The Psychopharmacology Algorithm Project at the Harvard South Shore Program: An Update on Bipolar Depression

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This updated version of the bipolar depression algorithm of the Psychopharmacology Algorithm Project at the Harvard South Shore Program aims to provide an organized, sequential, and evidence-supported approach for the treatment of that disorder. After initial evaluation and diagnosis, the psychiatrist should first assess whether there is an urgent indication for ECT. If ECT is not indicated, and the patient has psychotic symptoms, then an antipsychotic should be part of the medication regimen. Next, if the patient is not currently treated with mood stabilizers, there is a slight preference for lithium. If lithium is not effective or tolerated, treatment with quetiapine or lamotrigine should be initiated. If the patient is currently taking other mood stabilizers, their dosage should be optimized, and the clinician should consider adding or switching to lithium, quetiapine, or lamotrigine. Next, if the patient is not at especially high risk of mood destabilization, an antidepressant can be added in the bipolar depressed patient who has failed trials of lithium, quetiapine, and lamotrigine. Rapid-cycling depressed patients may require combinations of two or three mood stabilizers. ECT, along with other psychopharmacological options, could be reconsidered for the treatment of refractory bipolar depressed patients. (HARV REV PSYCHIATRY 2010;18:36–55.)

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Bipolar depression is distinct from unipolar depression. It is the predominant mood state for patients with bipolar disorder and is associated with significant morbidity and mortality. Although the diagnostic criteria for bipolar and unipolar major depressive episodes are identical in the current Diagnostic and Statistical Manual of Mental Disorders, the episodes differ in terms of their biological correlates, suicide risks, neuropsychological aspects, natural history, rapidity of onset, and response to pharmacotherapeutic agents. The situation is further complicated by differences between bipolar I and bipolar II disorders, as well as by the possible presence or absence of rapid cycling among patients with bipolar depression—further influencing prognosis and treatment.

Bipolar depression continues to present a treatment challenge for the prescribing physician. Algorithms can be helpful in guiding the clinician in considering and selecting appropriate, evidence-supported pharmacotherapeutic treatment. This article provides an update of previous algorithms developed by the Psychopharmacology Algorithm Project at the Harvard South Shore Program (PAPHSS). An updated algorithm for the treatment of psychotic depression has recently been published.

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PAPHSS is an Internet-based, interactive system (http://www.mhc.com/Algorithms/) developed to provide clinical consultation incorporating evidence-derived recommendations. The depression algorithms began with published precursors in 1988 and 1993, leading to the initial online version of the Algorithm for the Pharmacotherapy of Depression in 1996, which included algorithms for the treatment of major subtypes of depression. Since then, these algorithms, including those developed for the pharmacotherapy of schizophrenia and anxiety disorders, have been widely circulated and periodically updated.

CONSTRUCTING THE ALGORITHM

The PAPHSS algorithms are designed to approximate the cognitive process employed by a psychopharmacology consultant who is asked what should be done next to help a patient who is not responding to current treatment. Each step in the algorithm contains a question whose aim is to allow the consultant to efficiently further characterize the clinical situation and past treatment history of the patient. The answers to the questions lead either to additional questions or to a treatment recommendation derived from the evidence base or peer-reviewed expert opinion.

In formulating recommendations, the consultant considers the quality and quantity of evidence for efficacy, tolerability, and short- and long-term safety of the different treatment options. Long-term safety and tolerability are strong priorities because bipolar disorder is a chronic illness, and the treatment selected is likely to be continued over a very long period.

After review of the initial PAPHSS algorithm for bipolar depression (published in 1999) and associated references, a new PubMed search was conducted to find all relevant studies published since 1999. Keywords pertaining to all available psychopharmacological agents were entered to obtain a large list of references. A Boolean (AND) search was then done to combine this list with the keywords “bipolar depression.” All resultant studies in English were selected. Other relevant studies or reviews referenced in those articles were also examined. The algorithm was then updated based on that material.

HOW TO USE THE ALGORITHM

In a patient who presents with depression, the clinician initially conducts an assessment and makes a criteria-based DSM-IV diagnosis, noting comorbidities on Axes I and II. During this process the clinician screens for any medical or neurological contributors to the depression. If organic conditions are present, they are identified and treated. For example, thyroid dysfunction and other endocrine abnormalities should be addressed. Pregnant patients will have special needs, and active substance abuse can also influence treatment. The latter should be treated—and sufficient time allowed, if possible, for elimination of the problematic substances—prior to making a final diagnosis of bipolar depression and initiating pharmacological treatment. Anxiety and eating disorders should also be identified, as these may affect medication choices.

One important issue of diagnostic relevance concerns the subset of depressed patients who have not yet been diagnosed with bipolar disorder. By definition, patients diagnosed with bipolar depression meet criteria for a major depressive episode and have a history of manic or hypomanic episodes. Some “unipolar” depressed patients, however, may have two or more hypomanic or manic symptoms and may have a mixed state and belong in the bipolar spectrum.

Also, younger patients, some of whom may go on to exhibit future manic or hypomanic symptoms, may present with a depressive episode and be diagnosed with unipolar depression. It is important to attempt to diagnose these patients appropriately. A “pre-bipolar” presentation should be suspected in patients with (1) a family history of bipolar disorder, (2) a younger age of onset, (3) a family history of completed suicide, (4) past poor response to antidepressants, (5) a history of treatment-emergent agitation, irritability, or suicidality, or (6) current or past postpartum psychosis. The presence of a high number of these factors may indicate that the patient may be more appropriately treated as having bipolar, rather than unipolar, depression. Pediatricians and primary care physicians, in particular, should be careful not to miss the diagnosis of bipolar depression and to start these patients on antidepressants—which may possibly destabilize mood and worsen the course of the disorder.

Once the diagnosis of bipolar depression is made or strongly suspected, the algorithm can be used to guide psychopharmacological treatment. If the patient responds to the proposed treatment at a particular node in the algorithm, then that treatment can be continued, with no need to move to the next node of the algorithm. A treatment should not be considered to have failed unless it has had an adequate trial. Dosage issues will be discussed, based on available evidence, at the relevant points in the algorithm. In general, the recommended medication should be continued at an appropriate dose for at least four weeks. Patients should be reassessed at least weekly during the acute phase. Clinicians should consider using an objective rating scale to measure improvement; the Montgomery-Åsberg Depression Rating Scale (MADRS) may be the most sensitive.

If the recommended treatment fails to adequately treat the patient’s depression, then there should be another review of the diagnosis as discussed above before continuing with the algorithm. It should be kept in mind, however, that many
treatments for bipolar depression discussed in this algorithm have small effect sizes in many studies; hence the lack of response may be related to the failure of the chosen treatment rather than to misdiagnosis.

At all nodes there will be one or more preferred treatment recommendations and some other options; their relative merits will be discussed. Sometimes there will be minimal differences separating preferred and less preferred choices. There is no expectation that the user should always follow the preferred recommendation. If—after considering the treatment options proposed, including their evidence base, risks, and benefits—one of the less preferred options (or even a not-discussed option) seems more suitable for the individual patient, then that treatment should be pursued. At any node, however, if the clinician employs an option other than one of the preferred recommendations, and if the patient remains depressed, the clinician should not continue on to the next node of the algorithm. Instead, the clinician should start a new consultation at the beginning and find the node (and recommendations) appropriate to the new situation of the patient.

