The Texas Implementation of Medication Algorithms Update for Treatment of Bipolar I Disorder

Roy H. Perlis, M.D., and Paul E. Keck, Jr., M.D.

The Texas Implementation of Medication Algorithms (TIMA) for the treatment of bipolar I disorder have been updated on the basis of the rapidly evolving database of new, primarily pharmacologic treatments for this potentially devastating illness. The revision of the previous algorithms incorporates data from research studies, published and unpublished, that have appeared since the previous algorithms were developed in 2000.[1] The authors and panel members have constructed a thoughtful, thorough scaffold upon which to hang treatment recommendations. The authors based their treatment recommendations on the graded quality of empirical evidence of efficacy but attempted to incorporate interpretations of effectiveness, safety, and tolerability data. Importantly, their recommendations were also based on the assumption of an unrestricted formulary—thus, for example, the recommendation that the best-tolerated form of a medication should always be utilized.

There are a number of notable aspects to this update. While it is tempting to jump directly to the pharmacotherapies themselves, the guidelines also nicely specify general principles of treatment, reminding us that the goals of treatment are to help people with bipolar I disorder get not just better but well. Structured psychotherapies are also endorsed, where clinically appropriate, although they are explicitly not a focus of these algorithms.

Where the 2000 algorithm focused on mood elevation, the newer algorithm provides specific approaches to managing the 3 key phases of bipolar I disorder: manic, hypomanic, or mixed; depressed; and maintenance. The algorithm for the treatment of the manic or mixed phase of bipolar disorder is perhaps the most straightforward, since the largest number of placebo-controlled trials has been conducted with agents in this phase of illness. Several shifts in the recommendations will be apparent to clinicians. The relegation of olanzapine to Stage 1B (i.e., as an alternative to first-line treatments) represents an important acknowledgment that efficacy is not the only consideration in treatment selection; the new algorithm directly addresses concerns about weight gain and metabolic syndrome. On the other hand, given the evidence that at least some of the other atypicals may have similar liability, reflected in the U.S. Food and Drug Administration (FDA) decision to relabel all drugs in the class, singling out olanzapine may be premature. Similarly, carbamazepine is not listed as a choice for combination treatment in Stage 2 because of concerns about drug interactions, although it could be used in conjunction with ziprasidone, since this latter agent has limited metabolism via inducible hepatic enzymes. Indeed, other first-line drugs (e.g., valproate) also require monitoring of blood levels and concern for interaction. Conversely, oxcarbazepine continues to appear (as a Stage 3 option) in this and other treatment guidelines despite an absence of data from rigorous randomized controlled trials in mania.

The algorithm for bipolar depression is likely to have been the most challenging since there are so few randomized controlled trials in this phase of illness. The authors offer a significantly different approach to depression than most previous guidelines (e.g., those of the American Psychiatric Association's bipolar workgroup[2]), which emphasize mood stabilizers and then, after perfunctory handwringing about antidepressant use, include standard antidepressants anyway. Beyond lithium, for which there are a number of placebo-controlled trials generally suggest-

From the Bipolar Clinical and Research Program, Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston, Mass. (Dr. Perlis); and the Psychopharmacology Research Program, Department of Psychiatry, University of Cincinnati College of Medicine and General Clinical Research Center and Mental Health Care Line, Cincinnati Veterans Affairs Medical Center, Cincinnati, Ohio (Dr. Keck).

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Corresponding author and reprints: Roy H. Perlis, M.D., Bipolar Clinical and Research Program, 15 Parkman St., WACC 812, Boston, MA 02114 (e-mail: rperlis@partners.org).

