

### Advances in Treatment of Bipolar Disorder

edited by Terence A. Ketter, M.D. In book series: *Review of Psychiatry*, no. 3. Oldham J, Riba MB, eds. American Psychiatric Publishing, Inc., Washington, D.C., 2005, 241 pages, \$36.95 (paper).

This volume belongs to the last group of American Psychiatric Association (APA) reviews that address annual advances in psychiatry. In this era of rapid advances and ever more rapid modes of communications, integration of historical perspectives, different presentations of mental conditions in different populations and individuals, and different properties and effects of many newer medications in various forms to choose from remains of value. The primary focus of this volume is on treatments supported by controlled studies in patients diagnosed with acute mania, acute bipolar depression, or rapid cycling—patients who need long-term maintenance, adjunctive medications, and psychotherapy. Special chapters are dedicated to findings in children and adolescents and in women. Research on the rapidly increasing over-60 population is scattered throughout the text, relatively limited, and not indexed.

A span of 24 years passed for the U.S. Food and Drug Administration (FDA) to approve monotherapy with lithium (1970), chlorpromazine (1973), and divalproex (1994). Between 2000 and 2004, however, 5 atypical antipsychotics were approved for monotherapy, and 3 were approved for adjunct therapy in 2003 and 2004. Seven anticonvulsants, including benzodiazepines, are being studied in various presentations of bipolar disorder. New treatment opportunities are bringing major challenges and opportunities to the practitioner in rapid succession.

Assessment and treatment of bipolar disorder are indeed complex. The average clinician will be inclined to depend to a large extent on his or her successful outcome experiences, professional consensus in his or her community, professional organizations, and managed care restrictions. At best, the clinician will make an effort to acquire knowledge about the quality of research done with new medications, baseline laboratory testing required, optimal doses and levels, side effects, risks and benefits, drug-drug interactions, and augmentation value in different populations. Though it is vital to understand research findings in clinical decision making, statistics and scales used in research are generally of little interest to many clinicians.

The tables that list the drugs that are now available for the conditions discussed in this book, with a variety of characteristics and dosages, are very useful. Clinicians may find a chapter in which the data of over 100 research projects are cited rather labor intensive, though convincing, reading. They will also come away with awareness of the uncertainties in the field and research yet to be undertaken.

Gary Sachs, M.D., describes with brilliantly simple clarity and detail how the scientist arrives at assessing quality of results that the researcher has gathered. He gives due credit to naturalistic effectiveness reports and points out the limitations of randomized clinical trials with their many exclusion criteria for entry into a study, limited time spans during which subjects are generally studied, and, at times, sample sizes with insufficient power for statistical analysis. Dr. Sachs analyzes shortcomings of several studies by well-recognized researchers, pointing out, for example, that absence of baseline mania rating scale scores in depressed bipolar patients weakened outcomes and determination of “treatment-emergent affective switch” (TEAS). TEAS is a term that has been introduced within the past few years to describe the manic or hypomanic condition evoked by antide-

pressants in depressed bipolar patients. Another study weakness he elucidates is including patients already on lithium treatment and those who are nonresponsive to lithium in a study designed to determine the antidepressant effects of lithium. He describes how a category A lamotrigine study avoided the above study discrepancies.

Dr. Sachs also describes several large studies (category A, B, and C) in the 21st century that included the atypical antipsychotics as monotherapy or combined therapy with antidepressants. Studies by the Stanley Foundation Bipolar Network (SFBN) and the National Institute of Mental Health (NIMH)-sponsored Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) and many other studies leave the field of depression in bipolar illness (compared to unipolar depression) with as yet controversial evidence. It seems to me, inexperienced as I am in this type of research, that it is an inordinate challenge to consistently and clearly distinguish these diagnoses before TEAS occurs. I surmise, from the data presented here from over 100 publications, that a subgroup who responds well to antidepressants would do well to remain on antidepressants for longer than they were in some of the studies, and that those prone to experience TEAS are more prone to recurrences of TEAS and need different treatments. Several atypical antipsychotics have shown efficacy in monotherapy and are recommended along with any antidepressant that may be prescribed. Subclasses of patients are, as yet, not well-defined to be of use in clinical decision making but give food for thought for future research. Gary Sachs' chapter is quite comprehensive in that it also includes studies of risks and benefits of electroconvulsive therapy, adjunctive dopamine receptor agonists, omega-3 fatty acids, phototherapy, magnetic stimulation, and sleep deprivation.

For the clinician who is not interested in reading the research part of this review, I highly recommend pages 100 through 102 concerning evidence-based practices.

The 5 authors who contributed to the chapter on treatment of rapid-cycling bipolar disorder discuss evidence and potential side effects and consequences of lithium and divalproex as well as carbamazepine, lamotrigine, olanzapine, and quetiapine; each discussion is followed separately by practical considerations in using these medications. Rapid-cycling bipolar disorder appears to be an underdiagnosed, undertreated, and mistreated condition with no available long-term studies but reported worsening after short-term studies. Appropriate assessment is an issue here, and the condition is often perceived as recurrent or treatment-refractory major depression. This chapter has over 30 references.

