THE JOURNAL OF
CLINICAL PSYCHIATRY
PSYCHIATRIST.COM
2011

The History of Psychopharmacology
NCDEU
Festschrift Collection
~50 Years~

THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

THE JOURNAL OF CLINICAL PSYCHIATRY

2011

Physicians Postgraduate Press, Inc.

THE JOURNAL OF CLINICAL PSYCHIATRY

2011

Physicians Postgraduate Press, Inc.

Mission Statement

Our primary mission is to provide lifelong learning for the physician through evidence-based, peer-reviewed scientific information about the diagnosis and treatment of behavioral health and neuropsychiatric disorders.

General

The Journal of Clinical Psychiatry (print ISSN 0160-6689; online ISSN 1555-2101) is published monthly by Physicians Postgraduate Press, Inc., PO Box 752870, Memphis, TN 38175-2870, and is the official publication of the American Society of Clinical Psychopharmacology. Periodicals postage paid at Memphis, TN, and additional mailing offices. POSTMASTER: Send address changes to Circulation Department, Physicians Postgraduate Press, Inc., PO Box 752870, Memphis, TN 38175-2870.

Editorial

The Journal of Clinical Psychiatry
PO Box 752870
Memphis, TN 38175-2870, USA

phone: 901-273-2707
e-mail: **JCPeditorial@psychiatrist.com**

Manuscript Submission

All manuscript types and letters to the editor should be submitted electronically at **www.psychiatrist.com/authors/esubmissions.htm**.

Book Reviews

Press release agents and physicians interested in reviewing books should contact the Book Review Editor at **bookreviews@psychiatrist.com**.

Instructions for Authors

Available at **www.psychiatrist.com/authors/index.htm**.

Indexing

The Journal of Clinical Psychiatry is indexed in MEDLINE/PubMed, EMBASE/Excerpta Medica, Psychological Abstracts, Current Contents, Science Citation Index, Hospital Literature Index, Biological Abstracts, Cumulative Index to Nursing and Allied Health Literature, International Nursing, PsycINFO, Chemical Abstracts, Adolescent Mental Health Abstracts, Alcohol and Alcohol Science Problems Database, Social Sciences Citation Index.

Circulation

Subscription Rates	US	Int'l
Individuals: Print + Online	$156.00	$207.00
Individuals: Online Only	$99.00	$99.00
Single issues	$45.00	$45.00
Institutional pricing	Contact **subscriptions@psychiatrist.com**	

Address Changes

Submit address changes at least 6 weeks in advance by mail or e-mail to:

Circulation Department
Physicians Postgraduate Press, Inc.
PO Box 752870
Memphis, TN 38175-2870

e-mail: **addresschange@psychiatrist.com**

Article copies and back issues

Individual articles and single copies of back issues may be purchased by contacting our Circulation Department.

phone: 800-489-1001 ext 4
901-751-3800 ext 4

fax: 901-273-2747
e-mail: **orders@psychiatrist.com**

Single article copies may also be purchased online at PSYCHIATRIST.COM.

Multiple copies of articles and reprints may be purchased by contacting our Permissions Editor at **permissions@psychiatrist.com**.

Claims

Publisher will replace missing issues within 4 months of the publication date, subject to availability. Issues claimed outside the 4-month deadline may not be honored. Claims can be submitted by mail; fax 901-273-2747 Attn: Circulation; or emailed to **claims@psychiatrist.com**.

To ensure correct processing of your claim, please supply as much information as possible, including your complete mailing address and your customer number if available.

Copyright/Financial Disclosure

The Journal of Clinical Psychiatry requires the express transfer of copyright to Physicians Postgraduate Press, Inc., so that the author(s) and Physicians Postgraduate Press, Inc., are protected from misuse of copyrighted material. Each author must sign and submit the required "Authorship Statement, Copyright Transfer, Financial Disclosure, and Acknowledgment Permission" form, available at **www.psychiatrist.com/authors/index.htm**.

Permissions Requests

All editorial material published in *The Journal of Clinical Psychiatry* is the property of Physicians Postgraduate Press, Inc., unless specifically stated.

1. Requests for permission to publish may be submitted by regular mail, fax, or e-mail. Please include full name, address, phone number, fax number, and e-mail address.
2. Send requests to:

   Physicians Postgraduate Press, Inc.
   Attn: Permissions Editor
   850 Ridge Lake Blvd, Suite 300
   Memphis, TN 38120

   fax: (920) 457-0501
   e-mail: **permissions@psychiatrist.com**
3. Permission will not be granted until the article has been published in *The Journal of Clinical Psychiatry*.
4. Permission is not granted to place the full text of *The Journal of Clinical Psychiatry* articles on other Web sites.

Information Required for a Permissions Request

1. Requestor's Information:
   - Person's name, title, telephone, fax, and e-mail (if available)
   - Company's name and postal address
2. Article Information:
   - Article title
   - First bylined author
   - Volume number and issue dates
   - Page range of article
   - The copyrighted item to be used from the article, ie, the specific chart, table, figure, graph, or other illustration, abstract, quote, or full article
3. Intended Use of the Requested Item:
   - Title of the work in which the item is to appear
   - Author/editor/compiler
   - Publisher, with full address
   - Edition number
   - Publication year
   - Approximate press run of work
   - Form of reproduction (print, online, language)
   - Sponsorship, funding, or retail price (if a book)
   - Intended audience(s)

Embargo

Articles are embargoed until they are published online at PSYCHIATRIST.COM. Contact **JCPembargo@psychiatrist.com**.

Advertising

Principles

Physicians Postgraduate Press, Inc., adheres to the highest ethical standards when interspersing advertisements throughout the journal: (1) placement is held in the strictest confidence; (2) ads on a specific drug or topic are not placed immediately adjacent to editorial material of the same; (3) for non-premium positions, ads are rotated throughout the book from issue to issue.

Contacts:

- For print ads, send an e-mail to **journalads@psychiatrist.com**.
- For Classified or Conference ads, either in print format or through the journal's Web site, send an e-mail to **journalads@psychiatrist.com**.
- For online ads posted either on the journal's Web site or in an E-Lert, send an e-mail to **webads@psychiatrist.com**.

Rate Sheets

Available online through the journal's home page at PSYCHIATRIST.COM under "Information for Advertisers."

BPA WORLDWIDE BUSINESS

Disclaimer

Acceptance of any and all advertising in this publication, or any other material published by Physicians Postgraduate Press, Inc., does not imply endorsement by Physicians Postgraduate Press, Inc.

Disclaimer

The Journal of Clinical Psychiatry is owned and published by Physicians Postgraduate Press, Inc., 850 Ridge Lake Blvd, Suite 300, Memphis, TN 38120. All articles appearing in this publication, including editorials, letters, and book reviews, represent the opinions of the authors and do not necessarily reflect the official policy or opinions of Physicians Postgraduate Press, Inc., or the institution with which the author is affiliated, unless this is clearly specified. Physicians Postgraduate Press, Inc., disclaims any liability to any party for the accuracy, completeness, or availability of any and all Physicians Postgraduate Press, Inc., publications and other material, or for any damages arising out of the use or nonuse of this publication, and any and all Physicians Postgraduate Press, Inc., publications (and other material), and any information contained therein.

THE JOURNAL OF
CLINICAL PSYCHIATRY
2011

THE HISTORY OF PSYCHOPHARMACOLOGY
NCDEU
FESTSCHRIFT COLLECTION
~50 YEARS~

ARTICLES

© COPYRIGHT 2011 PHYSICIANS POSTGRADUATE PRESS, INC.

NCDEU's Golden Anniversary

This June marked the 50th annual NCDEU meeting, cosponsored by the National Institute of Mental Health (NIMH) and the American Society of Clinical Psychopharmacology (ASCP). Begun a half century ago as the Early Clinical Drug Evaluation Unit (ECDEU), a psychopharmacology research program of NIMH, the meeting provided a forum for the pioneers in this new therapeutic area to meet and discuss common interests. ECDEU grew in scope and attendees, and its name later evolved to New Clinical Drug Evaluation Unit, which conveys little information. The acronym *NCDEU*, however, is widely recognized and highly regarded.

I first attended NCDEU as an investigator in an NIMH-sponsored collaborative study of fluphenazine decanoate in 1974. From then until 2010 I have missed only 1 meeting—which conflicted with my wedding. NCDEU is a regular and valued fixture on my annual calendar.

From its inception as a forum for NIMH and university clinical researchers, ECDEU/NCDEU has grown to encompass representatives of pharmaceutical and device manufacturers, physicians from the US Food and Drug Administration, employees of clinical research organizations and research sites, and other interested clinicians and investigators. The meeting provides an informal but scintillating venue for creativity and collaboration. Retaining its primary focus on clinical psychopharmacology research, NCDEU has expanded to include psychosocial interventions, health economics, outcomes research, ethics, public policy, and much more. Many fertile seeds have taken root at NCDEU and subsequently yielded fruit to nourish the practice of Psychiatry.

The 50th anniversary meeting of NCDEU provided an opportunity for some of the field's leaders to look back and forward at progress in important areas of psychopharmacology and clinical science. In this issue and throughout the next year, *JCP* will publish a number of Festschrift articles to celebrate NCDEU, the pioneers in psychopharmacology, and progress in our robust field. We are honored to bring you the reviews, work, and thought of some of the leading figures in Psychiatry.

ASCP, this journal's partner, is a recent but natural cosponsor with NIMH of the NCDEU annual meeting. ASCP's leadership role is likely to expand in the meeting's future. ASCP and *JCP* look forward to our growing partnership and involvement in NCDEU and Psychiatry's promising future.

Alan J. Gelenberg, MD
Editor in Chief
agelenberg@psu.edu
doi:10.4088/JCP.10f06326whi

Jonathan O. Cole, MD (1925–2009): Innovator in Clinical Psychopharmacology and of the ECDEU/NCDEU Tradition

Nina R. Schooler, PhD

To honor the 50th anniversary of the ECDEU/NCDEU meetings, *The Journal of Clinical Psychiatry* is publishing a series of articles reviewing the past and anticipating the future in clinical psychopharmacology. This note is designed to provide a brief account of Jonathan Cole's key role in initiating the meeting that has become the New Clinical Drug Evaluation Unit (NCDEU).

Jonathan O. Cole, MD, was a unique leader in the creation of the field of clinical psychopharmacology. Obituaries from the American College of Neuropsychopharmacology[1] and the Collegium Internationale Neuro-Psychopharmacologicum,[2] the leading organizations in the field, and a memorial celebration of his life in September 2009 paid tribute to his seminal contributions. He was a distinguished administrator—Chief of the Psychopharmacology Service Center (PSC) at the National Institute of Mental Health (NIMH) and Superintendent of the Boston State Hospital. He was a much revered teacher of generations of residents at the McLean Hospital in Boston, Massachusetts. His textbooks, written in collaboration with Alan F. Schatzberg, MD, communicated these teachings to countless individuals who never had the opportunity to learn directly from his prodigious knowledge of the field.[3] He was an imaginative and rigorous researcher. One of his early publications on treatment of schizophrenia (1964) was formally authored by the National Institute of Mental Health Psychopharmacology Service Center Collaborative Study Group and is indexed under "Anonymous" by the National Library of Medicine.[4] This was the first in a series of seminal multicenter collaborative studies he initiated at the PSC.[5,6] His later contributions to the treatment of depression with medications remain as valid and insightful today as when they were published.[7]

In 1960, as Chief of the PSC, Jon Cole was using a variety of means to "jump start" the then nascent field of clinical psychopharmacology. As he recounted the story later, one strategy was to claim research already being supported by NIMH as clinical psychopharmacology.[8] A lasting contribution was to establish the Early Clinical Drug Evaluation Unit (ECDEU) program at universities and clinical centers around the country. Started with 15 grantees in 1950, the program was designed to provide open-ended support that would allow investigators to design and conduct research to examine the new medications quickly as they became available. Given that the discovery of chlorpromazine as a medication to treat psychosis had been serendipitous, the idea was that researchers poised to translate new discoveries into treatment through observation and rapid initiation of experiments would speed discovery into practice. The

Submitted: *November 18, 2010; accepted November 22, 2010*
J Clin Psychiatry 2011;72(3):286–287 (doi:10.4088/JCP.10com06726).
Corresponding author: *Nina R. Schooler, PhD, Department of Psychiatry and Behavioral Sciences at SUNY Downstate Medical Center, 450 Clarkson Ave Box 1203, Brooklyn NY 11203 (nina.schooler@gmail.com).*

studies conducted by the ECDEU investigators were often small; sometimes they were placebo controlled and sometimes open. They relied heavily on the clinical acumen and impressions of the investigators to document both the efficacy and the safety of the drugs being studied. The leaders of these units came together once or twice a year for closed meetings to share their findings (and problems) in conducting research in this new area. From its inception, the ECDEU program was international; Pierre Deniker, MD, of France, one of the discoverers of the potential of chlorpromazine as a psychiatric treatment, was one of the original ECDEU investigators. These small, closed meetings were the beginning of the ECDEU/NCDEU tradition. As recounted by Cole at the 25th anniversary of the NCDEU meeting,[8] the meeting gradually expanded. Pharmaceutical company representatives were invited to attend sessions at which their drugs were being discussed, investigators who no longer had support continued to attend, the US Food and Drug Administration sent representatives, and international investigators joined the meeting.

In 1976, the meeting was renamed the NCDEU (New Clinical Drug Evaluation Unit) Meeting. Many of the important characteristics embedded in the evolving program designed by Jonathan Cole continue in the renamed meeting. These include the early recognition of the value of multicenter studies[4–6]; the NCDEU meeting as a venue that supports partnership and collaboration among academia, government, and industry; and the recognition of the NCDEU meeting as the setting to report and discuss methodological advances.

At the 25th anniversary of ECDEU/NCDEU, Jon Cole[8] said, "If I am partially responsible for the development of the unique and excellent program, I am glad." That statement reflects his characteristic modesty about his accomplishments. To the contrary, the ECDEU program was his unique vision to establish a community of investigators dedicated to development of a new field. The ECDEU/NCDEU meeting represents a continuing demonstration of his accomplishment in providing a focused and open forum. The expanding community of academic researchers, pharmaceutical industry scientists and drug developers, United States and international regulatory authorities, and others involved in medication development in psychiatry continues to meet to report on findings, discuss methodological advances, and interact informally. The meeting now includes a special program dedicated to support and development of new investigators in the field. His spirit of modesty, honest, and unpretentious communication and the single agenda of the pursuit of new knowledge established a tone for the meeting that remains the NCDEU goal going forward, despite the more complex array of problems and constituents. NCDEU at 50 represents a fitting legacy to Jonathan Cole's early vision.

Author affiliation: From the Department of Psychiatry and Behavioral Sciences at SUNY Downstate Medical Center, Brooklyn, New York.
Potential conflicts of interest: Dr Schooler is a consultant for and has received honoraria from Eli Lilly & Company, Hoffman La Roche, Merck, H Lundbeck A/S, Ortho-McNeil Janssen, Pfizer Inc, and Dainippon Sumitomo; and has received grant/research support from Astra Zeneca, Bristol Meyers Squibb, H Lundbeck A/S, OrthoMcNeil Janssen, and Pfizer Inc.
Funding/support: None reported.

REFERENCES

1. Katz MM. Jonathan O. Cole. *Neuropsychopharmacology*. 2010;35(13):2647. doi:10.1038/npp.2009.232 PubMed
2. Gershon S. Obituary Jonathan O. Cole, MD 1925-2009. http://cinp.org/en/member-login/obituaries/jonathan-o-cole-md-1925-2009/. Accessed November 23, 2010.
3. Schatzberg AF, Cole JO, DeBattista C. *Manual of Clinical Psychopharmacology*. Arlington, VA: American Psychiatric Publishing Inc; 2010.
4. National Institute of Mental Health Psychopharmacology Service Center Collaborative Study Group. Phenothiazine treatment in acute schizophrenia: effectiveness. *Arch Gen Psychiatry*. 1964;10:246–261. PubMed
5. Prien RF, Cole JO. High dose chlorpromazine therapy in chronic schizophrenia. Report of National Institute of Mental Health—Psychopharmacology Research Branch Collaborative Study Group. *Arch Gen Psychiatry*. 1968;18(4):482–495. PubMed
6. Raskin A, Schulterbrandt JG, Reatig N, et al. Differential response to chlorpromazine, imipramine, and placebo: a study of subgroups of hospitalized depressed patients. *Arch Gen Psychiatry*. 1970;23(2):164–173. PubMed
7. Cole JO. Where are those new antidepressants we were promised? *Arch Gen Psychiatry*. 1988;45(2):193–194. PubMed
8. Cole JO. The ECDEU-NCDEU Program. *Psychopharmacol Bull*. 1986;22:3–5.

What's Next After 50 Years of Psychiatric Drug Development: An FDA Perspective

Thomas P. Laughren, MD

This article discusses changes in psychiatric drug development from a US Food and Drug Administration (FDA) standpoint. It first looks back at changes that have been influenced by regulatory process and then looks forward at FDA initiatives that are likely to affect psychiatric drug development in the future.

FDA protects the public health by ensuring the safety and efficacy of drug products introduced into the US market. FDA works with drug sponsors during development, and, when applications are submitted, reviews the safety and efficacy data and the proposed labeling. Drug advertising and promotion and postmarketing surveillance also fall within FDA's responsibility.

Among the many changes in psychiatric drug development over the past 50 years, several have been particularly influenced by FDA. Populations studied have expanded diagnostically and demographically, and approved psychiatric indications have become more focused on the clinical entities actually studied, including in some cases specific symptom domains of recognized syndromes. Trial designs have become increasingly complex and informative, and approaches to data analysis have evolved to better model the reality of clinical trials.

This article addresses 2 general areas of innovation at FDA that will affect psychiatric drug development in years to come. Several programs falling under the general heading of the Critical Path Initiative, ie, biomarkers, adaptive design, end-of-phase 2A meetings, and data standards, are described. In addition, a number of important safety initiatives, including Safety First, the Sentinel Initiative, the Safe Use Initiative, and meta-analysis for safety, are discussed.

J Clin Psychiatry 2010;71(9):1196–1204

Submitted: *May 19, 2010; accepted May 20, 2010*
(doi:10.4088/JCP.10m06262gry).
Corresponding author: *Thomas P. Laughren, MD, Division of Psychiatry Products, Center for Drug Evaluation and Research, US Food and Drug Administration, 10903 New Hampshire Ave, Silver Spring, MD 20993 (thomas.laughren@fda.hhs.gov).*

Drug development for psychiatric products has changed substantially over the past 50 years. This article will discuss this evolution from the standpoint of US Food and Drug Administration (FDA)'s role in this process and will then describe FDA initiatives that will have important effects on psychiatric drug development in the future.

FDA'S ROLE IN DRUG DEVELOPMENT

FDA's primary role is to protect public health by ensuring the safety and efficacy of drug and biologic products and also medical devices that are introduced into the US market.[1] This communication will be limited to FDA's role in drug development. FDA's authority to regulate drug development derives from the Federal Food, Drug, and Cosmetic Act (FD&C Act).[2] Regarding efficacy, the FD&C Act states that approval of a drug requires "substantial evidence" from "adequate and well-controlled investigations."[3] *Substantial evidence*, although not well-defined in the statute, is generally interpreted to mean sufficient evidence, but not necessarily overwhelming evidence. *Adequate and well-controlled investigations* are defined in FDA's regulations[4] that identify an array of study designs that can meet this standard, ranging from historical control to double-blind, placebo-controlled trials. For psychopharmacologic drug products, however, it is generally accepted that the most easily interpretable design is the placebo-controlled trial.[5] The FD&C Act describes the requirement for safety as follows: (1) must "include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling" and (2) "the results of tests show that such drug is safe under such conditions."[3] The safety requirement is interpreted to mean that a drug development program must have included all safety testing that would generally be considered necessary to adequately assess the safety of the new drug product, and that the results of these tests must establish that the new drug is reasonably safe, given the seriousness of the condition being treated and the circumstances of use. Both of these requirements are, of course, matters of judgment. What can be considered sufficient safety testing is an evolving standard that becomes better defined as we continue to learn about the adverse effects that drugs can have, eg, there is a recent requirement that prospective suicidality assessments must be included in psychopharmacologic drug studies. FDA also has a major role in deciding how the package insert (labeling) is written and in regulating drug advertising and promotion, which are largely based on the specific language included in the package insert.

FDA has oversight over the IND (investigational new drug) process under which new drug products are studied and developed in human subjects.[6] Once a drug sponsor has developed a product to the point where it is ready to be introduced into humans, ie, there is sufficient information about

its chemistry, manufacturing, and controls (CMC) and sufficient nonclinical safety data to justify safe human use, it must apply for an IND. From that point forward, FDA oversees all human trials with that product; every protocol must be submitted before it is initiated and serious unexpected adverse events that occur must be reported promptly. FDA then determines at each point in development that continued testing in humans is justified. Once a drug sponsor has completed its development and submits a new drug application (NDA),[7] FDA has the responsibility for carefully reviewing all aspects of this complex package of CMC, nonclinical, pharmacokinetic, and clinical data to determine whether or not the new product can be approved and marketed. FDA continues to have oversight over drug products after they reach the marketplace. This oversight includes assessment and monitoring of additional trials a sponsor decides to conduct, evaluation of new safety signals that emerge from postmarketing use of a drug, evaluation of new claims arising from continued development, and monitoring of drug advertising and promotion.

There is often confusion about certain activities that FDA does not regulate, in particular, off-label use. Once approved, a drug product generally may be used by prescribers for any use they deem justified, even if the use is not FDA approved. In rare circumstances, however, FDA may restrict the use of a drug to prescribers who have had training in the drug's use or who carry out particular safety assessments. The drug clozapine is marketed under a restricted distribution system requiring that all patients and prescribers must be registered and that a white blood cell count must be obtained at a specified frequency to identify neutropenia as soon as feasible. In labeling, FDA also identifies safety information that can affect use, eg, warnings about certain off-label uses. The antipsychotic drugs have a box warning alerting prescribers to a risk of excess mortality associated with the use of these drugs in patients with dementia, even though they are not approved for use in this population.[8] Some drugs are recommended for use only in patients who have failed alternative treatments.

EVOLUTION IN REGULATORY ASPECTS OF PSYCHIATRIC DRUG DEVELOPMENT OVER THE PAST 50 YEARS

There have been many changes in psychiatric drug development programs over the past 50 years, including the illnesses studied, the nature of the claims sought, the diversity of patients included in clinical studies, and the complexity of trial designs and data analysis. Many of these changes were a result of the evolution of this research field, but in some instances these changes resulted from FDA initiatives and regulatory actions. This section will briefly review these changes and bring the reader to where we are at present from a regulatory perspective in psychopharmacologic research.

Increasing Specificity of Targeted Indications

Drug product labels from 20+ years ago reveal that psychiatric drug indications at that time were often quite broad and general, eg, drugs were approved for the treatment of anxiety or depression, or in the case of schizophrenia, for the "management of the manifestations of psychosis." This was true despite the fact that the development programs in these instances were quite narrow, focusing, for example, on patients with generalized anxiety disorder, major depressive disorder, and schizophrenia. Since that time, labeling claims have gradually shifted to more narrow indications focusing on the clinical entities actually studied in these programs. This change in focus came about at least in part because of FDA's efforts to prevent drug sponsors from promoting their drugs for indications not studied in their development programs. Development programs have now been conducted and drugs have now been approved for essentially all of the anxiety disorders, including generalized anxiety disorder, obsessive compulsive disorder, panic disorder, social anxiety disorder, and posttraumatic stress disorder. In addition to multiple approvals for major depressive disorder (MDD), including recent approvals for 2 atypical antipsychotics as adjunctive therapy in patients with MDD not adequately responding to other antidepressants, drugs are now approved for bipolar depression, seasonal affective disorder, and treatment-resistant depression. A selective serotonin reuptake inhibitor (SSRI) is approved for treating bulimia and PMDD, a number of atypical antipsychotics are now approved for treating bipolar mania, and a number of new drugs and new formulations of older drugs are approved for treating attention-deficit/hyperactivity disorder (ADHD).

In addition to a broader array of approved indications, FDA has endorsed, and drug sponsors have pursued, other clinical entities for which drug approvals have not yet been accomplished. The entity "psychosis of Alzheimer's disease" has been accepted by FDA as a legitimate drug target,[9] as have psychotic depression, cognitive deficits in schizophrenia,[10] and negative symptoms in schizophrenia.[11] The latter 2 clinical entities represent a departure from the usual focus in psychopharmacologic drug development programs on *DSM*-recognized diseases and syndromes to a focus on specific symptom domains or symptom clusters that are part of a broader syndrome. FDA has traditionally resisted focusing on specific symptoms of a recognized entity as legitimate drug targets, out of concern for "pseudospecificity,"[12] ie, a concern that the claim is artificially narrow and is constructed purely for reasons of establishing a market niche. An example of a pseudospecific claim would be for hallucinations in schizophrenia for a drug that in fact is effective in treating an array of positive symptoms. On the other hand, as noted, FDA has accepted a more narrow focus for certain targets, eg, cognitive deficits in schizophrenia and negative symptoms in schizophrenia, since these are well-recognized aspects of this condition that are not well addressed by currently approved drugs that treat mostly the positive symptoms. FDA has, in fact, already approved drugs for certain more narrow targets, eg, certain intramuscular formulations of atypical antipsychotics for agitation in schizophrenia and bipolar disorder, clozapine for suicidality in schizophrenia, and 2 atypical

antipsychotic drugs for treating irritability associated with autistic disorder.

Broadening of Diversity of Populations Studied

There has also been a broadening of the populations included in drug development programs, including both demographic diversity and comorbidity. Inclusion of broad populations in development programs is important because it increases the ability to generalize the findings to the population that will eventually be treated with a new compound after approval and marketing. FDA has encouraged inclusion of broader populations through guidance documents and special initiatives. An International Conference on Harmonisation (ICH) guidance on the elderly[13] encourages including the elderly in development programs for drugs likely to be used in elderly patients, and an FDA guidance on gender[14] encourages including both genders in drug development. FDA has also launched several initiatives intended to increase the study of drugs in pediatric patients to provide clinicians with better information on use of drugs in this population for which much prescribing is currently off-label. The Food and Drug Administration Modernization Act (FDAMA 1997)[15] gave FDA authority to grant additional market exclusivity to companies that conduct studies in pediatric patients, and this authority was continued in the Best Pharmaceuticals for Children Act (BPCA) of 2001. The Pediatric Research Equity Act of 2003 (PREA) gave FDA authority to actually require pediatric studies in certain situations. In addition, the Food and Drug Administration Amendments Act of 2007 (FDAAA) reauthorized FDA's authority for both granting exclusivity and requiring pediatric studies in certain instances.[16] These programs have led to approvals of psychiatric drugs for the treatment of MDD, obsessive-compulsive disorder, schizophrenia, and bipolar disorder in pediatric patients. Current regulations (21 CFR 314.50) require analysis of safety and effectiveness findings by age, gender, and race.[17]

The study of drug treatment in certain psychiatric conditions with comorbid conditions that historically have been viewed as potentially problematic has led to approvals of labeling that assures clinicians of the safety of certain compounds in patients with these comorbid conditions, eg, sertraline in patients with comorbid acute coronary syndrome and atomoxetine in patients with comorbid Tourette's disorder. Although progress has been made in increasing the diversity of the populations studied in psychiatric drug development programs, more effort is needed to expand the range of patients included in trials.

Evolution of Clinical Trial Designs

Trial designs have also changed considerably over the past 20 to 30 years. Earlier development programs for psychiatric drugs generally involved relatively short-term studies (3–6 weeks) comparing a flexible-dose of new drug, often titrated to response, and placebo. Recent trials more often include fixed-dose designs and active controls for assay sensitivity. FDA has encouraged fixed-dose designs because these can provide clinicians with useful dose response information.[18] Examples of where these programs have been useful include risperidone and desvenlafaxine for which, in both instances, the dose response curve for effectiveness showed no added benefit for higher doses, but clearly more adverse effects for those doses were observed. There have been suggestions that this design leads to a higher failure rate than flexible-dose studies, perhaps because the multiple active drug arms raise expectations of benefit and thereby enhance placebo response.[19] Other analyses have not observed this difference.[20] An active control arm is used to show that a trial has "assay sensitivity," ie, the ability to distinguish effective from ineffective treatments. The active control arm is, in a sense, an insurance policy for a drug sponsor, as the interpretation of a "failed" 3-way study including an active control that also fails to beat placebo is different from a 2-way trial where new drug fails to beat placebo, a "negative" trial in FDA's view. Increasingly, companies are conducting "add-on" studies in which a second drug is added to an initial drug to which patients have had a partial but suboptimal response. Such studies have been done in MDD, generalized anxiety disorder, bipolar mania, and schizophrenia.

A study design of interest, but rarely used, is a study in nonresponders in which failures on a treatment are randomized to the failed treatment and the new drug. Such a study in nonresponders to typical antipsychotic drugs led to the approval of clozapine.[21]

Some programs have included fixed combination designs. These are studies comparing a combination of drugs with the 2 separate drugs in the combination. Symbyax (fluoxetine/olanzapine) was studied in this way and is approved for both bipolar depression and treatment-resistant depression.

At FDA's urging, it has now become standard for companies to conduct maintenance studies, not typically as part of an initial program, but postmarketing (phase 4), using a "randomized withdrawal" design, in which responders from an open-label run-in period on a drug are randomly assigned to continuation of that drug or to placebo, with time to relapse as the endpoint of interest.

Finally, there have now been a few large simple trials for psychiatric drugs, primarily to answer questions about comparative risk, eg, the Zodiac trial for ziprasidone versus olanzapine to observe for cardiovascular risk[22] and the Sertindole Cohort Prospective (SCoP) Study for sertindole versus risperidone to examine cardiovascular risk.[23]

Increasing Innovation in Data Analysis Approaches

Approaches to data analysis have also evolved. For many years, analysis using the last observation carried forward (LOCF) was the standard approach to dealing with missing data in evaluating drug trials at FDA. In more recent years, the advantages of other models, in particular the mixed model repeated measures (MMRM) approach, have been recognized,[24] and these MMRM approaches are currently preferred for analyzing psychopharmacologic trial data in

© Copyright 2011 Physicians Postgraduate Press, Inc.

the division of psychiatry products at FDA. It is important in using any model, including the MMRM model, to assess for whether or not the assumptions of the model are satisfied. In the case of the MMRM approach, it is assumed that dropouts are missing at random (MAR). It is critical, therefore, to obtain as complete information as possible on why patients leave these trials early.

WHAT TO EXPECT FROM FDA OF THE FUTURE WITH REGARD TO PSYCHIATRIC DRUG DEVELOPMENT

FDA has launched a number of initiatives in recent years that will undoubtedly affect the landscape of drug development in years to come, including psychiatric drug development programs. This article will focus on changes that generally fall into 2 areas: (1) critical path initiatives and (2) safety initiatives.

Critical Path Initiative

The Critical Path Initiative (CPI) is FDA's strategy for modernizing the approaches by which FDA-regulated products are developed, manufactured, evaluated, and used.[25] This effort was launched in March 2004 to address an observed decline in the number of product applications being submitted to FDA, despite an abundance of important breakthroughs in biomedical science and an ever increasing number of resources being devoted to developing such products. For drug products, the target of this initiative is the "critical path," ie, the pathway from discovery of a new compound of interest to ultimate launch of that product. The goal was to diagnose the roadblocks in this path and find solutions. The initial announcement requested an identification of specific activities along this path that could help to modernize product development sciences. There was a robust response to this request, and, in March 2006, FDA released a report[26] that included a list of 76 opportunities for development projects that could lead to advances in product development. These opportunities included projects in the areas of biomarkers, trial design, analysis, bioinformatics, among others. Numerous projects are now underway. This section will summarize several areas of interest that should impact positively on drug development within the area of psychopharmacology in years to come.

Biomarkers. Despite substantial progress in psychopharmacology over the last 50 years, there is abundant evidence for a current problem in psychiatric drug development. There have been no real "breakthrough" drugs since the SSRIs/SNRIs and the atypical antipsychotics. Most psychiatric new drug approvals in recent years have not been "novel" compounds, but rather, active enantiomers of already approved racemic mixtures, active metabolites of parent drugs that have activity very similar to the parent, or other "me-too" drugs (ie, members of the same class with minor differences). Such modestly different drugs can sometimes have important advantages, but major gains are rare. The newer drugs have generally not been found to be any more effective than older drugs, eg, as suggested by the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study for antipsychotics,[27] and the Agency for Healthcare Research and Quality (AHRQ) analysis for antidepressants.[28] Only 37% of patients with MDD experienced a remission with the initial drug used for treatment in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial.[29] Polypharmacy also continues to be very common in psychopharmacology,[30] suggesting that the need for more effective agents is apparent. Also of concern is the high failure rates for registration trials in psychopharmacology, eg, about a 50% failure rate in depression trials[5] and a rising failure rate in schizophrenia trials.[31] A fundamental problem is the fact that there is only a limited understanding of psychiatric disorders at a biologic level, so that psychiatric disorders are defined on the basis of symptoms rather than biologically. It is difficult to design drugs for diseases that we do not understand at a biologic level.

It is a widely held view that biomarkers might help in psychiatric drug development. FDA defines *biomarkers* as "measurable characteristics that reflect physiological, pharmacological, or disease processes in animals or humans."[26(pR-9)] Although biomarkers have many potential applications in drug development, the focus in this article will be on finding biomarkers that can predict efficacy or risk associated with psychiatric drug treatment, although markers that signal a low likelihood of spontaneous improvement (response in a placebo group) could also be very useful. The main goal of biomarker application in predicting efficacy and risk is to subgroup the population into responders/nonresponders and into those at risk/not at risk for some adverse event of interest. Our limited understanding of the biology of psychiatric disorders greatly limits our search for target markers. Examples of possible biomarkers include imaging measures, serum assays, genetic assays (genomic markers), physiologic measures, histopathological findings, psychological tests, and demographic variables (age, gender, race).

There are 2 principal ways a biomarker (B) could subdivide the population, ie, on the basis of differences in exposure (by far the best developed group of biomarkers) or differences in pharmacodynamic response. In either case, the differences could divide patients on the basis of either efficacy or risk. For example, if marker positive patients (B+) differ from marker negative patients (B–) by having higher exposures to a drug, that difference could translate into a difference in efficacy, eg, better efficacy in B+ patients, or a difference in risk, eg, a greater risk in B+ patients. Similarly, a pharmacodynamic difference between B+ and B– patients, unrelated to exposure, could be reflected by differences in efficacy or risk.

There are already many examples of genomic biomarkers that predict exposure, ie, pharmacokinetic differences based on different activities in metabolizing enzymes. Information about individual differences in levels of several polymorphic enzymes, with resulting differences in drug

exposures, is reflected in labeling for a number of drugs. These enzymes include CYP2C9, CYP2B6, CYP2C19, and CYP2D6. Atomoxetine, a selective norepinephrine reuptake inhibitor approved for the treatment of ADHD, is cleared predominantly by CYP2D6, and 2D6 poor metabolizers (PMs) have 10-fold higher plasma levels of atomoxetine than 2D6 extensive metabolizers (EMs).[32] Since the clinical relevance of this difference in exposure is not clear, the labeling for atomoxetine mentions the availability of genetic tests to determine 2D6 metabolizer status, but does not require such testing. Another example of a drug affected by 2D6 metabolizer status is codeine, an analgesic. Codeine is metabolized to the active species, morphine, by CYP2D6, and the drug has little or no effect in 2D6 PMs, who produce little active analgesic. On the other hand, 2D6 ultrametabolizers (UMs) produce toxic levels of morphine, and there have been reports of deaths in infants breastfeeding from mothers who are 2D6 UMs who have been given codeine.[33] It is also known that 2D6 PMs have approximately 8-fold increases in plasma levels of desipramine after exposure to desipramine, compared to 2D6 EMs.[34] Thus, genomic biomarkers have already had a substantial impact on the prescribing of medications, including psychiatric drugs.

There are fewer examples of biomarkers that predict differences in pharmacodynamic responses, and most are in the oncology area where the diseases are often understood at a molecular level. There are several oncology drugs for which biomarkers predict better efficacy for marker positive patients. The HER2 gene expresses a cell surface receptor that is needed for growth of breast cancer cells, and this gene is overexpressed in about 20% of breast cancers.[35] Trastuzumab (Herceptin) is an antibody that blocks this cell surface receptor. There is a kit available for identifying this subgroup of breast cancer patients, and clinical trials and other data suggest that it is primarily this subgroup that benefits from Herceptin treatment.[36] Labeling recommends Herceptin only for this HER2 positive subgroup of breast cancer patients.[37] For psychiatric drugs, there are some early findings suggesting that biomarkers may help in predicting responsiveness to drugs. One such example is for SSRIs and serotonin genes. Several studies suggest that an allele of the polymorphic serotonin transporter gene (5-HTTLPR) is associated with an SSRI response in Caucasians.[38] Data from the STAR*D trial suggest that a polymorphism in the *HTR2A* receptor gene is associated with a positive response to citalopram, an SSRI.[39] Although these findings are not as robust as the findings for several oncology drugs, they nevertheless give some encouragement that searching for biomarkers for psychiatric drug response may be fruitful.

On the safety side, there is an example of a biomarker that is a fairly strong predictor of the occurrence of serious skin reactions (Stevens Johnson syndrome [SJS] and toxic epidermal necrolysis [TEN]) in patients receiving the drug carbamazepine. The incidence of SJS/TEN is approximately 1–6/10,000 in Caucasians treated with carbamazepine compared to a much higher incidence of 30/10,000 in some Asian countries.[40] There is a strong association between the HLA-B* 1502 variant and the occurrence of SJS/TEN with carbamazepine in Asian populations.[41] The positive predictive value of this marker for SJS/TEN is 0.1 (ie, about 10% of patients who are positive for this marker develop SJS/TENS when treated with carbamazepine), and the negative predictive value is 1.0 (ie, there are no cases of SJS/TENS in patients who are negative for this marker). The labeling for carbamazepine recommends testing for this variant in Asian patients, and recommends an alternative drug if the test is positive for the allele, unless there is some compelling reason not to choose an alternate drug.

Although there are not, as yet, biomarkers that reliably predict responsiveness to psychiatric drugs, there is much interest in exploring for such markers. Consequently, it is important to plan for development programs involving biomarkers, and to try to address the practical issues and questions that emerge in such endeavors. Pharmaceutical sponsors are of course very interested in knowing what is required to get potentially useful biomarker information into a drug label. One critical issue is the need for hypothesis testing to establish a biomarker as a predictor of responsiveness. Before deciding on what hypotheses to test in definitive trials to support labeling, it is important to conduct enough pilot work to establish the best path forward. If, for example, it appears, based on pilot data, that a drug may work only in a subset of the population, it may be difficult to show that it is effective in a broad population, eg, patients with a *DSM-IV* diagnosis of schizophrenia. In that case, it may be preferable to study the drug initially in a subgroup of that larger population defined by some biomarker, eg, a genomic marker G, rather than the usual approach of testing in the broad population first. If this trial in the G+ subgroup were successful, it would then be important to examine the response in the G– population. If the drug is shown to work only in the G+ patients, and not to work at all in G– patients, this finding would support labeling targeting G+ patients. If, on the other hand, a sponsor wishes to obtain both a broad claim for a drug in the overall population, but, in addition, a specific claim in G+ patients, eg, a claim that this subgroup is particularly responsive, a different strategy would be needed. The sponsor would need to test the drug first in the overall population, and if successful, then in G+ patients. It is important to emphasize that it will always to necessary to examine the response in G– patients, even if not a formal test. If a drug works equally well in both G+ and G– patients, there would, of course, be no reason to include this genomic information in the label.

There are also other issues that need to be addressed in considering the use of biomarker information in drug development programs. Adaptive designs may be appropriate to increase the power for looking at a particular subgroup. The completeness of the biomarker information is also an important issue. Ideally, one would have biomarker information on the entire sample of patients, and randomization would be stratified on this basis. It is also important for sponsors to

understand that, if a drug is going to be labeled as needing testing of a biomarker, it will generally be necessary to assure the availability of a Center for Devices and Radiological Health (CDRH)–approved diagnostic kit. Thus, it would be necessary to have a parallel program underway in CDRH for the development and marketing of this kit.

Adaptive designs. *Adaptive design* is a term generally intended to refer to changes in the design or analysis of a clinical trial guided by examination of the accumulated data at an interim point with the goal of making the trial more efficient. Greater efficiency might mean fewer patients, shorter duration, greater likelihood of demonstrating an effect if one exists, or a more informative trial in other ways, eg, better information on dose response. FDA recently released a draft guidance on "adaptive design clinical trials for drugs and biologics" that is intended to assist sponsors in planning and conducting adaptive design clinical studies.[42] A study with an adaptive design includes a prospective plan for a modification of some aspect of the design or hypothesis testing based on an interim look at the data. The types of possible modifications are wide-ranging, and include changes in randomization procedure, treatment regimens, sample size, schedule of patient evaluations, primary endpoint, secondary endpoints, concomitant medications, and analytic methods. It is critical that whatever modifications are made are assessed for their effect on Type I error rate and that any needed adjustments are made. FDA will be focused on ensuring that Type I error is controlled. FDA encourages the consideration of adaptations to improve the efficiency of drug development. The division of psychiatry products also encourages such adaptive planning, and we expect to see the increasing use of such designs in psychiatric drug development programs in the future.

End-of-Phase 2A meetings. FDA is now offering End-of-Phase 2A meetings (EOP2A) to sponsors to provide early guidance on trial design for later phases of development.[43] The focus is on using clinical trial simulation and quantitative modeling based on prior knowledge (eg, on the drug, the disease, placebo response) to help in dose selection and other design features for future trials. The appropriate time for these meetings would be in early phase 2 after completion of an initial proof of concept study in patients. The basis for these discussions could be information of varying types, including biomarkers, surrogate endpoints, prior clinical trials data, or preclinical data. The information could come from a sponsor's resources or from FDA's own archived data. Sponsors need to take the initiative in requesting an EOP2A meeting, and would then interact with FDA staff in planning the meeting. Although there have not been any EOP2A meetings for psychiatric drug development programs to date, it is hoped that these meetings will begin to have an important role in psychiatric drug development programs of the future, as data resources and psychiatric disease understanding improve. With recent advances in genetics and neuroscience, there is reason to be hopeful that mental disorders can be reconceptualized in a way that is more conducive to drug discovery and development in this area.[44]

Data standards. One of the challenges of FDA's regulatory role is reviewing massive amounts of data generated during the development of drug products. This task has been facilitated in recent years by the transition from a paper to an electronic environment. This transition has been helped by agreement on specifications for an electronic common technical document (e-CTD).[45] There remain, however, obstacles to the efficient review of data, in particular, the very different formats used by different pharmaceutical sponsors for storing and sending data to FDA. These differences not only complicate the review of individual applications but also make it much more difficult to conduct meta-analyses across applications to look for safety signals that may not be detectable in individual programs. Differences in data standards include differences in file names, variable names, coding terminology, and data structures. In order to address this problem, FDA has begun to adopt standards established by the Clinical Data Interchange Standards Consortium (CDISC),[46] a nonprofit group whose goal is the development of such standards. One such standard that FDA has adopted is the Study Data Tabulation Model (SDTM) for clinical trial data. SDTM is a major advance, however, it is a 2-dimensional (flat file) structure that does not lend itself to addressing the complex relationships among data elements that characterize clinical reality. So an additional goal is to add another element to the overall model, ie, one developed by Health Level Seven International (HL7), a standards development organization for health care information exchange.[47] HL7 standards have been adopted internationally for health care information exchange and electronic health records (EHRs), and offer the advantage of 3-dimensional or even multidimensional representation of data. The resulting model will hopefully have the combined advantages of both individual elements.

Safety Initiatives and New FDA Authorities Regarding Safety Matters

One of FDA's responsibilities is to monitor the safety of its regulated products after marketing. For years, the mainstay of FDA safety monitoring has been the voluntary spontaneous reporting system, currently known as AERS (Adverse Event Reporting System). FDA does have a data mining capability with AERS to do proportionality analyses in order to sharpen its signal detection capability. Such data-mining explorations determine whether certain drugs have a greater proportion of their overall AERS reports representing a particular type of adverse event compared to other drugs, which would suggest that these drugs have a greater potential for this adverse event than comparator drugs. The methods for this data-mining approach are illustrated in an analysis of diabetes-related adverse events associated with the use of different antipsychotic agents in the AERS database; the analysis found important differences among the various drugs in the signal for such events.[48] FDA also has limited cooperative agreements with different outside groups to conduct observational studies to follow up on certain safety

© Copyright 2011 Physicians Postgraduate Press, Inc.

questions of interest, and has also relied on sponsors and the medical literature to learn about new risks emerging after a drug product has been marketed. Although these systems have been successful in identifying a number of new risks for drugs, they have not always been as efficient and timely as one would like. Consequently, FDA has launched a number of initiatives to enhance its ability to detect new safety signals and better understand drug risks. Recent legislation has also given FDA new authority to ask sponsors to conduct safety studies in certain circumstances.

New safety authorities under FDAAA 2007. FDAAA 2007 provided FDA with a number of new authorities, and several relate specifically to safety.[49] First, FDA can, in certain circumstances, require the conduct of studies and trials focused on specific safety issues. Second, FDA can now require sponsors to make certain safety-related labeling changes. Finally, FDA can require sponsors to develop and comply with risk evaluation and mitigation strategies (REMS), which are programs targeting a particular safety issue for a particular drug to ensure that it is detected and managed appropriately. The simplest REMS would be a medication guide, a patient-oriented document to provide patients and their families useful information about how to safely use a drug product. More complicated REMS might involve restricted distribution systems, focused monitoring and assessments, and even patient registries that would permit systematic tracking and assessment of all patients who receive a particular medication. Clozapine, for example, is available only under a program that restricts use to patients for whom health care providers are willing to register the patient and ensure that required blood testing is conducted; this is essentially a registry.

Safety First. FDA has always been concerned about and focused on the safety of drug and other FDA-regulated products. Safety First should be viewed as a renewal of FDA's commitment to this responsibility.[50] For drug products, this is an overall framework for integrating and implementing the policies, procedures, practices, and technology needed to meet this responsibility throughout a drug's lifecycle. Safety First will incorporate the implementation of FDA's new authorities under FDAAA 2007 and follow-up on various Institute of Medicine (IOM) reports and other activities related to ensuring the safety of drug products. Part of the implementation of this effort has been the creation of safety teams within each review division that include, at a minimum, a deputy for safety and a safety project manager. Safety issues will be formally tracked in the same way that drug applications are currently tracked to ensure they are fully addressed.

Sentinel Initiative. This initiative was launched by FDA in May 2008, in response to a mandate under FDAAA 2007, and is intended to complement existing systems FDA uses to track reports of adverse events linked to its regulated products. The Sentinel Initiative would enable FDA to actively query diverse automated health care data holders—like electronic health record systems, administrative and insurance claims databases, and registries—to evaluate possible medical product safety issues quickly and securely.[51] This system, unlike AERS, would be an active surveillance system that would allow for not only signal detection, but also signal strengthening and validation. It would also involve the use of linked automated health care data from multiple sources, unlike FDA's current contracts that are limited to single databases. It would be a resource for conducting observational studies using existing databases.

Safe Use Initiative. It is often said that FDA "does not regulate the practice of medicine" and this is certainly true. Nevertheless, FDA is concerned about unnecessary injuries and deaths that result from medication errors, many of which are preventable. The S*afe Use Initiative* is intended to foster public and private collaborations within the health care community in order to reduce preventable harm by identifying these risks and implementing interventions with partners in the community.[52] These partners include federal agencies, health care professionals and professional societies, pharmacies, hospitals, and other health care entities, patients, caregivers, consumers, and their representative organizations. Pilot programs are underway, and this initiative can be expected to expand FDA's collaborations with the community in years to come.

Meta-analyses for safety assessment. One approach FDA has used in recent years to detect signals for relatively uncommon serious adverse events is to conduct meta-analyses of placebo-controlled registration trials for which it has complete access to the trial data through NDAs and supplements. There are a number of examples of such analyses, including several in the area of psychiatric drugs. Because of concerns about possible treatment-emergent suicidality (suicidal ideation or behavior) in association with the use of antidepressants, 2 meta-analyses were conducted of placebo-controlled antidepressant trials. One of these involved pediatric trials[53] and the second involved trials in adults.[54] These meta-analyses confirmed a signal for treatment-emergent suicidality, in particular at the younger end of the age spectrum, and current antidepressant labeling has a box warning alerting clinicians to this risk. Meta-analyses of placebo-controlled registration trials were also conducted for the atypical antipsychotics. One of these examined mortality in elderly patients with dementia being treated for psychosis and other behavioral symptoms, and found an excess risk of mortality compared to placebo in these patients being treated with atypical antipsychotic drugs.[55] Other meta-analyses of placebo-controlled registration trials in this same population for certain drugs in the atypical class found an excess risk of cerebrovascular adverse events (strokes and transient ischemic attacks) for drug compared to placebo.[56] These adverse event findings are reflected in the labels for antipsychotic drugs. It can be anticipated that additional meta-analyses to explore adverse event signals will be conducted for psychiatric drug trials, and such analyses will be facilitated by the increasing standardization of clinical trials data that are submitted to FDA.

© Copyright 2011 Physicians Postgraduate Press, Inc.

CONCLUDING COMMENTS

FDA has helped to shape psychiatric drug development programs over the past 50 years and will continue to do so as the field progresses. Changes over the past 50 years that have had regulatory impact include expansion of the illnesses studied and the claims sought, increasing diversity in the populations studied, and innovation in both study design and data analysis. Several initiatives by FDA will have broad impact in drug development, including an impact on psychiatric drug development and practice. The Critical Path Initiative (CPI) includes a number of programs intended to increase the efficiency of drug development. One area of great interest under CPI is that of biomarkers, and there is hope that biomarkers might also streamline psychiatric drug development, both by identifying responsive subgroups and by identifying patients at particular risk for drug side effects. Other CPI initiatives include adaptive design, End-of-Phase 2A meetings, and data standards. Adaptive designs could help in a number of ways, by providing greater efficiency and increased chances of successful programs. End-of-Phase 2A meetings should help to make better use of available data and emerging understanding of psychiatric disease to better design later phase 2 and phase 3 clinical trials. Establishing data standards for NDA submissions could increase the efficiency of FDA reviews and facilitate meta-analyses that could help in assessing possible drug class risks. FDA has also launched a number of safety initiatives intended to ensure the safety of marketed products. FDA has new safety-related authorities under FDAAA 2007, and has moved to elevate safety considerations in FDA's organizational structure. The Sentinel Initiative promises to increase FDA's ability to detect safety signals by making more efficient use of large postmarketing databases, and the Safe Use Initiative seeks to reduce medication errors for marketed products by forming partnerships within the health care community. FDA's increasing use of meta-analyses for safety should help to assess safety concerns for drug classes. All of these initiatives can be expected to have important effects on psychiatric drug development and practice as well.

Drug names: atomoxetine (Strattera), carbamazepine (Carbatrol, Equetro, and others), citalopram (Celexa and others), clozapine (Clozaril, FazaClo, and others), codeine (Butalbital and others), desipramine (Norpramin and others), desvenlafaxine (Pristiq), fluoxetine (Prozac and others), imipramine (Tofranil and others), morphine (Apokyn, Kadian, and others), olanzapine (Zyprexa and others), olanzapine and fluoxetine (Symbyax), risperidone (Risperdal and others), sertraline (Zoloft and others), trastuzumab (Herceptin), ziprasidone (Geodon).

Author affiliation: US Food and Drug Administration, Silver Spring, Maryland.

Author contribution: Dr Laughren's contribution to the article was made in his private capacity. No official support or endorsement by the Food and Drug Administration is intended or should be inferred.

Potential conflicts of interest: None reported.

Funding/support: None reported.

REFERENCES

1. About FDA. US Food and Drug Administration Web site. http://www.fda.gov/AboutFDA/WhatWeDo/WhatFDARegulates/default.htm. Updated December 2, 2009. Accessed May 19, 2010.
2. Federal Food, Drug, and Cosmetic Act (FD&C Act). US Food and Drug Administration Web site. http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/default.htm. Updated March 5, 2010. Accessed May 19, 2010.
3. Sec 505. [21 USC §355] New Drugs. FD&C Act Chapter 5: Drugs and Devices. US Food and Drug Administration Web site. http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/FDCActChapterVDrugsandDevices/ucm108125.htm. Updated April 30, 2009; accessed May 19, 2010.
4. CFR—Code of Federal Regulations Title 21. US Food and Drug Administration Web site. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.126&SearchTerm=adequate%20and%20well%2Dcontrolled%20investigations. Updated April 1, 2009. Accessed May 19, 2010.
5. Laughren TP. The scientific and ethical basis for placebo-controlled trials in depression and schizophrenia: an FDA perspective. *Eur Psychiatry*. 2001;16(7):418–423. doi:10.1016/S0924-9338(01)00600-9 PubMed
6. Code of Federal Regulations Title 21. Part 312. Investigational New Drug Application. US Food and Drug Administration Web site. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312. Updated April 1, 2009. Accessed May 19, 2010.
7. Code of Federal Regulations Title 21. Part 314. Applications for FDA approval to market a new drug. US Food and Drug Administration Web site. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=314. Updated April 1, 2009. Accessed May 19, 2010.
8. MedWatch the FDA Safety Information and Adverse Event Reporting Program. Antipsychotics, Conventional and Atypical. US Food and Drug Administration Web site. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm110212.htm. Updated June 19, 2009. Accessed May 19, 2010.
9. Laughren TP. A regulatory perspective on psychiatric syndromes in Alzheimer disease. *Am J Geriatr Psychiatry*. 2001;9(4):340–345. PubMed
10. Buchanan RW, Davis M, Goff D, et al. A summary of the FDA-NIMH-MATRICS workshop on clinical trial design for neurocognitive drugs for schizophrenia. *Schizophr Bull*. 2005;31(1):5–19. doi:10.1093/schbul/sbi020 PubMed
11. Laughren T, Levin R. Food and Drug Administration perspective on negative symptoms in schizophrenia as a target for a drug treatment claim. *Schizophr Bull*. 2006;32(2):220–222. doi:10.1093/schbul/sbi039 PubMed
12. Laughren TP. Comorbid mood disorders and medical illness: a Food and Drug Administration perspective. *Biol Psychiatry*. 2003;54(3):195–199. doi:10.1016/S0006-3223(03)00529-8 PubMed
13. Guideline for Industry. Studies in Support of Special Populations: Geriatrics. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129519.pdf. Accessed May 19, 2010.
14. Center for Drug Evaluation and Research. Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072044.pdf. Accessed May 19, 2010.
15. US Food and Drug Administration. Food and Drug Administration Modernization Act of 1997 §111 of Title I; Federal Food, Drug, and Cosmetic Act §505A, 21USC §355a.
16. US Food and Drug Administration. Pediatric Drug Development. FDA Amendments Act of 2007. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.
17. US Food and Drug Administration. CFR: Code of Federal Regulations Title 21. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.50.
18. International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use. Dose-Response Information to Support Drug Registration. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073115.pdf.
19. Khan A, Khan SR, Walens G, et al. Frequency of positive studies among fixed and flexible dose antidepressant clinical trials: an analysis of the Food and Drug Administration summary basis of approval reports. *Neuropsychopharmacology*. 2003;28(3):552–557. doi:10.1038/sj.npp.1300059 PubMed
20. Papakostas GI, Fava M. Does the probability of receiving placebo

influence clinical trial outcome? a meta-regression of double-blind, randomized clinical trials in MDD. *Eur Neuropsychopharmacol*. 2009; 19(1):34–40. doi:10.1016/j.euroneuro.2008.08.009 PubMed
21. Kane J, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. *Arch Gen Psychiatry*. 1988;45(9):789–796. PubMed
22. Clinical Trials.gov. Large Simple Trial (LST) Of Cardiovascular Safety Of Ziprasidone And Olanzapine- (Zodiac). http://clinicaltrials.gov/ct2/show/NCT00418171. Accessed May 19, 2010.
23. Peuskens J, Tanghøj P, Mittoux A, et al. The Sertindole Cohort Prospective (SCoP) study. http://www.ncbi.nlm.nih.gov/pubmed/18384186. Accessed May 19, 2010.
24. Siddiqui O, Hung HMJ, O'Neill R. MMRM vs LOCF: a comprehensive comparison based on simulation study and 25 NDA datasets. *J Biopharm Stat*. 2009;19(2):227–246. doi:10.1080/10543400802609797 PubMed
25. US Food and Drug Administration. Critical Path Initiative. http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/default.htm. Accessed May 19, 2010.
26. US Food and Drug Administration. Critical Path Initiative. http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/UCM077254.pdf. Accessed May 19, 2010.
27. Lieberman JA, Stroup TS, McEvoy JP, et al. Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353(12):1209–1223. doi:10.1056/NEJMoa051688 PubMed
28. Agency for Healthcare Research and Quality. Treatment of Depression: Newer Pharmacotherapies. http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=hserta&part=A9274. Accessed May 19, 2010.
29. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006;163(11):1905–1917. doi:10.1176/appi.ajp.163.11.1905 PubMed
30. Mojtabai R, Olfson M. National trends in psychotropic medication polypharmacy in office-based psychiatry. *Arch Gen Psychiatry*. 2010;67(1): 26–36. doi:10.1001/archgenpsychiatry.2009.175 PubMed
31. Kemp AS, Schooler NR, Kalali AH, et al. What is causing the reduced drug placebo difference in recent schizophrenia clinical trials and what can be done about it? *Schizophr Bull*. 2008. doi:10.1093/schbul/sbn110 PubMed
32. Sauer JM, Ring BJ, Witcher JW. Clinical pharmacokinetics of atomoxetine. *Clin Pharmacokinet.* 2005;44(6):571–590. doi:10.2165/00003088-200544060-00002 PubMed
33. Madadi P, Ross CJD, Hayden MR, et al. Pharmacogenetics of neonatal opioid toxicity following maternal use of codeine during breastfeeding: a case-control study. *Clin Pharmacol Ther*. 2009;85(1):31–35. doi:10.1038/clpt.2008.157 PubMed
34. Brøsen K, Otton SV, Gram LF. Imipramine demethylation and hydroxylation: impact of the sparteine oxidation phenotype. *Clin Pharmacol Ther.* 1986;40(5):543–549. PubMed
35. Burstein HJ. The distinctive nature of HER2-positive breast cancers. *N Engl J Med.* 2005;353(16):1652–1654. doi:10.1056/NEJMp058197 PubMed
36. Desmedt C, Sperinde J, Piette F, et al. Quantitation of HER2 expression or HER2:HER2 dimers and differential survival in a cohort of metastatic breast cancer patients carefully selected for trastuzumab treatment primarily by FISH. *Diagn Mol Pathol*. 2009;18(1):22–29. doi:10.1097/PDM.0b013e31818ebc69 PubMed
37. US National Library of Medicine, National Institutes of Health. Daily Med: Herceptin (trastuzumab) kit for intravenous use (Genentech). http://dailymed.nlm.nih.gov/dailymed/search.cfm?startswith=herceptin&x=14&y=10. Accessed May 19, 2010.
38. Serretti A, Kato M, De Ronchi D, et al. Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with selective serotonin reuptake inhibitor efficacy in depressed patients. *Mol Psychiatry*. 2007;12(3):247–257. PubMed
39. McMahon FJ, Buervenich S, Charney D, et al. Variation in the gene encoding the serotonin 2A receptor is associated with outcome of antidepressant treatment. *Am J Hum Genet*. 2006;78(5):804–814. doi:10.1086/503820 PubMed
40. Tennis P, Stern RS. Risk of serious cutaneous disorders after initiation of use of phenytoin, carbamazepine, or sodium valproate: a record linkage study. *Neurology.* 1997;49(2):542–546. PubMed
41. Hung SI, Chung WH, Jee SH, et al. Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. *Pharmacogenet Genomics*. 2006;16(4):297–306. doi:10.1097/01.fpc.0000199500.46842.4a PubMed
42. US Food and Drug Administration. Newly Added Guidance Documents. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm121568.htm. Accessed May 19, 2010.
43. US Food and Drug Administration. Guidance for Industry: End-of-Phase 2A Meetings. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079690.pdf. Accessed May 19, 2010.
44. Insel TR, Wang PS. Rethinking mental illness. *JAMA*. 2010;303(19): 1970–1971. doi:10.1001/jama.2010.555 PubMed
45. Guidance for Industry Providing Regulatory Submissions in Electronic Format: Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications. US Food and Drug Administration Web site. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf. Accessed May 19, 2010.
46. Clinical Data Interchange Standards Consortium. http://www.cdisc.org. Accessed May 19, 2010.
47. Health Level Seven International (HL7). http://www.hl7.org/about/index.cfm. Accessed May 19, 2010.
48. DuMouchel W, Fram D, Yang X, et al. Antipsychotics, glycemic disorders, and life-threatening diabetic events: a Bayesian data-mining analysis of the FDA adverse event reporting system (1968–2004). *Ann Clin Psychiatry*. 2008;20(1):21–31. doi:10.1080/10401230701844612 PubMed
49. US Food and Drug Administration. http://inside.fda.gov:9003/downloads/ProgramsInitiatives/Drugs/SafetyFirst/ucm055469.pdf. Accessed July 8. 2010.
50. Department of Health and Human Services. Food and Drug Administration. Report to Congress. Changing the Future of Drug Safety: FDA Initiatives to Strengthen and Transform the Drug Safety System. http://www.fda.gov/downloads/Safety/SafetyofSpecificProducts/UCM184046.pdf. Accessed May 19, 2010.
51. US Food and Drug Administration. FDA's Sentinel Initiative. http://www.fda.gov/Safety/FDAsSentinelInitiative/default.htm. Accessed May 19, 2010.
52. US Food and Drug Administration. Safe Use Initiative. http://www.fda.gov/Drugs/DrugSafety/ucm187806.htm. Update December 12, 2009. Accessed May 19, 2010.
53. Hammad TA, Laughren TP, Racoosin JA. Suicidality in pediatric patients treated with antidepressant drugs. *Arch Gen Psychiatry*. 2006;63(3): 332–339. doi:10.1001/archpsyc.63.3.332 PubMed
54. Stone M, Laughren T, Jones ML, et al. Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. *BMJ*. 2009;339:b2880. doi:10.1136/bmj.b2880 PubMed
55. US Food and Drug Administration. Information for Healthcare Professionals: Conventional Antipsychotics. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124830.htm. Updated November 5, 2009. Accessed May 19, 2010.
56. US Food and Drug Administration. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm153478.htm. Accessed May 19, 2010.

Evolution of Psychopharmacology Trial Design and Analysis: Six Decades in the Making

Andrew C. Leon, PhD

Objective: The evolution of trial design and analysis during the lifespan of psychopharmacology is examined.

Background: The clinical trial methodology used to evaluate psychopharmacologic agents has evolved considerably over the past 6 decades. The first and most productive decade was characterized by case series, each with a small number of patients. These trials used nonstandardized clinical observation as outcomes and seldom had a comparison group. The crossover design became widely used to examine acute psychiatric treatments in the 1950s and 1960s. Although this strategy provided comparison data, it introduced problems in study implementation and interpretation. In 1962, the US Food and Drug Administration began to require "substantial evidence of effectiveness from adequate and well-controlled studies." Subsequent decades saw remarkable advances in clinical trial design, assessment, and statistical analyses. Standardized instruments were developed and parallel groups, double-blinding, and placebo controls became the benchmark. Sample sizes increased and data analytic procedures were developed that could accommodate the problems of attrition. Randomized withdrawal designs were introduced in the 1970s to examine maintenance therapies. Ethical principles for research became codified in the United States at that time. A wave of regulatory approvals of novel antipsychotics, antidepressants, and anticonvulsants came in the 1980s and 1990s, each based on data from randomized double-blind, parallel-group, placebo-controlled clinical trials. These trial designs often involved fixed-dose comparisons based, in part, on a greater appreciation that much of the benefit and harm in psychopharmacology was dose related.

Conclusions: Despite the progress in randomized controlled trial (RCT) design, the discovery of new mechanisms of action and blockbuster interventions has slowed during the past decade.

J Clin Psychiatry 2011;72(3):331–340

Submitted: *October 28, 2010; accepted December 9, 2010 (doi:10.4088/JCP.10r06669).*

Corresponding author: *Andrew C. Leon, PhD, Weill Cornell Medical College, Department of Psychiatry, Box 140, 525 East 68th St, New York, NY 10065 (acleon@med.cornell.edu).*

The development of psychopharmacologic agents over the past 6 decades has been characterized by a paradoxical relationship between medication discovery and clinical trial methodology. The methodology during the most productive decade, 1949–1958, was primitive. Since then, there have been tremendous advances in clinical trial design, assessment, and statistical analyses. Yet, despite numerous innovations in methodology, the discovery of new mechanisms of action and blockbuster interventions seems to have slowed—especially during the past decade. In an effort to understand this phenomenon, the evolution of trial design and analysis during the lifespan of psychopharmacology is examined here.

Initially, the historical context is considered by describing the development of regulatory policy and the early use of clinical trials in medicine. The initial psychopharmacology trials are then reviewed, focusing not on the results, but instead on methodology. Developments over the decades are then examined, culminating with a discussion of the more recent advances in design and analysis. This is not meant to be a comprehensive review of clinical trials in psychopharmacology, but instead a survey of trials that exemplify methodology and its progression over time.

MILESTONES IN US DRUG REGULATION

The US Congress passed the Pure Food and Drugs Act in 1906 to prohibit interstate commerce of misbranded and adulterated foods, drinks, and drugs.[1] The act, motivated in part by problems in the meat packing industry, did not prohibit false therapeutic claims; instead, it focused on ingredients and expanded the authority of the Bureau of Chemistry of the US Department of Agriculture, which was the forerunner of the US Food and Drug Administration (FDA).

There are times that misfortune drives regulatory progress. In 1937, for example, the S. E. Massengill Company of Bristol, Tennessee, prepared a new elixir formulation of sulfanilamide in an effort to provide a palatable alternative to the pill preparation. Tragically, the product contained the solvent diethylene glycol, which killed 107 people, mostly children.[1] This prompted Congress to pass the Federal Food, Drug, and Cosmetic Act in 1938, which required that a manufacturer show that a drug is safe.[1]

In the early 1960s, the sedative and antiemetic thalidomide, which was marketed in Europe, was shown to cause severe birth defects. Frances Kelsey, MD, PhD, a pharmacologist and an FDA medical officer, led efforts to keep thalidomide from the US market. Largely through her efforts the public demanded stronger regulation of drugs. In 1962, Congress passed the Kefauver-Harris Amendments to Federal Food, Drug, and Cosmetic Act, which required that a manufacturer provide *substantial evidence of effectiveness from adequate and well-controlled studies*.[2] In addition, it strengthened drug safety efforts and, most importantly, required that the FDA

approve a drug prior to its marketing.[1] The profound effect of this amendment on psychopharmacology clinical trial methodology will become apparent below.

Experimental Therapeutics

The first randomized controlled clinical trial (RCT) in medicine examined streptomycin for pulmonary tuberculosis and was published in 1948.[3] It applied the randomized study design from agriculture to medical research. It was a randomized controlled, double-blinded clinical trial with 107 participants who were randomly assigned to bed rest either alone or with streptomycin. The 6-month mortality rates were reduced nearly 75%: 27% (bed rest alone) versus 7% (bed rest and medication). Undoubtedly, the difference would have been even much greater had 12- or 24-month mortality been examined.

Initial Psychopharmacology Trials

The initial trials in psychopharmacology involved case series, each with a small number of patients. Cade reported the antimanic properties of lithium based on a series of 10 cases in Australia in 1949.[4] In 1952, the initial psychiatric study of chlorpromazine, which was previously used for nausea in surgical patients, involved 20 patients with psychosis and reported symptomatic improvement.[5] Chlorpromazine was approved by the FDA in 1954 for psychosis. Imipramine has a molecular structure similar to that of chlorpromazine and for that reason was initially tested as an antipsychotic in 1957 with several hundred cases.[6] Although that effort did not demonstrate effectiveness for psychosis, observation of about 12 of the cases with depression revealed the antidepressant property of imipramine. Iproniazid, a monoamine oxidase inhibitor (MAOI), was used for tuberculosis and clinical observation on the tuberculosis wards reported that patients expressed joy and optimism, despite their prognosis. In 1957, a case series of patients with depression showed beneficial effects of iproniazid.[7]

The decade from 1949 to 1958 is unparalleled in the history of psychopharmacology, with the discovery of the first mood stabilizer, the first antipsychotic, and 2 antidepressants, a tricyclic and an MAOI. Yet, none of these case series involved a control. These 4 highly influential case series represent the successes, but do not reveal how many other series showed no effectiveness or revealed safety problems. Further, they do not reveal how many case series were eventually shown to be false positives.

Placebo-Controlled Trials

In 1955, Beecher described placebo response rates across a wide range of indications including anesthesia for surgery, highlighting the need for trials to include a comparator.[8] He stated, "Many a drug has been extolled on the basis of clinical impression when the only power it had was that of a placebo."[8(p1605)] The need for both a control group and double-blinding in experimental research was articulated in 1958.[9]

The first controlled study of lithium involved a placebo-controlled crossover trial.[10] Thirty-eight subjects with mania were enrolled for two 2-week periods. Some cases were open; some blinded. Emotional and motor levels were each rated on a simplistic 3-point scale: +, ++, +++. Among those who were crossed from placebo to lithium, 75% were less manic, whereas none were less manic among those who went from lithium to placebo. Despite this strong evidence, lithium was not approved by the FDA until 1970, due in part to concerns about toxicity.

The first, placebo-controlled trial of chlorpromazine included 12 chronic schizophrenic male inpatients.[11] It was a blinded, crossover study in which subjects were randomized to 1 of 2 sequences with three 6-week periods—chlorpromazine/plcebo/placebo or placebo/placebo/chlorpromazine. No rating scales were used. Based on clinical observation, chlorpromazine significantly reduced "pathological activity." A randomized placebo-controlled trial that specifically recruited subjects with depression showed strong effects of imipramine in 1959.[12]

However, there were many case series results that failed to be confirmed in controlled trials. For instance, 4 case series reported strong antipsychotic properties of reserpine, the Indian herb *Rawoulfia*: 64% marked to moderate improvement,[13] 62%,[14] 46%,[15] and 70%.[16] Yet, none of these had a control. Subsequent controlled trials of reserpine showed no difference from placebo.[17] Another showed no benefit of reserpine, relative to placebo, as an add-on to electroconvulsive therapy.[18]

With the genesis of psychopharmacology, both the National Institute of Mental Health (NIMH) and the Department of Veterans Affairs (VA) set up psychopharmacology research units in the late 1950s. This stimulated the initial stage in the evolution of standards for RCT design and analysis. For instance, Jonathan O. Cole, MD, Director of the NIMH Psychopharmacology Services Center, published recommendations for reporting the results of trials, in which patient selection, evaluation of change, description of treatment setting, and toxicity reactions were all discussed.[19] However, there was no mention of statistics or data analysis.

At the time, study participants were most often inpatients and, when controls were used, crossover designs were the norm. The complexity of the crossover studies escalated. For example, there was a double-blind trial comparing placebo (P), BW203 (B), and chlorpromazine (C).[20] Thirty-six psychotic inpatients were each randomized to 1 of 6 sequences of three 4-week periods: P-B-C, P-C-B, B-P-C, B-C-P, C-P-B, C-B-P. The improvement rates of 62% (placebo), 50% (BW203), and 54% (chlorpromazine) demonstrated that placebo was significantly superior to BW203, undoubtedly the reason that the agent is not familiar to us today.

