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### **Bipolar Disorders Expert Column**

## **Update of the Texas Implementation of Medication Algorithms for Bipolar I Disorder**

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### **Overview**

Many new compounds for the treatment of bipolar I disorder (BDI) have become available since the last algorithm update of 2000, and further research has been completed and published for existing compounds. The purpose of the 2004 Consensus Conference was to review the Texas Implementation Medication Algorithms (TIMA) for patients with bipolar I disorder (BDI) and to update the algorithm with new evidence-based recommendations.<sup>[1]</sup> The panel that presented the conference consisted of national experts in the treatment of bipolar disorder, pharmacists, representatives from the state system, and consumers. Treatment options were reviewed for hypomania/mania, mixed symptoms, depression, and maintenance treatments, and were evaluated on the basis of an assessment of efficacy, safety issues, and adverse effects in the treatment of BDI. When possible, evaluations were based on evidence from well-controlled studies, and each study was judged on its own merits.

### **Guiding Principles of The Texas Implementation of Medication Algorithms (TIMA)**

Algorithms were developed after examining the quality and quantity of efficacy data, expert opinion, consumer input, and safety and tolerability issues. Certain treatment options were placed lower in the algorithm due to concerns about safety and tolerability, despite strong efficacy evidence,

These algorithms were intended to provide systematic guidance on possible treatment options for BDI. Medication guidelines should be used to help the clinician and patient develop the most effective medication strategy with the fewest side effects, and are not meant to be rigid or choice-limiting. Although it is recommended that the algorithms be followed as linearly as possible, these guidelines are meant to provide flexibility at each stage of choosing treatments for each patient. The main goals of the algorithms are symptomatic remission, full return of psychosocial functioning, and prevention of relapse and recurrence.

### **General Principles<sup>[1]</sup>**

- Medication decisions should not be based only on efficacy and tolerability, but also on patient history and preference.
- If a choice of formulations exists, treatment should be started with an agent that offers the best tolerability profile.
- If possible, clinicians with their patients should develop a treatment plan that includes the patient's significant others (including family and spouse) at the initiation of treatment and throughout the course of treatment.
- Psychoeducation or cognitive therapy focused on bipolar disorder, treatment, and relapse is encouraged.<sup>[2-4]</sup>

- Patients should be seen at least every 2 weeks during initiation of acute treatment to assess treatment outcomes, and healthcare practitioners should encourage patient adherence by making medication adjustments and correcting tolerability issues in a timely manner.
- Patients who achieve symptom remission and a satisfactory clinical response after acute treatment should continue to receive treatment with the same regimen, with dose changes made as necessary for tolerability.
- When discontinuing medications, eliminate treatments with the greatest side-effect burden first, and taper medications gradually unless it is medically necessary to stop abruptly. Use an overlap and taper strategy when adding new medications.

Other general treatment principles are discussed in detail in the current update to the algorithms.<sup>[1]</sup>

Limited data are available for the treatment of comorbid conditions. Patients with BDI often experience comorbid psychiatric disorders, such as substance abuse or substance dependence and anxiety disorders. The TIMA guidelines recommend appropriate concurrent or additional treatment as needed once the patient is stabilized using the algorithms. Clinicians should follow the general treatment guidelines outlined in the TIMA update when treating comorbid psychiatric disorders.