The flowchart for the current algorithm for treating acute bipolar depression is presented in Figure 1. At each clinical decision point, the clinician should consult the accompanying text to review the evidence in support of the recommendations. The flowchart should not be used as the sole basis for determining the algorithm’s recommendations.

Although this algorithm focuses on pharmacotherapy, the role of nonpharmacological treatments of bipolar depressed patients should not be overlooked. Best practice includes the use of psychotherapeutic, psychosocial, and family interventions. Current evidence suggests that clear benefits can be derived from these treatments. If there is inadequate response to pharmacological treatments at any step of the algorithm, nonpharmacological interventions should be reevaluated—and if possible, enhanced—while other medications are being considered. Psychotherapy is often a slow process: in the study by Miklowitz and colleagues of an intensive psychosocial intervention for bipolar disorder, it took a mean of 169 days to reach an effective result.

INITIAL EVALUATION

Node 1: Is Electroconvulsive Therapy Urgently Indicated?

An initial decision needs to be made as to whether ECT is urgently needed. ECT is a highly effective treatment for bipolar depression, with a 65%–80% response rate. For many patients, ECT may be considered as first-line treatment.

ECT is urgently indicated in patients with severe suicidality, catatonia, insufficient oral intake, and medical conditions (e.g., pregnancy) that may limit the use of psychotropics. Many such patients also require other treatment interventions such as hospitalization, close monitoring for safety, and the provision of adequate medical care. When rapid response is essential, ECT is the treatment of choice. Bipolar depressed patients may show response to ECT more rapidly than those with unipolar depression—a response that does not appear to be secondary to hypomanic induction.

In patients with a history of medication-refractory bipolar depression, response rates may be closer to 50%. Nevertheless, despite this lower response rate, ECT may still be viewed as a treatment of “first resort” in these patients because of the morbidity and mortality associated with prolonging the course of illness through the pursuit of medication options that will likely not be effective. Interestingly, patients with the longest duration of depressive episodes may be the most likely to respond to ECT.

Node 2: Are Psychotic Symptoms Present?

In patients with bipolar depression with psychotic features, and for whom ECT is not urgently indicated or is intolerable, refused, or unavailable, the inclusion of an antipsychotic in the regimen is presumed to be necessary. Unfortunately, no studies have used antipsychotics to specifically target psychotic symptoms in the bipolar depressed patient. In unipolar psychotic depression, most evidence supports the need for an antipsychotic in combination with an antidepressant. It cannot be assumed, however, that the treatment of bipolar psychotic depression should be the same as unipolar psychotic depression; for example, it may be that the use of an antidepressant is less desirable, as will be discussed below.

Given that patients with mood disorders have a high vulnerability to tardive dyskinesia, first-generation antipsychotics (FGAs) should be avoided; the use of second-generation antipsychotics (SGAs) is recommended instead. Another reason for limiting the use of FGAs is the concern—although the data are mixed—that continued use of an FGA in bipolar patients may predispose to depression.

Emerging data and current practice support the increased use of particular SGAs in patients with bipolar disorder. It may be reasonable to prefer quetiapine (see discussion below) because the evidence that it improves primary depressive symptoms in acute bipolar depression is the strongest, but other SGAs could be considered here since the algorithm’s focus at this node is to target psychotic symptoms. There are no comparative efficacy data, however, to...
**Diagnosis of Bipolar Depression**

- **Urgent indication for ECT present?**
  - **No**
  - **Yes**
    - **(1) ECT recommended. If refused or unsuccessful go to the next question**

- **Is the patient psychotic?**
  - **No**
  - **Yes**
    - **(2) Include antipsychotic in regimen**

**Current medications?**

- **(4) Lithium (+/- others)**
- **(5) Valproate, carbamazepine, lamotrigine, etc.**
- **(3) No mood stabilizers**
- **(6) Quetiapine**
- **(7) Olanzapine, OFC, or antidepressant**

- **Lithium level >0.8 mEq/L?**
  - **No**
  - **Yes (or intolerable)**
    - **Adjust level to >0.8 mEq/L**
    - **(8) Try quetiapine or lamotrigine**

- **Has the patient had an adequate trial of lithium?**
  - **No**
  - **Yes**
    - **Start/add lithium**
    - **(9) Try quetiapine or lamotrigine (whichever has not yet been tried)**

- **Has there been a trial of quetiapine or lamotrigine?**
  - **No**
  - **Yes**

- **Does patient have a history of rapid-cycling?**
  - **No**
  - **Yes**
    - **Avoid antidepressants**

- **Is patient at high risk of manic/hypomanic switch?**
  - **No**
  - **Yes**
    - **Has patient had trials of antidepressants?**
      - **No**
      - **Yes**
        - **Avoid antidepressants**

**Tried combinations of mood stabilizers?**

- **No**
- **(10) Make sure patient is on adequate dose of mood stabilizer first, then try bupropion (2nd choice SSRI’s). Low dose, go slow strategy, and increase patient contact.**
- **Yes**
  - **(11) Try mood stabilizer combinations, and combinations with quetiapine**
  - **(12) ECT or other strategies for refractory bipolar depression**

**FIGURE 1.** Flowchart of the algorithm for bipolar depression. ECT, Electroconvulsive therapy; OFC, olanzapine-fluoxetine combination; SSRI, selective serotonin reuptake inhibitor.
guide the clinician in this choice. In any event, given the high risk of adverse metabolic effects with olanzapine, we do not recommend it as a first-line treatment for bipolar depression with psychotic symptoms.

TREATMENT WITH MOOD STABILIZERS AND QUETIAPINE

After the initial evaluation to assess whether to begin treatment with ECT or whether to add an antipsychotic, the algorithm has five possible branches (Nodes 3–7), depending upon the patient’s current medication regimen.

Node 3: Is the Patient Currently Not on a Mood Stabilizer?

What is a mood stabilizer? There is no consensus definition accepted among researchers and clinicians. The most inclusive definition is that a mood stabilizer decreases symptoms acutely in any single phase of bipolar disorder while not inducing or worsening other phases. More conservatively, however, Bauer and Mitchner41 proposed a “two-by-two” definition: a mood stabilizer is an agent that has efficacy in treating and preventing both manic and depressive episodes. In reviewing 101 studies, they concluded (in 2004) that only lithium qualified by this definition. Since then, increasing evidence has suggested that quetiapine may soon meet the two-by-two criteria. Other medications with aspirations to the “mood stabilizer” label, such as several anticonvulsants, remain short of qualifying.

The ideal choice for treating a patient with acute bipolar depression who is not currently on a mood stabilizer would be a medication that is effective for this phase of the disorder and that can prevent future episodes of any phase. Lithium and quetiapine therefore appear to be the leading choices, with a slight preference for lithium. We will discuss the reasons for supporting lithium and quetiapine at this node and also consider other treatments supported by significant evidence—namely, lamotrigine and the olanzapine/fluoxetine combination. Finally, we will briefly note the options of valproate, carbamazepine, and oxcarbazepine (which are not favored here).

