Progress in the Treatment of Bipolar Depression: Advances and Challenges

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A discussion of the pharmacologic management of bipolar depression, including emerging treatments and expert recommendations.

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Some of the most challenging facets of bipolar disorder involve the management of its depressive symptoms. This article will focus on the pharmacologic management of this phase of bipolar disorder, describing the evidence base for controlled studies, emerging treatments, and expert recommendations.

An unmet need exists for acute and maintenance treatments that target depressive symptoms in bipolar disorder. Depression predominates over the course of both bipolar I (BP I) and bipolar II (BP II) disorders, occurring more than 3 times as frequently as manic and hypomanic symptoms combined in BP I, and nearly 40 times as frequently as hypomania in BP II. Patients repeatedly attribute greater impairment in their work, family life, and psychosocial functioning to depressive symptoms than to mania. Even more problematic, the majority of attempted suicides occur in states of depression, in which the rate is 20 times higher than in the general population.

A significant challenge facing clinicians is the misdiagnosis or underdiagnosis of bipolar depression. Perhaps this is because it presents itself less dramatically and is more difficult to recognize. A large French multicentered study of patients experiencing a major depressive episode, as classified by DSM-IV, found that when systematic methods for identifying hypomania were employed, the rate of BP II disorder nearly doubled, increasing from 22% to 40% of such patients. Similarly, when the Mood Disorder Questionnaire was used in a primary care clinic, more than one fifth of patients receiving antidepressants for the treatment of depression screened positive for bipolar disorder. Before this assessment, bipolar disorder had not been diagnosed in the majority of these patients. It is clear that early discrimination between bipolar disorder and other psychiatric illnesses, particularly major depressive disorder, is essential to minimize misdiagnosis and provide safe and effective care.

Acute and maintenance effects of lamotrigine

A rigorous and methodical evaluation of a pharmacologic treatment for bipolar depression emerged in 1999, when Calabrese and associates published the first randomized, parallel group, placebo-controlled trial of lamotrigine in the treatment of patients with BP I depression. Conducted over 7 weeks, the study randomized patients to lamotrigine 50 mg/d (n = 66), lamotrigine 200 mg/d (n = 63), or placebo (n = 66). Significant improvements were seen in patients receiving both dosages of lamotrigine over patients in the placebo group in observed change on the Hamilton Depression Rating Scale (HAM-D) total scores. On the Montgomery-sberg Depression Rating Scale (MADRS) total score, significant improvement over placebo was evident for only the lamotrigine 200 mg/d group (P < .05). However, a responder analysis—where response is defined as 50% or greater improvement in MADRS total score—showed that 54% of the patients receiving lamotrigine 200 mg/d and 48% of the patients receiving lamotrigine 50 mg/d met criteria for response. Response rates for patients treated with both dosages of lamotrigine were significantly greater than the 29% response rate observed for placebo-treated patients (P < .05).

Not all controlled studies of lamotrigine have demonstrated superior efficacy over placebo. Some trial results suggested improvement with lamotrigine in the core symptoms of depression but failed to detach from placebo on the primary outcome measure. Collectively, results demonstrated that lamotrigine was effective in treating bipolar depression, although dosages of 200 mg/d may be
needed for maximum benefit. In terms of safety, lamotrigine has generally been shown to have a sideeffect profile similar to that of placebo. The primary concern is the rare development of a serious rash, such as Stevens-Johnson syndrome and toxic epidermal necrolysis.10

Perhaps even more challenging than the acute relief of depressive symptoms in bipolar disorder is the prevention of depression recurrence. To address this concern, lamotrigine was studied over an 18-month period in recently depressed patients with BP I.11 After completing an open-label phase with lamotrigine for 8 to 16 weeks, 463 patients were randomized to lamotrigine, 50, 200, or 400 mg/d; lithium, 0.8 to 1.1 mEq/L/d; or placebo.

Both lamotrigine and lithium were more effective than placebo at delaying the time to intervention for any mood episode, and lamotrigine (but not lithium) was more effective than placebo at delaying the time to intervention for a depressive episode. In a complementary fashion, lithium (but not lamotrigine) was superior to placebo at delaying the time to intervention for a manic episode. Similar results were observed in another 18-month maintenance study that evaluated recently manic or hypomanic patients.12 Taken together, these studies support the use of lamotrigine for the prophylaxis of depressive episodes in bipolar disorder.

