

# The Texas Implementation of Medication Algorithms: Update to the Algorithms for Treatment of Bipolar I Disorder

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**Background:** A panel consisting of academic psychiatrists and pharmacist administrators of the Texas Department of State Health Services (formerly Texas Department of Mental Health and Mental Retardation), community mental health physicians, advocates, and consumers met in May 2004 to review new evidence in the pharmacologic treatment of bipolar I disorder (BDI). The goal of the consensus conference was to update and revise the current treatment algorithm for BDI as part of the Texas Implementation of Medication Algorithms, a statewide quality assurance program for the treatment of major psychiatric illness. The guidelines for evaluating possible medications, the criteria for selection and ranking, and the updated algorithms are described.

**Method:** Principles from previous consensus conferences were reviewed and amended. Medication algorithms for the acute treatment of hypomanic/manic or mixed and depressive episodes in BDI were developed after examining recent efficacy and safety and tolerability data. Recommendations for maintenance treatments were developed.

**Results:** The panel updated the 2 primary algorithms (hypomanic/manic/mixed and depressive) based on clinical evidence for efficacy, tolerability, and safety developed since 2000. Expert consensus was utilized where clinical evidence was limited. Prevention of new episodes or prophylaxis treatment recommendations were developed based on recent data from longer-term trials. Maintenance recommendations are provided as levels versus a specified staged algorithm, as for acute treatment, due to the relatively limited database to inform treatment.

**Conclusions:** These algorithms for the treatment of BDI represent the recommendations based on the most recent evidence available. These recommendations are meant to provide a framework for clinical decision making, not to replace clinical judgment. As with any algorithm, treatment practices will evolve beyond the recommendations of this consensus conference as new evidence and additional medications become available.

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This article describes the results of consensus proceedings to update treatment algorithms for patients with bipolar I disorder (BDI) being treated in the Texas public mental health system. The revised algorithms will be used in the Texas Implementation of Medication Algorithms (TIMA) initiative, which mandates the use of treatment guidelines for the priority patient population in state-funded inpatient and outpatient settings in Texas. Changes in this version include treatment recommendations for patients presenting with hypomanic, manic, or mixed episodes or depressive episodes and the addition of medications recently studied in patients with BDI in clinical trials. Additionally, the panel includes evidence-based recommendations for maintenance treatment for patients with BDI. Consistent with past methodologies of the Texas Medication Algorithm Project, an expert consensus panel format was utilized to update previous versions of the algorithms.<sup>1-5</sup>

Academic psychiatrists and clinical psychopharmacology specialists in the area of bipolar disorder were identified and invited to attend a 2-day conference in Dallas, Texas, in May 2004. Additionally, pharmacist administra-

tors of the Texas Department of State Health Services (TDSHS) (formerly the Texas Department of Mental Health and Mental Retardation), physicians from community mental health settings (inpatient and outpatient), advocates, and consumers were invited to join the consensus panel. In structured presentations, the group reviewed the newest available evidence (both published and completed analyses) to guide selections of treatments for hypomania/mania, mixed symptoms, depression, maintenance treatment, and issues regarding safety and adverse effects in the treatment of BDI. The evidence base utilized included data presented at national conferences (peer reviewed abstracts) but not yet peer reviewed for publication and readily available to the general public.

The consensus panel based the decision process on evidence from well-controlled studies when available. The consensus panel used a method similar to that utilized by the Agency for Healthcare Research and Quality in the development of depression guidelines.<sup>6</sup> A rating system of A, B, and C is used to evaluate the quality of data available to support a recommendation: "A"—randomized, blinded, placebo-controlled trials; "B"—open, controlled trials, large case series, and/or large retrospective analyses; and "C"—preliminary but unconfirmed findings from smaller case reports, case series, and expert consensus.<sup>6</sup> These levels of evidence are based on the quality of a given study. Thus each study is graded on its own merits. The determination of the number of grade A studies needed to make an algorithm recommendation depended on evaluation of the relative quantity and quality of evidence in certain treatment domains. For example, 1 level A study was in some cases viewed as supportive, given the limited well-controlled studies available.

Ordered treatment recommendations (i.e., algorithms) were developed after weighing the quantity and quality of evidence (both efficacy and effectiveness data) in support of a treatment, expert opinion, consumer input, and safety and tolerability issues. Safety and tolerability issues affected placement of certain treatments in the algorithm. For example, a level A treatment may be placed after a treatment with less developed evidence of treatment efficacy because of safety concerns. When the panel could not reach consensus, or inadequate evidence existed to reach a consensus, no opinion was rendered. Rather, when potential treatments had the possibility of equivalent efficacy and tolerability or no data suggesting superiority, they were included as multiple options within a single stage of treatment. It was also possible that a minority opinion could be expressed, even though overall consensus was reached on a staging recommendation. Minority opinions are noted in the text.

The consensus conference and the work done by the panel were not supported in any way by the pharmaceutical industry. Individual panel members' relationships with pharmaceutical companies, unrelated to this work, are de-

scribed in the financial disclosure statement at the end of the article. The panel did not work from a restricted formulary. With the support of TDSHS administration, the panel was asked to consider all available medications currently used in the treatment of BDI and to recommend where each available treatment should be used in the course of treating a patient. The algorithms are flexible so that when equally efficacious medications are available at a given stage, the practitioner is able to make decisions on the basis of individual patient history, preference, economics, or other practice priorities.

While the goal of this conference was to develop medication algorithms, it is not the intention of these authors to minimize the potential necessity and impact of other adjunctive therapies including psychotherapy, psychosocial interventions, and alternative and complementary treatments in the treatment of BDI. General principles derived from the consensus conference are presented first, as well as specific recommendations that govern application of these guidelines. The treatment algorithms and maintenance guidelines are then presented.

## **TREATMENT OVERVIEW FOR BIPOLAR I DISORDER**

The goal of the consensus panel was to integrate available research information and clinical consensus into user-friendly, hierarchical decision trees of medication options. Similar to previous versions, these algorithms were developed for the treatment of BDI only, due to the limited controlled studies available to support a standardized treatment plan for patients with other related diagnoses, including bipolar II disorder and schizoaffective disorder, bipolar type.<sup>7,8</sup> Studies defining appropriate treatment choices for these patients are ongoing in mood disorder research programs.

The adoption of treatment guidelines in the TDSHS system is not intended to substitute for clinician judgment or choice but to provide systematic guidance and structure regarding the array of potential treatment options for this patient population. The following general principles are intended to enumerate the philosophy and specific implementation strategies endorsed by the panel. The majority of principles discussed are similar to the last update of the Texas algorithm for bipolar disorder.<sup>9</sup>

### **General Principles**

- The goals of treatment are (1) symptomatic remission, (2) full return of psychosocial functioning, and (3) prevention of relapses and recurrences.
- The algorithm development process was guided by the goal of weighing evidence regarding effectiveness, tolerability, and safety. These core principles apply to clinical decisions for individuals as well.

- The treatment options recommended at the various points in the algorithms are based on available data from controlled clinical trials, open trials and retrospective data analyses, case reports and expert clinical consensus, as well as consumer input and safety and tolerability issues. The later stages in the algorithm typically are supported by less evidence and involve more complicated regimens, whereas the earlier stages involve simpler treatments in terms of safety, tolerability, ease of use, side effect profiles, etc. The treatment algorithms will be revised periodically as more controlled scientific studies (level A) and new information argue for adjustment.