Lithium. Lithium has demonstrated positive, though modest, efficacy in various studies.25,42,43 The benefits of lithium treatment appear to exist for patients across the life span.44,45 Recent community surveys suggest that lithium monotherapy is more likely to be maintained over time than other medication regimens used in bipolar disorder.46 Furthermore, large reviews of lithium treatment have consistently shown lithium to have a significant antisuicidal effect and to decrease long-term mortality.17,48 Other investigators have shown that lithium's antisuicidal effect appears to be distinct from its mood-stabilizing effects.49 Notably, the Systemic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study did not find lithium to have an antisuicidal effect as measured by “suicide events”—suicide attempts plus a small number of completed suicides50—though it must be noted that the sample had a low risk of suicidal tendencies. Some studies suggest that lithium has significant and unique neuroprotective effects in bipolar disorder.51–53

One area of concern with the use of lithium is the possibility that abrupt lithium discontinuation may worsen the natural course of bipolar disorder, leading to increased manic and depressive relapses.54 In a group of patients who were stable for years, 50% relapsed within 8 months after abrupt lithium discontinuation, versus within 37 months with gradual discontinuation.55 Consequently, if lithium treatment is initiated, it should be done with the expectation that it would be continued as a long-term maintenance agent and that it would be tapered off gradually if and when it needed to be discontinued.56,57 Initial and ongoing discussions with the patient about this issue are important.

When lithium is used for acute bipolar depression, a target serum lithium level of >0.8 mEq/L is proposed. Lithium was less effective as a monotherapy in one controlled study when the level was ≤0.8 mEq/L.58 A recent review59 and a new study60 concluded, however, that depressive recurrences are more likely (64% vs. 12%)61 if patients are maintained at high lithium levels rather than levels below 0.6 mEq/L. Although lower lithium levels were thus associated with better prophylaxis against depression, switches to mania were more common at those levels.60 Based on this latest analysis, we propose a target maintenance level of 0.6–0.75 mEq/L. In view of the potentially greater risk for mania at that level, some patients may need to be maintained either at the higher lithium level or at a lower level with another antimanic agent added.

Lithium, of course, has many side effects, both common and infrequent, that contribute to its avoidance by many clinicians and refusal by some patients. Training, clinical experience, and the availability of useful references on the shelf, such as the Lithium Encyclopedia for Clinical Practice,62 can help with overcoming these difficulties.

Quetiapine. One of only two Food and Drug Administration (FDA)-approved agents for acute bipolar depression, quetiapine may also be considered for initial treatment of acute bipolar depression in the patient not currently on a mood stabilizer. The first large (n = 511), eight-week, placebo-controlled, industry-supported study of quetiapine for bipolar depression (BOLDER I, by the BipOLar DEpRes-sion study group) showed clear separation from placebo in one week for patients being treated with either 300 mg or 600 mg of quetiapine per day.63 Significant response
(≥50% improvement in MADRS scores) at both doses was noted in 58% of quetiapine patients, compared to 36% of patients taking placebo. Significant effects were also noted in Hamilton Depression (HAM-D) and Anxiety (HAM-A) scores. Improvements were noted in core depressive symptoms and (as expected) in sleep and appetite symptoms. The authors noted that clinical effects were greater in patients with bipolar I versus bipolar II depression. A significant response was also noted in a subgroup of patients with rapid cycling.

A second, similar study (BOLDER II) replicated these findings (although with a relatively lower magnitude of response, attributable to a higher response in the placebo group). A better response was noted in bipolar II patients in this second study. Of note, however, in terms of depressive symptoms as measured by MADRS scores, impressive improvements were noted primarily in sleep and appetite scores, with much less robust improvements in primary depressive symptoms such as apparent sadness, pessimistic thoughts, and suicidal thoughts. Subsequent analyses of data from the above studies (BOLDER I & II) found improvements in quality-of-life measures and in anxiety in quetiapine-treated patients compared to placebo.

More recently, placebo-controlled studies comparing quetiapine versus paroxetine (20 mg/day) and quetiapine versus lithium (at a mean level of 0.6 mEq/L) found greater response with quetiapine than with placebo and somewhat better response with quetiapine than with the active comparators. A placebo-controlled, two-year maintenance study in bipolar patients initially stabilized on quetiapine and then randomized to either lithium or quetiapine monotherapy found good results with quetiapine. As of this writing, however, the two lithium comparison studies are available in posters only, so the full details have yet to be published.

With these positive findings regarding the effectiveness of quetiapine for acute bipolar depression, and with FDA approval for this indication, why would it not be the first-line treatment—on a par with, or even exceeding, lithium in that role? Indeed, in the comparison of quetiapine and lithium, quetiapine was statistically superior to placebo, whereas lithium was only numerically and nonsignificantly efficacious when compared to placebo. At this point, the answer is that despite the possibility that quetiapine may come to equal or replace lithium as the first-line treatment for bipolar depression, it seems premature to make that call right now. The one monotherapy-maintenance study is still unpublished; the weight gain, metabolic side effects, and sedation of quetiapine are significant liabilities that need to be taken into account; and the risks may actually have been underestimated. Recent news reports indicate that some unpublished quetiapine trials in the 1990s found high rates of clinically significant weight gain. Sudden cardiac death is another recently appreciated risk (probably associated with all antipsychotics in a dose-related manner) that requires consideration. The risk is approximately doubled and was found to be independent of weight gain and psychiatric diagnosis, including bipolar disorder. Quetiapine also has not been demonstrated to have some of the other benefits of lithium, such as suicide prevention and neuroprotective effects. On the other side of the equation, however—as noted earlier—lithium has its own significant side effects, including weight gain, hypothyroidism, diabetes insipidus syndrome, and (very rarely) renal failure. Taking all of the above information into account, we slightly favor initial treatment with lithium rather than quetiapine. Because of the chronic and episodic nature of bipolar disorder, whatever is used for acute treatment should also have the ability to decrease the risk of further episodes and to reduce long-term functional impairments. These considerations should play a central role in decisions regarding the choice of treatment, and the weight of evidence and decades of clinical experience in these aspects still lean in the direction of lithium.

Lamotrigine. Lamotrigine monotherapy has emerged as a possible alternative to lithium and quetiapine in treating acute bipolar depression in patients not currently on mood stabilizers. The evidence, however, appears to be mixed. On the positive side, a double-blind, placebo-controlled study of lamotrigine (50 mg/day, 200 mg/day, or placebo) in bipolar I depression (n = 195) found favorable results. At 50 mg there was some improvement on the MADRS, the Clinical Global Impressions—Severity (CGI-S) and the CGI-Improvement (CGI-I) scales, but improvement was nonsignificant on the 17-item Ham-D. On 200 mg, the results were better: 51% of patients showed improvement on the CGI-I, versus 41% with 50 mg and 26% with placebo. A small, placebo-controlled, crossover study of patients with refractory (mostly rapid-cycling) bipolar depression also found a similar percentage response rate in the CGI-I scale. Results from multiple open-label or otherwise less controlled studies have also supported the use of lamotrigine for treating depression in patients with bipolar disorder.