Inclusion Criteria

The inclusion criteria in the early studies were often rather broad perhaps, in part, because the diagnostic nosology of the era, *DSM-I* (1952) and *DSM-II* (1968), were narrative

based. It was not until Feighner criteria in 1972,[21] Research Diagnostic Criteria in 1978,[22] and *DSM-III* in 1980[23] that nosology became criterion based. In fact, some of the early trials used medication response for diagnostic classification, an approach later referred to as *pharmacologic dissection*.[24] In one such study, 180 subjects with schizophrenia, affective disorders, or other diagnoses showed 7 patterns of response to imipramine including mood elevation, reduction of anxiety, agitated disorganization, and so on.[25] A highly influential example of this approach to diagnoses in clinical trials was a study of imipramine treating 35 inpatients with depression, which found that the recovery rates were markedly different for nondelusional (66.7%) and delusional (23.1%) patients.[26] This study has informed subsequent RCT exclusion criteria and can be thought of as an early example of empirical basis for personalized treatment.

Standards for the study design and analysis continued to evolve. Max Hamilton, MD, a psychiatrist and namesake of a rating scale for depression, published a text that comprised 12 of his lectures covering a range of areas in clinical research design and analysis including stages of experimentation, design of experiments, measurement of variability, tests of statistical significance, *t* test, χ^2, ANOVA, correlation, selecting cases and treatment, and problems in design and analysis.[27]

Innovation in Psychopharmacology Trials

On the heels of the case series and the small RCT paradigm of the 1950s, the scale and complexity changed in the 1960s. Consider, for instance, a VA cooperative study that included 805 subjects with schizophrenia from 37 VA hospitals.[28] It was a double-blinded randomized crossover study with two 12-week periods that compared chlorpromazine, promazine, phenobarbital, and placebo. This study was quite innovative in that it included 2 phenothiazines and an active control (phenobarbital) and used 3 rating scales. The superiority of chlorpromazine was well-documented in this study.

A trial that compared tetrabenazine and chlorpromazine for chronic schizophrenia included 2 novel components: a 6-week washout period and a 2-week placebo lead-in period.[29] However, it did not use randomized treatment assignment; instead, it assigned subjects to the 2 groups (12 weeks of either tetrabenazine or chlorpromazine) matched on age, clinical assessment, behavioral rating, and previous leucotomy. This, like other studies of the time, presented results indicating significant symptomatic improvement *within* each group, but no significant *between* group effect. Such findings highlight the importance of including a comparison group.

After a decade or so of psychopharmacologic research, the standards for design and analysis continued to advance. In a 1962 manuscript on the evaluation of psychopharmacologic agents, Jonathan O. Cole, MD, described methods for each of several diagnostic groups.[30] One area addressed was the conduct of trials for outpatient samples with depression. Several of the topics covered represent challenges faced in contemporary psychopharmacology: substantial dropout rates with outpatients, the high rate of placebo response, comparative effectiveness, and the response of different subtypes to different agents (ie, personalized treatment). The publication of this comprehensive discussion of clinical trial methodology coincided with the 1962 Kefauver-Harris Amendment to Federal Food, Drug, and Cosmetic Act, which, as stated above, required *substantial evidence of effectiveness from adequate and well-controlled studies*.[2] Although, it is not clear that the publication was motivated by the new legislation, it was at this point in time that the trend in psychopharmacology was shifting from crossover trials to parallel-group designs.

Some studies of that era sought solutions to clinical challenges that we continue to grapple with today. For example, a 9-week placebo-controlled trial of mepazine as an add-on to phenothiazines had cognition as its primary outcome. It did not use clinical observation, but validated scales (Wechsler Adult Intelligence Scale and Hospital Adjustment Scale) to assess outcome.[31] Despite several earlier reports of clearer thinking with mepazine, no group differences were found in this randomized controlled trial.

A landmark study of phenothiazine treatments for acute schizophrenia was conducted during this period.[32] It was a 9-site, randomized, parallel groups, controlled trial that randomized 463 *newly admitted* patients to 6 weeks of chlorpromazine, thioridazine, fluphenazine, or placebo. There were 3 objectives:

(1) Efficacy of thioridazine and fluphenazine relative to placebo.
(2) The noninferiority of thioridazine and fluphenazine to chlorpromazine (although the term *noninferiority* was not used).
(3) Relative safety and tolerability of chlorpromazine, thioridazine, and fluphenazine.

It was this seminal study that developed and first used the now ubiquitous Clinical Global Impressions (CGI)-Severity and CGI-Improvement scales. Participants in this study were terminated due to treatment complications or failures, and the termination rates differed across the cells: active (20%) and placebo (41%). The analyses, which included only the completers, showed significantly greater marked/moderate improvement for the active cells (pooled 75%) versus placebo (23%); however, there were no differences among drugs. In stark contrast to the style used today, the results included the following: "Details on statistical analyses are not reported here. Any differences or relationships reported in this paper, unless otherwise stated, were found to be statistically significant."[32(p252)]

The randomized withdrawal design was introduced into the field of psychopharmacology with 3 trials in the early 1970s. A double-blind lithium discontinuation study in manic-depression (N = 50) and recurrent depression

(N = 34) found a significant prophylactic effect of lithium.[33] A small double-blind discontinuation study of lithium in manic-depression and recurrent depression (N = 18) found no difference between lithium and placebo in 2-year relapse rates.[34] A double-blind discontinuation study of recurrent depression compared lithium (N = 22), imipramine (N = 21), and placebo (N = 13) over 2 years.[35] Imipramine had a significantly superior prophylactic effect over placebo.

A NEW WAVE OF DEVELOPMENT IN PSYCHOPHARMACOLOGY

With the 1980s and 1990s came a new wave of regulatory approvals of novel antipsychotics, antidepressants, and anticonvulsants, each based on data from randomized double-blind, parallel-group, placebo-controlled clinical trials. Many of these studies built on the appreciation, developed in the prior decade, that much of the benefit and harm in psychopharmacology was dose related and, therefore, there is a need to apply fixed-dose comparison designs that allow for a brief period of titration. This shift was influenced in part by a letter describing limitations in the interpretation of a therapeutic window for antipsychotics from a flexible-dose study.[36] Dose comparison studies examined haloperidol for acute schizophrenia as well as fluphenazine decanoate[37] and haloperidol decanoate[38] for relapse prevention and provided an opportunity to look closely at extrapyramidal symptoms of haloperidol.[39]

The early fluoxetine studies used dose-escalating schedules in which a dose could range from 20 mg to 80 mg; yet, about 80% of participants got at least 60 mg within 2 weeks.[40,41] However, it was the fixed-dose, dose-response studies that helped identify optimal dosing of fluoxetine with regard to both efficacy and adverse events.[42,43] Furthermore, a study of nonresponders to 3 weeks of 20 mg of fluoxetine compared those who were then randomized to 5 additional weeks of either 20 mg or 60 mg. It found no added benefit of switching to 60 mg and significantly greater attrition due to "adverse experience" for the higher dose.[44]

Identifying the appropriate target population for an intervention is critical. For instance, clozapine was a promising antipsychotic, but the risk of agranulocytosis posed a serious obstacle to regulatory approval. The strategy used to demonstrate the efficacy of clozapine and gain approval in the United States was to conduct a trial in treatment-resistant patients. The pivotal trial recruited participants who had previously failed to respond to at least 3 different neuroleptics.[45] They were initially given 6 weeks lead-in of haloperidol. Only participants who *prospectively* failed to adequately improve during those 6 weeks were then randomized to receive 6 weeks of clozapine or chlorpromazine in a double-blind fashion. Although the response rate was modest for clozapine (30%), it was substantially greater than chlorpromazine (4%).

After a nearly 30-year gap in large-scale double-blind, placebo-controlled drug development employing random assignment to parallel groups for bipolar disorder, maintenance trials of anticonvulsants began a new era. For example, randomized controlled trials compared efficacy and safety of divalproex sodium, lithium carbonate, and placebo[46] and lamotrigine, lithium carbonate, and placebo.[47] Mood stabilizers like valproate typically were shown to have acute efficacy for mania prior to the evaluation of a maintenance effect. Furthermore, the maintenance trials focused on participants recently treated for mania or hypomania.[48] Up until this new era began, the depressed phase of bipolar disorder received considerably less attention, despite its overrepresentation in the course of the illness. Lamotrigine trials provide an exception to this in that the drug was shown to have some evidence of efficacy for acute bipolar depression[49] and subsequently found to provide maintenance therapy for recently depressed participants.[50] As with studies of many psychiatric disorders, trials for bipolar disorder are highly selective, excluding those with psychiatric or other medical comorbidity and alcohol or substance abuse and sometimes those with mixed states or rapid cycling. As a result, the generalizability of results is limited. Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)[51] and Lithium Treatment–Moderate dose Use Study (LiTMUS) for bipolar disorder[52] each sought to broaden the inclusion criteria.

The field realized the limitations of short-term treatment. Therefore another design was used to investigate treatment during various phases of an illness—sequentially examining acute, continuation, and maintenance phases of treatment. Each phase enrolls successive subsets of participants who met inclusion criteria based on response status in the prior phase. The acute and maintenance phases are each double-blind randomized studies in and of themselves, with randomization at the start of the respective phase. For example, 2 such programs were conducted in chronic depression, one compared sertraline and imipramine[53–55] and the other compared nefazodone and cognitive behavioral analysis system of psychotherapy (CBASP) alone and in combination.[56,57] Each of these programs also included a phase in which acute phase nonresponders were switched to another active agent for acute treatment.[58,59]

The role of psychotherapy augmentation for those not fully responding to an antidepressant was examined in the REVAMP Study. Participants with chronic depression who prospectively failed to respond to algorithm-guided medication were randomized to receive the next level antidepressant either alone or in combination with CBASP or brief supportive psychotherapy.[60]

Although several psychotropic agents have demonstrated efficacy in placebo-controlled trials, there has been limited empirical evidence to guide the choice among efficacious agents for a particular indication. For that reason, among others, the NIMH supported large comparative effectiveness trials including Sequenced Treatment Alternatives to Relieve Depression (STAR*D) and Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) for schizophrenia. These trials involved longer periods of treatment and more

generalizable samples than typically included to date. The CATIE study compared atypical antipsychotics (olanzapine, quetiapine, risperidone, ziprasidone) with the first-generation antipsychotic, perphenazine. The 57-site study enrolled 1,493 participants and used a novel outcome, "time until all cause discontinuation."[61] STAR*D examined treatments for adult outpatients with a nonpsychotic major depressive disorder who did not achieve remission on citalopram therapy. The study used equipoise-stratified randomization[62] in which the participants could opt out of a treatment strategy (switch or augmentation), but not the particular interventions within a strategy.[63] Separate studies examined antidepressant switch strategies (bupropion-SR vs sertraline vs venlafaxine-XR) with 727 participants[64] and antidepressant augmentation strategies (bupropion-SR vs buspirone) with 565 participants.[65]

DESIGNS FOR FUTURE TRIALS IN PSYCHOPHARMACOLOGY

There are 2 promising designs that have been seldom used in psychopharmacology: adaptive design and noninferiority trials. An adaptive design is a "multistage study design that uses accumulating data to decide how to modify aspects of the study without undermining the validity and integrity of the trial."[66(p425)] It is imperative that changes are based on prespecified criteria. For instance, in a dose-finding study, the least effective dose(s) could be dropped after the initial 15% or 20% of planned subjects have completed the study. Alternatively, the randomization allocation ratio might be modified, based on a priori criteria, such that substantially more subjects are randomized to the dose with most promising results to date. Such designs must guard against inflation of type I error and have safeguards that prevent the investigators from learning details of interim results that could have bearing on the remainder of the trial. An independent data monitoring committee might be used to review the interim data and, based on a priori adaptive criteria, convey a general message regarding which changes should be implemented, but not convey the specific results.

Most trials in psychopharmacology use a superiority design, hypothesizing a difference between treatment groups. In contrast, a noninferiority trial is used to show that one cell is *no worse than* the other. It would seem that comparative effectiveness trials could benefit from using the noninferiority design. For example, there would be important policy implications if a trial demonstrated that an inexpensive generic was no worse than a brand name medication. However, there are several fundamental challenges of noninferiority design including demonstration of assay sensitivity, choosing a well-defined margin of noninferiority, and the substantial sample sizes.[67]

Ethical Issues

As a part of the 1962 Kefauver-Harris Amendments, the FDA required that informed consent be obtained from all human research subjects in clinical trials that are submitted as part of the drug approval process.[1] In 1964, the World Medical Association issued the Declaration of Helsinki that set forth ethical principles for human experimentation. Ethical standards became codified in the United States in the 1970s. The US Congress passed the National Research Act in 1974. This established the commission that issued Belmont Report in 1979,[68] which outlined ethical principles that continue to serve as the basis for the Federal Regulations for protection of human subjects. Despite the standards, ethical perspectives on placebo controls in clinical trials vary from institutional review board (IRB) to IRB and cross-nationally. Policies regarding placebo remain an evolving area in need of harmonization.

IMPACT OF STATISTICAL REASONING ON RESEARCH IN PSYCHOPHARMACOLOGY

The standards for design and analysis were influenced by the initial statisticians involved in psychopharmacology studies. Samuel W. Greenhouse, PhD, was the first statistician at NIMH (1954–1966). C. James Klett, PhD, and John E. Overall, PhD, each played major roles in shaping the quality of the psychopharmacology research of Department of Veterans Affairs Cooperative Studies Program from the late 1950s and beyond. Eugene M. Laska, PhD, joined Rockland State (now the Nathan Kline Institute) as a statistician in 1964. In addition, statisticians were regularly included on NIMH review committees by the 1970s and 1980s; and, in this way, design rigor played a more prominent role in the awarding of research funds. Furthermore, the FDA initiated the multidisciplinary Advisory Committees in 1970s that included biostatisticians.

Data Analyses

The data analytic techniques used in the 1950s and 1960s included χ^2 tests, *t* tests, analysis of variance, and analysis of covariance. Each of these is useful for comparison of intervention groups in RCTs, yet none adequately accommodates the problem of attrition. The Kaplan-Meier product limit estimate was developed to account for censored cases as a survival analytic approach to cancer research.[69] Due to the influence of Joseph L. Fleiss, PhD, a prominent biostatistician at Columbia University School of Public Health and the New York State Psychiatric Institute, survival analysis was applied to a trial for mania.[70]

Attrition

The initial approach to attrition in psychopharmacology was to limit analyses to participants with complete data. This was a reasonable strategy in the 1950s when studies enrolled only inpatients and dropout was rare, seldom more than 5%, and typically due to death or a rare hospital discharge. Last observation carried forward (LOCF) came into use in the early 1960s, if not before. Another approach involved the replacement of each dropout with a newly randomized subject.

However, the attrition rates became substantially higher over the decades, exceeding 30% in antidepressant trials and 50% in antipsychotic trials.[71] In order to minimize the bias in estimates of the treatment effects in trials with substantial attrition, it is critical to classify participants based on *intention to treat* (ie, randomized assignment), rather than by actual treatment received. This was described by A. Bradford Hill in 1961,[72] yet to this day some investigators resist the proposal to attempt assessing all randomized participants for entire course of RCT, regardless of adherence to study medication, which is arguably the most appropriate implementation of the principle of intention to treat.[73] It was not until the 1980s that statistical strategies accommodated participants with incomplete data.[74,75] Mixed-effects models were introduced in 1982,[74] used in psychopharmacology shortly thereafter,[76–78] but not widely disseminated until the software became accessible, in part with funding from NIMH.[79–82]

The NIMH Treatment of Depression Collaborative Research Program was one of the earliest large trials to apply mixed-effects models, albeit as secondary analyses, in order to include participants with incomplete data.[83] The study randomly assigned 255 subjects to one of four 16-week treatments: cognitive behavior therapy, interpersonal psychotherapy, imipramine hydrochloride plus clinical management, and placebo plus clinical management.[84] It is also noteworthy that this was the first study to develop and incorporate a pharmacotherapy treatment manual to standardize the delivery of a psychopharmacologic intervention in a clinical trial.[85]

Sample Size Determination

Until fairly recently, sample size determination was conducted in rather ad hoc fashion. Even though algorithms and tables for sample size estimates were published in the 1960s,[86,87] sample sizes were typically selected based on 2 criteria: the number of participants included in prior trials and the budget. Power analyses did not become routine until specialized software became available in the 1990s. The need for power analyses for planning clinical trials has now become widely accepted. The concept of the effect size, a fundamental component of power analyses, has gained better understanding. The magnitude of a treatment effect in a completed RCT can be described with an effect size, such as the number needed to treat or area under the curve, each more intuitive than the conventional Cohen *d*.[88] The FDA Division of Psychiatry Products interprets *substantial evidence* primarily as a statistically significant treatment effect. However, a finding that is accompanied by a clinically meaningful effect size carries additional weight.

Assessment

In the 1950s, outcome measures in trials primarily involved clinical observation. There was no standardization across studies. The need for standardized, psychometrically validated assessment tools spurred the development of ratings scales such as the Hamilton Depression Rating Scale,[89] Brief Psychiatric Rating Scale,[90] Montgomery-Asberg Depression Rating Scale,[91] Positive and Negative Syndrome Scale (PANSS),[92] Panic Disorder Severity Scale,[93] Inventory of Depressive Symptomatology,[94] Young Mania Rating Scale,[95] and Clinician-Administered Posttraumatic Stress Disorder Scale.[96] The Early Clinical Drug Evaluation Unit (ECDEU) led an effort to promote uniformity in choice among the many new rating scales by publishing the ECDEU Assessment Manual.[97] More recently the American Psychiatric Association compiled the comprehensive *Handbook of Psychiatric Measures*.[98]

Guidelines for Clinical Trial Design

The momentum for design and analysis standards gained ground, in part, with publications from the NIMH[99] and the American College of Neuropsychopharmacology (ACNP).[100] The FDA published 3 of the initial guidance documents in 1977: General Considerations for the Clinical Evaluation of Drugs,[101] Guidelines for the Clinical Evaluation of Antidepressant Drugs,[102] and Guidelines for the Clinical Evaluation of Antianxiety Drugs.[103] Regulatory guidance continued with the International Conference on Harmonisation (ICH), which published the E9—Statistical Principles for Clinical Trials[104] and E10—Choice of Control Group and Related Issues in Clinical Trials.[105] The FDA continues to develop guidance documents, most recently releasing 2 drafts that are germane to psychopharmacology: Non-Inferiority Clinical Trials[106] and Adaptive Design Clinical Trials for Drugs and Biologics.[107]

A major advance in standardizing content of clinical trial reports came with the introduction of the Consolidated Standards of Reporting Trials (CONSORT).[108] It not only includes the now ubiquitous CONSORT chart showing the flow of participants from screening to study completion, but also presented a 25-item checklist that describes content of various sections of the manuscript including the Title, Abstract, Introduction, Methods, Results, and Discussion. The CONSORT Statement was updated in 2001 and 2010.[109–111]

There had been concern about selective reporting of positive trials and suppression of negative results. This was highlighted, for instance, by the FDA briefing document for the 2004 advisory committee meeting on suicidality and pediatric antidepressant use in which previously unseen negative results were revealed. [112] As part of the 1997 Food and Drug Administration Modernization Act, registration of some clinical trials and presentation of a protocol summary were required in a national database, ClinicalTrials.gov. In 2007, the FDA extended this mandate to include reporting of results and adverse events of completed trials. The International Committee of Medical Journal Editors (ICMJE) initiated a policy that requires investigators to register interventional studies at an acceptable public trials registry (such as ClinicalTrials.gov) as a condition of consideration for publication. It has been a requirement of this journal since 2007.

CONCLUSIONS

Six decades of trials in psychopharmacology were accompanied by major advances in research methodology. The early trials involved a single site, most often an academic medical center that enrolled chronic inpatients who had few, if any, treatment options. Those trials needed a small number of participants to detect the large treatment effects seen with severely ill, treatment naive patients. The patients were very well known to their clinicians, many spending months to years as inpatients in one facility. The clinicians' familiarity with the clinical status of each patient allowed for nonstandardized clinical observations of outcome such as "fewer windows were broken on the ward." The long-term doctor-patient relationships also provided opportunity for serendipity, which formed the foundation for discovery in psychopharmacology in its early decades.

Trial designs evolved from case series with no control to crossover designs to randomized, double-blind, parallel-group placebo-controlled trials. The trials of acute treatment became longer over the decades, initially offering as few as 2 to 4 weeks of treatment and now offering 8 to 12 to 26 weeks. More recently the observed treatment effects have become smaller, requiring multisite, and, more often, multinational and multicontinental studies to provide the number of participants necessary for adequate statistical power.

The paradox that motivated this article was the apparent inconsistency between 6 decades of advances in RCT technology (design, analysis, and assessment) and the slowing of discovery of psychopharmacology. In the decade from 1949 to 1958, 4 major discoveries laid the foundation of psychopharmacology, with lithium, the first mood stabilizer, chlorpromazine, the first antipsychotic, and imipramine and iproniazid, the first antidepressants, each with different mechanisms of action. Why has the discovery of blockbusters slowed today? It could simply stem from retrospective recall bias: were the discovery rates truly much higher in the 1950s? Is this phenomenon a function of publication bias filtering the negative trials or a nostalgic reconstructionist view of the history of psychopharmacology? Are the effect sizes truly shrinking, as has been postulated,[113] or is this phenomenon, in part, a function of trial conduct? Perhaps there is a need for more precise assessment procedures with greater emphasis on reliability and rater training and competence.[114–116] Could it be that today's mental health care delivery system limits the opportunity for serendipitous discovery, a driving force in early psychopharmacology? In my interviews of several who helped shape the field, I was repeatedly told that an insufficient amount of time is spent in phase 2 development to determine the correct drug, the proper dose, and the appropriate patient population. This suggests that the hurried effort to advance the development and regulatory approval of psychopharmacologic compounds could, in fact, have set the stage to miss potential blockbusters that were inadequately tested.

An immediate challenge faced in the field is to make progress in the development and identification of personalized treatments,[117] perhaps through the application of biomarkers. The concept of identifying moderators of the between-treatment effect size was articulated for clinical trials in psychiatry[118] and will no doubt be applied in the effort to uncover personalized treatments.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), buspirone (BuSpar and others), clozapine (Clozaril, FazaClo, and others), divalproex sodium (Depakote and others), fluoxetine (Prozac and others), haloperidol (Haldol and others), imipramine (Tofranil and others), lamotrigine (Lamictal and others), lithium (Lithobid and others), olanzapine (Zyprexa), quetiapine (Seroquel), reserpine (Serpalan), risperidone (Risperdal and others), sertraline (Zoloft and others), tetrabenazine (Xenazine), venlafaxine (Effexor and others), ziprasidone (Geodon).

Author affiliation: Weill Cornell Medical College, New York, New York.

Potential conflicts of interest: **Dr Leon** has served on Independent Data Safety Monitoring Boards for AstraZeneca, Sunovion, and Pfizer; has served as a consultant to NIMH, MedAvante, and Roche; has equity in MedAvante; and receives research funding from NIMH.

Funding/support: This research was supported, in part, by grants from the National Institute of Mental Health (MH068638 and MH092606).

Previous presentation: Portions of this manuscript were presented at the 50th Anniversary of NIMH, New Clinical Drug Evaluation Unit (NCDEU) Meeting; June 12–17, 2010; Boca Raton, FL.

Acknowledgments: Each of the following graciously shared their experiences in interviews with the author: Ross J. Baldessarini, MD; Jack D. Barchas, MD; Charles L. Bowden, MD; Joseph R. Calabrese, MD; Eric J. Cassell, MD; John M. Davis, MD; Alexander Glassman, MD; Joel B. Greenhouse, PhD; John M. Kane, MD; Donald F. Klein, MD; C. James Klett, PhD; Stephen R. Marder, MD; James H. Kocsis, MD; Eugene M. Laska, PhD; Thomas P. Laughren, MD; Jerome Levine, MD; John E. Overall, PhD; William Z. Potter, MD, PhD; A. John Rush, MD; Nina R. Schooler, PhD; Joanne B. Severe, MS; George M. Simpson, MD; Rosemary Stevens, PhD; and Robert Temple, MD. Beatrix Haustein, MBA, and Stéphanie Duhoux, PhD, each translated research literature.

REFERENCES

1. US Food and Drug Administration. US Food and Drug Administration: History. 2010. http://www.fda.gov/AboutFDA/WhatWeDo/History/FOrgsHistory/CDER/CenterforDrugEvaluationandResearchBrochureandChronology/ucm114470.htm#1906. Accessed November 23, 2010.
2. US Food and Drug Administration. *Federal Food, Drug, and Cosmetic, As Amended, FDA 93-1051*. Washington, DC: Superintendent of Documents, US Government Printing Office; 1993.
3. Medical Research Council. Streptomycin treatment of pulmonary tuberculosis. *BMJ*. 1948;2(4582):769–782.doi:10.1136/bmj.2.4582.769 PubMed
4. Cade JFJ. Lithium salts in the treatment of psychotic excitement. *Med J Aust*. 1949;2(10):518–520.
5. Delay J, Deniker P, Harl JM. Utilisation en therapeutique psychiatrique dune phenothiazine daction centrale elective (4560-Rp). *Presse Med*. 1952;60(64):1369.
6. Kuhn V. Uber die Behandlung depressiver zustande mit einem iminodibenzylderival (G 22355). *Schweiz Med Wochenschr*. 1957;(35–36):1135–1140. PubMed
7. Loomer HP, Saunders JC, Kline NS. A clinical and pharmacodynamic evaluation of iproniazid as a psychic energizer. *Psychiatr Res Rep Am Psychiatr Assoc*. 1957;8:129–141. PubMed
8. Beecher HK. The powerful placebo. *J Am Med Assoc*. 1955;159(17):1602–1606. PubMed
9. Modell W, Houde RW. Factors influencing clinical evaluation of drugs; with special reference to the double-blind technique. *J Am Med Assoc*. 1958;167(18):2190–2199. PubMed
10. Schou M, Juel-Nielsen N, Stromgren E, et al. The treatment of manic psychoses by the administration of lithium salts. *J Neurol Neurosurg Psychiatry*. 1954;17(4):250–260.doi:10.1136/jnnp.17.4.250 PubMed
11. Cutler RP, Monroe JJ, Anderson TE. Effects of tranquilizers upon pathological activity in psychotic patients. *AMA Arch Neurol Psychiatry*. 1957;78(1):61–68. PubMed

12. Ball JR, Kiloh LG. A controlled trial of imipramine in treatment of depressive states. *BMJ*. 1959;2(5159):1052–1055.doi:10.1136/bmj.2.5159.1052 PubMed
13. Noce RH, Williams DB, Rapaport W. Reserpine (Serpasil) in the management of the mentally ill. *J Am Med Assoc*. 1955;158(1):11–15. PubMed
14. Barsa JA, Kline NS. Combined reserpine-chlorpromazine therapy in disturbed psychotics. *Am J Psychiatry*. 1955;111(10):780. PubMed
15. Hollister LE, Krieger GE, Kringel A, et al. Treatment of chronic schizophrenic reactions with reserpine. *Ann N Y Acad Sci*. 1955;61(1):92–100. doi:10.1111/j.1749-6632.1955.tb42455.x PubMed
16. Kinross-Wright V. Chlorpromazine and reserpine in the treatment of psychoses. *Ann N Y Acad Sci*. 1955;61(1):174–182. doi:10.1111/j.1749-6632.1955.tb42464.x PubMed
17. Campden-Main BC, Wegielski Z. The control of deviant behavior in chronically disturbed psychotic patients by the oral administration of reserpine. *Ann N Y Acad Sci*. 1955;61(1):117–122.doi:10.1111/j.1749-6632.1955.tb42458.x PubMed
18. Goller ES. A controlled trial of reserpine in chronic schizophrenia. *J Ment Sci*. 1960;106:1408–1412. PubMed
19. Cole JO. Recommendations for reporting studies of psychiatric drugs. *Public Health Rep*. 1957;72(7):638–645. PubMed
20. Fleming BG, Currie JD. Investigation of a new compound, BW203, and of chlorpromazine in the treatment of psychosis. *J Ment Sci*. 1958;104(436):749–757. Pub Med
21. Feighner JP, Robins E, Guze SB, et al. Diagnostic criteria for use in psychiatric research. *Arch Gen Psychiatry*. 1972;26(1):57–63. PubMed
22. Spitzer RL, Endicott J, Robins E. Research Diagnostic Criteria: rationale and reliability. *Arch Gen Psychiatry*. 1978;35(6):773–782. PubMed
23. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition. Washington, DC: American Psychiatric Association; 1980.
24. Quitkin FM, McGrath PJ, Stewart JW, et al. Phenelzine and imipramine in mood reactive depressives: further delineation of the syndrome of atypical depression. *Arch Gen Psychiatry.* 1989;46(9):787–793. PubMed
25. Klein DF, Fink M. Psychiatric reaction patterns to imipramine. *Am J Psychiatry*. 1962;119:432–438. PubMed
26. Glassman AH, Kantor SJ, Shostak M. Depression, delusions, and drug response. *Am J Psychiatry*. 1975;132(7):716–719. PubMed
27. Hamilton M. *Lectures on the Methodology of Clinical Research*. Edinburgh, Scotland: E&S Livingstone; Williams & Wilkins; 1961.
28. Casey JF, Bennett IF, Lindley CJ, et al. Drug therapy in schizophrenia: a controlled study of the relative effectiveness of chlorpromazine, promazine, phenobarbital, and placebo. *Arch Gen Psychiatry*. 1960;2:210–220. PubMed
29. Ashcroft GW, MacDougall EJ, Barker PA. A comparison of tetrabenazine and chlorpromazine in chronic schizophrenia. *J Ment Sci*. 1961;107:287–293. PubMed
30. Cole JO. Evaluation of drug treatments in psychiatry. *J New Drugs*. 1962;2:264–275. PubMed
31. Whittier JR, Klein DF, Levine G, et al. Mepazine (Pacatal): clinical trial with placebo control and psychological study. *Psychopharmacologia*. 1960;1(4):280–287.doi:10.1007/BF00404225 PubMed
32. National Institute of Mental Health Psychopharmacology Service Center Collaborative Study Group. Phenothiazine treatment in acute schizophrenia; effectiveness. *Arch Gen Psychiatry*. 1964;10:246–261. PubMed
33. Baastrup PC, Poulsen JC, Schou M, et al. Prophylactic lithium: double blind discontinuation in manic-depressive and recurrent-depressive disorders. *Lancet*. 1970;2(7668):326–330.doi:10.1016/S0140-6736(70)92870-9 PubMed
34. Melia PI. Prophylactic lithium: a double-blind trial in recurrent affective disorders. *Br J Psychiatry*. 1970;116(535):621–624.doi:10.1192/bjp.116.535.621 PubMed
35. Prien RF, Caffey EM Jr, Klett CJ. Prophylactic efficacy of lithium carbonate in manic-depressive illness: report of the Veterans Administration and National Institute of Mental Health collaborative study group. *Arch Gen Psychiatry*. 1973;28(3):337–341. PubMed
36. Van Putten T, Marder SR. Variable dose studies provide misleading therapeutic windows. *J Clin Psychopharmacol*. 1986;6(4):249–250. doi:10.1097/00004714-198608000-00025 PubMed
37. Marder SR, Van Putten T, Mintz J, et al. Low- and conventional-dose maintenance therapy with fluphenazine decanoate: two-year outcome. *Arch Gen Psychiatry*. 1987;44(6):518–521. PubMed
38. Kane JM, Davis JM, Schooler N, et al. A multidose study of haloperidol decanoate in the maintenance treatment of schizophrenia. *Am J Psychiatry*. 2002;159(4):554–560.doi:10.1176/appi.ajp.159.4.554 PubMed
39. Van Putten T, Marder SR, Mintz J. A controlled dose comparison of haloperidol in newly admitted schizophrenic patients. *Arch Gen Psychiatry*. 1990;47(8):754–758. PubMed
40. Chouinard G. A double-blind controlled clinical trial of fluoxetine and amitriptyline in the treatment of outpatients with major depressive disorder. *J Clin Psychiatry*. 1985;46(3 Pt 2):32–37. PubMed
41. Feighner JP, Cohn JB. Double-blind comparative trials of fluoxetine and doxepin in geriatric patients with major depressive disorder. *J Clin Psychiatry*. 1985;46(3 Pt 2):20–25. PubMed
42. Fabre LF, Putman HP 3rd. A fixed-dose clinical trial of fluoxetine in outpatients with major depression. *J Clin Psychiatry*. 1987;48(10):406–408. PubMed
43. Wernicke JF, Dunlop SR, Dornseif BE, et al. Fixed-dose fluoxetine therapy for depression. *Psychopharmacol Bull*. 1987;23(1):164–168. PubMed
44. Dornseif BE, Dunlop SR, Potvin JH, et al. Effect of dose escalation after low-dose fluoxetine therapy. *Psychopharmacol Bull*. 1989;25(1):71–79. PubMed
45. Kane J, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. *Arch Gen Psychiatry*. 1988;45(9):789–796. PubMed
46. Bowden CL, Calabrese JR, McElroy SL, et al; Divalproex Maintenance Study Group. A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. *Arch Gen Psychiatry*. 2000;57(5):481–489.doi:10.1001/archpsyc.57.5.481 PubMed
47. Bowden CL, Calabrese JR, Sachs G, et al; Lamictal 606 Study Group. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. *Arch Gen Psychiatry*. 2003;60(4):392–400.doi:10.1001/archpsyc.60.4.392 PubMed
48. Bowden CL, Brugger AM, Swann AC, et al; The Depakote Mania Study Group. Efficacy of divalproex vs lithium and placebo in the treatment of mania. *JAMA*. 1994;271(12):918–924.doi:10.1001/jama.271.12.918 PubMed
49. Calabrese JR, Bowden CL, Sachs GS, et al. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression: Lamictal 602 Study Group. *J Clin Psychiatry*. 1999;60(2):79–88.doi:10.4088/JCP.v60n0203 PubMed
50. Calabrese JR, Bowden CL, Sachs G, et al; Lamictal 605 Study Group. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *J Clin Psychiatry*. 2003;64(9):1013–1024.doi:10.4088/JCP.v64n0906 PubMed
51. Sachs GS, Thase ME, Otto MW, et al. Rationale, design, and methods of the systematic treatment enhancement program for bipolar disorder (STEP-BD). *Biol Psychiatry*. 2003;53(11):1028–1042.doi:10.1016/S0006-3223(03)00165-3 PubMed
52. Nierenberg AA, Sylvia LG, Leon AC, et al; Litmus Study Group. Lithium treatment: moderate dose use study (LiTMUS) for bipolar disorder: rationale and design. *Clin Trials*. 2009;6(6):637–648. doi:10.1177/1740774509347399 PubMed
53. Rush AJ, Koran LM, Keller MB, et al. The treatment of chronic depression, part 1: study design and rationale for evaluating the comparative efficacy of sertraline and imipramine as acute, crossover, continuation, and maintenance phase therapies. *J Clin Psychiatry*. 1998;59(11):589–597. doi:10.4088/JCP.v59n1106 PubMed
54. Keller MB, Gelenberg AJ, Hirschfeld RM, et al. The treatment of chronic depression, part 2: a double-blind, randomized trial of sertraline and imipramine. *J Clin Psychiatry*. 1998;59(11):598–607.doi:10.4088/JCP.v59n1107 PubMed
55. Keller MB, Kocsis JH, Thase ME, et al. Maintenance phase efficacy of sertraline for chronic depression: a randomized controlled trial. *JAMA*. 1998;280(19):1665–1672.doi:10.1001/jama.280.19.1665 PubMed
56. Keller MB, McCullough JP, Klein DN, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. *N Engl J Med*. 2000;342(20):1462–1470.doi:10.1056/NEJM200005183422001 PubMed
57. Klein DN, Santiago NJ, Vivian D, et al. Cognitive-behavioral analysis system of psychotherapy as a maintenance treatment for chronic depression. *J Consult Clin Psychol*. 2004;72(4):681–688.doi:10.1037/0022-006X.72.4.681 PubMed
58. Thase ME, Rush AJ, Howland RH, et al. Double-blind switch study of imipramine or sertraline treatment of antidepressant-resistant chronic depression. *Arch Gen Psychiatry*. 2002;59(3):233–239.doi:10.1001/archpsyc.59.3.233 PubMed
59. Schatzberg AF, Rush AJ, Arnow BA, et al. Chronic depression: medication (nefazodone) or psychotherapy (CBASP) is effective when the other is

not. *Arch Gen Psychiatry*. 2005;62(5):513–520.doi:10.1001/archpsyc.62.5.513 PubMed
60. Kocsis JH, Gelenberg AJ, Rothbaum BO, et al; REVAMP Investigators. Cognitive behavioral analysis system of psychotherapy and brief supportive psychotherapy for augmentation of antidepressant nonresponse in chronic depression: the REVAMP Trial. *Arch Gen Psychiatry*. 2009;66(11):1178–1188.doi:10.1001/archgenpsychiatry.2009.144 PubMed
61. Lieberman JA, Stroup TS, McEvoy JP, et al; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353(12):1209–1223.doi:10.1056/NEJMoa051688 PubMed
62. Lavori PW, Rush AJ, Wisniewski SR, et al. Strengthening clinical effectiveness trials: equipoise-stratified randomization. *Biol Psychiatry*. 2001;50(10):792–801.doi:10.1016/S0006-3223(01)01223-9 PubMed
63. Rush AJ, Fava M, Wisniewski SR, et al; STAR*D Investigators Group. Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. *Control Clin Trials*. 2004;25(1):119–142.doi:10.1016/S0197-2456(03)00112-0 PubMed
64. Rush AJ, Trivedi MH, Wisniewski SR, et al; STAR*D Study Team. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *N Engl J Med*. 2006;354(12):1231–1242.doi:10.1056/NEJMoa052963 PubMed
65. Trivedi MH, Fava M, Wisniewski SR, et al; STAR*D Study Team. Medication augmentation after the failure of SSRIs for depression. *N Engl J Med*. 2006;354(12):1243–1252.doi:10.1056/NEJMoa052964 PubMed
66. Dragalin V. Adaptive designs: terminology and classification. *Drug Inf J*. 2006;40:425–435.
67. Leon AC. Comparative effectiveness clinical trials in psychiatry: superiority, noninferiority and the role of active comparators [published online ahead of print February 8, 2011]. *J Clin Psychiatry*. doi:10.4088/JCP.10m06089whi.
68. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont report: ethical principles and guidelines for the protection of human subjects of research*. http://ohsr.od.nih.gov/guidelines/belmont.html. Updated April 18, 1979. Accessed December 20, 2010.
69. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53(282):457–481. doi:10.2307/2281868
70. Fleiss JL, Dunner DL, Stallone F, et al. The life table: a method for analyzing longitudinal studies. *Arch Gen Psychiatry*. 1976;33(1):107–112. PubMed
71. Leon AC, Mallinckrodt CH, Chuang-Stein C, et al. Attrition in randomized controlled clinical trials: methodological issues in psychopharmacology. *Biol Psychiatry*. 2006;59(11):1001–1005.doi:10.1016/j.biopsych.2005.10.020 PubMed
72. Hill AB. *Principles of Medical Statistics*. 7th ed. New York, NY: Oxford University Press; 1961.
73. Lavori PW. Clinical trials in psychiatry: should protocol deviation censor patient data? *Neuropsychopharmacology*. 1992;6(1):39–48, discussion 49–63. PubMed
74. Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics*. 1982;38(4):963–974.doi:10.2307/2529876 PubMed
75. Jennrich RI, Schluchter MD. Unbalanced repeated-measures models with structured covariance matrices. *Biometrics*. 1986;42(4):805–820. doi:10.2307/2530695 PubMed
76. Gibbons RD, Hedeker D, Waternaux C, et al. Random regression models: a comprehensive approach to the analysis of longitudinal psychiatric data. *Psychopharmacol Bull*. 1988;24(3):438–443. PubMed
77. Hedeker D, Gibbons RD, Waternaux C, et al. Investigating drug plasma levels and clinical response using random regression models. *Psychopharmacol Bull*. 1989;25(2):227–231. PubMed
78. Hedeker D, Gibbons RD, Davis JM. Random regression models for multicenter clinical trials data. *Psychopharmacol Bull*. 1991;27(1):73–77. PubMed
79. Hedeker D. MIXOR: a Fortran program for mixed-effects ordinal probit and logistic regression. *Technical Report, Prevention Research Center*. Chicago, IL: School of Public Health, University of Illinois at Chicago; 1992.
80. Hedeker D. MIXREG: a Fortran program for mixed-effects linear regression with autocorrelated errors. *Technical Report, Prevention Research Center*. Chicago, IL: School of Public Health, University of Illinois at Chicago; 1992.
81. Hedeker D, Gibbons RD. MIXREG: a computer program for mixed-effects regression analysis with autocorrelated errors. *Comput Methods Programs Biomed*. 1996;49(3):229–252.doi:10.1016/0169-2607(96)01723-3 PubMed
82. Hedeker D, Gibbons RD. MIXOR: a computer program for mixed-effects ordinal regression analysis. *Comput Methods Programs Biomed*. 1996;49(2):157–176.doi:10.1016/0169-2607(96)01720-8 PubMed
83. Gibbons RD, Hedeker D, Elkin I, et al. Some conceptual and statistical issues in analysis of longitudinal psychiatric data: application to the NIMH treatment of Depression Collaborative Research Program dataset. *Arch Gen Psychiatry*. 1993;50(9):739–750. PubMed
84. Elkin I, Shea MT, Watkins JT, et al. National Institute of Mental Health Treatment of Depression Collaborative Research Program: general effectiveness of treatments. *Arch Gen Psychiatry*. 1989;46(11):971–982, discussion 983. PubMed
85. Fawcett J, Epstein P, Fiester SJ, et al; NIMH Treatment of Depression Collaborative Research Program. Clinical management—imipramine/placebo administration manual. *Psychopharmacol Bull*. 1987;23(2):309–324. PubMed
86. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. New York, NY: Academic Press; 1969.
87. Overall JE, Dalal SN. Design of experiments to maximize power relative to cost. *Psychol Bull*. 1965;64(5):339–350.doi:10.1037/h0022527 PubMed
88. Kraemer HC, Kupfer DJ. Size of treatment effects and their importance to clinical research and practice. *Biol Psychiatry*. 2006;59(11):990–996. doi:10.1016/j.biopsych.2005.09.014 PubMed
89. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56–62.doi:10.1136/jnnp.23.1.56 PubMed
90. Overall JE. The Brief Psychiatric Rating Scale. *Psychopharmacol Bull*. 1988;24:97–99.
91. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.doi:10.1192/bjp.134.4.382 PubMed
92. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261–276. PubMed
93. Shear MK, Brown TA, Barlow DH, et al. Multicenter collaborative Panic Disorder Severity Scale. *Am J Psychiatry*. 1997;154(11):1571–1575. PubMed
94. Rush AJ, Gullion CM, Basco MR, et al. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol Med*. 1996;26(3):477–486.doi:10.1017/S0033291700035558 PubMed
95. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. 1978;133(5):429–435. doi:10.1192/bjp.133.5.429 PubMed
96. Blake DD, Weathers FW, Nagy LM, et al. The development of a Clinician-Administered PTSD Scale. *J Trauma Stress*. 1995;8(1):75–90. doi:10.1002/jts.2490080106 PubMed
97. Guy W. *ECDEU Assessment Manual For Psychopharmacology*. Rockville, MD: Department of Health, Education, and Welfare; 1976.
98. Rush AJ, First MB, Blacker D, American Psychiatric Association. *Task Force for the Handbook of Psychiatric Measures. Handbook of Psychiatric Measures*. 2nd ed. Washington, DC: American Psychiatric Publishing.; 2008.
99. Levine J, Schiele BC, Bouthilet L. *Principles and Problems in Establishing the Efficacy of Psychotropic Agents*. Chevy Chase, MD: National Institute of Mental Health; 1971.
100. Prien RF, Robinson DS, National Institute of Mental Health, American College of Neuropsychopharmacology. *Clinical Evaluation of Psychotropic Drugs: Principles and Guidelines*. New York, NY: Raven Press; 1994.
101. Food and Drug Administration. General Considerations for the Clinical Evaluation of Drugs. 1977. http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/WomensHealthResearch/UCM131196.pdf. Accessed January 28, 2011.
102. Food and Drug Administration. Guidelines for the Clinical Evaluation of Antidepressant Drugs; 1977. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071299.pdf. Updated February 1997. Accessed December 20, 2010.
103. Food and Drug Administration. Guidelines for the Clinical Evaluation of Antianxiety Drugs 1977. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071295.pdf. Updated February 1997. Accessed December 20, 2010.
104. Food and Drug Administration Conference on Harmonisation I. E9—Statistical Principles for Clinical Trials 1998. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073137.pdf. Updated September 1998. Accessed December 20, 2010.
105. Food and Drug Administration Conference on Harmonization I. E10—Choice of Control Group and Related Issues in Clinical Trials 2001. http://www.fda.gov/downloads/Drugs/

GuidanceComplianceRegulatoryInformation/Guidances/ucm073139.pdf. Updated May 2001. Accessed December 20, 2010.
106. Food and Drug Administration. Non-Inferiority Clinical Trials: Draft Guidance for Industry; 2010. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM202140.pdf. Updated March 2010. Accessed December 20, 2010.
107. Food and Drug Administration. Adaptive Design Clinical Trials for Drugs and Biologics: Draft Guidance for Industry; 2010. http://www.fda.gov/downloads/Drugs/guidancecomplianceregulatoryinformation/guidances/ucm201790.pdf. Updated February 2010. Accessed December 20, 2010.
108. Begg C, Cho M, Eastwood S, et al. Improving the quality of reporting of randomized controlled trials: the CONSORT statement. *JAMA*. 1996;276(8):637–639.doi:10.1001/jama.276.8.637 PubMed
109. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet*. 2001;357(9263):1191–1194.doi:10.1016/S0140-6736(00)04337-3 PubMed
110. Schulz KF, Altman DG, Moher DCONSORT; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *PLoS Med*. 2010;7(3):e1000251.doi:10.1371/journal.pmed.1000251 PubMed
111. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340:c869. PubMed
112. Food and Drug Administration. (2004). Briefing document for February 2, 2004 Meeting of Psychopharmacological Drugs Advisory Committee (PDAC) and Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee (Peds AC). http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4065b1-04-Tab02-Laughren-Jan5.pdf. Accessed January 28, 2011.
113. Walsh BT, Seidman SN, Sysko R, et al. Placebo response in studies of major depression: variable, substantial, and growing. *JAMA*. 2002;287(14):1840–1847.doi:10.1001/jama.287.14.1840 PubMed
114. Kraemer HC. To increase power in randomized clinical trials without increasing sample size. *Psychopharmacol Bull*. 1991;27(3):217–224. PubMed
115. Leon AC, Marzuk PM, Portera L. More reliable outcome measures can reduce sample size requirements. *Arch Gen Psychiatry*. 1995;52(10):867–871. PubMed
116. Kobak KA, Kane JM, Thase ME, et al. Why do clinical trials fail? the problem of measurement error in clinical trials: time to test new paradigms? *J Clin Psychopharmacol*. 2007;27(1):1–5.doi:10.1097/JCP.0b013e31802eb4b7 PubMed
117. Leon AC. Two clinical trial designs to examine personalized treatments for psychiatric disorders [article published online ahead of print July 13, 2010]. *J Clin Psychiatry*. 2010. PubMed
118. Kraemer HC, Wilson GT, Fairburn CG, et al. Mediators and moderators of treatment effects in randomized clinical trials. *Arch Gen Psychiatry*. 2002;59(10):877–883.doi:10.1001/archpsyc.59.10.877 PubMed

Developments in Pediatric Psychopharmacology: Focus on Stimulants, Antidepressants, and Antipsychotics

Christoph U. Correll, MD; Christopher J. Kratochvil, MD; and John S. March, MD, MPH

Most major psychiatric disorders have an onset in childhood or adolescence in a sizeable proportion of patients, and earlier onset disorders often have a severe and chronic course that can seriously disrupt sensitive developmental periods, with lifelong adverse consequences. Accordingly, psychopharmacologic treatments have been increasingly utilized in severely ill youth. However, the increased use of psychopharmacologic treatments in pediatric patients has also raised concerns regarding a potential overdiagnosis and overtreatment of youth, without adequate data regarding the pediatric efficacy and safety of psychotropic agents. Over the past decade, a remarkable number of pediatric randomized controlled trials have been completed, especially with psychostimulants, antidepressants, and antipsychotics. For these frequently used agents, effect sizes against placebo have typically been at least moderate, with most numbers-needed-to-treat well below 10 for response, indicating clinical significance as well. Nevertheless, data also point to a greater and/or different profile of susceptibility to adverse effects in pediatric compared to adult patients, as well as to a role for nonpharmacologic treatments, given alone or combined with pharmacotherapy, for many of the youth. Taken together, these results highlight the need for a careful assessment of the risk-benefit relationship of psychopharmacologic treatments in patients who cannot be managed sufficiently with nonpharmacologic interventions and for routine, proactive adverse effect monitoring and management. Although considerable progress has been made, there is still enormous need for additional data and funding of pediatric psychopharmacology trials. It is hoped that the field will acquire the necessary resources to propel pediatric clinical psychopharmacology to new levels of insight by linking it with, but not replacing it by, pharmacoepidemiologic and biomarker approaches and advances.

J Clin Psychiatry 2011;72(5):655–670

Submitted: *April 11, 2011; accepted April 14, 2011 (doi:10.4088/JCP.11r07064).*
Corresponding author: *Christoph U. Correll, MD, Division of Psychiatry Research, The Zucker Hillside Hospital, 75-59 263rd St, Glen Oaks, NY 11004 (ccorrell@lij.edu).*

As part of a series honoring the 50th anniversary of the Early Clinical Drug Evaluation Unit (ECDEU)–New Clinical Drug Evaluation Unit (NCDEU) Annual Meeting, this article will address the pharmacologic treatment of youth with psychostimulants, antidepressants, and antipsychotics. In the spirit of providing a synopsis of past achievements, current challenges, and outstanding solutions, we will also summarize the current evidence for the efficacy and safety of these major pharmacologic drug classes in youth, identify knowledge gaps, and outline future directions in the clinical use and research of these medications in pediatric patients.

PSYCHOTROPIC MEDICATION USE IN YOUTH: A DEBATED ISSUE

Despite increasing recognition that psychiatric disorders that are generally treated in adulthood often have an onset before age 18 years, including unipolar depression,[1] bipolar disorder,[2] and schizophrenia,[3] the use of psychopharmacologic medications in youth with these conditions has been controversial. Although data suggest that psychiatric disorders are often more severe, chronic, and unresponsive to therapies and associated with greater functional impairment and disease burden if their onset occurs during childhood or adolescence compared to adulthood,[1,3,4] a number of concerns have been raised regarding the number of psychotropic medication prescriptions received by children and adolescents and the appropriateness of the diagnoses used to justify such use. There has been significant debate about a potential overdiagnosis of psychiatric disorders in childhood, particularly of bipolar disorder,[5–7] as well as allegations of overmedicating behaviors of prescribers.[8–17] The concern is that psychotropic medications, especially antipsychotics, are used too early, before or instead of attempts to address the youngsters' psychiatric symptomatology with more resource-intensive psychotherapeutic, behavioral, and family interventions.[18] The debate has also been fueled by decades of prescribing despite a dearth of efficacy and safety data for major psychiatric drug classes in youth, resulting in a general need to rely on extrapolations from studies in adults.[19]

DEVELOPMENTAL PSYCHOPHARMACOLOGY: DIFFERENCES THAT MATTER

The debate about the appropriateness and potentially underrecognized risks of psychotropic medication use in youth is accentuated by findings suggesting that psychotropic medications may have developmentally dependent effects that differ from those observed in adults. For example, research has suggested that tricyclic antidepressants are much less effective in youth than in adults.[20] Furthermore, a syndrome of paradoxical hyperactivity, agitation, and/or aggressiveness has been described in response to treatment with benzodiazepines or antihistamines, in a small subgroup of susceptible youth.[21,22] Similarly, pharmacokinetic differences have also been identified. Compared to adults, children

and adolescents have active tissue growth, increased reproductive hormone release during adolescence, a higher ratio of liver organ-to-tissue mass, greater intracellular and extracellular tissue water and glomerular filtration rates, lower protein binding, and reduced fat tissue mass.[23] Clinically, these differences usually mean that for some medications higher doses per kilogram weight are required in pediatric populations than in adults to achieve similar efficacy and that more frequent dosing per day may be required in younger children. In addition to other less well-known pharmacodynamic aspects, these pharmacokinetic differences between children and adolescents and adults might be one reason for a generally observed greater likelihood of a number of adverse effects in youths than in adults. For example, these quantitative differences include higher rates of nausea and activation with antidepressants[24]; higher rates of sedation, weight gain, prolactin elevation, and withdrawal dyskinesia with antipsychotics[24–26]; greater weight gain with mood stabilizers[26]; and higher rates of sudden cardiac death during stimulant treatment,[27] although the latter finding has not always been confirmed[28] and may be related to a greater prevalence of inborn structural and functional cardiac abnormalities in youth compared to individuals with attention-deficit/hyperactivity disorder (ADHD) who survived into adulthood.[29]

However, in addition to these quantitative differences, some adverse events might also differ qualitatively. In addition to the already described paradoxical agitation in response to benzodiazepines and sedatives, other examples include dysphoria in response to psychostimulants[30] and suicidal thoughts or behaviors in response to antidepressants.[31] While these qualitatively different responses do not affect all patients, there appear to be subgroups of patients who possibly either are genetically predisposed to metabolize these medications differently, leading to metabolites with different biological activity,[32] or differ in terms of receptor configuration and downstream pathways, due to an immaturity of the central nervous functioning or isolated pathway alterations. Taken together, the potential for age-dependent quantitative and qualitative differences in efficacy and adverse event profiles in youth compared to adults points toward the urgent need for carefully conducted large and long-term trials of psychotropic mediations in pediatric patients.

DEVELOPMENTS IN PEDIATRIC PSYCHOPHARMACOLOGY

Due to worries regarding insufficient knowledge about the complex and potentially enduring effects of psychotropic medications taken during periods of enormous biological and psychological development, it is important to evaluate how far the field of pediatric psychopharmacology has come and which gaps still need to be addressed.[33] Over the past 40 years, the field of pediatric psychopharmacology has evolved from an unduly long reliance on case reports and uncontrolled case series[33] to the conduct of methodologically problematic crossover and open-label studies and, more recently, to larger cohort studies and adequately powered, randomized, placebo-controlled and, less so, active comparator trials.[3,26,31,34,35] More recently, multisite studies have been conducted that compare the efficacy and safety of psychotherapy with a pharmacologic treatment and the combination of both treatment modalities against placebo.[36] Moreover, more complex equipoise randomization designs, placebo run-in phases, discontinuation designs, and large practical and adaptive trials are slowly entering the area of pediatric psychopharmacology. However, despite the fact that, like in adults, polypharmacy with psychotropic medications is common in youth with severe psychiatric disorders,[24,37,38] trials comparing different pharmacologic augmentation and combination strategies are scarce.

Due to the wide range of development and psychopathology encountered during childhood and adolescence, the validity and reliability of assessments can be affected in this population. Therefore, the development and validation of age-appropriate rating scales and determination of age-dependent thresholds for abnormal values and severity levels are necessary. Given that in psychiatry patient and clinician support measures will not yield to surrogate endpoints until our understanding of fundamental biology has progressed significantly,[39] this process is even more important. Moreover, questions and tasks must be age-appropriate and sometimes gender-appropriate (particularly in adolescence) and may not always be uniformly applicable.

Regarding side effect assessments, a review of 196 pediatric psychopharmacology articles published over more than 2 decades revealed that there was no common method used for eliciting or reporting adverse event data.[40] This appropriately prompted an increased focus on standardized assessment methods for acute and long-term adverse effects in youth,[41,42] as these inconsistencies in ascertaining and reporting data on medication safety in pediatric patients are a major current limitation. However, even regarding biological measures or organic side effects, the field has only slowly adopted the use of developmentally appropriate measures and thresholds. This is particularly pertinent for the assessment and tracking of age-inappropriate weight gain and abnormalities in cardiometabolic parameters, including effects on blood pressure, glucose, and lipids.[43]

The emergence of larger-scale conduct of psychopharmacology trials in children and adolescents can be attributed to the recognition that exposing a limited number of youngsters in controlled and well-supervised settings was more ethical than not conducting these studies, leading to the exposure of a much larger number of youngsters to largely untested medications in general clinical practice. Similarly, the field matured, accepting that a placebo control[44,45] in a limited number of patients was more ethical than using an active comparator of often similarly uncertain efficacy and safety or than remaining in doubt about the true efficacy and safety of a new compound or an agent that had been tested in detail only in adults. In this context, the initiative by the US Food

© Copyright 2011 Physicians Postgraduate Press, Inc.

and Drug Administration (FDA) to incentivize pharmaceutical companies to conduct pediatric studies in select drugs by granting a 6-month patent extension for adequate safety data in at least 100 youth followed for 6 months has contributed to the increase in an acute phase, placebo-controlled efficacy database as well as in 6- to 12-month open-label extension study–based safety and tolerability data. Additionally, new drugs with a likelihood of use in the pediatric population have recently been required to be tested in pediatric trials either prior to FDA approval or as a part of a postapproval commitment. In Europe, the European Medicines Agency has taken this a step further, requiring a pediatric investigational plan to be submitted with every submission of a medication for a new indication.

CONTROLLED EVIDENCE BASE FOR STIMULANTS, ANTIDEPRESSANTS, AND ANTIPSYCHOTICS IN YOUTH

Over the last decade, there has been a sharp increase in the number, size, and quality of psychopharmacologic studies in youth. Case series and open-label and crossover studies have been replaced by randomized controlled trials (RCTs) including many of the major medication classes, especially psychostimulants, antidepressants, and antipsychotics.

Psychostimulants

Given conservative estimates of ADHD prevalence rates of 3% to 7% in US children,[46] 60% to 85% continuation into adolescence, and up to 60% into adulthood,[47–49] and given the serious functional impairment associated with ADHD in youth as well as in adults,[50] effective management strategies for this early childhood–onset disorder are important.

Efficacy in ADHD. There is strong support for the efficacy of pharmacotherapy, especially of psychostimulants, as a first-line treatment for ADHD.[51] All stimulant medications currently approved for ADHD are either methylphenidate or amphetamine derivatives, both of which enhance the neurotransmission of dopamine and, to a lesser extent, of norepinephrine. Over the last decades, the pediatric database for the acute and long-term safety and efficacy of stimulants has continually grown, including more recently research in preschoolers and adolescents. In addition, data supporting the efficacy and safety of nonstimulant medications for ADHD have also increased significantly over the past decade.[51]

A meta-analysis of randomized, controlled pediatric studies of 2 FDA-approved treatments for ADHD, atomoxetine and stimulants, yielded a moderate effect size for atomoxetine of 0.63 and a large effect sizes of 0.99 and 0.95 for immediate- and extended-release stimulants, respectively.[52] These effect sizes translate into response rates of approximately 65% to 75% after the first stimulant trial (compared to 4%–30% with placebo) and 80% to 90% after 2 different, consecutive stimulant trials.[55] The calculated numbers needed to treat (NNTs) for study-defined response were 3 to 5 for stimulants and 4 for atomoxetine.[146] A third, more recently FDA-approved agent, the α_2 agonist guanfacine XR, had medium to large effect sizes of 0.43 to 0.86 in the 2 double-blind, placebo-controlled registration trials.[53,54] Moreover, recently, extended-release clonidine was also FDA-approved for monotherapy and as an adjunctive treatment in addition to stimulants.[51]

More recently, research has focused on improving the delivery mechanisms of stimulant medications to extend the duration of action. As a result, treatment can increasingly be individualized, having available multiple different formulations, including short-, intermediate-, and long-acting stimulants, as well as a variety of administration options, such as capsules, sprinkleable capsules, tablets, chewable tablets, oral solution, and transdermal patches.[51]

Three high-quality studies comparing stimulant treatment with psychosocial interventions have further advanced the field (Table 1). The Multimodal Treatment Study of Children With ADHD (MTA) was a seminal, longitudinal, 4-arm trial in 579 children aged 7 to 9.9 years with ADHD, combined type.[56] Patients were randomly assigned to manualized pharmacotherapy (consisting of immediate-release methylphenidate tid; final dose: 32.1 ± 15.4 mg/d), manualized behavioral intervention, combination of manualized pharmacotherapy (final dose: 28.9 ± 13.7 mg/d) plus behavioral intervention, or community treatment. Dose titration of methylphenidate was based on the patients' weight, on parent and teacher rating scale–reported efficacy, and on tolerability.[56] Alternative medications were allowed for patients with inadequate response to the initial methylphenidate trial. The behavioral treatment was structured and rigorous, including a 35-session parent training group; an 8-week, 5-days-per-week, 9-hours-per-day summer treatment program; and school-based treatment with 10 to 16 sessions of biweekly teacher consultation accompanied by 12 weeks of paraprofessionals directly working with the child.

Results indicated that all 4 treatment groups improved, but that the greatest improvement in ADHD symptoms occurred in the medication-only or the combined medication/psychosocial treatment groups. Combined treatment did not yield significantly greater benefits than medication management alone for core ADHD symptoms. Effect sizes for methylphenidate were moderate, ie, 0.52 for parent-reported efficacy and 0.75 for teacher-reported efficacy. In addition, modest advantages were found for specific non-ADHD symptoms and other functional outcomes. Rates of "excellent success" were 68% for combination treatment, 56% for medication treatment, 34% for psychosocial treatment, and 25% for community control treatment. This translates into NNTs of 3 for combination treatment, 4 for medication treatment, and 12 for psychosocial treatment, representing large effect sizes for combination treatment and medication treatment alone and very small effects of questionable clinical significance for behavioral treatment alone when compared with community control treatment that

Table 1. Randomized Studies Comparing Psychostimulants With a Psychosocial Intervention, a Combination of the Two, and a Control Condition

Study	Sample Size	Age Range (y)	% Males	Diagnosis	Treatment	Study Duration	Conclusion
Multimodal Treatment Study of Children With ADHD (MTA)[56–58]	579	7–9.9	80	ADHD	Subjects were randomly assigned to a manualized medication management program, an intensive psychosocial treatment, a combination of the two, or community treatment	14 mo	Combined treatment did not yield significantly greater benefits than medication management alone for core ADHD symptoms. Rates of "excellent success" were 68% for combination treatment, 56% for medication treatment, 34% for psychosocial treatment, and 25% for community control treatment
New York Montreal Study of Long-Term Methylphenidate and Multimodal Psychosocial Treatment in Children with ADHD[59,60]	133	7–9	93	ADHD	Study of children who responded to short-term methylphenidate, then were randomly assigned to methylphenidate alone, methylphenidate plus psychosocial treatment (parent training and counseling, social skills training, psychotherapy, and educational assistance), or methylphenidate with a psychosocial attention control treatment	2 y	Combined treatment did not lead to superior functioning compared to methylphenidate alone, and all treatment groups demonstrated significant improvement that continued over 2 y. Investigators concluded there was no support for routinely adding psychosocial interventions to stimulants for ADHD
Preschool ADHD Treatment Study (PATS)[61–63]	303	3–5.5	76	ADHD	Fewer than 10% of the children responded to an initial course of parent training, and ultimately 165 were initiated on pharmacotherapy. Mean optimal dose of immediate-release methylphenidate, dosed tid, was 14.2 mg/d	70 wk	While methylphenidate was effective, the effect size was smaller than that found in school-aged children in the study, perhaps due at least in part to the conservative dosing. Moderate to severe adverse effects occurred in 30% of preschoolers, including emotional outbursts, initial insomnia, repetitive behaviors/thoughts, decreased appetite, and irritability. A total of 11% discontinued methylphenidate due to intolerable adverse effects, compared to < 1% of school-aged children in MTA

Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

could consist of medication and/or behavioral treatment.[149] In subsequent analyses at 3 years[57] and 8 years,[58] there were no differences in outcome on the basis of initial treatment assignment anymore, but rather baseline functioning was the most consistent predictor. However, treatment had not been controlled beyond the 14 months of the active study, indicating that outcomes seem to differ only when effective and evidence based treatments are maintained according to at least somewhat controlled protocols or guidelines.

A second study that investigated medication, psychosocial, and combination treatment for ADHD was the New York Montreal Study of Long-Term Methylphenidate and Multimodal Psychosocial Treatment in Children with ADHD (Table 1).[59] In this 2-year study, 133 children aged 7 to 9 years with ADHD who had responded to short-term methylphenidate treatment were randomly assigned to treatment with methylphenidate, methylphenidate plus psychosocial treatment (parent training and counseling, social skills training, psychotherapy, and educational assistance), or methylphenidate plus a psychosocial attention control treatment. Consistent with the MTA results, combination treatment was not superior to methylphenidate alone, and all treatment groups demonstrated significant improvement that was generally maintained over 2 years, although after 1 year, all patients were single-blindedly assigned to pill placebo, with reinitiation of methylphenidate as needed.[60]

A third seminal, National Institute of Mental Health (NIMH)–funded stimulant study in ADHD was the Preschool ADHD Treatment Study (PATS), which enrolled 303 moderately to severely impaired preschoolers aged 3–5.5 years with ADHD (Table 1).[61,62] Fewer than 10% of the children responded to an initial course of parent training, and ultimately 165 were randomly assigned to 14 months of either placebo or immediate-release methylphenidate (1.25 mg, 2.5 mg, 5 mg, or 7.5 mg tid), using a titration schedule modeled after MTA. This study was needed, as stimulants were used clinically for children below the age of 6 years, and only a few, small randomized studies had been conducted in preschoolers that used immediate-release methylphenidate at relatively low doses (< 0.6 mg/kg compared to 0.3–1.0 mg/kg used in studies of older children), and at potentially too infrequent intervals (ie, qd or bid dosing, rather than tid dosing that might be necessary in younger children who have a faster drug metabolism). PATS subjects received 1 week of treatment with each dose during an initial, double-blind, crossover titration phase, and 22% of subjects responded

best to 7.5 mg tid (final most efficacious dose: 14.22 ± 8.1 mg/d, or 0.7 ± 0.4 mg/kg/d).[61,62]

Comparing PATS with MTA results revealed age group differences. Compared to school-aged children, preschoolers responded to lower weight-adjusted optimal doses of immediate-release methylphenidate (0.7 mg/kg/d compared to 1.0 mg/kg/d) and had slower clearance of a single dose of methylphenidate,[30] more emotional adverse events (eg, proneness to crying, irritability, and crabbiness), more study withdrawal due to adverse effects (11% vs < 1%), and smaller effect sizes for response (ie, 0.35 and 0.43 based on parent ratings for parent- and teacher-reported efficacy, respectively, compared to 0.52 for parents and 0.75 for teachers in the MTA study). Thus, results from this study suggested that in preschoolers with ADHD, clinicians should utilize slower titration and smaller doses of stimulants and monitor adverse effects more closely.[63]

Efficacy in disruptive behavior disorders. A meta-analysis of pharmacologic treatments for maladaptive aggression in youth (mean age: 9.1 years, 84.2% male) identified 18 RCTs with stimulants (16 with methylphenidate, 1 combination study of methylphenidate and mixed amphetamine salts, and 1 combination of methylphenidate, dextroamphetamine, and pemoline).[64] The primary diagnoses included ADHD (13 studies), disruptive behavior disorders (3 studies), autism (2 studies), and mental retardation (1 study), and all but 6 studies allowed for comorbid diagnoses of conduct disorder, oppositional defiant disorder, or ADHD. The average trial duration was 27.2 days, and the weighted average dose of methylphenidate was 0.93 mg/kg/d. Consistent with a prior meta-analysis on this topic, in which stimulants had an effect size of 0.84,[65] stimulants had a pooled mean effect size for pediatric aggression of 0.78, a medium to large effect size.[64] However, crossover studies were included in these calculations that are less methodologically sound, and, to date, no head-to-head comparison between stimulants and antipsychotics, the other medication class with a large effect size for aggression, exists. In a recently completed systematic review of placebo-controlled efficacy of stimulants for rating scale–based aggression, stimulants (6 studies, 907 patients) had a pooled effect size of 0.6 and an NNT for response of 4.[147]

Stimulant tolerability. All stimulant formulations have roughly similar adverse event profiles, including a potential for delayed onset of sleep, appetite suppression, weight loss, headache, abdominal pain, stomach upset, growth delays, and increases in pulse as well as blood pressure.[34,51,61] Less common adverse effects that might require management include tics and emotional lability/irritability. Emotional outbursts and irritability might be more frequent in younger children and those with developmental delays.[30] Concerns about the cardiovascular safety of psychostimulants have prompted specific recommendations to obtain historical and physical information to identify at-risk children with structural cardiac abnormalities and premedication cardiovascular symptomatology. However, potentially medication-related changes in pulse and blood pressure have also been observed in children with ADHD without preexisting cardiac abnormalities. For example, in a 10-year Florida Medicaid claims study, stimulant-treated patients with ADHD had 20% more emergency room visits and 21% more office visits for cardiac symptoms than patients not receiving stimulants.[28] However, cardiac mortality was not increased in patients currently receiving stimulants or those with a history of stimulant use. Likewise, Gould et al[27] reported similar rates of sudden death in pediatric patients taking psychostimulants compared to children in the general population, with 11 sudden deaths reported between 1992 and 2005. However, in a matched case-control study comparing data for 564 reports of sudden death in 7- to 19-year-olds with the deaths of 564 same-aged children who died in a motor vehicle accident, a significant association of stimulant use with sudden death emerged (odds ratio = 7.4; 95% CI, 1.4–74.9).[27] Nevertheless, absence of autopsy data in most cases and the possibility of non–medication-related effects complicate the interpretation of these results.

Antidepressants

As shown by the fact that approximately 2% of children and adolescents in the United States receive a prescription for a selective serotonin reuptake inhibitor (SSRI), clinicians consider antidepressants acceptable treatments for children and adolescents with mood, anxiety, and obsessive-compulsive disorders.[31] Randomized placebo-controlled trials are generally thought to indicate that SSRIs and selective serotonin and noradrenergic reuptake inhibitors (SNRIs) are effective in youth with mood, anxiety, and obsessive-compulsive disorders.[31] As family physicians and, to a lesser extent, pediatricians have become more comfortable using these medications in the pediatric population, prescribing rates continue to increase despite concerns about adverse events.