### Choice of Treatment

- Eligibility and point of entry into an algorithm for an individual patient should be determined by the clinician based on a review of relevant psychiatric factors (e.g., symptom severity, suicidality, comorbidity), general medical factors (e.g., concomitant medications or illnesses, age), and prior treatment history and response.
- In all decisions regarding medication options, the clinician should consider both those options with the greatest evidence in support of their efficacy and tolerability and options that have been effective for a particular individual in the past. If a patient responded well to and tolerated a specific pharmacotherapy during a previous mood episode, that same treatment is usually recommended again. Clinicians are advised to move, as much as possible, linearly down the algorithm. However, patient history and preference may dictate initiating treatments from an advanced algorithm stage, then potentially moving to an earlier algorithm stage at a later time.
- When a choice exists between different formulations of a recommended medication (i.e., a specific chemical entity), treatment should be initiated with the form that is most likely to be tolerated. As new formulations of medications become available, they should be incorporated into the algorithm based on whether they offer therapeutic advantages for patients.

### Patient/Clinician Relationship

- The clinician and the patient should engage in an adequate discussion regarding available treatment options and specific medications, including target symptoms, dosing strategies, side effect profiles, drug interactions, potential toxicity, safety in overdose, and cost implications. When clinical considerations make several medications equivalent, clinician and/or patient preference may define which option is selected.
- When possible, clinicians should develop a treatment plan with the patient that involves significant others

in the patient's life. Family and extended family participation is encouraged not only at initial assessment, but also throughout the patient's treatment, and may be especially helpful in monitoring the patient's progress and response to treatments.

- Patients should be encouraged to participate in their treatment by keeping a daily mood chart or completing the symptom and side effect monitoring forms included as part of the TIMA bipolar disorder education package.
- Participation in formal psychoeducation or cognitive therapy regarding bipolar disorder, treatments, and relapse prevention is encouraged due to recent evidence supporting these treatments as an effective complement to pharmacologic treatments.<sup>10-14</sup>

### Visit Frequency

- At entry into an acute treatment algorithm, relatively frequent (e.g., at least every 2 weeks) follow-up appointments for further evaluation and assessment should be scheduled to optimize treatment outcomes by encouraging patient adherence with treatment, making medication dose changes in a timely manner, and rapidly identifying and correcting potential problems or tolerability issues associated with treatment.

### Clinical Management

- These algorithms are intended for both outpatients and inpatients, although modifications for acute inpatient stabilization are anticipated, such as more aggressive dose titration and monitoring and use of combination therapy earlier than in outpatient settings.
- All patients with BDI who achieve a satisfactory acute clinical response (and optimal symptom remission) should receive continuation phase treatment with the same agent(s), with dosage adjustments as needed to allow adequate tolerability.<sup>15</sup> Ongoing discussions of tolerability and adherence are necessary for optimal management.
- In general, when discontinuing medications, those with greatest side effect burden(s) should be discontinued first. Discontinue medications gradually (2-4 weeks minimum) unless medical necessity requires a faster taper. When adding a new medication, use an "overlap and taper" strategy.
- Adequate documentation should be completed for each algorithm stage and treatment choice (i.e., critical decision points). If algorithm stages are skipped or if treatment is different from the algorithm(s), the rationale should be documented.
- At baseline and throughout treatment, the patient should be evaluated for possible inclusion in psychosocial interventions.

- Use of the algorithms for treatment of patients with BDI assumes that a thorough evaluation and diagnosis was made and that selection of treatment(s) is appropriate for a given patient. If a patient completes adequate trials of 2 algorithm stages without observable positive outcomes, it may be helpful to reassess medication compliance, and the patient should be re-evaluated for accuracy of diagnosis as well as potential mitigating factors such as other psychiatric comorbidities, including substance abuse.

### TREATMENT ALGORITHMS FOR BIPOLAR I DISORDER

The panel developed 2 stand-alone medication algorithms for acute treatment of BDI for patients presenting as primarily hypomanic/manic/mixed or as primarily depressed. This is a modification from the previous version, which recommended add-on treatments for depressive symptoms, to be used in conjunction with a primary mania algorithm. This change was recommended by the panel to simplify use of the algorithms.

The panel unanimously and strongly recommends that all patients with BDI receive continuous treatment with an antimanic agent.<sup>15,16</sup> For the purposes of the algorithm, antimanic agents are medications either that are approved by the U.S. Food and Drug Administration (FDA) for the treatment of mania or that have evidence of being effective for the treatment of mania. The term *mania* here is taken to include hypomania, mania, and mixed episodes. The use of various agents for acute and maintenance treatment is addressed separately in each section. Although early stages include monotherapy, later stages quickly move to more complex medication combinations that may involve greater risk of side effects and require closer monitoring and attention by the clinician. In clinical practice, the majority of patients receive more than 1 medication. Patients progress through the stages if inadequate symptom improvement or intolerable medication side effects occur. It is also reasonable to try alternate combinations within a given stage (e.g., Stage 1, 1[2], 1[3]). The stages, along with critical research citations, consensus opinion, and issues regarding discussion of safety and tolerability for that treatment strategy, are presented in turn.

Clinicians should take into consideration the following clinical caveats:

- Severely ill patients should be seen more often than patients who are less ill. Less ill but symptomatic patients should be seen frequently (every 2 weeks is recommended during periods of medication changes).
- A single week of improvement may not represent a stable effect. Since the recommendation to go to continuation phase assumes a stable acute response,

patients should be evaluated for at least 2 weeks following the first week of acute “response” to ensure stability of improvement before progressing to the continuation phase of treatment.

- In the continuation phase for hypomania/mania/mixed symptoms, patients should be seen at least monthly for the first 3 months, then every 2 to 3 months thereafter. Following 4 to 6 months of stability, a patient would be considered in maintenance phase treatment. Telephone calls and nonphysician clinicians should be used as appropriate to maximize the frequency of patient contact and optimize patient outcomes.

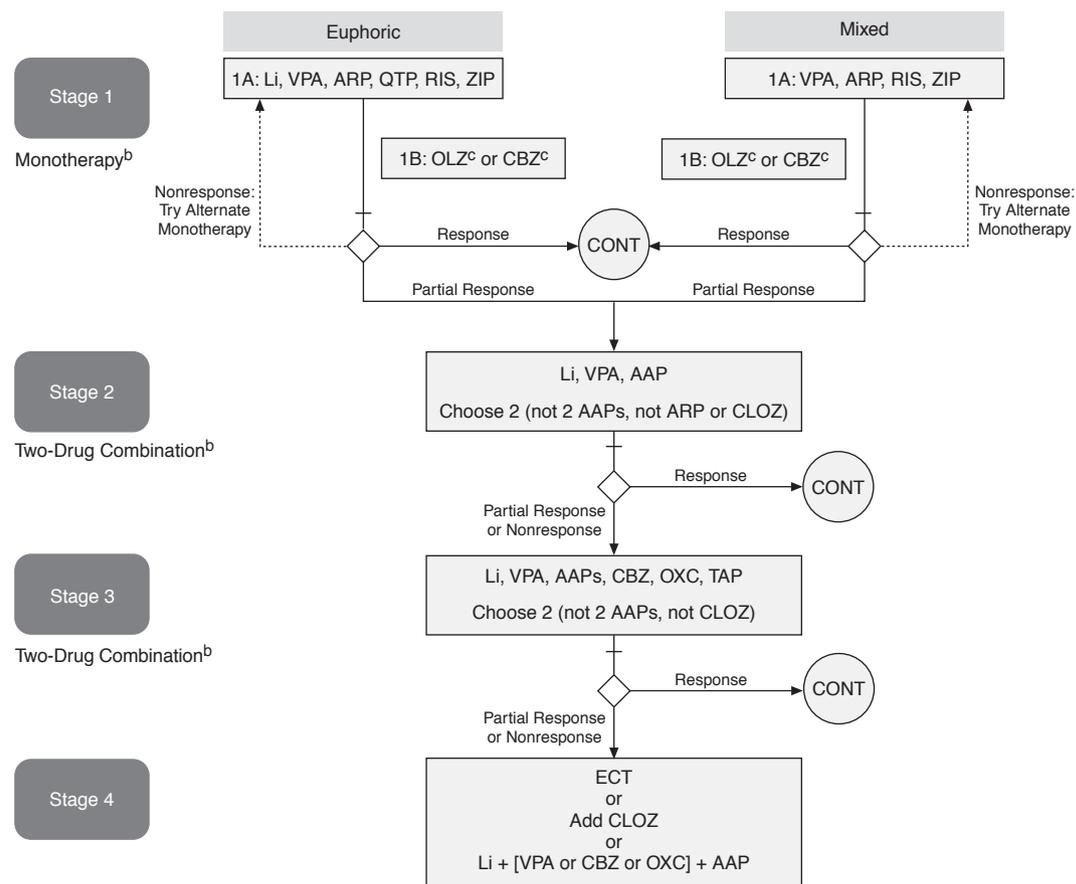
The aim of treatment is symptom remission and wellness (normalization of function) rather than just symptom improvement. Although not all patients achieve remission, every effort should be made to ensure the greatest potential maximal benefit for each patient. Therefore, once a response is seen, further tactical (e.g., dosage adjustment or augmentation) or strategic (e.g., addition of medication, psychotherapy, or rehabilitative services) options should be considered to optimize response.