These relatively positive findings about lamotrigine had been countered, however, by a recently published report of four large, industry-supported, double-blind, placebo-controlled clinical trials studying lamotrigine treatment in acutely depressed bipolar I and II patients. None of these studies found a statistical difference between lamotrigine and placebo in the primary measures of efficacy. A meta-analysis of these four negative or failed studies plus the first positive study noted above found an overall modest benefit for lamotrigine over placebo. A high placebo response rate was found in the moderately ill patients, and there was no separation of lamotrigine from placebo in this group. In
more severely ill patients, however—those with a 17-item HAM-D score >24—lamotrigine was found to be superior to placebo, with a number needed to treat of 6.5. The response rates for lamotrigine were actually the same in the moderately and severely ill groups (~45%), but the placebo response rate was much higher in the moderately ill group than in the other. These results suggest that sampling issues, rather than efficacy of lamotrigine, reduced the effect size in the moderately ill population. Lamotrigine worked equally well in bipolar I and II subtypes.

The efficacy of lamotrigine as maintenance therapy in delaying the recurrence of mood episodes, especially depression, is fairly robust. Two large, 18-month studies\(^{82,83}\) showed efficacy, enabling lamotrigine to obtain FDA approval for maintenance use. One of these studies\(^{85}\) compared lithium and lamotrigine for maintenance against depressive relapse. It favored lamotrigine; the results may have been influenced, however, by the sample, which was enriched with patients whose depression had responded acutely to lamotrigine before enlisting in the study. They were then assigned to continued lamotrigine versus switching to lithium. (The two-year quetiapine vs. lithium maintenance study mentioned earlier was similarly enriched with quetiapine responders.)\(^{99}\)

Despite earlier concerns that lamotrigine, as an agent with possible antidepressant activity, may cause switches to mania,\(^{84}\) subsequent studies have not shown any significant propensity for mood destabilization.\(^{80,85–87}\) Incidence of serious rash may also be less than previously found (in particular, when faster dosage titration was used). The rate now appears to be 0.1% or less.\(^{88,89}\) Lamotrigine does not cause other adverse effects commonly associated with alternative agents used for bipolar depression. Unlike lithium, quetiapine, and valproate, it is not associated with weight gain and may actually decrease weight.\(^{90}\) It is also less likely to cause unwanted neurocognitive side effects and sedation.\(^{91}\)

Lamotrigine has shown no efficacy in treating mania,\(^{6}\) which distances it from the “two by two” definition of mood stabilizers and makes it less desirable than lithium or quetiapine for acute bipolar depression in patients not currently on mood stabilizers. It also has no apparent benefit for suicidal ideation or behaviors; in fact, like all anticonvulsants, it carries a new black-box warning about possible increased risk of suicidality.

**Olanzapine-fluoxetine combination.** Another FDA-approved treatment for acute bipolar depression is the olanzapine-fluoxetine combination (OFC). A large \(n = 788\), placebo-controlled, industry-sponsored study comparing placebo, olanzapine, and OFC in patients with bipolar I depression demonstrated a significant reduction in MADRS scores in the OFC group.\(^{92}\) Olanzapine monotherapy also demonstrated a statistically significant response, but the effect size was considered clinically insignificant; although marked improvements were seen in appetite and sleep, the impact on the core symptoms of depression was small. The antidepressant effects of OFC seen in this study may have been primarily secondary to fluoxetine rather than olanzapine: there was no fluoxetine-alone control group to check for this possibility. Another study, comparing OFC to lamotrigine (no placebo arm), showed similar response and remission rates in the two groups, with OFC treatment resulting in quicker reduction of depressive symptoms.\(^{93}\) Lamotrigine was much better tolerated overall, however, and OFC treatment was associated with much greater increases in measured metabolic parameters.

Despite apparent effectiveness in patients with acute bipolar depression, the use of OFC is not recommended at this early step of the algorithm. One reason relates to longer-term tolerability: olanzapine is associated with a high risk of metabolic syndrome and therefore, if continued as maintenance treatment, places the patient at risk for increased morbidity and mortality from this syndrome. Also, as mentioned earlier, the increased risk of sudden cardiac death associated with antipsychotic medications remains an important concern.\(^{72}\) Another factor is that the long half-life of fluoxetine’s active metabolite, norfluoxetine, could possibly prolong a manic episode if the patient switches into mania while taking OFC. This last concern is only speculative, however; the switch rate to mania found in a 24-week, open-label extension study of OFC was only about 6%.\(^{94}\) In the acute phase of this study, the risk of polarity switch was also low—the same as placebo.\(^{92}\)

If a physician decides to forgo the use of FDA-approved agents such as quetiapine or OFC in favor of using a non-approved medication (e.g., lithium or lamotrigine) for the treatment of acute bipolar depression, the physician should discuss with the patient the rationale for proceeding in that way. The risks, benefits, and alternatives to this proposed off-label treatment should be mentioned, and the discussion should be documented.

**Other medications.** The use of other antipsychotics as monotherapy for acute bipolar depression is not yet supported by the available evidence. Aripiprazole, which has been studied in two eight-week, controlled trials \(n = 374\), failed to demonstrate a statistically significant response in total MADRS score at week 8.\(^{85}\) Although multiple small, open-label, prospective\(^{96–98}\) and retrospective\(^{100–102}\) studies have found some response to mostly adjunctive aripiprazole in bipolar depressed patients, the lack of randomization, blinding, and placebo comparisons leaves the results merely suggestive. Akathisia was a frequently reported adverse effect that limited aripiprazole’s use in some patients. With regard to other second-generation antipsychotics (ziprasidone, risperidone), only one published report\(^{103}\) of response
to ziprasidone (involving use of a high dose = 320 mg/day) is found in the literature. Further controlled studies are required to shed light on the possible use of aripiprazole, ziprasidone, or risperidone in patients with acute bipolar depression.

Finally, other anticonvulsant options that might be considered for initial treatment of acute bipolar depression include valproate, carbamazepine, and oxcarbazepine.

A small (n = 25), placebo-controlled study of valproate in patients with bipolar depression found that those treated with valproate (mean serum concentrations, 81 ± 19.2 mcg/mL) showed a statistically significant improvement as measured by the 17-item HAM-D. Another more recent, placebo-controlled, pilot study (n = 18) also suggested efficacy for valproate in bipolar depression. Larger controlled studies are not yet available to further evaluate the possible role of valproate for bipolar depression. In any event, due to its severe teratogenicity and recently discovered cognitive toxicity for children exposed in utero, valproate should be avoided, especially as a first-line agent, in women with child-bearing potential.

Very little evidence supports the use of carbamazepine for bipolar I depression. One placebo-controlled trial (971 mg/daily; plasma level = 9 mcg/mL) found that 15 of 24 patients responded at least to a "mild" degree. We could find no reports of oxcarbazepine monotherapy in the treatment of bipolar depression. There are two small studies of oxcarbazepine as an adjunctive treatment added to lithium for general mood stabilization. Further research is needed to determine if there is a role for oxcarbazepine in acute bipolar depression.

Nodes 4, 5, 6: Is the Patient Currently on a Mood Stabilizer or Quetiapine?

If the patient has acute bipolar depression that has occurred or persisted despite current treatment with a mood stabilizer or quetiapine, one would first evaluate adherence and ensure optimum therapeutic dosing of the existing medication. Node 4 addresses the lithium recommendation.