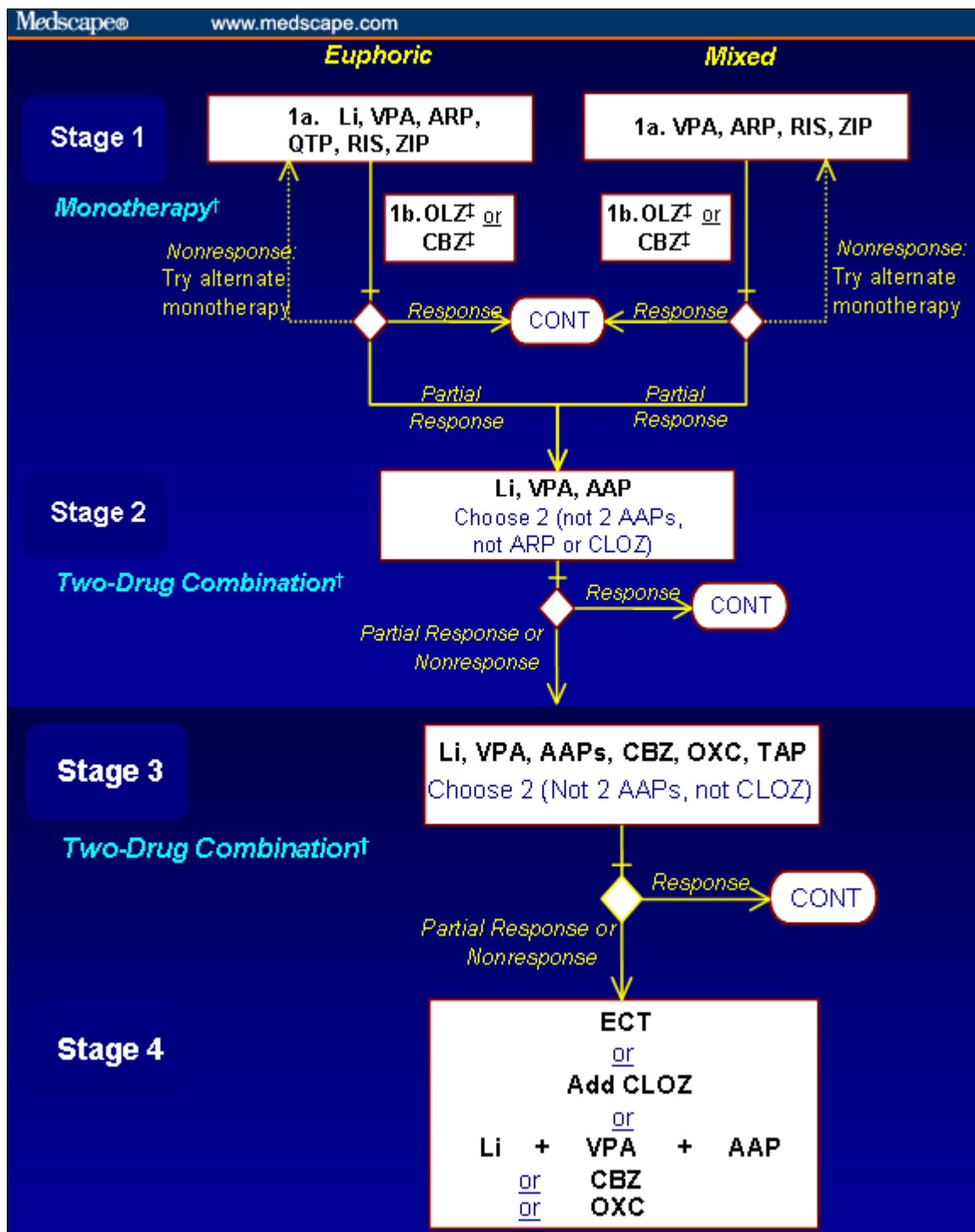
### **Treatment Algorithms for BDI**

The panel has developed stand-alone medication algorithms for the acute treatment of BDI, one for patients who are primarily hypomanic/manic or mixed, and one for patients who are primarily depressed. For the first time, the panel also developed recommendations for maintenance treatment.

The panel agreed that all patients with BDI should receive continuous treatment with an antimanic agent, defined as any medication approved by the Food and Drug Administration (FDA) specifically for the treatment of mania or medication with proven efficacy in the treatment of mania. In the past few years, many new atypical antipsychotic medications have been studied for treatment of mania. Because these agents figure prominently in the new algorithms, and because of the potential health implications of long-term exposure, the panel recommends that the American Diabetes Association guideline for the use of atypical antipsychotics<sup>[5]</sup> or the Mount Sinai Conference Monitoring Guideline for patients with schizophrenia receiving antipsychotic medications<sup>[6]</sup> be used to monitor patients taking atypical antipsychotics. Also, severely ill patients should be seen more frequently than those who are less ill. Finally, a single week of improvement may not indicate a stable response, and patients should be monitored for at least 2 weeks following an acute response to ensure stability before moving to continuation phase. Once patients reach continuation phase, patients should be seen at least monthly for the first 3 months of continuation treatment, with follow-up visits every 2 to 3 months during maintenance treatment (following 4 to 6 months of stability).