Within a stage, all medication decisions are based on clinician choice and patient preference. Decision points are defined by reaching reasonable doses and duration of times on a specified medication regimen at a given stage. Throughout the algorithm, the 4 elements for making medication choices are efficacy (improvement in symptoms), tolerability (side effects), safety, and serum concentrations where applicable. The reasons to consider treatment response, tolerability, and safety are self-evident. Serum concentrations are recommended when applicable to ensure that adequate dosing is achieved prior to trying alternative medications, addressing side effects, or assessing drug interactions.

#### Algorithm for Treatment of Acute Episodes of Hypomania/Mania/Mixed in Bipolar I Disorder (Figure 1)

Application of the algorithm assumes that the patient received a thorough evaluation and a diagnosis of BDI and that medication treatment is clinically indicated. Medications that had sufficient evidence to indicate efficacy for treatment of hypomania, mania, and mixed symptoms at the time of the consensus conference (spring 2004) are included. The clinician may choose to use adjunctive medications such as benzodiazepines or related medications for acute management of associated symptoms (e.g., agitation or insomnia).

**Stage 1A.** Stage 1A includes different monotherapy options for those patients presenting with euphoric or irritable hypomanic or manic symptoms, or mixed symptoms. For patients presenting with euphoric or irritable

Figure 1. Algorithm for Treatment of Acute Hypomanic/Manic/Mixed Episodes in Patients With Bipolar I Disorder<sup>a</sup>

<sup>a</sup>It is appropriate to try > 1 combination at a given level. New trials from each stage can be labeled Stage 2 (1), Stage 2 (2), etc.

<sup>b</sup>Use targeted adjunctive treatment as necessary before moving to next stage:

Agitation/Aggression—clonidine, sedatives

Insomnia—hypnotics

Anxiety—benzodiazepines, gabapentin

<sup>c</sup>Safety and other concerns led to placement of OLZ and CBZ as alternate first-stage choices.

Abbreviations: AAP = atypical antipsychotic, ARP = aripiprazole, CBZ = carbamazepine, CLOZ = clozapine, CONT = continuation,

ECT = electroconvulsive therapy, Li = lithium, OLZ = olanzapine, OXC = oxcarbazepine, QTP = quetiapine, RIS = risperidone, TAP = typical antipsychotic, VPA = valproate, ZIP = ziprasidone.

mania or hypomania, clinicians may choose from lithium, valproate, aripiprazole, quetiapine, risperidone, and ziprasidone. For mixed or dysphoric hypomania or mania, clinicians may choose among valproate, aripiprazole, risperidone, and ziprasidone.

The efficacy of lithium as an antimanic agent is well established. However, data suggest that the presence of dysphoric or mixed symptoms predicts less robust treatment response to lithium.<sup>17</sup> Therefore, lithium is recommended only as monotherapy for euphoric or irritable mania. Valproate is recommended as a monotherapy option for any presentation of hypomania or mania.<sup>18,19</sup> Divalproex is the FDA-approved form of valproate/valproic acid for the treatment of mania. Divalproex has a more favorable side effect profile and generally better tolerability than valproate/valproic acid.<sup>20</sup> Two recent cross-

sectional retrospective studies suggest that women may be at risk of developing oligomenorrhea and hyperandrogenism soon after starting valproate,<sup>21,22</sup> although this risk is lower than suggested by earlier, smaller studies.<sup>23</sup>

Most members of the class of newer-generation atypical antipsychotics are included as Stage 1 monotherapy options based on completion of 2 adequately powered, placebo-controlled, randomized level A trials. Aripiprazole has 2 multicenter, randomized, double-blind, placebo-controlled trials that support its efficacy for both manic and mixed acute episodes.<sup>24,25</sup> Quetiapine is recommended as monotherapy for euphoric hypomanic or manic symptoms based on 2 multicenter, double-blind, placebo-controlled, randomized trials, 1 compared with haloperidol and 1 compared with lithium.<sup>26,27</sup> No controlled evidence exists for use in acute mixed presentations.

Three multicenter, randomized, double-blind, placebo-controlled trials support risperidone monotherapy.<sup>28-30</sup> Ziprasidone has 2 multicenter, randomized, double-blind, placebo-controlled, monotherapy trials in inpatients with mania or mixed episodes, which support its antimanic properties.<sup>31,32</sup>

Evidence supports that the atypical antipsychotics share a common antimanic "class effect."<sup>33</sup> Individual choice between agents should be based on consideration of individual patient history and characteristics, potential side effects, and individual therapeutic responses to a given medication. While the class effect is clear, individual response can be variable. Lack of response to one atypical agent should not preclude additional trials with other members of this class.

The panel recognizes that the atypical antipsychotics are a relatively new group of medications and, with greater patient exposure, the field is learning about potential health implications that were not recognized early on. Antipsychotics may adversely affect glucose levels and precipitate diabetes mellitus. The extent to which these effects are related solely to drug-induced weight gain is unclear.<sup>34-37</sup> Although more reports of diabetes during treatment with clozapine or olanzapine have been published, epidemiologic studies provide conflicting data regarding the relative risk of different atypical antipsychotics to produce diabetes mellitus.<sup>36</sup> In March 2004, the FDA issued a safety alert requiring revisions in the labeling of all atypical antipsychotics to discuss the increased risk of glucose irregularities, including risk of diabetes mellitus, hyperglycemia, dyslipidemia, and weight gain, in patients taking atypical antipsychotics.<sup>38</sup> The TIMA Bipolar Disorder Consensus Panel recommends that the American Diabetes Association (ADA) et al. guideline for the use of atypical antipsychotics be followed for all patients initiating or receiving these agents.<sup>37</sup> The Texas public health system recently adopted the Mount Sinai Conference monitoring guideline for patients with schizophrenia receiving antipsychotic medications to allow easier nonfasting blood monitoring.<sup>39</sup> The Mount Sinai guideline provides additional recommendations regarding QT prolongation and prolactin elevations. The key point is that routine monitoring should occur for patients receiving atypical or typical antipsychotic treatment. It should be noted that the risk of long-term neurologic side effects associated with atypical antipsychotics, although less frequent than with typical antipsychotics, is still unknown.

**Stage 1B.** The consensus panel placed olanzapine and carbamazepine as potential monotherapy options within a substage, titled Stage 1B. This placement was due to concern about greater potential adverse events or complexity associated with these treatments. The efficacy data support viewing these treatments as first-line options, but the panel believes safety and tolerability issues warrant some separation from other first-line choices.