If the patient remains depressed, there will be different options, depending on the current medication and the response level (i.e., nonresponse vs. partial, but unsatisfactory response). Nodes 5 and 6 address these scenarios. There will be options to switch to a different treatment or to augment the current regimen with another medication. These decisions to switch versus augment involve complex considerations, but the following general guidelines should be helpful in reviewing the recommendations in Nodes 5 and 6 and beyond.

First, if the patient continues to be depressed while taking carbamazepine, lithium, quetiapine, or valproate—all of which have some antimanic efficacy—the question arises as to whether to substitute another drug or to supplement the existing drug. If the potential next treatment for the depression also has some antimanic efficacy, it could be substituted for the existing treatment. Thus, for example, valproate could be replaced with lithium. In this way, polytherapy can be minimized until it proves to be necessary. But if the new agent chosen to treat the depression has little or no efficacy for mania—for example, lamotrigine—it should be added rather than substituted.

Second, what if the patient has had a partial improvement in depression? Many physicians switch medications when the patient has not improved at all on the first one, and augment when there is a partial response to the first treatment. However, the partial response in question might not have resulted from the pharmacological effects of the first medication. It could have been a placebo response related to nonpharmacological aspects of care or other nonspecific factors. Whether that is so will require an educated guess; reviewing the situation with the patient may be helpful, for he or she may have a strong opinion about whether the improvement was due to the medication.

Third, if the patient is taking lamotrigine, which has little antimanic efficacy, and one chooses to introduce lithium or quetiapine next, it could be either added or substituted. Substitution is an option because these agents treat or prevent both the depressed and manic phases.

Fourth, if an antidepressant is to be introduced, it should always be added to the existing mood stabilizer.

Node 4: Is the Patient Taking Lithium?

If the patient is on lithium and is depressed, then, as discussed in Node 3 above, the level should be adjusted to >0.8 mEq/L if tolerated. If no improvement results, the clinician should proceed to Node 8.

Node 5: Is the Patient on Lamotrigine, Valproate, or Carbamazepine?

If the patient is taking lamotrigine, valproate, carbamazepine, or another putative mood stabilizer, then the dose of the existing medication should first be adjusted to its optimal level.

If using lamotrigine. In one study lamotrigine at 200 mg/day was more effective than at 50 mg/day. Although doses higher than 200 mg/day have been used to treat seizure disorders, most of the controlled studies in bipolar depression have used 200 mg. No evidence supports the use of higher doses in psychiatric treatment. A therapeutic serum level has not yet been established for this agent.

If the depression persists and the lamotrigine dose has been optimized, the preferred options are to add or switch to
either lithium or quetiapine. For the reasons given in Node 3 (the patient on no mood stabilizer), a switch to lithium is, by a narrow margin, the first-line recommendation. There is one placebo-controlled study \( (n = 124) \) wherein lamotrigine (titrated to 200 mg/day) added to lithium produced a better result than lithium alone in acute bipolar depression: 52% improved, versus 32% on placebo\(^{12} \) (see Node 8: persisting depression on lithium monotherapy, where this evidence applies better). This study does suggest that a switch to lithium might not be as efficacious as the combination. However, as the best option for potential monotherapy treatment, lithium arguably deserves an opportunity to be tried as a monotherapy before adding lithium to lamotrigine. If lithium fails, lamotrigine can be added at the next node. Alternatively, lithium could be added to lamotrigine here, and if the patient improves, an attempt could be made later to withdraw the lamotrigine.

A second recommended option would be to add or switch to quetiapine. There are no studies of switching to quetiapine or of adding quetiapine to lamotrigine for the treatment of acute bipolar depression after failure on lamotrigine. However, like lithium, quetiapine is effective for both acute mania and depression. The general considerations in comparing lithium, quetiapine, and OFC were presented at Node 3.

Finally, for reasons to be discussed at Node 9, antidepressants could be considered but are not recommended at this point in the algorithm.

If using valproate. When valproate is the current medication in use, the dose should be adjusted to reach the higher end of the therapeutic range (50–100 mcg/mL). At that point, despite the limited evidence of efficacy for acute bipolar depression (as discussed earlier), it may be reasonable to continue the valproate for 1–2 weeks (if tolerated) in order to see—before considering the options below—if any antidepressant response is developing. It is notable that in maintenance therapy, valproate may reduce the risk of new depressive episodes,\(^{113,114} \) although the evidence base for valproate in maintenance appears weaker than for lithium.\(^{6} \)

If the valproate level has been optimized and the depression persists, the options include: adding or switching to lithium; adding or switching to quetiapine; adding lamotrigine (switching is less desirable because lamotrigine is weak in preventing mania); and adding an antidepressant. For the reasons given in Node 3 (the patient on no mood stabilizer), a switch to lithium is the first-line recommendation. However, if the history suggests that valproate has been more effective than lithium in preventing mania in a particular patient, then the addition of lithium is recommended.

A second reasonable option would be to add or switch to quetiapine. There are no studies of adding quetiapine to valproate for the treatment of acute bipolar depression that persists despite treatment with valproate. Like lithium, however, quetiapine is effective as monotherapy for both acute mania and depression. As an adjunctive treatment, quetiapine added to the effectiveness of both valproate and lithium in two large, placebo-controlled, one-year maintenance studies\(^{115,116} \) (and received FDA approval for this use in 2008). The general considerations in comparing lithium, quetiapine, and OFC were presented at Node 3.

The addition of lamotrigine to valproate has not been studied in acute bipolar depression, and it is important to note that the combination poses a risk of drug-drug interaction. Glucuronidation of lamotrigine is inhibited by valproate, which can increase the risk of dangerous rash. Dosing adjustments can address this problem, as specified in the package insert. Reservations regarding the acute efficacy of lamotrigine, as discussed in Node 3, should be taken into account.

Finally, for reasons to be discussed at Node 9, antidepressants are again not recommended at this point in the algorithm.

If using carbamazepine. If the patient with acute bipolar depression is being treated with carbamazepine, the dose should first be adjusted to obtain a serum level of 4–12 mcg/mL. This step helps to protect against mania if other agents with limited efficacy for mania prevention are introduced later for their potential antidepressant effects. As noted earlier, carbamazepine probably has little efficacy for bipolar depression, so as soon as the level is within the target range, the clinician should proceed to introduce lithium, quetiapine, or another medication, as in the valproate and lamotrigine discussions above.

Node 6: Is the Patient on Quetiapine Monotherapy?

If the patient is on quetiapine monotherapy for acute bipolar depression and is not responding, optimizing the dose to 300–600 mg daily and waiting for up to six weeks—if there is a partial response that has not yet plateaued—is recommended. If the patient fails to achieve a satisfactory response, the options include: add or switch to lithium, lamotrigine, or OFC, or add an antidepressant. Again, as at Nodes 3 and 5, the introduction of lithium is slightly favored.

Node 7: Is the Patient on an Antidepressant, Olanzapine Monotherapy, or OFC?

If the patient is on an antidepressant, OFC, or olanzapine monotherapy and is in an acute bipolar depression, we recommend treating as at Node 3 (no mood stabilizer) with
lithium or, as a second choice, quetiapine for the reasons discussed earlier. The antidepressant, OFC, or olanzapine should be tapered while lithium is started. Gradual taper is recommended if the patient has been on these agents for many weeks; a more rapid discontinuation can be attempted if these agents have only recently been started. The taper should preferably not be shorter than one week in order to avoid the possible risk of further destabilizing the patient’s illness.