### **Algorithm for Treatment of Acute Episodes of Hypomania/Mania or Mixed Episodes in Bipolar I Disorder**

This algorithm has 2 possible entry points, 1 for patients with hypomania/mania and 1 for patients with mixed symptoms (Figure 1).



**Figure 1.**

Algorithm for treatment of bipolar I disorder - currently hypomanic/manic.\*

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\*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.

†Use targeted adjunctive treatment as necessary before moving to next stage: Agitation/Aggression - clonidine, sedatives; Insomnia - hypnotics; Anxiety - benzodiazepines, gabapentin.

‡Safety and other concerns led to placement of OLZ and CBZ as alternate first-stage choices.

*AAP = atypical antipsychotic; ARP = aripiprazole; BUP = bupropion; CBZ = carbamazepine; CLOZ = clozapine; CONT = continuation; ECT = electroconvulsive therapy; Li = lithium; LTG = lamotrigine; OFC = olanzapine-fluoxetine combination; OLZ = olanzapine; OXC = oxcarbazepine; QTP = quetiapine; RIS = risperidone; TAP = typical antipsychotic; VEN = venlafaxine; VPA = valproate; ZIP = ziprasidone*

**Stage 1A. Monotherapy.** For hypomanic/manic patients, lithium,<sup>[1]</sup> valproate,<sup>[7,8]</sup> aripiprazole,<sup>[9,10]</sup> quetiapine,<sup>[11,12]</sup> risperidone,<sup>[13-15]</sup> or ziprasidone<sup>[16,17]</sup> are recommended as first-choice treatments. For patients experiencing mixed episodes, valproate, aripiprazole, risperidone, or ziprasidone are recommended as agents with the strongest evidence of efficacy in the treatment of mixed symptoms.

**Stage 1B. Monotherapy alternates.** Due to safety and tolerability concerns, the panel placed olanzapine and carbamazepine at Stage 1B. The efficacy data for these medications support their placement as Stage 1 treatment options (see Suppes et al, 2002)<sup>[18-20]</sup>; however, concerns about health risks, including obesity and other metabolic issues (olanzapine),<sup>[5,21,22]</sup> and complexity of dosing and drug interactions (carbamazepine) led the panel to place olanzapine and carbamazepine at a substage of Stage 1.

Targeted adjunctive treatment, such as hypnotic agents for insomnia or benzodiazepines for anxiety, should be used as necessary before moving between stages on the algorithm. If the patient does not tolerate the first Stage 1 option, it is recommended that the clinician switch to another Stage 1 option rather than proceed to Stage 2. When changing medications, it is recommended that an overlap and taper method be used unless it is medically necessary to stop the medication abruptly. If a patient is tolerating a medication but has not achieved full symptom remission or continues to have residual symptoms, the panel recommends combination therapy (Stage 2).

**Stage 2. Two-drug combinations.** Combination therapy is commonly used in the treatment of BDI and is the recommended starting stage for more severely ill patients (eg, inpatients). The panel recommends choosing a combination from lithium, valproate, and the atypical antipsychotics (not aripiprazole or clozapine<sup>[23-26]</sup> and not a combination of 2 atypical antipsychotics). Lithium or valproate in combination with each other or with an atypical antipsychotic is recommended. At this stage, aripiprazole in combination is not included due to lack of data, and clozapine in combination is also not included due to concerns about medical monitoring efforts and side effects. Within this stage, clinicians are encouraged to try more than one combination if the first medication combination is not effective or well tolerated.

**Stage 3. Two-drug combinations.** Stage 3 includes Stage 2 options as well as carbamazepine,<sup>[1]</sup> oxcarbazepine,<sup>[27-30]</sup> and typical antipsychotics. Clinicians should pair atypical antipsychotics with anticonvulsants or lithium. Although strong evidence supports the efficacy of the typical antipsychotics in the treatment of BDI, concerns about potentially serious neurologic side effects and the long-term risk of tardive dyskinesia led to their placement at Stage 3.<sup>[31]</sup> Clozapine is excluded from Stage 3 because of safety and tolerability concerns.