Efficacy in major depressive disorder, obsessive-compulsive disorders, and anxiety disorders. In a review of 27 published and unpublished studies, Bridge and colleagues[31] examined the relative risks and benefits of antidepressant medications (SSRIs, nefazodone, venlafaxine, and mirtazapine) in youth with major depressive disorder (MDD) (N = 15), obsessive-compulsive disorder (OCD) (N = 6), and non-OCD anxiety disorders (N = 6). The NNT for MDD was 10 (95% CI, 7–15), for OCD was 6 (95% CI, 4–8), and for non-OCD anxiety was 3 (95% CI, 2–5), corresponding to a small, a medium, and a large effect size, respectively. For OCD and non-OCD anxiety disorders, younger and older subjects responded equally well. Conversely, for children younger than 12 years with MDD, only fluoxetine showed benefit over placebo. In most studies, the within-group response rate for medication hovered around 60% across trials independent of age, gender, or diagnosis. Interestingly, what distinguished a positive from a negative MDD trial was the size of the placebo response rate: the larger the placebo response, the greater the likelihood of a negative study. Given that an increased number of sites

Table 2. Randomized Studies Comparing Antidepressants With a Psychosocial Intervention, a Combination of the Two, and a Control Condition

Study	Sample Size	Age Range (y)	% Males	Diagnosis	Treatment	Study Duration	Conclusion
Pediatric OCD Treatment Study (POTS)[69]	112	7–17	50	OCD	Randomly assigned to CBT alone, medical management with sertraline alone, the combination of the two, or pill placebo	12 wk	All 3 active treatments superior to placebo in reducing OCD symptoms, although the remission rate for combined treatment was 53.6%; for CBT alone, 39.3%; for sertraline alone, 21.4%; and for placebo, 3.6%
Child/Adolescent Anxiety Multimodal Study (CAMS)[71,72]	488	7–17	50	Separation anxiety disorder, social phobia, or generalized anxiety disorder	Randomly assigned to sertraline, CBT, their combination, or pill placebo	12 wk	All 3 active treatments were significantly superior to placebo. Response rate for combination treatment was 81%, followed by both CBT alone (60%) and sertraline alone (55%), compared to only 24% with placebo
Treatment for Adolescents With Depression Study (TADS)[67,73–81]	439	12–17	46	MDD	Randomly assigned to fluoxetine with medical management, weekly CBT, their combination, or pill placebo	12 wk (acute phase)	Adolescents who received fluoxetine or combination therapy had significant improvements at 12 wk, while those receiving CBT alone did not separate from placebo. Response rates at 12 wk were 71.0% for combination treatment, 60.6% for fluoxetine, 43.2% for CBT, and 34.4% for placebo. By the end of 9 mo of treatment, response rates for combination (81.3%), fluoxetine (71.6%), and CBT (68.5%) were virtually identical
Treatment of SSRI-Resistant Depression in Adolescents (TORDIA)[82–85]	334	12–18	30	MDD (had not responded to a 2-mo trial with an SSRI)	Randomly assigned to a second, different SSRI (paroxetine, citalopram, or fluoxetine); a different SSRI plus CBT; venlafaxine; or venlafaxine plus CBT	12 wk	The 2 arms with CBT plus medication demonstrated a higher response rate (54.8%) than a medication switch alone (40.5%), with no difference in response rate between venlafaxine and a second SSRI

Abbreviations: CBT = cognitive-behavioral therapy, MDD = major depressive disorder, OCD = obsessive-compulsive disorder, SSRI = selective serotonin reuptake inhibitor.

predicted a poor response, it is likely that method variance—perhaps reflecting baseline inflation, rater unreliability, and early dropout—rather than lack of efficacy accounts for the large number of failed trials in pediatric major depression. Consistent with this interpretation, all 3 fluoxetine MDD trials—2 of which were funded by the NIMH[66,67] and 1 of which, funded by Eli Lilly, was conducted using academic sites[68]—were strongly positive, with placebo response rates around 35%, which is at the low end of a range that in negative trials approached 60%.

It is heuristically valuable in this regard to examine 4 very high quality, NIMH-funded studies in OCD, anxiety disorders, and adolescent MDD that compared specific antidepressants with cognitive-behavioral therapy (CBT), their combination, and placebo (Table 2).

The NIMH-funded Pediatric OCD Treatment Study (POTS) randomly assigned 112 patients with OCD aged 7 to 17 years to treatment with CBT, medical management with sertraline, the combination of the two, or pill placebo (Table 2).[69] All 3 active treatments were superior to placebo in reducing OCD symptoms, although clinical remission rates were 53.6% for combined treatment, 39.3% for CBT alone, and 21.4% for sertraline alone, compared to only 3.6% for placebo only. This translated into NNTs of 2 for the combination treatment and 3 for CBT (both representing large effect sizes), as well as 6 for sertraline, which was identical to the results in the aforementioned meta-analysis,[31] representing a moderate effect size. Thus, the POTS findings support an initial treatment approach for youth with OCD to consist of either CBT or sertraline as monotherapy or a combination of the two.

In a study by the Research Unit on Pediatric Psychopharmacology (RUPP) Anxiety Study Group,[70] 128 youth aged 6 to 17 years with social phobia, separation anxiety disorder, or generalized anxiety disorder (GAD) were enrolled who had failed to improve with 3 weeks of a psychosocial intervention. Patients were then randomly assigned to 8 weeks of fluvoxamine dosed up to 300 mg/d or placebo. In this trial, fluvoxamine was significantly superior to placebo on both the Pediatric Anxiety Rating Scale and the Clinical Global Impressions-Improvement scale. Response rates were 76% with fluvoxamine versus 29% with placebo, resulting in a large effect sized NNT of only 2, being slightly more effective compared to the NNT of 3 in the previously cited meta-analysis.[31]

One of the most relevant studies in pediatric anxiety disorders was the recently completed Child/Adolescent Anxiety Multimodal Study (CAMS).[71,72] In CAMS, 488 patients aged

© Copyright 2011 Physicians Postgraduate Press, Inc.

7 to 17 years with separation anxiety disorder, social phobia, or GAD were randomly assigned to sertraline, CBT, their combination, or pill placebo.[71] All 3 active treatments were significantly superior to placebo. The highest response rate, based on a rating of much or very much improved on the Clinical Global Impressions-Severity of Illness scale, was observed in the combination treatment (81%), followed by both CBT alone (60%) and sertraline alone (55%), compared to a response rate of only 24% with placebo.[72] These results translate into an NNT of 2 for the combination treatment and 3 for CBT alone, representing large effect sizes, and 4 for sertraline alone, representing a moderate effect size.

In the Treatment for Adolescents With Depression Study (TADS), 439 adolescents aged 12–17 years with moderate to severe depression were randomly assigned to one of 4 treatments: fluoxetine with medical management, weekly CBT, their combination, and pill placebo (Table 2).[67,73] Adolescents who received fluoxetine or combination therapy had significant improvements in depression ratings at 12 weeks, whereas those receiving CBT alone did not separate from placebo. Response rates at 12 weeks were 71.0% for combination treatment, 60.6% for fluoxetine, 43.2% for CBT, and 34.4% for placebo. The corresponding NNTs for response with combination of CBT plus fluoxetine and with fluoxetine monotherapy were 3 (95% CI, 2–4) and 4 (95% CI, 3–8), respectively,[67] large effect sizes that were much more favorable than the NNT of 10 in the aforementioned meta-analysis.[31] Younger and less severely/chronically ill youth who were less suicidal and less hopeless and who had less melancholic features or other comorbidities benefited more.[74] Notably, the mean duration of the current depressive episode prior to randomization was as long as 70 weeks, indicating little likelihood of spontaneous remission in these moderately to severely ill teens with MDD.[75] While this study demonstrated the key role of pharmacotherapy in the treatment of adolescent MDD, the combination treatment was most successful acutely for a number of secondary outcomes, including the treatment of patients with comorbid ADHD[76] and the reduction of suicidal events.[77,78] Of note, by the end of 9 months[79,80] and 1 year[81] of treatment, combination, fluoxetine, and CBT responses were virtually identical, and patients staying in the study generally retained their benefits.

A second trial comparing pharmacotherapy and psychotherapeutic intervention in pediatric depression was the Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) study,[82,83] which focused on more chronically depressed and treatment-resistant youth than TADS. This 12-week study randomly assigned 334 adolescents aged 12 to 18 years with MDD and lack of response to a 2-month initial trial with an SSRI to switch to one of 4 conditions: a different SSRI (citalopram, fluoxetine, or paroxetine); a different SSRI plus CBT; an antidepressant of a different class (venlafaxine); or venlafaxine plus CBT (Table 2).[82] The 2 arms with CBT plus medication demonstrated a higher response rate (54.8%) than a medication switch alone (40.5%), with no difference in response rate between switch to a second SSRI or venlafaxine.[82] This difference in response rates translates into an NNT of 7 in favor of the combination treatment over antidepressants alone in chronically depressed adolescents. TORDIA demonstrated that for adolescents with depression who do not respond to an initial SSRI, a switch to another antidepressant, combined with CBT, should be considered. Even if CBT is not feasible, simply changing medications yielded a 40.5% improvement, and within- and outside-class switches were equally effective. However, venlafaxine was associated with greater increases in pulse and diastolic blood pressure and more frequent skin problems than other SSRIs.[82] At 24-week follow-up, 38.9% of the 334 adolescents enrolled in the study achieved remission without differences based on initial treatment assignment.[84] Response at week 12, as well as lower baseline depression, hopelessness, and self-reported anxiety, suicidal ideation, and family conflict, mediated remission status at week 24.[84] Of patients who responded by week 12, 19.6% had a relapse of depression by week 24. At 72-week follow-up, an estimated 61.1% of the randomized youths had reached remission, but of the 130 remitted youth at week 24, 25.4% relapsed in the subsequent year.[85] Randomly assigned treatment during the first 12 weeks did not influence remission rate or time to remission, but patients assigned to SSRIs had a significantly more rapid decline in self-reported depressive symptoms and suicidal ideation than those assigned to venlafaxine.[85] Moreover, more severe depression, greater dysfunction, and alcohol or drug use at baseline mediated lack of remission. Of note, the depressive symptom trajectory in remitters had already separated from that of nonremitters by the first 6 weeks of treatment.[85]

Antidepressant tolerability. Adverse effects in youth treated with SSRIs and SNRIs include 3 main categories: nonpsychiatric, psychiatric, and suicidal events. Nonpsychiatric adverse events, such as nausea or headache, are typically transient and easily managed by slowing titration or dose reduction.[51] Psychiatric adverse events, such as switch into mania or "behavioral activation" (an ill-defined mixture of agitation, restlessness, insomnia, and affective instability) are less frequent, but of potentially greater importance for the child's functioning. Fortunately, conversion to mania is rare, and behavioral activation symptoms, which are also uncommon, typically respond to dose reduction.[51]

Suicidal events (classified as worsening ideation, an interrupted attempt, or an actual attempt) have become an adverse effect focus in antidepressant-treated youth.[83,86–88] In September 2004, an FDA Advisory Committee reviewed results of a meta-analysis of 24 controlled clinical trials of 9 antidepressants, which included approximately 4,400 pediatric patients.[89] While there were no completed suicides, the cumulative risk for suicidality (suicidal thinking or behavior), collected as spontaneous adverse event reports, was approximately 4% with antidepressants versus approximately 2% with placebo. In this respect, the Bridge et al[31] meta-analysis extended the earlier report,[89] identifying a small, but nontrivial, increase in risk of 0.7% (95% CI,

0.1%–1.3%), corresponding to a number needed to harm (NNH) of 143, which is larger, indicating lower risk, than the NNH of 50 identified in the earlier FDA analysis and the NNH of 43 in TADS. This very small and clinically undetectable effect is nonetheless of public health importance because of the large number of nonfatal suicidal events—approximately 2 million—occurring in youth in the United States each year. Importantly, however, completed suicides are fortunately very rare, and there were no completed suicides in the FDA sample of 4,400 patients, the TADS sample, or the Bridge et al[31] meta-analyzed studies, and epidemiologic evidence suggests that youth with depression receiving antidepressants are at lower risk for death by suicide than untreated youth.[73]

In the TADS, suicidality information was systematically collected, both at baseline and during follow-up, and about 30% of youth endorsed recent thoughts or behaviors related to self-harm before randomization, with combined treatment showing a statistically significant excess at baseline.[67] During the study, all 4 treatment groups (CBT, fluoxetine, their combination, and pill placebo) led to a systematically assessed decrease in suicidality, although fluoxetine demonstrated the smallest reduction.[67] To our knowledge, this is the only high-quality examination of ideation as contrasted to events, which shows that the impact of medication is not only on behavior. With respect to suicidal events, data from the TADS indicate that adding depression-specific CBT to fluoxetine eliminates the fluoxetine-associated risk for suicidal events specifically and psychiatric adverse events more generally.[73] In both instances, the risk from fluoxetine alone was double that for combined treatment, which was equivalent to those for CBT and placebo.[67,73] Of note, the NNH for suicidal events in the POTS, RUPP Anxiety, and CAMS trials was at infinity; that is, there were no suicidal events in these studies, indicating that the risk is largely confined to MDD trials. An examination of those trials (buttressed by the CAMS finding) that used sertraline as the active treatment found the same result.[87] In addition, the risk for a suicidal event in female subjects was about twice that for males, and adolescents were at higher risk than children, suggesting that depressed female adolescents represent the highest risk group.

Taken together, these studies identify a positive benefit-to-risk ratio for short-term treatment with SSRI or SNRI medication in adolescents and, perhaps, children with MDD and in patients of all ages with anxiety and OCD. Despite a large number of negative industry-sponsored trials, it is highly likely that the positive risk-benefit ratio is a class effect for both benefits and adverse events in patients treated with SSRIs and SNRIs. Adding CBT to medication management substantially enhances benefits and minimizes adverse events of most types. While supporting data are not definitive, the reduction in suicidal events in depressed teens obtained by adding CBT to medication is quite striking. Withholding medication is clearly not a reasonable solution. The 25% reduction in prescriptions or antidepressants that accompanied the black box warning was associated with a 25% increase in completed suicide rate,[90] presumably because these medications effectively treat depression and consequently reduce depression-associated mortality from suicide.[91]

Antipsychotics

On the basis of the broadened use of second-generation antipsychotics (SGAs), in particular, antipsychotic prescribing has increased substantially in youth.[10,11] This fact has increased the importance of scrutinizing the efficacy and safety of antipsychotics in youth across different indications. The debate about antipsychotic prescribing in children and adolescents has been fueled by the fact that antipsychotics are being used largely for nonpsychotic disorders and off-label indications[9,10,13]; by disagreement about the validity of psychiatric diagnoses during childhood, particularly bipolar disorder[6,92]; by concerns about a possible lack of psychosocial interventions and their replacement by antipsychotics, especially for the treatment of disruptive and aggressive spectrum disorder[93,94]; and by reports about more frequent and more severe antipsychotic adverse effects that can have long-term psychological and physical health implications when occurring during critical phases of development.[95,96]

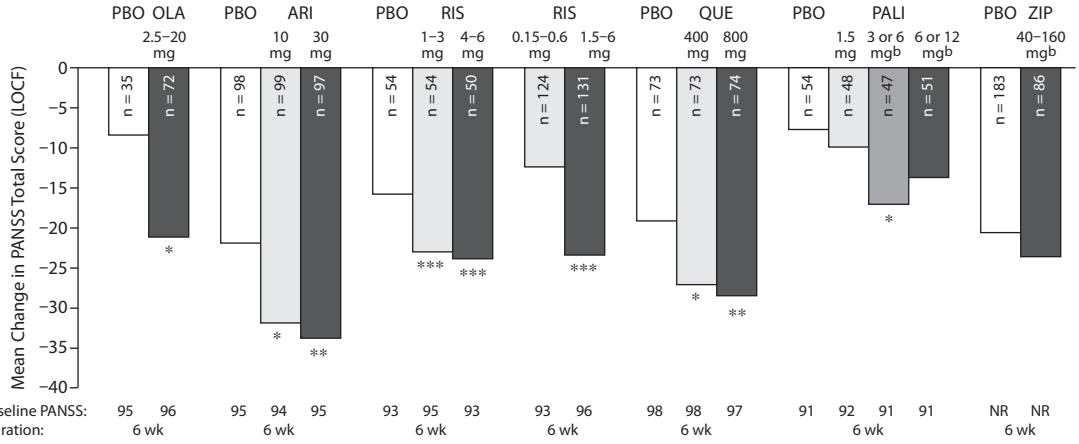
However, as concerns about antipsychotic prescribing in youth have increased, so has the controlled database for antipsychotics in youth with schizophrenia, bipolar mania, and autistic disorder.[97] These studies, mostly completed in the last 5 years, have been the basis for the FDA approval of the 4 most prescribed SGAs in youth. As of April 2011, aripiprazole, olanzapine, quetiapine, and risperidone have FDA-approved pediatric indications for bipolar mania (age 10–17 years; olanzapine: 13–17 years) and for schizophrenia (age 13–17 years). Moreover, paliperidone was also just approved by the FDA for adolescents with schizophrenia aged 13 to 17 years. In addition, aripiprazole and risperidone have an indication for irritability/aggression associated with autistic disorder (age 6–17 years), and controlled trial data exist for disruptive behavior disorders (mostly with risperidone) and tic disorders.[98]

Efficacy in pediatric schizophrenia/psychosis. More recently, after the sole availability of a few older, small, and underpowered active-controlled trials with first-generation antipsychotics, one of which included a placebo arm with 8 to 15 patients in each treatment arm,[3] 7 randomized, placebo-controlled antipsychotic trials have been completed in patients with pediatric schizophrenia.[99,102,136,139,140]

In one 6-week, international, multisite, placebo-controlled trial each (N = 107 to 302 per study), aripiprazole (10 mg or 30 mg),[139] olanzapine (2.5–20 mg),[136] quetiapine (400 mg or 800 mg),[99] paliperidone (1.5 mg, 3 mg or 6 mg [dependent on weight] and 6 mg or 12 mg [dependent on weight]),[102] and risperidone (1–3 mg or 4–6 mg)[140] were all superior to placebo in adolescents (aged 13–17 years) regarding the primary outcome, the change in the PANSS total score (Figure 1). In an additional trial, risperidone

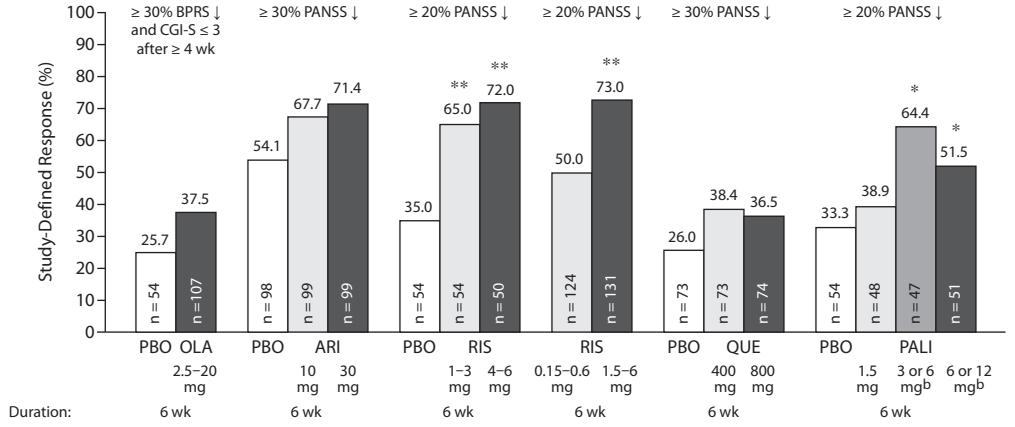
© Copyright 2011 Physicians Postgraduate Press, Inc.

Figure 1. Improvement in PANSS Total Score From 7 Randomized, Placebo-Controlled Trials in Pediatric Patients With Schizophrenia (aged 13–17 y)[a]



[a]Doses expressed as daily doses.
[b]Dependent on weight.
*$P < .05$ vs placebo.
**$P < .01$ vs placebo.
***$P < .001$ vs placebo.
Abbreviations: ARI = aripiprazole, LOCF = last observation carried forward, NR = not reported, OLA = olanzapine, PALI = paliperidone, PANSS = Positive and Negative Syndrome Scale, PBO = placebo, QUE = quetiapine, RIS = risperidone, ZIP = ziprasidone.

Figure 2. Study-Defined Response Rates in Pediatric Patients With Schizophrenia[a]

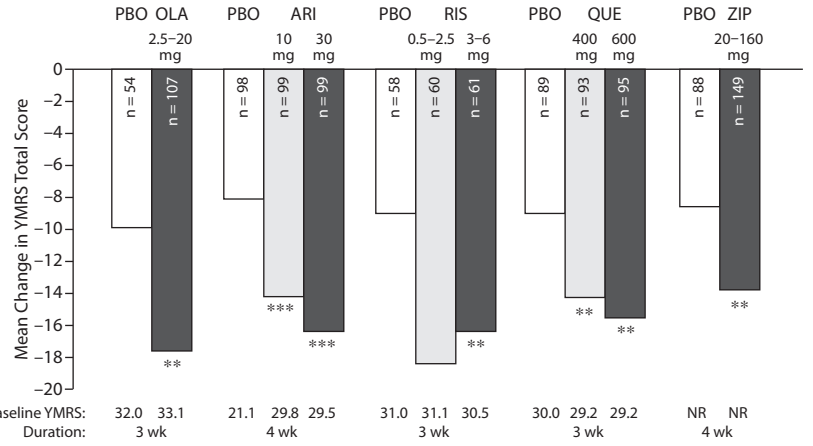


[a]Doses expressed as daily doses.
[b]Dependent on weight.
*$P < .05$ vs placebo.
**$P < .001$ vs placebo.
Abbreviations: ARI = aripiprazole, BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, OLA = olanzapine, PALI = paliperidone, PANSS = Positive and Negative Syndrome Scale, PBO = placebo, QUE = quetiapine, RIS = risperidone.

(1.5–6 mg) was superior to a pseudoplacebo of risperidone (0.15–0.6 mg).[101] By contrast, paliperidone (1.5 mg and 6 mg or 12 mg [dependent on weight]) did not separate from placebo, but response rates were significantly superior in both the medium- and high-dose arms.[102] Moreover, according to data available to date, one trial comparing ziprasidone with placebo (40–80 mg/d target dose in patients weighing < 45 kg and 80–160 mg in the others; see Figure 1) was discontinued by the sponsor due to lack of efficacy as determined in an interim analysis that revealed significant regional differences with higher placebo response rates in South America and Asia than in the United States and Europe.[100,138] Of note, the only studies/dose arms that failed in pediatric schizophrenia had a weight-based dosing schedule. Pooled NNTs based on the response rates for each of these SGAs ranged from 4 with risperidone to 10 with quetiapine, translating into moderate to small effect sizes, which were statistically significant except for olanzapine, which included the fewest participants (Figure 2).

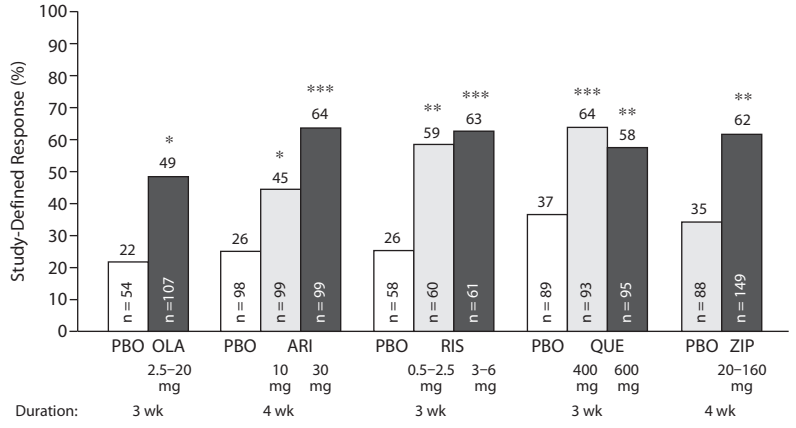
In all, 7 head-to-head trials compared antipsychotics in youth with schizophrenia or psychosis.[3,103–105] Across these active-controlled studies with modest sample sizes per treatment group (ranging from 11–42) and short durations (4–8 weeks), no differences in efficacy were observed

Figure 3. Improvement in YMRS Total Score From 5 Randomized, Placebo-Controlled Trials in Pediatric Patients With Bipolar I Disorder (aged 10–17 y)[a]



[a]Doses expressed as daily doses.
**$P < .01$ vs placebo.
***$P < .001$ vs placebo.
Abbreviations: ARI = aripiprazole, NR = not reported, OLA = olanzapine, PBO = placebo, QUE = quetiapine, RIS = risperidone, YMRS = Young Mania Rating Scale, ZIP = ziprasidone.

Figure 4. Response Rates (≥50% reduction in YMRS total score) in Pediatric Patients With Bipolar I Disorder Mania[a]



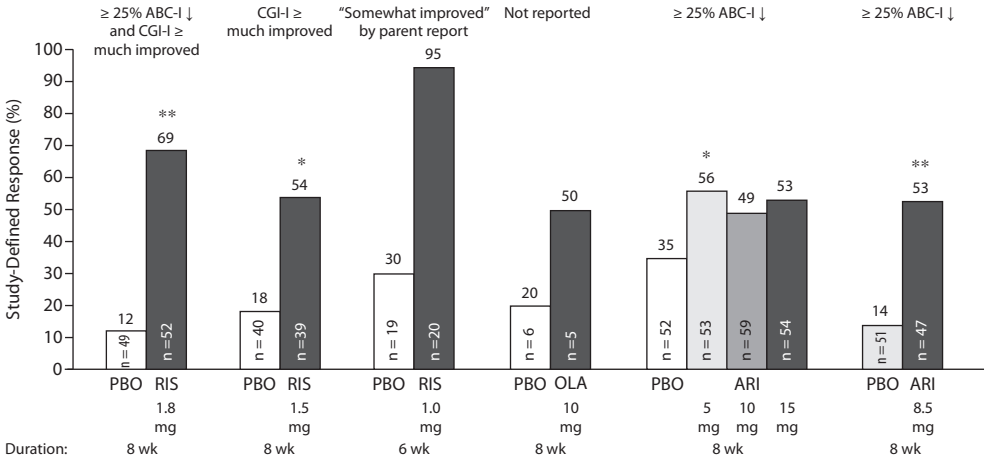
[a]Doses expressed as daily doses.
*$P < .05$ vs placebo.
**$P < .01$ vs placebo.
***$P < .001$ vs placebo.
Abbreviations: ARI = aripiprazole, OLA = olanzapine, PBO = placebo, QUE = quetiapine, RIS = risperidone, YMRS = Young Mania Rating Scale, ZIP = ziprasidone.

among nonclozapine antipsychotics.[3,103–105] This includes investigator-initiated and federally funded, active-controlled trials, all showing that symptom response was not significantly different between olanzapine and risperidone,[103,104] between olanzapine or risperidone and haloperidol[103] or molindone,[104] or between olanzapine and quetiapine.[105] By contrast, in small-scale studies with only 10 to 21 patients per treatment group, lasting between 6 and 12 weeks, clozapine was superior to haloperidol,[106] standard dosing of olanzapine,[107] or "high-dose" (up to 30 mg) olanzapine,[108] with an NNT of 3 for response in the latter study, representing a large effect size.

Efficacy in pediatric bipolar I disorder with manic or mixed episode. Eight, mostly recent, RCTs demonstrated efficacy of SGAs in pediatric patients with bipolar I mania. Five RCTs in youths (aged 10–17 years) showed superior efficacy of antipsychotic monotherapy compared to placebo regarding reduction in the Young Mania Rating Scale (YMRS) score.[26] In 1 international, multisite, placebo-controlled trial each, lasting either 3 weeks (olanzapine, risperidone, quetiapine) or 4 weeks (aripiprazole, ziprasidone), aripiprazole (10 mg or 30 mg),[141] olanzapine (2.5–20 mg),[142] quetiapine (400 mg or 600 mg),[143] risperidone (0.5–2.5 mg or 3–6 mg),[144] and ziprasidone (20–160 mg)[145] were all superior to placebo in children and adolescents (age 10–17 years; 13–17 years for olanzapine) regarding the primary outcome, the change in the YMRS total score (Figure 3).[26] In pediatric bipolar I disorder mania, NNTs of the pooled dose arms for "response" (defined as at least a 50% reduction in the YMRS total score) compared to placebo (Figure 4) ranged from 3 to 4, corresponding to large to moderate effect sizes.

Few head-to-head studies between antipsychotics and conventional mood stabilizers have been conducted. In 1 placebo-controlled trial, quetiapine (mean dose: 450 mg) added to valproic acid was superior in adolescents with bipolar I mania to valproic acid monotherapy.[109] In 1 active-controlled trial, quetiapine and valproate were equally effective regarding the YMRS change, but quetiapine was superior regarding a 50% reduction in the YMRS score, and speed of response was faster with quetiapine.[110] In an additional, recent study comparing risperidone with valproic acid, risperidone was also superior to the mood stabilizer.[111] This superiority of SGAs compared to mood stabilizers for pediatric mania was recently confirmed in a systematic review and indirect comparison of placebo-controlled trials with either SGAs or lithium/antiepileptics.[26] However, more direct head-to-head comparator trials are needed, as well as those including additional nonpharmacologic strategies. Moreover, the relative efficacy of 2 mood stabilizers compared with 1 antipsychotic is unknown. Furthermore, the efficacy of SGAs for bipolar depression in youth is currently unclear.[148]

Figure 5. Study-Defined Response Rates in 5 Randomized, Placebo-Controlled Trials of Pediatric Patients With Autism[a]



[a]Doses expressed as daily doses.
*$P < .05$ vs placebo.
**$P < .001$ vs placebo.
Abbreviations: ABC-I = Aberrant Behavior Checklist-Irritability subscale, ARI = aripiprazole, CGI-I = Clinical Global Impressions-Improvment scale, OLA = olanzapine, PBO = placebo, RIS = risperidone.

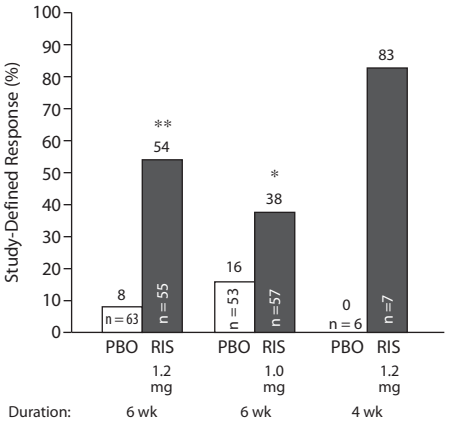
Efficacy in autistic disorder. Eight RCTs in pediatric patients with autism spectrum disorders have been completed.[112–117] In 5 adequately powered (> 30 patients), randomized, placebo-controlled trials, risperidone[113–115] and aripiprazole (5–15 mg[116] or 5 mg, 10 mg, and 15 mg[117]) showed superior efficacy compared to placebo regarding the primary outcome, the irritability subscale score of the Aberrant Behavior Checklist (ABC), in pediatric patients with autistic disorder. While stereotypic behaviors improved also, the core deficits of verbal and nonverbal communication were not altered by antipsychotic treatment. The pooled effect sizes against placebo were moderate to large, ie, 0.7 to 0.8 for risperidone[113–115] and 0.5 to 0.8 with aripiprazole.[116,117] NNTs for study-defined "response" in autism spectrum disorders ranged from 2 to 4 for risperidone,[113–115] 4 in a small study of 11 patients treated with olanzapine,[118] and 4 to 7 in 2 studies[116,117] with aripiprazole, with greater efficacy in the higher dose arms in the flexible-dose study[117] (Figure 5). In addition to the acute phase trials, in 2 placebo-controlled relapse prevention studies, risperidone was significantly superior to placebo in maintaining efficacy in the ABC irritability subscore.[119,120]

To date, only 1 randomized study,[121] by the RUPP Autism Network, has examined the effects of parent training added to risperidone versus risperidone monotherapy for maladaptive and irritable behavior. The study was conducted in 124 children (aged 4–13 years) with pervasive developmental disorders plus frequent tantrums, self-injury, and aggression. In this 24-week study, risperidone plus parent training resulted in a greater reduction of maladaptive behaviors than medication treatment alone. Moreover, risperidone dose requirements were lower in the combination treatment group.[121] While these results were encouraging, Clinical Global Impressions scale scores did not differ, and head-to-head studies of pharmacologic and nonpharmacologic treatments, alone and in combination, for aggressive behaviors associated with autism-spectrum disorders are sorely needed.

Efficacy in disruptive behavior disorders. Across 8 placebo-controlled studies in youth with aggressive behaviors associated with conduct disorder, disruptive behavior disorders, ADHD, and/or mental retardation/subaverage IQ superiority, all involving risperidone, the antipsychotic was superior to placebo regarding the study-defined response measure.[57,122–126] Because the scales used in these studies differed, only study-defined response rates are displayed (Figure 6),[122,124,125] translating into NNTs of 2–5, representing moderate to large effect sizes. In 1 additional, active-controlled trial, molindone was found to be as effective as thioridazine for conduct disordered youth.[127] Finally, risperidone also showed superior efficacy for relapse prevention compared to placebo in 1 large, 6-month placebo-substitution trial.[128] Although a number of RCTs found psychosocial and behavioral interventions to be successful for reducing aggressive and externalizing behaviors in youth,[129,130] studies comparing antipsychotics with behavioral intervention, combination, and placebo are lacking. The same is true of studies that investigate the best sequencing approach between psychotropic and behavioral interventions.

Efficacy in Tourette's disorder. Superiority of risperidone compared to placebo was shown in 2 randomized, placebo-controlled trials of youths with Tourette's disorder (N = 54), with either risperidone[131] or ziprasidone,[132] with an NNT of 4 for risperidone. Although a recent RCT found a behavioral intervention to be successful for reducing tics in Tourette's disorder,[133] studies comparing antipsychotics with

Figure 6. Study-Defined Response Rates (CGI-I ≥ much improved) in 3 Randomized, Placebo-Controlled Trials of Pediatric Patients With Disruptive Behavior Disorders[a]



[a]Doses expressed as daily doses.
*$P < .05$ vs placebo.
**$P < .001$ vs placebo.
Abbreviations: CGI-I = Clinical Global Impressions-Improvment scale, PBO = placebo, RIS = risperidone.

behavioral intervention, the combination of the two, and placebo are lacking.

Antipsychotic tolerability. Studies comparing antipsychotic adverse effect rates in children and adolescents with those in similar studies of adults indicated that youth were at higher risk for developing a number of antipsychotic-induced side effects.[19,96,134–136] These included higher rates of sedation, extrapyramidal side effects (except for akathisia), withdrawal dyskinesia, prolactin elevation, weight gain, and at least some metabolic abnormalities.

By contrast, tardive dyskinesia[137] and diabetes[19,135] were less likely to occur in youth compared to adults. However, this finding is likely due to the short follow-up periods in youth and presence of an accumulated risk and added lag time in adults, raising concerns about a potential shortening of the time until these long-term complications occur when antipsychotic treatment is initiated during childhood.

In the era of first-generation antipsychotic use, extrapyramidal side effects and tardive dyskinesia were the predominant adverse effect concerns with first-generation antipsychotics.[137] Since the introduction of SGAs (ie, clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, iloperidone, asenapine, and lurasidone [in order of introduction into the US market]), concerns about neuromotor side effects have largely been replaced by worries about cardiometabolic side effects, such as weight gain and dysregulation of the lipid and glucose homeostasis.[19,25,96] Recent studies suggest that youth are more prone to rapid and significant weight gain with antipsychotics, and that this weight gain extends to antipsychotics that in adults are generally considered weight neutral, yet that the metabolic effects vary across antipsychotics despite ubiquitous elevation in all body composition parameters with all studied SGAs.[96] Although more research is needed, this suggests that weight-independent, direct metabolic effects seem to exist that vary across individual antipsychotics. Long-term studies of general antipsychotic tolerability and, especially, cardiovascular and metabolic outcomes are needed. Finally, efforts are required at increasing appropriate monitoring and management of adverse antipsychotic effects in youth.

Table 3. Areas of Pediatric Psychopharmacology Research Requiring Further Attention

Studies including large and generalizable samples
Long-term, longitudinal studies that track therapeutic and adverse effects over time and relate outcomes to different stages of development
Strategies overcoming the limitations created by high dropout rates in long-term studies
Well-powered placebo-controlled studies
Well-powered active-controlled pharmacologic monotherapy and, especially, combination treatment studies
Well-powered comparative pharmacologic and nonpharmacologic studies, in monotherapy and in combination
Linkage of efficacy and effectiveness outcomes
Identification of meaningful and simple effectiveness measures
Identification of clinical and, especially, biological response predictors that would allow for an individualization or, at least, stratification of treatment based on baseline or early intratreatment variables
Broader-based utilization of novel technologies, eg, electronic medical record and centralized video rating in remote, diverse, nonacademic settings
Utilization of increasingly sophisticated biological assessments, including "omics" platforms
Increasing use of adaptive designs, smart trials, research networks, and large registries
Dissemination and application of research findings into measurement-based, evidence- and guideline-driven assessment and treatment delivery in clinical practice settings
Increasing linkage of basic, clinical, and services research initiatives, involving a number of translational steps that will ultimately help to improve the diagnosis, treatment, and outcomes of youth with severe psychiatric conditions

FUTURE DIRECTIONS AND CONCLUSIONS

Although considerable progress has been made, especially relative to the previous abundant absence of randomized controlled trial data, pediatric psychopharmacology still remains a stepchild of adult pharmacology, and more, larger, and longer studies need to be funded and conducted in youth.

Areas that require further work and innovation span a number of priority areas summarized in Table 3. Moreover, the field needs stakeholders—academia, industry, the NIMH, the FDA, and consumer groups—to support practical clinical trials and, where those are not possible, observational studies, conducted in generalizable treatment settings and patients to generate precise benefit and risk estimates of treatments in clinically important patient subgroups.[39] Moreover, practical clinical trials can provide a robust platform to study moderators and mediators and biomarkers and biosignatures of treatment outcome, as well as to test the multistage treatment strategies utilizing dynamic treatment regimens that are required to achieve the goal of increasingly personalized treatment of psychiatrically ill youth.

In conclusion, while especially the last decade has seen a large increase in our knowledge about the safety and efficacy of psychopharmacologic treatments in youth, a number of challenges remain to be addressed, and more work is clearly needed. It is hoped that in 10 years, the field will have been able to acquire and utilize the necessary resources to propel the area of pediatric clinical psychopharmacology to new levels of insight by linking it with, but not replacing it by, pharmacoepidemiologic or biological approaches and advances.

Drug names: aripiprazole (Abilify), asenapine (Saphris), atomoxetine (Strattera), citalopram (Celexa and others), clonidine (Catapres, Duraclon, and others), clozapine (Clozaril, FazaClo, and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), guanfacine (Intuniv, Tenex, and others), haloperidol (Haldol and others), iloperidone (Fanapt), lithium (Lithobid and others), lurasidone (Latuda), methylphenidate (Focalin, Daytrana, and others), mirtazapine (Remeron and others), molindone (Moban), olanzapine (Zyprexa), paliperidone (Invega), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), risperidone (Risperdal and others), sertraline (Zoloft and others), valproic acid (Depakene, Stavzor, and others), venlafaxine (Effexor and others), ziprasidone (Geodon).

Author affiliations: Division of Psychiatry Research, The Zucker Hillside Hospital, North Shore-Long Island Jewish Health System, Glen Oaks; Albert Einstein College of Medicine, Bronx; The Feinstein Institute for Medical Research, Manhasset; and Hofstra North Shore LIJ School of Medicine, Hempstead, New York (Dr Correll); Department of Psychiatry, University of Nebraska Medical Center, Omaha (Dr Kratochvil); and Department of Psychiatry and Behavioral Sciences, Duke Child and Family Study Center, Durham, North Carolina (Dr March).

Potential conflicts of interest: **Dr Correll** has been a consultant and/or advisor to or has received honoraria from Actelion, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Cephalon, Eli Lilly, IntraCellular Therapies, Ortho-McNeil/Janssen/Johnson & Johnson, Merck, Otsuka, Pfizer, and Sepracor/Sunovion and has received grant support from the Feinstein Institute for Medical Research, the National Institute of Mental Health (NIMH), the National Alliance for Research in Schizophrenia and Depression (NARSAD), and Ortho-McNeil/Janssen/Johnson & Johnson. **Dr Kratochvil** has received grant support from Eli Lilly and Shire; has been a consultant for Eli Lilly, Neuroscience Education Institute, Theravance, Seaside, Quintiles, and Pfizer; is Editor of the *Brown University Child & Adolescent Psychopharmacology Update*; received study drug for an NIMH-funded study from Eli Lilly and Abbott; and received royalties from Oxford Press. **Dr March** has served as a consultant or scientific advisor to Pfizer, Eli Lilly, GlaxoSmithKline, Bristol-Myers Squibb, Johnson & Johnson, Psymetrix, Attention Therapeutics, Avenir, Alkermes, Vivus, Scion, and MedAvante; has received research support from Eli Lilly and Pfizer; has received study drug for an NIMH-funded study from Eli Lilly and from Pfizer; is an equity holder in MedAvante; receives royalties from Guilford Press, Oxford University Press, and MultiHealth Systems; and receives research support from NARSAD, NIMH, and National Institute on Drug Abuse. Dr March has not engaged in promotional work, eg, speakers bureau or training, for over 15 years. Dr March's conflict of interest is fully reported to Duke University and is viewable at http://www.dcri.duke.edu/research/coi.jsp, and a conflict of interest management plan has been established.

Funding/support: None reported.

REFERENCES

1. Chang K. Challenges in the diagnosis and treatment of pediatric bipolar depression. *Dialogues Clin Neurosci*. 2009;11(1):73–80. PubMed
2. Perlis RH, Miyahara S, Marangell LB, et al; STEP-BD Investigators. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Biol Psychiatry*. 2004;55(9):875–881. doi:10.1016/j.biopsych.2004.01.022 PubMed
3. Kumra S, Oberstar JV, Sikich L, et al. Efficacy and tolerability of second-generation antipsychotics in children and adolescents with schizophrenia. *Schizophr Bull*. 2008;34(1):60–71. doi:10.1093/schbul/sbm109 PubMed
4. Perlis RH, Dennehy EB, Miklowitz DJ, et al. Retrospective age at onset of bipolar disorder and outcome during two-year follow-up: results from the STEP-BD study. *Bipolar Disord*. 2009;11(4):391–400. doi:10.1111/j.1399-5618.2009.00686.x PubMed
5. Olfson M, Crystal S, Gerhard T, et al. Mental health treatment received by youths in the year before and after a new diagnosis of bipolar disorder. *Psychiatr Serv*. 2009;60(8):1098–1106. doi:10.1176/appi.ps.60.8.1098 PubMed
6. Moreno C, Laje G, Blanco C, et al. National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. *Arch Gen Psychiatry*. 2007;64(9):1032–1039. doi:10.1001/archpsyc.64.9.1032 PubMed
7. Blader JC, Carlson GA. Increased rates of bipolar disorder diagnoses among US child, adolescent, and adult inpatients, 1996–2004. *Biol Psychiatry*. 2007;62(2):107–114. doi:10.1016/j.biopsych.2006.11.006 PubMed
8. Cooper WO, Hickson GB, Fuchs C, et al. New users of antipsychotic medications among children enrolled in TennCare. *Arch Pediatr Adolesc Med*. 2004;158(8):753–759. doi:10.1001/archpedi.158.8.753 PubMed
9. Cooper WO, Arbogast PG, Ding H, et al. Trends in prescribing of antipsychotic medications for US children. *Ambul Pediatr*. 2006;6(2):79–83. doi:10.1016/j.ambp.2005.11.002 PubMed
10. Olfson M, Blanco C, Liu L, et al. National trends in the outpatient treatment of children and adolescents with antipsychotic drugs. *Arch Gen Psychiatry*. 2006;63(6):679–685. doi:10.1001/archpsyc.63.6.679 PubMed
11. Olfson M, Crystal S, Huang C, et al. Trends in antipsychotic drug use by very young, privately insured children. *J Am Acad Child Adolesc Psychiatry*. 2010;49(1):13–23. PubMed
12. Patel NC, Sanchez RJ, Johnsrud MT, et al. Trends in antipsychotic use in a Texas Medicaid population of children and adolescents: 1996 to 2000. *J Child Adolesc Psychopharmacol*. 2002;12(3):221–229. doi:10.1089/104454602760386905 PubMed
13. Zito JM, Safer DJ, de Jong-van den Berg LT, et al. A three-country comparison of psychotropic medication prevalence in youth. *Child Adolesc Psychiatry Ment Health*. 2008;2(1):26. doi:10.1186/1753-2000-2-26 PubMed
14. Zito JM, Safer DJ, DosReis S, et al. Psychotropic practice patterns for youth: a 10-year perspective. *Arch Pediatr Adolesc Med*. 2003;157(1):17–25. PubMed
15. Zito JM, Safer DJ, Sai D, et al. Psychotropic medication patterns among youth in foster care. *Pediatrics*. 2008;121(1):e157–e163. doi:10.1542/peds.2007-0212 PubMed
16. Zito JM, Tobi H, de Jong-van den Berg LT, et al. Antidepressant prevalence for youths: a multi-national comparison. *Pharmacoepidemiol Drug Saf*. 2006;15(11):793–798. doi:10.1002/pds.1254 PubMed
17. Gerhard T, Chavez B, Olfson M, et al. National patterns in the outpatient pharmacological management of children and adolescents with autism spectrum disorder. *J Clin Psychopharmacol*. 2009;29(3):307–310. doi:10.1097/JCP.0b013e3181a20c8a PubMed
18. Crystal S, Olfson M, Huang C, et al. Broadened use of atypical antipsychotics: safety, effectiveness, and policy challenges. *Health Aff (Millwood)*. 2009;28(5):w770–w781. doi:10.1377/hlthaff.28.5.w770 PubMed
19. Correll CU, Penzner JB, Parikh UH, et al. Recognizing and monitoring adverse events of second-generation antipsychotics in children and adolescents. *Child Adolesc Psychiatr Clin N Am*. 2006;15(1):177–206. doi:10.1016/j.chc.2005.08.007 PubMed
20. Ryan ND, Varma D. Child and adolescent mood disorders—experience with serotonin-based therapies. *Biol Psychiatry*. 1998;44(5):336–340. doi:10.1016/S0006-3223(98)00163-2 PubMed
21. Massanari M, Novitsky J, Reinstein LJ. Paradoxical reactions in children associated with midazolam use during endoscopy. *Clin Pediatr (Phila)*. 1997;36(12):681–684. doi:10.1177/000992289703601202 PubMed
22. Kanegaye JT, Favela JL, Acosta M, et al. High-dose rectal midazolam for pediatric procedures: a randomized trial of sedative efficacy and agitation. *Pediatr Emerg Care*. 2003;19(5):329–336. doi:10.1097/01.pec.0000092578.40174.85 PubMed
23. Paxton JW, Dragunow M. Pharmacology. In: Werry JS, Aman MG, eds. *Practitioner's Guide to Psychoactive Drugs for Children and Adolescents.* New York, NY: Plenum Medical; 1993:23–55.
24. Safer DJ, Zito JM. Treatment-emergent adverse events from selective serotonin reuptake inhibitors by age group: children versus adolescents. *J Child Adolesc Psychopharmacol*. 2006;16(1–2):159–169. doi:10.1089/cap.2006.16.159 PubMed
25. Correll CU. Antipsychotic use in children and adolescents: minimizing adverse effects to maximize outcomes. *J Am Acad Child Adolesc Psychiatry*. 2008;47(1):9–20. doi:10.1097/chi.0b013e31815b5cb1 PubMed
26. Correll CU, Sheridan EM, DelBello MP. Antipsychotic and mood stabilizer efficacy and tolerability in pediatric and adult patients with bipolar I mania: a comparative analysis of acute, randomized, placebo-controlled trials. *Bipolar Disord*. 2010;12(2):116–141. doi:10.1111/j.1399-5618.2010.00798.x PubMed

27. Gould MS, Walsh BT, Munfakh JL, et al. Sudden death and use of stimulant medications in youths. *Am J Psychiatry*. 2009;166(9):992–1001. doi:10.1176/appi.ajp.2009.09040472 PubMed
28. Winterstein AG, Gerhard T, Shuster J, et al. Cardiac safety of central nervous system stimulants in children and adolescents with attention-deficit/hyperactivity disorder. *Pediatrics*. 2007;120(6):e1494–e1501. doi:10.1542/peds.2007-0675 PubMed
29. Gerhard T, Winterstein AG, Olfson M, et al. Pre-existing cardiovascular conditions and pharmacological treatment of adult ADHD. *Pharmacoepidemiol Drug Saf*. 2010;19(5):457–464. PubMed
30. Wigal T, Greenhill L, Chuang S, et al. Safety and tolerability of methylphenidate in preschool children with ADHD. *J Am Acad Child Adolesc Psychiatry*. 2006;45(11):1294–1303. doi:10.1097/01.chi.0000235082.63156.27 PubMed
31. Bridge JA, Iyengar S, Salary CB, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *JAMA*. 2007;297(15):1683–1696. doi:10.1001/jama.297.15.1683 PubMed
32. de Leon J, Nikoloff DM. Paradoxical excitation on diphenhydramine may be associated with being a CYP2D6 ultrarapid metabolizer: three case reports. *CNS Spectr*. 2008;13(2):133–135. PubMed
33. DeVeaugh-Geiss J, March J, Shapiro M, et al. Child and adolescent psychopharmacology in the new millennium: a workshop for academia, industry, and government. *J Am Acad Child Adolesc Psychiatry*. 2006;45(3):261–270. doi:10.1097/01.chi.0000194568.70912.ee PubMed
34. May DE, Kratochvil CJ. Attention-deficit hyperactivity disorder: recent advances in pediatric pharmacotherapy. *Drugs*. 2010;70(1):15–40. doi:10.2165/11530540-000000000-00000 PubMed
35. March JS, Silva SG, Compton S, et al. The case for practical clinical trials in psychiatry. *Am J Psychiatry*. 2005;162(5):836–846. doi:10.1176/appi.ajp.162.5.836 PubMed
36. Greenhill LL, Vitiello B, Riddle MA, et al. Review of safety assessment methods used in pediatric psychopharmacology. *J Am Acad Child Adolesc Psychiatry*. 2003;42(6):627–633. doi:10.1097/01.CHI.0000046841.56865.37 PubMed
37. dosReis S, Zito JM, Safer DJ, et al. Multiple psychotropic medication use for youths: a two-state comparison. *J Child Adolesc Psychopharmacol*. 2005;15(1):68–77. doi:10.1089/cap.2005.15.68 PubMed
38. Bhangoo RK, Lowe CH, Myers FS, et al. Medication use in children and adolescents treated in the community for bipolar disorder. *J Child Adolesc Psychopharmacol*. 2003;13(4):515–522. doi:10.1089/104454603322724904 PubMed
39. March JS, Silva SG, Compton S, et al. The case for practical clinical trials in psychiatry. *Am J Psychiatry*. 2005;162(5):836–846. doi:10.1176/appi.ajp.162.5.836 PubMed
40. Greenhill LL, Vitiello B, Riddle MA, et al. Review of safety assessment methods used in pediatric psychopharmacology. *J Am Acad Child Adolesc Psychiatry*. 2003;42(6):627–633. doi:10.1097/01.CHI.0000046841.56865.37 PubMed
41. Greenhill LL, Vitiello B, Abikoff H, et al. Developing methodologies for monitoring long-term safety of psychotropic medications in children: report on the NIMH conference, September 25, 2000. *J Am Acad Child Adolesc Psychiatry*. 2003;42(6):651–655. doi:10.1097/01.CHI.0000046842.56865.EC PubMed
42. Vitiello B, Riddle MA, Greenhill LL, et al. How can we improve the assessment of safety in child and adolescent psychopharmacology? *J Am Acad Child Adolesc Psychiatry*. 2003;42(6):634–641. doi:10.1097/01.CHI.0000046840.90931.36 PubMed
43. Correll CU. Monitoring and management of antipsychotic-related metabolic and endocrine adverse effects in children and adolescents. *Int Rev Psychiatry*. 2008;20(4):195–201. doi:10.1080/09540260801889179 PubMed
44. Olfson M, Blanco C, Liu L, et al. National trends in the outpatient treatment of children and adolescents with antipsychotic drugs. *Arch Gen Psychiatry*. 2006;63(6):679–685. doi:10.1001/archpsyc.63.6.679 PubMed
45. March J, Kratochvil C, Clarke G, et al. AACAP 2002 research forum: placebo and alternatives to placebo in randomized controlled trials in pediatric psychopharmacology. *J Am Acad Child Adolesc Psychiatry*. 2004;43(8):1046–1056. doi:10.1097/01.chi.0000129606.83206.77 PubMed
46. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000.
47. Barkley RA, Fischer M, Edelbrock CS, et al. The adolescent outcome of hyperactive children diagnosed by research criteria: I. an 8-year prospective follow-up study. *J Am Acad Child Adolesc Psychiatry*. 1990;29(4):546–557. doi:10.1097/00004583-199007000-00007 PubMed
48. Barkley RA, Fischer M, Smallish L, et al. The persistence of attention-deficit/hyperactivity disorder into young adulthood as a function of reporting source and definition of disorder. *J Abnorm Psychol*. 2002;111(2):279–289. doi:10.1037/0021-843X.111.2.279 PubMed
49. Biederman J, Faraone S, Milberger S, et al. A prospective 4-year follow-up study of attention-deficit hyperactivity and related disorders. *Arch Gen Psychiatry*. 1996;53(5):437–446. PubMed
50. Adler LA, Sutton VK, Moore RJ, et al. Quality of life assessment in adult patients with attention-deficit/hyperactivity disorder treated with atomoxetine. *J Clin Psychopharmacol*. 2006;26(6):648–652. doi:10.1097/01.jcp.0000239797.21826.70 PubMed
51. Vaughan BS, March JS, Kratochvil CJ. The evidence-based pharmacological treatment of paediatric ADHD. *Int J Neuropsychopharmacol*. 2011;1–13. doi:10.1017/S1461145711000095 PubMed
52. Faraone SV. Using meta-analysis to compare the efficacy of medications for attention-deficit/hyperactivity disorder in youths. *P T*. 2009;34(12):678–694. PubMed
53. Biederman J, Melmed RD, Patel A, et al; SPD503 Study Group. A randomized, double-blind, placebo-controlled study of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. *Pediatrics*. 2008;121(1):e73–e84. doi:10.1542/peds.2006-3695 PubMed
54. Sallee FR, McGough J, Wigal T, et al: SPD503 STUDY GROUP. Guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder: a placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2009;48(2):155–165. doi:10.1097/CHI.0b013e318191769e PubMed
55. Pliszka SR. Non-stimulant treatment of attention-deficit/hyperactivity disorder. *CNS Spectr*. 2003;8(4):253–258. PubMed
56. The MTA Cooperative Group. Multimodal Treatment Study of Children with ADHD. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry*. 1999;56(12):1073–1086. doi:10.1001/archpsyc.56.12.1073 PubMed
57. Jensen PS, Arnold LE, Swanson JM, et al. 3-year follow-up of the NIMH MTA study. *J Am Acad Child Adolesc Psychiatry*. 2007;46(8):989–1002. doi:10.1097/CHI.0b013e3180686d48 PubMed
58. Molina BS, Hinshaw SP, Swanson JM, et al; MTA Cooperative Group. The MTA at 8 years: prospective follow-up of children treated for combined-type ADHD in a multisite study. *J Am Acad Child Adolesc Psychiatry*. 2009;48(5):484–500. doi:10.1097/CHI.0b013e31819c23d0 PubMed
59. Klein RG, Abikoff H, Hechtman L, et al. Design and rationale of controlled study of long-term methylphenidate and multimodal psychosocial treatment in children with ADHD. *J Am Acad Child Adolesc Psychiatry*. 2004;43(7):792–801. doi:10.1097/01.chi.0000128798.91601.fe PubMed
60. Abikoff H, Hechtman L, Klein RG, et al. Symptomatic improvement in children with ADHD treated with long-term methylphenidate and multimodal psychosocial treatment. *J Am Acad Child Adolesc Psychiatry*. 2004;43(7):802–811. doi:10.1097/01.chi.0000128791.10014.ac PubMed
61. Greenhill L, Kollins S, Abikoff H, et al. Efficacy and safety of immediate-release methylphenidate treatment for preschoolers with ADHD. *J Am Acad Child Adolesc Psychiatry*. 2006;45(11):1284–1293. doi:10.1097/01.chi.0000235077.32661.61 PubMed
62. Abikoff HB, Vitiello B, Riddle MA, et al. Methylphenidate effects on functional outcomes in the Preschoolers with Attention-deficit/hyperactivity disorder Treatment Study (PATS). *J Child Adolesc Psychopharmacol*. 2007;17(5):581–592. doi:10.1089/cap.2007.0068 PubMed
63. Pliszka S; AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2007;46(7):894–921. doi:10.1097/chi.0b013e318054e724 PubMed
64. Pappadopulos E, Woolston S, Chait A, et al. Pharmacotherapy of aggression in children and adolescents: efficacy and effect size. *J Can Acad Child Adolesc Psychiatry*. 2006;15(1):27–39. PubMed
65. Connor DF, Glatt SJ, Lopez ID, et al. Psychopharmacology and aggression. I: a meta-analysis of stimulant effects on overt/covert aggression-related behaviors in ADHD. *J Am Acad Child Adolesc Psychiatry*. 2002;41(3):253–261. doi:10.1097/00004583-200203000-00004 PubMed
66. Emslie GJ, Rush AJ, Weinberg WA, et al. A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Arch Gen Psychiatry*. 1997;54(11):1031–1037. PubMed
67. March J, Silva S, Petrycki S, et al; Treatment for Adolescents With Depression Study (TADS) Team. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA*. 2004;292(7):807–820. doi:10.1001/jama.292.7.807 PubMed
68. Emslie GJ, Heiligenstein JH, Wagner KD, et al. Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. *J Am Acad Child Adolesc Psychiatry*. 2002;41(10):1205–1215. doi:10.1097/00004583-200210000-00010 PubMed
69. Pediatric OCD Treatment Study (POTS) Team. Cognitive-behavior therapy, sertraline, and their combination for children and adolescents with obsessive-compulsive disorder: the Pediatric OCD Treatment Study (POTS) randomized controlled trial. *JAMA*. 2004;292(16):1969–1976.

doi:10.1001/jama.292.16.1969 PubMed
70. The Research Unit on Pediatric Psychopharmacology Anxiety Study Group. Fluvoxamine for the treatment of anxiety disorders in children and adolescents. *N Engl J Med*. 2001;344(17):1279–1285. doi:10.1056/NEJM200104263441703 PubMed
71. Compton SN, Walkup JT, Albano AM, et al. Child/Adolescent Anxiety Multimodal Study (CAMS): rationale, design, and methods. *Child Adolesc Psychiatry Ment Health*. 2010;4(1):1. doi:10.1186/1753-2000-4-1 PubMed
72. Walkup JT, Albano AM, Piacentini J, et al. Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. *N Engl J Med*. 2008; 359(26):2753–2766. doi:10.1056/NEJMoa0804633 PubMed
73. March JS, Vitiello B. Clinical messages from the Treatment for Adolescents With Depression Study (TADS). *Am J Psychiatry*. 2009;166(10):1118–1123. doi:10.1176/appi.ajp.2009.08101606 PubMed
74. Curry J, Rohde P, Simons A, et al; TADS Team. Predictors and moderators of acute outcome in the Treatment for Adolescents with Depression Study (TADS). *J Am Acad Child Adolesc Psychiatry*. 2006;45(12):1427–1439. doi:10.1097/01.chi.0000240838.78984.e2 PubMed
75. Treatment for Adolescents with Depression Study (TADS) Team. The Treatment for Adolescents With Depression Study (TADS): demographic and clinical characteristics. *J Am Acad Child Adolesc Psychiatry*. 2005; 44(1):28–40. doi:10.1097/01.chi.0000145807.09027.82 PubMed
76. Kratochvil CJ, May DE, Silva SG, et al. Treatment response in depressed adolescents with and without co-morbid attention-deficit/hyperactivity disorder in the Treatment for Adolescents with Depression Study. *J Child Adolesc Psychopharmacol*. 2009;19(5):519–527. doi:10.1089/cap.2008.0143 PubMed
77. Emslie G, Kratochvil C, Vitiello B, et al; TADS Team. Treatment for Adolescents with Depression Study (TADS): safety results. *J Am Acad Child Adolesc Psychiatry*. 2006;45(12):1440–1455. doi:10.1097/01.chi.0000240840.63737.1d PubMed
78. Vitiello B, Silva SG, Rohde P, et al. Suicidal events in the Treatment for Adolescents With Depression Study (TADS). *J Clin Psychiatry*. 2009;70(5):741–747. doi:10.4088/JCP.08m04607 PubMed
79. March JS, Silva S, Petrycki S, et al; The TADS Team. The Treatment for Adolescents With Depression Study (TADS): long-term effectiveness and safety outcomes. *Arch Gen Psychiatry*. 2007;64(10):1132–1143. doi:10.1001/archpsyc.64.10.1132 PubMed
80. Kennard BD, Silva SG, Tonev S, et al. Remission and recovery in the Treatment for Adolescents with Depression Study (TADS): acute and long-term outcomes. *J Am Acad Child Adolesc Psychiatry*. 2009;48(2): 186–195. doi:10.1097/CHI.0b013e31819176f9 PubMed
81. March J, Silva S, Curry J, et al; Treatment for Adolescents With Depression Study (TADS) Team. The Treatment for Adolescents With Depression Study (TADS): outcomes over 1 year of naturalistic follow-up. *Am J Psychiatry*. 2009;166(10):1141–1149. doi:10.1176/appi.ajp.2009.08111620 PubMed
82. Brent D, Emslie G, Clarke G, et al. Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: the TORDIA randomized controlled trial. *JAMA*. 2008;299(8):901–913. doi:10.1001/jama.299.8.901 PubMed
83. Vitiello B. Combined cognitive-behavioural therapy and pharmacotherapy for adolescent depression: does it improve outcomes compared with monotherapy? *CNS Drugs*. 2009;23(4):271–280. doi:10.2165/00023210-200923040-00001 PubMed
84. Emslie GJ, Mayes T, Porta G, et al. Treatment of Resistant Depression in Adolescents (TORDIA): week 24 outcomes. *Am J Psychiatry*. 2010; 167(7):782–791. doi:10.1176/appi.ajp.2010.09040552 PubMed
85. Vitiello B, Emslie G, Clarke G, et al. Long-term outcome of adolescent depression initially resistant to selective serotonin reuptake inhibitor treatment: a follow-up study of the TORDIA sample. *J Clin Psychiatry*. 2011;72(3):388–396. doi:10.4088/JCP.09m05885blu PubMed
86. Posner K, Oquendo MA, Gould M, et al. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry*. 2007;164(7):1035–1043. doi:10.1176/appi.ajp.164.7.1035 PubMed
87. March JS, Klee BJ, Kremer CM. Treatment benefit and the risk of suicidality in multicenter, randomized, controlled trials of sertraline in children and adolescents. *J Child Adolesc Psychopharmacol*. 2006;16(1–2):91–102. doi:10.1089/cap.2006.16.91 PubMed
88. Brent DA, Greenhill LL, Compton S, et al. The Treatment of Adolescent Suicide Attempters study (TASA): predictors of suicidal events in an open treatment trial. *J Am Acad Child Adolesc Psychiatry*. 2009;48(10): 987–996. doi:10.1097/CHI.0b013e3181b5dbe4 PubMed
89. Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. *Arch Gen Psychiatry*. 2006;63(3): 332–339. doi:10.1001/archpsyc.63.3.332 PubMed
90. Gibbons RD, Brown CH, Hur K, et al. Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. *Am J Psychiatry*. 2007;164(9):1356–1363. doi:10.1176/appi.ajp.2007.07030454 PubMed
91. Gibbons RD, Hur K, Bhaumik DK, et al. The relationship between antidepressant medication use and rate of suicide. *Arch Gen Psychiatry*. 2005; 62(2):165–172. doi:10.1001/archpsyc.62.2.165 PubMed
92. Blader JC, Carlson GA. Increased rates of bipolar disorder diagnoses among US child, adolescent, and adult inpatients, 1996–2004. *Biol Psychiatry*. 2007;62(2):107–114. doi:10.1016/j.biopsych.2006.11.006 PubMed
93. Pathak P, West D, Martin BC, et al. Evidence-based use of second-generation antipsychotics in a state Medicaid pediatric population, 2001–2005. *Psychiatr Serv*. 2010;61(2):123–129. doi:10.1176/appi.ps.61.2.123 PubMed
94. Wilson D. Poor children likelier to get antipsychotics. *New York Times*. December 11, 2009. http://www.nytimes.com/2009/12/12/health/12medicaid.html?pagewanted=all. Accessed April 15, 2011.
95. Correll CU. Antipsychotic use in children and adolescents: minimizing adverse effects to maximize outcomes. *J Am Acad Child Adolesc Psychiatry*. 2008;47(1):9–20. doi:10.1097/chi.0b013e31815b5cb1 PubMed
96. Correll CU, Manu P, Olshanskiy V, et al. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA*. 2009;302(16):1765–1773. doi:10.1001/jama.2009.1549 PubMed
97. Vitiello B, Correll C, van Zwieten-Boot B, et al. Antipsychotics in children and adolescents: increasing use, evidence for efficacy and safety concerns. *Eur Neuropsychopharmacol*. 2009;19(9):629–635. doi:10.1016/j.euroneuro.2009.04.008 PubMed
98. Jensen PS, Buitelaar J, Pandina GJ, et al. Management of psychiatric disorders in children and adolescents with atypical antipsychotics: a systematic review of published clinical trials. *Eur Child Adolesc Psychiatry*. 2007;16(2):104–120. doi:10.1007/s00787-006-0580-1 PubMed
99. Findling RL, Kline K, Mckenna K, et al. Efficacy and safety of quetiapine in adolescents with schizophrenia: a 6-week, double-blind, randomized, placebo-controlled trial. Presented at: 55th Annual Meeting of the American Academy of Child and Adolescent Psychiatry; October 28–November 2, 2008; Chicago, IL.
100. Findling RL, Cavus I, Pappadopulos E, et al. Efficacy and safety of ziprasidone in adolescents with schizophrenia. Presented at: 2nd Biannual Meeting of the Schizophrenia International Research Society (SIRS); April 10–14, 2010; Venice, Italy.
101. Haas M, Eerdekens M, Kushner S, et al. Efficacy, safety and tolerability of two risperidone dosing regimens in adolescent schizophrenia: double-blind study. *Br J Psychiatry*. 2009;194(2):158–164. doi:10.1192/bjp.bp.107.046177 PubMed
102. Singh V, Vijapurkar U, Robb A, et al. Efficacy, safety and tolerability of paliperidone ER in adolescent patients with schizophrenia. Poster presented at: 65th Annual Meeting of the Society of Biological Psychiatry; May 20–22, 2010; New Orleans, LA.
103. Sikich L, Hamer RM, Bashford RA, et al. A pilot study of risperidone, olanzapine, and haloperidol in psychotic youth: a double-blind, randomized, 8-week trial. *Neuropsychopharmacology*. 2004;29(1):133–145. doi:10.1038/sj.npp.1300327 PubMed
104. Sikich L, Frazier JA, McClellan J, et al. Double-blind comparison of first- and second-generation antipsychotics in early-onset schizophrenia and schizo-affective disorder: findings from the Treatment of Early-Onset Schizophrenia Spectrum Disorders (TEOSS) study. *Am J Psychiatry*. 2008;165(11):1420–1431. doi:10.1176/appi.ajp.2008.08050756 PubMed
105. Arango C, Robles O, Parellada M, et al. Olanzapine compared to quetiapine in adolescents with a first psychotic episode. *Eur Child Adolesc Psychiatry*. 2009;18(7):418–428. doi:10.1007/s00787-009-0749-5 PubMed
106. Kumra S, Frazier JA, Jacobsen LK, et al. Childhood-onset schizophrenia: a double-blind clozapine-haloperidol comparison. *Arch Gen Psychiatry*. 1996;53(12):1090–1097. PubMed
107. Shaw P, Sporn A, Gogtay N, et al. Childhood-onset schizophrenia: a double-blind, randomized clozapine-olanzapine comparison. *Arch Gen Psychiatry*. 2006;63(7):721–730. doi:10.1001/archpsyc.63.7.721 PubMed
108. Kumra S, Kranzler H, Gerbino-Rosen G, et al. Clozapine and "high-dose" olanzapine in refractory early-onset schizophrenia: a 12-week randomized and double-blind comparison. *Biol Psychiatry*. 2008;63(5):524–529. doi:10.1016/j.biopsych.2007.04.043 PubMed
109. Delbello MP, Schwiers ML, Rosenberg HL, et al. A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania. *J Am Acad Child Adolesc Psychiatry*.