**Node 8: Is the Patient Still Depressed After an Adequate Trial of Lithium?**

If the lithium level has been optimized and the patient remains depressed, the main options are to add quetiapine, lamotrigine, OFC, or an antidepressant. This choice is a difficult one. Quetiapine is robustly effective as an acute monotherapy, and it has maintenance efficacy as an add-on to another mood stabilizer (FDA approved), but as we have discussed, it adds metabolic and other side-effect risks that can be a problem over the long term. Lamotrigine, as noted at Node 5, has one (n = 124) positive study as an add-on to lithium in bipolar I and II depression. Fifty-two percent of patients met criteria for response, versus 32% on placebo (number needed to treat = 5), and 8% switched to mania/hypomania, versus 3% on placebo. As noted at Node 3, lamotrigine’s maintenance efficacy is reasonably established; it is FDA approved for this indication; and it is well tolerated for most patients. Antidepressants are the popular choice for many practicing clinicians but are increasingly viewed negatively by experts because of apparent lack of acute efficacy and suggestions of destabilizing effects on the course of some bipolar patients (see Note 9 discussion of the benefits and risks of antidepressants). OFC has severe, long-term metabolic side effects. The balance of considerations used in this algorithm favors adding quetiapine or lamotrigine (see earlier discussions regarding these agents). Since there is no strong reason to prefer one over the other, the clinician should choose whichever seems to be most appropriate for the individual patient at this node.

**Node 9: Has the Patient Tried Lithium Combined with Either Lamotrigine or Quetiapine?**

If the patient is still symptomatic after treatment with lithium and after adding either lamotrigine or quetiapine, then whichever agent (i.e., quetiapine or lamotrigine) has not been used would be recommended next.

TREATMENT WITH ANTIDEPRESSANTS

**Should an Antidepressant Be Used? A Brief Review of the Evidence**

The use of antidepressants in bipolar depression is controversial. The data continue to be frequently reviewed and discussed. Are antidepressants effective in the treatment of bipolar depression? If so, do risks of antidepressant-induced mania or long-term mood destabilization outweigh the potential benefits?

Historically, antidepressants have been used to treat bipolar depression (more in bipolar II than in bipolar I patients; see below), and previous algorithms have proposed that antidepressants may be effective and tolerable when added to a mood stabilizer. Efficacy studies (most with bipolar II depression) have demonstrated potential responses to tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and bupropion. In most of these studies, antidepressants were added as an adjunct to a mood stabilizer.

A meta-analysis of 12 randomized trials of antidepressants for bipolar depression concluded that antidepressants (usually when added to a mood stabilizer or olanzapine) can be effective in treating bipolar depression. The addition of an antidepressant (either bupropion or paroxetine) did not appear to increase the chances of “durable recovery,” using euthymia for eight or more weeks as the primary outcome measure. Other depression outcome measures, even transient recovery, did not favor the antidepressant, even at a trend level. Poor response to antidepressants has also been observed in other studies.

In subsequent research, the STEP-BD project (Systematic Treatment Enhancement Program for Bipolar Disorder), sponsored by the National Institute of Mental Health, included a double-blind, placebo-controlled(n = 125 completed treatment), 26-week study comparing patients treated with a mood stabilizer plus an antidepressant to patients treated with a mood stabilizer plus placebo. The addition of an antidepressant (either bupropion or paroxetine) did not increase the incidence of manic switches, it may not decrease the risk of cycle acceleration, and antidepressant use could still be associated with an increased frequency of mood episodes. The risk may vary with the antidepressant: when bupropion,
sertraline, and venlafaxine were compared, bupropion was least associated with subsequent mania. The risk was slightly higher with sertraline and significantly higher with venlafaxine, though the presence of more rapid-cyclers in the venlafaxine group may have contributed to this result.

Of 228 patients given an adjunctive antidepressant for bipolar depression in the Stanley Foundation Bipolar Network sample, only 16% had a sustained response that continued for one year. Manic or hypomanic switches occurred in 19% of the patients during the acute phase of treatment (ten weeks) and in 37% of the patients who participated in the one-year continuation phase. The STEP-BD sample had only a 10% switch rate, but the patients who participated in that study probably had a low risk of switching. Other studies have also found low switch risks.

Antidepressants appear to be better tolerated in patients with bipolar II, versus bipolar I, depression; that is, the risk of an antidepressant-induced switch into mania appears to be lower in patients with bipolar II. Also, when manic switches do occur with antidepressant therapy, the severity of mood elevation appears to be milder in patients with bipolar II disorder. Interestingly, a recent study of treatment-naive, rapid-cycling, bipolar II patients treated with citalopram monotherapy showed an overall decrease in mood instability. This study was very small, however—with only nine subjects—which limits generalizability. A more substantial and intriguing finding was reported in a study of venlafaxine monotherapy for bipolar II depression. Eighty-three patients with a “low hypomanic switch rate” and no recent psychosis or substance abuse were randomized to venlafaxine (mean dose = 185 mg/day) or lithium (mean dose = 966 mg/day; serum level = 0.64 mEq/L) for 12 weeks in an open-label trial. Response rate was 58% for venlafaxine versus 20% for lithium ($p < 0.0005$). There was no significant difference in switch rates (2 with venlafaxine; 1 with lithium) but were more dropouts with lithium. The study shortcomings were its open-label design, lack of placebo control, and lack of long-term follow-up. Nevertheless, the study suggests that even if venlafaxine is problematic in bipolar I depression, it may be different in carefully selected bipolar II patients. More generally, antidepressants may prove to have more of a role in the treatment of bipolar II depression, though further controlled research is needed.

Node 10: Using Antidepressants in Non-rapid-cycling Bipolar Depression

In view of the preceding examination of the effectiveness and safety of antidepressants, this algorithm proposes that patients with bipolar depression should undergo trials of lithium, quetiapine, and lamotrigine (sometimes in combination) prior to initiating antidepressant therapy. Even then, to decrease the risk of manic switch, an antidepressant should be used only if the patient is concomitantly treated with a therapeutic dose of a mood stabilizer. In this revision of the algorithm, monotherapy with antidepressants is not recommended for any patients.

Prior to considering antidepressant therapy, patients at high risk of switching into mania should be identified. These patients include, but are not limited to, bipolar depressed patients with (1) even minimal coexisting manic symptoms at baseline (e.g., motor activation, pressured speech, or racing thoughts), (2) a history of recent, frequent, severe, or dangerous manic/hypomanic episodes, (3) a history of antidepressant-induced mania/hypomania, or (4) a history of substance abuse. These features suggest a relative disadvantage to antidepressant use; if antidepressants are prescribed, close monitoring is necessary.

There seems to be no clear choice among antidepressants in terms of efficacy. Some SSRIs seemed effective in earlier studies, but not more recently. The bupropion efficacy data are weak. Perhaps the choice is best made based on safety issues, in which context bupropion has a slight edge. Bupropion and SSRIs have low rates of manic induction. Bupropion is less likely to impair sexual functioning, though it is contraindicated if there is a history of seizures or an eating disorder. MAOIs could occasionally be an appropriate choice, especially in the anergic depressed patient. Antidepressants with adrenergic properties, such as venlafaxine and TCAs, should probably be avoided, especially in bipolar I patients, given their possibly higher risk of manic switch and their possible association with more severe switches.