### Atypical antipsychotics for acute bipolar depression

In addition to lamotrigine, the atypical antipsychotics olanzapine13 and quetiapine14 have been evaluated in randomized, placebo-controlled trials for the treatment of bipolar depression. The antidepressant efficacy of olanzapine was studied over the course of 8 weeks in patients with BP I disorder who were experiencing a major depressive episode.13 Patients were randomized to olanzapine (n = 370), an olanzapine-fluoxetine combination (n = 86), or placebo (n = 377). The monotherapy group received a mean modal olanzapine dosage of 9.7 mg/d. The combination group received a mean modal olanzapine dosage of 7.4 mg/d and a fluoxetine dosage of 39.3 mg/d.

Beginning at week 1 and continuing throughout the duration of the study, patients receiving olanzapine and the olanzapine-fluoxetine combination demonstrated significantly greater mean improvement over placebo in MADRS total scores. Olanzapine monotherapy was superior to placebo on measures of response (39.0% vs 30.4%; P = .02) and remission (32.8% vs 24.5%; P = .02).

However, when fluoxetine was added to olanzapine, the antidepressant efficacy became even more vigorous. The combination of olanzapine and fluoxetine was significantly better on all efficacy measures of depression than either olanzapine monotherapy or placebo, including higher rates of response (56.1%; P = .006 vs olanzapine, P < .001 vs placebo), remission (MADRS < 12; 48.8%; P = .07 vs olanzapine, P < .001 vs placebo), study completion, and times to response and remission. Treatment with olanzapine was associated with somnolence, weight gain, increased appetite, dry mouth, and asthenia. The side-effect profile of the olanzapine-fluoxetine combination was similar to that seen with olanzapine monotherapy, except for higher rates of nausea and diarrhea. Weight gain, cholesterol levels, and nonfasting glucose levels were higher in patients taking olanzapine or an olanzapine-fluoxetine combination, compared with placebo. No differences were observed among the 3 groups in the rate of treatment-emergent glucose elevations of 200 mg/dL or greater.

To date, quetiapine is the only other atypical antipsychotic studied in the treatment of bipolar depression.14 In an 8-week trial termed the BOLDER (BipOLar DEpRession) I study, patients with BP I and BP II disorder were randomly assigned to receive quetiapine, 600 mg/d (n = 180); quetiapine, 300 mg/d (n = 181); or placebo (n = 181). Patients with BP II disorder were not excluded as in the olanzapine-fluoxetine trial and composed 34% of the study population.

As early as week 1, both dosages of quetiapine resulted in significantly greater mean improvement in MADRS total scores compared with placebo and at all time points in the intent-to-treat group of patients (P < .001). The mean change in MADRS total score from baseline to last assessment was -16.73 in the 600 mg/d group, -16.39 in the 300 mg/d group, and -10.26 in the placebo group (P < .001 for both quetiapine dosages vs placebo). The response rate was approximately 58% for patients treated with either dosages of quetiapine, compared with 36.1% for placebo (P < .001). Remission rates were also significantly higher in patients treated with quetiapine, namely 52.9% for quetiapine at both 600 and 300 mg/d, compared with 28.4% for placebo (P < .001).

Adverse effects that occurred at significantly higher rates with the drug than with placebo included dry mouth, sedation, somnolence, dizziness, constipation, headache, and weight gain.

Cross-study comparisons of olanzapine and quetiapine should be interpreted with caution because of methodologic and sample differences. However, some distinct differences have emerged among...
atypical antipsychotics in their efficacy for treating symptoms of bipolar depression. The magnitude of clinical effect in comparison to placebo can be calculated through measurement of Cohen’s d effect size.\textsuperscript{15} The effect size for 600 mg/d of quetiapine was 1.09 in patients with BP I depression and 0.91 for a dosage of 300 mg/d. Since both values were 0.8 or greater, they were considered to represent a large treatment effect. Olanzapine, on the other hand, achieved an effect size of 0.32, but this increased to 0.68 when it was combined with fluoxetine. Other notable differences in medications relate to findings on the MADRS individual item analysis. Patients receiving quetiapine or an olanzapine-fluoxetine combination improved on the core mood items of depression: representing apparent sadness, reporting sadness, inability to feel, and pessimistic thoughts. Olanzapine monotherapy was not more effective than placebo at improving the core mood items of depression. In addition, both dosages of quetiapine were found to reduce suicidal thoughts compared with placebo, whereas both olanzapine groups did not differ from placebo in reducing suicidal thinking. A replication study of quetiapine in the treatment of bipolar depression (BOLDER II) has recently been completed.\textsuperscript{16} The results are yet to be formally published, but a preliminary analysis showed for a second time that quetiapine monotherapy at dosages of both 300 and 600 mg/d was superior to placebo at improving depressive symptoms. In contrast to the BOLDER I study, treatment effect sizes in the replication study were found to decrease in the BP I subgroup of patients. However, significantly greater mean improvement compared to placebo on the MADRS was observed not only in the BP I subgroup but also in patients with BP II disorder.