Olanzapine has 3 positive monotherapy multicenter, randomized, double-blind, placebo-controlled trials (see Suppes et al. 2002<sup>9</sup>). Consensus panel members placed it within a substage due to concerns regarding the long-term safety of using this agent.<sup>35,37,40-42</sup> In recent studies, significant weight gain, as defined by > 7% of the baseline body weight, was associated with olanzapine therapy.<sup>43</sup> In a secondary analysis of a 3-week, double-blind, placebo-controlled study with a 49-week follow-up, the data indicated that although olanzapine showed significant efficacy, patients' body mass indices (BMIs) had increased by an average of 7.9%, and 50% of the patients met or exceeded the criterion for obesity compared with 30% who met or exceeded the obesity criterion at baseline.<sup>44</sup> Additionally, blood pressure, pulse rates, non-fasting serum glucose levels, and serum cholesterol levels were also substantially and temporally associated with weight gain.<sup>44</sup> The clinical significance of weight gain during antipsychotic therapy is substantial; the risk of cardiovascular-related mortality increases with each point increase in the BMI.<sup>45,46</sup> Additionally, obesity is a risk factor for diabetes mellitus.<sup>47</sup>

Historically, evidence supporting the use of carbamazepine for acute hypomanic, manic, or mixed symptoms was based on small, open combination trials (see Suppes et al. 2002<sup>9</sup>). Recently, 2 multicenter, randomized, double-blind, placebo-controlled trials with extended-release carbamazepine capsules support its efficacy as monotherapy for acute manic or mixed symptoms in bipolar disorder.<sup>48,49</sup> Extended-release carbamazepine is the FDA-approved form of carbamazepine for the treatment of mania.

Carbamazepine is placed within Stage 1B due to concerns about complexity of dosing, the potential for drug interactions through hepatic enzyme induction (including autoinduction), and tolerability issues, including the need for blood monitoring. Current available data and clinical experience are inadequate to determine the degree to which side effects and tolerability may be improved with the extended-release formulation.

**Stages 1A and 1B.** Generally, in the case of partial response with good tolerance or response with residual symptoms, the recommendation is to add a medication (move to combination therapy, i.e., Stage 2) versus switching. If the patient is intolerant in Stage 1, the recommendation is to try an alternative antimanic agent within Stage 1. When changing medications, the recommendation is to cross over (overlap and taper), using abrupt discontinuation only when medically necessary.<sup>15</sup>

**Stage 2.** The widespread reliance on combination therapy in the treatment of BDI is reflected by the placement of this approach in Stage 2 (see Suppes et al. 2002<sup>9</sup>). Consistent with past algorithm recommendations, clinicians are offered an array of potential agents from which to choose a 2-drug combination. Specifically, they are

asked to choose a combination of 2 drugs from the following options: lithium, valproate, olanzapine, quetiapine, risperidone, and ziprasidone. The panel does not recommend the use of 2 atypical antipsychotics, but rather suggests the combination of lithium plus valproate or lithium or valproate plus an atypical antipsychotic. Clozapine is recommended later in the algorithm due to monitoring and safety concerns and the general agreement that it be reserved for use in treatment-resistant patients. Carbamazepine is not listed in this stage due to a higher risk of drug interactions than other medications.

Support for combinations that include lithium, valproate, and atypical antipsychotic medications comes from a growing body of literature supporting the use of these drugs in combination for symptoms of bipolar disorder only partially responsive to monotherapies.<sup>50-60</sup> Placebo-controlled trials have been completed using lithium or valproate plus an atypical antipsychotic. These trials support greater efficacy for the combination with improved clinical response and time to response in acute mania or mixed states. Common practice consists of using Stage 2 for more severely ill patients with BDI versus starting with monotherapy (Stage 1). Once symptoms resolve, consideration may be given to longer-term treatment with monotherapy (Stage 1).

In a double-blind, placebo-controlled trial, patients receiving olanzapine with either valproate or lithium had a greater decrease in manic and depressive symptoms than those receiving valproate or lithium monotherapy.<sup>53</sup> A similar large, multicenter, randomized, double-blind, placebo-controlled trial has been completed for quetiapine,<sup>56</sup> and a smaller placebo-controlled add-on trial has been completed in adolescents.<sup>57</sup> Two large, multicenter, randomized, double-blind, placebo-controlled add-on trials have been completed for risperidone.<sup>58,59</sup> A recent double-blind, placebo-controlled study supports that ziprasidone in combination with lithium reduces manic symptoms faster than lithium alone early in the course of treatment, although impact of adjunctive ziprasidone at 3 weeks is limited.<sup>60</sup> It should be noted that aripiprazole was excluded from this stage because there are no combination trials with aripiprazole available at this time.

Within Stage 2, clinicians are encouraged to try other 2-drug combinations if a first attempt at combination therapy is inadequately tolerated or does not result in remission of symptoms and restoration of optimal functioning.

**Stage 3.** Stage 3 consists of 2-drug combination treatments with a larger set of medication choices, including aripiprazole as an atypical antipsychotic option, carbamazepine, oxcarbazepine, and older typical antipsychotic medications in addition to medications recommended in Stage 2. Clozapine is not recommended at this stage due to monitoring and safety concerns.

Typical antipsychotics are a large group of medications associated with significant acute neurologic side effect

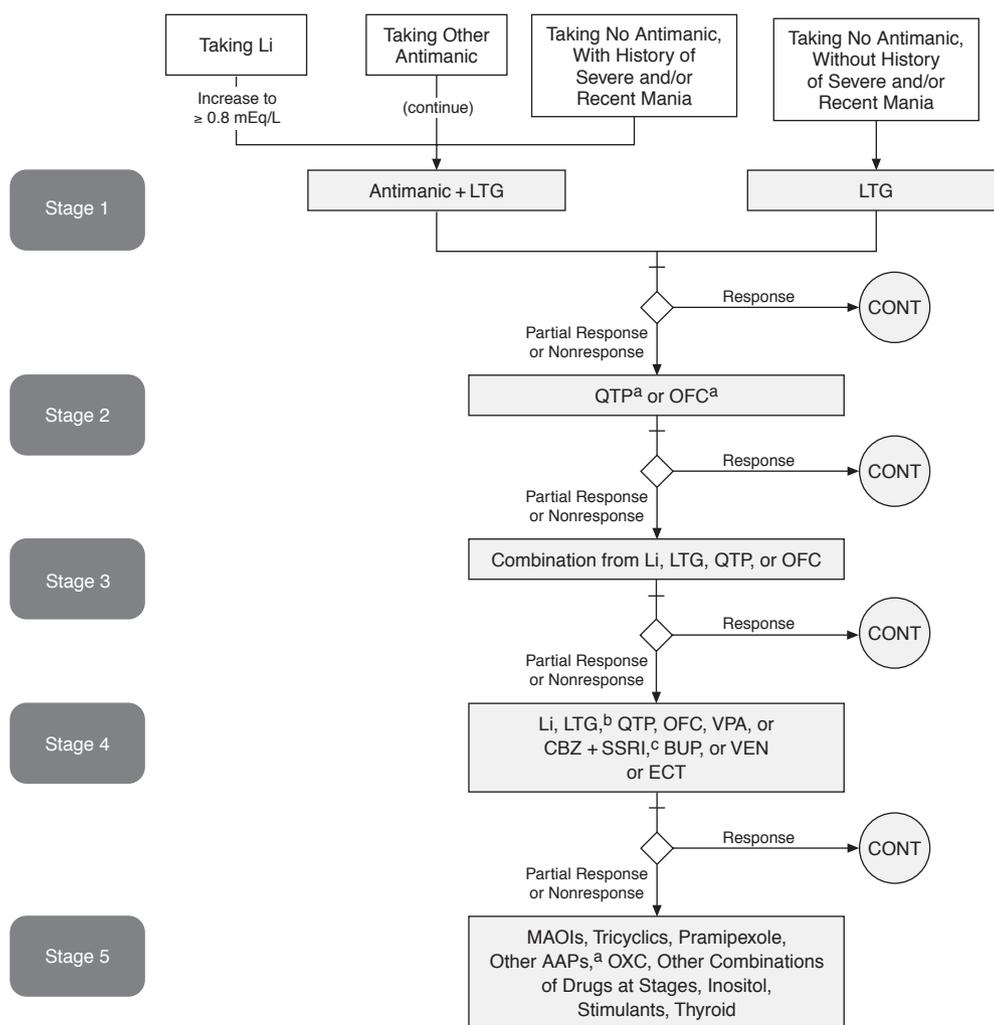
risks and long-term risks of tardive dyskinesia. The panel recognizes that these medications are still in use and that a patient may benefit from a drug from this class.<sup>16</sup> In multicenter, double-blind, randomized head-to-head trials, haloperidol was as effective at reducing mania as aripiprazole,<sup>61</sup> olanzapine,<sup>62</sup> and risperidone,<sup>30</sup> but in each of these trials, haloperidol showed a much greater rate of extrapyramidal symptoms than the comparators. In a double-blind trial, valproate plus haloperidol or other conventional antipsychotics was more efficacious, and allowed lower antipsychotic drug dosage, than antipsychotic drug alone.<sup>63</sup> Additionally, in a randomized, double-blind, placebo-controlled trial, haloperidol plus lithium or divalproex was as effective as risperidone plus lithium or divalproex in reducing mania, but a greater number of patients receiving haloperidol had significant increases in ratings of extrapyramidal symptoms than either the risperidone or placebo group.<sup>58</sup> Based on the long-term risk profile, the atypical antipsychotics are recommended for long-term use over this older group of medications.