When treating a patient with bipolar depression, antidepressants should be started at a low dose and increased gradually while monitoring for possible induction of hypomania or mania. Patient contact should be increased during the antidepressant trial.6 The risk of manic induction should be discussed with the patient, and he or she (and family members when appropriate) should be educated about the warning signs of emerging mania or hypomania; an irritable dysphoric state may be the precursor to a manic switch.

If the patient responds to the antidepressant (or seems to respond: given the high placebo-response rates, it can be hard to know if the drug was the determining factor), how long should it be continued? This question is at least as controversial as the question of whether to use antidepressants at all. As noted earlier, it has been hard to prove the effectiveness of antidepressants, and their side effects (even beyond the question of switch risk) can be significant. Many practice guidelines (e.g., the American Psychiatric Association and Canadian Network for Mood and Anxiety Treatments) have recommended that antidepressants be stopped within the first three to six months after remission.
of the depressive episode. This recommendation is based, however, on little, mostly indirect evidence. A retrospective chart review comparing 25 patients who stopped antidepressants to 19 who stayed on them found an increased risk of relapse to depression (and about the same as the risk of mania) in the group who discontinued.\footnote{153} A study involving patients in the Stanley Foundation Bipolar Network sample evaluated 84 bipolar patients who were given an antidepressant and stayed on it for at least two months and improved. A total of 549 patients had received antidepressants, so the 84 patients represented 15\% of that population, suggesting that the antidepressants were not very effective. This smaller group of patients was followed prospectively for a year. About half stopped the antidepressant and half stayed on it. The group that continued with the antidepressant had fewer depressive relapses and no increases in mania.\footnote{154} Therefore, if patients are fortunate enough to improve on an antidepressant, the decision whether to continue will need to be based on individualized considerations such as past history of sustained response without switching, history of only mild hypomanic episodes (as in bipolar II), and history of failure on multiple non-antidepressant regimens. The best long-term results, with the least switching, may prove to be in the patients who achieve full remission on the antidepressant.\footnote{155}

RAPID-CYCLING BIPOLAR DISORDER: NODE 11

Rapid-cycling bipolar disorder, defined as bipolar disorder with four or more mood episodes per year, is especially difficult to treat. When longer-term effectiveness of mood stabilizers is studied in rapid-cycling patients, no clear advantage is noted from any single mood stabilizer compared to others.\footnote{156,157} These patients, who are at especially high risk for mood destabilization from treatment with antidepressants, should probably not be treated with antidepressants. Instead, combinations of two or three mood stabilizers may be required. Both lamotrigine\footnote{158} and lithium\footnote{159} have demonstrated some utility in this group of patients. They may be used together or in combination with valproate (cautiously if combining valproate and lamotrigine, given the glucuronidation interaction and increased risk of rash). Recent data support the use of quetiapine in patients with bipolar I and II depression with a history of rapid cycling.\footnote{160,161} Olanzapine may also have a modest effect in this group.\footnote{162,163} Combinations of these second-generation antipsychotics with mood stabilizers may be required.

REFRACTORY BIPOLAR DEPRESSION: NODE 12

If the patient’s depression is refractory to the above treatments, further (not yet used) combinations of multiple agents (e.g., mood stabilizers, quetiapine, and antidepressants) should be tried.\footnote{164} OFC may have an appropriate role here. If these regimens are found to be ineffective, then other approaches need to be considered.

A trial of ECT should be considered in refractory patients (see discussion at Node 1 regarding evidence of efficacy); maintenance treatment may be required. Clinical drawbacks, however, include potential memory impairments in certain patients (e.g., patients who have diminished cognitive reserve, are older, or require bilateral ECT).\footnote{165} Other limitations include the lack of availability of ECT for many patients (particularly for outpatients) and the increased costs of care if ECT is not initiated early in the course of inpatient therapy.\footnote{166}

If ECT is not helpful, acceptable, or tolerable, other options may be considered. Because of differences in the subjects treated in the available studies, the varying quality of the studies, and insufficient confirmatory data, it is impossible to make unequivocal recommendations in favor of any particular treatments. These agents, listed below in alphabetical order and not in order of recommendation, include aripiprazole, clozapine, modafinil, omega-3 fatty acids, pramipexole, and topiramate. The clinician should be guided by considerations of safety and efficacy in choosing a treatment for any particular patient.

Aripiprazole, as previously discussed, failed to show efficacy as monotherapy in two controlled trials.\footnote{95} However, also as noted, multiple noncontrolled studies have found some response to mostly adjunctive aripiprazole in bipolar depressed patients, including patients with varying degrees of treatment resistance.\footnote{96–102}

Clozapine, a second-generation antipsychotic with a good evidence base for treating refractory schizophrenia, may also be considered for refractory bipolar depression. Although no controlled studies use clozapine to target bipolar depression, small studies that have included patients with treatment-resistant bipolar disorder have suggested a possible mood-stabilizing effect in these patients.\footnote{165,166} A 48-month follow-up study also demonstrated improvement in treatment-resistant patients with psychotic bipolar disorder who were treated with clozapine,\footnote{167} and a long-term study showed a decrease in rehospitalization rates from bipolar depressive episodes with clozapine as an add-on medication.\footnote{168} A consideration in selecting clozapine would be a possible benefit regarding suicidality, a major concern in bipolar depressed patients. Although data for this effect specifically in patients with bipolar disorder are lacking, treatment with clozapine has been shown to decrease suicide risk in patients with schizophrenia and schizoaffective disorder.\footnote{169–171}

Modafinil, when added to a mood stabilizer, with or without an antidepressant, has been shown in one study to be potentially effective in treating acute bipolar depression.\footnote{172}
That placebo-controlled trial \((n = 85)\) found a numerically greater effect on energy-related symptoms of the Inventory of Depressive Symptomatology scale than on the scale’s other items. Fifty-nine percent improved on the energy subscale, versus 44% in the total IDS scale. These figures compared to 31% and 23%, respectively, with the placebo. Thus, the effect of modafinil may have been primarily on energy symptoms rather than on mood per se. It has also been suggested that the patient sample may have been enriched with a subgroup of patients with fatigue and energy complaints who were referred because of the opportunity to be on a stimulating medication.\(^\text{173}\) Anergic bipolar depressed patients may consequently be especially appropriate candidates for modafinil treatment. Concerns have been raised that since modafinil acts at the same site as cocaine, it should be used with caution in patients with substance abuse disorders—a common comorbidity in bipolar patients.\(^\text{174}\)

Omega-3 fatty acids have been studied for the treatment of bipolar depression. One randomized, placebo-controlled study \((n = 116)\) failed to show a difference between ethyl-eicosapentaenoate versus placebo in patients receiving mood-stabilizing medications.\(^\text{175}\) Another small, controlled study \((n = 75)\) did find significant improvement in HAM-D and CGI scores compared to placebo.\(^\text{176}\) This study focused, however, on mildly to moderately depressed patients. Ethyl-eicosapentaenoate was generally well tolerated in both studies.