2002;41(10):1216–1223. doi:10.1097/00004583-200210000-00011 PubMed
110. DelBello MP, Kowatch RA, Adler CM, et al. A double-blind randomized pilot study comparing quetiapine and divalproex for adolescent mania. *J Am Acad Child Adolesc Psychiatry*. 2006;45(3):305–313. doi:10.1097/01.chi.0000194567.63289.97 PubMed
111. Pavuluri MN, Henry DB, Findling RL, et al. Double-blind randomized trial of risperidone versus divalproex in pediatric bipolar disorder. *Bipolar Disord*. 2010;12(6):593–605. doi:10.1111/j.1399-5618.2010.00850.x PubMed
112. McDougle CJ, Stigler KA, Erickson CA, et al. Atypical antipsychotics in children and adolescents with autistic and other pervasive developmental disorders. *J Clin Psychiatry*. 2008;69(suppl 4):15–20. PubMed
113. McCracken JT, McGough J, Shah B, et al; Research Units on Pediatric Psychopharmacology Autism Network. Risperidone in children with autism and serious behavioral problems. *N Engl J Med*. 2002;347(5):314–321. doi:10.1056/NEJMoa013171 PubMed
114. Shea S, Turgay A, Carroll A, et al. Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. *Pediatrics*. 2004;114(5):e634–e641. doi:10.1542/peds.2003-0264-F PubMed
115. Nagaraj R, Singhi P, Malhi P. Risperidone in children with autism: randomized, placebo-controlled, double-blind study. *J Child Neurol*. 2006;21(6):450–455. PubMed
116. Marcus RN, Owen R, Kamen L, et al. A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. *J Am Acad Child Adolesc Psychiatry*. 2009;48(11):1110–1119. doi:10.1097/CHI.0b013e3181b76658 PubMed
117. Owen R, Sikich L, Marcus RN, et al. Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. *Pediatrics*. 2009;124(6):1533–1540. doi:10.1542/peds.2008-3782 PubMed
118. Hollander E, Wasserman S, Swanson EN, et al. A double-blind placebo-controlled pilot study of olanzapine in childhood/adolescent pervasive developmental disorder. *J Child Adolesc Psychopharmacol*. 2006;16(5):541–548. doi:10.1089/cap.2006.16.541 PubMed
119. Research Units on Pediatric Psychopharmacology Autism Network. Risperidone treatment of autistic disorder: longer-term benefits and blinded discontinuation after 6 months. *Am J Psychiatry*. 2005;162(7):1361–1369. doi:10.1176/appi.ajp.162.7.1361 PubMed
120. Troost PW, Lahuis BE, Steenhuis MP, et al. Long-term effects of risperidone in children with autism spectrum disorders: a placebo discontinuation study. *J Am Acad Child Adolesc Psychiatry*. 2005;44(11):1137–1144. doi:10.1097/01.chi.0000177055.11229.76 PubMed
121. Aman MG, McDougle CJ, Scahill L, et al; the Research Units on Pediatric Psychopharmacology Autism Network. Medication and parent training in children with pervasive developmental disorders and serious behavior problems: results from a randomized clinical trial. *J Am Acad Child Adolesc Psychiatry*. 2009;48(12):1143–1154. doi:10.1097/CHI.0b013e3181bfd669 PubMed
122. Aman MG, De Smedt G, Derivan A, et al; Risperidone Disruptive Behavior Study Group. Double-blind, placebo-controlled study of risperidone for the treatment of disruptive behaviors in children with subaverage intelligence. *Am J Psychiatry*. 2002;159(8):1337–1346. doi:10.1176/appi.ajp.159.8.1337 PubMed
123. Armenteros JL, Lewis JE, Davalos M. Risperidone augmentation for treatment-resistant aggression in attention-deficit/hyperactivity disorder: a placebo-controlled pilot study. *J Am Acad Child Adolesc Psychiatry*. 2007;46(5):558–565. doi:10.1097/chi.0b013e3180323354 PubMed
124. Snyder R, Turgay A, Aman M, et al; Risperidone Conduct Study Group. Effects of risperidone on conduct and disruptive behavior disorders in children with subaverage IQs. *J Am Acad Child Adolesc Psychiatry*. 2002;41(9):1026–1036. doi:10.1097/00004583-200209000-00002 PubMed
125. Van Bellinghen M, De Troch C. Risperidone in the treatment of behavioral disturbances in children and adolescents with borderline intellectual functioning: a double-blind, placebo-controlled pilot trial. *J Child Adolesc Psychopharmacol*. 2001;11(1):5–13. doi:10.1089/104454601750143348 PubMed
126. Findling RL, McNamara NK, Branicky LA, et al. A double-blind pilot study of risperidone in the treatment of conduct disorder. *J Am Acad Child Adolesc Psychiatry*. 2000;39(4):509–516. doi:10.1097/00004583-200004000-00021 PubMed
127. Greenhill LL, Solomon M, Pleak R, et al. Molindone hydrochloride treatment of hospitalized children with conduct disorder. *J Clin Psychiatry*. 1985;46(8, Pt 2):20–25. PubMed
128. Reyes M, Buitelaar J, Toren P, et al. A randomized, double-blind, placebo-controlled study of risperidone maintenance treatment in children and adolescents with disruptive behavior disorders. *Am J Psychiatry*. 2006;163(3):402–410. doi:10.1176/appi.ajp.163.3.402 PubMed
129. Wilson SJ, Lipsey MW. School-based interventions for aggressive and disruptive behavior: update of a meta-analysis. *Am J Prev Med*. 2007;33(suppl):S130–S143. doi:10.1016/j.amepre.2007.04.011 PubMed
130. Fossum S, Handegård BH, Martinussen M, et al. Psychosocial interventions for disruptive and aggressive behaviour in children and adolescents: a meta-analysis. *Eur Child Adolesc Psychiatry*. 2008;17(7):438–451. doi:10.1007/s00787-008-0686-8 PubMed
131. Scahill L, Leckman JF, Schultz RT, et al. A placebo-controlled trial of risperidone in Tourette syndrome. *Neurology*. 2003;60(7):1130–1135. PubMed
132. Sallee FR, Kurlan R, Goetz CG, et al. Ziprasidone treatment of children and adolescents with Tourette's syndrome: a pilot study. *J Am Acad Child Adolesc Psychiatry*. 2000;39(3):292–299. doi:10.1097/00004583-200003000-00010 PubMed
133. Piacentini J, Woods DW, Scahill L, et al. Behavior therapy for children with Tourette disorder: a randomized controlled trial. *JAMA*. 2010;303(19):1929–1937. doi:10.1001/jama.2010.607 PubMed
134. Safer DJ. A comparison of risperidone-induced weight gain across the age span. *J Clin Psychopharmacol*. 2004;24(4):429–436. doi:10.1097/01.jcp.0000130558.86125.5b PubMed
135. Correll CU, Carlson HE. Endocrine and metabolic adverse effects of psychotropic medications in children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 2006;45(7):771–791. doi:10.1097/01.chi.0000220851.94392.30 PubMed
136. Kryzhanovskaya L, Schulz SC, McDougle C, et al. Olanzapine versus placebo in adolescents with schizophrenia: a 6-week, randomized, double-blind, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2009;48(1):60–70. doi:10.1097/CHI.0b013e3181900404 PubMed
137. Correll CU, Kane JM. One-year tardive dyskinesia rates in children and adolescents treated with second-generation antipsychotics: a systematic review. *J Child Adolesc Psychopharmacol*. 2007;17(5):647–655. doi:10.1089/cap.2006.0117 PubMed
138. Safety and tolerability of ziprasidone in adolescents with schizophrenia. http://clinicaltrials.gov/ct2/show/NCT00265382. Updated August 31, 2010. Accessed April 19, 2011.
139. Findling RL, Robb A, Nyilas M, et al. A multiple-center, randomized, double-blind, placebo-controlled study of oral aripiprazole for treatment of adolescents with schizophrenia. *Am J Psychiatry*. 2008;165(11):1432–1441. doi:10.1176/appi.ajp.2008.07061035 PubMed
140. Haas M, Unis AS, Armenteros J, et al. A 6-week, randomized, double-blind, placebo-controlled study of the efficacy and safety of risperidone in adolescents with schizophrenia. *J Child Adolesc Psychopharmacol*. 2009;19(6):611–621. doi:10.1089/cap.2008.0144 PubMed
141. Findling RL, Nyilas M, Forbes RA, et al. Acute treatment of pediatric bipolar I disorder, manic or mixed episode, with aripiprazole: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2009;70(10):1441–1451. doi:10.4088/JCP.09m05164yel PubMed
142. Tohen M, Kryzhanovskaya L, Carlson G, et al. Olanzapine versus placebo in the treatment of adolescents with bipolar mania. *Am J Psychiatry*. 2007;164(10):1547–1556. doi:10.1176/appi.ajp.2007.06111932 PubMed
143. DelBello MP, Findling RL, Acevedo LD, et al. Efficacy of quetiapine in children and adolescents with bipolar mania: a 3-week double-blind, randomized, placebo-controlled trial. Presented at: 54th Annual Meeting of the American Academy of Child and Adolescent Psychiatry; October 24–29, 2007; Boston, MA.
144. Haas M, Delbello MP, Pandina G, et al. Risperidone for the treatment of acute mania in children and adolescents with bipolar disorder: a randomized, double-blind, placebo-controlled study. *Bipolar Disord*. 2009;11(7):687–700. doi:10.1111/j.1399-5618.2009.00750.x PubMed
145. DelBello MP, Findling RL, Wang PP, et al. Efficacy and safety of ziprasidone in pediatric bipolar disorder. Presented at: 63rd Annual Meeting of the Society of Biological Psychiatry; May 1–3, 2008; Washington, DC.
146. Montañés-Rada F, Gangoso-Fermoso AB, Martínez-Granero MA. Drugs for attention deficit hyperactivity disorder [in Spanish]. *Rev Neurol*. 2009;48(9):469–481. PubMed
147. Correll CU. Systematic review of randomized controlled trials of pharmacologic treatments for youth with maladaptive aggression and related best practice recommendations. Presented at: 57th Annual Meeting of the American Academy of Child and Adolescent Psychiatry; October 26–31, 2010; New York, NY.
148. DelBello MP, Chang K, Welge JA, et al. A double-blind, placebo-controlled pilot study of quetiapine for depressed adolescents with bipolar disorder. *Bipolar Disord*. 2009;11(5):483–493. doi:10.1111/j.1399-5618.2009.00728.x PubMed
149. Swanson JM, Kraemer HC, Hinshaw SP, et al. Clinical relevance of the primary findings of the MTA: success rates based on severity of ADHD and ODD symptoms at the end of treatment. *J Am Acad Child Adolesc Psychiatry*. 2001;40(2):168–179. PubMed

Geriatric Psychopharmacology: Evolution of a Discipline

Barnett S. Meyers, MD, and Dilip V. Jeste, MD

The development of geriatric psychopharmacology was built on advances in geriatric psychiatry nosology and clinical pharmacology and on increased investment in aging research by the National Institute of Mental Health and by academic institutions. Application of the US Food and Drug Administration's geriatric labeling rule provided further impetus. Developments in the knowledge about 3 principal classes of medications (antidepressants, antipsychotics, and treatments for Alzheimer's disease) illustrate the trajectory of geriatric psychopharmacology research. Nonetheless, the loss of information about age effects that has resulted from applying age exclusion criteria in studies limited to either younger adults or geriatric patients is regrettable. Antidepressant trials have moved from studying younger and medically well "geriatric" samples to focusing on "older old" persons and those with significant medical comorbidity including coronary artery disease, cerebrovascular disease, and dementia. Increased specificity is reflected in studies of relationships between specific neuropsychological deficits, specific brain abnormalities, and antidepressant responsiveness. Clinical trials in older adults have demonstrated that the efficacy of antipsychotic medications continues across the lifespan, but that sensitivity to specific side effects changes in older age, with poor tolerability frequently mitigating the benefits of treatment. Treatments for Alzheimer's disease have fallen within the purview of geriatric psychopharmacology. The research focus is increasingly shifting from treatments to slow the course of cognitive decline to studies of early diagnosis and of interventions designed to prevent the development of deficits in vulnerable individuals. The importance of geriatric psychopharmacology will grow further as the average lifespan increases all over the world.

J Clin Psychiatry 2010;71(11):1416–1424

Submitted: *August 10, 2010; accepted August 30, 2010.*
(doi:10.4088/JCP.10r06485gry).
Corresponding author: *Dilip V. Jeste, MD, University of California, San Diego, 9500 Gilman Dr, No 0664, San Diego, CA 92093 (djeste@ucsd.edu).*

The history of geriatric psychopharmacology can be best understood in relationship to 4 parallel developments that occurred during the last quarter of the 20th century: (1) the development and publication of standardized criteria as a foundation for reliable psychiatric diagnosis during the 1970s[1–4]; (2) the identification, study, and subsequent US Food and Drug Administration (FDA) approval of medications to treat the indications of psychiatric syndromes and disorders[5]; (3) the development of an infrastructure and funding mechanisms within the National Institute of Mental Health (NIMH) to develop academically based investigator-scholars in geriatric mental health; and (4) the increasing awareness of the "graying of America,"[6] the call to address this "demographic imperative" by augmenting the knowledge base in geriatrics at academic centers,[7] and an increasing focus on geriatric mental illness.[8] Applied to the disciplines of pharmacology and therapeutics, these events led to the development of scientists and programs of study devoted to investigating disorders of later life and the efficacy and tolerability of medications in geriatric patients. It can be argued that focused geriatric studies might have had a paradoxical effect of limiting our ability to identify aging effects. Specifically, our ability to determine the contributions of factors related to chronological aging has been limited by the segregation of studies of older adults from those of younger samples. A broadening of age inclusion criteria in psychopharmacology studies supported by industry and the NIMH would be required to more precisely identify aging effects on efficacy and tolerability.

A decade passed before these NIMH investments bore fruit. Sufficient information was available in the 1980s to support the launch of peer-reviewed journals devoted to geriatric psychiatry, such as *International Journal of Geriatric Psychiatry* in 1985, *International Psychogeriatrics* in 1989, and the US-based *American Journal of Geriatric Psychiatry* in 1993. The development of a knowledge base also led to the publication of early textbooks of geriatric psychopharmacology,[9–12] including the first of 4 editions of a textbook devoted to clinical geriatric psychopharmacology.[13] The historical forces that contributed to our current knowledge can be best understood by reading the too-often overlooked introduction sections of geriatric psychiatry texts that review the evolution of the discipline.[14]

This article provides a historical overview of developments that contributed to advances in geriatric psychopharmacology followed by a description of the trajectories of research advances in 3 principal classes of medications: antidepressants, antipsychotics, and medications used to treat Alzheimer's disease. An exhaustive review of developments in all classes of medications or of each medication in the classes discussed is beyond the scope of this review. We focus on prototypical medication classes to describe the trajectory of research in geriatric psychopharmacology generally.

Changes in the FDA Drug Approval and Labeling Process

To obtain FDA approval for standard indications, industry trials typically focus recruitment on patients who would

be at the greatest likelihood of benefiting from a medication and are at lowest risk for suffering adverse events. Therefore, phase 3 studies did not typically include either geriatric patients or patients with significant medical comorbidity to minimize the risk for adverse outcomes. The "geriatric use" rule of 1997[15] required industry to provide supplemental data on specific classes of medications used to treat geriatric patients. "Psychotropic medications" were included among the classes covered by the geriatric use rule. The conceptualization of geriatric patients as a "special population" that required additional empirically derived labeling instructions for drug approval required industry to specifically study the effects of older age on a medication's pharmacologic properties. Nevertheless, application of the geriatric use rule does not require the inclusion of statistically meaningful numbers of older adults or patients with aging-related medical comorbidity in phase 3 studies. Meaningful data on geriatric use would require the inclusion of a broad and representative age range of subjects in single studies or meta-analyses that addressed age effects across mixed-aged adult and geriatric studies. Such data remain unavailable. Also, the requirement for geriatric labeling does not specifically address psychopharmacologic issues related to significant comorbidity that challenge geriatric psychiatrists.

Applications of Advances in Psychopharmacology to Geriatric Psychopharmacology

Although this review focuses on geriatric psychopharmacology, the discussions of specific medication classes have been informed increasingly by parallel developments in pharmacologic research. Geriatric psychopharmacology has benefited from discoveries ranging from the identification of neurotransmitters and their physiologic effects to developments in our understanding of pharmacodynamic effects and pharmacokinetic processes. For example, the development of an assay to assess the cumulative serum anticholinergic activity associated with medication use[16] was followed by the correlation of increased activity with anticholinergic side effects in geriatric patients.[17] Similarly, evidence that aging is associated with decreased dopamine functioning in corticostriatal pathways[18] explained the association between older age and the increased prevalence of both extrapyramidal symptoms and tardive dyskinesia that had been observed with treatment using conventional antipsychotic medications.[19,20] Despite aging-related decreases in renal and hepatic function, the "pharmacokinetic assumption" that aging would result in high concentrations of *most* psychotropic medications has not been supported empirically.[21] An aging-related slowing of demethylation required for the metabolism of medications such as diazepam and the tertiary amine tricyclic antidepressants (TCAs) stands as the major exception to the absence of clinically significant age effects on drug metabolism.[22] The dearth of pharmacokinetic studies that include a broad age range continues to limit our knowledge of both the pharmacodynamic and pharmacokinetic effects of aging and has contributed to the hope that population pharmacokinetics will clarify the effects of aging on medication effects.[23,24]

Definition of *Geriatric*

As noted above, the inclusion of physically healthy participants over the age of 60 in efficacy studies does not address either the efficacy or the tolerability of medications in patients with comorbid medical conditions that are commonly seen in older persons. Also, defining *geriatric* on the basis of chronological age fails to capture both the nonlinearity of changes in physiologic processes and the increased biologic heterogeneity that is associated with aging.[25,26] The standard "geriatric" cutoff age of 65 years or older is arbitrary and evolves out of regulatory definitions rather than empirical studies of the aging process. It is not surprising that the earliest geriatric studies included the "lowest-hanging fruit," ie, younger ambulatory patients. Thus, the seminal acute and maintenance antidepressant trials conducted in the 1980s by Georgotas and colleagues recruited medically well outpatients and applied an inclusion criterion of age 55 or older.[27–29] Early reviews[30] pointed to the need for randomized controlled trials (RCTs) of antidepressants in the older old to guide treatment of "truly" geriatric patients. As discussed in later sections, recent studies have focused on more "geriatric" questions; this has included requiring age 70 or above for inclusion and studying the efficacy of medications in patients with comorbid conditions.[30]

ANTIDEPRESSANTS

Efficacy for Major Depression

Early NIMH-supported RCTs demonstrated the efficacy of both nortriptyline and phenelzine for the acute and continuation treatment of geriatric depression.[27,28] Although a small-sample early report failed to demonstrate the efficacy of nortriptyline for maintenance therapy,[29] results from an extension of this trial were positive,[31] but never published because of the premature death of Dr Anastasios Georgotas, the lead investigator. Subsequently, a large-scale NIMH trial demonstrated the clear superiority of nortriptyline maintenance for recurrent geriatric depression among patients 60 and older.[32] By 1994, a sufficient number of controlled studies demonstrating efficacy and tolerability were available for the NIMH Consensus Development Conference to recommend secondary amine TCAs as the first-line treatment among TCAs for geriatric depression.[33]

The FDA approval of fluoxetine in 1987 was followed by approval of other medications in the selective serotonin reuptake inhibitor (SSRI) class. Eli Lilly received a specific indication for fluoxetine as a treatment for major geriatric depression in 1999 based on statistical separation from placebo in a large-sample trial.[34] Although approvals for the treatment of geriatric depression have not been obtained for other SSRIs, completion of acute and continuation/maintenance trials in older adults has become standard during the development of new antidepressants. A sufficient number

of trials have been completed for the publication of meta-analysis demonstrating that second-generation antidepressants are effective[35] and have an efficacy that is comparable to that of TCAs, although side effect profiles tend to favor SSRIs over the classical TCAs.[36,37] Poorer tolerability to TCAs among older adults results, in part, from aging-related increases in sensitivity to the anticholinergic and α_1-blocking properties of these medications. These changes in pharmacodynamic sensitivity are thought to mediate aging-related increased risks for orthostatic hypotension and falls associated with TCA treatment.[21]

Efficacy in the Older Old

The trial conducted by Roose and colleagues[38] in "old-old" patients addressed the dearth of efficacy in data in older geriatric patients by applying an inclusion criterion of age 75 and above. Although results on the primary outcome measures were negative, secondary analyses revealed that more severely depressed participants and those with early-onset depression were more likely to benefit from the antidepressant. These results point to the heterogeneity of geriatric depression and indicate that neuropsychological factors and underlying aging-related changes in brain structures may diminish the efficacy of antidepressants.[39,40] The finding by Reynolds et al[41] that comorbid anxiety and the severity of medical comorbidity moderated the efficacy of SSRI maintenance treatment in patients 70 and older added to knowledge about how aging-related factors moderate antidepressant efficacy.

Efficacy in Psychotic Depression

Early studies in the United Kingdom[42] and United States[43] reported that approximately 45% of older adults hospitalized for depression have associated delusions. Trials of antidepressants demonstrating that delusional depression was associated with a poor response to classical TCAs[44–46] were followed by the observation that older patients with delusional depression had a 2-fold greater 1-year mortality than patients with nondelusional major depression.[47] Although an early RCT demonstrated the efficacy of combining a TCA with a conventional antipsychotic in younger adults,[48] the first RCT of combination treatment in geriatric patients with psychotic major depression was negative.[49] A recent RCT of delusional depression using high doses of the better-tolerated SSRI class of antidepressants in combination with an atypical antipsychotic demonstrated comparable efficacy in young adults and older participants, who comprised more than 50% of the sample.[50]

Depression Associated With Comorbidity

Conceptualization of comorbidity rather than chronological age as central to the definition of *geriatric* stimulated RCTs conducted in depressed patients with comorbid conditions. Early approaches to depression with medical comorbidity used stimulants, such as methylphenidate, to improve nonspecific symptoms, including anergy, lack of motivation, and fatigue. Despite open trials suggesting that psychostimulants may improve symptoms associated with debilitation[51] and "negative symptoms" in patients with dementia,[52] RCTs have not demonstrated efficacy among patients who meet criteria for major depression.[53]

Most antidepressant trials in patients with Alzheimer's disease and major depression have been negative,[54] which has been attributed to high placebo response rates, instability of depressive symptoms in dementia patients, and insensitivity of symptoms caused by dementia to antidepressant effects.[55] Provisional diagnostic criteria have been proposed to better capture the major depression that occurs in association with Alzheimer's disease.[56,57] Nevertheless, the validity of these criteria must be established and reliable scales for assessing depression in these patients must be developed before the sensitivity of depression in dementia to antidepressants can be meaningfully assessed.

The past decade has seen an increasing focus on investigating whether specific types and locations of central nervous abnormalities moderate responsiveness to antidepressants. Studies of specific neuropsychological deficits and associated underlying neuropathology have been promising. The construct of "vascular depression" was developed to describe major depression associated with particular clinical characteristics, including apathy, excess disability, and impairment in executive functioning.[58] A similar clinical syndrome was contemporaneously described among older patients with major depression associated with diffuse white matter hyperintensities attributed to small vessel cerebrovascular disease.[59] Studies of geriatric depression associated with executive functioning have demonstrated that patients with impaired executive function performances have both diminished antidepressant response[60,61] and pathology in white matter tracts in corticostriatal pathways.[62,63] Further analysis of the data from the study of the "old-old"[38] complemented these findings by demonstrating that the size of drug-placebo differences had been diminished in the RCT because of negative interaction between the SSRI and the presence of executive impairment among participants.[64] Parallel findings were reported from an RCT of magnetic resonance imaging–defined vascular major depression, which demonstrated that the presence of white matter hyperintensities and executive impairment independently predicted a diminished antidepressant response to the SSRI.[65] Thus, the trajectory of geriatric antidepressant trials has moved from examining the nonspecific construct of chronological age to demonstrating the moderating effect of specific neurobiological factors on response to antidepressants.

Studies of the relationships between both recent cerebrovascular accidents[66] and coronary artery disease (CAD)[67] with depression have demonstrated a higher prevalence of major depression in patients with these vascular disorders and poorer outcomes if depression is present. Antidepressant trials in patients with poststroke depression have demonstrated efficacy for acute treatment with the secondary amine TCA nortriptyline,[68,69] prophylactic efficacy of both

nortriptyline and escitalopram,[70] and decreases in long-term mortality from vascular disease in patients who underwent a short-term course of poststroke antidepressant treatment, whether or not depression had been present initially.[71] Trials conducted in patients with major depression and CAD have demonstrated the efficacy of antidepressants,[71,72] particularly in patients with more severe and recurrent forms of depression.[4] Inclusion in these trials was based on the concurrent medical condition rather than chronological age, an approach consistent with emphasizing aging-related medical conditions rather than chronological age as moderators of treatment response.

ANTIPSYCHOTICS

Although antipsychotic medications are effective for treating bipolar mania and, in some instances, bipolar depression, RCTs in geriatric patients have been limited to patients with schizophrenia and the psychiatric complications of dementia.

Schizophrenia

Early double-blind studies demonstrated the efficacy of conventional antipsychotic medications in older patients with schizophrenia.[73–75] However, texts written as early as the 1970s[76–78] warned that α_1-, cholinergic- and histaminic-blocking properties of low-potency medications and the stronger dopamine-blocking properties of high-potency conventional antipsychotics made older patients particularly vulnerable to the development of clinically significant side effects. Subsequent research demonstrated that both a "late-onset" subtype of schizophrenia, which is marked by positive symptoms, and the positive symptoms of early-onset patients who have aged are responsive to conventional antipsychotic drugs,[79,80] although lower doses are needed to treat positive symptoms in older patients than in younger adults.[81] Studies of relationships between age and both the frequencies and types of extrapyramidal symptoms (EPS) associated with conventional antipsychotic treatment demonstrated that older patients are more likely than younger patients to experience dystonic reactions, but that antipsychotic-induced parkinsonism, including tremor and rigidity, is common in older patients.[82] The increased incidence, prevalence, severity, and persistence of tardive dyskinesia (TD) in older patients treated with conventional antipsychotic medications[19,83–85] have been a major factor limiting the use of these medications in geriatric psychiatry. Although investigators have pointed out the difficulty of distinguishing between risks for TD conferred by chronological age and those due to prolonged exposure, presumed aging-related brain changes[81,82] and the frequency and severity of TD in older patients supported the replacement of conventional antipsychotics with atypical antipsychotic medications for treating older patients with schizophrenia.

The FDA approval of clozapine in 1989 provided the first atypical antipsychotic medication and a treatment associated with a lower risk for EPS and TD. However, clozapine can be particularly problematic for older patients due to increased vulnerability of older patients to antimuscarinic, hypotensive, and sedative side effects and to the development of agranulocytosis during clozapine treatment.[86] Therefore, clozapine has been used primarily to treat psychotic disorders in patients who have EPS-predisposing comorbid conditions, such as Parkinson's disease and Lewy body disease, both of which increase their sensitivity to developing EPS in response to antipsychotic treatment. The small number of RCTs conducted with atypical antipsychotic medications in older patients with schizophrenia indicate that target doses of these medications are generally well tolerated and effective.[87,88] Also, seniors treated with atypical antipsychotics have demonstrated greater adherence and lower risk of TD than those who receive conventional agents.[89,90]

Older age is known to be associated with an increased prevalence of both obesity and type II diabetes, diminished glucose tolerance, and hyperlipidemia even in the absence of antipsychotic medication treatment. Nonetheless, concerns about metabolic side effects of atypical antipsychotic medications may limit their use in older patients.[91,92] The exclusion of a comparison group of older patients from most controlled studies of schizophrenia, including the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE),[93] has precluded systematic analysis of how older age affects the incidence or severity of metabolic abnormalities during atypical antipsychotic treatment. However, a 12-week trial of olanzapine in psychotic depression demonstrated that young adults and participants 60 years and older had statistically significant and comparable elevations in triglycerides and cholesterols over a 12-week period.[50] While available data support the use of atypical antipsychotic medications in older patients with schizophrenia, sound practice dictates regular monitoring of metabolic parameters and interventions to address metabolic abnormalities that develop.

Antipsychotic Treatment of the Psychiatric Complications of Dementia

Agitation and psychotic symptoms are common in Alzheimer's disease, with prevalence estimates ranging between 30% and 70%.[94–96] The demonstration of untoward consequences of these psychiatric complications, including earlier institutionalization[97] and increased caregiver burden,[98] supported assessing the efficacy of interventions to reduce psychiatric comorbidity. Conventional antipsychotics were prescribed to treat these complications, but meta-analysis and systematic reviews demonstrated only modest benefits.[99,100] A small RCT with haloperidol demonstrated the importance of appropriate dosing and careful monitoring to keep patients within the narrow therapeutic window associated with clinical improvement without problematic EPS.[101] Epidemiologic evidence of a relationship between psychotropic medications and incidence of hip fractures among nursing home residents[102] changed the treatment of psychiatric complications of dementia and increased the role

of geriatric psychiatrists in long-term care. Demonstration of a dose-dependent hip fracture risk and the subsequent finding that the intensity of pharmacotherapy administered to nursing home residents was predicted by the size of the primary care physicians' practices rather than by identifiable patient characteristics[103] led to federal legislation to regulate prescribing of psychopharmacologic agents in facilities that treat Medicare recipients. State inspection agencies welcomed the involvement of geriatric psychiatrists as nursing home consultants to monitor psychotropic prescribing to assure that residents were not treated with legislatively defined "unnecessary medications" or doses.

The introduction of atypical antipsychotic medications in the 1990s was associated with industry's conducting RCTs to test the efficacy of second-generation compounds that would avoid the problems of sedation and orthostatic hypotension associated with low-potency conventional agents and the EPS associated with high-potency agents. Positive placebo-controlled RCTs with both risperidone[104] and olanzapine[105] were reported, with both dose-finding placebo-controlled studies again demonstrating the presence of a narrow therapeutic dosing window for older patients with dementia. The CATIE Alzheimer's trial[106] compared the effectiveness of 3 atypical antipsychotic medications to placebo for psychiatric complications of dementia using time to discontinuation due to either lack of efficacy or poor tolerability as the primary outcome measure. Although the times to discontinuation due to lack of efficacy were longer among participants randomized to both olanzapine and risperidone than in subjects who received placebo, this greater efficacy was "offset" by the higher discontinuation rate among subjects who received active medication.[106] CATIE Alzheimer's trial results highlight the importance of monitoring patients to determine relative benefits versus risks of antipsychotic treatment and of considering nonpharmacologic interventions to manage psychiatric symptoms associated with dementia. A subsequent analysis of pooled data across many atypical antipsychotic RCTs demonstrating a greater mortality rate among patients who had received active medication than those who had been randomized to placebo[107] led to an FDA black box warning and the end of industry-supported trials of atypical antipsychotic medications in dementia patients. In view of these safety concerns, an APA consensus statement on the treatment of Alzheimer's disease[108] and an American College of Neuropsychopharmacology White Paper[109] were published to evaluate the risk:benefit ratio for using atypical antipsychotics to treat psychiatric complications of dementia.

Research into treating the behavioral complications of dementia has been further limited by the absence of standard criteria for defining constructs such as agitation and of tools to assess severity. The FDA pointed out that "agitation" cannot be considered an approvable indication until consensus diagnostic criteria and reliable assessment tools are developed.[110] In contrast, the publication of criteria for the psychosis of Alzheimer's disease[111] led to FDA approval of this indication, although the greater mortality risk with atypical medications is an obstacle to the use of those drugs for this syndrome.

ALZHEIMER'S DISEASE TREATMENTS

Studies of Alzheimer's disease treatments have increasingly fallen within the purview of geriatric psychopharmacology. Early treatments were both nonspecific and largely ineffective. Dihydroergotoxine, a vasodilator with mild monamine oxidase inhibitor properties, was approved for treatment of "senile mental decline" in the 1970s, which was consistent with the then-prevalent assumption that underlying vascular disease played a pathogenic role in late life–onset dementias; however, benefits of dihydroergotoxine were minimal, and trial results are difficult to interpret because standardized diagnostic criteria and reliable assessment tools were not available.[112]

Laboratory studies of brains of patients with Alzheimer's disease in the late 1970s demonstrated that concentrations of brain acetylcholine (ACh) were correlated with both the severity of cognitive impairment and the numbers of senile plaques in dementia patients.[113] These findings were followed by the demonstration of degenerated cholinergic pathways in Alzheimer's disease,[114,115] leading up to the hypothesis that deficiency in ACh was central to the cognitive impairment of Alzheimer's disease.[116] Initial attempts to supply damaged neurons with choline, a precursor of the neurotransmitter ACh, were both impractical and ineffective. Subsequent studies that attempted to slow the metabolism of available ACh led to the development of the cholinesterase inhibitor class of antidementia medications. RCTs using cholinesterase inhibitors in systematically diagnosed patients with mild to moderate dementia have been largely positive in terms of slowing the rate of cognitive decline over a period of up to 2 years,[117,118] with some variability in evidence supporting one or another medication in this class for patients at specific stages of disease or with other types of dementia. Although donepezil has received approval for moderate to severe as well as mild dementia, an absence of head-to-head studies demonstrating the clear superiority of one agent over another is consistent with considering the 4 approved cholinesterase inhibitors as comparably effective overall. The use of tacrine, the first cholinesterase inhibitor approved to treat Alzheimer's disease, has been limited because of a high risk for hepatotoxicity that is not associated with alternative agents. Paradoxically, demonstration of the efficacy of cholinesterase inhibitors in 6-month studies has discouraged the conduct of longer term placebo-controlled trials on ethical grounds. While data from the available open-label add-on trials suggest possible benefits from continued treatment with anti-Alzheimer's medications in some patients,[119] no definitive recommendations for continued treatment can be made without large-scale RCTs of longer duration.

Memantine, a partial antagonist of the *N*-methyl-D-aspartate glycine receptor, has been studied for Alzheimer's disease based on the underlying theory that the excitatory

properties of glycine contribute to the death of damaged Alzheimer's disease neurons. The 2 pivotal memantine trials for moderate to severe Alzheimer's disease conducted in the United States were led by geriatric psychiatrists,[119,120] demonstrating the extension of geriatric psychopharmacology studies into disorders involving structural brain disease.

Alzheimer's disease investigators have recognized that the effective treatment must occur early, before neurons are irreversibly damaged by the deposition of abnormal amyloid and tau protein. The demonstration that radioligand imaging identifies abnormal brain amyloid deposits in patients with mild Alzheimer's disease[121,122] and recent evidence that abnormalities in concentrations of cerebrospinal fluid amyloid and phosphorylated tau predict the development of Alzheimer's disease provide an early-detection foundation for future interventions.[123] Early interventions with novel pharmacologic strategies, including immunization and amyloid-modifying medications that are under development, have the potential for postponing the onset or reducing the risk of Alzheimer's disease in vulnerable individuals.

Putative Cognitive Enhancers for the Psychiatric Complications of Alzheimer's Disease

RCTs designed to study whether specific medications decrease the rate of cognitive decline in Alzheimer's disease patients have led to secondary analyses of whether improvement in psychiatric symptoms is greater in participants who received active medication compared to those allocated to placebo. Analyses for improvement in psychopathology in association with cholinesterase inhibitors[124–126] and memantine[127] have generated mixed results, and hypothesis-driven RCTs that demonstrate the efficacy of putative cognitive enhancers for specific psychiatric phenomena remain unavailable.

GERIATRIC PSYCHOPHARMACOLOGY: THE FUTURE

The impact on psychiatric disorders of physiologic changes associated with normal aging and of aging-related diseases is consistent with considering geriatric psychiatry as being probably the most "medical" of the psychiatric subspecialties. The central role of medical issues in treating older psychiatric patients was used to support classifying geriatric psychiatry within the purview of liaison psychiatry a quarter century ago.[128] Furthermore, geriatric psychiatry is also at the boundary between psychiatry and neurology. The contributions of structural brain changes associated with aging and of aging-related brain disease to the so-called functional psychiatric conditions support considering geriatric psychiatry as a model for integrating psychiatry, neurology, and neuroscience[129] in a combined discipline of "neuropsychiatry."[130] For these reasons, geriatric psychopharmacology is the discipline that is best suited to study relationships between both general medical and neurologic conditions that are associated with aging and classical psychiatric disorders. Research in geriatric psychopharmacology has increasingly demonstrated that both physical and psychosocial factors influence the phenomenology and treatment response of psychiatric disorders in later life. The trajectory of research in this arena has been increasingly specific. The accumulation of new data about how specific medical and neurologic lesions contribute to psychiatric symptoms allows geriatric psychopharmacology to ask more precise questions about moderators of outcome. From this perspective, geriatric psychopharmacology has evolved into the prototypical psychiatric discipline for addressing questions at the boundaries between structure and function and between pathologic processes and psychiatric treatment. With the rapidly changing demographics, in view of the lengthening lifespan all over the world, the importance of geriatric psychopharmacology is expected to grow progressively over the next quarter century.

Drug names: clozapine (Clozaril, FazaClo, and others), diazepam (Valium and others), donepezil (Aricept and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), memantine (Namenda), nortriptyline (Pamelor, Aventyl, and others), olanzapine (Zyprexa), phenelzine (Nardil), risperidone (Risperdal and others), tacrine (Cognex).

Author affiliations: Department of Psychiatry, Weill Cornell Medical College, White Plains, New York (Dr Meyers); and Department of Psychiatry, University of California, San Diego (Dr Jeste).

Potential conflicts of interest: **Dr Meyers** has been a consultant to Forest, has provided legal consultation for AstraZeneca, and has received medications donated by Eli Lilly and Pfizer for his RO1 grant funded by the National Institute of Mental Health. **Dr Jeste** received medications donated by AstraZeneca, Bristol-Myers Squibb, Eli Lilly, and Janssen for his RO1 grant for a study of atypical antipsychotics in older people funded by the National Institute of Mental Health.

Funding/support: This work was supported, in part, by National Institute of Mental Health grants MH085943 and MH082425 (Dr Meyers) and MH080002 and MH071536 (Dr Jeste).

REFERENCES

1. Feighner JP, Robins E, Guze SB, et al. Diagnostic criteria for use in psychiatric research. *Arch Gen Psychiatry*. 1972;26(1):57–63. PubMed
2. Wing JK, Cooper JE, Sartorius N. *Measurement and Classification of Psychiatric Symptoms: An Instruction Manual for the PSE and Catego Program*. New York, NY: Cambridge University Press; 1974.
3. Spitzer RL, Endicott J, Robins E. *Research Diagnostic Criteria (RDC) for a Selected Group of Functional Disorders*. 2nd ed. New York, NY: New York State Psychiatric Institute; 1975.
4. American Psychiatric Association. *Diagnostic and Statistical Manual for Mental Disorders*, Third Edition. Washington, DC: American Psychiatric Association Press; 1980.
5. Drug Reference for FDA Approved Psychiatric Drugs. Epocrates Inc. http://www.neurotransmitter.net/drug_reference.html. Updated April 4, 2008. Accessed September 1, 2010.
6. Butler R. *Why Survive? Being Old in America*. Baltimore, MD: Johns Hopkins University Press; 1975.
7. Hazzard WR. Geriatric education programs in North Carolina: response to the demographic imperative. *N C Med J*. 1989;50(2):92–93. PubMed
8. Jeste DV, Alexopoulos GS, Bartels SJ, et al. Consensus statement on the upcoming crisis in geriatric mental health: research agenda for the next 2 decades. *Arch Gen Psychiatry*. 1999;56(9):848–853.doi:10.1001/archpsyc.56.9.848 PubMed
9. Fann WE, Maddox GL. *Drug Issues in Geropsychiatry*. Baltimore, MD: Williams and Wilkins; 1974.
10. Raskin A, Robinson DS, Levine J. *Age and the Pharmacology of Psychoactive Drugs*. New York, NY: Elsevier; 1981.
11. Jarvick LF, Greenblatt DJ, Harman D. *Clinical Pharmacology and the Aged Patient*. New York, NY: Raven Press; 1981.
12. Jenike MA. *Handbook of Geriatric Psychopharmacology*. Littleton, MA: PSG Publishing Co, Inc; 1985.

13. Salzman C. *Clinical Geriatric Psychopharmacology*. 1st ed. New York, NY: McGraw-Hill; 1984.
14. Meyers BS. Introduction. In: Sadavoy J, Jarvik LF, Grossberg GT, et al, eds. *Comprehensive Textbook of Geriatric Psychiatry*. 3rd ed. New York, NY: WW Norton; 2004:Xix–XIiii.
15. Federal Register. Specific requirements on content and format of labeling for human prescription drugs; addition of "geriatric use" subsection in the labeling (62 FR45313). US Food and Drug Administration. http://federalregister.gov/a/97-22701. Updated August 27, 1997. Accessed September 1, 2010.
16. Tune L, Coyle JT. Serum levels of anticholinergic drugs in treatment of acute extrapyramidal side effects. *Arch Gen Psychiatry*. 1980;37(3): 293–297. PubMed
17. Mulsant BH, Gharabawi GM, Bossie CA, et al. Correlates of anticholinergic activity in patients with dementia and psychosis treated with risperidone or olanzapine. *J Clin Psychiatry*. 2004;65(12):1708–1714. doi:10.4088/JCP.v65n1217 PubMed
18. McGeer PL, McGeer EG, Suzuki JS. Aging and extrapyramidal function. *Arch Neurol*. 1977;34(1):33–35. PubMed
19. Jeste DV, Wyatt RJ. Aging and tardive dyskinesia. In: Miller NE, Cohen GD, eds. *Schizophrenia and Aging: Schizophrenia, Paranoid and Schizophreniform Disorders in Later Life*. New York, NY: Guilford Press; 1987:275–286.
20. Jeste DV, Rockwell E, Harris MJ, et al. Conventional vs newer antipsychotics in elderly patients. *Am J Geriatr Psychiatry*. 1999;7(1):70–76. PubMed
21. Meyers BS, Young RC. Psychopharmacology. In: Sadavoy J, Jarvik LF, Grossberg GT, et al, eds. *Comprehensive Textbook of Geriatric Psychiatry*. 3rd ed. New York, NY: WW Norton; 2004.
22. DeVane CL, Pollock BG. Pharmacokinetic considerations of antidepressant use in the elderly. *J Clin Psychiatry*. 1999;60(suppl 20):38–44. PubMed
23. Pollock BG. The pharmacokinetic imperative in late-life depression. *J Clin Psychopharmacol*. 2005;25(suppl 1):S19–S23.doi:10.1097/01.jcp.0000162809.69323.66 PubMed
24. Uchida H, Mamo DC, Mulsant BH, et al. Increased antipsychotic sensitivity in elderly patients: evidence and mechanisms. *J Clin Psychiatry*. 2009;70(3):397–405.doi:10.4088/JCP.08r04171 PubMed
25. Federal Register. Specific requirements on content and format of labeling for human prescription drugs; addition of "geriatric use" subsection in the labeling (62 FR45313). US Food and Drug Administration. http://federalregister.gov/a/97-22701. Updated August 27, 1997. Accessed September 1, 2010.
26. Rowe JW. Aging and renal function. *Annu Rev Gerontol Geriatr*. 1980;1:161–179.
27. Georgotas A, McCue RE, Hapworth W, et al. Comparative efficacy and safety of MAOIs versus TCAs in treating depression in the elderly. *Biol Psychiatry*. 1986;21(12):1155–1166.doi:10.1016/0006-3223(86)90222-2 PubMed
28. Georgotas A, McCue RE, Cooper TB, et al. How effective and safe is continuation therapy in elderly depressed patients? factors affecting relapse rate. *Arch Gen Psychiatry*. 1988;45(10):929–932. PubMed
29. Georgotas A, McCue RE, Cooper TB. A placebo-controlled comparison of nortriptyline and phenelzine in maintenance therapy of elderly depressed patients. *Arch Gen Psychiatry*. 1989;46(9):783–786. PubMed
30. Salzman C, Schneider L, Lebowitz B. Antidepressant treatment of very old patients. *Am J Geriatr Psychiatry*. 1993;1(1):21–29. doi:10.1097/00019442-199300110-00004
31. Meyers BS, Kakuma T, Ippolito L. Nortriptyline maintenance for geriatric depression: an expansion of the Georgotas studies. Presented as a poster at the 37th Annual NCDEU Meeting; May 1997; Boca Raton, FL.
32. Reynolds CF 3rd, Frank E, Perel JM, et al. Nortriptyline and interpersonal psychotherapy as maintenance therapies for recurrent major depression: a randomized controlled trial in patients older than 59 years. *JAMA*. 1999;281(1):39–45.doi:10.1001/jama.281.1.39 PubMed
33. Salzman C. Pharmacological treatment of depression. In: Schneider LS, Reynolds CFI, Lebowitz BD, et al, eds. *Diagnosis and Treatment of Treatment in Late Life: Results of the NIH Consensus Development Conference*. Washington, DC: American Psychiatric Association Press; 1994:181–244.
34. Tollefson GD, Bosomworth JC, Heiligenstein JH, et al; The Fluoxetine Collaborative Study Group. A double-blind, placebo-controlled clinical trial of fluoxetine in geriatric patients with major depression. *Int Psychogeriatr*. 1995;7(1):89–104.doi:10.1017/S1041610295001888 PubMed
35. Nelson JC, Delucchi K, Schneider LS. Efficacy of second generation antidepressants in late-life depression: a meta-analysis of the evidence. *Am J Geriatr Psychiatry*. 2008;16(7):558–567.doi:10.1097/01.JGP.0000308883.64832.ed PubMed
36. Mottram P, Wilson K, Strobl J. Antidepressants versus placebo for the depressed elderly. *Cochrane Database Syst Rev*. 2001;(3):CD000651.
37. Mottram P, Wilson K, Strobl JJ. Antidepressants for depressed elderly. *Cochrane Database Syst Rev*. 2006;(1):CD003491. PubMed
38. Roose SP, Sackeim HA, Krishnan KR, et al; Old-Old Depression Study Group. Antidepressant pharmacotherapy in the treatment of depression in the very old: a randomized, placebo-controlled trial. *Am J Psychiatry*. 2004;161(11):2050–2059.doi:10.1176/appi.ajp.161.11.2050 PubMed
39. Sneed JR, Roose SP, Keilp JG, et al. Response inhibition predicts poor antidepressant treatment response in very old depressed patients. *Am J Geriatr Psychiatry*. 2007;15(7):553–563.doi:10.1097/JGP.0b013e3180302513 PubMed
40. Meyers BS. Optimizing the use of data generated by geriatric depression treatment studies during a time of diminishing resources. *Am J Geriatr Psychiatry*. 2007;15(7):545–552.doi:10.1097/JGP.0b013e3180959df5 PubMed
41. Reynolds CF 3rd, Dew MA, Pollock BG, et al. Maintenance treatment of major depression in old age. *N Engl J Med*. 2006;354(11):1130–1138. doi:10.1056/NEJMoa052619 PubMed
42. Post F. *The Significance of Affective Symptoms in Old Age*. New York, NY: Oxford University Press; 1962.
43. Meyers BS. Late-life delusional depression: acute and long-term treatment. *Int Psychogeriatr*. 1995;7(suppl):113–124.doi:10.1017/S1041610295002390 PubMed
44. Friedman C, De Mowbray MS, Hamilton VJ. Imipramine (Tofranil) in depressive states: a controlled trial with inpatients. *J Ment Sci*. 1961;107:948–953. PubMed
45. Hordern A, Holt NF, Burt CG, et al. Amitriptyline in depressive states: phenomenology and prognostic considerations. *Br J Psychiatry*. 1963;109(463):815–825.doi:10.1192/bjp.109.463.815 PubMed
46. Glassman AH, Perel JM, Shostak M, et al. Clinical implications of imipramine plasma levels for depressive illness. *Arch Gen Psychiatry*. 1977;34(2):197–204. PubMed
47. Murphy E. The prognosis of depression in old age. *Br J Psychiatry*. 1983;142(2):111–119.doi:10.1192/bjp.142.2.111 PubMed
48. Spiker DG, Weiss JC, Dealy RS, et al. The pharmacological treatment of delusional depression. *Am J Psychiatry*. 1985;142(4):430–436. PubMed
49. Mulsant BH, Sweet RA, Rosen J, et al. A double-blind randomized comparison of nortriptyline plus perphenazine versus nortriptyline plus placebo in the treatment of psychotic depression in late life. *J Clin Psychiatry*. 2001;62(8):597–604.doi:10.4088/JCP.v62n0804 PubMed
50. Meyers BS, Flint AJ, Rothschild AJ, et al; STOP-PD Group. A double-blind randomized controlled trial of olanzapine plus sertraline vs olanzapine plus placebo for psychotic depression: the Study of Pharmacotherapy of Psychotic Depression (STOP-PD). *Arch Gen Psychiatry*. 2009;66(8):838–847.doi:10.1001/archgenpsychiatry.2009.79 PubMed
51. Chiarello RJ, Cole JO. The use of psychostimulants in general psychiatry: a reconsideration. *Arch Gen Psychiatry*. 1987;44(3):286–295. PubMed
52. Galynker I, Ieronimo C, Miner C, et al. Methylphenidate treatment of negative symptoms in patients with dementia. *J Neuropsychiatry Clin Neurosci*. 1997;9(2):231–239. PubMed
53. Satel SL, Nelson JC. Stimulants in the treatment of depression: a critical overview. *J Clin Psychiatry*. 1989;50(7):241–249. PubMed
54. Rosenberg PB, Drye LT, Martin BK, et al; DIADS-2 Research Group. Sertraline for the treatment of depression in Alzheimer disease. *Am J Geriatr Psychiatry*. 2010;18(2):136–145.doi:10.1097/JGP.0b013e3181c796eb PubMed
55. Meyers BS. Depression and dementia: comorbidities, identification, and treatment. *J Geriatr Psychiatry Neurol*. 1998;11(4):201–205. PubMed
56. Olin JT, Katz IR, Meyers BS, et al. Provisional diagnostic criteria for depression of Alzheimer disease: rationale and background. *Am J Geriatr Psychiatry*. 2002;10(2):129–141. PubMed
57. Olin JT, Schneider LS, Katz IR, et al. Provisional diagnostic criteria for depression of Alzheimer disease. *Am J Geriatr Psychiatry*. 2002;10(2):125–128. PubMed
58. Alexopoulos GS, Meyers BS, Young RC, et al. Clinically defined vascular depression. *Am J Psychiatry*. 1997;154(4):562–565. PubMed
59. Krishnan KR, Hays JC, Blazer DG. MRI-defined vascular depression. *Am J Psychiatry*. 1997;154(4):497–501. PubMed
60. Kalayam B, Alexopoulos GS. Prefrontal dysfunction and treatment response in geriatric depression. *Arch Gen Psychiatry*. 1999;56(8):713–718. doi:10.1001/archpsyc.56.8.713 PubMed
61. Alexopoulos GS, Meyers BS, Young RC, et al. Executive dysfunction

and long-term outcomes of geriatric depression. *Arch Gen Psychiatry*. 2000;57(3):285–290.doi:10.1001/archpsyc.57.3.285 PubMed
62. Alexopoulos GS, Kiosses DN, Heo M, et al. Executive dysfunction and the course of geriatric depression. *Biol Psychiatry*. 2005;58(3):204–210. doi:10.1016/j.biopsych.2005.04.024 PubMed
63. Alexopoulos GS, Murphy CF, Gunning-Dixon FM, et al. Microstructural white matter abnormalities and remission of geriatric depression. *Am J Psychiatry*. 2008;165(2):238–244.doi:10.1176/appi.ajp.2007.07050744 PubMed
64. Sneed JR, Culang ME, Keilp JG, et al. Antidepressant medication and executive dysfunction: a deleterious interaction in late-life depression. *Am J Geriatr Psychiatry*. 2010;18(2):128–135.doi:10.1097/JGP.0b013e3181c796d2 PubMed
65. Sheline YI, Pieper CF, Barch DM, et al. Support for the vascular depression hypothesis in late-life depression: results of a 2-site, prospective, antidepressant treatment trial. *Arch Gen Psychiatry*. 2010;67(3):277–285. doi:10.1001/archgenpsychiatry.2009.204 PubMed
66. Robinson RG, Lipsey JR, Rao K, et al. Two-year longitudinal study of post-stroke mood disorders: comparison of acute-onset with delayed-onset depression. *Am J Psychiatry*. 1986;143(10):1238–1244. PubMed
67. Glassman AH, Shapiro PA. Depression and the course of coronary artery disease. *Am J Psychiatry*. 1998;155(1):4–11. PubMed
68. Lipsey JR, Robinson RG, Pearlson GD, et al. Nortriptyline treatment of post-stroke depression: a double-blind study. *Lancet*. 1984;1(8372): 297–300.doi:10.1016/S0140-6736(84)90356-8 PubMed
69. Robinson RG, Schultz SK, Castillo C, et al. Nortriptyline versus fluoxetine in the treatment of depression and in short-term recovery after stroke: a placebo-controlled, double-blind study. *Am J Psychiatry*. 2000;157(3):351–359.doi:10.1176/appi.ajp.157.3.351 PubMed
70. Robinson RG, Jorge RE, Moser DJ, et al. Escitalopram and problem-solving therapy for prevention of poststroke depression: a randomized controlled trial. *JAMA*. 2008;299(20):2391–2400.doi:10.1001/jama.299.20.2391 PubMed
71. Jorge RE, Robinson RG, Arndt S, et al. Mortality and poststroke depression: a placebo-controlled trial of antidepressants. *Am J Psychiatry*. 2003;160(10):1823–1829.doi:10.1176/appi.ajp.160.10.1823 PubMed
72. Roose SP, Laghrissi-Thode F, Kennedy JS, et al. Comparison of paroxetine and nortriptyline in depressed patients with ischemic heart disease. *JAMA*. 1998;279(4):287–291.doi:10.1001/jama.279.4.287 PubMed
73. Honigfeld G, Rosenblum MP, Blumenthal IJ, et al. Behavioral improvement in the older schizophrenic patient: drug and social therapies. *J Am Geriatr Soc*. 1965;13:57–72. PubMed
74. Tsuang MM, Lu LM, Stotsky BA, et al. Haloperidol versus thioridazine for hospitalized psychogeriatric patients: double-blind study. *J Am Geriatr Soc*. 1971;19(7):593–600. PubMed
75. Branchey MH, Lee JH, Amin R, et al. High- and low-potency neuroleptics in elderly psychiatric patients. *JAMA*. 1978;239(18):1860–1862. doi:10.1001/jama.239.18.1860 PubMed
76. Salzman C. Geriatric psychopharmacology in the elderly. In: Shader RI, Dimascio A, eds. *Psychotropic Drug Side Effects*. Baltimore, MD: William and Wilkins; 1970:261–279.
77. Davis JM, Fann WE, El-Yossef NK, et al. Clinical problems in treating the aged with psychotropic drugs. In: Eisdoref C, Fann WE, eds. *Psychopharmacology and Aging*. New York, NY: Plenum Press; 1971:41–54.
78. Stotsky B. Psychoactive drugs for geriatric patients with psychiatric disorders. In: Gershon S, Raskin A, eds. *Aging*. Vol. 2. New York, NY: Raven Press; 2010:229–258.
79. Harris MJ, Jeste DV. Late-onset schizophrenia: an overview. *Schizophr Bull*. 1988;14(1):39–55. PubMed
80. Howard R, Rabins PV, Seeman MV, et al; The International Late-Onset Schizophrenia Group. Late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: an international consensus. *Am J Psychiatry*. 2000;157(2):172–178.doi:10.1176/appi.ajp.157.2.172 PubMed
81. Jeste DV, Lacro JP, Gilbert PL, et al. Treatment of late-life schizophrenia with neuroleptics. *Schizophr Bull*. 1993;19(4):817–830. PubMed
82. Caligiuri MR, Jeste DV, Lacro JP. Antipsychotic-induced movement disorders in the elderly: epidemiology and treatment recommendations. *Drugs Aging*. 2000;17(5):363–384.doi:10.2165/00002512-200017050-00004 PubMed
83. Woerner MG, Kane JM, Lieberman JA, et al. The prevalence of tardive dyskinesia. *J Clin Psychopharmacol*. 1991;11(1):34–42.doi:10.1097/00004714-199102000-00005 PubMed
84. Saltz BL, Woerner MG, Kane JM, et al. Prospective study of tardive dyskinesia incidence in the elderly. *JAMA*. 1991;266(17):2402–2406. doi:10.1001/jama.266.17.2402 PubMed
85. Smith JM, Baldessarini RJ. Changes in prevalence, severity, and recovery in tardive dyskinesia with age. *Arch Gen Psychiatry*. 1980;37(12): 1368–1373. PubMed
86. Alvir JM, Lieberman JA, Safferman AZ, et al. Clozapine-induced agranulocytosis: incidence and risk factors in the United States. *N Engl J Med*. 1993;329(3):162–167.doi:10.1056/NEJM199307153290303 PubMed
87. Jeste DV, Barak Y, Madhusoodanan S, et al. International multisite double-blind trial of the atypical antipsychotics risperidone and olanzapine in 175 elderly patients with chronic schizophrenia. *Am J Geriatr Psychiatry*. 2003;11(6):638–647. PubMed
88. Jeste DV, Lacro JP, Bailey A, et al. Lower incidence of tardive dyskinesia with risperidone compared with haloperidol in older patients. *J Am Geriatr Soc*. 1999;47(6):716–719. PubMed
89. Dolder CR, Lacro JP, Dunn LB, et al. Antipsychotic medication adherence: is there a difference between typical and atypical agents? *Am J Psychiatry*. 2002;159(1):103–108.doi:10.1176/appi.ajp.159.1.103 PubMed
90. Dolder CR, Jeste DV. Incidence of tardive dyskinesia with typical versus atypical antipsychotics in very high risk patients. *Biol Psychiatry*. 2003;53(12):1142–1145.doi:10.1016/S0006-3223(03)00170-7 PubMed
91. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. *Diabetes Care*. 2004;27(2):596–601.doi:10.2337/diacare.27.2.596 PubMed
92. Jin H, Meyer JM, Jeste DV. Atypical antipsychotics and glucose dysregulation: a systematic review. *Schizophr Res*. 2004;71(2–3):195–212. doi:10.1016/j.schres.2004.03.024 PubMed
93. Lieberman JA, Stroup TS, McEvoy JP, et al; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353(12):1209–1223.doi:10.1056/NEJMoa051688 PubMed
94. Rabins PV, Mace NL, Lucas MJ. The impact of dementia on the family. *JAMA*. 1982;248(3):333–335.doi:10.1001/jama.248.3.333 PubMed
95. Wragg RE, Jeste DV. Overview of depression and psychosis in Alzheimer's disease. *Am J Psychiatry*. 1989;146(5):577–587. PubMed
96. Cohen-Mansfield J. Agitated behaviors in the elderly: II. Preliminary results in the cognitively deteriorated. *J Am Geriatr Soc*. 1986;34(10):722–727. PubMed
97. Ferris SH, Steinberg G, Shulman E, et al. Institutionalization of Alzheimer's disease patients: reducing precipitating factors through family counseling. *Home Health Care Serv Q*. 1987;8(1):23–51. doi:10.1300/J027v08n01_03 PubMed
98. Victoroff J, Mack WJ, Nielson KA. Psychiatric complications of dementia: impact on caregivers. *Dement Geriatr Cogn Disord*. 1998;9(1):50–55. doi:10.1159/000017022 PubMed
99. Sunderland T, Silver MA. Neuroleptics in the treatment of dementia. *Int J Geriatr Psychiatry*. 1988;3(2):79–88. doi:10.1002/gps.930030203
100. Schneider LS, Pollock VE, Lyness SA. A metaanalysis of controlled trials of neuroleptic treatment in dementia. *J Am Geriatr Soc*. 1990;38(5): 553–563. PubMed
101. Devanand DP, Marder K, Michaels KS, et al. A randomized, placebo-controlled dose-comparison trial of haloperidol for psychosis and disruptive behaviors in Alzheimer's disease. *Am J Psychiatry*. 1998; 155(11):1512–1520. PubMed
102. Ray WA, Griffin MR, Schaffner W, et al. Psychotropic drug use and the risk of hip fracture. *N Engl J Med*. 1987;316(7):363–369.doi:10.1056/NEJM198702123160702 PubMed
103. Ray WA, Federspiel CF, Schaffner W. A study of antipsychotic drug use in nursing homes: epidemiologic evidence suggesting misuse. *Am J Public Health*. 1980;70(5):485–491.doi:10.2105/AJPH.70.5.485 PubMed
104. Katz IR, Jeste DV, Mintzer JE, et al; Risperidone Study Group. Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. *J Clin Psychiatry*. 1999;60(2):107–115. PubMed
105. Street JS, Clark WS, Gannon KS, et al. Olanzapine treatment of psychotic and behavioral disturbances associated with Alzheimer's disease in nursing care facilities: a double-blind, randomzied, placebo-controlled trial. The HGEU Study Group. *Arch Gen Psychiatry*. 2000;57:968–976. PubMed doi:10.1001/archpsyc.57.10.968
106. Schneider LS, Tariot PN, Dagerman KS, et al; CATIE-AD Study Group. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med*. 2006;355(15):1525–1538.doi:10.1056/NEJMoa061240 PubMed
107. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized

placebo-controlled trials. *JAMA*. 2005;294(15):1934–1943.doi:10.1001/jama.294.15.1934 PubMed
108. Rabins PV, Blacker D, Rovner BW, et al; APA Work Group on Alzheimer's Disease and Other Dementias, Steering Committee on Practice Guidelines. American Psychiatric Association Practice Guideline for the Treatment of Patients With Alzheimer's Disease and Other Dementias: Second Edition. *Am J Psychiatry*. 2007;164(suppl):5–56. PubMed
109. Jeste DV, Blazer D, Casey DE, et al. ACNP White Paper: update on use of antipsychotic drugs in elderly persons with dementia. *Neuropsychopharmacology*. 2008;33(5):957–970.doi:10.1038/sj.npp.1301492 PubMed
110. Division of Neuropharmacological Drug Products of FDA Issues Paper. March 9, 2000 Meeting of the Psychopharmacological Drugs Advisory Committee on the various psychiatric and behavioral disturbances associated with dementia. US Food and Drug Administration. http://www.fda.gov/ohrms/dockets/DOCKETS/00n0088/bkg0001.pdf. Accessed September 1, 2010.
111. Jeste DV, Finkel SI. Psychosis of Alzheimer's disease and related dementias: diagnostic criteria for a distinct syndrome. *Am J Geriatr Psychiatry*. 2000;8(1):29–34.doi:10.1097/00019442-200002000-00004 PubMed
112. Hollister LE, Yesavage J. Ergoloid mesylates for senile dementias: unanswered questions. *Ann Intern Med*. 1984;100(6):894–898. PubMed
113. Perry EK, Tomlinson BE, Blessed G, et al. Correlation of cholinergic abnormalities with senile plaques and mental test scores in senile dementia. *BMJ*. 1978;2(6150):1457–1459.doi:10.1136/bmj.2.6150.1457 PubMed
114. Whitehouse PJ, Price DL, Clark AW, et al. Alzheimer disease: evidence for selective loss of cholinergic neurons in the nucleus basalis. *Ann Neurol*. 1981;10(2):122–126.doi:10.1002/ana.410100203 PubMed
115. Coyle JT, Price DL, DeLong MR. Alzheimer's disease: a disorder of cortical cholinergic innervation. *Science*. 1983;219(4589):1184–1190. doi:10.1126/science.6338589 PubMed
116. Bartus RT, Dean RL 3rd, Beer B, et al. The cholinergic hypothesis of geriatric memory dysfunction. *Science*. 1982;217(4558):408–414. doi:10.1126/science.7046051 PubMed
117. Cummings JL. Cholinesterase inhibitors: a new class of psychotropic compounds. *Am J Psychiatry*. 2000;157(1):4–15. PubMed
118. Farlow M. A clinical overview of cholinesterase inhibitors in Alzheimer's disease. *Int Psychogeriatr*. 2002;14(suppl 1):93–126. doi:10.1017/S1041610203008688 PubMed
119. Reisberg B, Doody R, Stöffler A, et al; Memantine Study Group. Memantine in moderate-to-severe Alzheimer's disease. *N Engl J Med*. 2003;348(14):1333–1341.doi:10.1056/NEJMoa013128 PubMed
120. Tariot PN, Farlow MR, Grossberg GT, et al; Memantine Study Group. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. *JAMA*. 2004;291(3):317–324.doi:10.1001/jama.291.3.317 PubMed
121. Shoghi-Jadid K, Small GW, Agdeppa ED, et al. Localization of neurofibrillary tangles and beta-amyloid plaques in the brains of living patients with Alzheimer disease. *Am J Geriatr Psychiatry*. 2002;10(1):24–35. PubMed
122. Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol*. 2004;55(3):306–319.doi:10.1002/ana.20009 PubMed
123. De Meyer G, Shapiro F, Vanderstichele H, et al; Alzheimer's Disease Neuroimaging Initiative. Diagnosis-independent Alzheimer disease biomarker signature in cognitively normal elderly people. *Arch Neurol*. 2010;67(8):949–956.doi:10.1001/archneurol.2010.179 PubMed
124. Cummings JL, Back C. The cholinergic hypothesis of neuropsychiatric symptoms in Alzheimer's disease. *Am J Geriatr Psychiatry*. 1998;6(suppl 1):S64–S78.doi:10.1097/00019442-199821001-00009 PubMed
125. Mega MS, Masterman DM, O'Connor SM, et al. The spectrum of behavioral responses to cholinesterase inhibitor therapy in Alzheimer disease. *Arch Neurol*. 1999;56(11):1388–1393.doi:10.1001/archneur.56.11.1388 PubMed
126. Trinh NH, Hoblyn J, Mohanty S, et al. Efficacy of cholinesterase inhibitors in the treatment of neuropsychiatric symptoms and functional impairment in Alzheimer disease: a meta-analysis. *JAMA*. 2003;289(2):210–216.doi:10.1001/jama.289.2.210 PubMed
127. Cummings JL, Schneider E, Tariot PN, et al; Memantine MEM-MD-02 Study Group. Behavioral effects of memantine in Alzheimer disease patients receiving donepezil treatment. *Neurology*. 2006;67(1):57–63. doi:10.1212/01.wnl.0000223333.42368.f1 PubMed
128. Lipowski ZJ. The need to integrate liaison psychiatry and geropsychiatry. *Am J Psychiatry*. 1983;140(8):1003–1005. PubMed
129. Martin JB. The integration of neurology, psychiatry, and neuroscience in the 21st century. *Am J Psychiatry*. 2002;159(5):695–704.doi:10.1176/appi.ajp.159.5.695 PubMed
130. Yudofsky SC, Hales RE. Neuropsychiatry and the future of psychiatry and neurology. *Am J Psychiatry.* 2002;159(8):1261–1264. doi:10.1176/appi.ajp.159.8.1261 PubMed

Past and Present Progress in the Pharmacologic Treatment of Schizophrenia

John M. Kane, MD, and Christoph U. Correll, MD

Despite treatment advances over the past decades, schizophrenia remains one of the most severe psychiatric disorders that is associated with a chronic relapsing course and marked functional impairment in a substantial proportion of patients. In this article, a historical overview of the pharmacologic advances in the treatment of schizophrenia over the past 50 years is presented. This is followed by a review of the current developments in optimizing the treatment and outcomes in patients with schizophrenia. Methodological challenges, potential solutions, and areas of particular need for further research are highlighted. Although treatment goals of response, remission, and recovery have been defined more uniformly, a good "effectiveness" measure mapping onto functional outcomes is still lacking. Moreover, the field must advance in transferring measurement-based approaches from research to clinical practice. There is an ongoing debate regarding whether and which first- or second-generation antipsychotics should be used. However, especially when considering individual adverse effect profiles, the differentiation into first- and second-generation antipsychotics as unified classes cannot be upheld, and a more differentiated view and treatment selection are required. The desired, individualized treatment approach needs to consider current symptoms, comorbid conditions, past therapeutic response, and adverse effects, as well as patient choice and expectations. Acute and long-term goals and effects of medication treatment should be balanced. To date, clozapine is the only evidence-based treatment for refractory patients, and the role of antipsychotic polypharmacy and other augmentation strategies remains unclear, at best. To discover novel treatments with enhanced/broader efficacy and improved tolerability, and to enable personalized treatment, the mechanisms underlying illness development and progression, symptomatic improvement, and side effect development need to be elucidated.

J Clin Psychiatry 2010;71(9):1115–1124

Submitted: *May 20, 2010; accepted July 9, 2010 (doi:10.4088/JCP.10r06264yel).*
Corresponding author: *John M. Kane, MD, Zucker Hillside Hospital, 75-59 263rd St, Glen Oaks, NY 11004 (psychiatry@lij.edu).*

This article is part of a series honoring the 50th anniversary of the NCDEU Annual Meeting. This meeting has fostered, facilitated, documented, and disseminated a vast growth in our knowledge of clinical psychopharmacology and our ability to apply that knowledge to improving the lives of millions of people. We will try to put some of the historical development in the context of present challenges and future needs and opportunities.

EARLY BEGINNINGS AND THE ROLE OF THE EARLY CLINICAL DRUG EVALUATION UNITS

When the first meeting of the Early Clinical Drug Evaluation Units (later, the *New* Clinical Drug Evaluation Unit [NCDEU]) took place in 1959, it had been approximately 5 years since the introduction of chlorpromazine in the United States, and clinical trial methodology was in its formative stages.

In 1952, a French surgeon was exploring strategies to reduce surgical shock. He thought that antihistamines might be an effective approach. He noticed, however, that an antihistamine that he was using, chlorpromazine, had a powerful effect on mental state. A psychiatrist, Pierre Deniker, heard about these observations and decided to try chlorpromazine in some of his most difficult-to-manage patients. The results were remarkable. After some reluctance on the part of academic psychiatrists and psychologists in the United States to support testing of the drug, its value was demonstrated among patients in state institutions, and ultimately chlorpromazine was approved by the US Food and Drug Administration (FDA) in 1954. By 1964, approximately 50 million people around the world had been treated with this medication, and a revolution in the management of psychotic disorders was underway.

The somewhat serendipitous observation that chlorpromazine had pronounced "calming" activity even in individuals with psychotic signs and symptoms was one of the great advances in 20th century medicine. Although other drugs (eg, reserpine) had been used with some success to treat psychosis,[1] the safety index and overall effectiveness of chlorpromazine, and subsequently other dopamine receptor antagonists, radically changed our ability to treat schizophrenia and other psychotic disorders on a wide scale.

The pace of new discoveries regarding effective psychotropic medications in the 1950s and 1960s was staggering. At the same time, tension remained between the psychodynamic and biologic perspectives regarding the etiology and treatment of the major psychiatric illnesses. Considerable efforts were made to study the impact of psychotropic drugs, and increasingly sophisticated methodologies were brought to bear as clinical trials in medicine underwent rapid development.

In 1949, the World Health Organization published the sixth revision of the *International Statistical Classification of Diseases* (*ICD*), which for the first time included a section on

mental disorders.[2] The first official *Diagnostic and Statistical Manual of Mental Disorders* was published in 1952 by the American Psychiatric Association (APA).[3] Diagnostic criteria were not really specified for discrete disorders until the third edition of *DSM*,[4] which attempted to improve the validity and reliability of psychiatric diagnosis. This, in turn, had enormous implications for clinical practice, clinical research, and drug development.

The ECDEU, which were established by the National Institute of Mental Health (NIMH), served as unique platforms for clinical investigation. They were designed to provide stable funding for investigators studying new drugs. The Psychopharmacology Research Branch, which provided funding and guidance for these units, played a critical role in the advancement of the field.

An example of a seminal contribution by Jerry Levine, William Petrie, and Nina Schooler of NIMH, with colleagues from the Biometric Laboratory at George Washington University, was the first publication of the *ECDEU Assessment Manual for Psychopharmacology* in 1976.[5] The development and testing of assessment instruments that could be demonstrated to be both valid and reliable for the measurement of therapeutic effects on a variety of disease categories was a major advance.

A NEW ERA OF EVIDENCE-BASED PSYCHOPHARMACOLOGY AND THE ROLE OF THE NIMH PSYCHOPHARMACOLOGY SERVICE CENTER

In 1969, Donald Klein and John Davis published a seminal work entitled *Diagnosis and Drug Treatment of Psychiatric Disorders*.[6] In the introduction, they wrote,

> This simple dichotomy between medical and nonmedical practitioners does less than justice to the complicated therapeutic scene. The medical practitioners are divided largely into 2 polar camps: the analytical and psychological versus the organic and directive. The first group developed an ideology that rejects the use of organic treatments and directive methods as usually ineffective, symptomatic at best, and destructive of the growth potential of the patient by fostering pathological dependence. This stand was reinforced by the obvious ineffectiveness of most organic therapies, complicated by the addictive potential and social incapacitation often produced by sedative agents. The directive and organic group, on the other hand, emphasized short-term manipulative and symptom-relieving procedures, deriding or ignoring concern with the resolution of intrapsychic conflict and patient maturity. Unfortunately, the positive contributions of both groups were obscured by their respective biophobic and psychophobic attitudes. One might speculate that the fierce adherence of each group to its methods in the face of the remarkable lack of systematic comparative studies attests to a profound insecurity as to the value of one's procedures, dealt with by a compensatory evangelism.
>
> We may be fortunate to be entering a period in which rational comparative study will become standard for therapeutic decision. Although clinical hunches and results of clinical experience are important factors in the termination of proper treatment, the findings of research studies, particularly those which are done with controlled double-blind technique, provide the behavioral scientific data for informed decision. Also important is the evidence available on the interaction of the somatic therapies with other treatment forms, such as psychological and social therapies. This book is an initial effort to organize and present such material to the psychiatric practitioner for his critical review.

With the establishment of The National Institute of Mental Health Psychopharmacology Service Center, a series of cooperative studies led by Jonathan Cole was conducted.[7] They included both private and public hospitals and initially compared chlorpromazine, fluphenazine, and thioridazine with placebo. All 3 drugs were found to be equally effective and more efficacious than placebo. A second NIMH Cooperative Study[8] compared chlorpromazine, acetophenazine, and fluphenazine. No specific drug showed a consistent pattern of superiority across the 57 dependent variables that were assessed.

By 1969, when Klein and Davis published their review,[6] they identified 126 controlled studies comparing antipsychotic drugs and placebo in which the medications were found to be more effective and 26 comparisons in which they were not. The authors also examined the role of dose adequacy and found that most of those studies that found chlorpromazine to be ineffective used very small doses, and all 23 studies that employed doses over 500 mg were positive. Similarly, in all studies, which were judged to be methodologically rigorous, the phenothiazine derivatives (and reserpine) were shown to be more effective than controls.

NEUROMOTOR SIDE EFFECT CONCERN

Shortly after the introduction of the phenothiazines, concerns about adverse neurologic effects—first "parkinsonism" and subsequently tardive dyskinesia—took on considerable saliency. Theories as to minimum effective dosage utilized subtle parkinsonism as a measure of adequate dosing.[9] However, both the frequency and potential functional consequences (including attendant stigma) associated with adverse neurologic effects became an important focus of attention.[10–12] Given the frequency of extrapyramidal symptoms (EPS) and likelihood of underdiagnosis,[13–15] debate ensued as to whether the use of prophylactic antiparkinsonian medication should be routinely recommended. At the same time, antiparkinsonian agents were associated with their own burden of adverse effects.

In the 1980s, the concern about tardive dyskinesia became even more intense with increasing medicolegal issues and the publication of 2 APA Task Force Reports.[16,17] Ultimately, prospective studies began to clarify both the incidence of and risk factors for tardive dyskinesia. The incidence was generally found to be 5% per year of cumulative antipsychotic drug

exposure with first-generation antipsychotics.[18,19] Increasing age, particularly the postmenopausal phase in women, was associated with higher risk, as was vulnerability to early occurring extrapyramidal side effects.[20]

ANTIPSYCHOTIC DOSE FINDING AND BLOOD LEVELS IN FLUX

Phases in dosage recommendations also ensued over the coming decades with trials of very high doses[21] and trials of very low doses,[22] with, as usual, mixed results. In general, however, once blood levels of psychotropic drugs became widely available, it became apparent that very high doses provided no added value for the average patient and that measuring blood drug levels might help to some degree in explaining the heterogeneity of response.[23] Measurement of blood drug levels never really caught on in routine clinical practice, and even now they play much less of a role in research than they did in the 1980s (for reasons that are not entirely clear). The identification of dopamine as a key neurotransmitter in the mechanism of action of antipsychotic drugs and the discovery of various dopamine receptors in specific brain regions led to renewed enthusiasm about finding more "rational" pharmacologic agents and again setting the stage for further progress in understanding dosage requirements and heterogeneity of response. A number of studies emphasized the feasibility of utilizing substantially lower doses in the maintenance phase of treatment than had been commonly employed.[24,25] Interestingly, the most informative studies examining dose-response relationships in maintenance treatment and relapse prevention utilized long-acting injectable formulations. This was particularly important in eliminating the potential confound of poor or partial adherence with dosing requirements.[22] Although these studies emphasized the feasibility of utilizing lower than customary doses, they also established thresholds below which relapse rates increased substantially.