Oxcarbazepine, which is structurally similar to carbamazepine, has fewer rigorously controlled trials than other antimanic agents supporting its efficacy for treatment of bipolar disorder.<sup>64-68</sup> Studies in epileptic patients suggest that some patients who do not tolerate carbamazepine improve when they are switched to oxcarbazepine.<sup>69-71</sup> The panel placed it lower in the algorithm because of limited well-controlled studies.

**Stage 4.** Stage 4 introduces the option of electroconvulsive therapy (ECT) treatment, as well as clozapine or 3-drug combinations. Electroconvulsive therapy is an effective treatment for acute mania,<sup>72,73</sup> but safety, tolerability, and patient acceptance issues warrant its placement at a later stage in the algorithm. Clozapine is an effective antimanic therapy in treatment-resistant patients with bipolar disorder (see Suppes et al. 2002<sup>9</sup>), but general clinical consensus is to attempt treatment with other atypical antipsychotic medications before initiating clozapine. Safety considerations (see Stage 1) and medical monitoring required during clozapine treatment suggest that this option be utilized only after multiple other medication trials have failed to achieve adequate response. The third option in Stage 4 includes combinations of 3 drugs: lithium, an anticonvulsant (valproate, carbamazepine, or oxcarbazepine), and an atypical antipsychotic.

Throughout all the stages, the consensus committee recommends periodic evaluation and treatment for any associated symptoms that may mask treatment response, including symptoms of anxiety, insomnia, and agitation. Persistent limited response also suggests reevaluating adherence, reconsidering the diagnosis, evaluating for potential substance use or abuse, and ruling out potential medical issues.

Figure 2. Algorithm for Treatment of Acute Depressive Episodes in Patients With Bipolar I Disorder



<sup>a</sup>Note safety issue described in text.

<sup>b</sup>Lamotrigine has limited antimanic efficacy and, in combination with an antidepressant, may require the addition of an antimanic.

<sup>c</sup>SSRIs include citalopram, escitalopram, fluoxetine, paroxetine, sertraline, and fluvoxamine.

Abbreviations: AAP = atypical antipsychotic, BUP = bupropion, CBZ = carbamazepine, CONT = continuation, ECT = electroconvulsive therapy,

Li = lithium, LTG = lamotrigine, MAOI = monoamine oxidase inhibitor, OFC = olanzapine-fluoxetine combination, OXC = oxcarbazepine,

QTP = quetiapine, SSRI = selective serotonin reuptake inhibitor, VEN = venlafaxine, VPA = valproate.

### Algorithm for Treatment of Acute Depressive Episodes in Bipolar I Disorder (Figure 2)

Since the last revision of the Texas algorithms for treatment of bipolar disorder, new data have emerged on the acute treatment of bipolar depression. A significant change in this version is that the algorithm for treatment of bipolar depression is now a stand-alone guideline, distinct from recommendations for treating patients who are acutely hypomanic, manic, or mixed. However, both the quantity and quality of research assessing treatment of bipolar depression continue to lag behind related work in the treatment of bipolar mania. Consequently, the recommendations and ordering of treatments for bipolar depression are generally based on fewer well-controlled studies,

with a relatively greater weight of expert consensus on the decision-making process.

The panel actively debated the ordering of Stages 1 through 4. In particular, the suggestion of using quetiapine and olanzapine-fluoxetine combination alone (Stage 2) or in combination (Stage 3) was discussed. The recommendation that these stages precede the current common clinical practice of using an antimanic agent plus an antidepressant was discussed and eventually agreed upon based on the quality and sample size of studies (see below), with the proviso that replication studies are needed. A minority opinion was expressed that treatments in Stage 4 should precede those in Stages 2 and 3.

After reviewing all of the studies discussed below, the majority of panel members agreed that the quality of the studies with recent compounds (e.g., quetiapine and olanzapine-fluoxetine combination) and the moderate to large effect sizes observed in these studies supported the higher placement of medications less traditionally used for the treatment of bipolar depression than in the 2000 bipolar depression algorithm.<sup>9</sup> The panel reached consensus on an overall lower placement for adjunctive antidepressants (with the exception of olanzapine-fluoxetine combination) in light of the superior quality of newer studies of bipolar depression. Large, multicenter, double-blind, placebo-controlled trials using antidepressant and antimanic combination therapy are needed to help resolve this issue.

The panel preferentially ordered depression treatments with the least likelihood of causing mood destabilization. All patients with bipolar disorder, currently depressed, should have mood stabilizer treatment optimized before initiation of antidepressant treatments.<sup>74-76</sup> For this reason, there are multiple entry points into Stage 1 of the bipolar depression algorithm. For those patients already taking lithium, the panel recommends that the lithium dose be optimized (serum level  $\geq 0.8$  mEq/L), if tolerated, to determine whether additional antidepressant treatments are necessary.<sup>74</sup> All patients with a recent and/or severe history of mania should receive or add an effective antimanic agent (see algorithm for treatment of hypomania/mania and mixed episodes) for treatment of bipolar depression.

**Stage 1.** This stage has multiple entry points. If depressive symptoms persist after mood stabilizer treatment is optimized, the panel recommends the addition of lamotrigine. Lamotrigine monotherapy is recommended as a first-stage option only for those patients without a recent and/or severe history of manic symptoms.