**Challenges in the treatment of bipolar depression**

Improving tolerability and treatment effectiveness remain crucial challenges when using pharmacologic agents for the management of bipolar depression. Thirty-four percent of patients receiving olanzapine,\textsuperscript{13} 22% of patients receiving quetiapine,\textsuperscript{14} and 18% of patients receiving lamotrigine\textsuperscript{7} discontinued treatment because of adverse events, lack of efficacy, or relapse into a mood episode. In the lamotrigine study, the rate of withdrawals due to adverse events was similar with active drug and placebo. In the olanzapine trial, patients receiving olanzapine monotherapy were most likely to discontinue treatment because of excessive somnolence, and had higher dropout rates because of adverse events than did patients who received an olanzapine-fluoxetine combination or placebo. Analysis of dropouts in patients who received quetiapine also showed higher rates of withdrawal because of sedation and somnolence. Such data help to answer the question, “When is it best to use lamotrigine or an atypical antipsychotic in the acute treatment of bipolar depression?” In our experience, nonresponders to lamotrigine are typically responders to quetiapine and vice versa. Those who may respond best to quetiapine are typically agitated, restless, anxious, and suicidal patients who benefit from the anxiolytic and sedating properties of quetiapine. Likewise, nonresponders to quetiapine usually demonstrate symptoms of fatigue, psychomotor retardation, and hypersomnolence; these patients may benefit most from lamotrigine. While these observations are speculative, they could assist the physician in determining which initial agent to prescribe based on the available data linking differences in dropout rates to adverse events. In the trials of lamotrigine,\textsuperscript{7} quetiapine,\textsuperscript{14} and the olanzapine-fluoxetine combination\textsuperscript{13} the response rates approximated 50%. These figures are similar to the response rate (47%) reported in the recent Sequenced Treatment Alternatives to Relieve Depression (STAR*D) effectiveness trial\textsuperscript{17} of unipolar depression. Still, this indicates that available treatments for bipolar depression appear to be effective for only about 50% of patients, leaving significant numbers of individuals with debilitating symptoms, including suicidality. Even among patients who had achieved recovery from a bipolar mood episode, a recent Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) report determined that when followed prospectively, 144 (22.4%) of 644 patients experienced a depressive recurrence within 1 year.\textsuperscript{18} A greater percentage of days depressed over the past year, residual depressive symptoms at recovery, and a higher lifetime number of depressive episodes were all indications of recurrence of depressive episodes. Data from the STEP-BD report support the need for alternative therapeutic agents that offer complete recovery from a major depressive episode and can sustain these effects over the maintenance phase. Other treatment strategies for bipolar depression that have been evaluated in controlled trials are
reviewed elsewhere. In this article, we have included a summary of agents studied in the depressed phase of bipolar disorder based on the strength of trial methodology.

Not to be overlooked is the use of lithium, a cornerstone in the management of bipolar disorder, with proven antidepressant effects dating back more than 30 years. Placebo-controlled studies of lithium, however, have generally enrolled small numbers of patients and are limited by methodologic concerns, such as use of crossover designs. A more recent study of lithium indicates that higher blood levels may be most useful, since no additional antidepressant benefit was achieved by the administration of paroxetine or imipramine when blood levels of lithium were maintained above 0.8 mEq/L. With long-term use, another advantage of lithium is its ability to protect patients from suicide.

The anticonvulsants carbamazepine and divalproex have also been studied in placebo-controlled trials of acute bipolar depression, albeit studies involving these drugs have enrolled only limited numbers of patients. Use of a doubleblind, placebo-controlled, off-on-off design found that treatment with carbamazepine achieved response in 63% (15/24) of bipolar patients at an average dosage of 971 mg/d. The results of a placebo-controlled trial of divalproex in BPI depression have been published. The data from this trial (which consisted of 25 patients) indicated that the rate of improvement over time in depressive symptoms was about twice as high in patients who received divalproex as it was in those who received placebo.