In the chapter about treatment of bipolar disorder in children and adolescents, the reader is reminded of the fact that this is a very young field with little evidence from research and no FDA-approved medication specifically for this age group. The 3 authors of the chapter emphasize that much needs to be established, including an integration of psychotherapies, pharmacotherapy, and psychoeducation. Studies are generally on small samples. These studies reveal, for example, that lithium treatment in adolescents with manic episodes reduces comorbid substance abuse and reduces manic symptoms in children, as judged by the Children's Global Assessment Scale score.

The authors of this chapter also note that a high percentage of relapse with manic episodes has been observed with discontinuation of valproate treatment as well as lithium. Side effects of both medications are especially distressing in this young population. Lamotrigine and topiramate have shown promise in treating bipolar and attention-deficit/hyperactivity disorder symptoms, but with undesirable side effects.

Moreover, these authors note that atypical antipsychotics have been shown to be effective in children with bipolar disorder. This treatment has yet to be further studied in order to get FDA approval in this population. Combination therapies have been shown to be more effective than monotherapy. Psychotherapy and pharmacologic intervention are proposed to prevent the development of bipolar disorder in adulthood. This chapter is accompanied by over 100 references that include several case and clinical case series.

The final chapter offers the reader a review of over 100 references relating to differences between men and women in onset, course, manifestations, and treatments of bipolar disorder. The authors deal comprehensively with mood, treatments, and side effects across the menstrual cycle, pregnancy, and breastfeeding, but have omitted menopause and the recent studies and review articles dealing with our aging population, of which women constitute the majority.

The current and next generations of medical students and residents will be considerably better versed than many current practitioners in research methods by which evidence-based practices are determined. For the latter, this book is a chore to read, but its conclusions are of great value. Reading this review will also help the clinician, educator, and researcher, all of whom should have this book on their shelves to facilitate updating, teaching, and research as needed. Practitioners in geriatric psychiatry, though, are on their own to attend to evidence-based practices for the population over the age of 60.

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**What Your Patients Need to Know About  
 Psychiatric Medications**

*by Robert E. Hales, M.D., M.B.A.; Stuart C. Yudofsky, M.D.;  
 and Robert H. Chew, Pharm.D. American Psychiatric  
 Publishing, Inc., Washington, D.C., 2005, 356 pages,  
 \$64.00 (paper), spiral-bound, CD-ROM included.*

Phrased as a statement, the title of this book is also an implied question that all readers should ponder: "What (do) your patients need to know (about psychiatric medications in general and about the ones they are taking/or might take in particular)?"

While I would like to think that this is a question explicitly addressed each time we prescribe for a patient, feedback from colleagues suggests otherwise. Given the hectic pace of clinical practice, it is essential to adopt an educational and safety protocol to follow when prescribing psychiatric medications for patients. The authors have tackled this challenge head on and have

written a text that does a remarkable job of organizing vital information for physicians and for their patients.

Beginning with a thoughtful introduction to the challenges of meaningful communication with patients about their psychiatric medications, the book goes on to systematically cover the major groups and their indications. For each category, there is an overview of the class, followed by the particulars of the specific medications. The general discussion explains the diagnostic categories and indications for the medications and provides a brief history of how they have been used. I particularly like the way the authors subdivide the groups into categories and then present the details of the various medications in a standard format. Just looking at the table of contents provides a helpful summary of the way to think about these medications: antianxiety medications, medications for the treatment of insomnia, selective serotonin reuptake inhibitors and mixed-action antidepressants, tricyclic antidepressants, monoamine oxidase inhibitors, mood stabilizers, first-generation antipsychotics, second-generation antipsychotics, medications for the treatment of attention-deficit/hyperactivity disorder in adults, stimulants, and cognitive enhancers.

Is this a book for psychiatrists, for primary care doctors, and for others who prescribe psychiatric medications, or is it for the patients who take the medications? I say "yes" to all of the above. While not a substitute for a textbook of psychopharmacology, this book is so user-friendly that it is apt to be consulted routinely for a quick check of the essential points when prescribing. Similarly, by copying the key pages and giving them to patients, doctors will provide them with the necessary information and encourage informed discussion and appropriate questions.

Along with the dosing information, common side effects, adverse reactions, and precautions, each section discusses possible drug interactions, use in pregnancy, overdose risks, and any special considerations, thoughtfully leaving space for handwritten notes that patients might make as they read or talk with their doctors. As an additional plus, the book comes with a CD-ROM that contains all the text and handouts in a printable form.

Obviously, it is incumbent on us as physicians to ensure that our patients understand the reasons that particular medications are being prescribed and the various risks, benefits, and caveats associated with them. The three authors are well-respected and appropriate experts on these topics. Together they have produced a book that does such an outstanding job of filling the void in prescribing psychiatric medications that it is likely to become standard fare in offices and clinics. In the process, countless patients will benefit, becoming better informed partners in their own care.

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