The use of lamotrigine for treatment of bipolar I depression is recommended based on data from 2 open-label adjunctive trials and 2 placebo-controlled monotherapy trials of lamotrigine in the acute treatment of bipolar patients. In one small, open-label clinical case series of bipolar I and II patients, 65% of patients were rated much or very much improved on the Clinical Global Impressions scale (CGI) overall improvement score after add-on treatment with lamotrigine.<sup>77</sup> In a second open-label, prospective trial, 68% of patients presenting as depressed showed a moderate to marked response after 24 weeks of add-on treatment with lamotrigine.<sup>78</sup>

Two monotherapy trials have also been published. In one study,<sup>79</sup> lamotrigine monotherapy at 200 mg/day achieved significant reductions in depression compared with placebo by the end of week 3, as measured by the Montgomery-Asberg Depression Rating Scale (MADRS)<sup>80</sup> total score, the CGI-Severity of Illness<sup>81</sup> and the CGI-Improvement<sup>81</sup> scores, but not the Hamilton Rating Scale for Depression (HAM-D)<sup>82,83</sup> scores. In addition, lamotrigine was superior to placebo on 6 of the 10 individual

MADRS items of depressive symptoms (including apparent sadness, reported sadness, inner tension, lassitude, inability to feel, and suicidal thoughts). Although this study did not separate from placebo on its primary outcome measure (HAM-D), it was the first large-scale randomized controlled trial in BDI depression, and the lamotrigine group separated from placebo on all secondary measures. A second, smaller placebo-controlled, double-blind study in treatment-resistant bipolar depression found lamotrigine superior to placebo.<sup>84</sup> Overall tolerability and safety were good using the recommended slow titration schedule. Initiating at a higher dose or titrating more rapidly is not recommended as this raises the likelihood of causing serious, potentially lethal, rashes. At recommended titration rates, medically serious rashes occur in less than 0.1% of patients, and nonserious rash rates ranged from 3.9% to 13.4%.<sup>85</sup>

**Stage 2.** Stage 2 options for patients with bipolar depression include quetiapine monotherapy and olanzapine-fluoxetine combination treatment. Although onset of action appears to be faster than with lamotrigine, the overall weight of evidence and tolerability data in long-term use favor lamotrigine placement at Stage 1. An overlap and taper strategy is recommended in moving from Stage 1 to Stage 2.

Olanzapine-fluoxetine combination is the only treatment with an FDA indication for the acute treatment of bipolar I depression, based on a double-blind, placebo-controlled study.<sup>86</sup> There was a significant response by the end of week 1, which was sustained throughout the 8-week trial. Eight of the 10 depressive symptoms on the MADRS scale improved significantly relative to placebo in patients taking olanzapine-fluoxetine combination. The side effects profile of olanzapine-fluoxetine combination is similar to that of olanzapine monotherapy, and the safety issues discussed earlier regarding olanzapine are also pertinent here (see Stage 1, mania).

In a recent study of acutely depressed patients with bipolar I and II, quetiapine monotherapy at doses of 300 and 600 mg/day was significantly more effective than placebo, beginning at week 1 and continuing throughout the 8-week study.<sup>87</sup> The 600-mg dose was effective in 9 of the 10 depressive symptoms on the MADRS, and the 300-mg dose was effective in 8 of the 10 symptoms. Titration began with 50 mg/day and increased by 100 mg/day to 300 or 600 mg/day (by day 4 or 7, respectively). Tolerability was reasonable, although sedation and somnolence were present in about 55% of patients, and resulted in about 11% of patients dropping out of the study prematurely, mostly during the first week. Overall, 26% of patients assigned to the 600-mg group and 16% of patients in the 300-mg group dropped out prematurely due to side effects.

Note that earlier recommendations to utilize the ADA guidelines<sup>37</sup> or the Mount Sinai Conference guidelines<sup>39</sup> when using atypical antipsychotics apply in Stage 2.

**Stage 3.** Stage 3 treatment includes the combination of any 2 of the 4 agents already introduced in this treatment guideline, namely lithium, lamotrigine, quetiapine, and olanzapine-fluoxetine combination. Clinicians should note that olanzapine-fluoxetine combination is a 2-drug combination, and its use with another medication results in a 3-drug combination. Earlier safety concerns with the atypical antipsychotics should be noted. These recommendations are relatively low risk for mania induction or cycle acceleration and reflect acute strategies that may be particularly effective in longer-term treatment. Evidence for the use of these combination strategies is limited at this stage, and inclusion is based on monotherapy trials.

**Stage 4.** This stage includes a variety of other treatment options, including ECT and combinations that include the use of lithium, lamotrigine, quetiapine, olanzapine-fluoxetine combination, valproate, or carbamazepine in combination with an SSRI medication, bupropion, or venlafaxine<sup>76,86,88</sup> (see Suppes et al. 2002<sup>9</sup>). Selective serotonin reuptake inhibitors (SSRIs) include citalopram, escitalopram, fluoxetine, paroxetine, sertraline, and fluvoxamine. Although these medications are in common use, controlled studies of their use in patients with BDI are limited.<sup>88-91</sup> Limited data suggest that the risk of mania induction with venlafaxine may exceed that with paroxetine.<sup>91</sup> Recent double-blind data support this observation in that venlafaxine was associated with a greater switch rate than sertraline or bupropion.<sup>92</sup> In combination with antimanic agents, the relative switch potential is fairly low with newer antidepressants, about 5% to 12%, similar to placebo.<sup>93,94</sup> Nonetheless, mania induction remains a possibility and must be discussed with the patient. Recent concerns about exacerbation of depression and suicidal ideation with antidepressants highlight the need for care when using these agents. However, there is evidence that inadequate treatment of depressive symptoms with antidepressants, either by not being prescribed or by being given at subtherapeutic doses, could contribute to the likelihood of suicide.<sup>95</sup> Please note that Stage 4 allows the combination of lamotrigine plus an antidepressant. Given the limited efficacy of lamotrigine in preventing new manic episodes, the addition of an antimanic is recommended for this combination.

Electroconvulsive therapy has been shown to be effective in bipolar depression, including treatment-refractory bipolar depression, but limited controlled data are available for the treatment of bipolar depression.<sup>96,97</sup>

**Stage 5.** Stage 5 offers a variety of treatment options with limited empirical evidence in support of their use, but which are listed as options based on expert opinion and clinical consensus. The exception is the inclusion of monoamine oxidase inhibitor (MAOI) medications, which have controlled evidence in support of their utility, but are placed at this stage due to serious safety (dietary

**Figure 3. Guidelines for Maintenance Treatment: Most Recent Episode Hypomanic/Manic/Mixed**

It is an option to remain on well-tolerated, effective, acute-phase treatments. Available evidence supports the options presented for prevention of new episodes or maintenance treatment.

Level I:	Patients With Frequent, Recent, or Severe Mania	Lithium or Valproate
	Patients Without Frequent, Recent, or Severe Mania	Lithium, Valproate, or Lamotrigine
	Alternative	Olanzapine <sup>a</sup>

Level II: Aripiprazole<sup>b</sup>

Level III: Carbamazepine or Clozapine<sup>a</sup>

Level IV: Quetiapine,<sup>b</sup> Risperidone,<sup>b</sup> or Ziprasidone<sup>b</sup>

Level V: Typical Antipsychotics,<sup>a</sup> Oxcarbazepine,<sup>b</sup> ECT

<sup>a</sup>Safety issues warrant careful consideration of this option for potential long-term use.

<sup>b</sup>Relatively limited information is currently available on this agent in long-term use.

restrictions and drug interactions) and compliance concerns with their use (see Suppes et al. 2002<sup>9</sup>). Due to evidence suggesting some degree of efficacy in bipolar depression (see Suppes et al. 2002<sup>9</sup>), tricyclic antidepressants are included at this lower stage despite (1) a relatively less favorable side effect profile, (2) a relatively narrow therapeutic index, and (3) evidence suggesting increased switches into mania relative to newer antidepressants.<sup>75,88,94,98</sup> Additional Stage 5 suggestions are other atypical antipsychotics not already included, and pramipexole,<sup>99,100</sup> which has 2 small positive, double-blind, placebo-controlled add-on studies in bipolar depression. Other options include trials of new combinations of drugs included in the algorithm, as well as inositol, stimulants, and thyroid supplementation.