Pramipexole, a dopamine agonist, has been studied in two small \((n = 22, 21)\), placebo-controlled studies\(^\text{177,178}\) (one exclusively of bipolar II depression)\(^\text{178}\) in patients already on therapeutic doses of a mood stabilizer. Both showed pramipexole to be superior to placebo, with impressive effect sizes \((0.77 \text{ and } 1.1, \text{ respectively})\).\(^\text{179}\) Rapid cyclers were excluded from these studies due to concern that the dopamine agonist posed a risk of manic switches for them. Pramipexole was well tolerated in both studies.

Topiramate, an anticonvulsant, was found to be comparable to bupropion for bipolar depression in one small, preliminary, noncontrolled study when either one was added to a mood stabilizer.\(^\text{137}\) Both agents were well tolerated, and no manic switches were noted. Placebo-controlled studies of topiramate are needed in order to confirm these findings.

Finally, a recent, comprehensive review of mostly open studies of vagus nerve stimulation for treatment-resistant depression (which included both unipolar and bipolar patients) suggests a possible benefit from this treatment.\(^\text{180}\) If future, controlled studies confirm the efficacy of this treatment in bipolar depressed patients, it could prove to be especially beneficial in view of its advantage in relation to medication compliance problems, its probable safety in specific populations (e.g., pregnant women), and its positive effects on sleep architecture.

**COMPARISONS TO OTHER ALGORITHMS AND RECOMMENDATIONS**

A review of treatment guidelines that were available prior to 2005\(^\text{181}\) highlights the ongoing need for updated algorithms that incorporate newer evidence applicable to the clinical setting. The present algorithm for treating acute bipolar depression differs from the earlier version of the PAPHSS algorithm and other published algorithms. Some of the pertinent characteristics of other algorithms and guidelines are presented in Table 1. In contrast to some of the alternative algorithms, the current PAPHSS algorithm proposes (1) early consideration of ECT, (2) early addressing of psychotic symptoms, (3) optimization of lithium therapy prior to trying quetiapine or lamotrigine in both bipolar I and II depressed patients, (4) low priority of the olanzapine-fluoxetine combination because of its long-term metabolic side effects, and (5) use of antidepressants only very late in the algorithm, if at all (since they are to be avoided, if possible, with rapid-cycling patients and others with a relatively higher risk of mood destabilization). This algorithm places perhaps more emphasis on long-term safety, tolerability, and effectiveness in the options preferred at each decision point, rather than focusing on short-term efficacy as reflected in registration trials that enabled FDA approval. A shift to this “more conservative prescribing” approach has been advocated in general medicine\(^\text{187}\) and seems fully applicable in psychopharmacology.

**FINAL COMMENT**

The aim of this algorithm is to organize the available evidence in a format that is accessible and pertinent to the prescribing clinician who has to make treatment decisions about particular patients, but algorithms themselves, along with the reasoning behind them, should never be a substitute for clinical judgment.

Notwithstanding the development of this and other algorithms and the careful analysis and evaluation that are incorporated into them, the treatment of patients with bipolar depression remains a challenge for both clinicians and patients. Despite the growing body of research evidence and the many review articles that have been written about such treatment, a considerable degree of uncertainty remains about which of the treatments constitute first-, second-, or third-line therapies. Psychiatrists will need to remain open to emerging evidence.
Table 1. Characteristics of Other Algorithms and Guidelines for the Treatment of Acute Bipolar Depression

<table>
<thead>
<tr>
<th>Algorithm or guideline</th>
<th>Year</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychopharmacology Algorithm Project at the Harvard South Shore Program (^7)</td>
<td>1999*</td>
<td>Early division between bipolar I and II patients Recommended use of Li or LMTG in bipolar I patients, with earlier resort to addition of antidepressants Recommended antidepressant monotherapy in some bipolar II patients</td>
</tr>
<tr>
<td>Expert Consensus Guideline Series (^{182})</td>
<td>2000</td>
<td>Early use of an antidepressant (including SNRI) added to a mood stabilizer in severe depression Mood stabilizer alone for mild to moderate depression Li is the mood stabilizer of choice, followed by VPA or LMTG</td>
</tr>
<tr>
<td>American Psychiatric Association Practice Guidelines (^18)</td>
<td>2002</td>
<td>Recommended Li or LMTG as first-line treatment May use adjunctive antidepressants, but did not recommend antidepressant monotherapy</td>
</tr>
<tr>
<td>World Federation of Societies of Biological Psychiatry guidelines (^{183})</td>
<td>2002</td>
<td>Antidepressant (bupropion or SSRI) in combination with mood stabilizer, preferably Li or LMTG, recommended as first-line treatment Mood-stabilizer combinations (in addition to antidepressants) recommended as second-line treatment</td>
</tr>
<tr>
<td>British Association for Psychopharmacology guidelines (^{184})</td>
<td>2003</td>
<td>In patients already on mood stabilizer, optimize serum level; if no response, then add antidepressant If no prior medication, then start with combination antidepressant (SSRI) and antimanic agent (Li, VPA, or an antipsychotic) Taper off antidepressant once depression subsides</td>
</tr>
<tr>
<td>Texas Implementation of Medication Algorithm (^{122})</td>
<td>2005</td>
<td>For bipolar I, begin with LMTG (± antimanic drug), then move to QTP or OFC if needed Li, LMTG, QTP, OFC combinations before using adjunctive antidepressants Emphasis placed on using treatments with lowest likelihood of mood destabilization ECT considered in later stages</td>
</tr>
<tr>
<td>Goodwin &amp; Jamison (^6)</td>
<td>2007</td>
<td>For bipolar I: Early combination of Li and LMTG recommended; then add QTP; if no response, change QTP to OFC; if no response, change OFC to an antidepressant while maximizing antimanic agents Early consideration of ECT or of antidepressant/antimanic combination for severe depression Antidepressants otherwise reserved for cases of failure of 2 mood stabilizers or a mood stabilizer plus QTP</td>
</tr>
<tr>
<td>Canadian Network for Mood and Anxiety Treatments Guidelines (^{162})</td>
<td>2007</td>
<td>First-line treatments: Li, LMTG, QTP monotherapy; OLZ or VPA plus SSRI; Li or VPA plus bupropion Second-line treatments: switch from or combine Li, LMTG, or QTP, or add SSRI or bupropion</td>
</tr>
<tr>
<td>European College of Neuropsychopharmacology consensus meeting (^{185})</td>
<td>2007</td>
<td>Reviews data, but no clear hierarchy of recommendations or guidelines</td>
</tr>
<tr>
<td>International Consensus Group (^{166})</td>
<td>2008</td>
<td>Endorses use of Li, LMTG, or QTP monotherapy as first-line treatments for acute bipolar I depression, citing evidence for efficacy of these agents Not an algorithm, but recommendations said to be based on the principle of selecting treatment based on factors such as symptom profile and patient and family history</td>
</tr>
</tbody>
</table>

\(^*\)This is the earlier version of the PAPHSS algorithm.

Li, lithium; LMTG, lamotrigine; OFC, olanzapine/fluoxetine combination; OLZ, olanzapine; QTP, quetiapine; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; VPA, valproate/divalproex.
and evolving changes in practice in order to continue providing safe and effective treatment for bipolar depressed patients.

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