**Stage 4. Last stage.** Stage 4 recommendations are based on less well-controlled trials or effective treatments with safety, tolerability, or patient acceptability issues. Options at this stage consist of electroconvulsive therapy (ECT), medication combinations including clozapine add-on therapy, and 3-drug combinations. Three-drug combinations are recommended using the following formula: lithium + (valproate or carbamazepine or oxcarbazepine) + atypical antipsychotic. The use of multiple atypical antipsychotics is not suggested; instead, a combination of lithium with an anticonvulsant and an atypical antipsychotic is recommended. Clozapine should be considered for more treatment-resistant patients or those whose course is marked by mania or mood lability and who have been nonresponsive or only partially responsive to other medication options.

## Algorithm for Treatment of Acute Depressive Episodes in Bipolar I Disorder

Unlike the last version of the algorithms, this revision includes a stand-alone treatment algorithm for BDI depression (Figure 2). Research into this treatment area is still at its early stages, and the stages in this algorithm are based on fewer well-controlled studies, with a relatively greater weight of expert consensus used in the decision-making process. Another change from the previous version is the placement of antidepressants at Stage 4 instead of Stage 1. Although consensus was reached on the placement of these medications, a minority opinion was expressed that Stage 4 treatments should precede those in Stages 2 and 3.

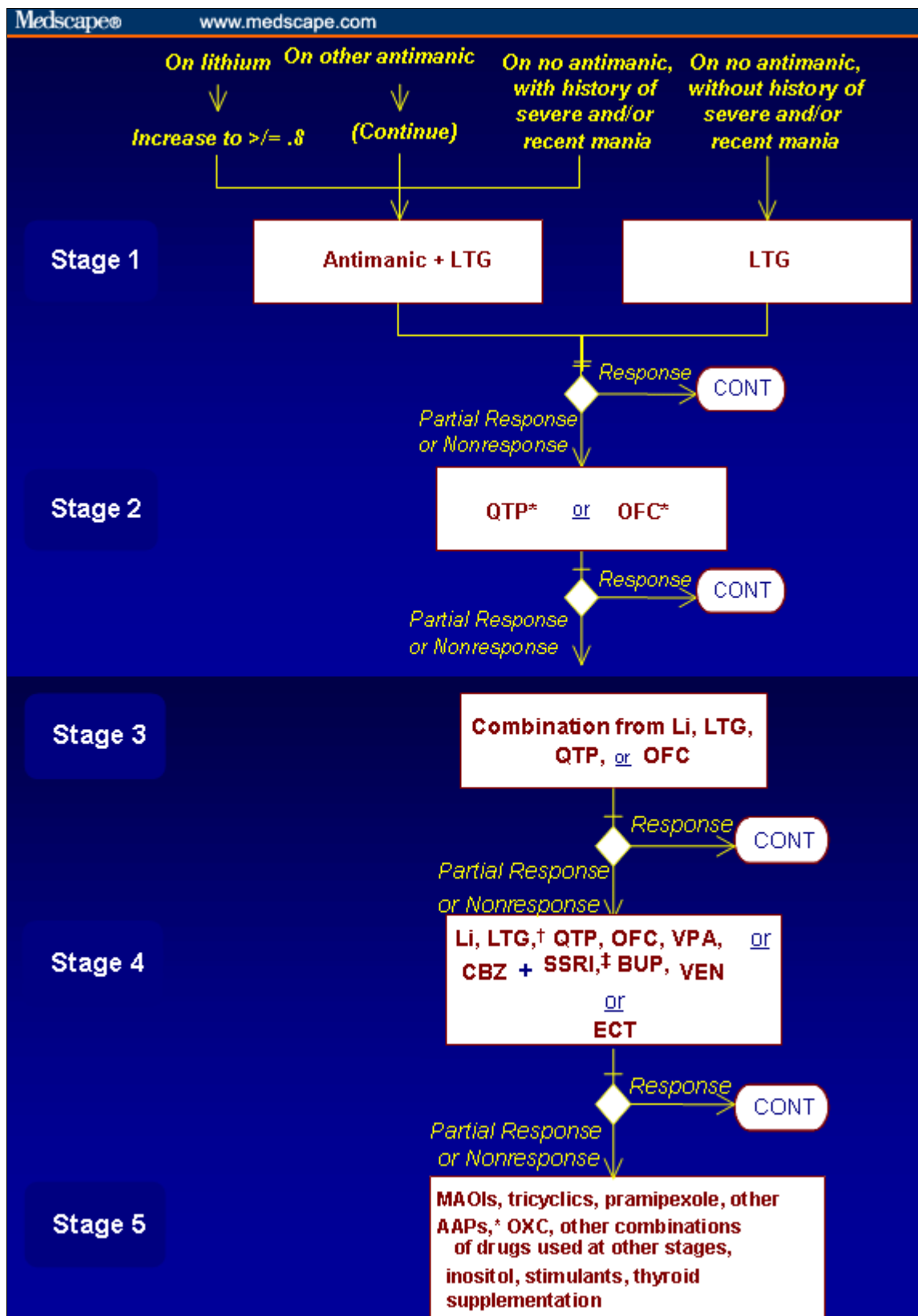


Figure 2.

Algorithm for the treatment of BDI - currently depressed.\*

From Suppes T, et al. *J Clin Psychiatry*. 2005;66:870-886.<sup>[1]</sup> Copyright 2005, Physicians Postgraduate

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\*Note safety issue described in text.

†LTG has limited antimanic efficacy and, in combination with an antidepressant, may require the addition of an antimanic.

‡SSRIs include citalopram, escitalopram, fluoxetine, paroxetine, sertraline, and fluvoxamine.

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

**Stage 1.** For patients currently taking lithium but still experiencing depressive symptoms, it is recommended that lithium serum levels be optimized to 0.8 mEq/L, if tolerated, before entry into the algorithm. These levels may be adequate to treat the depression in some patients.<sup>[32]</sup> Patients who are not receiving an antimanic but have a history of severe or recent mania should start on an antimanic agent. Patients who are currently receiving another antimanic agent should continue on it. Once antimanic treatment is optimized, the panel recommends adding lamotrigine. Lamotrigine monotherapy is recommended only for patients with no history of severe or recent manic symptoms. Evidence from both adjunctive-treatment trials and placebo-controlled trials supports the use of lamotrigine in the treatment of bipolar depression.