**Guidelines for Maintenance Treatment After Hypomania/Mania/Mixed Episodes (Figure 3)**

While the need for ongoing long-term treatment for the vast majority of patients has been recognized for many years,<sup>15,16</sup> relatively few controlled prophylactic or maintenance trials using rigorous methodology had been completed until recently. Due to differences in illness course and available studies after episodes of mood elevation compared with depression,<sup>101</sup> the panel developed different maintenance treatment recommendations based on the polarity of the most recent episode. Most available data are regarding maintenance treatment after mood elevation episodes and are discussed in this section, whereas recommendations for maintenance treatment after depressive

episodes are discussed in a separate section below. For those patients who are stabilized after treatment for acute hypomanic, manic, or mixed episodes, maintenance treatment should be initiated. Due to the need for ongoing treatment, medication changes are often made based on development of subsyndromal symptoms. Thus, while acute-phase treatments are routinely continued following an episode, medication changes are common in outpatient care and often made during long-term follow-up.

The recommendation following an acute episode is continuation of acute treatment medications, followed by simplification of drug regimen and/or transition to treatments with the best documented efficacy and tolerability for maintenance therapy. Well-tolerated, effective acute-phase treatments are reasonable and acceptable options for maintenance treatment.

It should be noted that the current guideline focuses on the use of monotherapy for long-term treatment, reflecting the studies to date. Longer-term placebo-controlled studies involving single medications generally have low study completion rates. The role of combination treatment versus monotherapy in maintenance treatment remains to be determined. As most patients in clinical practice receive combination therapy, there is a compelling need for such studies.

Medications are found, hierarchically ordered by quality and quantity of evidence, in the maintenance treatment recommendations. The terminology of *levels* is utilized here to reflect the overall limited study data in this area. The panel weighed available data and expert consensus in the recommendations for maintenance treatment. As with acute mania, the use of levels represents the sequencing of interventions from those with the most substantial evidence balanced with tolerability and safety concerns to those with less evidence and/or greater safety and tolerability concerns.

**Level I.** For those with a history of frequent, recent, or severe mania, lithium or valproate is recommended.<sup>102–106</sup> For those without frequent, recent, or severe mania, lamotrigine is an acceptable choice.<sup>103,107</sup> In a recent 18-month study, patients with a current or recent manic or hypomanic episode were stabilized on lamotrigine and then randomized to lithium, lamotrigine, or placebo. Investigators found that while lithium and lamotrigine both significantly prolonged time to a new episode, lithium was significantly more effective in preventing new manic symptoms and lamotrigine in preventing new depressive symptoms.<sup>103</sup> Lithium has the most positive evidence in maintenance studies of bipolar disorder. In another 3-group study,<sup>108</sup> valproate and lithium were compared with placebo in a 52-week, double-blind trial. While neither treatment was significantly different from placebo on the primary endpoint, time to mood episode recurrence, valproate was superior to lithium on several secondary outcome measures, including survival time in the study.<sup>108</sup>

In a recent 47-week double-blind study,<sup>106</sup> BDI patients taking olanzapine or valproate had similar rates of bipolar relapse, although olanzapine was more efficacious in preventing new manic symptoms, but those patients taking olanzapine had a greater number of adverse events, including greater weight gain and increase in total cholesterol. Olanzapine has 3 additional recent double-blind studies supporting its use in relapse prevention following an acute manic or mixed episode.<sup>109,110,112</sup> Olanzapine is recommended as an alternate choice because of safety concerns with long-term use.<sup>106,109–112</sup>

**Level II.** Aripiprazole is recommended based on a randomized, double-blind, placebo-controlled, 6-month maintenance study in which patients received open-label aripiprazole until stable, then were randomized to either placebo or aripiprazole for the 6-month follow-up.<sup>113</sup> With a primary endpoint of time to relapse, aripiprazole performed significantly better than placebo. Patients receiving aripiprazole reported more anxiety and nervousness than those receiving placebo. Based on this study, aripiprazole received FDA approval in 2005 for the maintenance treatment of BDI, most recent episode manic or mixed.

**Level III.** Carbamazepine is recommended as a maintenance treatment. Double-blind studies comparing carbamazepine and lithium found greater effectiveness for lithium, but some degree of effectiveness for carbamazepine.<sup>102</sup> Another double-blind study found that neither lithium nor carbamazepine monotherapy was effective in treatment-resistant patients, although the combination of lithium and carbamazepine was more effective.<sup>50</sup> A recent 6-month, open-label study following two 3-week acute studies supports the use of beaded extended-release carbamazepine for prophylaxis in recently manic or mixed bipolar patients.<sup>114</sup> Clozapine is also recommended for treatment-resistant patients based on a 1-year randomized study comparing clozapine add-on treatment to treatment as usual.<sup>115</sup> Long-term use of clozapine requires ongoing monitoring for safety, as well as interventions to counteract adverse events that may occur with sustained use.<sup>37,39</sup>

**Level IV.** Quetiapine,<sup>116–118</sup> risperidone,<sup>52,119</sup> and ziprasidone<sup>120,121</sup> are all recommended as potential maintenance treatments. However, most of the maintenance observations with these drugs have been open, uncontrolled studies conducted in combination with other established agents. Additionally, while the safety profile has been good in long-term use, the number of patients with systematic data is still limited.

**Level V.** Treatments with smaller, uncontrolled studies in support of their use for maintenance treatment include typical antipsychotics<sup>16</sup> (see earlier section regarding adverse events and safety issues) and oxcarbazepine.<sup>68,122</sup> Electroconvulsive therapy is also included at this level as a potential maintenance treatment.<sup>123,124</sup>

**Figure 4. Guidelines for Maintenance Treatment: Most Recent Episode Depressed**

It is an option to remain on well-tolerated, effective, acute-phase treatments. Available evidence supports the options presented for maintenance treatment.

Level I:	Patients With Recent and/or Severe History of Mania	Lamotrigine Combined With Antimanic Agent
	All Other Patients	Lamotrigine Monotherapy

Level II: Lithium

Level III: Combination of an Antimanic and Antidepressant That Has Been Effective in the Past, Including Olanzapine-Fluoxetine Combination<sup>a</sup>

Level IV: Valproate, Carbamazepine, Aripiprazole,<sup>b</sup> Clozapine,<sup>a</sup> Olanzapine,<sup>a</sup> Quetiapine,<sup>b</sup> Risperidone,<sup>b</sup> Ziprasidone<sup>b</sup>

Level V: Typical Antipsychotics,<sup>a</sup> Oxcarbazepine,<sup>b</sup> ECT

<sup>a</sup>Safety issues warrant careful consideration of this option for potential long-term use.

<sup>b</sup>Relatively limited information is currently available on this agent in long-term use.

### Guidelines for Maintenance Treatment After Depressive Episodes (Figure 4)

To date, data regarding maintenance treatment after a depressive episode are limited. As with maintenance options for patients with recent hypomanic, manic, or mixed episodes, the panel organized these maintenance treatments by strength of evidence and safety and tolerability. As discussed previously, the evidence for maintenance therapy after a depressive episode is not as strong or clear as the evidence for maintenance therapy after an acute manic episode. Expert consensus necessarily played a greater role in selection of the maintenance treatment recommendations following a depressive episode than those following a hypomanic, manic, or mixed episode. Clinicians and patients also have the option of remaining on well-tolerated, effective acute-phase treatments and adjusting doses as necessary to permit adequate tolerability.

Due to the risks of mania induction and cycle acceleration, antidepressant monotherapy is not recommended as an appropriate maintenance treatment for patients with BDI, most recent episode depressed. The long-term use of antidepressants in conjunction with a mood stabilizer in patients with BDI continues to be an area of controversy.<sup>125</sup> A recent retrospective case-control study suggests that the overall course of illness may be improved for a subset of patients who respond to and tolerate adjunctive antidepressants by maintaining the antidepressant and mood stabilizer combination therapy used to treat the acute depression.<sup>126</sup> The relative risks and benefits of continuing versus discontinuing adjunctive anti-

depressants remain to be fully evaluated in a prospective study.<sup>127</sup>

Data regarding maintenance treatments are generally based on their use following manic rather than depressive episodes. The lack of continuity between different levels of these recommendations reflects our limited understanding and knowledge of overall best practices due to the small number of controlled studies.