Two unpublished studies have evaluated the antidepressant effects of divalproex in patients with BP I, BP II, or bipolar disorder not otherwise specified. In the first trial, conducted over 8 weeks, patients treated with divalproex showed improvement over placebo at weeks 2 and 5, but not at the study’s end point, as assessed by mean change in HAM-D total score. In a 6-week trial of divalproex extended release, significant improvement over placebo was demonstrated on the MADRS despite the small sample size of 18 patients.

Taken as a whole, the evidence for divalproex and carbamazepine as monotherapy in the treatment of acute bipolar depression is less substantial than the evidence that exists for lithium, lamotrigine, or the antipsychotics quetiapine and olanzapine. For this reason, expert guidelines often suggest divalproex and carbamazepine as third- or fourth-line treatments.

Expert recommendations

Algorithms for the acute treatment of depressive episodes in bipolar disorder have been developed by the American Psychiatric Association, the Texas Implementation of Medication Algorithms Panel, and the Canadian Network for Mood and Anxiety Treatments. Expert recommendations concur that antidepressants should not be used as monotherapy in BP I depression. It is generally agreed that mood stabilizer treatment should be optimized before beginning a specific antidepressant regimen.

For patients taking lithium, this entails reaching a blood level equal to 0.8 mEq/L, and for patients with a history of severe or recent mania, beginning or continuing an antimanic agent. For patients not taking an antimanic agent or for those without a history of severe or recent mania, lamotrigine would be an appropriate initial choice. Next step treatments include switching to quetiapine or a combination of olanzapinefluboxetine. If patients still remain symptomatic, treatment strategies would incorporate combinations of lithium, lamotrigine, divalproex, carbamazepine, quetiapine, olanzapine, selective serotonin reuptake inhibitors (SSRIs), or bupropion. Electroconvulsive therapy has also shown positive results in treatment of bipolar depression, including treatment-refractory states.

Treatment with the SSRI venlafaxine has been associated with higher rates of mania or hypomania, as has treatment with tricyclic antidepressants. Long-term use of antidepressants in bipolar disorder is an ongoing controversy. Benefits from the addition of an antidepressant may be limited to the first 6 months of treatment, with some investigators advocating the withdrawal of antidepressants after resolution of the acute depressive episode. Still others argue that antidepressants should not be discontinued if they were used successfully in conjunction with a mood stabilizer during an acute depressive episode. This is based on retrospective data indicating that withdrawal of the antidepressant was associated with significantly higher 1-year relapse rates.

Depressive symptoms are a prominent concern in the care of patients with bipolar disorder. Accurate diagnosis and rapid introduction of treatment in the acute phase are essential to achieving favorable outcomes. There is solid evidence for the use of atypical antipsychotics, lithium, and anticonvulsants in the initial management of bipolar depression. How frequently traditional antidepressants should be prescribed in bipolar disorder and the appropriate duration of their use remains unclear.

For now, the task is to better define optimal treatments that are effective for a majority of patients,
that are well tolerated, that do not result in cycling, and are successful at maintaining a lasting response. Given the limitations or partial efficacy of the reviewed monotherapies, future investigation of combined pharmacotherapies for acute bipolar depression seems warranted. Focusing our attention on the depressed phase of bipolar disorder remains the fundamental challenge.

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Drugs Mentioned in This Article

Amitriptyline (Elavil, Norfranil, others)
Bupropion (Wellbutrin, Zyban)
Carbamazepine (Carbatrol, Tegretol, others)
Citalopram (Celexa)
Desipramine (Norpramin, others)
Divalproex (Depacon, Depakene, Depakote)
Escitalopram (Lexapro)
Fluoxetine (Prozac, Sarafem)
Gabapentin (Neurontin)
Imipramine (Endep, Tofranil, others)
Lamotrigine (Lamictal)
Lithium (Eskalith, Lithane, others)
Moclobemide (Manerix)
Olanzapine (Zyprexa)
Paroxetine (Paxil)
Pramipexole (Mirapex)
Quetiapine (Seroquel)
Riluzole (Rilutek)
Risperidone (Risperdal)
Sertraline (Zoloft)
Topiramate (Topamax)
Tranylcypromine (Parnate)
Venlafaxine (Effexor)
Zonisamide (Zonegran)

References


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