Concerns regarding dose-response (and dose-tolerability) relationships were also an important focus in evaluating comparative data between first- and second-generation antipsychotics. Although some reviews and meta-analyses had suggested that some of the apparent superiority of second- versus first-generation antipsychotics was due to unnecessarily high dosages of first-generation medications,[26] other reviews have not supported this conclusion.[27,28] It has been shown that even low doses of haloperidol, ie, 4 mg/d, in the acute treatment of chronic patients are associated with a significant risk of EPS.[29] Moreover, in 2 recent first-episode studies, haloperidol treatment of 3 mg/d was associated with significantly greater relapse rates[30] or all-cause discontinuation rates[31] than the second-generation comparators.

MAINTENANCE TREATMENT AND RELAPSE PREVENTION

In the late 1950s,[32,33] investigators began to systematically examine the consequences of controlled phenothiazine withdrawal. It became increasingly apparent that patients receiving placebo experienced significantly higher rates of rehospitalization than patients continuing to receive medication.[34]

By 1969, Klein and Davis were already recommending that "all patients who have an acute schizophrenic psychosis should be maintained on phenothiazine, possibly with an adjunctive antidepressant, indefinitely."[6(p160)] However, others did not share this view, and it took many years to establish a consensus as to the need for maintenance treatment, particularly in the early phases of a schizophrenia illness.

The increasing concern about tardive dyskinesia in the 1980s led to a reevaluation of the overall benefit-to-risk ratio of maintenance or relapse prevention treatment. There were renewed efforts to establish minimum effective dosage and/or the value of "intermittent" or "targeted" treatment, all of which were intended to reduce cumulative medication exposure, with the hope of reducing the incidence of tardive dyskinesia. These results helped to further clarify the need for continuous maintenance treatment for the average patient and confirmed a threshold of drug activity that was necessary to prevent or delay relapse.[35]

ADDRESSING NONADHERENCE

In the 1970s, long-acting injectable fluphenazine enanthate and fluphenazine decanoate were approved. Fluphenazine decanoate ultimately became the more widely used agent because of better tolerability.[36] This provided a strategy to help patients overcome the challenges of consistent medication-taking in the face of a complex illness often resulting in poor insight and impaired cognitive functioning.[37,38] Despite the promise of this approach, the use of long-acting injectable medications never became as popular in the United States as it did in many other countries. However, the current availability of more and newer agents in long-acting formulations[39] in combination with ever increasing needs to control the costs associated with relapse and rehospitalization might yet impact utilization rates.

TREATMENT-REFRACTORY ILLNESS AND CLOZAPINE

With the development and testin g of clozapine in Europe, early observations suggested a novel compound had been developed with a qualitatively different clinical profile. Most clinicians were impressed with the relative absence of drug-induced extrapyramidal effects, although some debate arose as to the incidence of akathisia. In addition, early observations indicated the potential of clozapine to have some therapeutic benefit among patients who had failed to respond to other agents. At the same time, a series of cases of agranulocytosis associated with clozapine were reported in Finland and elsewhere.[40] This led to a delay in the further development of clozapine in the United States. However, once a large clinical trial was conducted demonstrating the clear superiority of clozapine over chlorpromazine in treatment-

refractory schizophrenia patients,[41] the benefit-to-risk ratio (with the requirement for weekly blood monitoring) was felt to be sufficient to justify FDA approval with the narrow indication for treatment-resistant patients in 1990. Since then, the singular role of clozapine in treatment-refractory patients with schizophrenia has been confirmed.[42]

To some extent, clozapine served as a prototype and a stimulus for the development of other new drugs with the receptor-binding profiles that might replicate clozapine's unique clinical attributes. This created a number of challenges, particularly in various domains of drug development as well as in clinical design and methodology. It might be said that a major focus of work in the past decade has been to clarify the extent to which any, some, or all of the second-generation (sometimes referred to as *atypical*, a term that we believe has outlived its usefulness) medications are superior to any, some, or all of the first-generation antipsychotics.

In this context, a reemphasis on the study of dose-response relationships and dose equivalency between drugs has occurred,[43] as did a partial reevaluation of the public health importance of drug-induced parkinsonism and tardive dyskinesia.[44]

ATTENTION TO FIRST-EPISODE SCHIZOPHRENIA

Beginning in the mid 1980s, the field started to focus on patients with a first episode of schizophrenia.[45] The increased attention on first-episode patients seemed warranted in order to evaluate treatment outcomes that were not confounded by the effects of prior treatment, multiple relapses, and chronic illness. Studies revealed cognitive and psychosocial deficits that were present at illness onset,[46] a long duration of untreated psychosis prior to first mental health contact and treatment,[47] and increased sensitivity to medication side effects,[48] but also a better treatment response compared to more chronically ill patients.[49] These results, representing a mixture of putative pathophysiologic processes and environmental effects, were greeted with efforts to shorten the duration of untreated psychosis through outreach, which has been associated with some degree of improved outcomes.[50]

However, despite interventions during the first episode of schizophrenia, the overwhelming majority of patients was found to relapse in the subsequent years,[51] with medication discontinuation significantly increasing risk, and the achievement of at least 2 years of concurrent symptomatic and psychosocial recovery has remained as low as 15%.[52] The documented low recovery rates revitalized efforts at testing an integrated, personalized, and evidence-based psychopharmacologic and psychosocial intervention package against treatment as usual in first-episode patients in 2 parallel NIMH-funded Recovery After an Initial Schizophrenia Episode (RAISE) projects (http://www.nimh.nih.gov/health/topics/schizophrenia/raise/index.shtml) to evaluate if the functional outcome trajectory can be modified early in the illness phase. In addition, as part of the move toward the early treatment of schizophrenia, and the response to new FDA incentives, the efficacy of antipsychotics has also been tested and validated in recent years in a series of placebo-controlled studies in adolescents with schizophrenia.[53]

THE PRODROME TO SCHIZOPHRENIA: EARLY RECOGNITION AND PREVENTION EFFORTS

Stimulated by first-episode research and the related recognition of a symptomatic, "prodromal" phase preceding the first full psychotic episode, early identification and intervention even during the prepsychotic illness phase became an area of increasing research attention beginning in the 1990s. The development of specific assessment tools and delineation of criteria for individuals considered at clinical high risk for psychosis[54,55] were followed by the examination of conversion rates in at-risk cohorts followed naturalistically. However, despite initially encouraging results concerning the predictive validity of the psychosis risk syndrome criteria, recent studies have reported declining conversion rates,[56] highlighting the need for further investigations. Throughout a series of mostly small, randomized, controlled studies, several pharmacologic and nonpharmacologic interventions, involving omega-3 fatty acids, second-generation antipsychotics, and cognitive-behavioral therapy, have been found to delay or prevent the onset of psychosis, at least as long as the active treatment was provided.[57] However, recent discussions of potentially including the psychosis risk syndrome in *DSM-V* have been met with criticism for fear of a high rate of false-positives; an overmedicalization of ill-defined and nonspecific psychopathology; insufficient time and training in clinical settings to utilize complex, research-based instruments for the identification of high-risk individuals; and the resultant risk of stigma and the unnecessary use of treatments with a potential for significant long-term side effects.[57]

COMPARATIVE EFFICACY AND EFFECTIVENESS OF FIRST-GENERATION AND SECOND-GENERATION ANTIPSYCHOTICS

With the introduction of second-generation antipsychotics, findings of lower EPS burden and tardive dyskinesia risk were coupled with expectations of superior efficacy for positive, negative, and cognitive symptoms. Initial efficacy studies seemed to confirm the superiority of second-generation antipsychotics, but the comparator consisted predominantly of haloperidol, used at moderate to high doses and often without anticholinergic cotreatment, which made early treatment discontinuation and secondary negative symptom presentations more likely in haloperidol-treated patients. Since then, a series of acute phase and longer-term studies have been completed, including large efficacy-effectiveness hybrid trials[31,58–60] that compared first- and second-generation antipsychotics. These data have been evaluated and interpreted in a number of different ways. Interpretations include that

© Copyright 2011 Physicians Postgraduate Press, Inc.

there is no difference between first- and second-generation antipsychotics, that second-generation antipsychotics are superior to first-generation antipsychotics, that some second-generation antipsychotics are superior to either all or some first-generation antipsychotics, in general, or in certain efficacy and/or side effect domains, or in patient subgroups that are not yet easily identified prior to choosing a specific agent. Because such a number of divergent interpretations have been offered, this indicates that blanket statements do not do justice to the complex clinical situation and database.

Taken together, the evidence seems to suggest that in refractory patients, clozapine is superior to first-generation antipsychotics[61–63] and second-generation antipsychotics (although the latter was hardly confirmed by a recent meta-analysis,[64] which was attributed to inappropriately low clozapine doses). Compared to first-generation antipsychotics, only 3 second-generation antipsychotics (amisulpride, olanzapine, and risperidone) were superior based on Positive and Negative Syndrome Scale (PANSS) score change differences,[61] but these were also the medications studied at a time when first-generation antipsychotics predominated, whereas the newer second-generation antipsychotics were tested mostly at a time of predominant second-generation antipsychotic use. While this could have introduced a cohort sampling bias, the differences between nonclozapine antipsychotics were very modest, with effect sizes as low as 0.1 to 0.3. Similarly, differences between second-generation antipsychotics studied head-to-head were either nonexistent or also marginal, favoring in some comparisons risperidone (vs quetiapine and ziprasidone) or olanzapine (vs aripiprazole, quetiapine, risperidone, and ziprasidone), with the same low effect size difference of only 0.1 to 0.3.[59–61] Moreover, the differences between second-generation antipsychotics were even more restricted when not analyzing mean total PANSS score differences, but analyzing discontinuation of medication due to inefficacy.[61] Thus, differences in design, including active or placebo control, dosing, and sponsorship,[65–67] may have a greater impact on efficacy outcomes than the actual choice of nonclozapine antipsychotics.

The CATIE [Clinical Antipsychotic Trials of Intervention Effectiveness] and CUtLASS [Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study] studies seemed to suggest that there are generally no differences between second-generation antipsychotics and first-generation antipsychotics in all-cause discontinuation, especially when analyzing quality of life[60] and patients who had switched antipsychotics.[68] However, these conclusions have been challenged on the basis of insufficient sample sizes to make noninferiority claims.[69] Moreover, in first-episode samples, all-cause discontinuation rates and relapse rates were significantly higher at 1 and 2 years, respectively, with modestly dosed haloperidol compared to the respective second-generation antipsychotic comparators.[31] Even in chronically ill samples, relapse rates were also significantly higher in first-generation antipsychotics, although haloperidol doses were higher than currently recommended.[70]

The clinical effectiveness of first-generation antipsychotics, a measure of objective and subjective outcomes encompassing symptom-based and functional effects, is challenged by increased acute[71] and chronic[72] extrapyramidal side effects and related symptoms of dysphoria, compared to second-generation (atypical) antipsychotics. Even though at chlorpromazine equivalents below 600 mg/d there was no increased EPS rate with typical versus atypical antipsychotics, at those doses, the efficacy of second-generation antipsychotics was superior.[27] Furthermore, while masking of EPS can be achieved with prophylactic anticholinergic treatment,[58] the risk of tardive dyskinesia is not reduced, but rather potentially increased,[72] and recent data suggest that anticholinergic medication load is associated with decreased efficacy of cognitive remediation treatment.[73]

Ultimately, we feel that the controversy regarding the most likely oversimplified dichotomy between first- and second-generation antipsychotics has resulted in progress, in that it stimulated the conduct of large trials and examination of effectiveness outcomes beyond symptom reduction. These trials have generated new and important data, but also highlighted methodological challenges. These challenges include the definition of clinically meaningful endpoints, the effect of baseline medication and past treatment history, the limitation of available treatments used at a more chronic illness phase, and the importance of differences in acute and long-term adverse effects. All of these data point to the need for new treatments with novel mechanisms, tailored approaches that map onto the pathophysiology of the disease process (that may vary between patients and between different illness stages), and biologic dissection of patients into meaningful subgroups that can inform a stratified or, even, individualized treatment selection.

SHIFTING ADVERSE EVENT FOCUS TO PHYSICAL HEALTH

Over the last decade and coinciding with the predominant use of second-generation antipsychotics, there has been a shift in side effect concerns from parkinsonism and tardive dyskinesia to physical health risks and outcomes.[74–76] The relevance of antipsychotic-related weight gain was highlighted by data suggesting that severely mentally ill patients die on average 25 years earlier than the general population, and that this is predominantly due to premature cardiovascular and cerebrovascular mortality,[77] both of which are related to weight gain, obesity, and associated metabolic abnormalities. Reasons for the increased prevalence of the cardiovascular risk factors, morbidity, and mortality in the mentally ill are complex, but include effects of the psychiatric illness and poor lifestyle behaviors, but also weight gain and metabolic abnormalities conferred by psychiatric treatments, particularly second-generation antipsychotics. For a while, the discussion seemed to focus on having to decide between a higher risk for EPS and tardive dyskinesia with first-generation antipsychotics and a greater risk for weight gain

and long-term cardiometabolic consequences with second-generation antipsychotics. Increasingly, however, the field has been moving to a more differentiated view, recognizing that neither second- nor first-generation antipsychotics are homogeneous classes regarding adverse effect risk. Thus, although clozapine and olanzapine, 2 second-generation antipsychotics, are among the most weight gain–producing and metabolically problematic antipsychotics, the low-potency first-generation antipsychotic chlorpromazine is also associated with considerable adverse cardiometabolic effects.[78] Furthermore, high- and mid-potency first-generation antipsychotics most likely have a similar cardiometabolic risk potential as low-risk second-generation antipsychotics, such as aripiprazole and ziprasidone, yet, in treatment-naive and first-episode patients, all antipsychotics, even those considered more neutral in chronic patients, are associated with considerable weight gain.[79–81]

As a result of the antipsychotic-related cardiometabolic effects, the traditional role of psychiatrists as health care providers who have little to do with the somatic well being of their patients has been challenged. The redefinition of the psychotropic medication prescriber and psychiatric health care provider as at least an orchestrator/facilitator of integrated medical care and as the focal point of health care monitoring in patients receiving medications with cardiometabolic impact is still in process.[82] Despite the warning of the FDA in 2003 about the diabetes risk associated with antipsychotics, which was shortly followed by monitoring guidelines for weight, blood pressure, and fasting glucose and lipids in antipsychotic-treated patients,[83] a series of recent database and audit studies confirmed a concerning low rate of metabolic monitoring that in one study was similar to the background monitoring in a nonpsychiatric control population prescribed albuterol.[84,85] In addition to insufficient monitoring, several studies have shown that mentally ill patients receive substandard medical care targeting coronary heart disease risk factors in psychiatric settings[86–88] and addressing diabetes or myocardial infarction in medical settings.[89,90] While patient nonadherence with medical appointments and interventions might contribute to this problem, the field needs to effectively address the suboptimal monitoring and management behaviors of mental and medical health care providers, as well as systems issues of fragmented care and poor access to care.

RAISING THE BAR FOR OUTCOMES

In addition to a broadened focus on physical health, outcomes other than symptomatic improvement have become standard in the field. These include more standardized approaches to measuring response, remission, and recovery.[91–94] In addition, subjective well-being[95,96] and quality of life,[54] cognition,[97–99] and psychosocial performance, including employment,[100–102] have become endpoints of interest and goals for patients, families, clinicians, and researchers. To move toward these important goals, it has become clear that the field needs to study and engage in the routine application of measurement-based psychiatry, clinical and shared decision-making, psychoeducation, and adherence management, as well as in the integration of rational psychosocial treatment elements in the often too one-sided pharmacologic treatment planning.[103]

TARGETING INDIVIDUALIZED TREATMENT

Individualized treatment based on reliable probabilities of outcome for a specific patient is an important treatment goal. Unfortunately, this goal is still largely out of reach, due to the heterogeneity of patients and treatment response, most likely related to mostly unknown genetic, structural, and functional physiologic differences between patients and within patients over time. Efforts at increasing the predictability of outcomes have included clinically driven nosologic and phenomenological approaches, but these have not really succeeded. Current approaches that do not yet have clinical applicability include the use of genetics, neuroimaging, neurocognition, and blood- or tissue-based biomarkers and sets of biomarkers, also called *biosignatures*.[104,105] Similarly, developments are underway to define biomarkers as surrogate endpoints in drug development and approval.[106]

However, there is a powerful clinical tool that uses the patients' own response pattern to predict outcomes. This intraindividual test of early response/nonresponse as a predictor of subsequent response[107,108] or of dysphoric response[109] was studied briefly in the 1980s. As much as 15 to 20 years later, these findings have been revisited and expanded upon, stimulated by analyses showing that, at least at a group level, the majority of antipsychotic response occurs within the first few weeks[110,111] and, even, days[112] after antipsychotic initiation. Building on these findings, a series of post hoc analyses[113–117] plus a recent prospective study[118] showed that nonresponse at study endpoint can be predicted with high sensitivity, specificity, and predictive power by presence of less than a minimal response equivalent to less than 20% reduction in the PANSS[119] or Brief Psychiatric Rating Scale[120] total score at 2 weeks after antipsychotic initiation. However, having identified this general response pattern, questions remain as to whether response patterns are similar in likely more heterogeneous first-episode schizophrenia samples and in treatment-refractory patients, whether a limited set of specific symptom items that could be used in clinical practice is equally valid and reliable, what one can learn from symptom trajectories at an individual patient level, and what alternative treatments are likely to be more successful after early nonresponse has been identified.

CHALLENGES, UNMET NEEDS, AND FUTURE DIRECTIONS

A number of unmet needs and challenges exist in schizophrenia. These include methodological and practical problems, such as the decreasing ability to separate

© Copyright 2011 Physicians Postgraduate Press, Inc.

medication effects from placebo, with resultant high rates of "failed" trials and/or the need to increase sample sizes. Unmet needs also include areas of psychopathology that are insufficiently impacted with currently available treatments, such as negative symptoms and cognitive dysfunction, as well as problems with adherence to treatment guidelines and the adoption of best clinical practices, for example by the routine adoption of measurement-based treatment strategies. More work is also needed regarding the conduct of sufficiently large or long-term comparative effectiveness studies; the identification of simple, meaningful, and measurable effectiveness outcome measures; and the best ways to translate evidence into clinical practice. All of these areas seem to be amenable to incremental steps of improvement.

However, to qualitatively change outcomes in schizophrenia, there is a need for the detection of valid biomarkers and biosignatures that map onto the underlying pathophysiology of the disease. In this context, the discovery of mechanisms and predictors of efficacy and tolerability is required to guide the rational treatment selection. Our increasing technological sophistication makes biomarker studies more feasible in an age when clinical classification might be replaced by genomic, proteomic, or metabolomic approaches, to name but a few. The resultant developments are expected to greatly facilitate the much needed discovery of mechanistically novel treatments that either work in a complementary way, enabling also rational combination treatments, or are particularly effective for specific symptom domains and readily separable subgroups of patients. The resultant new treatments will hopefully speed up or increase the magnitude of symptom reduction across all relevant domains of schizophrenia, enhance relapse prevention, and bolster efficacy for nonresponders and currently refractory patients, while reducing the likelihood of developing key adverse effects. Finally, the primary or secondary prevention of psychosis is an important goal that will depend, in part, on uncovering mechanisms underlying the susceptibility for and progression toward psychosis, so that neuroprotective and low-risk agents can be investigated in samples that can be characterized as being at true risk for psychosis in a highly reliable way.[49]

To discuss the specific agents under development for these various treatment targets is beyond the scope of this review, but compounds are being explored with a variety of putative mechanisms of action. These include metabotropic glutamate agonists, α-nicotinic receptor agonists, muscarinic agonists, histamine-3 receptor antagonists, glycine transporter inhibitors, ampakines, phosphodiesterase-10 inhibitors, D_1 agonists, D_3 antagonists, 5-HT_{2A} antagonists, and partial dopamine agonists, among others.[121–124]

SUMMARY AND CONCLUSION

In summary, building on more than 5 decades of pharmacotherapy research and clinical practice in schizophrenia, in which the ECDEU and NCDEU played a major role, the field has finally entered a phase that promises to develop and test the necessary tools that will enable more targeted and, ultimately, individualized treatment approaches. The hope is that a more detailed mechanistic understanding of the factors involved in the development, progression, and amelioration of the disease process will give rise to a number of new treatment approaches and that the focus will shift from symptomatic to disease-modifying and, ideally, curative interventions. Being in the midst of these developments, it is important to realize how far we have come, what role the prior advancements have played in our current state of knowledge, and what still needs to be accomplished to further improve the outcome of patients suffering from schizophrenia.

Drug names: albuterol (Proventil and others), aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), olanzapine (Zyprexa), quetiapine (Seroquel), reserpine (Serpalan and others), risperidone (Risperdal and others), ziprasidone (Geodon).

Author affiliations: The Zucker Hillside Hospital, North Shore—Long Island Jewish Health System, Glen Oaks, New York; and Albert Einstein College of Medicine, Bronx, New York.

Potential conflicts of interest: **Dr Kane** has been a consultant to AstraZeneca, Boehringer Ingelheim, Cephalon, Dainippon Sumitomo, Eisai, Lundbeck, Johnson & Johnson, Merck, Myriad, Novartis, Wyeth, Janssen, Pfizer, Eli Lilly, Bristol-Myers Squibb, Otsuka, Vanda, Proteus, Takeda, Targacept, Intracellular Therapeutics, and Rules Based Medicine; has received honoraria for lectures from Otsuka, Eli Lilly, Bristol-Myers Squibb, and Janssen; and is a stock shareholder in MedAvante. **Dr Correll** has been a consultant and/or advisor to Actelion, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, Janssen/Johnson & Johnson, GlaxoSmithKline, Hoffmann-La Roche, Medicure, Otsuka, Pfizer, Schering-Plough, Supernus, Takeda, and Vanda and has received honoraria from Boehringer-Ingelheim, GlaxoSmithKline, Lundbeck, Ortho-McNeil, and Janssen.

Funding/support: Supported by the Zucker Hillside Hospital Advanced Center for Intervention and Services Research for the Study of Schizophrenia (MH074543-01) from the National Institute of Mental Health, Bethesda, Maryland.

REFERENCES

1. Armitage SG, Greenberg PD, Olsen AL, et al. The effects of reserpine on schizophrenic patients. *AMA Arch Neurol Psychiatry*. 1956;76(2):198–204. PubMed
2. World Health Organization. *International Statistical Classification of Diseases, Injuries, and Causes of Death. Sixth Revision.* Geneva, Switzerland: World Health Organization; 1949.
3. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Washington, DC: American Psychiatric Association; 1952.
4. American Psychiatric Association. Committee on Nomenclature and Statistics. *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition. Washington, DC: American Psychiatric Association; 1980.
5. Guy W. *ECDEU Assessment Manual for Psychopharmacology*. Department of Health, Education, and Welfare publication (ADM) 76-388. Rockville, MD: National Institute of Mental Health; 1976.
6. Klein DF, Davis JM. *Diagnosis and Drug Treatment of Psychiatric Disorders*. Baltimore, MD: The Williams & Wilkins Company; 1969.
7. Guttmacher MS. Phenothiazine treatment in acute schizophrenia; effectiveness: National Institute of Mental Health Psychopharmacology Service Center Collaborative Study Group. *Arch Gen Psychiatry*. 1964;10(3):246–261. PubMed
8. Clinical effects of three phenothiazines in "acute" schizophrenia. Publication Rep No 6. Bethesda, MD: US Public Health Service; 1966.
9. Haase HJ. Occurrence and interpretation of psychomotor parkinsonism in megaphen or largactil prolonged therapy. *Nervenarzt*. 1954;25(12):486–492. PubMed
10. Van Putten T. Why do schizophrenic patients refuse to take their drugs? *Arch Gen Psychiatry*. 1974;31(1):67–72. PubMed
11. Van Putten T, Mutalipassi LR, Malkin MD. Phenothiazine-induced

decompensation. *Arch Gen Psychiatry*. 1974;30(1):102–105. PubMed
12. Van Putten T. The many faces of akathisia. *Compr Psychiatry*. 1975;16(1):43–47.doi:10.1016/0010-440X(75)90019-X PubMed
13. Rifkin A, Quitkin F, Klein DF. Akinesia: a poorly recognized drug-induced extrapyramidal behavioral disorder. *Arch Gen Psychiatry*. 1975;32(5):672–674.
14. Rifkin A. The risks of long-term neuroleptic treatment of schizophrenia: especially depression and akinesia. *Acta Psychiatr Scand Suppl*. 1981;63(S291):129–136.doi:10.1111/j.1600-0447.1981.tb02465.x PubMed
15. Rifkin A, Quitkin F, Kane JM, et al. Are prophylactic antiparkinson drugs necessary? a controlled study of procyclidine withdrawal. *Arch Gen Psychiatry*. 1978;35(4):483–489. PubMed
16. Baldessarini RJ, Cole JO, Davis JM, et al. Tardive dyskinesia: summary of a task force report of the American Psychiatric Association. *Am J Psychiatry*. 1980;137(10):1163–1172.
17. Kane JM, Jeste DV, Barnes TRE, et al. *American Psychiatric Association Task Force Report on Tardive Dyskinesia*. Washington, DC: American Psychiatric Press; 1992.
18. Kane JM, Woerner M, Weinhold P, et al. A prospective study of tardive dyskinesia development: preliminary results. *J Clin Psychopharmacol*. 1982;2(5):345–349.doi:10.1097/00004714-198210000-00012 PubMed
19. Morgenstern H, Glazer WM. Identifying risk factors for tardive dyskinesia among long-term outpatients maintained with neuroleptic medications: results of the Yale Tardive Dyskinesia Study. *Arch Gen Psychiatry*. 1993;50(9):723–733. PubMed
20. Kane JM, Smith JM. Tardive dyskinesia: prevalence and risk factors, 1959 to 1979. *Arch Gen Psychiatry*. 1982;39(4):473–481. PubMed
21. Quitkin F, Rifkin A, Klein DF. Very high dosage vs standard dosage fluphenazine in schizophrenia: a double-blind study of nonchronic treatment-refractory patients. *Arch Gen Psychiatry*. 1975;32(10):1276–1281. PubMed
22. Kane JM, Rifkin A, Woerner M, et al. Low-dose neuroleptic treatment of outpatient schizophrenics. I: preliminary results for relapse rates. *Arch Gen Psychiatry*. 1983;40(8):893–896. PubMed
23. Kane JM, Rifkin A, Quitkin F, et al. Antipsychotic drug blood levels and clinical outcome. In: Klein DF, Gittelman-Klein R, eds. *Progress in Psychiatric Drug Treatment*. New York, NY: Brunner Mazel; 1976:399–408.
24. Baldessarini RJ, Davis JM. What is the best maintenance dose of neuroleptics in schizophrenia? *Psychiatry Res*. 1980;3(2):115–122. doi:10.1016/0165-1781(80)90028-1 PubMed
25. Baldessarini RJ, Cohen BM, Teicher MH. Significance of neuroleptic dose and plasma level in the pharmacological treatment of psychoses. *Arch Gen Psychiatry*. 1988;45(1):79–91. PubMed
26. Geddes J, Freemantle N, Harrison P, et al. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. *BMJ*. 2000;321(7273):1371–1376.doi:10.1136/bmj.321.7273.1371 PubMed
27. Leucht S, Wahlbeck K, Hamann J, et al. New generation antipsychotics versus low-potency conventional antipsychotics: a systematic review and meta-analysis. *Lancet*. 2003;361(9369):1581–1589.doi:10.1016/S0140-6736(03)13306-5 PubMed
28. Leucht S, Corves C, Arbter D, et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet*. 2009;373(9657):31–41.doi:10.1016/S0140-6736(08)61764-X PubMed
29. Zimbroff DL, Kane JM, Tamminga CA, et al; Sertindole Study Group. Controlled, dose-response study of sertindole and haloperidol in the treatment of schizophrenia. *Am J Psychiatry*. 1997;154(6):782–791. PubMed
30. Schooler N, Rabinowitz J, Davidson M, et al; Early Psychosis Global Working Group. Risperidone and haloperidol in first-episode psychosis: a long-term randomized trial. *Am J Psychiatry*. 2005;162(5):947–953. doi:10.1176/appi.ajp.162.5.947 PubMed
31. Kahn RS, Fleischhacker WW, Boter H, et al; EUFEST study group. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. *Lancet*. 2008;371(9618):1085–1097.doi:10.1016/S0140-6736(08)60486-9 PubMed
32. Good WW, Sterling M, Holtzman WH. Termination of chlorpromazine with schizophrenia patients. *Am J Psychol*. 1958;115(5):443–448. PubMed
33. Engelhardt DM, Rosen B, Freedman N, et al. Phenothiazines in prevention of psychiatric hospitalization. II: duration of treatment exposure. *JAMA*. 1963;186:981–983. PubMed
34. Engelhardt DM, Rosen B, Freedman N, et al. Phenothiazines in prevention of psychiatric hospitalization. IV: delay or prevention of hospitalization—a reevaluation. *Arch Gen Psychiatry*. 1967;16(1):98–101. PubMed
35. Kane JM. Schizophrenia. *N Engl J Med*. 1996;334(1):34–41.doi:10.1056/NEJM199601043340109 PubMed
36. Kane JM, Quitkin F, Rifkin A, et al. Comparison of the incidence and severity of extrapyramidal side effects with fluphenazine enanthate and fluphenazine decanoate. *Am J Psychiatry*. 1978;135(12):1539–1542. PubMed
37. Adams CE, Fenton MKP, Quraishi S, et al. Systematic meta-review of depot antipsychotic drugs for people with schizophrenia. *Br J Psychiatry*. 2001;179(4):290–299.doi:10.1192/bjp.179.4.290 PubMed
38. Haddad PM, Taylor M, Niaz OS. First-generation antipsychotic long-acting injections v oral antipsychotics in schizophrenia: systematic review of randomised controlled trials and observational studies. *Br J Psychiatry Suppl*. 2009;52(52):S20–S28.doi:10.1192/bjp.195.52.s20 PubMed
39. Fleischhacker WW. Second-generation antipsychotic long-acting injections: systematic review. *Br J Psychiatry Suppl*. 2009;52(52):S29–S36. doi:10.1192/bjp.195.52.s29 PubMed
40. Griffith RW, Saameli K. Clozapine and agranulocytosis [letter]. *Lancet*. 1975;2(7936):657.doi:10.1016/S0140-6736(75)90135-X PubMed
41. Kane JM, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. *Arch Gen Psychiatry*. 1988;45(9):789–796. PubMed
42. Essali A, Al-Haj Haasan N, Li C, et al. Clozapine versus typical neuroleptic medication for schizophrenia. *Cochrane Database Syst Rev*. 2009; (1) CD000059. PubMed
43. Davis JM, Chen N. Dose response and dose equivalence of antipsychotics. *J Clin Psychopharmacol*. 2004;24(2):192–208.doi:10.1097/01.jcp.0000117422.05703.ae PubMed
44. Rosenheck RA. Evaluating the cost-effectiveness of reduced tardive dyskinesia with second-generation antipsychotics. *Br J Psychiatry*. 2007;191(3):238–245.doi:10.1192/bjp.bp.106.035063 PubMed
45. Kane JM, Rifkin A, Quitkin F, et al. Fluphenazine vs placebo in patients with remitted, acute first-episode schizophrenia. *Arch Gen Psychiatry*. 1982;39(1):70–73. PubMed
46. Bilder RM, Goldman RS, Robinson D, et al. Neuropsychology of first-episode schizophrenia: initial characterization and clinical correlates. *Am J Psychiatry*. 2000;157(4):549–559.doi:10.1176/appi.ajp.157.4.549 PubMed
47. Loebel AD, Lieberman JA, Alvir JM, et al. Duration of psychosis and outcome in first-episode schizophrenia. *Am J Psychiatry*. 1992;149(9):1183–1188. PubMed
48. Robinson DG, Woerner MG, Delman HM, et al. Pharmacological treatments for first-episode schizophrenia. *Schizophr Bull*. 2005;31(3):705–722.doi:10.1093/schbul/sbi032 PubMed
49. Robinson DG, Woerner MG, Alvir JM, et al. Predictors of treatment response from a first episode of schizophrenia or schizoaffective disorder. *Am J Psychiatry*. 1999;156(4):544–549. PubMed
50. Melle I, Larsen TK, Haahr U, et al. Prevention of negative symptom psychopathologies in first-episode schizophrenia: two-year effects of reducing the duration of untreated psychosis. *Arch Gen Psychiatry*. 2008;65(6):634–640.doi:10.1001/archpsyc.65.6.634 PubMed
51. Robinson DG, Woerner MG, Alvir JM, et al. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Arch Gen Psychiatry*. 1999;56(3):241–247.doi:10.1001/archpsyc.56.3.241 PubMed
52. Robinson DG, Woerner MG, McMeniman M, et al. Symptomatic and functional recovery from a first episode of schizophrenia or schizoaffective disorder. *Am J Psychiatry*. 2004;161(3):473–479.doi:10.1176/appi.ajp.161.3.473 PubMed
53. Kumra S, Oberstar JV, Sikich L, et al. Efficacy and tolerability of second-generation antipsychotics in children and adolescents with schizophrenia. *Schizophr Bull*. 2008;34(1):60–71.doi:10.1093/schbul/sbm109 PubMed
54. Yung AR, McGorry PD. The initial prodrome in psychosis: descriptive and qualitative aspects. *Aust N Z J Psychiatry*. 1996;30(5):587–599. doi:10.3109/00048679609062654 PubMed
55. Miller TJ, McGlashan TH, Woods SW, et al. Symptom assessment in schizophrenic prodromal states. *Psychiatr Q*. 1999;70(4):273–287. doi:10.1023/A:1022034115078 PubMed
56. Yung AR, Stanford C, Cosgrave E, et al. Testing the ultra high risk (prodromal) criteria for the prediction of psychosis in a clinical sample of young people. *Schizophr Res*. 2006;84(1):57–66.doi:10.1016/j.schres.2006.03.014 PubMed
57. Correll CU, Hauser M, Auther AM, et al. Research in people with psychosis risk syndrome: a review of the current evidence and future directions. *J Child Psychol Psychiatry*. 2010;51(4):390–431.doi:10.1111/j.1469-7610.2010.02235.x PubMed

58. Rosenheck R, Perlick D, Bingham S, et al; Department of Veterans Affairs Cooperative Study Group on the Cost-Effectiveness of Olanzapine. Effectiveness and cost of olanzapine and haloperidol in the treatment of schizophrenia: a randomized controlled trial. *JAMA*. 2003;290(20):2693–2702.doi:10.1001/jama.290.20.2693 PubMed
59. Lieberman JA, Stroup TS, McEvoy JP, et al; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353(12):1209–1223.doi:10.1056/NEJMoa051688 PubMed
60. Jones PB, Barnes TR, Davies L, et al. Randomized controlled trial of the effect on Quality of Life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). *Arch Gen Psychiatry*. 2006;63(10):1079–1087.doi:10.1001/archpsyc.63.10.1079 PubMed
61. Leucht S, Komossa K, Rummel-Kluge C, et al. A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. *Am J Psychiatry*. 2009;166(2):152–163.doi:10.1176/appi.ajp.2008.08030368 PubMed
62. McEvoy JP, Lieberman JA, Stroup TS, et al; CATIE Investigators. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *Am J Psychiatry*. 2006;163(4):600–610.doi:10.1176/appi.ajp.163.4.600 PubMed
63. Lewis SW, Barnes TR, Davies L, et al. Randomized controlled trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. *Schizophr Bull*. 2006;32(4):715–723.doi:10.1093/schbul/sbj067 PubMed
64. Leucht S, Arbter D, Engel RR, et al. How effective are second-generation antipsychotic drugs? a meta-analysis of placebo-controlled trials. *Mol Psychiatry*. 2009;14(4):429–447.doi:10.1038/sj.mp.4002136 PubMed
65. Woods SW, Gueorguieva RV, Baker CB, et al. Control group bias in randomized atypical antipsychotic medication trials for schizophrenia. *Arch Gen Psychiatry*. 2005;62(9):961–970.doi:10.1001/archpsyc.62.9.961 PubMed
66. Kemmler G, Hummer M, Widschwendter C, et al. Dropout rates in placebo-controlled and active-control clinical trials of antipsychotic drugs: a meta-analysis. *Arch Gen Psychiatry*. 2005;62(12):1305–1312.doi:10.1001/archpsyc.62.12.1305 PubMed
67. Heres S, Davis J, Maino K, et al. Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation antipsychotics. *Am J Psychiatry*. 2006;163(2):185–194.doi:10.1176/appi.ajp.163.2.185 PubMed
68. Essock SM, Covell NH, Davis SM, et al. Effectiveness of switching antipsychotic medications. *Am J Psychiatry*. 2006;163(12):2090–2095.doi:10.1176/appi.ajp.163.12.2090 PubMed
69. Kraemer HC, Glick ID, Klein DF. Clinical trials design lessons from the CATIE study. *Am J Psychiatry*. 2009;166(11):1222–1228.doi:10.1176/appi.ajp.2009.08121809 PubMed
70. Leucht S, Barnes TR, Kissling W, et al. Relapse prevention in schizophrenia with new-generation antipsychotics: a systematic review and exploratory meta-analysis of randomized, controlled trials. *Am J Psychiatry*. 2003;160(7):1209–1222.doi:10.1176/appi.ajp.160.7.1209 PubMed
71. Fischer-Barnicol D, Lanquillon S, Haen E, et al; Working Group Drugs in Psychiatry. Typical and atypical antipsychotics—the misleading dichotomy: results from the Working Group Drugs in Psychiatry (AGATE). *Neuropsychobiology*. 2008;57(1–2):80–87.doi:10.1159/000135641 PubMed
72. Correll CU, Leucht S, Kane JM. Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies. *Am J Psychiatry*. 2004;161(3):414–425.doi:10.1176/appi.ajp.161.3.414 PubMed
73. Vinogradov S, Fisher M, Warm H, et al. The cognitive cost of anticholinergic burden: decreased response to cognitive training in schizophrenia. *Am J Psychiatry*. 2009;166(9):1055–1062.doi:10.1176/appi.ajp.2009.09010017 PubMed
74. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS Drugs*. 2005;19(suppl 1):1–93.doi:10.2165/00023210-200519001-00001 PubMed
75. Fleischhacker WW, Cetkovich-Bakmas M, De Hert M, et al. Comorbid somatic illnesses in patients with severe mental disorders: clinical, policy, and research challenges. *J Clin Psychiatry*. 2008;69(4):514–519.doi:10.4088/JCP.v69n0401 PubMed
76. Leucht S, Burkard T, Henderson J, et al. Physical illness and schizophrenia: a review of the literature. *Acta Psychiatr Scand*. 2007;116(5):317–333.doi:10.1111/j.1600-0447.2007.01095.x PubMed
77. Colton CW, Manderscheid RW. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. *Prev Chronic Dis*. 2006;3(2):A42. PubMed
78. Lieberman JA, Phillips M, Gu H, et al. Atypical and conventional antipsychotic drugs in treatment-naive first-episode schizophrenia: a 52-week randomized trial of clozapine vs chlorpromazine. *Neuropsychopharmacology*. 2003;28(5):995–1003. PubMed
79. Zipursky RB, Gu H, Green AI, et al. Course and predictors of weight gain in people with first-episode psychosis treated with olanzapine or haloperidol. *Br J Psychiatry*. 2005;187(6):537–543.doi:10.1192/bjp.187.6.537 PubMed
80. Perez-Iglesias R, Crespo-Facorro B, Martinez-Garcia O, et al. Weight gain induced by haloperidol, risperidone and olanzapine after 1 year: findings of a randomized clinical trial in a drug-naïve population. *Schizophr Res*. 2008;99(1–3):13–22.doi:10.1016/j.schres.2007.10.022 PubMed
81. Correll CU, Manu P, Olshanskiy V, et al. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA*. 2009;302(16):1765–1773.doi:10.1001/jama.2009.1549 PubMed
82. Lambert TJ, Newcomer JW. Are the cardiometabolic complications of schizophrenia still neglected? barriers to care. *Med J Aust*. 2009;190(suppl):S39–S42. PubMed
83. American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; et al. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care*. 2004;27(2):596–601.doi:10.2337/diacare.27.2.596 PubMed
84. Morrato EH, Druss B, Hartung DM, et al. Metabolic testing rates in 3 state Medicaid programs after FDA warnings and ADA/APA recommendations for second-generation antipsychotic drugs. *Arch Gen Psychiatry*. 2010;67(1):17–24.doi:10.1001/archgenpsychiatry.2009.179 PubMed
85. Morrato EH, Nicol GE, Maahs D, et al. Metabolic screening in children receiving antipsychotic drug treatment. *Arch Pediatr Adolesc Med*. 2010;164(4):344–351. PubMed
86. Nasrallah HA, Meyer JM, Goff DC, et al. Low rates of treatment for hypertension, dyslipidemia and diabetes in schizophrenia: data from the CATIE schizophrenia trial sample at baseline. *Schizophr Res*. 2006;86(1–3):15–22.doi:10.1016/j.schres.2006.06.026 PubMed
87. Correll CU, Harris JL, Pantaleon Moya RA, et al. Low-density lipoprotein cholesterol in patients treated with atypical antipsychotics: missed targets and lost opportunities. *Schizophr Res*. 2007;92(1–3):103–107.doi:10.1016/j.schres.2007.01.004 PubMed
88. Correll CU, Druss BG, Lombardo I, et al. Findings of a national cardiometabolic screening program in 10,084 psychiatric outpatients. *Psychiatr Serv*. In press.
89. Druss BG, Bradford WD, Rosenheck RA, et al. Quality of medical care and excess mortality in older patients with mental disorders. *Arch Gen Psychiatry*. 2001;58(6):565–572.doi:10.1001/archpsyc.58.6.565 PubMed
90. Frye RL. Optimal care of patients with type 2 diabetes mellitus and coronary artery disease. *Am J Med*. 2003;115(suppl 8A):93S–98S.doi:10.1016/j.amjmed.2003.09.015 PubMed
91. Andreasen NC, Carpenter WT Jr, Kane JM, et al. Remission in schizophrenia: proposed criteria and rationale for consensus. *Am J Psychiatry*. 2005;162(3):441–449.doi:10.1176/appi.ajp.162.3.441 PubMed
92. Kane JM, Leucht S. Unanswered questions in schizophrenia clinical trials. *Schizophr Bull*. 2008;34(2):302–309.doi:10.1093/schbul/sbm143 PubMed
93. Leucht S, Heres S, Hamann J, et al. Methodological issues in current antipsychotic drug trials. *Schizophr Bull*. 2008;34(2):275–285.doi:10.1093/schbul/sbm159 PubMed
94. Liberman RP, Kopelowicz A, Ventura J, et al. Operational criteria and factors related to recovery from schizophrenia. *Int Rev Psychiatry*. 2002;14(4):256–272. doi:10.1080/0954026021000016905
95. Naber D, Karow A, Lambert M. Subjective well-being under the neuroleptic treatment and its relevance for compliance. *Acta Psychiatr Scand suppl*. 2005;111(427):29–34. doi:10.1111/j.1600-0447.2005.00542.x
96. Lambert M, Schimmelmann BG, Naber D, et al. Prediction of remission as a combination of symptomatic and functional remission and adequate subjective well-being in 2960 patients with schizophrenia. *J Clin Psychiatry*. 2006;67(11):1690–1697.doi:10.4088/JCP.v67n1104 PubMed
97. Green MF, Penn DL, Bentall R, et al. Social cognition in schizophrenia: an NIMH workshop on definitions, assessment, and research opportunities. *Schizophr Bull*. 2008;34(6):1211–1220.doi:10.1093/schbul/sbm145 PubMed
98. Harvey PD, Green MF, Bowie C, et al. The dimensions of clinical and cognitive change in schizophrenia: evidence for independence of

improvements. *Psychopharmacology (Berl)*. 2006;187(3):356–363. doi:10.1007/s00213-006-0432-1 PubMed
99. Keefe RS, Vinogradov S, Medalia A, et al. Report from the Working Group Conference on Multisite Trial Design for Cognitive Remediation in Schizophrenia [published online ahead of print March 1, 2010]. *Schizophr Bull*. doi:10.1093/schbul/sbq010 PubMed
100. Lehman AF, Goldberg R, Dixon LB, et al. Improving employment outcomes for persons with severe mental illnesses. *Arch Gen Psychiatry*. 2002;59(2):165–172.doi:10.1001/archpsyc.59.2.165 PubMed
101. McGurk SR, Schiano D, Mueser KT, et al. Implementation of the thinking skills for work program in a psychosocial clubhouse. *Psychiatr Rehabil J*. 2010;33(3):190–199.doi:10.2975/33.3.2010.190.199 PubMed
102. Evans JD, Bond GR, Meyer PS, et al. Cognitive and clinical predictors of success in vocational rehabilitation in schizophrenia. *Schizophr Res*. 2004;70(2–3):331–342.doi:10.1016/j.schres.2004.01.011 PubMed
103. Dixon LB, Dickerson F, Bellack AS, et al; Schizophrenia Patient Outcomes Research Team (PORT). The 2009 schizophrenia PORT psychosocial treatment recommendations and summary statements. *Schizophr Bull*. 2010;36(1):48–70.doi:10.1093/schbul/sbp115 PubMed
104. Nasrallah HA, Keshavan MS, Benes FM, et al. Proceedings and data from The Schizophrenia Summit: a critical appraisal to improve the management of Schizophrenia. *J Clin Psychiatry*. 2009;70(suppl 1):4–46. PubMed
105. Falkai P, Mike O, Inez MG, et al; MEOS Consortium. A roadmap to disentangle the molecular etiology of schizophrenia. *Eur Psychiatry*. 2008;23(4):224–232.doi:10.1016/j.eurpsy.2008.02.006 PubMed
106. Lathia CD, Amakye D, Dai W, et al. The value, qualification, and regulatory use of surrogate end points in drug development. *Clin Pharmacol Ther*. 2009;86(1):32–43.doi:10.1038/clpt.2009.69 PubMed
107. Nedopil N, Pflieger R, Rüther E. The prediction of acute response, remission and general outcome of neuroleptic treatment in acute schizophrenic patients. *Pharmacopsychiatria*. 1983;16(6):201–205. doi:10.1055/s-2007-1019499 PubMed
108. Bartkó G, Herczeg I, Békésy M. Predicting outcome of neuroleptic treatment on the basis of subjective response and early clinical improvement. *J Clin Psychiatry*. 1987;48(9):363–365. PubMed
109. Awad AG, Voruganti LN. Neuroleptic dysphoria: revisiting the concept 50 years later. *Acta Psychiatr Scand suppl*. 2005;111(s427):6–13. doi:10.1111/j.1600-0447.2005.00539.x PubMed
110. Agid O, Kapur S, Arenovich T, et al. Delayed-onset hypothesis of antipsychotic action: a hypothesis tested and rejected. *Arch Gen Psychiatry*. 2003;60(12):1228–1235.doi:10.1001/archpsyc.60.12.1228 PubMed
111. Leucht S, Busch R, Hamann J, et al. Early-onset hypothesis of antipsychotic drug action: a hypothesis tested, confirmed and extended. *Biol Psychiatry*. 2005;57(12):1543–1549.doi:10.1016/j.biopsych.2005.02.023 PubMed
112. Agid O, Kapur S, Warrington L, et al. Early onset of antipsychotic response in the treatment of acutely agitated patients with psychotic disorders. *Schizophr Res*. 2008;102(1–3):241–248.doi:10.1016/j.schres.2008.03.016 PubMed
113. Correll CU, Malhotra AK, Kaushik S, et al. Early prediction of antipsychotic response in schizophrenia. *Am J Psychiatry*. 2003;160(11):2063–2065.doi:10.1176/appi.ajp.160.11.2063 PubMed
114. Leucht S, Busch R, Kissling W, et al. Early prediction of antipsychotic nonresponse among patients with schizophrenia. *J Clin Psychiatry*. 2007;68(3):352–360.doi:10.4088/JCP.v68n0301 PubMed
115. Chang YC, Lane HY, Yang KH, et al. Optimizing early prediction for antipsychotic response in schizophrenia. *J Clin Psychopharmacol*. 2006;26(6):554–559.doi:10.1097/01.jcp.0000246211.95905.8c PubMed
116. Ascher-Svanum H, Nyhuis AW, Faries DE, et al. Clinical, functional, and economic ramifications of early nonresponse to antipsychotics in the naturalistic treatment of schizophrenia. *Schizophr Bull*. 2008;34(6):1163–1171.doi:10.1093/schbul/sbm134 PubMed
117. Kinon BJ, Chen L, Ascher-Svanum H, et al. Predicting response to atypical antipsychotics based on early response in the treatment of schizophrenia. *Schizophr Res*. 2008;102(1–3):230–240.doi:10.1016/j.schres.2008.02.021 PubMed
118. Kinon BJ, Chen L, Ascher-Svanum H, et al. Early response to antipsychotic drug therapy as a clinical marker of subsequent response in the treatment of schizophrenia. *Neuropsychopharmacology*. 2010;35(2):581–590.doi:10.1038/npp.2009.164 PubMed
119. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261–276. PubMed
120. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychol Rep*. 1962;10(3):799–812. doi:10.2466/PR0.10.3.799-812
121. Guidotti A, Auta J, Davis JM, et al. GABAergic dysfunction in schizophrenia: new treatment strategies on the horizon. *Psychopharmacology (Berl)*. 2005;180(2):191–205.doi:10.1007/s00213-005-2212-8 PubMed
122. Mansvelder HD, van Aerde KI, Couey JJ, et al. Nicotinic modulation of neuronal networks: from receptors to cognition. *Psychopharmacology (Berl)*. 2006;184(3-4):292–305.doi:10.1007/s00213-005-0070-z PubMed
123. Conn PJ, Tamminga C, Schoepp DD, et al. Schizophrenia: moving beyond monoamine antagonists. *Mol Interv*. 2008;8(2):99–107. doi:10.1124/mi.8.2.7 PubMed
124. Sellin AK, Shad M, Tamminga C. Muscarinic agonists for the treatment of cognition in schizophrenia. *CNS Spectr*. 2008;13(11):985–996. PubMed

The Pharmacologic Treatment of Bipolar Disorder

Gary S. Sachs, MD; Jamie M. Dupuy, MD; and Curtis W. Wittmann, MD

Over the past half century, substantial clinical trial data have accumulated to guide clinical management of bipolar disorder, and 13 medications have gained US Food and Drug Administration approval for the treatment of mania or bipolar depression or the maintenance treatment of bipolar disorder. While the number of studies has grown and many controversies related to pharmacologic treatment of bipolar disorder are not yet resolved, the task of transforming the accumulated evidence into useful guidance for clinical practice becomes more manageable and less error prone by limiting consideration to the highest quality studies. Therefore, this article emphasizes points of relative clarity by highlighting findings supported by double-blind, placebo-controlled clinical trials with samples of at least 100 subjects. A MEDLINE search was conducted and augmented by a manual search of bibliographies, textbooks, and abstracts from recent scientific meetings for randomized controlled trials published in English between 1950 and April 2010 with at least 100 subjects. Keywords used in the search included *randomized controlled trial*, *mania*, *hypomania*, *depression*, *relapse prevention*, *placebo*, *antidepressant*, *switch*, and *maintenance treatment of bipolar disorder*. A paradigm for implementing evidence-based treatment is offered along with consideration of patterns emerging across clinical trials.

J Clin Psychiatry 2011;72(5):704–715

Submitted: *August 24, 2011; accepted March 29, 2011 (doi:10.4088/JCP.10m06523).*
Corresponding author: *Gary S. Sachs, MD, Massachusetts General Hospital, Clinical Psychopharmacology Unit, WACC 815, 50 Staniford St, Boston, MA 02114 (sachsg@aol.com).*

The past half century has seen meaningful growth in the number and quality of studies pertaining to the management of bipolar disorders. The quality of data presented at NCDEU and other academic meetings has advanced from case series and pilot studies to fully powered pivotal trials and recent large-scale effectiveness studies such as those carried out by the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) group, the Stanley Foundation, the Bipolar Affective disorder: Lithium/ANti-Convulsant Evaluation (BALANCE) group, and the Bipolar Trials Network. The list of evidence-based treatments now includes 13 US Food and Drug Administration (FDA)–approved medications for bipolar disorder.

The yields of drug development efforts directed at meeting the immense needs of patients and families impacted by the common but poorly understood conditions now referred to as *bipolar disorders* are far from satisfying, but do comprise a more scientifically valid basis for clinical decision making than was available through the end of the 20th century. As the admittedly dim light of efficacy and effectiveness data gradually illuminates the clinical landscape, even limited visibility offers opportunities to improve patient care. While acknowledging the continued controversy and uncertainties, this review seeks to emphasize well-established points and areas of general agreement that can provide direction for managing the care of patients with bipolar disorder.

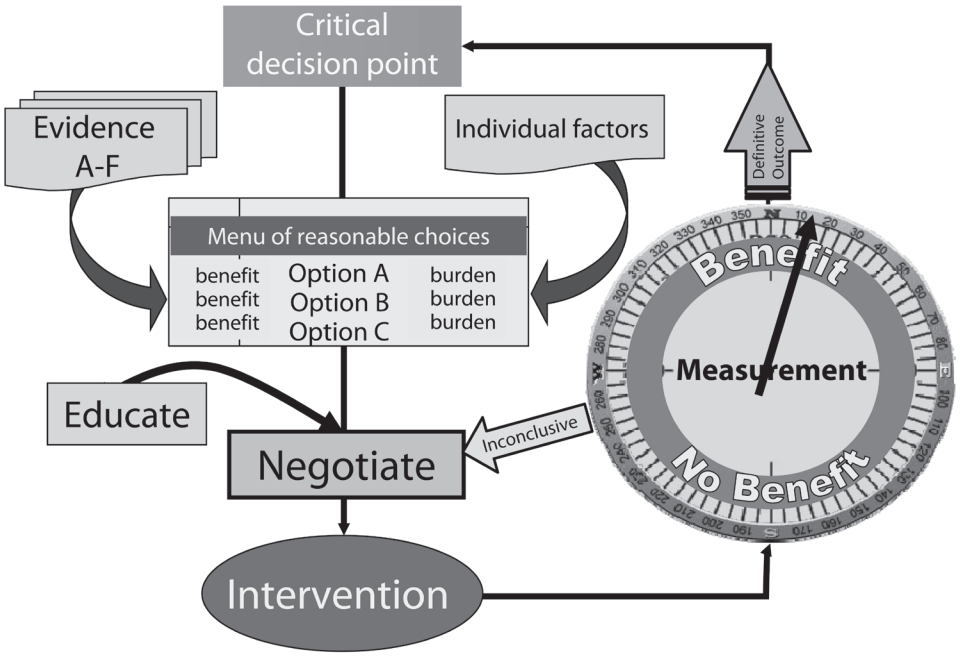
CONTEXT FOR PHARMACOLOGIC TREATMENT OF BIPOLAR DISORDER

Bipolar disorders are chronic multidimensional conditions afflicting about 3% to 6% of the population.[1–3] Although the illness is often familial, the causes of bipolar disorders remain elusive, and no pathognomonic markers have been identified. Diagnosis is made on the basis of purely clinical criteria. The complexity of symptomatology associated with bipolar disorder often leads to confusion and frustration, which undermine confidence in treatment decisions. A basic fund of knowledge related to bipolar disorder and *DSM-IV* nosology is presented below to facilitate the process of clinical assessment, which is the foundation for management of bipolar illness. After discussion of these issues, an approach is offered to guide the integration of clinical knowledge and evidence from clinical trials.

Typically in bipolar disorder the onset of affective episodes occurs during adolescence or the early adult years.[4,5] Uncertainty frequently plagues the diagnosis, and despite the often dramatic psychopathology observed or reported by patients with bipolar disorders, the rates of false-positive and false-negative diagnosis are high. Field trials suggest that the diagnostic criteria for current acute mania in *DSM-IV* are highly reliable. However, assessment of current hypomania is much less reliable, and it is difficult to determine the reliability of assessments for prior manic or hypomanic episodes, especially when a patient is currently depressed.

The subsequent course of illness is highly variable. Most individuals experience an irregular course in which acute abnormal mood states alternate with periods of full or partial remission lasting weeks to years. While abnormal mood elevation is the cardinal diagnostic feature of bipolar disorders, most patients find depression to be more frequent, and more disabling, than hypomania or mania. Furthermore, abnormal mood states are seldom the only expression of the complex pathophysiology underlying bipolar disorders. In addition to the full syndromal episodes, patients with bipolar disorders often experience functional impairment due to interepisode subsyndromal affective symptomatology,[2,6]

Figure 1. Schema for Iterative Collaborative Measure-Based Care[a]



[a]Adapted with permission from Sachs.[28]

comorbid nonaffective psychopathology[7–16] (eg, anxiety disorders, substance misuse, cognitive impairment), and general medical conditions[17–22] (eg, obesity, migraine headache, inflammatory disorders).

Bipolar disorder ranks as the sixth leading cause of disability worldwide and is associated with increased mortality[23–25] relative to the general population. Suicide accounts for a small fraction of the excess mortality associated with bipolar disorder. Mortality ratios comparing patients with bipolar disorder to the general population reveal elevated death rates due to a number of general medical conditions including heart disease, stroke, and infections.[26,27] The shortened life span of patients with severe mental illnesses like bipolar disorder represents a major health care disparity.

A PARADIGM FOR INTEGRATION OF MEASUREMENT AND MANAGEMENT

The complexity and variability associated with bipolar disorder lead to an understandable desire for a systematic approach to treatment. Stakeholder feedback obtained by the National Institute of Mental Health (NIMH) prior to the start of the STEP-BD made clear that algorithmic care is unattractive to patients and family members as well as clinicians. There is, however, a desire to move clinical practice beyond the guidance of population-based results to personalized care. In response, STEP-BD included a disease management program based on a collaborative chronic care model in which clinicians were encouraged to use their experience and judgment in light of the best available evidence[28] (Figure 1). This model is not the only or necessarily the best model of care. It is presented here because it has been implemented across multiple treatment centers, and, although it is not prescriptive, its use resulted in high rates of treatment concordant with recognized treatment guidelines and in encouraging outcomes.[29]

Table 1. STEP-BD Collaborative Care Model: Principles of Treatment[a]

1. Define critical decision points on the basis of formal diagnostic assessment
2. Formulate a menu of reasonable options for each individual that offers proven treatments first
3. Engage patients in shared decision making and other collaborative care strategies
4. Integrate measurement into management
5. Revise the menu of reasonable choices on the bases of response and tolerability

[a]Based on Sachs.[30]
Abbreviation: STEP-BD = Systematic Treatment Enhancement Program for Bipolar Disorder.

The STEP-BD Collaborative Care model involves 5 main principles[30] (Table 1). The model starts with the assumption that the patient meets formal diagnostic criteria for bipolar disorder, agrees to at least 1 treatment objective, and confronts a critical clinical decision point. These decision points are most commonly related to management of acute episodes (depression, hypomania, mania, or mixed), but may be relapse prevention, return to employment, control of rapid cycling, desire to conceive a child, or management of a treatment-limiting adverse effect.

Table 2. Simplified Levels of Evidence[a]

Category A	Double-blind placebo-controlled trial with adequate sample[b]
Category B	Double-blind comparison studies with adequate sample[b]
Category C	Open comparison trials with adequate sample[b]
Category D	Uncontrolled observation or controlled study with ambiguous result
Category E	No published evidence (± class effect)
Category F	Available evidence negative or considered a failed trial

[a]Based on Sachs.[28]
[b]Statistical power ≥ 0.8 to detect meaningful differences at $P < .05$.

In this model, clinicians formulate a personalized menu of reasonable choices based on consideration of both the best available evidence pertaining to the current decision point and the clinician's knowledge of the patient as an individual. Evidence-based practice recognizes an implicit duty to at least offer proven treatments first.[31] Clinicians can meet this duty by maintaining a working knowledge of the proven treatments defined in Table 2 as "category A" treatments and by being aware of the key individual characteristics of their patients that pertain to choice of treatment. At a minimum this will include a patient's history of prior treatment response, adverse effect tolerance, pertinent general medical conditions, and personal preferences. Essential to collaborative care is the concept of having a plan with shared decision making and communication with other professionals and those the patient designates as supports. Including the patient as an active agent in his or her own care requires an engaged, well-informed patient and negotiation skills. Given the opportunity, patients and their care providers are often motivated to make a well-informed selection from the menu of reasonable choices and participate in a variety of self-management strategies. The outcome of each intervention is then evaluated on the basis of routine measures. The measures for assessing the benefit of an intervention may consist of formal scales or judgments made in reference to a patient's personal goals.

When interventions are carried out to a definitive endpoint (declaring that a treatment is effective, ineffective, or intolerable), it is possible to make progress toward optimizing an individual's treatment plan. Indecisive outcomes, however, may result when tolerable interventions are curtailed without adequate dose or duration or are simply rejected as unacceptable. Integrating measurement into the management facilitates personalized evidence-based treatment decisions.

Several lines of evidence support the rationale of retaining well-tolerated, efficacious treatments and replacing treatments that are ineffective and/or poorly tolerated.[32–34] Keeping records of these outcomes facilitates optimization of an individual's treatment plan through iterative revision of the menu of reasonable choices. No currently available biomarker or group of biomarkers offers a better means of guiding treatment decisions.

Importantly, several studies indicate that a patient's record of response to treatment has impressive predictive value. For subjects (N = 3,369) enrolled in 10 placebo-controlled pivotal trials for bipolar depression, Calabrese et al[35] examined the value of "early response" (defined as improvement in the depression scale score of at least 20% from baseline after 2 weeks of treatment) for predicting the probability of response and remission at the end of each study (7–10 weeks of treatment).

The most compelling finding in this analysis was the high negative predictive value associated with not meeting the criteria for early improvement. Across all of the 10 active treatment groups as well as the placebo groups, subjects with less than 20% improvement after 2 weeks of treatment had only a 10%–20% chance of meeting remission criteria at the end of the study.[35] The consistency of this pattern observed across large placebo-controlled studies for bipolar depression suggests that a determination of the need for dose adjustment or a declaration of the treatment as ineffective could be made with acceptable confidence as rapidly as every 2 weeks.

EVIDENCE: DECISION MAKING GUIDANCE AND BENCHMARK METRICS

Implicit in the general consensus that the principles of evidence-based medicine provide the best guidance for clinical practice is the idea of offering proven treatments before unproven treatments.[31] Utilizing this principle necessitates a working knowledge of medical evidence and consideration of appropriate metrics. Consumers of medical evidence can assess the clinical meaning of published studies by evaluating the quality of the evidence, by gauging the effect size of various interventions, and by establishing benchmarks applicable to routine clinical practice. Simple metrics are offered below to integrate these processes into meaningful guidance for clinical decision making and metrics for evaluating outcomes in routine practice.

For the purposes of this review, we conducted a MEDLINE search augmented by a manual search of bibliographies, textbooks, and abstracts from recent scientific meetings to identify randomized studies of mania, hypomania, depression, or maintenance treatment of bipolar disorder with at least 100 subjects. Although areas remain for which few or no high-quality data are available, the knowledge base pertaining to clinical care of patients with bipolar disorder has grown substantially over the past 2 decades. The daunting task of transforming the accumulated evidence into useful guidance becomes more manageable and less error prone by limiting consideration to the highest quality studies. Results from studies with sufficient methodological rigor to allow valid causal inference, referred to here as *category A evidence*, represent the highest standard for evidence-based medicine (Table 2). Category A evidence is derived from randomized double-blind placebo-controlled studies with sample sizes adequate to detect differences that are statistically significant and clinically relevant. Formal power calculations to determine sample size adequacy can be complicated. A simple

rule of thumb, however, is often sufficient to help clinicians judge the adequacy of sample size in mood disorder treatment studies. Clinical trials with fewer than 100 subjects are unlikely to meet criteria for category A evidence.

This simple benchmark establishes a lower bound on the range of studies we include as having high-quality evidence.

EVIDENCE REVIEW: MANIA

Cade's 1949 publication[36] on the calming effects of lithium was a landmark event setting the stage for an era of progress in psychopharmacology. This case series was followed by persuasive, albeit small, placebo-controlled crossover studies. The first parallel-group placebo-controlled trial for demonstrating the acute antimanic efficacy of lithium did not appear in the literature until 1994.[37]

As seen in Table 3, category A studies for acute mania now demonstrate the efficacy of 8 dopamine-blocking agents (olanzapine,[46,47] ziprasidone,[53,54] risperidone,[49–52] haloperidol,[49] quetiapine,[55–60] aripiprazole,[61–63] paliperidone,[66] and asenapine[64,65]) and 3 non–dopamine-blocking agents (lithium,[37–39] valproate,[37,40] and carbamazepine[42,43]).

Due to the less stringent standards of the mid–20th century, chlorpromazine has FDA approval for mania but lacks a placebo-controlled trial establishing its antimanic efficacy. In a comparison of lithium to chlorpromazine (n = 255), Prien et al[38] found both to be effective for mania, but chlorpromazine (mean dose = 1,000 mg) was more effective in severely ill and agitated patients, while lithium (mean dose = 1,800 mg) was associated with fewer adverse effects.

The available data indicate that 3 weeks of monotherapy treatment with any of these FDA-approved agents is significantly more beneficial than placebo treatment, but seldom sufficient to achieve a complete remission of manic symptoms. After 3 weeks of treatment under the controlled conditions of a randomized controlled trial (RCT), the mean mania rating scale score for subjects receiving any one of the proven antimanic agents still exceeds the minimum symptom score required for study entry at baseline.* This finding highlights the need for sustained treatment and provides a rationale for combination treatment.

While there are undoubtedly individual differences in response to antimanic agents, the preponderance of accumulated evidence does not indicate important differences in overall efficacy. Nearly all direct comparisons between active agents yield no statistically significant differences in overall antimanic efficacy (lithium vs chlorpromazine,[38] haloperidol vs risperidone,[49] olanzapine vs divalproex,[68] olanzapine vs haloperidol,[69] aripiprazole vs haloperidol,[70] quetiapine vs lithium,[39] quetiapine vs hapoleridol[67]). Two exceptions to this pattern are noteworthy. Tohen et al[71] found olanzapine to have a small, but statistically significant efficacy advantage over divalproex. This advantage was, however, at least partially offset by disadvantages in tolerability. Conversely, the comparison of aripiprazole and haloperidol reported by Vieta et al[70] found no difference in efficacy, but a significant advantage for aripiprazole in overall effectiveness due to its greater tolerability.

Number needed to treat (NNT) analyses of the positive category A studies show that for a mania RCT to yield 1 additional responsive subject above the placebo response rate, it is necessary to treat 3 to 6 subjects with a proven antimanic agent. The desire to compare results across studies by comparing effect size is understandable, but making comparisons of the NNT across studies is of questionable validity. An NNT analysis does correct results for placebo response, but does not overcome the methodological limitations that prevent drawing conclusions based on comparisons of treatment other than those available within a single randomized study. Comparing outcomes across placebo-controlled monotherapy mania studies is confounded by differences in study samples as well as study procedures. For instance, the antimanic efficacy of risperidone appears twice as robust in study results based on a sample accessioned in India[52] compared to results obtained in a separate study that used nearly the same treatment protocol but enrolled its sample exclusively at sites in the United States.[51]

Category A studies suggest that adding a dopamine-blocking antimanic agent confers about the same increment of extra benefit over placebo whether used as monotherapy or administered as an adjunct to valproate or lithium.[72,73] Valproate was also superior to placebo as an adjunct to antipsychotic treatment.[74]

The available data are as yet insufficient to conclusively prove that 2 agents are superior to monotherapy, because the advantage of adding a second active agent has been demonstrated only in samples that restricted enrollment to subjects with inadequate response to prior treatment. Nonetheless, combination treatment is a reasonable approach for more severely ill patients, since the preponderance of evidence

Table 3. Summary of Category A Acute Mania Studies[a]

At Least 1 Positive Trial	Only Negative or Failed Trials	Negative Study[b]
Lithium[37–39]	Lamotrigine[c]	✓
Valproate[37,40]	Gabapentin[41]	
Carbamazepine[42,43]	Oxcarbazepine[44]	
	Topiramate[45]	✓
Olanzapine[46,47]	Licarbazepine[48]	
Risperidone[49–52]		
Ziprasidone[53,54]		
Haloperidol[49]		
Quetiapine[55–60]		
Aripiprazole[61–63]		
Asenapine[64,65]		
Paliperidone[66]		

[a]Statistical power ≥ 0.8 to detect meaningful differences at $P < .05$.
[b]Interpreted as a "negative study" because the study drug failed to separate from placebo and the study included an active comparator that did separate from placebo.
[c]G.S.S., GlaxoSmithKline data on file, 2000.

*References 37, 39, 46, 47, 51–54, 57, 58, 61–67.

© Copyright 2011 Physicians Postgraduate Press, Inc.

from these studies shows lower dropout rates among subjects receiving 2 active treatments than those receiving placebo and 1 active treatment.[75,76]

In addition, placebo-controlled adjunct studies have established the efficacy of adding valproate to dopamine-blocking agents[74] and the efficacy of adding risperidone, haloperidol, olanzapine,[49] or quetiapine[55] to the non–dopamine-blocking agents lithium and valproate.

Category A placebo-controlled clinical trials comparing gabapentin, lamotrigine, topiramate, oxcarbazepine, and licarbazepine to placebo have to date produced only negative results or failed studies (references 41, 44, 45, 48, and 77 and G.S.S., GlaxoSmithKline data on file, 2000). These results do not support a class effect for anticonvulsants as antimanic agents.

Table 4. Summary of Category A Acute Bipolar Depression Efficacy Studies[a]

At Least 1 Positive Trial	Only Negative or Failed Trials	Negative Study[b]
Lamotrigine[83]	Imipramine[84]	
Olanzapine[80]	Paroxetine[85]	✓
Olanzapine and fluoxetine[80]	Lithium[86]	✓
Quetiapine[85–89]	Aripiprazole[90]	
	Ziprasidone[91]	
	Bifeprunox[92]	
	Lithium + paroxetine[78]	
	Lithium + imipramine[78]	
	Mood stabilizer + paroxetine[93]	
	Mood stabilizer + bupropion[93]	

[a]Statistical power ≥ 0.8 to detect meaningful differences at $P < .05$.
[b]Interpreted as a "negative study" because the study drug failed to separate from placebo and the study included an active comparator that did separate from placebo.

EVIDENCE REVIEW: DEPRESSION

A variety of scientific, ethical, and practical design issues have long hampered efforts to address basic clinical questions related to bipolar depression, and consequently most studies examined adjunctive treatment.[78–80] Early studies suggesting benefit of monoamine oxidase inhibitors (MAOIs) are limited by small sample size and classification of outcomes based solely on change in depression scale scores.[81,82] Thus, reported response rates were not corrected for subjects who experienced treatment-emergent switch to hypomania or mania. Recent parallel-group double-blind studies of bipolar depression have improved methodology, and results for monotherapy including lithium, atypical antipsychotics, and standard antidepressants are becoming available.