**Level I.** Lamotrigine is recommended in combination with an antimanic agent for those patients with recent and/or severe manic history. For all others, lamotrigine monotherapy is a reasonable maintenance treatment.<sup>107,128,129</sup> In a recent study,<sup>128</sup> patients with a current or recent depressive episode were stabilized on lamotrigine and then randomized to receive lamotrigine, lithium, or placebo monotherapy for 18 months to compare the long-term efficacy of lamotrigine and lithium in preventing mood episodes. Investigators found that lamotrigine and lithium were superior to placebo for prolonging the time to relapse, with lamotrigine more effective against depression and lithium more effective against mania.<sup>128</sup> This study was the companion study to one mentioned above for maintenance treatment after a manic episode.<sup>103</sup> Recent studies suggest a greater likelihood of recurrence into the most recent episode type; thus, lamotrigine is placed prior to lithium for those patients with the most recent episode depressed.

**Level II.** Lithium has multiple studies in support of its long-term efficacy and has an FDA indication for maintenance treatment of bipolar disorder.<sup>16,103,107,128</sup> As well, older studies support the use of lithium maintenance after depressive episodes.<sup>16</sup> Importantly for maintenance treatment, naturalistic (uncontrolled) evidence supports a decrease in suicidal actions with the use of lithium.<sup>130,131</sup>

**Level III.** An antimanic agent and antidepressant combination that has been effective for the patient in the past, including the olanzapine-fluoxetine combination, is recommended here. While lower on the acute treatment algorithm, based on recent controlled data these combinations are considered here. Open extension data (olanzapine-fluoxetine combination) and case-controlled data (antimanic plus antidepressant) support longer-term efficacy for this combination type.<sup>111,126</sup> The ADA<sup>37</sup> or Mount Sinai Conference<sup>39</sup> guidelines should be followed for ongoing monitoring for safety, as well as for interventions to counteract adverse events that may occur with sustained use.

**Level IV.** Valproate,<sup>104,108</sup> carbamazepine,<sup>50,102,114</sup> and atypical antipsychotics (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone)\* all have some evidence supporting their use in the maintenance treatment of bipolar depression. The only atypical anti-

\*References 8, 52, 106, 109–111, 113, 115–121.

psychotic with well-controlled maintenance trials is olanzapine, which was as effective as lithium and valproate and significantly better than placebo.<sup>109,110,112</sup> Concerns regarding medical monitoring and safety in long-term use led to lower placement of the atypical antipsychotics in this ranking of maintenance options.

**Level V.** Treatments with smaller and less controlled studies of their use in maintenance treatment include typical antipsychotics and oxcarbazepine.<sup>16,68,122</sup> Electroconvulsive therapy is also included at this level as a potential maintenance treatment.<sup>123,124</sup>

### ADDITIONAL TREATMENT INTERVENTIONS

The majority of patients in maintenance therapy are currently treated with 2 or more drugs, and many patients experience comorbid psychiatric disorders. In particular, treatment of co-occurring anxiety disorders and substance abuse or dependence may be needed. The treatment recommendations in this article in no way preclude additional treatments targeted at co-occurring illnesses in conjunction with medications discussed here. The panel believes that treatment of co-occurring conditions should follow the general treatment principles outlined in this update.

Rapid cycling occurs in about 20% of patients with bipolar disorder at some period in the course of illness. While no specific recommendations are made for rapid cycling, rapid cycling appears to be a nonspecific predictor of treatment nonresponse,<sup>132</sup> and combination therapy is frequently needed for these patients to reach remission.

This algorithm specifically addresses the treatment of bipolar I disorder. Due to the lack of research directly addressing patients with bipolar II disorder, ordered, evidence-based treatment recommendations are not available for this disorder, although recent prevalence data suggest that bipolar II disorder could be as common as bipolar I disorder.<sup>133</sup> The recently published Expert Consensus Guideline Series<sup>134</sup> captures current treatment approaches of experienced practitioners to bipolar II. Clinical considerations for treating bipolar II disorder generally coincide with those for treating bipolar I. Data currently exist supporting the use of lithium, lamotrigine, valproate, and antidepressant monotherapy.<sup>7,135</sup> The relative strength of these data is quite limited, with the strongest data to date in favor of lithium. Ongoing research addressing patients with bipolar II will become available in the next 2 to 3 years, at which time evidence-based guidelines may be developed.

The TIMA physician manual will be updated and will support implementation of these guidelines, including treatment tactics and recommendations for adjunctive treatments (e.g., interventions for insomnia, agitation, and other associated symptoms) (see TIMA Web site, <http://www.dshs.state.tx.us/mhprograms/TIMA.shtm>). The manual includes recommendations for side effect

management and modifications that may be required for inpatient use of the algorithms. Description of the psychoeducational program used in the Texas system and specific educational tools are also available at the Web site.

### CONCLUSIONS

The goals of this update are to affirm general principles of treatment and to update medication recommendations for the treatment of BDI. In this period of rapid advance of knowledge, one of the strengths of the algorithm approach is rapid incorporation of new high-quality scientific results. The current guidelines present recommendations for treatment of BDI based on available evidence and expert consensus, with input from national experts, TDSHS psychiatrists, patient advocates, and consumers. Additionally, a concise ranking of those treatments with evidence supporting their use in maintenance or prevention of relapse is provided.

This update has some notable differences from earlier versions, particularly that the use of atypical antipsychotics is recommended for virtually all phases of illness, with the caveat that we are still learning about relative risks and benefits of this class of medications. Additionally, recent studies led to the placement of traditional antidepressants at Stage 4 in the management of depressive symptoms, with other treatments with less risk of destabilization and more compelling evidence of efficacy preceding the use of antidepressants. Finally, due to differences in illness course and available studies after episodes of mood elevation compared with depression, different maintenance treatment recommendations are provided, based on the polarity of the most recent episode.

The algorithms and guidelines are a synthesis of current scientific evidence balanced with pragmatic clinical issues of safety and tolerability. Users can view these materials as a codification of available evidence and expert opinion intended to guide clinician decision making, but not as rigid or choice-limiting dictates. This is the fourth version of a Texas guideline for the treatment of bipolar disorder, and each version incorporates significant changes in response to increased treatment options, clinical research findings, and clinical experience. The remarkable changes in the Texas Medication Algorithms for BDI over the last 7 years are a reflection of the rate at which the field is advancing. The opportunity to update medication treatment algorithms in response to new developments is central to the strengths and limitations of medication algorithms. The Texas Medication Algorithm Project, now the Texas Implementation of Medication Algorithms, provides a mechanism to provide timely updates of medication algorithms for BDI. As the scientific findings in both acute and maintenance treatment of bipolar disorder continue to advance, these materials will be revised to reflect changes in our knowledge.

*Drug names:* aripiprazole (Abilify), bupropion (Wellbutrin and others), carbamazepine (Carbatol, Equetro, and others), citalopram (Celexa and others), clonidine (Catapres and others), clozapine (Clozaril, FazaClo, and others), divalproex (Depakote), escitalopram (Lexapro), fluoxetine (Prozac and others), gabapentin (Neurontin), haloperidol (Haldol and others), lamotrigine (Lamictal), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), olanzapine-fluoxetine (Symbyax), oxcarbazepine (Trileptal), paroxetine (Paxil, Pexeva, and others), pramipexole (Mirapex), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), topiramate (Topamax), valproic acid (Depakene and others), venlafaxine (Effexor), ziprasidone (Geodon).

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