<sup>[33,34]</sup> Safety and tolerability are good when the drug is administered at recommended titration rates, but initiating lamotrigine at a higher dose or titrating more rapidly is not recommended, as this increases the risk of serious rash.

**Stage 2.** Options at this stage include quetiapine or an olanzapine-fluoxetine combination (OFC). OFC is the only treatment with an FDA indication for the acute treatment of BDI-associated depression.<sup>[35]</sup> Quetiapine was recommended at this stage based on one large, well-powered, randomized, placebo-controlled trial.<sup>[36]</sup> Since the publication of the TIMA guidelines, a replication study for quetiapine has been completed, with strong results supporting its antidepressant properties.<sup>[37]</sup>

**Stage 3.** The same combination of medications recommended in Stages 1 and 2 are recommended in Stage 3. It should be noted that the olanzapine-fluoxetine combination is a 2-drug combination, and adding another medication creates a 3-drug combination.

**Stage 4.** The panel recommends lithium, lamotrigine, OFC, valproate, or carbamazepine in combination with a selective serotonin reuptake inhibitor, bupropion, or venlafaxine, or ECT. Recommendations at this stage are based primarily on limited controlled data and expert consensus. ECT is an effective treatment, but safety, tolerability, and patient acceptance issues led to its placement at a lower stage.

**Stage 5.** Treatment options at this stage have either limited empirical evidence or safety and tolerability concerns. Options at this stage are monoamine oxidase inhibitors, tricyclic antidepressants, atypical antipsychotics not previously included, pramipexole, inositol, stimulants, and thyroid supplementation. Other options include new combinations of drugs previously mentioned in the algorithm.

## Guidelines for Maintenance Treatment

Due to limited well-controlled data for maintenance treatments, medications are ordered hierarchically by quality and quantity of evidence ( [Table 1](#) ). Since controlled trials often use monotherapy while the majority of naturalistic treatment likely includes combination therapy, understanding of maintenance is still limited for evidence-based decisions. The term "level" is used to reflect the overall limited data available to inform maintenance treatment choices and the necessarily heavier weight given to expert consensus in ranking treatment options. The ordering of levels was designed to reflect Level I as having the most data, followed by Level II and so on.