The evidence review process identified 11 medication (monotherapy or combination) treatments for which category A studies have been conducted (Table 4). Positive category A evidence clearly supports the 2 FDA-approved treatments, quetiapine[85–89] and the combination of olanzapine and fluoxetine (OFC).[80] The same 3-arm study that established the efficacy of OFC also found olanzapine monotherapy had significantly better efficacy than placebo for bipolar depression. In that study, the combination of olanzapine and fluoxetine was statistically superior to olanzapine monotherapy as well as superior to placebo.[80] Two positive category A studies support the use of lamotrigine for acute bipolar depression.[83,94] Lamotrigine does not, however, have FDA approval and has had 4 additional negative or failed studies.[95]

To date, only 1 category A study is available with data comparing lithium to placebo as a treatment for acute bipolar depression. This study must be considered a negative study rather than a failed trial for lithium, because the study found no difference between lithium and placebo, while also finding statistically significant advantage for quetiapine over placebo.[86]

Whenever multiple proven treatments exist, the question arises of which treatment might be best for an individual patient. While matching treatments to individual patients remains an unfulfilled dream, in this instance there may be some clinically interesting pharmacogenetic light at the end of the proverbial tunnel. Perlis et al[96] found a differential pattern of response based on genotypes of subjects randomly assigned to treatment with OFC (n = 88) or lamotrigine (n = 85). A set of 19 candidate genes were genotyped. Response to OFC was significantly associated with single nucleotide polymorphisms (SNPs) within the dopamine D_3 receptor and histamine H_1 receptor (*HRH1*) genes. Response to lamotrigine was significantly associated with SNPs within the dopamine D_2 receptor, *HRH1*, dopamine β-hydroxylase, glucocorticoid receptor, and melanocortin 2 receptor genes. These findings are consistent with the notion that dopaminergic influences play an important role in bipolar I depression.

Several dopamine-blocking antimanic agents (bifeprunox,[92] aripiprazole,[90] and ziprasidone[91]) have produced negative or failed results in bipolar depression studies. This may reflect real differences in the action of these drugs in comparison to quetiapine and olanzapine, but may also result from simple deficiencies in the design and execution of the clinical trials. In addition to disadvantages related to inadequate knowledge of the therapeutic doses of these medications for bipolar depression, some of the trials were quite likely hampered by enrollment of inappropriate subjects and/or low quality ratings on study outcome measures.[97,98]

The role of standard antidepressants in bipolar depression remains controversial. Baldessarini et al[99] reported that despite the ongoing concern about prescribing unopposed antidepressant medication to bipolar patients, antidepressant medication is still the initial treatment for 50% of newly diagnosed patients with bipolar disorder in the United States. Unfortunately, there are few data to support the benefit of this common practice.

A meta-analysis of small double-blind studies is often cited as evidence supporting the adjunctive use of standard antidepressants as a class for the treatment of bipolar depression.[100] The utility of this meta-analysis as a guide to treatment is unclear for several reasons. First,

the class of drugs referred to as *antidepressants* is heterogeneous in structure and mechanism (selective serotonin reuptake inhibitor, serotonin-norepinephrine reuptake inhibitor, MAOI, etc). Second, data from studies of MAOI-type antidepressants constitute a large proportion of the positive data and, as noted above, tend to overestimate the benefit of treatment because subjects were considered antidepressant responders even if they switched to mania during the course of treatment. Third, no individual standard antidepressant has shown efficacy in a category A study as monotherapy nor as an adjunct to lithium or valproate. Furthermore, the results of recent efficacy and clinical effectiveness studies have not produced results that encourage use of standard antidepressants for bipolar depression.

In a double-blind study comparing placebo to standard antidepressants (bupropion or paroxetine) as adjuncts to mood stabilizers for bipolar depression, STEP-BD found no advantage for standard antidepressants over placebo.[93] Separately, STEP-BD used the same infrastructure and outcome measures to conduct a quasi-experimental analysis comparing outcome for STEP-BD subjects who did not participate in the randomized trial, but were prescribed antidepressant medications while participating in the study. This open comparison of the outcome for depressed bipolar patients treated with or without standard antidepressant medications also showed no advantage for adjunctive antidepressant medication.[101,102] It is important to note, since study results are often viewed as subject to the limitation of accession bias, that results from the sample receiving open treatment were remarkably similar to results obtained from subjects who consented to participate in the double-blind study. In both studies, the proportion of patients who achieved a durable recovery (defined as 8 consecutive weeks of euthymia) was less than 25%.

Another large effectiveness study conducted by the Stanley Foundation Bipolar Network reported similar discouraging results for standard antidepressants. Altshuler et al[103] found that only about 15% of bipolar depressed patients for whom an antidepressant was prescribed in open treatment met criteria for treatment response.

Very limited data are available to guide the treatment of depression in patients with bipolar II disorder. Suppes et al[104] reported that the benefit of quetiapine was significantly superior to placebo in the subset of more than 180 bipolar II subjects randomized in 2 bipolar depression studies. In a study with a smaller bipolar II sample, however, Suppes et al[88] found that the antidepressant benefit of quetiapine extended release reached statistical significance in bipolar I but not bipolar II subjects.

Amsterdam[33,105–108] has published several papers with small samples suggesting that patients with bipolar II might safely be treated with standard antidepressants. The small studies require follow-up in fully powered controlled trials, but do offer some support for the idea that there may be subsets of bipolar II patients who benefit from standard antidepressant medication, even as monotherapy.

TREATMENT-EMERGENT AFFECT SWITCH

Prior to the advent of modern antimanic and antidepressant medications, Emil Kraepelin recognized that patients with manic-depressive illness frequently make direct transitions from one affective state to another of opposite polarity, without an intervening period of recovery.[109] The possibility that pharmacologic agents capable of treating mania or depression might lead to treatment-induced mania or depression has long been a serious concern for the field.[110–116]

Unfortunately, we lack methods to confidently determine whether any given transition between pathological mood states is iatrogenic or due to the natural course of an individual's illness. Therefore, referring to *treatment-emergent depression, hypomania, mania,* or *mixed episodes* is more accurate than using terms such as *antidepressant-induced mania* or *neuroleptic-induced depression*.

Despite several trials that have reported rates of treatment-emergent affect switch (TEAS), the extent to which standard antidepressant medications are associated with treatment-emergent hypomania or mania remains highly controversial. Rather than rehashing this unsatisfying debate, a summary of the data can provide some practical guidance for clinical practice.

None of the medications with category A evidence of efficacy for bipolar depression has been associated with treatment-emergent hypomania/mania. STEP-BD found no evidence of TEAS associated with adjunctive use of bupropion or paroxetine compared to adjunctive placebo.[93] The Stanley Foundation Bipolar Network found that venlafaxine was associated with significantly higher rates of TEAS than bupropion or sertraline.[117] Furthermore, the same study found that among subjects randomly assigned to these 3 antidepressants, overall TEAS rates were significantly higher among bipolar I subjects compared to bipolar II subjects.[118] Defining TEAS as a Young Mania Rating Scale score > 13, they observed a TEAS rate of 12% (of 134) of bipolar I subjects versus 2% (of 48) of bipolar II subjects. Defining TEAS as a Clinical Global Impressions (CGI) mania score of ≥ 3 (mildly ill) produced observed rates of 22% in bipolar I subjects and 8% of bipolar II subjects.

These findings suggest that there may be important differences between agents classified as "antidepressants" in regard to the propensity to induce affective switch. On the other hand, the putative destabilizing effect of standard antidepressants may be a reflection of a relatively small vulnerable subgroup. When standard antidepressants are administered as adjuncts to an antimanic mood stabilizing agent, 80% to 90% of subjects do not experience TEAS.

A recent review by Frye et al[119] identified risk factors associated with TEAS: tricyclic antidepressant use, prior history of treatment-emergent mania, hyperthymic temperament, comorbid alcoholism, female gender, comorbid anxiety disorder, prepubertal onset, and bipolar I subtype (vs bipolar II). The effect sizes of most, if not all, of these factors are likely to be modest and have little predictive

power for individual care. Perhaps the least controversial recommendation that can be applied in clinical practice is to avoid repeating exposure to any class of medication that has been associated with a personal history of TEAS.

EVIDENCE REVIEW: MAINTENANCE, OR PREVENTION OF RECURRENCE

Although lithium was granted FDA approval as a prophylactic treatment for bipolar disorder in 1974, the first adequately powered parallel-group double-blind placebo-controlled RCT was not published until 2000.[120] This industry-sponsored study was designed as a pivotal trial to evaluate the prophylactic utility of divalproex versus placebo and included a lithium arm to establish assay sensitivity. Although widely considered a failed trial because differences on the a priori primary outcome measure did not reach statistical significance and no benefit of lithium was detected, the study did produce several important findings. Divalproex was not significantly better than placebo on the a priori primary outcome variable, time to any mood episode. Divalproex was, however, superior to placebo on some important secondary outcome variables including lower rates of discontinuation for a recurrent mood episode and discontinuation due to a depressive episode. Divalproex was also superior to lithium for protection against depressive symptoms and on Global Assessment Scale scores. More importantly, post hoc analyses suggested that the study failed because a substantial number of subjects were randomized who were not ill at the time of enrollment and therefore not necessarily responders to acute treatment with divalproex.

In light of this problem, subsequent successful maintenance treatment studies have employed designs in which the randomized sample is enriched with responders to open acute treatment with the study drug. Furthermore, in studies with enriched design, subjects randomly assigned to placebo are actually discontinuing treatment with the study drug that had been associated with sufficient improvement to qualify them for the double-blind phase of treatment. Meta-analyses of maintenance studies show that previously stable patients suffer high relapse rates following discontinuation of medication, especially when discontinuation is rapid.[121–130] These studies, which typically show survival curves with steep slopes for the placebo group in the first months after randomization, can more accurately be considered treatment-disruption studies. Recognition of this design issue has important ramifications for understanding clinical trial results.

In an NIMH-sponsored study designed to compare the benefit of prophylactic treatment with lithium at low (0.4–0.6 mmol/L) versus standard levels (0.8–1.0 mmol/L), Gelenberg et al[131] found a significant advantage for treatment at standard levels. The risk of relapse was 2.6 times higher in those randomly assigned to the lower range treatment. A reanalysis of these data suggested that the higher relapse rate associated with lithium treatment at the low level was really driven by the high relapse rate experienced by subjects who had an abrupt 50% reduction in their dose of lithium as a consequence of randomization to switch from the standard range to the low range. Furthermore, subjects who stayed at the standard range had no advantage over subjects who started and remained at the low range. Thus, an abrupt reduction of even 50% may adversely impact the course of illness in stable patients.

Table 5. Summary of Category A Prophylaxis Studies[a]

At Least 1 Positive Trial	Only Negative or Failed Trials	Negative Study[b]
Lithium[94,133,134]	Imipramine[84]	✓
Valproate[94,120,133,134]		
Lamotrigine[94,133,134]		
Olanzapine[34,135,136]		
Aripiprazole[137]		
Quetiapine[138]		
Ziprasidone[139]		
Risperidone[140]		

[a]Statistical power ≥ 0.8 to detect meaningful differences at $P < .05$.
[b]Interpreted as a "negative study" because the study drug failed to separate from placebo and the study included an active comparator that did separate from placebo.

Although most of the relapse prevention data come from studies of agents with acute antimanic activity, similar results are reported following treatment of acute bipolar depression.[94] In a small double-blind study, Ghaemi et al[132] found trends that reached borderline statistical significance indicating worsening course following discontinuation of effective antidepressant medications.

In a 3-arm prophylaxis study that randomized 117 bipolar I subjects but did not include placebo, Prien et al[84] reported that lithium and lithium plus imipramine were superior to imipramine alone in preventing recurrences of mania and found no significant differences between the 3 conditions for prevention of depression.

As seen in Table 5, category A studies support the use of lithium,[94,133,134] lamotrigine,[94,133,134] olanzapine,[34,135,136] aripiprazole,[137] quetiapine,[138] ziprasidone,[139] and the long-acting injectable form of risperidone[140] for preventing recurrence of acute episodes. These successful category A studies, however, all randomized patients who had experienced a remission of acute phase symptoms during treatment with the study medication prior to randomization. This methodological issue has important clinical implications. The data from these successful maintenance studies cannot support the practice of switching from acute phase treatments to a new maintenance treatment after resolution of an acute episode. Instead, the data provide persuasive argument against treatment disruption and support continued treatment with agents that were a part of a successful acute phase regimen.

The BALANCE study[141] was a large simple trial designed to compare long-term outcomes of treatment with lithium, valproate, and the combination of lithium and valproate in subjects who were not acutely ill, but warranted maintenance treatment. Consenting bipolar subjects all started 4 to 8 weeks of open treatment with the combination of lithium and

valproate. Subjects (n = 330) were then randomly assigned to continuing combination treatment, lithium monotherapy (by tapering off valproate) (plasma concentration, 0.4–1.0 mmol/L), or valproate monotherapy (by tapering off lithium) (750–1250 mg). The primary outcome was time to intervention (either medication or hospitalization), and patients could be randomized without necessarily being euthymic. Although the hazard ratio for combination therapy versus lithium monotherapy was 0.82 (95% CI = 0.58–1.17, *P* = .27), the difference was not statistically significant. The study did, however, find a significant advantage for combination treatment compared to valproate monotherapy (hazard ratio = 0.59, 95% CI = 0.42–0.83, *P* = .0023). This finding may not be generalizable due to the low valproate dosage used, but it at least informs practitioners that low-dose valproate maintenance treatment is of little merit.

Like other studies above, BALANCE used a discontinuation paradigm. Notably, the study was enriched only to the extent that randomized subjects were able to tolerate the combination of lithium and valproate rather than necessarily respond to combination treatment. The apparent disagreement between this study and the Bowden et al report[37] may simply reflect the difference in entry criteria, dosing, and definition of outcome, but it is also possible that maintaining therapeutic lithium levels protects against recurrence due to valproate discontinuation, while valproate as dosed in BALANCE does not protect against recurrence due to lithium discontinuation.

Individual factors reported as associated with relapse and poor outcome for bipolar disorders include early age at onset, psychosis,[142] psychiatric comorbidities,[143–145] residual mood symptoms,[146,147] history of frequent episodes,[143,148,149] and use of antidepressants.[111] In women with bipolar disorders, postpartum[150] and the menopause transition[151] are also periods of increased vulnerability to illness relapse. Consistent with early reports suggesting familial response to lithium,[152] Perlis and colleagues[153] have reported several genes with modest association to lithium response in both the STEP-BD and University College London cohorts. Large-scale genome-wide association studies have promise to identify predictors of individual response to specific prophylactic treatments.

CONCLUSIONS

Bipolar disorders are common chronic complex conditions. Accumulated clinical trial data now offer a scientific basis for clinical decision making. No clinically useful biomarkers have been identified for predicting treatment response. A systematic iterative approach to treatment in which measurement is integrated into the management plan offers a means to bridge from population-based recommendations to personalized care. The distinction between efficacy and effectiveness research includes at least tacit recognition of potential individual differences in response to treatment and the importance of care delivery systems.

Patients with acute mania vary widely in symptomatology and clinical urgency. Although dopamine-blocking agents appear to be preferable for more severely ill patients, non–dopamine-blocking antimanic agents may be more tolerable. Most often, treatment over a period of 3 to 4 weeks is insufficient to achieve full remission. The data support a class effect for dopamine-blocking agents but not anticonvulsants as treatment for acute mania.

Four treatments have positive category A evidence for the treatment of bipolar depression. There is no evidence that adding standard antidepressant medication destabilizes patients treated with agents that have proven antimanic efficacy.

All agents with proven efficacy for relapse prevention have gained approval based on studies that randomized patients who had already improved in response to study medication. This so-called enriched design is an important limitation on the generalizability of results from relapse prevention studies, but has consistently replicated the finding that abrupt discontinuation of treatment can destabilize bipolar patients.

More research and further refinement in methodology are needed to facilitate the translation of population-based data to personalized treatment.

Drug names: aripiprazole (Abilify), asenapine (Saphris), bupropion (Wellbutrin, Aplenzin, and others), carbamazepine (Carbatrol, Equetro, and others), fluoxetine (Prozac and others), gabapentin (Neurontin and others), haloperidol (Haldol and others), imipramine (Tofranil and others), lamotrigine (Lamictal and others), lithium (Lithobid and others), olanzapine (Zyprexa), oxcarbazepine (Trileptal and others), paliperidone (Invega), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), risperidone (Risperdal and others), topiramate (Topamax and others), venlafaxine (Effexor and others), ziprasidone (Geodon).

Author affiliations: Bipolar Clinic and Research Program, Massachusetts General Hospital, Boston (all authors); and United BioSource Corporation, Lexington (Dr Sachs), Massachusetts.

Potential conflicts of interest: **Dr Sachs** is an employee of United BioSource Corporation; has been a consultant for Forest, Merck, Sunovion, and Takeda; has received grant/research support from the National Institute of Mental Health and Repligen; has been on the speakers/advisory boards of AstraZeneca, Pfizer, and Otsuka; and is a stock shareholder in Concordant Rater Systems. **Drs Dupuy** and **Wittmann** report no financial or other relationships relevant to the subject of this article.

Funding/support: None reported.

REFERENCES

1. Angst J, Gamma A, Lewinsohn P. The evolving epidemiology of bipolar disorder. *World Psychiatry*. 2002;1(3):146–148. PubMed
2. Judd LL, Akiskal HS. The prevalence and disability of bipolar spectrum disorders in the US population: re-analysis of the ECA database taking into account subthreshold cases. *J Affect Disord*. 2003;73(1–2):123–131. doi:10.1016/S0165-0327(02)00332-4 PubMed
3. Kessler RC, Akiskal HS, Ames M, et al. Prevalence and effects of mood disorders on work performance in a nationally representative sample of US workers. *Am J Psychiatry*. 2006;163(9):1561–1568. doi:10.1176/appi.ajp.163.9.1561 PubMed
4. Perlis RH, Miyahara S, Marangell LB, et al; STEP-BD Investigators. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Biol Psychiatry*. 2004;55(9):875–881. doi:10.1016/j.biopsych.2004.01.022 PubMed
5. Leboyer M, Henry C, Paillere-Martinot ML, et al. Age at onset in bipolar affective disorders: a review. *Bipolar Disord*. 2005;7(2):111–118. doi:10.1111/j.1399-5618.2005.00181.x PubMed
6. Simon GE. Social and economic burden of mood disorders.

Biol Psychiatry. 2003;54(3):208–215. doi:10.1016/S0006-3223(03)00420-7 PubMed
7. Simon NM, Otto MW, Wisniewski SR, et al. Anxiety disorder comorbidity in bipolar disorder patients: data from the first 500 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Am J Psychiatry*. 2004;161(12):2222–2229. doi:10.1176/appi.ajp.161.12.2222 PubMed
8. Summers M, Papadopoulou K, Bruno S, et al. Bipolar I and bipolar II disorder: cognition and emotion processing. *Psychol Med*. 2006;36(12):1799–1809. doi:10.1017/S0033291706008804 PubMed
9. Chengappa KN, Levine J, Gershon S, et al. Lifetime prevalence of substance or alcohol abuse and dependence among subjects with bipolar I and II disorders in a voluntary registry. *Bipolar Disord*. 2000;2(3, pt 1):191–195. doi:10.1034/j.1399-5618.2000.020306.x PubMed
10. Goldberg JF, Garno JL, Leon AC, et al. A history of substance abuse complicates remission from acute mania in bipolar disorder. *J Clin Psychiatry*. 1999;60(11):733–740. doi:10.4088/JCP.v60n1103 PubMed
11. Brady KT, Lydiard RB. Bipolar affective disorder and substance abuse. *J Clin Psychopharmacol*. 1992;12(suppl):17S–22S. PubMed
12. Biederman J, Faraone SV, Wozniak J, et al. Parsing the association between bipolar, conduct, and substance use disorders: a familial risk analysis. *Biol Psychiatry*. 2000;48(11):1037–1044. doi:10.1016/S0006-3223(00)00906-9 PubMed
13. Winokur G, Turvey C, Akiskal H, et al. Alcoholism and drug abuse in three groups—bipolar I, unipolars and their acquaintances. *J Affect Disord*. 1998;50(2–3):81–89. doi:10.1016/S0165-0327(98)00108-6 PubMed
14. Venn HR, Gray JM, Montagne B, et al. Perception of facial expressions of emotion in bipolar disorder. *Bipolar Disord*. 2004;6(4):286–293. doi:10.1111/j.1399-5618.2004.00121.x PubMed
15. Clark L, Kempton MJ, Scarnà A, et al. Sustained attention-deficit confirmed in euthymic bipolar disorder but not in first-degree relatives of bipolar patients or euthymic unipolar depression. *Biol Psychiatry*. 2005;57(2):183–187. doi:10.1016/j.biopsych.2004.11.007 PubMed
16. Robinson LJ, Thompson JM, Gallagher P, et al. A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. *J Affect Disord*. 2006;93(1–3):105–115. doi:10.1016/j.jad.2006.02.016 PubMed
17. Evans DL, Charney DS, Lewis L, et al. Mood disorders in the medically ill: scientific review and recommendations. *Biol Psychiatry*. 2005;58(3):175–189. doi:10.1016/j.biopsych.2005.05.001 PubMed
18. McIntyre RS, Konarski JZ, Soczynska JK, et al. Medical comorbidity in bipolar disorder: implications for functional outcomes and health service utilization. *Psychiatr Serv*. 2006;57(8):1140–1144. doi:10.1176/appi.ps.57.8.1140 PubMed
19. Newcomer JW. Medical risk in patients with bipolar disorder and schizophrenia. *J Clin Psychiatry*. 2006;67(suppl 9):25–30, discussion 36–42. doi:10.4088/JCP.1106e16 PubMed
20. Wang PW, Sachs GS, Zarate CA, et al. Overweight and obesity in bipolar disorders. *J Psychiatr Res*. 2006;40(8):762–764. doi:10.1016/j.jpsychires.2006.01.007 PubMed
21. Arnold LM, Hudson JI, Keck PE, et al. Comorbidity of fibromyalgia and psychiatric disorders. *J Clin Psychiatry*. 2006;67(8):1219–1225. doi:10.4088/JCP.v67n0807 PubMed
22. Hamelsky SW, Lipton RB. Psychiatric comorbidity of migraine. *Headache*. 2006;46(9):1327–1333. doi:10.1111/j.1526-4610.2006.00576.x PubMed
23. McKenna MT, Michaud CM, Murray CJ, et al. Assessing the burden of disease in the United States using disability-adjusted life years. *Am J Prev Med*. 2005;28(5):415–423. doi:10.1016/j.amepre.2005.02.009 PubMed
24. Ustün TB, Ayuso-Mateos JL, Chatterji S, et al. Global burden of depressive disorders in the year 2000. *Br J Psychiatry*. 2004;184(5):386–392. doi:10.1192/bjp.184.5.386 PubMed
25. Murray CJ, Lopez AD, Jamison DT. The global burden of disease in 1990: summary results, sensitivity analysis and future directions. *Bull World Health Organ*. 1994;72(3):495–509. PubMed
26. Osby U, Brandt L, Correia N, et al. Excess mortality in bipolar and unipolar disorder in Sweden. *Arch Gen Psychiatry*. 2001;58(9):844–850. doi:10.1001/archpsyc.58.9.844 PubMed
27. Angst F, Stassen HH, Clayton PJ, et al. Mortality of patients with mood disorders: follow-up over 34–38 years. *J Affect Disord*. 2002;68(2–3):167–181. doi:10.1016/S0165-0327(01)00377-9 PubMed
28. Sachs GS. Strategies for improving treatment of bipolar disorder: integration of measurement and management. *Acta Psychiatr Scand Suppl*. 2004;110(422):7–17. doi:10.1111/j.1600-0447.2004.00409.x PubMed
29. Dennehy EB, Bauer MS, Perlis RH, et al. Concordance with treatment guidelines for bipolar disorder: data from the Systematic Treatment Enhancement Program for Bipolar Disorder. *Psychopharmacol Bull*. 2007;40(3):72–84. PubMed
30. Sachs G. *Managing Bipolar Affective Disorder*. London, UK: Science Press Ltd; 2004.
31. Klerman GL. The psychiatric patient's right to effective treatment: implications of Osheroff v. Chestnut Lodge. *Am J Psychiatry*. 1990;147(4):409–418. PubMed
32. Altshuler LL, Post RM, Hellemann G, et al. Impact of antidepressant continuation after acute positive or partial treatment response for bipolar depression: a blinded, randomized study. *J Clin Psychiatry*. 2009;70(4):450–457. doi:10.4088/JCP.08m04191 PubMed
33. Amsterdam JD, Shults J. Efficacy and safety of long-term fluoxetine versus lithium monotherapy of bipolar II disorder: a randomized, double-blind, placebo-substitution study. *Am J Psychiatry*. 2010;167(7):792–800. doi:10.1176/appi.ajp.2009.09020284 PubMed
34. Tohen M, Calabrese JR, Sachs GS, et al. Randomized, placebo-controlled trial of olanzapine as maintenance therapy in patients with bipolar I disorder responding to acute treatment with olanzapine. *Am J Psychiatry*. 2006;163(2):247–256. doi:10.1176/appi.ajp.163.2.247 PubMed
35. Kemp DE, Ganocy SJ, Brecher M, et al. Clinical value of early partial symptomatic improvement in the prediction of response and remission during short-term treatment trials in 3369 subjects with bipolar I or II depression. *J Affect Disord*. 2011;130(1–2):171–179. doi:10.1016/j.jad.2010.10.026 PubMed
36. Cade JF. Lithium salts in the treatment of psychotic excitement. *Med J Aust*. 1949;2(10):349–352. PubMed
37. Bowden CL, Brugger AM, Swann AC, et al; The Depakote Mania Study Group. Efficacy of divalproex vs lithium and placebo in the treatment of mania. *JAMA*. 1994;271(12):918–924. doi:10.1001/jama.271.12.918 PubMed
38. Prien RF, Caffey EM Jr, Klett CJ; Report of the Veterans Administration and National Institute of Mental Health Collaborative Study Group. Comparison of lithium carbonate and chlorpromazine in the treatment of mania. *Arch Gen Psychiatry*. 1972;26(2):146–153. PubMed
39. Bowden CL, Grunze H, Mullen J, et al. A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. *J Clin Psychiatry*. 2005;66(1):111–121. doi:10.4088/JCP.v66n0116 PubMed
40. Pope HG Jr, McElroy SL, Keck PE Jr, et al. Valproate in the treatment of acute mania: a placebo-controlled study. *Arch Gen Psychiatry*. 1991;48(1):62–68. PubMed
41. Pande AC, Crockatt JG, Janney CA, et al; Gabapentin Bipolar Disorder Study Group. Gabapentin in bipolar disorder: a placebo-controlled trial of adjunctive therapy. *Bipolar Disord*. 2000;2(3, pt 2):249–255. doi:10.1034/j.1399-5618.2000.20305.x PubMed
42. Weisler RH, Kalali AH, Ketter TA; SPD417 Study Group. A multicenter, randomized, double-blind, placebo-controlled trial of extended-release carbamazepine capsules as monotherapy for bipolar disorder patients with manic or mixed episodes. *J Clin Psychiatry*. 2004;65(4):478–484. doi:10.4088/JCP.v65n0405 PubMed
43. Weisler RH, Hirschfeld R, Cutler AJ, et al; SPD417 Study Group. Extended-release carbamazepine capsules as monotherapy in bipolar disorder: pooled results from two randomised, double-blind, placebo-controlled trials. *CNS Drugs*. 2006;20(3):219–231. doi:10.2165/00023210-200620030-00004 PubMed
44. Wagner KD, Kowatch RA, Emslie GJ, et al. A double-blind, randomized, placebo-controlled trial of oxcarbazepine in the treatment of bipolar disorder in children and adolescents. *Am J Psychiatry*. 2006;163(7):1179–1186. doi:10.1176/appi.ajp.163.7.1179 PubMed
45. Kushner SF, Khan A, Lane R, et al. Topiramate monotherapy in the management of acute mania: results of four double-blind placebo-controlled trials. *Bipolar Disord*. 2006;8(1):15–27. doi:10.1111/j.1399-5618.2006.00276.x PubMed
46. Tohen M, Sanger TM, McElroy SL, et al; Olanzapine HGEH Study Group. Olanzapine versus placebo in the treatment of acute mania. *Am J Psychiatry*. 1999;156(5):702–709. PubMed
47. Tohen M, Jacobs TG, Grundy SL, et al; The Olanzapine HGGW Study Group. Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. *Arch Gen Psychiatry*. 2000;57(9):841–849. doi:10.1001/archpsyc.57.9.841 PubMed
48. Study of licarbazepine in the treatment of manic episodes of bipolar disorder. ClinicalTrials.gov identifier: NCT00099229. http://clinicaltrials.gov/ct2/show/NCT00099229?term=NCT00099229&rank=1. Updated December 12, 2007. Accessed March 31, 2011.
49. Sachs GS, Grossman F, Ghaemi SN, et al. Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind, placebo-controlled comparison of efficacy and safety.

Am J Psychiatry. 2002;159(7):1146–1154. doi:10.1176/appi.ajp.159.7.1146 PubMed
50. Yatham LN, Grossman F, Augustyns I, et al. Mood stabilisers plus risperidone or placebo in the treatment of acute mania: international, double-blind, randomised controlled trial. *Br J Psychiatry*. 2003;182(2): 141–147. doi:10.1192/bjp.182.2.141 PubMed
51. Hirschfeld RM, Keck PE Jr, Kramer M, et al. Rapid antimanic effect of risperidone monotherapy: a 3-week multicenter, double-blind, placebo-controlled trial. *Am J Psychiatry*. 2004;161(6):1057–1065. doi:10.1176/appi.ajp.161.6.1057 PubMed
52. Khanna S, Vieta E, Lyons B, et al. Risperidone in the treatment of acute mania: double-blind, placebo-controlled study. *Br J Psychiatry*. 2005;187(3):229–234. doi:10.1192/bjp.187.3.229 PubMed
53. Keck PE Jr, Versiani M, Potkin S, et al; Ziprasidone in Mania Study Group. Ziprasidone in the treatment of acute bipolar mania: a three-week, placebo-controlled, double-blind, randomized trial. *Am J Psychiatry*. 2003;160(4):741–748. doi:10.1176/appi.ajp.160.4.741 PubMed
54. Potkin SG, Keck PE Jr, Segal S, et al. Ziprasidone in acute bipolar mania: a 21-day randomized, double-blind, placebo-controlled replication trial. *J Clin Psychopharmacol*. 2005;25(4):301–310. doi:10.1097/01.jcp.0000169068.34322.70 PubMed
55. Sachs G, Chengappa KN, Suppes T, et al. Quetiapine with lithium or divalproex for the treatment of bipolar mania: a randomized, double-blind, placebo-controlled study. *Bipolar Disord*. 2004;6(3):213–223. doi:10.1111/j.1399-5618.2004.00115.x PubMed
56. Yatham LN, Paulsson B, Mullen J, et al. Quetiapine versus placebo in combination with lithium or divalproex for the treatment of bipolar mania. *J Clin Psychopharmacol*. 2004;24(6):599–606. doi:10.1097/01.jcp.0000144887.66319.2f PubMed
57. Vieta E, Mullen J, Brecher M, et al. Quetiapine monotherapy for mania associated with bipolar disorder: combined analysis of two international, double-blind, randomised, placebo-controlled studies. *Curr Med Res Opin*. 2005;21(6):923–934. doi:10.1185/030079905X46340 PubMed
58. Ketter TA, Jones M, Paulsson B. Rates of remission/euthymia with quetiapine monotherapy compared with placebo in patients with acute mania. *J Affect Disord*. 2007;100(suppl 1):S45–S53. doi:10.1016/j.jad.2007.02.006 PubMed
59. Yatham LN, Vieta E, Young AH, et al. A double blind, randomized, placebo-controlled trial of quetiapine as an add-on therapy to lithium or divalproex for the treatment of bipolar mania. *Int Clin Psychopharmacol*. 2007;22(4):212–220. doi:10.1097/YIC.0b013e328080ca57 PubMed
60. Li H, Ma C, Wang G, et al. Response and remission rates in Chinese patients with bipolar mania treated for 4 weeks with either quetiapine or lithium: a randomized and double-blind study. *Curr Med Res Opin*. 2008;24(1):1–10. doi:10.1185/030079908X253933 PubMed
61. Keck PE Jr, Marcus R, Tourkodimitris S, et al; Aripiprazole Study Group. A placebo-controlled, double-blind study of the efficacy and safety of aripiprazole in patients with acute bipolar mania. *Am J Psychiatry*. 2003;160(9): 1651–1658. doi:10.1176/appi.ajp.160.9.1651 PubMed
62. Sachs G, Sanchez R, Marcus R, et al; Aripiprazole Study Group. Aripiprazole in the treatment of acute manic or mixed episodes in patients with bipolar I disorder: a 3-week placebo-controlled study. *J Psychopharmacol*. 2006;20(4): 536–546. doi:10.1177/0269881106059693 PubMed
63. Keck PE, Orsulak PJ, Cutler AJ, et al; CN138-135 Study Group. Aripiprazole monotherapy in the treatment of acute bipolar I mania: a randomized, double-blind, placebo- and lithium-controlled study. *J Affect Disord*. 2009;112(1-3):36–49. doi:10.1016/j.jad.2008.05.014 PubMed
64. McIntyre RS, Cohen M, Zhao J, et al. Asenapine in the treatment of acute mania in bipolar I disorder: a randomized, double-blind, placebo-controlled trial. *J Affect Disord*. 2010;122(1-2):27–38. doi:10.1016/j.jad.2009.12.028 PubMed
65. McIntyre RS, Cohen M, Zhao J, et al. A 3-week, randomized, placebo-controlled trial of asenapine in the treatment of acute mania in bipolar mania and mixed states. *Bipolar Disord*. 2009;11(7):673–686. doi:10.1111/j.1399-5618.2009.00748.x PubMed
66. Vieta E, Nuamah IF, Lim P, et al. A randomized, placebo- and active-controlled study of paliperidone extended release for the treatment of acute manic and mixed episodes of bipolar I disorder. *Bipolar Disord*. 2010;12(3): 230–243. doi:10.1111/j.1399-5618.2010.00815.x PubMed
67. McIntyre RS, Brecher M, Paulsson B, et al. Quetiapine or haloperidol as monotherapy for bipolar mania—a 12-week, double-blind, randomised, parallel-group, placebo-controlled trial. *Eur Neuropsychopharmacol*. 2005; 15(5):573–585.
68. Zajecka JM, Weisler R, Sachs G, et al. A comparison of the efficacy, safety, and tolerability of divalproex sodium and olanzapine in the treatment of bipolar disorder. *J Clin Psychiatry*. 2002;63(12):1148–1155. doi:10.4088/JCP.v63n1210 PubMed
69. Tohen M, Goldberg JF, Gonzalez-Pinto Arrillaga AM, et al. A 12-week, double-blind comparison of olanzapine vs haloperidol in the treatment of acute mania. *Arch Gen Psychiatry*. 2003;60(12):1218–1226. doi:10.1001/archpsyc.60.12.1218 PubMed
70. Vieta E, Bourin M, Sanchez R, et al; Aripiprazole Study Group. Effectiveness of aripiprazole v. haloperidol in acute bipolar mania: double-blind, randomised, comparative 12-week trial. *Br J Psychiatry*. 2005;187(3): 235–242. doi:10.1192/bjp.187.3.235 PubMeddoi:10.1016/j.euroneuro.2005.02.006 PubMed
71. Tohen M, Baker RW, Altshuler LL, et al. Olanzapine versus divalproex in the treatment of acute mania. *Am J Psychiatry*. 2002;159(6):1011–1017. doi:10.1176/appi.ajp.159.6.1011 PubMed
72. Ketter T, ed. Treatment of acute mania in bipolar disorder. *Advances in Treatment of Bipolar Disorder*. Washington, DC: American Psychiatric Publishing, Inc; 2005:11–24.
73. Perlis RH, Welge JA, Vornik LA, et al. Atypical antipsychotics in the treatment of mania: a meta-analysis of randomized, placebo-controlled trials. *J Clin Psychiatry*. 2006;67(4):509–516. doi:10.4088/JCP.v67n0401 PubMed
74. Müller-Oerlinghausen B, Retzow A, Henn FA, et al; European Valproate Mania Study Group. Valproate as an adjunct to neuroleptic medication for the treatment of acute episodes of mania: a prospective, randomized, double-blind, placebo-controlled, multicenter study. *J Clin Psychopharmacol*. 2000;20(2):195–203. doi:10.1097/00004714-200004000-00012 PubMed
75. Post RM, Ketter TA, Pazzaglia PJ, et al. Rational polypharmacy in the bipolar affective disorders. *Epilepsy Res Suppl*. 1996;11:153–180. PubMed
76. Freeman MP, Stoll AL. Mood stabilizer combinations: a review of safety and efficacy. *Am J Psychiatry*. 1998;155(1):12–21. PubMed
77. Rosa AR, Fountoulakis K, Siamouli M, et al. Is anticonvulsant treatment of mania a class effect? data from randomized clinical trials [published online ahead of print December 15, 2009]. *CNS Neurosci Ther*. 2009. doi:10.1111/j.1755-5949.2009.00089.x PubMed
78. Nemeroff CB, Evans DL, Gyulai L, et al. Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression. *Am J Psychiatry*. 2001;158(6):906–912. doi:10.1176/appi.ajp.158.6.906 PubMed
79. Sachs GS, Lafer B, Stoll AL, et al. A double-blind trial of bupropion versus desipramine for bipolar depression. *J Clin Psychiatry*. 1994;55(9): 391–393. PubMed
80. Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry*. 2003;60(11):1079–1088. doi:10.1001/archpsyc.60.11.1079 PubMed
81. Himmelhoch JM, Thase ME, Mallinger AG, et al. Tranylcypromine versus imipramine in anergic bipolar depression. *Am J Psychiatry*. 1991;148(7): 910–916. PubMed
82. Thase ME, Mallinger AG, McKnight D, et al. Treatment of imipramine-resistant recurrent depression, IV: A double-blind crossover study of tranylcypromine for anergic bipolar depression. *Am J Psychiatry*. 1992; 149(2):195–198. PubMed
83. van der Loos ML, Mulder PG, Hartong EG, et al; LamLit Study Group. Efficacy and safety of lamotrigine as add-on treatment to lithium in bipolar depression: a multicenter, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2009;70(2):223–231. doi:10.4088/JCP.08m04152 PubMed
84. Prien RF, Kupfer DJ, Mansky PA, et al. Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders: report of the NIMH Collaborative Study Group comparing lithium carbonate, imipramine, and a lithium carbonate-imipramine combination. *Arch Gen Psychiatry*. 1984;41(11):1096–1104. PubMed
85. McElroy SL, Weisler RH, Chang W, et al; EMBOLDEN II (Trial D1447C00134) Investigators. A double-blind, placebo-controlled study of quetiapine and paroxetine as monotherapy in adults with bipolar depression (EMBOLDEN II). *J Clin Psychiatry*. 2010;71(2):163–174. doi:10.4088/JCP.08m04942gre PubMed
86. Young AH, McElroy SL, Bauer M, et al; EMBOLDEN I (Trial 001) Investigators. A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I). *J Clin Psychiatry*. 2010;71(2):150–162. doi:10.4088/JCP.08m04995gre PubMed
87. Calabrese JR, Keck PE Jr, Macfadden W, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. *Am J Psychiatry*. 2005;162(7):1351–1360. doi:10.1176/appi.ajp.162.7.1351 PubMed

88. Suppes T, Datto C, Minkwitz M, et al. Effectiveness of the extended release formulation of quetiapine as monotherapy for the treatment of acute bipolar depression. *J Affect Disord*. 2010;121(1-2):106–115. doi:10.1016/j.jad.2009.10.007 PubMed
89. Thase ME, Macfadden W, Weisler RH, et al; BOLDER II Study Group. Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). *J Clin Psychopharmacol*. 2006;26(6):600–609. doi:10.1097/01.jcp.0000248603.76231.b7 PubMed
90. Thase ME, Jonas A, Khan A, et al. Aripiprazole monotherapy in nonpsychotic bipolar I depression: results of 2 randomized, placebo-controlled studies. *J Clin Psychopharmacol*. 2008;28(1):13–20. doi:10.1097/jcp.0b013e3181618eb4 PubMed
91. Sachs GS, Ice K, Chappell P, et al. Efficacy and safety of adjunctive oral ziprasidone for acute treatment of depression in patients with bipolar I disorder. *J Clin Psychiatry*. In press.
92. Multicenter, randomized, double-blind, placebo-controlled, parallel-group study of bifeprunox in the treatment of depression in outpatients with bipolar disorder. ClinicalTrials.gov identifier: NCT00134459. http://clinicaltrials.gov/ct2/results?term=NCT00134459. Updated July 6, 2009. Accessed March 31, 2011.
93. Sachs GS, Nierenberg AA, Calabrese JR, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. *N Engl J Med*. 2007;356(17):1711–1722. doi:10.1056/NEJMoa064135 PubMed
94. Calabrese JR, Bowden CL, Sachs G, et al; Lamictal 605 Study Group. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *J Clin Psychiatry*. 2003;64(9):1013–1024. doi:10.4088/JCP.v64n0906 PubMed
95. Geddes JR, Calabrese JR, Goodwin GM. Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials. *Br J Psychiatry*. 2009;194(1):4–9. doi:10.1192/bjp.bp.107.048504 PubMed
96. Perlis RH, Adams DH, Fijal B, et al. Genetic association study of treatment response with olanzapine/fluoxetine combination or lamotrigine in bipolar I depression. *J Clin Psychiatry*. 2010;71(5):599–605. doi:10.4088/JCP.08m04632gre PubMed
97. Sachs GS. Understanding why studies fail: what can you see through a third blind eye? Presented at the 15th Biennial Winter Workshop in Psychoses; November 15–18, 2009; Barcelona, Spain.
98. Sachs GS. Found in translation: concordance across global clinical trials. Presented at the 49th Annual NCDEU Meeting; June 29–July 2, 2009; Hollywood, Florida.
99. Baldessarini R, Henk H, Sklar A, et al. Psychotropic medications for patients with bipolar disorder in the United States: polytherapy and adherence. *Psychiatr Serv*. 2008;59(10):1175–1183. doi:10.1176/appi.ps.59.10.1175 PubMed
100. Gijsman HJ, Geddes JR, Rendell JM, et al. Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. *Am J Psychiatry*. 2004;161(9):1537–1547. doi:10.1176/appi.ajp.161.9.1537 PubMed
101. Sachs GS. STEP-BD Update: what have we learned. Presented at the 5th International Conference on Bipolar Disorder; June 12–14, 2003; Pittsburgh, Pennsylvania.
102. Goldberg JF, Brooks JO 3rd, Kurita K, et al. Depressive illness burden associated with complex polypharmacy in patients with bipolar disorder: findings from the STEP-BD. *J Clin Psychiatry*. 2009;70(2):155–162. doi:10.4088/JCP.08m04301 PubMed
103. Altshuler L, Suppes T, Black D, et al. Impact of antidepressant discontinuation after acute bipolar depression remission on rates of depressive relapse at 1-year follow-up. *Am J Psychiatry*. 2003;160(7):1252–1262. doi:10.1176/appi.ajp.160.7.1252 PubMed
104. Suppes T, Hirschfeld RM, Vieta E, et al. Quetiapine for the treatment of bipolar II depression: analysis of data from two randomized, double-blind, placebo-controlled studies. *World J Biol Psychiatry*. 2008;9(3):198–211. doi:10.1080/15622970701317265 PubMed
105. Amsterdam JD, Shults J. Fluoxetine monotherapy of bipolar type II and bipolar NOS major depression: a double-blind, placebo-substitution, continuation study. *Int Clin Psychopharmacol*. 2005;20(5):257–264. doi:10.1097/01.yic.0000171519.64080.c9 PubMed
106. Amsterdam JD, Shults J, Brunswick DJ, et al. Short-term fluoxetine monotherapy for bipolar type II or bipolar NOS major depression—low manic switch rate. *Bipolar Disord*. 2004;6(1):75–81. doi:10.1046/j.1399-5618.2003.00083.x PubMed
107. Amsterdam JD, Wang CH, Shwarz M, et al. Venlafaxine versus lithium monotherapy of rapid and non-rapid cycling patients with bipolar II major depressive episode: a randomized, parallel group, open-label trial. *J Affect Disord*. 2009;112(1–3):219–230. doi:10.1016/j.jad.2008.03.029 PubMed
108. Amsterdam JD, Wang G, Shults J. Venlafaxine monotherapy in bipolar type II depressed patients unresponsive to prior lithium monotherapy. *Acta Psychiatr Scand*. 2010;121(3):201–208. doi:10.1111/j.1600-0447.2009.01462.x PubMed
109. Kraepelin E. *Manic-Depressive Insanity and Paranoia*. Edinburgh, UK: E & S Livingstone; 1921.
110. Angst J. Switch from depression to mania—a record study over decades between 1920 and 1982. *Psychopathology*. 1985;18(2–3):140–154. doi:10.1159/000284227 PubMed
111. Ghaemi SN. Treatment of rapid-cycling bipolar disorder: are antidepressants mood destabilizers? *Am J Psychiatry*. 2008;165(3):300–302. doi:10.1176/appi.ajp.2007.07121931 PubMed
112. Goodwin FK. The biology of recurrence: new directions for the pharmacologic bridge. *J Clin Psychiatry*. 1989;50(suppl):40–44, discussion 45–47. PubMed
113. Wehr T, Goodwin FK. Tricyclics modulate frequency of mood cycles. *Chronobiologia*. 1979;6(4):377–385. PubMed
114. Wehr TA, Goodwin FK. Rapid cycling in manic-depressives induced by tricyclic antidepressants. *Arch Gen Psychiatry*. 1979;36(5):555–559. PubMed
115. Ahlfors UG, Baastrup PC, Dencker SJ, et al. Flupenthixol decanoate in recurrent manic-depressive illness: a comparison with lithium. *Acta Psychiatr Scand*. 1981;64(3):226–237. doi:10.1111/j.1600-0447.1981.tb00778.x PubMed
116. Zarate CA Jr, Tohen M. Double-blind comparison of the continued use of antipsychotic treatment versus its discontinuation in remitted manic patients. *Am J Psychiatry*. 2004;161(1):169–171. doi:10.1176/appi.ajp.161.1.169 PubMed
117. Post RM, Altshuler LL, Leverich GS, et al. Mood switch in bipolar depression: comparison of adjunctive venlafaxine, bupropion and sertraline. *Br J Psychiatry*. 2006;189(2):124–131. doi:10.1192/bjp.bp.105.013045 PubMed
118. Altshuler LL, Suppes T, Black DO, et al. Lower switch rate in depressed patients with bipolar II than bipolar I disorder treated adjunctively with second-generation antidepressants. *Am J Psychiatry*. 2006;163(2):313–315. doi:10.1176/appi.ajp.163.2.313 PubMed
119. Frye MA, Helleman G, McElroy SL, et al. Correlates of treatment-emergent mania associated with antidepressant treatment in bipolar depression. *Am J Psychiatry*. 2009;166(2):164–172. doi:10.1176/appi.ajp.2008.08030322 PubMed
120. Bowden CL, Calabrese JR, McElroy SL, et al; Divalproex Maintenance Study Group. A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. *Arch Gen Psychiatry*. 2000;57(5):481–489. doi:10.1001/archpsyc.57.5.481 PubMed
121. Baldessarini RJ, Tondo L. Recurrence risk in bipolar manic-depressive disorders after discontinuing lithium maintenance treatment: an overview. *Clin Drug Investig*. 1998;15(4):337–351. doi:10.2165/00044011-199815040-00010 PubMed
122. Baldessarini RJ, Tondo L, Floris G, et al. Reduced morbidity after gradual discontinuation of lithium treatment for bipolar I and II disorders: a replication study. *Am J Psychiatry*. 1997;154(4):551–553. PubMed
123. Baldessarini RJ, Tondo L, Ghiani C, et al. Illness risk following rapid versus gradual discontinuation of antidepressants. *Am J Psychiatry*. 2010;167(8):934–941. doi:10.1176/appi.ajp.2010.09060880 PubMed
124. Baldessarini RJ, Tondo L, Hennen J. Effects of lithium treatment and its discontinuation on suicidal behavior in bipolar manic-depressive disorders. *J Clin Psychiatry*. 1999;60(suppl 2):77–84, discussion 111–116. PubMed
125. Baldessarini RJ, Tondo L, Viguera AC. Discontinuing lithium maintenance treatment in bipolar disorders: risks and implications. *Bipolar Disord*. 1999;1(1):17–24. doi:10.1034/j.1399-5618.1999.10106.x PubMed
126. Faedda GL, Tondo L, Baldessarini RJ. Lithium discontinuation: uncovering latent bipolar disorder? *Am J Psychiatry*. 2001;158(8):1337–1339. doi:10.1176/appi.ajp.158.8.1337-a PubMed
127. Faedda GL, Tondo L, Baldessarini RJ, et al. Outcome after rapid vs gradual discontinuation of lithium treatment in bipolar disorders. *Arch Gen Psychiatry*. 1993;50(6):448–455. PubMed
128. Suppes T, Baldessarini RJ, Faedda GL, et al. Risk of recurrence following discontinuation of lithium treatment in bipolar disorder. *Arch Gen Psychiatry*. 1991;48(12):1082–1088. PubMed

129. Tondo L, Baldessarini RJ, Floris G, et al. Effectiveness of restarting lithium treatment after its discontinuation in bipolar I and bipolar II disorders. *Am J Psychiatry*. 1997;154(4):548–550. PubMed
130. Viguera AC, Whitfield T, Baldessarini RJ, et al. Risk of recurrence in women with bipolar disorder during pregnancy: prospective study of mood stabilizer discontinuation. *Am J Psychiatry*. 2007;164(12): 1817–1824, quiz 1923. doi:10.1176/appi.ajp.2007.06101639 PubMed
131. Gelenberg AJ, Kane JM, Keller MB, et al. Comparison of standard and low serum levels of lithium for maintenance treatment of bipolar disorder. *N Engl J Med*. 1989;321(22):1489–1493. doi:10.1056/NEJM198911303212201 PubMed
132. Ghaemi SN, Ostacher MM, El-Mallakh RS, et al. Antidepressant discontinuation in bipolar depression: a Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) randomized clinical trial of long-term effectiveness and safety. *J Clin Psychiatry*. 2010;71(4): 372–380. doi:10.4088/JCP.08m04909gre PubMed
133. Goodwin GM, Bowden CL, Calabrese JR, et al. A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder. *J Clin Psychiatry*. 2004;65(3):432–441. doi:10.4088/JCP.v65n0321 PubMed
134. Bowden CL, Calabrese JR, Sachs G, et al; Lamictal 606 Study Group. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. *Arch Gen Psychiatry*. 2003;60(4):392–400. doi:10.1001/archpsyc.60.4.392 PubMed
135. Tohen M, Greil W, Calabrese JR, et al. Olanzapine versus lithium in the maintenance treatment of bipolar disorder: a 12-month, randomized, double-blind, controlled clinical trial. *Am J Psychiatry*. 2005;162(7): 1281–1290. doi:10.1176/appi.ajp.162.7.1281 PubMed
136. Tohen M, Ketter TA, Zarate CA, et al. Olanzapine versus divalproex sodium for the treatment of acute mania and maintenance of remission: a 47-week study. *Am J Psychiatry*. 2003;160(7):1263–1271. doi:10.1176/appi.ajp.160.7.1263 PubMed
137. Keck PE Jr, Calabrese JR, McQuade RD, et al; Aripiprazole Study Group. A randomized, double-blind, placebo-controlled 26-week trial of aripiprazole in recently manic patients with bipolar I disorder. *J Clin Psychiatry*. 2006;67(4):626–637. doi:10.4088/JCP.v67n0414 PubMed
138. Vieta E, Suppes T, Eggens I, et al. Efficacy and safety of quetiapine in combination with lithium or divalproex for maintenance of patients with bipolar I disorder (international trial 126). *J Affect Disord*. 2008; 109(3):251–263. doi:10.1016/j.jad.2008.06.001 PubMed
139. Bowden CL, Vieta E, Ice KS, et al. Ziprasidone plus a mood stabilizer in subjects with bipolar I disorder: a 6-month, randomized, placebo-controlled, double-blind trial. *J Clin Psychiatry*. 2010;71(2):130–137. doi:10.4088/JCP.09m05482yel PubMed
140. Macfadden W, Alphs L, Haskins JT, et al. A randomized, double-blind, placebo-controlled study of maintenance treatment with adjunctive risperidone long-acting therapy in patients with bipolar I disorder who relapse frequently. *Bipolar Disord*. 2009;11(8):827–839. doi:10.1111/j.1399-5618.2009.00761.x PubMed
141. Geddes JR, Goodwin GM, Rendell J, et al; BALANCE investigators and collaborators. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. *Lancet*. 2010;375(9712):385–395. doi:10.1016/S0140-6736(09)61828-6 PubMed
142. Goodwin FK, Jamison KR, Ghaemi SN, eds. *Manic-Depressive Illness: Bipolar Disorders and Recurrent Depression*. 2nd ed. New York, NY: Oxford University Press; 2007.
143. Otto MW, Simon NM, Wisniewski SR, et al; STEP-BD Investigators. Prospective 12-month course of bipolar disorder in out-patients with and without comorbid anxiety disorders. *Br J Psychiatry*. 2006;189(1):20–25. doi:10.1192/bjp.bp.104.007773 PubMed
144. Baldassano CF. Illness course, comorbidity, gender, and suicidality in patients with bipolar disorder. *J Clin Psychiatry*. 2006; 67(suppl 11):8–11. PubMed
145. Judd LL, Schettler PJ, Akiskal HS, et al. Residual symptom recovery from major affective episodes in bipolar disorders and rapid episode relapse/recurrence. *Arch Gen Psychiatry*. 2008;65(4):386–394. doi:10.1001/archpsyc.65.4.386 PubMed
146. Perlis RH, Ostacher MJ, Patel JK, et al. Predictors of recurrence in bipolar disorder: primary outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Am J Psychiatry*. 2006;163(2):217–224. doi:10.1176/appi.ajp.163.2.217 PubMed
147. Marangell LB, Dennehy EB, Miyahara S, et al. The functional impact of subsyndromal depressive symptoms in bipolar disorder: data from STEP-BD. *J Affect Disord*. 2009;114(1–3):58–67. doi:10.1016/j.jad.2008.07.006 PubMed
148. Levin FR, Hennessy G. Bipolar disorder and substance abuse. *Biol Psychiatry*. 2004;56(10):738–748. PubMed
149. Nierenberg AA, Miyahara S, Spencer T, et al; STEP-BD Investigators. Clinical and diagnostic implications of lifetime attention-deficit/hyperactivity disorder comorbidity in adults with bipolar disorder: data from the first 1000 STEP-BD participants. *Biol Psychiatry*. 2005; 57(11):1467–1473. doi:10.1016/j.biopsych.2005.01.036 PubMed
150. Freeman MP, Smith KW, Freeman SA, et al. The impact of reproductive events on the course of bipolar disorder in women. *J Clin Psychiatry*. 2002;63(4):284–287. doi:10.4088/JCP.v63n0403 PubMed
151. Robertson Blackmore E, Craddock N, Walters J, et al. Is the perimenopause a time of increased risk of recurrence in women with a history of bipolar affective postpartum psychosis? a case series. *Arch Women Ment Health*. 2008;11(1):75–78. doi:10.1007/s00737-008-0215-2 PubMed
152. Grof P, Duffy A, Cavazzoni P, et al. Is response to prophylactic lithium a familial trait? *J Clin Psychiatry*. 2002;63(10):942–947. doi:10.4088/JCP.v63n1013 PubMed
153. Perlis RH, Smoller JW, Ferreira MA, et al. A genomewide association study of response to lithium for prevention of recurrence in bipolar disorder. *Am J Psychiatry*. 2009;166(6):718–725. doi:10.1176/appi.ajp.2009.08111633 PubMed

The Future of Psychopharmacology of Depression

Trina Chang, MD, and Maurizio Fava, MD

There are clear limitations to the currently approved pharmacotherapies of depression, including the fact that they are all essentially monoamine-based, have modest efficacy and a relatively slow onset of efficacy, and suffer from significant tolerability issues, particularly in the long term, including sexual dysfunction, weight gain, and cognitive impairments. This article reviews some of the most promising novel mechanisms that are not represented in compounds currently approved for depression in either the United States or Europe and that may represent the future of the psychopharmacologic treatment of depression, potentially addressing some of the efficacy and tolerability issues of antidepressants on the market. These potential antidepressant treatments include the multimodal serotonergic agents, the triple uptake inhibitors, the neurokinin-based novel therapies, the glutamatergic treatments, the nicotinic receptor–based treatments, the neurogenesis-based treatments, and antiglucocorticoid therapies. Some of these mechanisms appear to be more advanced in terms of drug development than others, but they all contribute to the global effort to develop more effective and better tolerated treatments for major depressive disorder.

J Clin Psychiatry 2010;71(8):971–975

Submitted: *May 5, 2010; accepted June 17, 2010 (doi:10.4088/JCP.10m06223blu).*
Corresponding author: *Maurizio Fava, MD, Depression Clinical and Research Program, Massachusetts General Hospital, 55 Fruit St, Bulfinch 351, Boston, MA 02114 (MFava@Partners.org).*

It has been more than 20 years since the last major revolution in antidepressant pharmacotherapy, the introduction of selective serotonin reuptake inhibitors (SSRIs). The SSRIs seemed to promise efficacy comparable to that of the antidepressants already on the market, namely, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), without the problematic side effects and drug interactions of those drug classes. Similar hopes were attached to their derivative compounds, the serotonin-norepinephrine reuptake inhibitors (SNRIs) and norepinephrine reuptake inhibitors (NERIs), and to other new antidepressants developed since then, such as bupropion and mirtazapine. Indeed, these new antidepressants have proven to be more tolerable and acceptable than TCAs and MAOIs: SSRIs accounted for more than half of all antidepressant prescriptions in 2006,[1] and, following their introduction, adult use of antidepressants nearly tripled from 1988–1994 to 1999–2004.[2] In the recent Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, a large "real-world" study of depression treatment, approximately half of all patients became symptom-free with one of the first 2 treatment strategies in the study.[3,4]

All the same, these newer medications represent only a limited advance beyond their predecessors. One major reason is that all existing pharmacotherapies of depression are essentially monoamine-based. While the effects of monoamine-based antidepressants may go well beyond the initial changes in monoamine system function and may lead to broader brain circuitry changes,[5] so far they have all been limited by relatively modest efficacy overall[6] and significant tolerability issues, particularly in the long term.[7]

The therapeutic efficacy limitations of these monoamine-based antidepressants include the following concerns: (1) relatively modest remission rates[8]; (2) relatively slow onset of efficacy and delayed time to remission, so that, of ultimate remitters, as many as half will not remit until 6 to 12 weeks of ongoing antidepressant therapy[9]; and (3) lower effectiveness for certain depressive symptoms such as sleep disturbances and fatigue than for others.[10]

The tolerability limitations of currently available antidepressant therapies are also of great significance. Among them are the following: (1) elevated rates of sexual dysfunction,[11] with the possible exceptions of bupropion,[12] vilazodone,[13] and agomelatine[14]; (2) modest yet troublesome rates of weight gain during long-term antidepressant treatment,[15] once again with the exception perhaps of bupropion,[16] NERIs such as reboxetine,[17] and agomelatine[18]; (3) relatively high rates of insomnia and/or daytime sleepiness[19–21]; (4) treatment-emergent anxiety and nervousness[21]; and (5) relatively high rates of cognitive, memory, and attentional difficulties during long-term antidepressant treatment.[22]

This article will review some of the most promising novel mechanisms that are not represented in compounds currently approved for depression in either the United States or Europe and that may represent the future of the psychopharmacologic treatment of depression, potentially addressing some of the efficacy and tolerability issues of antidepressants on the market.

MULTIMODAL SEROTONERGIC AGENTS

These compounds are an extension of the currently available SSRIs and SNRIs. They typically include elements of inhibition of the serotonin transporter and elements that either block serotonergic receptors, such as the serotonin 5-HT_{2A} receptor, and/or act as a partial agonist of serotonergic receptors, such as the 5-HT_{1A} receptors, within the same molecule. The advantage of the additional receptor effects is supported, for example, by the fact that partial agonism of the 5-HT_{1A} receptors has been shown to help with

SSRI-induced sexual dysfunction with buspirone augmentation.[23] One example of a multimodal serotonergic agent is vilazodone, which combines the effects of an SSRI with 5-HT_{1A} receptor partial agonist activity[13]; it has shown efficacy in major depressive disorder (MDD) trials and a relatively benign sexual profile.[13] Another example is a compound under development by Lundbeck (Lu AA21004), which combines SSRI activity with 5-HT_3 receptor antagonism and 5-HT_{1A} agonism and has shown efficacy in a proof-of-concept trial by Artigas et al.[24]

TRIPLE UPTAKE INHIBITORS

The triple uptake inhibitors (TUIs) are probably considered the "low-hanging fruit" in monoamine-based drug development, as they capitalize on known pharmacologic actions. These compounds typically combine inhibition of the serotonin, norepinephrine, and dopamine transporters, with the idea that targeting the dopamine transporter will enhance overall efficacy; address anhedonia, apathy, and cognitive impairment; and minimize residual fatigue and sleepiness, as suggested by the dopamine reuptake inhibitor modafinil augmentation studies of SSRIs.[25] In addition, given the usefulness of dopaminergic compounds in treating SSRI-induced sexual dysfunction,[26,27] TUIs are expected to be associated with lesser sexual dysfunction than SSRIs and SNRIs. Another postulated advantage of the TUIs is that the synergistic effect of the triple inhibition may allow robust effects on these 3 neurotransmitters without requiring a high occupancy of the serotonin transporter, thus minimizing SSRI-related side effects.[28] The only TUI currently available, the weight loss drug sibutramine, has modest dopamine reuptake–inhibiting properties through its metabolites,[29] in addition to its SNRI activity.[30]

One of the concerns that has perhaps limited the enthusiasm for this mechanism has traditionally been the risk for abuse related to the dopamine transporter inhibition. Yet, there are clear examples in the literature to the contrary: self-administration, used as a marker of abuse liability, was not observed in rats given a TUI,[31] while an anti–alcohol abuse effect was seen in another rodent study of a TUI developed by DOV.[32]

NEUROKININ-BASED NOVEL THERAPIES (NK_1 ANTAGONISTS)

Neurokinin (NK) receptors and their endogenous ligand, substance P (SP), have been shown to be highly expressed in areas of the brain involved in the regulation of mood.[33] The NK_1 receptor is the principal central nervous system (CNS) receptor for SP in humans[34] and, for that reason, has been the target of significant drug development in depression. Due to their novel, nonmonoaminergic mechanism, NK_1 antagonists have been of great interest as monotherapy or adjunctive treatments for treatment-resistant depression (TRD). In addition, SP and its preferred NK_1 receptor have been identified within brain areas known to be involved in the regulation of stress and anxiety responses, and aversive and stressful stimuli have been shown repeatedly to change SP brain tissue content as well as NK_1 receptor binding.[35] Therefore, one of the questions concerning NK_1 antagonists is whether drug development in depression should target, in particular, anxious depression or depression with high levels of stress, or whether relapse prevention, given the role of stress in triggering relapses, would be a more appropriate role for these compounds. With respect to NK_1 antagonism, it is unclear whether a minimum level of receptor occupancy has to be achieved to obtain a consistent therapeutic effect.

Despite an initial positive study with the NK_1 antagonist aprepitant (otherwise known as MK-869 or L-754030),[36] 5 subsequent double-blind, placebo-controlled trials of aprepitant failed to show greater efficacy for aprepitant than placebo.[37] Another Merck NK_1 antagonist compound showed promise in a proof-of-concept study,[38] but the results of a subsequent double-blind study comparing 2 doses of L-759274 with paroxetine 20 mg and placebo were also interpreted as inconclusive.[39] Finally, studies involving the use of NK_2-selective receptor antagonists as monotherapy for MDD are currently underway (www.clinicaltrials.gov: NCT00429260, NCT00336713, NCT00415142).

GLUTAMATE-BASED TREATMENTS

Glycine and glutamate serve as primary excitatory neurotransmitters in the CNS, where they participate in many functions through activation of several ionotropic receptors, including the *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA), and kainate receptors as well as the type I, II, and III metabotropic glutamate receptors.[40] It has been hypothesized that NMDA receptor antagonists may possess neuroprotective properties and, as a result, antidepressant effects.[41] Reports of rapid and sustained antidepressant effects following injections of the NMDA antagonist ketamine have generated significant interest in the field of depression, as has the announcement that another NMDA receptor antagonist targeting the NR2B subtype, traxoprodil (CP 101 606), has antidepressant effects in patients unresponsive to an SSRI.[42] Further interest in the development of new glutamatergic antidepressants has been spurred by a positive double-blind augmentation study of the NMDA antagonist and dopaminergic drug amantadine in depressed imipramine nonresponders[43] and by the robust improvement reported in an open trial in TRD of riluzole, an agent shown to inhibit the release of glutamic acid as well as noncompetitively inhibit the NMDA receptors.[44] More recently, however, a double-blind, placebo-controlled trial involving the use of the NMDA receptor antagonist memantine for the treatment of MDD did not reveal greater reduction in depressive symptom severity among patients receiving memantine than those receiving placebo.[45]

A major limitation in testing and potential development of NMDA antagonists as antidepressants is that some of these

agents may possess hallucinogenic properties and may even induce psychotic-like symptoms in subjects with or without a history of psychosis.[46,47]

Unlike NMDA antagonists such as amantadine, the potential role of AMPA, kainate, or metabotropic glutamate receptor antagonists in alleviating CNS diseases is not as well studied, although there is considerable interest in these compounds as well. Given the beneficial effects of glutamatergic agents such as memantine on cognition,[48] these agents are considered to be potentially effective in the treatment of cognitive dysfunction in depression or in the treatment of MDD presenting with prominent cognitive dysfunction.

NICOTINIC RECEPTOR–BASED TREATMENTS

The nicotinic receptor is an ionotropic receptor consisting of 5 subunits.[49] In the human CNS, 11 different subunits have been identified (α2–9, β2–4), with most nicotinic receptors consisting of a combination of α and β subunits.[49] The most abundant and widespread nicotinic receptors in the mammalian CNS are the α4β2, α3β4, α3β2, and α7 (ie, consisting of 5 α7 subunits).[50]

There is some evidence to suggest a potential role for nicotinic receptor antagonists in depression, since several antidepressants such as the tricyclic antidepressant imipramine also possess nicotinic receptor antagonist effects.[51] Recent findings have shown TC-5214, the *S*-(+)-enantiomer of mecamylamine, a noncompetitive nicotinic receptor antagonist (α4β2, α4β2, and α7), to be active in animal models of depression[52] and to be more effective than placebo in augmenting SSRIs in TRD in a phase 2b trial.[53]

In addition, it appears that the various nicotinic-receptor subtypes may be involved in different functions including memory, cognition, and behavioral reinforcement/addiction. For example, the α4β2[54] receptors have been reported to play a key role in acetylcholine-mediated dopamine release in areas involved in behavioral reinforcement and addiction, including the striatum, ventral tegmental area, and nucleus accumbens,[55] while the α7 receptors have been linked to cognitive functions, including learning and memory, in preclinical studies.[56] Therefore, developing specific nicotinic receptor ligands, such as α7 receptor agonists and α4β2 partial agonists, may offer opportunities to develop novel treatments for depression as well as treatments to target cognitive dysfunction and inattention in depression.

The main obstacle in the drug development of pronicotinergic-based treatments for depression is the abuse liability associated with nicotinic receptor agonism, which is thought to be secondary to nicotinic receptor–mediated dopamine release in mesolimbic brain areas associated with reward processing.[57]

NEUROGENESIS-BASED TREATMENTS

There is now good evidence for neuroplasticity impairments, in particular in adult neurogenesis and gliogenesis, that are caused by stress and that may contribute to mood disorders. Furthermore, studies show that a number of antidepressant therapies appear to increase neurogenesis.[58] These findings have contributed to the idea that novel antidepressant medication development could utilize adult neurogenesis and gliogenesis as preclinical cellular markers for predicting the antidepressant properties of novel compounds.[58] A recent positive, placebo-controlled, proof-of-concept trial of a combination therapy of buspirone plus melatonin, identified through a neurogenesis-based platform,[59] certainly supports the idea that this approach might identify novel non–monoamine-based antidepressant therapies.

ANTIGLUCOCORTICOID THERAPIES

Basic and clinical studies provide some evidence for elevated secretion of the hypothalamic neuropeptides corticotropin-releasing hormone (CRH) and vasopressin in depression and anxiety, with CRH predominantly acting through CRH_1 receptors to produce a number of anxiety- and depression-like symptoms. These findings suggest that CRH_1 receptors may be potential drug targets.[60] A recent report[60] summarized the results from clinical studies of 2 CRH_1 receptor antagonists: in the first study, originally designed as a safety and tolerability trial in MDD, the CRH_1 receptor antagonist NBI-30775/R121919 had a clinical profile comparable to that of the antidepressant paroxetine. In the second study, which investigated the effect of another CRH_1 receptor antagonist, NBI-34041, on stress hormone secretion in response to a psychosocial stressor, the administration of this compound reduced the stress-elicited secretion of cortisol. These preliminary studies do suggest that CRH_1 receptor antagonists and other types of antiglucocorticoid therapies may represent promising novel therapeutics in the psychopharmacology of depression.

OTHER POTENTIAL DIRECTIONS

Further expansions of the current armamentarium of drug treatments of depression will depend on the discovery of new pathways and targets for antidepressant treatment, but fortunately several other lines of psychiatric research hold promise for making these discoveries. For example, by identifying genes and gene products that are linked to increased vulnerability to mood disorders, psychiatric genetics could potentially unearth new mechanisms involved in the pathophysiology of depression. Similarly, neuroimaging studies are offering a new way of looking at the pathways involved in depression, while proteomics and neurohormonal research may lead to the discovery of other potential treatment targets. It is also likely that the use of biomarkers for treatment response may be coupled with the treatment development process so that treatments can be targeted for specific populations based on neurobiological characteristics. These approaches, combined with advances in

nonmedication treatments ranging from the development of variants of behavioral therapies to the greater interest in somatic treatments such as transcranial magnetic stimulation, make evident the great potential for improving on the successes of the most recent generation of antidepressants.

SUMMARY

There are clear limitations to the currently approved pharmacotherapies of depression, including the fact that they are all essentially monoamine-based, have modest efficacy and a relatively slow onset of efficacy, and suffer from significant tolerability issues, particularly in the long term, including sexual dysfunction, weight gain, and cognitive impairments. A number of promising novel mechanisms, which are not represented in compounds currently approved for depression in either the United States or Europe, may represent the future in the psychopharmacologic treatment of depression; the hope is that they will address some of the efficacy and tolerability issues of currently available antidepressants. These potential antidepressant treatments include the multimodal serotonergic agents, the triple uptake inhibitors, the neurokinin-based novel therapies, the glutamatergic treatments, the nicotinic receptor–based treatments, the neurogenesis-based treatments, and anti-glucocorticoid therapies. In addition, other lines of research such as psychiatric genetics and neuroimaging could point the way toward other potential new drug mechanisms. Some of these mechanisms appear to be more advanced in terms of drug development than others, but they all contribute to the global effort to develop more effective and better tolerated treatments for MDD.

Drug names: amantadine (Symmetrel and others), aprepitant (Emend), bupropion (Wellbutrin, Aplenzin, and others), buspirone (BuSpar and others), imipramine (Tofranil and others), memantine (Namenda), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), sibutramine (Meridia).

Author affiliation: Depression Clinical and Research Program, Massachusetts General Hospital, Boston.