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ing a modest antidepressant response, there are only single, i.e., unreplicated, positive placebo-controlled trials for lamotrigine, quetiapine, and olanzapine/fluoxetine combination in acute bipolar depression. Indeed, the data regarding lamotrigine were not uniformly positive, whereas the data for olanzapine monotherapy are strongly suggestive in the single placebo-controlled trial of this agent.[3] Although these agents are staged sequentially, it might have been more consistent with the limited database to consider these agents as coequal Stage 1 alternatives. Given the weight of lithium evidence, as well as recent epidemiologic data strongly suggesting an antisuicide benefit,[4] the authors might have chosen to place greater emphasis on lithium. Finally, despite the concerns about antidepressants and switch or cycling, the absolute risk with newer agents other than venlafaxine, when combined with mood stabilizers, appears to be low,[5] so it may be premature to relegate the addition of an antidepressant to a fourth-line treatment.

The maintenance treatment algorithm is also supported by data from relatively few randomized controlled trials. Most evidence to date suggests that while lithium, olanzapine, aripiprazole, and lamotrigine have evidence of maintenance efficacy, their spectrum of action may differ: the former 3 agents appear to be better at preventing manic than depressive recurrence, while the opposite may be true for lamotrigine. Beyond these 4 agents, the quality of evidence slips quickly to lower grades and the authors' interpretations of this limited evidence form the basis of recommendations at lower stages. Interestingly, many of the acute-phase recommendations appear to be driven in part by maintenance considerations: the first-line antimanic and antidepressant interventions are generally those that also are useful in maintenance. Such a "one-step-ahead" approach, while perhaps intuitive, is worth underscoring: whenever possible, use as acute treatment that which could be continued in maintenance if effective.

Lastly, the authors consider the difficult issue of comorbidity. Since patients with bipolar disorder are extremely likely to have a co-occurring psychiatric or medical disorder that affects treatment recommendation, this is no small issue. In many instances, the presence of a co-occurring disorder could lead to considerations that might override some stages in the algorithm. These commonly encountered clinical complications do not detract from the updated algorithms, but rather underscore the need to use them as a point of reference but not a rigid straightjacket in clinical decision making. A case in point is the role of antidepressants: for example, as anxiety comorbidity appears to be the norm rather than the exception in this disorder, and antidepressants are an effective intervention in many anxiety disorders, they may in some cases be worth the risk.

The limitations of the guidelines are primarily those of the evidence base itself. The concept of evidence-based practice is hard to question but falsely suggests that the process of identifying and analyzing pertinent studies is straightforward, comprehensive, and always yields consistent results. The problem of publication bias is well-established; the authors have made an effort to include unpublished data to address this limitation, but in the absence of a comprehensive registry of trials, negative trials are still likely to receive less emphasis. A related difficulty arises from the fact that many recent bipolar trials are FDA registration trials. Such industry-funded trials are often large and well-designed but may also be more likely to yield positive results than non–industry-funded studies or those in which authors have no competing interests.[6-8] Smaller trials using investigative drugs, particularly those that are off-patent or late in patent life, would tend to receive less weight. An example of such a drug in bipolar disorder might be pramipexole for depression, which has yielded positive results in 2 small placebo-controlled trials[9,10] but is not included in any evidence-based guidelines.

Our reliance on large industry-funded studies also means that certain clinically important questions are rarely addressed directly: Is "optimization" of lithium level truly an effective antidepressant intervention? Is combination therapy with an atypical antipsychotic and a mood stabilizer superior to an atypical antipsychotic alone? (The trials to date have primarily compared combinations to mood stabilizer monotherapy.) Perhaps most importantly, what are the optimum combinations of medications for maintenance treatment? Here the literature from randomized controlled trials in bipolar disorder is remarkably sparse so far.

Finally, a straightforward means of balancing efficacy, tolerability, and safety remains elusive in these and other evidence-based guidelines in psychiatry. This is particularly true for maintenance interventions, where the impact of adverse effects on functioning and quality of life may be most apparent. Means do exist for weighing efficacy, tolerability, and quality of life in a quantitative fashion,[11] although they are rarely applied in psychiatric trials.

Despite the limitations of the evidence base, these guidelines provide a useful and important contribution to both clinicians and clinical researchers in bipolar disorder. They mark an important step in beginning to integrate newer agents with mainstays of treatment such as lithium. They also highlight the gaps in our knowledge and the desperate need for new medications—or new studies of older medications and their combinations—to treat this often devastating disorder.

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