Well-tolerated and effective acute-phase treatments are acceptable and reasonable options for maintenance treatment. Although many patients stabilize on medications when acutely ill, it is common to adjust medications at later times, either due to tolerability issues, subsyndromal symptoms, or both. Recommendations for maintenance treatment address medication adjustments during ongoing vs acute treatment.

## Maintenance Treatment Guidelines: Most Recent Episode Hypomanic/Manic or Mixed

At Level I, lithium or valproate is recommended for patients with or without frequent, recent, or severe mania,<sup>[38-42]</sup> and lamotrigine is recommended for patients without frequent, recent, or severe mania (see Figure 3).<sup>[38,41]</sup> Olanzapine is recommended as an alternative treatment.<sup>[38]</sup> For Level II, aripiprazole is recommended on the basis of the results of one randomized, double-blind, placebo-controlled, 6-month maintenance study.<sup>[43]</sup> Level III recommendations are carbamazepine or clozapine. At Level IV, the other atypical antipsychotics not previously included are recommended (quetiapine, risperidone, or ziprasidone), and Level V includes typical antipsychotics, oxcarbazepine, and ECT.

### Maintenance Treatment Guidelines: Most Recent Episode Depressed

Similar to the recommendation set forth in the acute treatment algorithm, due to the risk of mania induction and cycle acceleration, antidepressant monotherapy is not recommended for maintenance treatment in BDI. The Level I recommendation for patients with a recent or severe history of mania is lamotrigine in combination with an antimanic agent ( [Table 2](#) ). For all other patients, lamotrigine monotherapy is recommended at Level I.<sup>[44,45]</sup> In a recent study, investigators found that lithium and lamotrigine were both more effective than placebo in prolonging relapse; however, lithium was more effective against mania, and lamotrigine more effective against depression.<sup>[41]</sup> Because of these results, lamotrigine is placed before lithium for patients most recently depressed. Lithium is recommended as Level II treatment on the basis of results of multiple studies supporting its long-term efficacy.<sup>[31,38,41,42,44]</sup> At Level III, the recommendation is for an antimanic agent and antidepressant combination that has been effective for the patient in the past. Level IV options are valproate, carbamazepine, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone. Level V includes typical antipsychotics, oxcarbazepine, and ECT.

### Conclusions

The goals of this TIMA update were to affirm the general principles of treatment and to incorporate newer evidence into the medication recommendations for BDI. Unlike the previous version of this algorithm, the current algorithm recommends use of atypical antipsychotics for nearly every stage of BDI. This recommendation is tempered by awareness of the lack of knowledge regarding long-term effects of the use of atypical antipsychotics and by the recommendation that monitoring guidelines be followed. The current algorithm also places antidepressants at a lower stage than the previous versions did. Finally, this version of the algorithm provides stand-alone recommendations for both acute hypomanic/manic/mixed and acute depressed episodes, as well as separate maintenance recommendations for the different episodes. As new studies are completed, algorithms will continue to change and provide a mechanism for ready communication.

**Table 1. Maintenance Treatment: Most Recent Episode Hypomanic/Manic/Mixed**

Levels	Treatment Options
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*
Level II	Aripiprazole <sup>†</sup>
Level III	Carbamazepine or clozapine*
Level IV	Quetiapine, <sup>†</sup> risperidone, <sup>†</sup> or ziprasidone <sup>†</sup>
Level V	Typical antipsychotics,* oxcarbazepine, <sup>†</sup> ECT

\*Safety issues warrant careful consideration of this option for potential long-term use.

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

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**Table 2. Maintenance Treatment: Most Recent Episode Depression**

Levels	Treatment Options
Level I	Patients with recent and/or severe history of mania: Lamotrigine combined with an 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*
Level IV	Valproate, carbamazepine, aripiprazole, <sup>†</sup> clozapine,* olanzapine,* quetiapine, <sup>†</sup> risperidone, <sup>†</sup> ziprasidone <sup>†</sup>
Level V	Typical antipsychotics,* oxcarbazepine, <sup>†</sup> ECT

\*Safety issues warrant careful consideration of this option for potential long-term use.

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

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