Potential conflicts of interest: **Dr Chang** has received grant/research support from GlaxoSmithKline and Harvard Medical School. **Dr Fava** has received research support from Abbott, Alkermes, Aspect Medical Systems, AstraZeneca, BioResearch, BrainCells, Bristol-Myers Squibb, Cephalon, Clinical Trials Solutions, Covidien, Eli Lilly, EnVivo, Forest, Ganeden Biotech, GlaxoSmithKline, Johnson & Johnson, Lichtwer, Lorex, Novartis, Organon, PamLab, Pfizer, Roche, RTC Logic, Sanofi-Aventis, Shire, Solvay, Synthelabo, and Wyeth-Ayerst; has been an advisor/consultant for Abbott, Affectis, Amarin, Aspect Medical Systems, AstraZeneca, Auspex, Bayer, Best Practice Project Management, BioMarin, Biovail, BrainCells, Bristol-Myers Squibb, CeNeRx, Cephalon, Clinical Trials Solutions, CNS Response, Compellis, Cypress, Dov, Eisai, Eli Lilly, EPIX, Euthymics Bioscience, Fabre-Kramer, Forest, GenOmind, GlaxoSmithKline, Gruenthal, Janssen, Jazz, Johnson & Johnson, Knoll, Labopharm, Lorex, Lundbeck, MedAvante, Merck, Methylation Sciences, Neuronetics, Novartis, Nutrition 21, Organon, PamLab, Pfizer, PharmaStar, Pharmavite, Precision Human Biolaboratory, Prexa, PsychoGenics, Psylin Neurosciences, Rexahn, Ridge Diagnostics, Roche, RCT Logic, Sanofi-Aventis, Sepracor, Schering-Plough, Solvay, Somaxon, Somerset, Synthelabo, Takeda, Tetragenex, TransForm, Transcept, Vanda, and Wyeth-Ayerst; has had speaking/publishing affiliations with Adamed, Advanced Meeting Partners, American Psychiatric Association, American Society of Clinical Psychopharmacology, AstraZeneca, Belvoir Media Group, Boehringer Ingelheim, Bristol-Myers Squibb, Cephalon, Eli Lilly, Forest, GlaxoSmithKline, Imedex, MGH Psychiatry Academy/Primedia, MGH Psychiatry Academy/Reed Elsevier, Novartis, Organon, Pfizer, PharmaStar, United BioSource, and Wyeth-Ayerst; has equity holdings in Compellis; holds a patent for SPCD and has a patent application for a combination of azapirones and bupropion in MDD; and has received copyright royalties for the MGH CPFQ, SFI, ATRQ, DESS, and SAFER.

Funding/support: Dr Chang is supported in part by a T-32 Research Training Grant MH-19126 through the American Psychiatric Association's Program for Minority Research Training in Psychiatry.

REFERENCES

1. Schappert SM, Rechtsteiner EA. *Ambulatory Medical Care Utilization Estimates for 2006. National Health Statistics Reports; no 8*. Hyattsville, MD: National Center for Health Statistics; 2006. http://www.cdc.gov/nchs/data/nhsr/nhsr008.pdf.
2. National Center for Health Statistics. *Health, United States, 2009: With Special Feature on Medical Technology.* Hyattsville, MD: Centers for Disease Control and Prevention; 2010. http://www.cdc.gov/nchs/data/hus/hus09.pdf
3. Rush AJ, Trivedi MH, Wisniewski SR, et al. STAR*D Study Team. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *N Engl J Med*. 2006;354(12):1231–1242. doi:10.1056/NEJMoa052963 PubMed
4. Trivedi MH, Fava M, Wisniewski SR, et al. STAR*D Study Team. Medication augmentation after the failure of SSRIs for depression. *N Engl J Med*. 2006;354(12):1243–1252. doi:10.1056/NEJMoa052964 PubMed
5. Hyman SE, Nestler EJ. Initiation and adaptation: a paradigm for understanding psychotropic drug action. *Am J Psychiatry*. 1996;153(2):151–162. PubMed
6. Papakostas GI, Thase ME, Fava M, et al. Are antidepressant drugs that combine serotonergic and noradrenergic mechanisms of action more effective than the selective serotonin reuptake inhibitors in treating major depressive disorder? a meta-analysis of studies of newer agents. *Biol Psychiatry*. 2007;62(11):1217–1227. doi:10.1016/j.biopsych.2007.03.027 PubMed
7. Cassano P, Fava M. Tolerability issues during long-term treatment with antidepressants. *Ann Clin Psychiatry*. 2004;16(1):15–25. PubMed
8. Machado M, Iskedjian M, Ruiz I, et al. Remission, dropouts, and adverse drug reaction rates in major depressive disorder: a meta-analysis of head-to-head trials. *Curr Med Res Opin*. 2006;22(9):1825–1837. doi:10.1185/030079906X132415 PubMed
9. Trivedi MH, Rush AJ, Wisniewski SR, et al. STAR*D Study Team. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry*. 2006;163(1):28–40. doi:10.1176/appi.ajp.163.1.28 PubMed
10. Nierenberg AA, Keefe BR, Leslie VC, et al. Residual symptoms in depressed patients who respond acutely to fluoxetine. *J Clin Psychiatry*. 1999;60(4):221–225. PubMed
11. Clayton AH, Pradko JF, Croft HA, et al. Prevalence of sexual dysfunction among newer antidepressants. *J Clin Psychiatry*. 2002;63(4):357–366. PubMed
12. Kavoussi RJ, Segraves RT, Hughes AR, et al. Double-blind comparison of bupropion sustained release and sertraline in depressed outpatients. *J Clin Psychiatry*. 1997;58(12):532–537. PubMed
13. Khan A. Vilazodone, a novel dual-acting serotonergic antidepressant for managing major depression. *Expert Opin Investig Drugs*. 2009;18(11):1753–1764. doi:10.1517/13543780903286396 PubMed
14. Kennedy SH, Rizvi S, Fulton K, et al. A double-blind comparison of sexual functioning, antidepressant efficacy, and tolerability between agomelatine and venlafaxine XR. *J Clin Psychopharmacol*. 2008;28(3):329–333. doi:10.1097/JCP.0b013e318172b48c PubMed
15. Fava M. Weight gain and antidepressants. *J Clin Psychiatry*. 2000;61 (suppl 11):37–41. PubMed
16. Croft H, Houser TL, Jamerson BD, et al. Effect on body weight of bupropion sustained-release in patients with major depression treated for 52 weeks. *Clin Ther*. 2002;24(4):662–672. doi:10.1016/S0149-2918(02)85141-4 PubMed
17. Silveira RO, Zanatto V, Appolinário JC, et al. An open trial of reboxetine in obese patients with binge eating disorder. *Eat Weight Disord*. 2005;10(4):e93–e96. PubMed
18. Kennedy SH, Rizvi SJ. Agomelatine in the treatment of major depressive disorder: potential for clinical effectiveness. *CNS Drugs*. 2010;24(6):479–499. doi:10.2165/11534420-000000000-00000 PubMed

19. Fava M. Daytime sleepiness and insomnia as correlates of depression. *J Clin Psychiatry*. 2004;65(suppl 16):27–32. PubMed
20. Thase ME. Treatment issues related to sleep and depression. *J Clin Psychiatry*. 2000;61(suppl 11):46–50. PubMed
21. Fava M, Hoog SL, Judge RA, et al. Acute efficacy of fluoxetine versus sertraline and paroxetine in major depressive disorder including effects of baseline insomnia. *J Clin Psychopharmacol*. 2002;22(2):137–147. doi:10.1097/00004714-200204000-00006 PubMed
22. Fava M, Graves LM, Benazzi F, et al. A cross-sectional study of the prevalence of cognitive and physical symptoms during long-term antidepressant treatment. *J Clin Psychiatry*. 2006;67(11):1754–1759. doi:10.4088/JCP.v67n1113 PubMed
23. Landén M, Eriksson E, Agren H, et al. Effect of buspirone on sexual dysfunction in depressed patients treated with selective serotonin reuptake inhibitors. *J Clin Psychopharmacol*. 1999;19(3):268–271. doi:10.1097/00004714-199906000-00012 PubMed
24. Artigas F, Dragheim M, Loft H, et al. A randomized, double-blind placebo-controlled, active-referenced study of Lu AA21004 in patients with major depression. Presented at: 22nd Annual Meeting of the European College of Neuropsychopharmacology; September 2009; Istanbul, Turkey.
25. Fava M, Thase ME, DeBattista C, et al. Modafinil augmentation of selective serotonin reuptake inhibitor therapy in MDD partial responders with persistent fatigue and sleepiness. *Ann Clin Psychiatry*. 2007;19(3):153–159. doi:10.1080/10401230701464858 PubMed
26. Clayton AH, Warnock JK, Kornstein SG, et al. A placebo-controlled trial of bupropion SR as an antidote for selective serotonin reuptake inhibitor–induced sexual dysfunction. *J Clin Psychiatry*. 2004;65(1):62–67. doi:10.4088/JCP.v65n0110 PubMed
27. Damsa C, Bumb A, Bianchi-Demicheli F, et al. "Dopamine-dependent" side effects of selective serotonin reuptake inhibitors: a clinical review. *J Clin Psychiatry*. 2004;65(8):1064–1068. doi:10.4088/JCP.v65n0806 PubMed
28. Skolnick P, Krieter P, Tizzano J, et al. Preclinical and clinical pharmacology of DOV 216,303, a "triple" reuptake inhibitor. *CNS Drug Rev*. 2006;12(2):123–134. doi:10.1111/j.1527-3458.2006.00123.x PubMed
29. Nakagawa T, Ukai K, Ohyama T, et al. Effects of sibutramine on the central dopaminergic system in rodents. *Neurotox Res*. 2001;3(3):235–247. doi:10.1007/BF03033262 PubMed
30. McNeely W, Goa KL. Sibutramine: a review of its contribution to the management of obesity. *Drugs*. 1998;56(6):1093–1124. doi:10.2165/00003495-199856060-00019 PubMed
31. Liang Y, Shaw AM, Boules M, et al. Antidepressant-like pharmacological profile of a novel triple reuptake inhibitor, (1S,2S)-3-(methylamino)-2-(naphthalen-2-yl)-1-phenylpropan-1-ol (PRC200-SS). *J Pharmacol Exp Ther*. 2008;327(2):573–583. doi:10.1124/jpet.108.143610 PubMed
32. McMillen BA, Shank JE, Jordan KB, et al. Effect of DOV 102,677 on the volitional consumption of ethanol by Myers' high ethanol-preferring rat. *Alcohol Clin Exp Res*. 2007;31(11):1866–1871. doi:10.1111/j.1530-0277.2007.00513.x PubMed
33. Bergström M, Hargreaves RJ, Burns HD, et al. Human positron emission tomography studies of brain neurokinin 1 receptor occupancy by aprepitant. *Biol Psychiatry*. 2004;55(10):1007–1012. doi:10.1016/j.biopsych.2004.02.007 PubMed
34. Hargreaves R. Imaging substance P receptors (NK1) in the living human brain using positron emission tomography. *J Clin Psychiatry*. 2002;63(suppl 11):18–24. PubMed
35. Ebner K, Singewald N. The role of substance P in stress and anxiety responses. *Amino Acids*. 2006;31(3):251–272. doi:10.1007/s00726-006-0335-9 PubMed
36. Kramer MS, Cutler N, Feighner J, et al. Distinct mechanism for antidepressant activity by blockade of central substance P receptors. *Science*. 1998;281(5383):1640–1645. doi:10.1126/science.281.5383.1640 PubMed
37. Keller M, Montgomery S, Ball W, et al. Lack of efficacy of the substance P (neurokinin1 receptor) antagonist aprepitant in the treatment of major depressive disorder. *Biol Psychiatry*. 2006;59(3):216–223. doi:10.1016/j.biopsych.2005.07.013 PubMed
38. Kramer MS, Winokur A, Kelsey J, et al. Demonstration of the efficacy and safety of a novel substance P (NK1) receptor antagonist in major depression. *Neuropsychopharmacology*. 2004;29(2):385–392. doi:10.1038/sj.npp.1300260 PubMed
39. Ranga K, Krishnan R. Clinical experience with substance P receptor (NK1) antagonists in depression. *J Clin Psychiatry*. 2002;63(suppl 11):25–29. PubMed
40. Waterhouse RN. Imaging the PCP site of the NMDA ion channel. *Nucl Med Biol*. 2003;30(8):869–878. doi:10.1016/S0969-8051(03)00127-6 PubMed
41. Stahl SM, Grady MM. Differences in mechanism of action between current and future antidepressants. *J Clin Psychiatry*. 2003;64(suppl 13):13–17. PubMed
42. Skolnick P, Popik P, Trullas R. Glutamate-based antidepressants: 20 years on. *Trends Pharmacol Sci*. 2009;30(11):563–569. doi:10.1016/j.tips.2009.09.002 PubMed
43. Rogóz Z, Skuza G, Daniel WA, et al. Amantadine as an additive treatment in patients suffering from drug-resistant unipolar depression. *Pharmacol Rep*. 2007;59(6):778–784. PubMed
44. Zarate CA Jr, Payne JL, Quiroz J, et al. An open-label trial of riluzole in patients with treatment-resistant major depression. *Am J Psychiatry*. 2004;161(1):171–174. doi:10.1176/appi.ajp.161.1.171 PubMed
45. Zarate CA Jr, Singh JB, Quiroz JA, et al. A double-blind, placebo-controlled study of memantine in the treatment of major depression. *Am J Psychiatry*. 2006;163(1):153–155. doi:10.1176/appi.ajp.163.1.153 PubMed
46. Smith EJ. Amantadine-induced psychosis in a young healthy patient. *Am J Psychiatry*. 2008;165(12):1613. doi:10.1176/appi.ajp.2008.08081228 PubMed
47. Riederer P, Lange KW, Kornhuber J, et al. Pharmacotoxic psychosis after memantine in Parkinson's disease. *Lancet*. 1991;338(8773):1022–1023. doi:10.1016/0140-6736(91)91888-2 PubMed
48. McKeage K. Memantine: a review of its use in moderate to severe Alzheimer's disease. *CNS Drugs*. 2009;23(10):881–897. doi:10.2165/11201020-000000000-00000 PubMed
49. Paterson D, Nordberg A. Neuronal nicotinic receptors in the human brain. *Prog Neurobiol*. 2000;61(1):75–111. doi:10.1016/S0301-0082(99)00045-3 PubMed
50. Shytle RD, Silver AA, Lukas RJ, et al. Nicotinic acetylcholine receptors as targets for antidepressants. *Mol Psychiatry*. 2002;7(6):525–535. doi:10.1038/sj.mp.4001035 PubMed
51. Arias HR, Rosenberg A, Targowska-Duda KM, et al. Tricyclic antidepressants and mecamylamine bind to different sites in the human α4β2 nicotinic receptor ion channel. *Int J Biochem Cell Biol*. 2010;42(6):1007–1018. doi:10.1016/j.biocel.2010.03.002 PubMed
52. Lippiello PM, Beaver JS, Gatto GJ, et al. TC-5214 (*S*-(+)-mecamylamine): a neuronal nicotinic receptor modulator with antidepressant activity. *CNS Neurosci Ther*. 2008;14(4):266–277. doi:10.1111/j.1755-5949.2008.00054.x PubMed
53. Dunbar G. Positive effects of the nicotinic channel blocker TC-5214 as augmentation treatment in patients with major depressive disorder who are inadequate responders to a first-line SSRI. Presented at: Nicotinic Acetylcholine Receptor-Based Therapeutics: Emerging Frontiers in Basic Research and Clinical Science, satellite meeting to the Society for Neuroscience; October 14–16, 2009; Chicago, IL.
54. Chen Y, Sharples TJ, Phillips KG, et al. The nicotinic α4β2 receptor selective agonist, TC-2559, increases dopamine neuronal activity in the ventral tegmental area of rat midbrain slices. *Neuropharmacology*. 2003;45(3):334–344. doi:10.1016/S0028-3908(03)00189-8 PubMed
55. Salminen O, Murphy KL, McIntosh JM, et al. Subunit composition and pharmacology of two classes of striatal presynaptic nicotinic acetylcholine receptors mediating dopamine release in mice. *Mol Pharmacol*. 2004;65(6):1526–1535. doi:10.1124/mol.65.6.1526 PubMed
56. Levin ED, Bettegowda C, Blosser J, et al. AR-R17779, and alpha7 nicotinic agonist, improves learning and memory in rats. *Behav Pharmacol*. 1999;10(6–7):675–680. doi:10.1097/00008877-199911000-00014 PubMed
57. Rice ME, Cragg SJ. Nicotine amplifies reward-related dopamine signals in striatum. *Nat Neurosci*. 2004;7(6):583–584. doi:10.1038/nn1244 PubMed
58. Banasr M, Duman RS. Regulation of neurogenesis and gliogenesis by stress and antidepressant treatment. *CNS Neurol Disord Drug Targets*. 2007;6(5):311–320. doi:10.2174/187152707783220929 PubMed
59. Barlow C, Hen R, Fava M, et al. Neurogenesis assays prospectively identify a novel clinically efficacious combination for the treatment of major depressive disorder. Presented at: 48th Annual Meeting of the American College of Neuropsychopharmacology; December 6–10, 2009; Hollywood, FL.
60. Holsboer F, Ising M. Central CRH system in depression and anxiety—evidence from clinical studies with CRH1 receptor antagonists. *Eur J Pharmacol*. 2008;583(2–3):350–357. doi:10.1016/j.ejphar.2007.12.032 PubMed

The Pharmacologic Treatment of Anxiety Disorders: A Review of Progress

Lakshmi N. Ravindran, MD, and Murray B. Stein, MD, MPH

Anxiety disorders, as a group, are among the most common mental health conditions and frequently cause significant functional impairment. Both psychotherapeutic and pharmacologic techniques are recognized to be effective management strategies. This review provides a discussion of the major classes of psychotropic medications investigated in clinical trials of the following anxiety disorders: panic disorder, social anxiety disorder, generalized anxiety disorder, posttraumatic stress disorder, and obsessive-compulsive disorder. Findings suggest that both selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors are useful first-line agents for most of the anxiety disorders, particularly given the frequent comorbidity with mood disorders. Highly serotonergic agents are preferred for obsessive-compulsive disorder. Other antidepressants, such as tricyclic antidepressants or monoamine oxidase inhibitors, are generally reserved as second- and third-line strategies due to tolerability issues. Evidence for other agents, including anticonvulsants and atypical antipsychotics, suggests that they may have an adjunctive role to antidepressants in cases of treatment resistance, while azapirones have been used effectively for generalized anxiety disorder, and a substantial body of evidence supports benzodiazepine use in panic disorder and generalized anxiety disorder. Despite notable advances, many patients with anxiety disorders fail to adequately respond to existing pharmacologic treatments. Increased research attention should be focused on systematizing pharmacologic and combined pharmacologic-psychosocial strategies to address treatment resistance and developing novel treatments for anxiety disorders.

J Clin Psychiatry 2010;71(7):839–854

Submitted: *May 4, 2010; accepted May 6, 2010.*
Online ahead of print: *June 11, 2010 (doi:10.4088/JCP.10r06218blu).*
Corresponding author: *Murray B. Stein, MD, MPH, 8939 Villa La Jolla Dr, Ste 200, La Jolla, CA 92037 (mstein@ucsd.edu).*

Historically, the anxiety disorders have received relatively little research attention. Recent epidemiologic findings, though, point to their being the commonest class of mental illness[1] and frequently comorbid with other conditions, both medical and psychiatric. As such, there has been increased focus on the need to develop effective treatments, both pharmacologic and psychological, to provide symptom relief.

There are currently 6 primary anxiety disorders identified in the *DSM-IV-R*: panic disorder, generalized anxiety disorder (GAD), social anxiety disorder, posttraumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), and specific phobia. With the exception of specific phobia (for which exposure therapy or occasional as-needed benzodiazepine use has been found to be most helpful), both pharmacotherapy and psychological therapies have been used as effective treatments for the other anxiety disorders. Although a discussion of effective psychotherapies for anxiety disorders is beyond the scope of this review, the use of cognitive-behavioral therapy (CBT) is currently the gold standard in this regard.[2–5] Herein, we provide a review of different psychotropic medications used to treat anxiety disorders with an emphasis on evidence derived from randomized controlled trials (RCTs).

TRICYCLIC ANTIDEPRESSANTS

Different classes of psychotropic medications have been investigated for the treatment of anxiety disorders, with the most frequently investigated class being the antidepressants. The oldest among these, the tricyclic antidepressants (TCAs), have been used in psychiatry since the late 1950s. The TCAs, with their 3-ring molecular structure, work by inhibiting both serotonin and norepinephrine reuptake from the synaptic cleft.[6] TCAs have varying levels of evidence to support their use in different anxiety disorders.

In panic disorder, the 2 TCAs that have been most investigated are clomipramine and imipramine. Evidence from several RCTs indicates that either medication is more effective than placebo in the acute treatment of panic disorder[7–13] by reducing the number of panic attacks, decreasing anticipatory anxiety, and in some cases reducing the need for concurrent benzodiazepine use.[14] There is also additional support for the use of maintenance imipramine or clomipramine to decrease the risk of relapse.[15,16] Further, head-to-head comparison with other classes of antidepressants suggests that TCAs are as effective as newer agents such as sertraline and paroxetine[17–19] for panic disorder.

In the only double-blind placebo-controlled trial of a TCA in GAD, Rickels et al[20] found imipramine to be an effective anxiolytic, although its success was somewhat hampered by the higher reported rate of adverse effects compared to diazepam, the active comparator. In contrast to the evidence base that exists for TCAs and the other anxiety disorders, there are no placebo-controlled studies for these agents in social anxiety disorder. A small (N = 15) open trial[21] of imipramine

did not find this agent to be an effective treatment for social anxiety disorder.

TCAs have also been investigated in PTSD. Amitriptyline was found to be superior to placebo in one 8-week trial[22] in combat veterans, but the overall response rate in both groups was quite low by the end of the study (36% amitriptyline vs 28% placebo). However, desipramine, a TCA that works primarily by blocking norepinephrine reuptake, was not found to be particularly effective in a small 8-week double-blind crossover trial,[23] although the 4-week treatment periods may have been too brief to assess a beneficial effect. Two RCTs have compared imipramine to phenelzine (see "Monoamine Oxidase Inhibitors and Reversible Monoamine Oxidase Inhibitors").

The majority of controlled evidence investigating TCAs in OCD involves studies of clomipramine, a TCA with potent inhibition of serotonin reuptake. Clomipramine is the only TCA approved by the US Food and Drug Administration (FDA) for treatment of OCD. In one of the first published RCTs of TCAs in OCD,[24] clomipramine was found to be superior to placebo in ameliorating severity of OCD symptoms, while nortriptyline was not. The superiority of clomipramine over placebo has been confirmed in a number of trials of both acute-phase and continuation treatment.[25–27] Investigators have also explored the efficacy of brief courses of intravenous (IV) clomipramine. For instance, Fallon et al[28] found IV clomipramine significantly more efficacious than IV placebo in OCD patients who had failed a course of oral clomipramine. However, the more widespread use of IV clomipramine as a treatment has been limited by the need for close medical supervision and cardiac monitoring during administration (reviewed in Ravindran et al[29]). In blinded clinical trials, results of head-to-head comparisons of oral clomipramine with newer agents show similar efficacy between agents, but some authors suggest that the novel agents (fluvoxamine,[30–32] paroxetine,[33] venlafaxine[34]) may be more tolerable. Finally, Noorbala et al[35] investigated whether combining TCAs might provide additional benefit over monotherapy with clomipramine. Subjects were randomly assigned in a double-blind fashion to receive clomipramine in combination with nortriptyline or clomipramine plus placebo. While both groups improved over time, there was an advantage for the combination group in terms of both efficacy and onset of improvement.

The major limiting factors to the more widespread use of TCAs at this time are their side effect profile, which includes prominent anticholinergic and antiadrenergic effects such as sedation, constipation, dry mouth, orthostatic hypotension, and sexual dysfunction, and their well-documented risk of toxicity in overdose. These factors, along with the ready availability of other effective but more tolerable agents, have largely relegated TCAs to third- or fourth-line agents for use in treatment resistance. The exception is the use of clomipramine in OCD, for which it is largely regarded as the gold standard treatment. However, its side effect profile means that it is often only considered following a trial of a more tolerable serotonergic agent such as a selective serotonin reuptake inhibitor (SSRI).

MONOAMINE OXIDASE INHIBITORS AND REVERSIBLE MONOAMINE OXIDASE INHIBITORS

The monoamine oxidase inhibitors (MAOIs) are another older class of antidepressants that has been investigated for anxiety disorders. They work by irreversibly inhibiting the enzyme monoamine oxidase, which is responsible for the breakdown of monoamines such as serotonin and norepinephrine, resulting in a net increase in the availability of these neurotransmitters in the synapse. Both open and double-blind placebo-controlled studies support the use of MAOIs for panic disorder.[36,37]

While no double-blind placebo-controlled trials of MAOIs exist to support their use in GAD, there is a well-established evidence base for their use in social anxiety disorder. Phenelzine, in particular, has support for its efficacy from 4 double-blind placebo-controlled trials in which alprazolam,[38] atenolol,[39] moclobemide,[40] and most recently cognitive-behavioral group therapy[41] were used as active comparators.

The use of MAOIs in PTSD is more mixed. Two RCTs comparing phenelzine to imipramine and placebo for treatment of PTSD found both drugs to be superior to placebo,[42,43] with one of the trials[43] suggestive of a slight advantage for phenelzine over imipramine. However, Shestatzky et al[44] were unable to replicate these positive results for phenelzine in their 10-week double-blind crossover trial.

There is a single placebo-controlled trial[45] of MAOIs in OCD in which fluoxetine was compared to phenelzine. Fluoxetine was found to be significantly more efficacious overall than both phenelzine and placebo, although a subgroup of patients with symmetry obsessions showed response to phenelzine.

As with TCAs, the use of MAOIs is often reserved for third- or fourth-line management of anxiety disorders. This is due in part to the need to maintain a low-tyramine diet to decrease the risk of hypertensive crises, the risk of drug-drug interactions, and the side effect burden of these medications compared to newer more tolerable agents.

More recently, the use of reversible monoamine oxidase inhibitors (RIMAs) has also been investigated. The main advantage of these agents over their older counterparts is that their reversible inhibition of monoamine oxidase means that they are not subject to the same stringent dietary requirements of the MAOIs, nor do they require a 2-week washout period before switching to other antidepressant classes.

Moclobemide is a RIMA available in a number of countries worldwide, although it is not currently approved for use in the United States. Double-blind parallel-group studies[46,47] have found moclobemide to be as effective as both clomipramine and fluoxetine in the acute treatment of panic disorder and have provided support for the benefits of maintenance therapy with moclobemide up to 1 year. Results of studies

with moclobemide in social phobia are generally positive; a number of open and double-blind controlled trials found moclobemide to be an effective treatment for social anxiety disorder with comparable efficacy to phenelzine and citalopram,[40,48–51] not only for short-term treatment but also for maintenance.[40,52,53] Noyes et al[54] conducted a double-blind trial comparing 5 different fixed doses of moclobemide to placebo for 12 weeks. Although the authors observed a trend toward efficacy for the higher doses at the 8-week mark, by the end of the trial, response rates between all active drug groups and placebo were similar. To our knowledge, there are no placebo-controlled trials of moclobemide in GAD, OCD, or PTSD, although 2 small open trials do suggest a utility for moclobemide in PTSD.[55,56] Overall, moclobemide has been observed to be a well-tolerated medication, with insomnia, dizziness, nausea, and headaches among the commonest side effects.

Brofaromine, another RIMA with additional effects via inhibition of serotonin reuptake, has been investigated in scientific trials of anxiety. As with moclobemide, brofaromine has been shown in double-blind RCTs to be superior to placebo[57] and as effective as clomipramine[58] or fluvoxamine[59] for panic disorder. In the 3 placebo-controlled RCTs of brofaromine in social anxiety disorder, active drug was judged superior in all cases.[60–62] Trials of brofaromine in PTSD are mixed, with 1 multicenter RCT[63] suggesting that brofaromine is more effective than placebo in subjects with PTSD of greater than 1 year's duration, but a subsequent trial[64] unable to detect differences in outcome between groups. There are no RCTs of brofaromine for GAD or OCD. Sleep disturbance, dry mouth, dizziness, and nausea are commonly reported adverse effects of brofaromine.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

The primary mechanism of action of the class of drugs known as selective serotonin reuptake inhibitors (SSRIs) is inhibition of reuptake at the presynaptic serotonin (5-HT) transporter pump, resulting in increased overall levels of brain 5-HT. There are currently 6 SSRIs available for clinical use: fluoxetine, sertraline, paroxetine (immediate release and controlled release formulations), fluvoxamine, citalopram, and, most recently, escitalopram. Although each SSRI may have different FDA indications for specific anxiety disorders, clinicians tend to treat them as having equal efficacy across the group. As a class, the SSRIs are considered first-line pharmacotherapy agents for each of the anxiety disorders due to their overall levels of efficacy, safety, and tolerability.

Fluoxetine, paroxetine, and sertraline all carry FDA approvals for use in panic disorder, but all 6 SSRIs have been investigated in RCTs for this disorder. Overall, SSRIs are considered effective agents in the acute treatment of panic disorder, with 3 meta-analytic reviews[65–67] finding their efficacy and tolerability to be comparable to those of TCAs, although Bakker et al[66] suggested that there were significantly fewer dropouts in trials involving SSRIs relative to those investigating TCAs. Randomized controlled trials have also supported the use of SSRIs for maintenance therapy and relapse prevention in panic disorder.[15,47,68]

Two large, positive, double-blind placebo-controlled trials[69,70] have been reported that support paroxetine use for GAD, and head-to-head RCTs[71–73] in GAD have reported comparable efficacy among sertraline, escitalopram, and venlafaxine XR. A double-blind discontinuation study[74] concluded that paroxetine was an effective agent for preventing relapse in GAD, noting that twice as many paroxetine-treated patients achieved remission compared to those randomly assigned to placebo, and placebo-treated patients were 5 times more likely to relapse during the discontinuation taper. Similarly, positive results for sertraline have been reported for short-term treatment of GAD,[75,76] even in populations categorized as moderately to severely ill.[77] Escitalopram is the other SSRI with published reports of efficacy in GAD for both acute and long-term treatment[78–80] and, along with paroxetine, is officially indicated for GAD. There are no RCTs of citalopram, fluvoxamine, or fluoxetine as monotherapy for GAD.

As with the other anxiety disorders, multiple trials have been published supporting the use of various SSRIs for both acute and continuation treatment of social anxiety disorder, although only paroxetine and sertraline have been FDA-approved for this indication. A number of meta-analyses have confirmed the utility of SSRIs, finding them significantly superior to placebo with respect to both efficacy and improvement in psychosocial function.[81–85] While 1 meta-analytic review[81] found SSRIs to have greater effect sizes than the RIMAs, another[82] found them comparable to benzodiazepines, while yet another[83] was unable to find significant differences in efficacy between SSRIs and any of the other drug classes examined. However, when issues of tolerability were brought into the equation, the consensus was that SSRIs should be the preferred first-line treatment for social anxiety disorder.[83,84] The only exception to the above literature is the single RCT investigating fluoxetine for social anxiety disorder.[86] In this placebo-controlled trial, no significant outcome differences were detected between the active drug and placebo, although authors did report a higher-than-usual placebo response. Other trials comparing fluoxetine to psychological therapy and placebo have found different results.[87] There are no RCTs of citalopram for social anxiety disorder.

Two SSRIs, sertraline and paroxetine, have FDA indications for PTSD that follow positive results from several large multicenter acute-phase RCTs.[88–91] However, 2 subsequent, much smaller studies[92,93] that primarily studied military veterans were unable to find similar benefits for sertraline. Longer-term studies[94,95] have nevertheless found sertraline to be effective at maintaining acute-phase gains and preventing relapse. No RCTs of fluvoxamine or escitalopram in PTSD have been reported, but there is a single double-blind trial comparing citalopram to sertraline and placebo.[96] In that study, sertraline demonstrated a significant advantage for treating avoidance/numbing type symptoms, but no other

outcome differences were noted between groups. Although a 2007 report published by the Institute of Medicine[296] concluded that there was insufficient evidence to support the efficacy of SSRIs in PTSD due to the moderate effect sizes (~0.5) seen in most pharmacotherapy trials, evidence from the above mentioned RCTs and meta-analyses,[97,98] taken with the frequent presence of comorbid depression in PTSD and prevalent nature of SSRI use, means that SSRIs will very likely continue to be a mainstay of PTSD treatment for the near future.

Several SSRIs (fluoxetine, fluvoxamine, paroxetine, and sertraline) carry official FDA indications for OCD, and as a class the SSRIs represent the first line of pharmacotherapeutic intervention for this disorder. Numerous large, well-controlled RCTs involving each SSRI have confirmed the efficacy of SSRIs for both acute-phase and continuation treatment of OCD.[99–113] A recent meta-analysis[114] noted that the efficacy of SSRIs relative to placebo could be seen between 6–13 weeks of treatment and further concluded that there were no within-class differences in efficacy. Trials of SSRIs in OCD have also underscored the importance of using doses in the upper end of the dosing spectrum for this population.[102,107,110,115] Although 3 earlier meta-analyses[116–118] comparing the effects of clomipramine to SSRIs for OCD found the TCA to be superior, results from all RCTs comparing the agents directly make the difference less clear. Nevertheless, despite the recognized efficacy of clomipramine for OCD, clinical guidelines generally recommend SSRIs as the first medication class to be tried because of the overall balance between efficacy and tolerability.[119–121]

Despite the prevalent use of SSRIs for anxiety disorders, concerns still exist about these medications. Common side effects upon initiation of these medications include nausea, dizziness, headaches, jitteriness, and both sleep and gastrointestinal disturbances—symptoms that are also commonly experienced as part of anxiety disorders and therefore often interpreted as a worsening of anxiety. As such, starting with lower than usual doses, gradual titration, and ongoing psychoeducation about side effects are necessary when using these medications in the anxiety disorder population. A discontinuation syndrome with SSRIs has also been documented and is more common with agents with a shorter half-life, such as paroxetine. Gradual tapering or switching to an SSRI with a long half-life, such as fluoxetine, may be helpful. There is also a risk of drug-drug interactions with SSRIs, particularly when they are combined with drugs that are also metabolized through the P450 enzyme system. Finally, there has been widespread recent media attention on the risk of increased suicidal ideation and behavior in youth started on these medications. This has resulted in a "black box warning" about use of these agents in children and people 24 years old or younger. Nevertheless, it has also been recognized that in more severe cases where there is also substantial functional impairment, the use of SSRIs may be appropriate and should be considered on the basis of clinical judgment.

SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS

There are currently 4 serotonin-norepinephrine reuptake inhibitors (SNRIs) available for clinical use: venlafaxine extended release (ER), desvenlafaxine, duloxetine, and milnacipran. The majority of research investigating SNRIs for anxiety disorders is based on venlafaxine ER, as the latter 3 have only more recently become available. With respect to anxiety disorders, venlafaxine ER is indicated for the treatment of GAD, panic disorder, and social anxiety disorder, while duloxetine has also been approved for GAD. Along with SSRIs, SNRIs, specifically venlafaxine, are considered alternate first-line agents for the treatment of the anxiety disorders discussed here.

Venlafaxine is an SNRI with a mechanism that involves differential reuptake of norepinephrine and serotonin at either end of its dose range. Large double-blind RCTs have been published examining the benefits of venlafaxine ER relative to placebo in the acute treatment of panic disorder. The first large trial[122] found that venlafaxine ER–treated subjects were not significantly more likely to be free from full-symptom panic attacks, but they were more likely to have overall decreased panic attack frequency, anticipatory anxiety, and avoidant behavior. A more recently published report[123] found no significant difference between venlafaxine ER and placebo on the primary outcome of freedom from panic attacks, although the active drug was significantly better on secondary outcomes. More favorable results have been seen in RCTs comparing venlafaxine to paroxetine. In these, venlafaxine ER dosed between 75–225 mg was found to be comparably efficacious and tolerable to paroxetine.[124,125] While these studies support the short-term treatment of panic disorder with venlafaxine ER, Ferguson and colleagues[126] published a report concluding that venlafaxine ER was significantly more effective than placebo in maintaining the gains of acute treatment and preventing relapse during a 6-month follow-up. Controlled investigations of the other SNRIs in panic disorder consist of 2 open trials of duloxetine[127] and milnacipran,[128] respectively.

The use of venlafaxine ER for short-term treatment of GAD is well established based on the results of several RCTs.[129–131] Head-to-head comparisons with different medication classes such as SSRIs[73,132] and pregabalin[133] report similar efficacy and tolerability. Longer-term studies[134,135] have also confirmed venlafaxine ER to be efficacious for relapse prevention. Similarly robust results have been found for duloxetine in GAD. Rynn et al[136] reported that duloxetine was superior to placebo not only on measures of efficacy but also with respect to improvement of functional impairment. In one comparison to venlafaxine,[137] both drugs were seen to be effective, but venlafaxine-treated subjects experienced a greater number of side effects during the tapering period. Another placebo-controlled trial[138] that compared duloxetine, dosed at either 20 or 60–120 mg/d, to venlafaxine found that all 3 active treatments were effective at treating psychic

© Copyright 2011 Physicians Postgraduate Press, Inc.

anxiety, but only venlafaxine and high-dose duloxetine (60–120 mg) were more beneficial than placebo for somatic anxiety. Like venlafaxine, duloxetine has also been shown to be effective for relapse prevention[139] of GAD. There are no published trials of either desvenlafaxine or milnacipran for GAD to date.

With the exception of a case-study report of duloxetine, the only literature on SNRIs for social anxiety disorder consists of trials of venlafaxine ER. Two large double-blind RCTs[140,141] found venlafaxine to be significantly more effective than placebo, while 2 other placebo-controlled trials[142,143] involving head-to-head comparisons with paroxetine concluded that both active drugs were similarly effective and tolerable. In a large 6-month study, Stein et al[144] showed that both low-dose (75 mg) and high-dose (150–225 mg) venlafaxine ER were comparable and superior to placebo; the authors hypothesized that this could mean that the noradrenergic actions of venlafaxine—which are essentially nonexistent at the 75-mg dose—were not the ones responsible for therapeutic benefit in social anxiety disorder.

In a 12-week multicenter placebo-controlled trial, Davidson and colleagues[145] found venlafaxine ER to be well tolerated and comparable in efficacy to sertraline for acute treatment of PTSD. Extending these findings, a 6-month RCT showed that venlafaxine was superior to placebo in improving overall posttraumatic symptoms, with specific benefits to the avoidance/numbing and hyperarousal symptom clusters.[146] To date, no reports of controlled trials of PTSD involving the other SNRIs have been published.

Findings from controlled trials of venlafaxine ER in OCD are mixed. Although a small placebo-controlled RCT[147] failed to find evidence of its efficacy, it should be noted that the doses of venlafaxine used in the study were relatively low (up to 225 mg/d). However, authors of a larger double-blind parallel-group study[148] comparing venlafaxine ER to paroxetine concluded that both medications were similarly efficacious and tolerable for treatment of OCD. The authors subsequently assigned nonresponders from the original trial to switch to the alternate antidepressant for a further 12 weeks. In this case, 42% of the original nonresponders eventually converted to responders, but the effect was more noteworthy for those switched to paroxetine rather than to venlafaxine.[149] A double-blind comparison of venlafaxine to clomipramine found both medications to be equally effective, but venlafaxine-treated patients reported fewer treatment-emergent adverse effects.[34] There are no published reports of controlled trials in OCD involving the other SNRIs.

Overall, there is excellent controlled evidence to suggest that SNRIs, particularly venlafaxine, are effective and well-tolerated agents for the anxiety disorders discussed above. These are the main factors explaining why they are considered reasonable alternate first-line agents to SSRIs. One disadvantage often cited with the use of venlafaxine in particular is the potential not only for side effects but for the emergence of adverse events, similar to the SSRI discontinuation syndrome, during tapering periods or times of noncompliance. The use of SNRIs in anxiety disorders is more thoroughly discussed in a recent review.[150]

OTHER ANTIDEPRESSANTS

The use of alternate antidepressants with unique mechanisms of action has also been investigated for anxiety disorders, although the literature is sparser. Mirtazapine works presynaptically to inhibit the α_2 heteroreceptors on serotonergic neurons and the α_2-adrenergic autoreceptors. It also works to selectively block serotonergic 5-HT_2 and 5-HT_3 receptors on the postsynaptic neuron, as well as having potent antagonist effects at histaminic H_1 receptors.[151] Three open trials[152–154] suggested a utility for mirtazapine in the short-term treatment of panic disorder, and a double-blind parallel-group study[155] found it to be comparably efficacious to fluoxetine; however, all 4 studies used small samples. An open trial conducted by Van Veen et al[156] suggested that mirtazapine might be useful for treatment of social anxiety disorder. A single double-blind placebo-controlled RCT[157] did reinforce this idea, but the population studied was limited to females with social anxiety disorder. In the only RCT[158] of mirtazapine in PTSD, authors were able to demonstrate symptom improvement on a global measure of change, but on no other outcome variables. Twelve weeks of open-label mirtazapine followed by an 8-week discontinuation period indicated that mirtazapine was helpful for OCD,[159] but further controlled trials of mirtazapine monotherapy in OCD are lacking. A single-blind placebo-controlled study[160] suggested that combining mirtazapine and citalopram might accelerate treatment response in OCD relative to citalopram alone; however, there were no overall differences in responder rates by the end of the trial period. At this time, there are no RCTs of mirtazapine for GAD.

Bupropion, a norepinephrine and dopamine reuptake blocker, has mixed findings from open trials in panic disorder,[161,162] but lacks data from placebo-controlled RCTs to make definitive conclusions. A single RCT[163] comparing bupropion extended release to escitalopram found both agents to effectively treat GAD, but no RCTs exist to support bupropion treatment of social anxiety disorder. On the basis of the results of 2 controlled trials,[164,165] bupropion was not found to be an effective treatment for PTSD. There are no controlled trials of bupropion in OCD, but in 1 open-label study,[166] it was not found to be particularly useful.

Nefazodone is an older antidepressant hypothesized to work via both antagonism of postsynaptic serotonin 5-HT_{2A} receptors and modest inhibition of presynaptic serotonin and norepinephrine reuptake. Positive findings from 3 small open trials[167–169] suggest a potential benefit for nefazodone in panic disorder, but no RCTs have confirmed this. Similarly, Hedges and colleagues[170] found promising results in the only open trial of nefazodone in GAD. By contrast, Van Ameringen et al[171] demonstrated that nefazodone was not an effective treatment for generalized social anxiety disorder in their placebo-controlled study. Two controlled studies[172,173]

of nefazodone in PTSD found it to be superior to placebo and as effective as sertraline. There are no controlled trials of nefazodone in OCD. Despite the potential utility of nefazodone in various anxiety disorders, worries about possible hepatotoxicity caused this drug to be withdrawn from the market in several countries. Although it is still available in the United States, these health concerns have likely contributed to the decline in research of this drug.

While the mechanism of action of trazodone is not entirely clear, it is thought to work similarly to nefazodone through weak reuptake inhibition of serotonin and norepinephrine and antagonism of 5-HT_{2A} receptors. Although a small (N = 11) single-blind trial[174] found trazodone to be helpful for panic disorder, Charney et al[175] found that it was neither well tolerated nor effective in their double-blind RCT comparing trazodone to imipramine and alprazolam. A double-blind placebo-controlled RCT of trazodone, imipramine, and diazepam for GAD found all active treatments to be helpful, with a slight superiority for both antidepressant agents.[20] In their small double-blind placebo-controlled trial, Pigott et al[176] did not find trazodone to be a useful agent for treatment of OCD.

ANTICONVULSANTS

Nonbenzodiazepine drugs with anticonvulsant activity are commonly used in the treatment of different psychiatric illnesses. On the basis of the hypothesis that clinical anxiety results from excessive neuronal activation of fear circuits, it has been theorized that anticonvulsant drugs may potentially reduce this excitation in a similar fashion to the way in which they decrease epileptic burst firing.[177] These drugs often differ significantly from each other with respect to chemical structure, and, further, their mechanisms of anxiolytic action are frequently poorly understood. Nevertheless, researchers have investigated their use in the different anxiety disorders with varying results. There are only 2 double-blind placebo-controlled trials of anticonvulsants in panic disorder, both with limited success. In the first RCT, which examined gabapentin compared to placebo for panic disorder, Pande et al[178] were unable to find an overall difference between treatment groups, but a post hoc analysis suggested that gabapentin had an advantage for treatment of the subgroup with more severe illness at baseline. More recently, Zwanzger and colleagues[179] were unable to detect differences in outcome between groups receiving tiagabine or placebo for 4 weeks. In an earlier controlled open trial,[180] carbamazepine was similarly found to display a lack of benefit for panic disorder. In contrast to these negative trials in patients with panic disorder, positive open trials and case series of valproate,[181,182] vigabatrin,[183] and levetiracetam[184] have been published but lack more controlled evidence to substantiate the findings.

For GAD, pregabalin has the greatest amount of support, with 6 positive double-blind placebo-controlled RCTs published. The first 4 of the trials focused on optimal dosing of the drug for the short-term treatment of GAD.[185–188] With the exception of 1 study,[185] all investigated doses of pregabalin (200–600 mg/d) were superior to placebo at decreasing overall anxiety (somatic and psychic), and improvements were frequently observed as early as the first week. Three[185,186,188] of the 4 trials used a benzodiazepine as an active comparator, and pregabalin was found similarly efficacious to these agents in these studies. In 2006, Montgomery et al[133] conducted a placebo-controlled trial comparing venlafaxine to 2 different doses of pregabalin in patients with moderate to severe GAD. All 3 active treatment groups showed significant improvement, with pregabalin showing a slightly earlier time to response than venlafaxine. Continuation treatment with pregabalin has also been shown to be an effective strategy at preventing relapse in GAD.[189] Tiagabine, a γ-aminobutyric acid (GABA) reuptake inhibitor with anticonvulsant properties, has had mixed results in GAD. A 10-week open trial[297] that randomly assigned patients to treatment with either tiagabine or paroxetine found that both drugs were well tolerated and similarly effective in reducing anxiety symptoms. However, Pollack and colleagues[190] failed to find a difference between tiagabine and placebo on the primary outcome analyses of their multicenter 8-week double-blind RCT. In a double-blind trial of males with GAD,[191] 68% of subjects receiving valproate were deemed responders compared to only 16% of those receiving placebo. Riluzole, a glutamate modulator, showed some promise as a treatment of GAD when results from an open trial[192] indicated that 80% of completers responded and 53% remitted, but further investigation is needed.

A variety of anticonvulsants have been investigated as potential treatments for social anxiety disorder. Although there was initial promise for levetiracetam,[193] 1 small and 1 large placebo-controlled trial[194,195] have since found it ineffective. Double-blind RCTs have also shown support for gabapentin[196] and for high-dose pregabalin (600 mg/d), although low-dose pregabalin (150 mg/d) was found to be no better than placebo.[197] Although there is a lack of controlled evidence, results of open trials indicate that valproate,[198] topiramate,[199] and tiagabine[200] may also be useful in social anxiety disorder.

Few controlled trials of anticonvulsants have been published in PTSD. A small pilot study[201] did find lamotrigine monotherapy to be helpful. A subsequent RCT[202] of topiramate monotherapy was similarly positive, but a double-blind study[203] of topiramate augmentation in patients with PTSD was unable to find such a benefit, although the elevated attrition rates in the latter study might have affected results. A large multicenter RCT[298] failed to find tiagabine to be an effective treatment for PTSD, and 2 negative RCTs of valproate in adult PTSD have now been published.[204,205]

There are no controlled studies of anticonvulsant monotherapy for OCD and only limited literature on augmentation with anticonvulsants. In a study by Onder et al,[206] subjects with OCD were randomly assigned to receive either fluoxetine alone or fluoxetine and gabapentin. Results showed that the combination treatment seemed to accelerate response,

although there were no statistical differences in outcome at endpoint. Case reports and a retrospective case series suggest a possible role for topiramate[207,208] and lamotrigine[209] in OCD, but no controlled trials have been published to date.

With the exception of pregabalin for GAD, the paucity of double-blind trials and the frequently mixed results would suggest that anticonvulsant monotherapy be largely reserved for cases of treatment resistance or possibly as augmentation of a more established first-line agent in the treatment of anxiety disorders.

ATYPICAL ANTIPSYCHOTICS

The introduction of the atypical antipsychotics into the psychiatric pharmacopoeia during the 1990s transformed the management of schizophrenia. That these drugs also had serotonergic properties and could be used to successfully augment antidepressant effects in mood disorders led to interest in uncovering a possible additional role for anxiety disorders. In their small (N = 10) open-label trial of olanzapine monotherapy in patients with treatment-refractory panic disorder, Hollifield et al[210] found that patients experienced a significant decrease in anticipatory anxiety by study end, with 50% of participants free of panic attacks. In a subsequent open trial[211] of SSRI augmentation with low-dose olanzapine in a similar population, 82% of subjects were deemed responders by study end, with a 58% remission rate in those who completed the trial. Risperidone monotherapy was compared to paroxetine in a recent randomized, rater-blinded study.[212] Both groups showed similar improvement, but a post hoc analysis suggested that risperidone might work slightly faster. Placebo-controlled studies of atypical antipsychotics in panic disorder are lacking.

In GAD, controlled evidence for atypical antipsychotics has so far been limited to augmentation studies. Olanzapine augmentation of fluoxetine resulted in a significantly greater proportion of responders than placebo, but the olanzapine-treated group also gained significantly more weight.[213] A double-blind RCT[214] of low-dose risperidone augmentation resulted in significantly greater reductions of both psychic and overall anxiety in the treatment group, but responder rates were not statistically different. A more recent double-blind RCT[215] also failed to find a difference between low-dose risperidone augmentation and placebo on primary endpoints, although post hoc analyses suggested a possible role for risperidone in subjects with more severe GAD. Despite the promising results of an open-label study of quetiapine augmentation[216] in treatment-refractory GAD, Simon and colleagues[217] were unable to find benefits to quetiapine augmentation of paroxetine CR in a placebo-controlled RCT. Open-label augmentation with aripiprazole, an atypical antipsychotic with partial agonism at both the D_2 and 5-HT_{1A} receptors, resulted in significant improvement in a small group of patients with refractory GAD and secondary depression diagnoses.[218] However, the authors were unable to determine whether the overall benefits were due to improvement of anxious or depressive symptoms. A small open trial[219] of ziprasidone augmentation has also shown promising results, but replication of the results in a larger controlled trial is needed.

A double-blind RCT[220] of olanzapine monotherapy for social anxiety disorder resulted in significantly better clinical outcome than placebo. Although weight gain was minimal and similar between groups, subjects receiving olanzapine had greater complaints of dry mouth and drowsiness. Authors of a small open trial[221] of quetiapine monotherapy in social anxiety disorder reported positive findings, but results of a subsequent RCT[222] failed to distinguish between active treatment and placebo on primary outcomes.

Controlled evidence of atypical antipsychotics in PTSD largely consists of augmentation trials, but with conflicting results. Of the trials investigating augmentation with risperidone, 3 trials[223–225] found the drug to benefit the reexperiencing or hyperarousal symptom clusters, but no improvements were seen in the avoidance/numbing cluster. Hamner et al[226] found risperidone specifically helpful for psychotic but not overall posttraumatic symptoms. Similarly, Rothbaum et al[227] was unable to find benefits for risperidone augmentation for overall posttraumatic symptoms or even individual symptom clusters. In contrast, the single RCT[228] of olanzapine augmentation showed significant reductions in overall scores of PTSD measures as well as improvements in sleep and depression. However, authors were concerned about the mean weight gain of 13 lb in subjects treated with olanzapine. Monotherapy with risperidone was investigated in an RCT[229] of women with PTSD, with the results showing benefit on the primary outcome measure (total score on the Treatment Outcomes Post-traumatic Stress Disorder Scale-8) but none of the secondary measures. Results of the single RCT[230] of olanzapine monotherapy for PTSD failed to demonstrate a beneficial effect, but that study was small and possibly underpowered.

Virtually all published trials of atypical antipsychotics in OCD consist of augmentation studies in patients who have not responded to a course of SSRIs, and results are mixed. While authors of several placebo-controlled RCTs found evidence to support augmentation with olanzapine,[231] risperidone,[232,233] and quetiapine,[234,235] other investigators failed to find these atypical antipsychotics efficacious for this purpose.[236–239] Head-to-head comparisons involving these agents have also been studied. A single-blind trial conducted by Maina et al[240] compared olanzapine and risperidone augmentation in subjects resistant to serotonin reuptake inhibitors. Both agents were found to be equally effective at reducing obsessive-compulsive symptoms, but the adverse event reports differed between groups, with the main complaints being amenorrhea in the risperidone group and weight gain in the olanzapine group. A double-blind placebo-controlled crossover trial comparing risperidone and haloperidol augmentation found them to be equally effective at treating obsessions, although risperidone was significantly better at improving depressive symptoms and was generally better tolerated.[241] Using findings from the above studies, a

recent meta-analysis by Bloch and colleagues[242] concluded that augmentation with atypical antipsychotics could be a helpful strategy for treatment-resistant OCD. Benefits were most evident with risperidone, but evidence was inconclusive for both olanzapine and quetiapine. A single pilot trial[243] of atypical antipsychotic monotherapy has been published using open-label aripiprazole, one of the newest atypical antipsychotics. Treatment with aripiprazole resulted in significant improvement in compulsive symptoms, and overall improvement showed a trend toward significance ($P = .06$). However, the results need to be replicated with a larger population under controlled conditions. An open-label study[244] of aripiprazole augmentation in a population with treatment-resistant OCD also showed promising results.

It is clear that the evidence base of atypical antipsychotics for anxiety disorders is still quite sparse. There is an urgent need for larger and more definitive trials to validate the common clinical strategy of augmenting antidepressants with these agents when managing anxiety disorders. Further, the worrisome side effect burden of these agents, which often includes substantial weight gain and other metabolic sequelae, also needs to be addressed in these studies to develop better ways of managing it, particularly since these side effects may have a considerable effect on both general medical health and compliance.

AZAPIRONES

Buspirone is a psychotropic medication that exerts its anxiolytic effect via partial agonism of the 5-HT_{1A} receptor. Buspirone is currently the only one of its class (the azapirones) to have regulatory approval in the United States, where it is indicated for the treatment of anxiety that would come closest to what we would currently define as GAD. However, published trials of buspirone for other anxiety disorders also exist. Findings for buspirone in panic disorder are generally unfavorable. Two randomized placebo-controlled trials have been published comparing buspirone to imipramine. In one,[245,] no significant differences were found between all 3 groups, while the other[246] found that only imipramine was superior to placebo. Similarly, a randomized head-to-head comparison of buspirone and clorazepate found the latter agent to be significantly more efficacious.[247]

There are several RCTs of buspirone in GAD. The vast majority of these are head-to-head or placebo-controlled trials comparing buspirone to benzodiazepines. Buspirone was generally found to be as efficacious and tolerable as the benzodiazepines. In the only RCT[129] comparing buspirone to a newer antidepressant, both venlafaxine and buspirone were found to be superior to be placebo, although venlafaxine demonstrated greater efficacy on one anxiety measure.

There are conflicting findings on the efficacy of buspirone in social anxiety disorder. Modest efficacy was found by Schneier and colleagues[248] in their 12-week open trial, but in a double-blind RCT, van Vliet et al[249] were unable to find outcome differences between buspirone and placebo.

A positive preliminary open trial[250] in PTSD suggested a possible role for buspirone in this disorder, but no RCTs have been published to substantiate this.

Controlled trials of buspirone in OCD also demonstrate mixed findings. While an early open trial[251] of buspirone monotherapy failed to demonstrate benefit for any of the 14 patients enrolled, a double-blind RCT[252] comparing buspirone to clomipramine found both agents to be similarly effective at improving obsessive-compulsive symptoms. Buspirone augmentation in patients with insufficient response to serotonin reuptake inhibitors has also been studied. Two open trials[253,254] of buspirone augmentation of an SSRI showed promising results, but subsequent findings from both open and double-blind trials failed to support this practice.[255–257]

While tolerability and low potential for dependence are advantages over benzodiazepine use, buspirone can often take a few weeks to show clinical effect. Further, its limited efficacy for anxiety disorders means that it is mainly relegated to use for uncomplicated GAD. However, since GAD is commonly comorbid with other anxiety and mood disorders, even here other antidepressants are the preferred first choice.

BENZODIAZEPINES

The benzodiazepines have been a mainstay of anxiety disorder treatment for many years. These drugs work by binding to a specific site on the GABA-A receptor, resulting in an enhanced effect of the inhibitory neurotransmitter GABA. Benzodiazepines have many properties including anxiolytic, anticonvulsant, muscle-relaxant, and sedative actions. The multiple benzodiazepines are usually classified by their elimination half-life into short-, intermediate-, and long-acting. Their tolerability and rapid onset of effect have contributed to their continued use in the anxiety disorders.

Several RCTs of benzodiazepines in panic disorder have been published supporting their use (reviewed in the American Psychiatric Association Practice Guidelines for the Treatment of Patients With Panic Disorder[258]). Alprazolam, a short-acting benzodiazepine, was the first medication to receive regulatory approval by the FDA for the treatment of panic disorder following the results of 2 large multicenter studies.[259,260] Not only has alprazolam been found to be significantly superior to placebo and comparable in efficacy to imipramine, but clinical improvement was also seen sooner with alprazolam than with imipramine.[260] Other studies have confirmed the utility of alprazolam for panic disorder[261–266] in reducing frequency of panic attacks, phobic avoidance, and anticipatory anxiety, as well as maintaining gains during continuation treatment.[267–269] Studies have also validated the utility of clonazepam, the other benzodiazepine FDA-approved for use in panic disorder,[264,270–272] as well as diazepam[261,273,274] and lorazepam.[275,276] Overall, meta-analytic comparisons of the different drug classes used in panic disorder found that benzodiazepines had similar

effect sizes compared to either SSRIs or TCAs.[67,277] There has also been interest in combining benzodiazepines with other agents to assess whether this affects response. Two trials[278,279] showed that coadministration of a benzodiazepine and SSRI conferred an earlier benefit compared to an SSRI alone, although this advantage was not sustained by trial end.

As with panic disorder, studies of benzodiazepines in GAD are numerous, and, as a result, alprazolam has been approved by the FDA for use in this disorder. One meta-analytic review[280] of pharmacologic agents used in GAD found benzodiazepines to be as effective as the azapirones, although compliance was noted to be greater with the benzodiazepines. A more recent meta-analysis[281] showed moderate effect sizes for benzodiazepines that were comparable to those of SSRIs and venlafaxine.

Three controlled trials of benzodiazepine monotherapy, all involving clonazepam, have been reported for social anxiety disorder. The first 2 trials[282,283] concluded that clonazepam was significantly superior to placebo in the acute treatment of social anxiety disorder. Connor et al[284] found that responders to 6 months' treatment with clonazepam were significantly less likely to relapse compared to those who switched to placebo, suggesting that continuation treatment with clonazepam is a safe and effective strategy for social anxiety disorder.

Limited evidence for benzodiazepine use in PTSD exists. In 1 double-blind crossover study,[285] alprazolam was helpful for nonspecific anxiety but not specific posttraumatic stress symptoms, while Cates et al[286] failed to find evidence that clonazepam was helpful to treat sleep disturbance in PTSD. Findings of 2 studies[287,288] investigating whether benzodiazepine administration in the aftermath of trauma might prevent PTSD development were negative, with investigators even suggesting the possibility of deleterious effects. Given the paucity of effective pharmacotherapies for PTSD, the use of benzodiazepines—which are so effective in the other fear-based anxiety disorders such as panic disorder and the phobias—in PTSD should be further explored with large-scale controlled studies.

Reports of controlled trials of benzodiazepines in OCD are few. A double-blind multiple crossover study[289] comparing psychotropic medications with different mechanisms found both clonazepam and clomipramine to be significantly superior to the control medication. The authors noted that the benefits of clonazepam over the other medications were seen within the first 3 weeks of its use. In contrast, a placebo-controlled RCT[290] failed to demonstrate the superiority of clonazepam over placebo with respect to either rates of response or degree of symptom improvement. Similarly, in a double-blind placebo-controlled RCT[291] of clonazepam augmentation of sertraline, no differences were detected between groups.

Enthusiasm for benzodiazepine use in anxiety disorder has waned in the face of several factors. Although these medications are often tolerated well and have the ability to provide rapid and effective relief of symptoms, clinicians are often concerned about more severe adverse effects such as oversedation, cognitive impairment, and psychomotor incoordination. Benzodiazepines are dangerous in overdose, and individuals discontinuing benzodiazepine use may experience uncomfortable withdrawal symptoms. Further, 2 of the most cited reasons for a general reluctance to use benzodiazepines are the risk of tolerance and dependence in long-term use. While this is certainly a risk, longer-term follow-up studies of patients receiving clonazepam or alprazolam for panic disorder showed little evidence of tolerance, while noting that a majority of patients maintained their treatment gains.[267,269,292,293] That being said, one population in whom it would be prudent to exercise more care is individuals with a history of substance abuse. Although not specifically prohibited in these cases, benzodiazepine use should be undertaken only after a frank discussion about the risks with an emphasis on the need for careful monitoring. Overall, benzodiazepines represent a valuable treatment option for anxiety, particularly for panic disorder, GAD, and, in some cases, social anxiety disorder. However, benzodiazepines are often overlooked in favor of other conventional agents for other reasons. Anxiety disorders are frequently comorbid with other psychiatric illnesses, particularly depressive disorders. Since benzodiazepines have no recognized antidepressant effects, the use of a conventional antidepressant agent in these cases is more appropriate. A popular strategy for using benzodiazepines in anxiety disorders is short-term use during initiation of an antidepressant agent, as these may take time to display therapeutic benefit. Not only does this coadministration have the benefit of providing some initial symptom relief, but it may also attenuate some of the more agitating side effects that can be seen when starting an antidepressant. Once patients are stabilized on treatment with antidepressants, clinicians will often opt to taper the benzodiazepine.

DISCUSSION

The pharmacologic management of anxiety disorders has made great progress over the last few decades; however, large gaps continue to exist in the literature and in practical implementation of the evidence. A number of clinical trials involving SSRIs have, by and large, been well powered and well replicated, but pilot studies or open trials involving other medication classes need to be replicated and investigated in larger populations to validate findings. There are a large number of augmentation studies with atypical antipsychotics for OCD, although, even here, the findings are not generally conclusive. With the exception of this instance, augmentation and combination studies of pharmacologic agents to systematically identify next-step strategies for cases of treatment resistance are generally few and far between. More recently, investigators[294,295] have been attempting to address this deficit.

There has also been an increased effort to delineate specific neurobiological dysfunctions underlying the different

anxiety disorders in the hope that this may help clinicians to better target symptoms with the appropriate pharmacologic agents and may also be of use in developing new drugs. Genetics and neuroimaging are 2 streams of research that will be of critical importance in extending this field further.

Although developing more effective psychotropic drugs would be helpful, it is also important to be open to using more novel therapies, such as repetitive transcranial magnetic stimulation, that could be employed either on their own or in combination with existing pharmacotherapeutic agents. Despite the gaps in the literature, findings from the above studies have provided invaluable information to clinicians, aiding them to more effectively provide symptom relief and improved quality of life for patients suffering from this often debilitating group of illnesses.

Drug names: alprazolam (Xanax, Niravam, and others), aripiprazole (Abilify), atenolol (Tenormin and others), bupropion (Aplenzin, Wellbutrin, and others), buspirone (BuSpar and others), carbamazepine (Carbatrol, Equetro, and others), citalopram (Celexa and others), clomipramine (Anafranil and others), clonazepam (Klonopin and others), clorazepate (Gen-Xene, Tranxene, and others), desipramine (Norpramin and others), desvenlafaxine (Pristiq), diazepam (Diastat, Valium, and others), duloxetine (Cymbalta), escitalopram (Lexapro), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), gabapentin (Neurontin and others), imipramine (Tofranil, Surmontil, and others), lamotrigine (Lamictal and others), levetiracetam (Keppra and others), lorazepam (Ativan and others), milnacipran (Savella), mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), phenelzine (Nardil), pregabalin (Lyrica), quetiapine (Seroquel), riluzole (Rilutek and others), risperidone (Risperdal and others), sertraline (Zoloft and others), tiagabine (Gabitril), topiramate (Topamax and others), trazodone (Oleptro and others), valproate (Depacon and others), venlafaxine (Effexor and others), vigabatrin (Sabril), ziprasidone (Geodon).

Author affiliations: Department of Psychiatry, University of Toronto, Ontario, Canada (Dr Ravindran); and Anxiety and Traumatic Stress Disorders Research Program, University of California San Diego, La Jolla (Dr Stein).

Potential conflicts of interest: **Dr Stein** receives or in the past 3 years has received research support from Eli Lilly, GlaxoSmithKline, and Hoffmann-LaRoche and is currently or in the past 3 years has been a consultant for AstraZeneca, BrainCells Inc, Bristol-Myers Squibb, Comprehensive Neuroscience, Eli Lilly, Forest, Hoffmann-LaRoche, Jazz, Johnson & Johnson, Mindsite, Pfizer, and Sepracor. **Dr Ravindran** reports no financial or other relationship relevant to the subject of this article.

Funding/support: Supported by grants from the National Institute of Mental Health (MH64122) and the US Department of Defense (W81XWH08-2-0159, supporting the INTRuST Clinical Consortium).

REFERENCES

1. Kessler RC, Berglund P, Demler O, et al. Lifetime prevalence and age-of-onset distributions of *DSM-IV* disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62(6):593–602. doi:10.1001/archpsyc.62.6.593 PubMed
2. Hofmann SG, Smits JA. Cognitive-behavioral therapy for adult anxiety disorders: a meta-analysis of randomized placebo-controlled trials. *J Clin Psychiatry*. 2008;69(4):621–632. PubMed
3. Norton PJ, Price EC. A meta-analytic review of adult cognitive-behavioral treatment outcome across the anxiety disorders. *J Nerv Ment Dis*. 2007;195(6):521–531. doi:10.1097/01.nmd.0000253843.70149.9a PubMed
4. Deacon BJ, Abramowitz JS. Cognitive and behavioral treatments for anxiety disorders: a review of meta-analytic findings. *J Clin Psychol*. 2004;60(4):429–441. doi:10.1002/jclp.10255 PubMed
5. Butler AC, Chapman JE, Forman EM, et al. The empirical status of cognitive-behavioral therapy: a review of meta-analyses. *Clin Psychol Rev*. 2006;26(1):17–31. doi:10.1016/j.cpr.2005.07.003 PubMed
6. Feighner JP. Mechanism of action of antidepressant medications. *J Clin Psychiatry*. 1999;60(suppl 4):4–11, discussion 12–13. PubMed
7. Modigh K, Westberg P, Eriksson E. Superiority of clomipramine over imipramine in the treatment of panic disorder: a placebo-controlled trial. *J Clin Psychopharmacol*. 1992;12(4):251–261. PubMed
8. Sheehan DV, Raj AB, Sheehan KH, et al. The relative efficacy of buspirone, imipramine and placebo in panic disorder: a preliminary report. *Pharmacol Biochem Behav*. 1988;29(4):815–817. doi:10.1016/0091-3057(88)90214-6 PubMed
9. Mavissakalian MR, Perel JM. Imipramine dose-response relationship in panic disorder with agoraphobia: preliminary findings. *Arch Gen Psychiatry*. 1989;46(2):127–131. PubMed
10. Taylor CB, Hayward C, King R, et al. Cardiovascular and symptomatic reduction effects of alprazolam and imipramine in patients with panic disorder: results of a double-blind, placebo-controlled trial. *J Clin Psychopharmacol*. 1990;10(2):112–118. doi:10.1097/00004714-199004000-00006 PubMed
11. Fahy TJ, O'Rourke D, Brophy J, et al. The Galway Study of Panic Disorder. I: clomipramine and lofepramine in *DSM-III-R* panic disorder: a placebo controlled trial. *J Affect Disord*. 1992;25(1):63–75. doi:10.1016/0165-0327(92)90094-M PubMed
12. Mavissakalian MR, Perel JM. Imipramine treatment of panic disorder with agoraphobia: dose ranging and plasma level-response relationships. *Am J Psychiatry*. 1995;152(5):673–682. PubMed
13. Broocks A, Bandelow B, Pekrun G, et al. Comparison of aerobic exercise, clomipramine, and placebo in the treatment of panic disorder. *Am J Psychiatry*. 1998;155(5):603–609. PubMed
14. Andersch S, Rosenberg NK, Kullingsjö H, et al. Efficacy and safety of alprazolam, imipramine and placebo in treating panic disorder: a Scandinavian multicenter study. *Acta Psychiatr Scand suppl*. 1991;83(S365):18–27. doi:10.1111/j.1600-0447.1991.tb03097.x PubMed
15. Lecrubier Y, Judge R. Collaborative Paroxetine Panic Study Investigators. Long-term evaluation of paroxetine, clomipramine and placebo in panic disorder. *Acta Psychiatr Scand*. 1997;95(2):153–160. doi:10.1111/j.1600-0447.1997.tb00389.x PubMed
16. Mavissakalian MR, Perel JM. Long-term maintenance and discontinuation of imipramine therapy in panic disorder with agoraphobia. *Arch Gen Psychiatry*. 1999;56(9):821–827. doi:10.1001/archpsyc.56.9.821 PubMed
17. Lecrubier Y, Bakker A, Dunbar G, et al. Collaborative Paroxetine Panic Study Investigators. A comparison of paroxetine, clomipramine and placebo in the treatment of panic disorder. *Acta Psychiatr Scand*. 1997;95(2):145–152. doi:10.1111/j.1600-0447.1997.tb00388.x PubMed
18. Bakker A, van Dyck R, Spinhoven P, et al. Paroxetine, clomipramine, and cognitive therapy in the treatment of panic disorder. *J Clin Psychiatry*. 1999;60(12):831–838. PubMed
19. Mavissakalian MR. Imipramine vs sertraline in panic disorder: 24-week treatment completers. *Ann Clin Psychiatry*. 2003;15(3–4):171–180. PubMed
20. Rickels K, Downing R, Schweizer E, et al. Antidepressants for the treatment of generalized anxiety disorder: a placebo-controlled comparison of imipramine, trazodone, and diazepam. *Arch Gen Psychiatry*. 1993;50(11):884–895. PubMed
21. Simpson HB, Schneier FR, Campeas RB, et al. Imipramine in the treatment of social phobia. *J Clin Psychopharmacol*. 1998;18(2):132–135. doi:10.1097/00004714-199804000-00005 PubMed
22. Davidson J, Kudler H, Smith R, et al. Treatment of posttraumatic stress disorder with amitriptyline and placebo. *Arch Gen Psychiatry*. 1990;47(3):259–266. PubMed
23. Reist C, Kauffmann CD, Haier RJ, et al. A controlled trial of desipramine in 18 men with posttraumatic stress disorder. *Am J Psychiatry*. 1989;146(4):513–516. PubMed
24. Thorén P, Asberg M, Cronholm B, et al. Clomipramine treatment of obsessive-compulsive disorder I: a controlled clinical trial. *Arch Gen Psychiatry*. 1980;37(11):1281–1285. PubMed
25. DeVeaugh-Geiss J, Landau P, Katz R. Preliminary results from a multicenter trial of clomipramine in obsessive-compulsive disorder. *Psychopharmacol Bull*. 1989;25(1):36–40. PubMed
26. Katz RJ, DeVeaugh-Geiss J, Landau P. Clomipramine in obsessive-compulsive disorder. *Biol Psychiatry*. 1990;28(5):401–414. doi:10.1016/0006-3223(90)90408-T PubMed
27. Hoehn-Saric R, McLeod DR, Zimmerli WD, et al. Symptoms and physiologic manifestations in obsessive compulsive patients before and after treatment with clomipramine. *J Clin Psychiatry*. 1993;54(7):272–276. PubMed
28. Fallon BA, Liebowitz MR, Campeas R, et al. Intravenous clomipramine for obsessive-compulsive disorder refractory to oral clomipramine: a placebo-controlled study. *Arch Gen Psychiatry*. 1998;55(10):918–924. doi:10.1001/archpsyc.55.10.918 PubMed
29. Ravindran LN, Jung SM, Ravindran AV. Intravenous anti-obsessive agents: a review. *J Psychopharmacol*. 2010;24(3):287–296. doi:10.1177/0269881108096508 PubMed

30. Freeman CP, Trimble MR, Deakin JF, et al. Fluvoxamine vs clomipramine in the treatment of obsessive compulsive disorder: a multicenter, randomized, double-blind, parallel group comparison. *J Clin Psychiatry*. 1994;55(7):301–305. PubMed
31. Koran LM, McElroy SL, Davidson JR, et al. Fluvoxamine versus clomipramine for obsessive-compulsive disorder: a double-blind comparison. *J Clin Psychopharmacol*. 1996;16(2):121–129. doi:10.1097/00004714-199604000-00004 PubMed
32. Mundo E, Maina G, Uslenghi C. Multicentre, double-blind, comparison of fluvoxamine and clomipramine in the treatment of obsessive-compulsive disorder. *Int Clin Psychopharmacol*. 2000;15(2):69–76. doi:10.1097/00004850-200015020-00002 PubMed
33. Zohar J, Judge R. OCD Paroxetine Study Investigators. Paroxetine vs clomipramine in the treatment of obsessive-compulsive disorder. *Br J Psychiatry*. 1996;169(4):468–474. doi:10.1192/bjp.169.4.468 PubMed
34. Albert U, Aguglia E, Maina G, et al. Venlafaxine vs clomipramine in the treatment of obsessive-compulsive disorder: a preliminary single-blind, 12-week, controlled study. *J Clin Psychiatry*. 2002;63(11):1004–1009. PubMed
35. Noorbala AA, Hosseini SH, Mohammadi MR, et al. Combination of clomipramine and nortriptyline in the treatment of obsessive-compulsive disorder: a double-blind, placebo-controlled trial. *J Clin Pharm Ther*. 1998;23(2):155–159. doi:10.1046/j.1365-2710.1998.00156.x PubMed
36. Sheehan DV, Ballenger J, Jacobsen G. Treatment of endogenous anxiety with phobic, hysterical, and hypochondriacal symptoms. *Arch Gen Psychiatry*. 1980;37(1):51–59. PubMed
37. Buigues J, Vallejo J. Therapeutic response to phenelzine in patients with panic disorder and agoraphobia with panic attacks. *J Clin Psychiatry*. 1987;48(2):55–59. PubMed
38. Gelernter CS, Uhde TW, Cimbolic P, et al. Cognitive-behavioral and pharmacological treatments of social phobia: a controlled study. *Arch Gen Psychiatry*. 1991;48(10):938–945. PubMed
39. Liebowitz MR, Schneier F, Campeas R, et al. Phenelzine vs atenolol in social phobia: a placebo-controlled comparison. *Arch Gen Psychiatry*. 1992;49(4):290–300. PubMed
40. Versiani M, Nardi AE, Mundim FD, et al. Pharmacotherapy of social phobia: a controlled study with moclobemide and phenelzine. *Br J Psychiatry*. 1992;161(3):353–360. doi:10.1192/bjp.161.3.353 PubMed
41. Blanco C, Heimberg RG, Schneier FR, et al. A placebo-controlled trial of phenelzine, cognitive behavioral group therapy, and their combination for social anxiety disorder. *Arch Gen Psychiatry*. 2010;67(3):286–295. doi:10.1001/archgenpsychiatry.2010.11 PubMed
42. Frank JB, Kosten TR, Giller EL Jr, et al. A randomized clinical trial of phenelzine and imipramine for posttraumatic stress disorder. *Am J Psychiatry*. 1988;145(10):1289–1291. PubMed
43. Kosten TR, Frank JB, Dan E, et al. Pharmacotherapy for posttraumatic stress disorder using phenelzine or imipramine. *J Nerv Ment Dis*. 1991;179(6):366–370. PubMed
44. Shestatzky M, Greenberg D, Lerer B. A controlled trial of phenelzine in posttraumatic stress disorder. *Psychiatry Res*. 1988;24(2):149–155. doi:10.1016/0165-1781(88)90057-1 PubMed
45. Jenike MA, Baer L, Minichiello WE, et al. Placebo-controlled trial of fluoxetine and phenelzine for obsessive-compulsive disorder. *Am J Psychiatry*. 1997;154(9):1261–1264. PubMed
46. Krüger MB, Dahl AA. The efficacy and safety of moclobemide compared to clomipramine in the treatment of panic disorder. *Eur Arch Psychiatry Clin Neurosci*. 1999;249(suppl 1):S19–S24. doi:10.1007/PL00014163 PubMed
47. Tiller JW, Bouwer C, Behnke K. International Panic Disorder Study Group. Moclobemide and fluoxetine for panic disorder. *Eur Arch Psychiatry Clin Neurosci*. 1999;249(suppl 1):S7–S10. doi:10.1007/PL00014164 PubMed
48. Bisserbe JC, Lépine JP. Moclobemide in social phobia: a pilot open study. GRP Group. Groupe de Recherche en Psychopharmacologie. *Clin Neuropharmacol*. 1994;17(suppl 1):S88–S94. PubMed
49. The International Multicenter Clinical Trial Group on Moclobemide in Social Phobia. Moclobemide in social phobia: a double-blind, placebo-controlled clinical study. *Eur Arch Psychiatry Clin Neurosci*. 1997;247(2):71–80. PubMed
50. Schneier FR, Goetz D, Campeas R, et al. Placebo-controlled trial of moclobemide in social phobia. *Br J Psychiatry*. 1998;172(1):70–77. doi:10.1192/bjp.172.1.70 PubMed
51. Atmaca M, Kuloglu M, Tezcan E, et al. Efficacy of citalopram and moclobemide in patients with social phobia: some preliminary findings. *Hum Psychopharmacol*. 2002;17(8):401–405. doi:10.1002/hup.436 PubMed
52. Versiani M, Amrein R, Montgomery SA. Social phobia: long-term treatment outcome and prediction of response—a moclobemide study. *Int Clin Psychopharmacol*. 1997;12(5):239–254. PubMed
53. Stein DJ, Cameron A, Amrein R, et al. Moclobemide Social Phobia Clinical Study Group. Moclobemide is effective and well tolerated in the long-term pharmacotherapy of social anxiety disorder with or without comorbid anxiety disorder. *Int Clin Psychopharmacol*. 2002;17(4):161–170. doi:10.1097/00004850-200207000-00002 PubMed
54. Noyes R Jr, Moroz G, Davidson JR, et al. Moclobemide in social phobia: a controlled dose-response trial. *J Clin Psychopharmacol*. 1997;17(4):247–254. doi:10.1097/00004714-199708000-00002 PubMed
55. Neal LA, Shapland W, Fox C. An open trial of moclobemide in the treatment of post-traumatic stress disorder. *Int Clin Psychopharmacol*. 1997;12(4):231–237. doi:10.1097/00004850-199707000-00008 PubMed
56. Onder E, Tural U, Aker T. A comparative study of fluoxetine, moclobemide, and tianeptine in the treatment of posttraumatic stress disorder following an earthquake. *Eur Psychiatry*. 2006;21(3):174–179. doi:10.1016/j.eurpsy.2005.03.007 PubMed
57. van Vliet IM, Westenberg HG, Den Boer JA. MAO inhibitors in panic disorder: clinical effects of treatment with brofaromine: a double blind placebo controlled study. *Psychopharmacology (Berl)*. 1993;112(4):483–489. doi:10.1007/BF02244898 PubMed
58. Bakish D, Saxena BM, Bowen R, et al. Reversible monoamine oxidase-A inhibitors in panic disorder. *Clin Neuropharmacol*. 1993;16(suppl 2):S77–S82. PubMed
59. van Vliet IM, den Boer JA, Westenberg HG, et al. A double-blind comparative study of brofaromine and fluvoxamine in outpatients with panic disorder. *J Clin Psychopharmacol*. 1996;16(4):299–306. doi:10.1097/00004714-199608000-00005 PubMed
60. van Vliet IM, den Boer JA, Westenberg HG. Psychopharmacological treatment of social phobia: clinical and biochemical effects of brofaromine, a selective MAO-A inhibitor. *Eur Neuropsychopharmacol*. 1992;2(1):21–29. doi:10.1016/0924-977X(92)90032-4 PubMed
61. Fahlén T, Nilsson HL, Borg K, et al. Social phobia: the clinical efficacy and tolerability of the monoamine oxidase -A and serotonin uptake inhibitor brofaromine: a double-blind placebo-controlled study. *Acta Psychiatr Scand*. 1995;92(5):351–358. doi:10.1111/j.1600-0447.1995.tb09596.x PubMed
62. Lott M, Greist JH, Jefferson JW, et al. Brofaromine for social phobia: a multicenter, placebo-controlled, double-blind study. *J Clin Psychopharmacol*. 1997;17(4):255–260. doi:10.1097/00004714-199708000-00003 PubMed
63. Katz RJ, Lott MH, Arbus P, et al. Pharmacotherapy of post-traumatic stress disorder with a novel psychotropic. *Anxiety*. 1994-1995;1(4):169–174. PubMed
64. Baker DG, Diamond BI, Gillette G, et al. A double-blind, randomized, placebo-controlled, multi-center study of brofaromine in the treatment of post-traumatic stress disorder. *Psychopharmacology (Berl)*. 1995;122(4):386–389. doi:10.1007/BF02246271 PubMed
65. Otto MW, Tuby KS, Gould RA, et al. An effect-size analysis of the relative efficacy and tolerability of serotonin selective reuptake inhibitors for panic disorder. *Am J Psychiatry*. 2001;158(12):1989–1992. doi:10.1176/appi.ajp.158.12.1989 PubMed
66. Bakker A, van Balkom AJ, Spinhoven P. SSRIs vs TCAs in the treatment of panic disorder: a meta-analysis. *Acta Psychiatr Scand*. 2002;106(3):163–167. doi:10.1034/j.1600-0447.2002.02255.x PubMed
67. Mitte K. A meta-analysis of the efficacy of psycho- and pharmacotherapy in panic disorder with and without agoraphobia. *J Affect Disord*. 2005;88(1):27–45. doi:10.1016/j.jad.2005.05.003 PubMed
68. Rapaport MH, Wolkow R, Rubin A, et al. Sertraline treatment of panic disorder: results of a long-term study. *Acta Psychiatr Scand*. 2001;104(4):289–298. doi:10.1034/j.1600-0447.2001.00263.x PubMed
69. Pollack MH, Zaninelli R, Goddard A, et al. Paroxetine in the treatment of generalized anxiety disorder: results of a placebo-controlled, flexible-dosage trial. *J Clin Psychiatry*. 2001;62(5):350–357. PubMed
70. Rickels K, Zaninelli R, McCafferty J, et al. Paroxetine treatment of generalized anxiety disorder: a double-blind, placebo-controlled study. *Am J Psychiatry*. 2003;160(4):749–756. doi:10.1176/appi.ajp.160.4.749 PubMed
71. Ball SG, Kuhn A, Wall D, et al. Selective serotonin reuptake inhibitor treatment for generalized anxiety disorder: a double-blind, prospective comparison between paroxetine and sertraline. *J Clin Psychiatry*. 2005;66(1):94–99. doi:10.4088/JCP.v66n0113 PubMed
72. Bielski RJ, Bose A, Chang CC. A double-blind comparison of escitalopram and paroxetine in the long-term treatment of generalized anxiety disorder. *Ann Clin Psychiatry*. 2005;17(2):65–69. doi:10.1080/10401230590932326 PubMed
73. Kim TS, Pae CU, Yoon SJ, et al. Comparison of venlafaxine extended release versus paroxetine for treatment of patients with generalized anxiety disorder. *Psychiatry Clin Neurosci*. 2006;60(3):347–351. doi:10.1111/j.1440-1819.2006.01512.x PubMed
74. Stocchi F, Nordera G, Jokinen RH, et al. Paroxetine Generalized Anxiety Disorder Study Team. Efficacy and tolerability of paroxetine for the long-term treatment of generalized anxiety disorder. *J Clin Psychiatry*. 2003;64(3):250–258. PubMed
75. Allgulander C, Dahl AA, Austin C, et al. Efficacy of sertraline in a 12-week trial for generalized anxiety disorder. *Am J Psychiatry*. 2004;161(9):1642–1649. doi:10.1176/appi.ajp.161.9.1642 PubMed

76. Brawman-Mintzer O, Knapp RG, Rynn M, et al. Sertraline treatment for generalized anxiety disorder: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2006;67(6):874–881. doi:10.4088/JCP.v67n0603 PubMed
77. Dahl AA, Ravindran A, Allgulander C, et al. Sertraline in generalized anxiety disorder: efficacy in treating the psychic and somatic anxiety factors. *Acta Psychiatr Scand*. 2005;111(6):429–435. doi:10.1111/j.1600-0447.2005.00529.x PubMed
78. Davidson JR, Bose A, Korotzer A, et al. Escitalopram in the treatment of generalized anxiety disorder: double-blind, placebo controlled, flexible-dose study. *Depress Anxiety*. 2004;19(4):234–240. doi:10.1002/da.10146 PubMed
79. Goodman WK, Bose A, Wang Q. Treatment of generalized anxiety disorder with escitalopram: pooled results from double-blind, placebo-controlled trials. *J Affect Disord*. 2005;87(2-3):161–167. doi:10.1016/j.jad.2004.11.011 PubMed
80. Allgulander C, Florea I, Huusom AK. Prevention of relapse in generalized anxiety disorder by escitalopram treatment. *Int J Neuropsychopharmacol*. 2006;9(5):495–505. doi:10.1017/S1461145705005973 PubMed
81. van der Linden GJ, Stein DJ, van Balkom AJ. The efficacy of the selective serotonin reuptake inhibitors for social anxiety disorder (social phobia): a meta-analysis of randomized controlled trials. *Int Clin Psychopharmacol*. 2000;15(suppl 2):S15–S23. PubMed
82. Fedoroff IC, Taylor S. Psychological and pharmacological treatments of social phobia: a meta-analysis. *J Clin Psychopharmacol*. 2001;21(3):311–324. doi:10.1097/00004714-200106000-00011 PubMed
83. Blanco C, Schneier FR, Schmidt A, et al. Pharmacological treatment of social anxiety disorder: a meta-analysis. *Depress Anxiety*. 2003;18(1):29–40. doi:10.1002/da.10096 PubMed
84. Stein DJ, Ipser JC, Balkom AJ. Pharmacotherapy for social phobia. *Cochrane Database Syst Rev*. 2004;(4):CD001206. PubMed
85. Hedges DW, Brown BL, Shwalb DA, et al. The efficacy of selective serotonin reuptake inhibitors in adult social anxiety disorder: a meta-analysis of double-blind, placebo-controlled trials. *J Psychopharmacol*. 2007;21(1):102–111. doi:10.1177/0269881106065102 PubMed
86. Kobak KA, Greist JH, Jefferson JW, et al. Fluoxetine in social phobia: a double-blind, placebo-controlled pilot study. *J Clin Psychopharmacol*. 2002;22(3):257–262. doi:10.1097/00004714-200206000-00005 PubMed
87. Davidson JR, Foa EB, Huppert JD, et al. Fluoxetine, comprehensive cognitive behavioral therapy, and placebo in generalized social phobia. *Arch Gen Psychiatry*. 2004;61(10):1005–1013. doi:10.1001/archpsyc.61.10.1005 PubMed
88. Brady K, Pearlstein T, Asnis GM, et al. Efficacy and safety of sertraline treatment of posttraumatic stress disorder: a randomized controlled trial. *JAMA*. 2000;283(14):1837–1844. doi:10.1001/jama.283.14.1837 PubMed
89. Davidson JR, Rothbaum BO, van der Kolk BA, et al. Multicenter, double-blind comparison of sertraline and placebo in the treatment of posttraumatic stress disorder. *Arch Gen Psychiatry*. 2001;58(5):485–492. doi:10.1001/archpsyc.58.5.485 PubMed
90. Marshall RD, Beebe KL, Oldham M, et al. Efficacy and safety of paroxetine treatment for chronic PTSD: a fixed-dose, placebo-controlled study. *Am J Psychiatry*. 2001;158(12):1982–1988. doi:10.1176/appi.ajp.158.12.1982 PubMed
91. Tucker P, Zaninelli R, Yehuda R, et al. Paroxetine in the treatment of chronic posttraumatic stress disorder: results of a placebo-controlled, flexible-dosage trial. *J Clin Psychiatry*. 2001;62(11):860–868. PubMed
92. Zohar J, Amital D, Miodownik C, et al. Double-blind placebo-controlled pilot study of sertraline in military veterans with posttraumatic stress disorder. *J Clin Psychopharmacol*. 2002;22(2):190–195. doi:10.1097/00004714-200204000-00013 PubMed
93. Friedman MJ, Marmar CR, Baker DG, et al. Randomized, double-blind comparison of sertraline and placebo for posttraumatic stress disorder in a Department of Veterans Affairs setting. *J Clin Psychiatry*. 2007;68(5):711–720. doi:10.4088/JCP.v68n0508 PubMed
94. Davidson J, Pearlstein T, Londborg P, et al. Efficacy of sertraline in preventing relapse of posttraumatic stress disorder: results of a 28-week double-blind, placebo-controlled study. *Am J Psychiatry*. 2001;158(12):1974–1981. doi:10.1176/appi.ajp.158.12.1974 PubMed
95. Londborg PD, Hegel MT, Goldstein S, et al. Sertraline treatment of posttraumatic stress disorder: results of 24 weeks of open-label continuation treatment. *J Clin Psychiatry*. 2001;62(5):325–331. PubMed
96. Tucker P, Potter-Kimball R, Wyatt DB, et al. Can physiologic assessment and side effects tease out differences in PTSD trials? a double-blind comparison of citalopram, sertraline, and placebo. *Psychopharmacol Bull*. 2003;37(3):135–149. PubMed
97. Stein DJ, Seedat S, van der Linden GJ, et al. Selective serotonin reuptake inhibitors in the treatment of post-traumatic stress disorder: a meta-analysis of randomized controlled trials. *Int Clin Psychopharmacol*. 2000;15(suppl 2):S31–S39. PubMed
98. Stein DJ, Ipser JC, Seedat S. Pharmacotherapy for post traumatic stress disorder (PTSD). *Cochrane Database Syst Rev*. 2006;(1):CD002795. PubMed
99. Chouinard G. Sertraline in the treatment of obsessive compulsive disorder: two double-blind, placebo-controlled studies. *Int Clin Psychopharmacol*. 1992;7(suppl 2):37–41. doi:10.1097/00004850-199210002-00007 PubMed
100. Montgomery SA, McIntyre A, Osterheider M, et al. The Lilly European OCD Study Group. A double-blind, placebo-controlled study of fluoxetine in patients with *DSM-III-R* obsessive-compulsive disorder. *Eur Neuropsychopharmacol*. 1993;3(2):143–152. doi:10.1016/0924-977X(93)90266-O PubMed
101. Tollefson GD, Rampey AH Jr, Potvin JH, et al. A multicenter investigation of fixed-dose fluoxetine in the treatment of obsessive-compulsive disorder. *Arch Gen Psychiatry*. 1994;51(7):559–567. PubMed
102. Tollefson GD, Birkett M, Koran L, et al. Continuation treatment of OCD: double-blind and open-label experience with fluoxetine. *J Clin Psychiatry*. 1994;55(suppl):69–76, discussion 77–78. PubMed
103. Greist J, Chouinard G, DuBoff E, et al. Double-blind parallel comparison of three dosages of sertraline and placebo in outpatients with obsessive-compulsive disorder. *Arch Gen Psychiatry*. 1995;52(4):289–295. PubMed
104. Greist JH, Jefferson JW, Kobak KA, et al. A 1 year double-blind placebo-controlled fixed dose study of sertraline in the treatment of obsessive-compulsive disorder. *Int Clin Psychopharmacol*. 1995;10(2):57–65. doi:10.1097/00004850-199506000-00001 PubMed
105. Mundo E, Bianchi L, Bellodi L. Efficacy of fluvoxamine, paroxetine, and citalopram in the treatment of obsessive-compulsive disorder: a single-blind study. *J Clin Psychopharmacol*. 1997;17(4):267–271. doi:10.1097/00004714-199708000-00005 PubMed
106. Kronig MH, Apter J, Asnis G, et al. Placebo-controlled, multicenter study of sertraline treatment for obsessive-compulsive disorder. *J Clin Psychopharmacol*. 1999;19(2):172–176. doi:10.1097/00004714-199904000-00013 PubMed
107. Montgomery SA, Kasper S, Stein DJ, et al. Citalopram 20 mg, 40 mg and 60 mg are all effective and well tolerated compared with placebo in obsessive-compulsive disorder. *Int Clin Psychopharmacol*. 2001;16(2):75–86. doi:10.1097/00004850-200103000-00002 PubMed
108. Romano S, Goodman W, Tamura R, et al. Long-term treatment of obsessive-compulsive disorder after an acute response: a comparison of fluoxetine vs placebo. *J Clin Psychopharmacol*. 2001;21(1):46–52. doi:10.1097/00004714-200102000-00009 PubMed
109. Bergeron R, Ravindran AV, Chaput Y, et al. Sertraline and fluoxetine treatment of obsessive-compulsive disorder: results of a double-blind, 6-month treatment study. *J Clin Psychopharmacol*. 2002;22(2):148–154. doi:10.1097/00004714-200204000-00007 PubMed
110. Hollander E, Allen A, Steiner M, et al. Paroxetine OCD Study Group. Acute and long-term treatment and prevention of relapse of obsessive-compulsive disorder with paroxetine. *J Clin Psychiatry*. 2003;64(9):1113–1121. PubMed
111. Kamijima K, Murasaki M, Asai M, et al. Paroxetine in the treatment of obsessive-compulsive disorder: randomized, double-blind, placebo-controlled study in Japanese patients. *Psychiatry Clin Neurosci*. 2004;58(4):427–433. doi:10.1111/j.1440-1819.2004.01278.x PubMed
112. Fineberg NA, Tonnoir B, Lemming O, et al. Escitalopram prevents relapse of obsessive-compulsive disorder. *Eur Neuropsychopharmacol*. 2007;17(6-7):430–439. doi:10.1016/j.euroneuro.2006.11.005 PubMed
113. Stein DJ, Andersen EW, Tonnoir B, et al. Escitalopram in obsessive-compulsive disorder: a randomized, placebo-controlled, paroxetine-referenced, fixed-dose, 24-week study. *Curr Med Res Opin*. 2007;23(4):701–711. doi:10.1185/030079907X178838 PubMed
114. Soomro GM, Altman D, Rajagopal S, et al. Selective serotonin re-uptake inhibitors (SSRIs) vs placebo for obsessive compulsive disorder (OCD). *Cochrane Database Syst Rev*. 2008;(1):CD001765. PubMed
115. Ninan PT, Koran LM, Kiev A, et al. High-dose sertraline strategy for nonresponders to acute treatment for obsessive-compulsive disorder: a multicenter double-blind trial. *J Clin Psychiatry*. 2006;67(1):15–22. doi:10.4088/JCP.v67n0103 PubMed
116. Stein DJ, Spadaccini E, Hollander E. Meta-analysis of pharmacotherapy trials for obsessive-compulsive disorder. *Int Clin Psychopharmacol*. 1995;10(1):11–18. doi:10.1097/00004850-199503000-00002 PubMed
117. Piccinelli M, Pini S, Bellantuono C, et al. Efficacy of drug treatment in obsessive-compulsive disorder: a meta-analytic review. *Br J Psychiatry*. 1995;166(4):424–443. doi:10.1192/bjp.166.4.424 PubMed
118. Ackerman DL, Greenland S. Multivariate meta-analysis of controlled drug studies for obsessive-compulsive disorder. *J Clin Psychopharmacol*. 2002;22(3):309–317. doi:10.1097/00004714-200206000-00012 PubMed
119. Baldwin DS, Anderson IM, Nutt DJ, et al. British Association for Psychopharmacology. Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British

Association for Psychopharmacology. *J Psychopharmacol*. 2005;19(6):567–596. doi:10.1177/0269881105059253 PubMed
120. American Psychiatric Association. *Practice Guidelines for the Treatment of Patients With Obsessive-Compulsive Disorder*. Washington, DC: American Psychiatric Association; 2007.
121. Bandelow B, Zohar J, Hollander E, et al. WFSBP Task Force on Treatment Guidelines for Anxiety, Obsessive-Compulsive and Post-Traumatic Stress Disorders. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders—first revision. *World J Biol Psychiatry*. 2008;9(4):248–312. doi:10.1080/15622970802465807 PubMed
122. Bradwejn J, Ahokas A, Stein DJ, et al. Venlafaxine extended-release capsules in panic disorder: flexible-dose, double-blind, placebo-controlled study. *Br J Psychiatry*. 2005;187(4):352–359. doi:10.1192/bjp.187.4.352 PubMed
123. Liebowitz MR, Asnis G, Mangano R, et al. A double-blind, placebo-controlled, parallel-group, flexible-dose study of venlafaxine extended release capsules in adult outpatients with panic disorder. *J Clin Psychiatry*. 2009;70(4):550–561. doi:10.4088/JCP.08m04238 PubMed
124. Pollack MH, Lepola U, Koponen H, et al. A double-blind study of the efficacy of venlafaxine extended-release, paroxetine, and placebo in the treatment of panic disorder. *Depress Anxiety*. 2007;24(1):1–14. doi:10.1002/da.20218 PubMed
125. Pollack M, Mangano R, Entsuah R, et al. A randomized controlled trial of venlafaxine ER and paroxetine in the treatment of outpatients with panic disorder. *Psychopharmacology (Berl)*. 2007;194(2):233–242. doi:10.1007/s00213-007-0821-0 PubMed
126. Ferguson JM, Khan A, Mangano R, et al. Relapse prevention of panic disorder in adult outpatient responders to treatment with venlafaxine extended release. *J Clin Psychiatry*. 2007;68(1):58–68. doi:10.4088/JCP.v68n0108 PubMed
127. Simon NM, Kaufman RE, Hoge EA, et al. Open-label support for duloxetine for the treatment of panic disorder. *CNS Neurosci Ther*. 2009;15(1):19–23. doi:10.1111/j.1755-5949.2008.00076.x PubMed
128. Blaya C, Seganfredo AC, Dornelles M, et al. The efficacy of milnacipran in panic disorder: an open trial. *Int Clin Psychopharmacol*. 2007;22(3):153–158. doi:10.1097/YIC.0b013e32802c7bf5 PubMed
129. Davidson JR, DuPont RL, Hedges D, et al. Efficacy, safety, and tolerability of venlafaxine extended release and buspirone in outpatients with generalized anxiety disorder. *J Clin Psychiatry*. 1999;60(8):528–535. PubMed
130. Rickels K, Pollack MH, Sheehan DV, et al. Efficacy of extended-release venlafaxine in nondepressed outpatients with generalized anxiety disorder. *Am J Psychiatry*. 2000;157(6):968–974. doi:10.1176/appi.ajp.157.6.968 PubMed
131. Nimatoudis I, Zissis NP, Kogeorgos J, et al. Remission rates with venlafaxine extended release in Greek outpatients with generalized anxiety disorder: a double-blind, randomized, placebo controlled study. *Int Clin Psychopharmacol*. 2004;19(6):331–336. doi:10.1097/00004850-200411000-00003 PubMed
132. Bose A, Korotzer A, Gommoll C, et al. Randomized placebo-controlled trial of escitalopram and venlafaxine XR in the treatment of generalized anxiety disorder. *Depress Anxiety*. 2008;25(10):854–861. doi:10.1002/da.20355 PubMed
133. Montgomery SA, Tobias K, Zornberg GL, et al. Efficacy and safety of pregabalin in the treatment of generalized anxiety disorder: a 6-week, multicenter, randomized, double-blind, placebo-controlled comparison of pregabalin and venlafaxine. *J Clin Psychiatry*. 2006;67(5):771–782. doi:10.4088/JCP.v67n0511 PubMed
134. Gelenberg AJ, Lydiard RB, Rudolph RL, et al. Efficacy of venlafaxine extended-release capsules in nondepressed outpatients with generalized anxiety disorder: a 6-month randomized controlled trial. *JAMA*. 2000;283(23):3082–3088. doi:10.1001/jama.283.23.3082 PubMed
135. Allgulander C, Hackett D, Salinas E. Venlafaxine extended release (ER) in the treatment of generalised anxiety disorder: twenty-four-week placebo-controlled dose-ranging study. *Br J Psychiatry*. 2001;179(1):15–22. doi:10.1192/bjp.179.1.15 PubMed
136. Rynn M, Russell J, Erickson J, et al. Efficacy and safety of duloxetine in the treatment of generalized anxiety disorder: a flexible-dose, progressive-titration, placebo-controlled trial. *Depress Anxiety*. 2008;25(3):182–189. doi:10.1002/da.20271 PubMed
137. Hartford J, Kornstein S, Liebowitz M, et al. Duloxetine as an SNRI treatment for generalized anxiety disorder: results from a placebo and active-controlled trial. *Int Clin Psychopharmacol*. 2007;22(3):167–174. doi:10.1097/YIC.0b013e32807fb1b2 PubMed
138. Nicolini H, Bakish D, Duenas H, et al. Improvement of psychic and somatic symptoms in adult patients with generalized anxiety disorder: examination from a duloxetine, venlafaxine extended-release and placebo-controlled trial. *Psychol Med*. 2009;39(2):267–276. doi:10.1017/S0033291708003401 PubMed
139. Davidson JR, Wittchen HU, Llorca PM, et al. Duloxetine treatment for relapse prevention in adults with generalized anxiety disorder: a double-blind placebo-controlled trial. *Eur Neuropsychopharmacol*. 2008;18(9):673–681. doi:10.1016/j.euroneuro.2008.05.002 PubMed
140. Rickels K, Mangano R, Khan A. A double-blind, placebo-controlled study of a flexible dose of venlafaxine ER in adult outpatients with generalized social anxiety disorder. *J Clin Psychopharmacol*. 2004;24(5):488–496. doi:10.1097/01.jcp.0000138764.31106.60 PubMed
141. Liebowitz MR, Mangano RM, Bradwejn J, et al. SAD Study Group. A randomized controlled trial of venlafaxine extended release in generalized social anxiety disorder. *J Clin Psychiatry*. 2005;66(2):238–247. doi:10.4088/JCP.v66n0213 PubMed
142. Allgulander C, Mangano R, Zhang J, et al. SAD 388 Study Group. Efficacy of Venlafaxine ER in patients with social anxiety disorder: a double-blind, placebo-controlled, parallel-group comparison with paroxetine. *Hum Psychopharmacol*. 2004;19(6):387–396. doi:10.1002/hup.602 PubMed
143. Liebowitz MR, Gelenberg AJ, Munjack D. Venlafaxine extended release vs placebo and paroxetine in social anxiety disorder. *Arch Gen Psychiatry*. 2005;62(2):190–198. doi:10.1001/archpsyc.62.2.190 PubMed
144. Stein MB, Pollack MH, Bystritsky A, et al. Efficacy of low and higher dose extended-release venlafaxine in generalized social anxiety disorder: a 6-month randomized controlled trial. *Psychopharmacology (Berl)*. 2005;177(3):280–288. doi:10.1007/s00213-004-1957-9 PubMed
145. Davidson J, Rothbaum BO, Tucker P, et al. Venlafaxine extended release in posttraumatic stress disorder: a sertraline- and placebo-controlled study. *J Clin Psychopharmacol*. 2006;26(3):259–267. doi:10.1097/01.jcp.0000222514.71390.c1 PubMed
146. Davidson J, Baldwin D, Stein DJ, et al. Treatment of posttraumatic stress disorder with venlafaxine extended release: a 6-month randomized controlled trial. *Arch Gen Psychiatry*. 2006;63(10):1158–1165. doi:10.1001/archpsyc.63.10.1158 PubMed
147. Yaryura-Tobias JA, Neziroglu FA. Venlafaxine in obsessive-compulsive disorder. *Arch Gen Psychiatry*. 1996;53(7):653–654. PubMed
148. Denys D, van der Wee N, van Megen HJ, et al. A double blind comparison of venlafaxine and paroxetine in obsessive-compulsive disorder. *J Clin Psychopharmacol*. 2003;23(6):568–575. doi:10.1097/01.jcp.0000095342.32154.54 PubMed
149. Denys D, van Megen HJ, van der Wee N, et al. A double-blind switch study of paroxetine and venlafaxine in obsessive-compulsive disorder. *J Clin Psychiatry*. 2004;65(1):37–43. doi:10.4088/JCP.v65n0106 PubMed
150. Dell'Osso B, Buoli M, Baldwin DS, et al. Serotonin norepinephrine reuptake inhibitors (SNRIs) in anxiety disorders: a comprehensive review of their clinical efficacy. *Hum Psychopharmacol*. 2010;25(1):17–29. doi:10.1002/hup.1074 PubMed
151. Gorman JM. Mirtazapine: clinical overview. *J Clin Psychiatry*. 1999;60(suppl 17):9–13, discussion 46–48. PubMed
152. Carpenter LL, Leon Z, Yasmin S, et al. Clinical experience with mirtazapine in the treatment of panic disorder. *Ann Clin Psychiatry*. 1999;11(2):81–86. doi:10.3109/10401239909147053 PubMed
153. Boshuisen ML, Slaap BR, Vester-Blokland ED, et al. The effect of mirtazapine in panic disorder: an open label pilot study with a single-blind placebo run-in period. *Int Clin Psychopharmacol*. 2001;16(6):363–368. doi:10.1097/00004850-200111000-00008 PubMed
154. Sarchiapone M, Amore M, De Risio S, et al. Mirtazapine in the treatment of panic disorder: an open-label trial. *Int Clin Psychopharmacol*. 2003;18(1):35–38. doi:10.1097/00004850-200301000-00006 PubMed
155. Ribeiro L, Busnello JV, Kauer-Sant'Anna M, et al. Mirtazapine vs fluoxetine in the treatment of panic disorder. *Braz J Med Biol Res*. 2001;34(10):1303–1307. doi:10.1590/S0100-879X2001001000010 PubMed
156. Van Veen JF, Van Vliet IM, Westenberg HG. Mirtazapine in social anxiety disorder: a pilot study. *Int Clin Psychopharmacol*. 2002;17(6):315–317. doi:10.1097/00004850-200211000-00008 PubMed
157. Muehlbacher M, Nickel MK, Nickel C, et al. Mirtazapine treatment of social phobia in women: a randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol*. 2005;25(6):580–583. doi:10.1097/01.jcp.0000186871.04984.8d PubMed
158. Davidson JR, Weisler RH, Butterfield MI, et al. Mirtazapine vs placebo in posttraumatic stress disorder: a pilot trial. *Biol Psychiatry*. 2003;53(2):188–191. doi:10.1016/S0006-3223(02)01411-7 PubMed
159. Koran LM, Gamel NN, Choung HW, et al. Mirtazapine for obsessive-compulsive disorder: an open trial followed by double-blind discontinuation. *J Clin Psychiatry*. 2005;66(4):515–520. doi:10.4088/JCP.v66n0415 PubMed
160. Pallanti S, Quercioli L, Bruscoli M. Response acceleration with mirtazapine augmentation of citalopram in obsessive-compulsive disorder patients without comorbid depression: a pilot study. *J Clin Psychiatry*. 2004;65(10):1394–1399. doi:10.4088/JCP.v65n1015 PubMed
161. Sheehan DV, Davidson J, Manschreck T, et al. Lack of efficacy of a new antidepressant (bupropion) in the treatment of panic disorder with phobias. *J Clin Psychopharmacol*. 1983;3(1):28–31. doi:10.1097/00004714-198302000-00006 PubMed

162. Simon NM, Emmanuel N, Ballenger J, et al. Bupropion sustained release for panic disorder. *Psychopharmacol Bull*. 2003;37(4):66–72. PubMed
163. Bystritsky A, Kerwin L, Feusner JD, et al. A pilot controlled trial of bupropion XL vs escitalopram in generalized anxiety disorder. *Psychopharmacol Bull*. 2008;41(1):46–51. PubMed
164. Hertzberg MA, Moore SD, Feldman ME, et al. A preliminary study of bupropion sustained-release for smoking cessation in patients with chronic posttraumatic stress disorder. *J Clin Psychopharmacol*. 2001;21(1):94–98. doi:10.1097/00004714-200102000-00017 PubMed
165. Becker ME, Hertzberg MA, Moore SD, et al. A placebo-controlled trial of bupropion SR in the treatment of chronic posttraumatic stress disorder. *J Clin Psychopharmacol*. 2007;27(2):193–197. doi:10.1097/JCP.0b013e318032eaed PubMed
166. Vulink NC, Denys D, Westenberg HG. Bupropion for patients with obsessive-compulsive disorder: an open-label, fixed-dose study. *J Clin Psychiatry*. 2005;66(2):228–230. doi:10.4088/JCP.v66n0211 PubMed
167. DeMartinis NA, Schweizer E, Rickels K. An open-label trial of nefazodone in high comorbidity panic disorder. *J Clin Psychiatry*. 1996;57(6):245–248. PubMed
168. Bystritsky A, Rosen R, Suri R, et al. Pilot open-label study of nefazodone in panic disorder. *Depress Anxiety*. 1999;10(3):137–139. doi:10.1002/(SICI)1520-6394(1999)10:3<137::AID-DA8>3.0.CO;2-7 PubMed
169. Papp LA, Coplan JD, Martinez JM, et al. Efficacy of open-label nefazodone treatment in patients with panic disorder. *J Clin Psychopharmacol*. 2000;20(5):544–546. doi:10.1097/00004714-200010000-00009 PubMed
170. Hedges DW, Reimherr FW, Strong RE, et al. An open trial of nefazodone in adult patients with generalized anxiety disorder. *Psychopharmacol Bull*. 1996;32(4):671–676. PubMed
171. Van Ameringen M, Mancini C, Oakman J, et al. Nefazodone in the treatment of generalized social phobia: a randomized, placebo-controlled trial. *J Clin Psychiatry*. 2007;68(2):288–295. doi:10.4088/JCP.v68n0215 PubMed
172. Davis LL, Jewell ME, Ambrose S, et al. A placebo-controlled study of nefazodone for the treatment of chronic posttraumatic stress disorder: a preliminary study. *J Clin Psychopharmacol*. 2004;24(3):291–297. doi:10.1097/01.jcp.0000125685.82219.1a PubMed
173. McRae AL, Brady KT, Mellman TA, et al. Comparison of nefazodone and sertraline for the treatment of posttraumatic stress disorder. *Depress Anxiety*. 2004;19(3):190–196. doi:10.1002/da.20008 PubMed
174. Mavissakalian M, Perel J, Bowler K, et al. Trazodone in the treatment of panic disorder and agoraphobia with panic attacks. *Am J Psychiatry*. 1987;144(6):785–787. PubMed
175. Charney DS, Woods SW, Goodman WK, et al. Drug treatment of panic disorder: the comparative efficacy of imipramine, alprazolam, and trazodone. *J Clin Psychiatry*. 1986;47(12):580–586. PubMed
176. Pigott TA, L'Heureux F, Rubenstein CS, et al. A double-blind, placebo controlled study of trazodone in patients with obsessive-compulsive disorder. *J Clin Psychopharmacol*. 1992;12(3):156–162. PubMed
177. Mula M, Pini S, Cassano GB. The role of anticonvulsant drugs in anxiety disorders: a critical review of the evidence. *J Clin Psychopharmacol*. 2007;27(3):263–272. doi:10.1097/jcp.0b013e318059361a PubMed
178. Pande AC, Pollack MH, Crockatt J, et al. Placebo-controlled study of gabapentin treatment of panic disorder. *J Clin Psychopharmacol*. 2000;20(4):467–471. doi:10.1097/00004714-200008000-00011 PubMed
179. Zwanzger P, Eser D, Nothdurfter C, et al. Effects of the GABA-reuptake inhibitor tiagabine on panic and anxiety in patients with panic disorder. *Pharmacopsychiatry*. 2009;42(6):266–269. doi:10.1055/s-0029-1241798 PubMed
180. Uhde TW, Stein MB, Post RM. Lack of efficacy of carbamazepine in the treatment of panic disorder. *Am J Psychiatry*. 1988;145(9):1104–1109. PubMed
181. Primeau F, Fontaine R, Beauclair L. Valproic acid and panic disorder. *Can J Psychiatry*. 1990;35(3):248–250. PubMed
182. Woodman CL, Noyes R Jr. Panic disorder: treatment with valproate. *J Clin Psychiatry*. 1994;55(4):134–136. PubMed
183. Zwanzger P, Baghai T, Boerner RJ, et al. Anxiolytic effects of vigabatrin in panic disorder. *J Clin Psychopharmacol*. 2001;21(5):539–540. doi:10.1097/00004714-200110000-00017 PubMed
184. Papp LA. Safety and efficacy of levetiracetam for patients with panic disorder: results of an open-label, fixed-flexible dose study. *J Clin Psychiatry*. 2006;67(10):1573–1576. doi:10.4088/JCP.v67n1012 PubMed
185. Feltner DE, Crockatt JG, Dubovsky SJ, et al. A randomized, double-blind, placebo-controlled, fixed-dose, multicenter study of pregabalin in patients with generalized anxiety disorder. *J Clin Psychopharmacol*. 2003;23(3):240–249. doi:10.1097/00004714-200306000-00005 PubMed
186. Pande AC, Crockatt JG, Feltner DE, et al. Pregabalin in generalized anxiety disorder: a placebo-controlled trial. *Am J Psychiatry*. 2003;160(3):533–540. doi:10.1176/appi.ajp.160.3.533 PubMed
187. Pohl RB, Feltner DE, Fieve RR, et al. Efficacy of pregabalin in the treatment of generalized anxiety disorder: double-blind, placebo-controlled comparison of BID vs TID dosing. *J Clin Psychopharmacol*. 2005;25(2):151–158. doi:10.1097/01.jcp.0000155820.74832.b0 PubMed
188. Rickels K, Pollack MH, Feltner DE, et al. Pregabalin for treatment of generalized anxiety disorder: a 4-week, multicenter, double-blind, placebo-controlled trial of pregabalin and alprazolam. *Arch Gen Psychiatry*. 2005;62(9):1022–1030. doi:10.1001/archpsyc.62.9.1022 PubMed
189. Feltner D, Wittchen HU, Kavoussi R, et al. Long-term efficacy of pregabalin in generalized anxiety disorder. *Int Clin Psychopharmacol*. 2008;23(1):18–28. doi:10.1097/YIC.0b013e3282f0f0d7 PubMed
190. Pollack MH, Roy-Byrne PP, Van Ameringen M, et al. The selective GABA reuptake inhibitor tiagabine for the treatment of generalized anxiety disorder: results of a placebo-controlled study. *J Clin Psychiatry*. 2005;66(11):1401–1408. doi:10.4088/JCP.v66n1109 PubMed
191. Aliyev NA, Aliyev ZN. Valproate (depakine-chrono) in the acute treatment of outpatients with generalized anxiety disorder without psychiatric comorbidity: randomized, double-blind placebo-controlled study. *Eur Psychiatry*. 2008;23(2):109–114. doi:10.1016/j.eurpsy.2007.08.001 PubMed
192. Mathew SJ, Amiel JM, Coplan JD, et al. Open-label trial of riluzole in generalized anxiety disorder. *Am J Psychiatry*. 2005;162(12):2379–2381. doi:10.1176/appi.ajp.162.12.2379 PubMed
193. Simon NM, Worthington JJ, Doyle AC, et al. An open-label study of levetiracetam for the treatment of social anxiety disorder. *J Clin Psychiatry*. 2004;65(9):1219–1222. doi:10.4088/JCP.v65n0909 PubMed
194. Zhang W, Connor KM, Davidson JR. Levetiracetam in social phobia: a placebo controlled pilot study. *J Psychopharmacol*. 2005;19(5):551–553. doi:10.1177/0269881105056526 PubMed
195. Stein MB, Ravindran LN, Simon NM, et al. Levetiracetam in generalized social anxiety disorder: a double-blind, randomized controlled trial. *J Clin Psychiatry*. 2009;71(5):627–631. PubMed
196. Pande AC, Davidson JR, Jefferson JW, et al. Treatment of social phobia with gabapentin: a placebo-controlled study. *J Clin Psychopharmacol*. 1999;19(4):341–348. doi:10.1097/00004714-199908000-00010 PubMed
197. Pande AC, Feltner DE, Jefferson JW, et al. Efficacy of the novel anxiolytic pregabalin in social anxiety disorder: a placebo-controlled, multicenter study. *J Clin Psychopharmacol*. 2004;24(2):141–149. doi:10.1097/01.jcp.0000117423.05703.e7 PubMed
198. Kinrys G, Pollack MH, Simon NM, et al. Valproic acid for the treatment of social anxiety disorder. *Int Clin Psychopharmacol*. 2003;18(3):169–172. doi:10.1097/00004850-200305000-00008 PubMed
199. Van Ameringen M, Mancini C, Pipe B, et al. An open trial of topiramate in the treatment of generalized social phobia. *J Clin Psychiatry*. 2004;65(12):1674–1678. doi:10.4088/JCP.v65n1213 PubMed
200. Dunlop BW, Papp L, Garlow SJ, et al. Tiagabine for social anxiety disorder. *Hum Psychopharmacol*. 2007;22(4):241–244. doi:10.1002/hup.846 PubMed
201. Hertzberg MA, Butterfield MI, Feldman ME, et al. A preliminary study of lamotrigine for the treatment of posttraumatic stress disorder. *Biol Psychiatry*. 1999;45(9):1226–1229. doi:10.1016/S0006-3223(99)00011-6 PubMed
202. Tucker P, Trautman RP, Wyatt DB, et al. Efficacy and safety of topiramate monotherapy in civilian posttraumatic stress disorder: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2007;68(2):201–206. doi:10.4088/JCP.v68n0204 PubMed
203. Lindley SE, Carlson EB, Hill K. A randomized, double-blind, placebo-controlled trial of augmentation topiramate for chronic combat-related posttraumatic stress disorder. *J Clin Psychopharmacol*. 2007;27(6):677–681. doi:10.1097/jcp.0b013e31815a43ee PubMed
204. Davis LL, Davidson JR, Ward LC, et al. Divalproex in the treatment of posttraumatic stress disorder: a randomized, double-blind, placebo-controlled trial in a veteran population. *J Clin Psychopharmacol*. 2008;28(1):84–88. doi:10.1097/JCP.0b013e318160f83b PubMed
205. Hamner MB, Faldowski RA, Robert S, et al. A preliminary controlled trial of divalproex in posttraumatic stress disorder. *Ann Clin Psychiatry*. 2009;21(2):89–94. PubMed
206. Onder E, Tural U, Gökbakan M. Does gabapentin lead to early symptom improvement in obsessive-compulsive disorder? *Eur Arch Psychiatry Clin Neurosci*. 2008;258(6):319–323. doi:10.1007/s00406-007-0798-z PubMed
207. Hollander E, Dell'Osso B. Topiramate plus paroxetine in treatment-resistant obsessive-compulsive disorder. *Int Clin Psychopharmacol*. 2006;21(3):189–191. doi:10.1097/01.yic.0000199453.54799.cc PubMed
208. Van Ameringen M, Mancini C, Patterson B, et al. Topiramate augmentation in treatment-resistant obsessive-compulsive disorder: a retrospective, open-label case series. *Depress Anxiety*. 2006;23(1):1–5. doi:10.1002/da.20118 PubMed
209. Uzun O. Lamotrigine as an augmentation agent in treatment-resistant obsessive-compulsive disorder: a case report. *J Psychopharmacol*. 2010;24(3):425–427. doi:10.1177/0269881108098809 PubMed
210. Hollifield M, Thompson PM, Ruiz JE, et al. Potential effectiveness and safety of olanzapine in refractory panic disorder. *Depress Anxiety*.

2005;21(1):33–40. doi:10.1002/da.20050 PubMed
211. Sepede G, De Berardis D, Gambi F, et al. Olanzapine augmentation in treatment-resistant panic disorder: a 12-week, fixed-dose, open-label trial. *J Clin Psychopharmacol*. 2006;26(1):45–49. doi:10.1097/01.jcp.0000195108.01898.17 PubMed
212. Prosser JM, Yard S, Steele A, et al. A comparison of low-dose risperidone to paroxetine in the treatment of panic attacks: a randomized, single-blind study. *BMC Psychiatry*. 2009;9(1):25. doi:10.1186/1471-244X-9-25 PubMed
213. Pollack MH, Simon NM, Zalta AK, et al. Olanzapine augmentation of fluoxetine for refractory generalized anxiety disorder: a placebo controlled study. *Biol Psychiatry*. 2006;59(3):211–215. doi:10.1016/j.biopsych.2005.07.005 PubMed
214. Brawman-Mintzer O, Knapp RG, Nietert PJ. Adjunctive risperidone in generalized anxiety disorder: a double-blind, placebo-controlled study. *J Clin Psychiatry*. 2005;66(10):1321–1325. doi:10.4088/JCP.v66n1016 PubMed
215. Pandina GJ, Canuso CM, Turkoz I, et al. Adjunctive risperidone in the treatment of generalized anxiety disorder: a double-blind, prospective, placebo-controlled, randomized trial. *Psychopharmacol Bull*. 2007;40(3):41–57. PubMed
216. Katzman MA, Vermani M, Jacobs L, et al. Quetiapine as an adjunctive pharmacotherapy for the treatment of non-remitting generalized anxiety disorder: a flexible-dose, open-label pilot trial. *J Anxiety Disord*. 2008;22(8):1480–1486. doi:10.1016/j.janxdis.2008.03.002 PubMed
217. Simon NM, Connor KM, LeBeau RT, et al. Quetiapine augmentation of paroxetine CR for the treatment of refractory generalized anxiety disorder: preliminary findings. *Psychopharmacology (Berl)*. 2008;197(4):675–681. doi:10.1007/s00213-008-1087-x PubMed
218. Menza MA, Dobkin RD, Marin H. An open-label trial of aripiprazole augmentation for treatment-resistant generalized anxiety disorder. *J Clin Psychopharmacol*. 2007;27(2):207–210. doi:10.1097/01.jcp.0000248620.34541.bc PubMed
219. Snyderman SH, Rynn MA, Rickels K. Open-label pilot study of ziprasidone for refractory generalized anxiety disorder. *J Clin Psychopharmacol*. 2005;25(5):497–499. doi:10.1097/01.jcp.0000177853.15910.de PubMed
220. Barnett SD, Kramer ML, Casat CD, et al. Efficacy of olanzapine in social anxiety disorder: a pilot study. *J Psychopharmacol*. 2002;16(4):365–368. doi:10.1177/026988110201600412 PubMed
221. Schutters SI, van Megen HJ, Westenberg HG. Efficacy of quetiapine in generalized social anxiety disorder: results from an open-label study. *J Clin Psychiatry*. 2005;66(4):540–542. doi:10.4088/JCP.v66n0420b PubMed
222. Vaishnavi S, Alamy S, Zhang W, et al. Quetiapine as monotherapy for social anxiety disorder: a placebo-controlled study. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31(7):1464–1469. doi:10.1016/j.pnpbp.2007.06.027 PubMed
223. Monnelly EP, Ciraulo DA, Knapp C, et al. Low-dose risperidone as adjunctive therapy for irritable aggression in posttraumatic stress disorder. *J Clin Psychopharmacol*. 2003;23(2):193–196. doi:10.1097/00004714-200304000-00012 PubMed
224. Reich DB, Winternitz S, Hennen J, et al. A preliminary study of risperidone in the treatment of posttraumatic stress disorder related to childhood abuse in women. *J Clin Psychiatry*. 2004;65(12):1601–1606. doi:10.4088/JCP.v65n1204 PubMed
225. Bartzokis G, Lu PH, Turner J, et al. Adjunctive risperidone in the treatment of chronic combat-related posttraumatic stress disorder. *Biol Psychiatry*. 2005;57(5):474–479. doi:10.1016/j.biopsych.2004.11.039 PubMed
226. Hamner MB, Faldowski RA, Ulmer HG, et al. Adjunctive risperidone treatment in post-traumatic stress disorder: a preliminary controlled trial of effects on comorbid psychotic symptoms. *Int Clin Psychopharmacol*. 2003;18(1):1–8. doi:10.1097/00004850-200301000-00001 PubMed
227. Rothbaum BO, Killeen TK, Davidson JR, et al. Placebo-controlled trial of risperidone augmentation for selective serotonin reuptake inhibitor-resistant civilian posttraumatic stress disorder. *J Clin Psychiatry*. 2008;69(4):520–525. doi:10.4088/JCP.v69n0402 PubMed
228. Stein MB, Kline NA, Matloff JL. Adjunctive olanzapine for SSRI-resistant combat-related PTSD: a double-blind, placebo-controlled study. *Am J Psychiatry*. 2002;159(10):1777–1779. doi:10.1176/appi.ajp.159.10.1777 PubMed
229. Padala PR, Madison J, Monnahan M, et al. Risperidone monotherapy for post-traumatic stress disorder related to sexual assault and domestic abuse in women. *Int Clin Psychopharmacol*. 2006;21(5):275–280. doi:10.1097/00004850-200609000-00005 PubMed
230. Butterfield MI, Becker ME, Connor KM, et al. Olanzapine in the treatment of post-traumatic stress disorder: a pilot study. *Int Clin Psychopharmacol*. 2001;16(4):197–203. doi:10.1097/00004850-200107000-00003 PubMed
231. Bystritsky A, Ackerman DL, Rosen RM, et al. Augmentation of serotonin reuptake inhibitors in refractory obsessive-compulsive disorder using adjunctive olanzapine: a placebo-controlled trial. *J Clin Psychiatry*. 2004;65(4):565–568. doi:10.4088/JCP.v65n0418 PubMed
232. McDougle CJ, Epperson CN, Pelton GH, et al. A double-blind, placebo-controlled study of risperidone addition in serotonin reuptake inhibitor-refractory obsessive-compulsive disorder. *Arch Gen Psychiatry*. 2000;57(8):794–801. doi:10.1001/archpsyc.57.8.794 PubMed
233. Hollander E, Baldini Rossi N, Sood E, et al. Risperidone augmentation in treatment-resistant obsessive-compulsive disorder: a double-blind, placebo-controlled study. *Int J Neuropsychopharmacol*. 2003;6(4):397–401. doi:10.1017/S1461145703003730 PubMed
234. Atmaca M, Kuloglu M, Tezcan E, et al. Quetiapine augmentation in patients with treatment resistant obsessive-compulsive disorder: a single-blind, placebo-controlled study. *Int Clin Psychopharmacol*. 2002;17(3):115–119. doi:10.1097/00004850-200205000-00004 PubMed
235. Denys D, de Geus F, van Megen HJ, et al. A double-blind, randomized, placebo-controlled trial of quetiapine addition in patients with obsessive-compulsive disorder refractory to serotonin reuptake inhibitors. *J Clin Psychiatry*. 2004;65(8):1040–1048. doi:10.4088/JCP.v65n0803 PubMed
236. Shapira NA, Ward HE, Mandoki M, et al. A double-blind, placebo-controlled trial of olanzapine addition in fluoxetine-refractory obsessive-compulsive disorder. *Biol Psychiatry*. 2004;55(5):553–555. doi:10.1016/j.biopsych.2003.11.010 PubMed
237. Carey PD, Vythilingum B, Seedat S, et al. Quetiapine augmentation of SRIs in treatment refractory obsessive-compulsive disorder: a double-blind, randomised, placebo-controlled study [ISRCTN83050762]. *BMC Psychiatry*. 2005;5(1):5. doi:10.1186/1471-244X-5-5 PubMed
238. Fineberg NA, Sivakumaran T, Roberts A, et al. Adding quetiapine to SRI in treatment-resistant obsessive-compulsive disorder: a randomized controlled treatment study. *Int Clin Psychopharmacol*. 2005;20(4):223–226. doi:10.1097/00004850-200507000-00005 PubMed
239. Kordon A, Wahl K, Koch N, et al. Quetiapine addition to serotonin reuptake inhibitors in patients with severe obsessive-compulsive disorder: a double-blind, randomized, placebo-controlled study. *J Clin Psychopharmacol*. 2008;28(5):550–554. doi:10.1097/JCP.0b013e318185e735 PubMed
240. Maina G, Pessina E, Albert U, et al. 8-week, single-blind, randomized trial comparing risperidone vs olanzapine augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder. *Eur Neuropsychopharmacol*. 2008;18(5):364–372. doi:10.1016/j.euroneuro.2008.01.001 PubMed
241. Li X, May RS, Tolbert LC, et al. Risperidone and haloperidol augmentation of serotonin reuptake inhibitors in refractory obsessive-compulsive disorder: a crossover study. *J Clin Psychiatry*. 2005;66(6):736–743. doi:10.4088/JCP.v66n0610 PubMed
242. Bloch MH, Landeros-Weisenberger A, Kelmendi B, et al. A systematic review: antipsychotic augmentation with treatment refractory obsessive-compulsive disorder. *Mol Psychiatry*. 2006;11(7):622–632. doi:10.1038/sj.mp.4001823 PubMed
243. Connor KM, Payne VM, Gadde KM, et al. The use of aripiprazole in obsessive-compulsive disorder: preliminary observations in 8 patients. *J Clin Psychiatry*. 2005;66(1):49–51. doi:10.4088/JCP.v66n0107 PubMed
244. Pessina E, Albert U, Bogetto F, et al. Aripiprazole augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: a 12-week open-label preliminary study. *Int Clin Psychopharmacol*. 2009;24(5):265–269. doi:10.1097/YIC.0b013e32832e9b91 PubMed
245. Pohl R, Balon R, Yeragani VK, et al. Serotonergic anxiolytics in the treatment of panic disorder: a controlled study with buspirone. *Psychopathology*. 1989;22(suppl 1):60–67. doi:10.1159/000284627 PubMed
246. Sheehan DV, Raj AB, Sheehan KH, et al. Is buspirone effective for panic disorder? *J Clin Psychopharmacol*. 1990;10(1):3–11. doi:10.1097/00004714-199002000-00002 PubMed
247. Schweizer E, Rickels K. Buspirone in the treatment of panic disorder: a controlled pilot comparison with clorazepate. *J Clin Psychopharmacol*. 1988;8(4):303. doi:10.1097/00004714-198808000-00033 PubMed
248. Schneier FR, Saoud JB, Campeas R, et al. Buspirone in social phobia. *J Clin Psychopharmacol*. 1993;13(4):251–256. doi:10.1097/00004714-199308000-00004 PubMed
249. van Vliet IM, den Boer JA, Westenberg HG, et al. Clinical effects of buspirone in social phobia: a double-blind placebo-controlled study. *J Clin Psychiatry*. 1997;58(4):164–168. PubMed
250. Duffy JD, Malloy PF. Efficacy of buspirone in the treatment of posttraumatic stress disorder: an open trial. *Ann Clin Psychiatry*. 1994;6(1):33–37. doi:10.3109/10401239409148837 PubMed
251. Jenike MA, Baer L. An open trial of buspirone in obsessive-compulsive disorder. *Am J Psychiatry*. 1988;145(10):1285–1286. PubMed
252. Pato MT, Pigott TA, Hill JL, et al. Controlled comparison of buspirone and clomipramine in obsessive-compulsive disorder. *Am J Psychiatry*. 1991;148(1):127–129. PubMed

253. Markovitz PJ, Stagno SJ, Calabrese JR. Buspirone augmentation of fluoxetine in obsessive-compulsive disorder. *Am J Psychiatry*. 1990;147(6):798–800. PubMed
254. Jenike MA, Baer L, Buttolph L. Buspirone augmentation of fluoxetine in patients with obsessive compulsive disorder. *J Clin Psychiatry*. 1991;52(1):13–14. PubMed
255. Pigott TA, L'Heureux F, Hill JL, et al. A double-blind study of adjuvant buspirone hydrochloride in clomipramine-treated patients with obsessive-compulsive disorder. *J Clin Psychopharmacol*. 1992;12(1):11–18. doi:10.1097/00004714-199202000-00003 PubMed
256. McDougle CJ, Goodman WK, Leckman JF, et al. Limited therapeutic effect of addition of buspirone in fluvoxamine-refractory obsessive-compulsive disorder. *Am J Psychiatry*. 1993;150(4):647–649. PubMed
257. Grady TA, Pigott TA, L'Heureux F, et al. Double-blind study of adjuvant buspirone for fluoxetine-treated patients with obsessive-compulsive disorder. *Am J Psychiatry*. 1993;150(5):819–821. PubMed
258. American Psychiatric Association. *Practice Guidelines for the Treatment of Patients With Panic Disorder*. 2nd ed. Washington, DC: American Psychiatric Association; 2009:1–90.
259. Ballenger JC, Burrows GD, DuPont RL Jr, et al. Alprazolam in panic disorder and agoraphobia: results from a multicenter trial. I: efficacy in short-term treatment. *Arch Gen Psychiatry*. 1988;45(5):413–422. PubMed
260. Cross-National Collaborative Panic Study, Second Phase Investigators. Drug treatment of panic disorder: comparative efficacy of alprazolam, imipramine, and placebo. *Br J Psychiatry*. 1992;160(2):191–202, discussion 202–205. doi:10.1192/bjp.160.2.191 PubMed
261. Dunner DL, Ishiki D, Avery DH, et al. Effect of alprazolam and diazepam on anxiety and panic attacks in panic disorder: a controlled study. *J Clin Psychiatry*. 1986;47(9):458–460. PubMed
262. Rizley R, Kahn RJ, McNair DM, et al. A comparison of alprazolam and imipramine in the treatment of agoraphobia and panic disorder. *Psychopharmacol Bull*. 1986;22(1):167–172. PubMed
263. Munjack DJ, Crocker B, Cabe D, et al. Alprazolam, propranolol, and placebo in the treatment of panic disorder and agoraphobia with panic attacks. *J Clin Psychopharmacol*. 1989;9(1):22–27. doi:10.1097/00004714-198902000-00005 PubMed
264. Tesar GE, Rosenbaum JF, Pollack MH, et al. Double-blind, placebo-controlled comparison of clonazepam and alprazolam for panic disorder. *J Clin Psychiatry*. 1991;52(2):69–76. PubMed
265. Lydiard RB, Lesser IM, Ballenger JC, et al. A fixed-dose study of alprazolam 2 mg, alprazolam 6 mg, and placebo in panic disorder. *J Clin Psychopharmacol*. 1992;12(2):96–103. doi:10.1097/00004714-199204000-00004 PubMed
266. Schweizer E, Patterson W, Rickels K, et al. Double-blind, placebo-controlled study of a once-a-day, sustained-release preparation of alprazolam for the treatment of panic disorder. *Am J Psychiatry*. 1993;150(8):1210–1215. PubMed
267. Curtis GC, Massana J, Udina C, et al. Maintenance drug therapy of panic disorder. *J Psychiatr Res*. 1993;27(suppl 1):127–142. doi:10.1016/0022-3956(93)90023-U PubMed
268. Pollack MH, Otto MW, Tesar GE, et al. Long-term outcome after acute treatment with alprazolam or clonazepam for panic disorder. *J Clin Psychopharmacol*. 1993;13(4):257–263. doi:10.1097/00004714-199308000-00005 PubMed
269. Schweizer E, Rickels K, Weiss S, et al. Maintenance drug treatment of panic disorder. I: results of a prospective, placebo-controlled comparison of alprazolam and imipramine. *Arch Gen Psychiatry*. 1993;50(1):51–60. PubMed
270. Beauclair L, Fontaine R, Annable L, et al. Clonazepam in the treatment of panic disorder: a double-blind, placebo-controlled trial investigating the correlation between clonazepam concentrations in plasma and clinical response. *J Clin Psychopharmacol*. 1994;14(2):111–118. PubMed
271. Rosenbaum JF, Moroz G, Bowden CL. Clonazepam Panic Disorder Dose-Response Study Group. Clonazepam in the treatment of panic disorder with or without agoraphobia: a dose-response study of efficacy, safety, and discontinuance. *J Clin Psychopharmacol*. 1997;17(5):390–400. doi:10.1097/00004714-199710000-00008 PubMed
272. Valença AM, Nardi AE, Nascimento I, et al. Double-blind clonazepam vs placebo in panic disorder treatment. *Arq Neuropsiquiatr*. 2000;58(4):1025–1029. PubMed
273. Noyes R Jr, Anderson DJ, Clancy J, et al. Diazepam and propranolol in panic disorder and agoraphobia. *Arch Gen Psychiatry*. 1984;41(3):287–292. PubMed
274. Noyes R Jr, Burrows GD, Reich JH, et al. Diazepam versus alprazolam for the treatment of panic disorder. *J Clin Psychiatry*. 1996;57(8):349–355. PubMed
275. Charney DS, Woods SW. Benzodiazepine treatment of panic disorder: a comparison of alprazolam and lorazepam. *J Clin Psychiatry*. 1989;50(11):418–423. PubMed
276. Schweizer E, Pohl R, Balon R, et al. Lorazepam vs alprazolam in the treatment of panic disorder. *Pharmacopsychiatry*. 1990;23(2):90–93. doi:10.1055/s-2007-1014489 PubMed
277. Wilkinson G, Balestrieri M, Ruggeri M, et al. Meta-analysis of double-blind placebo-controlled trials of antidepressants and benzodiazepines for patients with panic disorders. *Psychol Med*. 1991;21(4):991–998. doi:10.1017/S0033291700029986 PubMed
278. Goddard AW, Brouette T, Almai A, et al. Early coadministration of clonazepam with sertraline for panic disorder. *Arch Gen Psychiatry*. 2001;58(7):681–686. doi:10.1001/archpsyc.58.7.681 PubMed
279. Pollack MH, Simon NM, Worthington JJ, et al. Combined paroxetine and clonazepam treatment strategies compared to paroxetine monotherapy for panic disorder. *J Psychopharmacol*. 2003;17(3):276–282. doi:10.1177/02698811030173009 PubMed
280. Mitte K, Noack P, Steil R, et al. A meta-analytic review of the efficacy of drug treatment in generalized anxiety disorder. *J Clin Psychopharmacol*. 2005;25(2):141–150. doi:10.1097/01.jcp.0000155821.74832.f9 PubMed
281. Hidalgo RB, Tupler LA, Davidson JR. An effect-size analysis of pharmacologic treatments for generalized anxiety disorder. *J Psychopharmacol*. 2007;21(8):864–872. doi:10.1177/0269881107076996 PubMed
282. Munjack DJ, Baltazar PL, Bohn PB, et al. Clonazepam in the treatment of social phobia: a pilot study. *J Clin Psychiatry*. 1990;51(suppl):35–40, discussion 50–53. PubMed
283. Davidson JR, Potts N, Richichi E, et al. Treatment of social phobia with clonazepam and placebo. *J Clin Psychopharmacol*. 1993;13(6):423–428. doi:10.1097/00004714-199312000-00008 PubMed
284. Connor KM, Davidson JR, Potts NL, et al. Discontinuation of clonazepam in the treatment of social phobia. *J Clin Psychopharmacol*. 1998;18(5):373–378. doi:10.1097/00004714-199810000-00004 PubMed
285. Braun P, Greenberg D, Dasberg H, et al. Core symptoms of posttraumatic stress disorder unimproved by alprazolam treatment. *J Clin Psychiatry*. 1990;51(6):236–238. PubMed
286. Cates ME, Bishop MH, Davis LL, et al. Clonazepam for treatment of sleep disturbances associated with combat-related posttraumatic stress disorder. *Ann Pharmacother*. 2004;38(9):1395–1399. doi:10.1345/aph.1E043 PubMed
287. Gelpin E, Bonne O, Peri T, et al. Treatment of recent trauma survivors with benzodiazepines: a prospective study. *J Clin Psychiatry*. 1996;57(9):390–394. PubMed
288. Mellman TA, Bustamante V, Fins AI, et al. REM sleep and the early development of posttraumatic stress disorder. *Am J Psychiatry*. 2002;159(10):1696–1701. doi:10.1176/appi.ajp.159.10.1696 PubMed
289. Hewlett WA, Vinogradov S, Agras WS. Clomipramine, clonazepam, and clonidine treatment of obsessive-compulsive disorder. *J Clin Psychopharmacol*. 1992;12(6):420–430. doi:10.1097/00004714-199212000-00008 PubMed
290. Hollander E, Kaplan A, Stahl SM. A double-blind, placebo-controlled trial of clonazepam in obsessive-compulsive disorder. *World J Biol Psychiatry*. 2003;4(1):30–34. doi:10.3109/15622970309167908 PubMed
291. Crockett BA, Churchill E, Davidson JR. A double-blind combination study of clonazepam with sertraline in obsessive-compulsive disorder. *Ann Clin Psychiatry*. 2004;16(3):127–132. PubMed
292. Pollack MH. Long-term management of panic disorder. *J Clin Psychiatry*. 1990;51(suppl):11–13, discussion 50–53. PubMed
293. Worthington JJ 3rd, Pollack MH, Otto MW, et al. Long-term experience with clonazepam in patients with a primary diagnosis of panic disorder. *Psychopharmacol Bull*. 1998;34(2):199–205. PubMed
294. Simon NM, Otto MW, Worthington JJ, et al. Next-step strategies for panic disorder refractory to initial pharmacotherapy: a 3-phase randomized clinical trial. *J Clin Psychiatry*. 2009;70(11):1563–1570. doi:10.4088/JCP.08m04485blu PubMed
295. Improving treatment outcomes in pharmacotherapy of generalized social anxiety disorder. ClinicalTrials.gov Web site. http://clinicaltrials.gov/ct2/results?term=NCT00282828. Updated March 12, 2009.
296. Institute of Medicine. Treatment of PTSD: An Assessment of the Evidence. Washington, DC: National Academies Press; 2007
297. Rosenthal M. Tiagabine for the treatment of generalized anxiety disorder: a randomized, open-label, clinical trial with paroxetine as a positive control. *J Clin Psychiatry.* 2003;64(10):1245–1249. doi:10.4088/JCP.v64n1016 PubMed
298. Davidson JR, Brady K, Mellman TA, et al. The efficacy and tolerability of tiagabine in adult patients with post-traumatic stress disorder. *J Clin Psychopharmacol*. 2007;27(1):85–88. doi:10.1097/JCP.0b013e31802e5115 PubMed

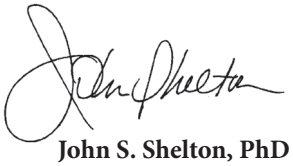
NCDEU Festschrift—Celebrating 50 Years

During the past year, the *Journal* has been pleased to publish a series of special articles celebrating the 50th anniversary of NCDEU (New Clinical Drug Evaluation Unit) of the National Institute of Mental Health. Each of these pieces has been written by world renowned researchers and has highlighted the importance of psychopharmacologic treatment of psychiatric disorders. These articles are gems and are the result of a thoughtful exploration of a variety of topics. It has been our privilege to publish them in *JCP*.

Individually, each article has a particular focus. Collectively, however, they demonstrate how far the field has progressed during the past half century. On a personal note, reading these articles brings a tremendous feeling of satisfaction, for many of the seminal articles about new and developing drug treatments appeared in the pages of *The Journal of Clinical Psychiatry* and its former title, *Diseases of the Nervous System*, during the course of our 72 years of dedicated service to the field.

This year marks a watershed change for the annual NCDEU meeting because it is being held under the auspices of the American Society of Clinical Psychopharmacology (ASCP), for which *JCP* is the official journal. Under the direction of the ASCP, this annual event will no doubt grow in size and stature and be filled with fascinating lectures and interesting posters.

We have an exciting offer to mark the end of this special series of publications. Subscribe to or renew your subscription to the *Journal*, and you will receive a free PDF collection of the articles. Visit psychiatrist.com/subscribe to learn more.



John S. Shelton, PhD
Publisher

doi:10.4088/JCP.11pn06967