# Treatment Options for Bipolar Depression

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Bipolar disorder is often misdiagnosed as major depressive disorder because of the high frequency of depressive symptomatology in many patients with bipolar disorder. Depressive episodes that are resistant to treatment may also be associated with a worse course of illness in bipolar disorder, but we do not yet understand all the factors in the connection between bipolar disorder and depression. The data on the effectiveness of antidepressants in the treatment of depression in bipolar disorder vary greatly, and there have been few prospective, randomized studies on the subject. From the data so far, the rates of induction of mania for selective serotonin reuptake inhibitors and lamotrigine seem similar to those seen with placebo. The optimal length of time to continue antidepressant treatment in patients with bipolar disorder has not yet been determined; however, research tends to indicate that a longer term of treatment (6 months or more) may aid in the prevention of relapse. Newer U.S. Food and Drug Administration–approved treatments for depression in bipolar disorder include a combination of olanzapine and fluoxetine, which is used for depressive episodes in bipolar disorder, and lamotrigine, which is used for maintenance treatment of bipolar I disorder. Psychoeducation has also been examined as a possible treatment for depression in bipolar disorder, and a study has shown that patients receiving psychoeducation plus medication may have a lower rate of relapse than patients who receive medication alone.
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Depression is a serious concern in patients with bipolar disorder. Many patients experience depressive symptoms more frequently than manic or hypomanic symptoms. In the National Institute of Mental Health Collaborative Depression Study,[1,2] patients with bipolar I disorder and patients with bipolar II disorder spent substantially more time with depressive symptoms than with manic/hypomanic symptoms or cycling/mixed symptoms. After patients sought treatment for an affective episode at 1 of the 5 centers involved in the naturalistic study, they were followed for a mean of 13 years. The 146 patients with bipolar I disorder spent 32% of the follow-up weeks with depressive symptoms, and the 86 patients with bipolar II disorder spent 50% of the time with depressive symptoms. In contrast, the patients with bipolar I disorder spent only 9% of the time with manic/hypomanic symptoms, and those with bipolar II disorder spent only 2% of the time with manic/hypomanic symptoms. It is possible that patients underreported manic and hypomanic symptomatology because they were only queried annually by phone and may not have accurately recalled short-lived or mild manic symptoms during the year; however, the fundamental predominance of depression in bipolar disorder is borne out by other data from the Stanley Foundation.[3]

Because of the predominance of depressive symptomatology, bipolar disorder is often diagnosed as major depressive disorder (unipolar depression), both in patients experiencing their first episode of depression and in those who have had recurring episodes. In a study[4] of 250 individuals presenting with a major depressive episode, when the investigators used strict DSM-IV criteria and regular clinical interviews, 72% of the individuals were diagnosed with unipolar depression, 6% with bipolar I disorder, and 22% with bipolar II disorder. When the patients were evaluated 4 weeks later using broader but evidence-based systematic criteria—including a semistructured interview, the Global Assessment of Functioning, the Hypomania Checklist, and a questionnaire for affective temperaments—the proportion of patients diagnosed with unipolar depression decreased to 45%, the proportion diagnosed with bipolar II disorder increased to 40%, and the proportion diagnosed with bipolar I disorder remained the same. The misdiagnosis of bipolar disorder as unipolar depression can cause problems with treatment because patients might receive inadequate treatment, i.e., antidepressants alone and not mood stabilizers.

Factors that are not commonly thought of as related to depression may be linked to it by mechanisms that we do not yet understand and may play a role in recurrence. For example, Fagiolini et al.[5] found that patients with bipolar disorder who were obese had a significantly shorter time

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to recurrence of depression than patients who were not obese; however, time to recurrence of manic episodes did not differ between patients who were obese and those who were not obese.

## TREATMENT OPTIONS FOR DEPRESSION IN BIPOLAR DISORDER

### Mood Stabilizers

Not only do patients with bipolar disorder experience depressive symptoms more frequently than manic or hypomanic symptoms, but the presence of depression seems to be associated with a worse course of illness in bipolar disorder. My colleagues and I[6] conducted a double-blind, placebo-controlled study comparing the effectiveness of divalproex, lithium, and placebo in maintenance treatment of patients with bipolar I disorder. Patients were randomly assigned to receive divalproex (N = 187), lithium (N = 91), or placebo (N = 94) for 1 year. We anticipated that improvement in manic symptoms would contribute more to overall improvement in bipolar disorder than would improvement in depressive symptoms. However, our results suggested the opposite finding. Neither divalproex nor lithium was significantly more effective than placebo in preventing premature termination from the study because of mania, but divalproex was significantly ($p = .02$) more effective than placebo in preventing early termination because of depression or because of any mood episode overall.

It has been reported that patients with bipolar disorder have a higher risk of suicide when they are depressed than when they are manic, hypomanic, or in a mixed state.[7] Studies have looked at the relationship between treatments for bipolar disorder and the risk of suicide attempts; however, these studies are limited by the infrequency of suicide attempts in treated patients with bipolar disorder. A retrospective review by Goodwin et al.[8] reported greater rates of suicide attempts that resulted in hospitalization for carbamazepine-treated and divalproex-treated patients compared with patients taking lithium. But a problem with retrospective studies is that it is often difficult to control for the type and severity of illness and the nonrandom fashion in which the particular medications were used. These studies indicate some possible differences between medications, but in the absence of prospective randomized data, these results are suggestive rather than conclusive.

### Antidepressant Augmentation of Mood Stabilizers

There have been few placebo-controlled, randomized studies on traditional antidepressants in the short-term treatment of depression in bipolar disorder. My colleagues and I conducted further analyses[9] of the patients who became depressed during our study[6] of maintenance treatment with mood stabilizers described above. Patients who became depressed during the course of the first study[6] were given a selective serotonin reuptake inhibitor (SSRI, either sertraline or paroxetine) in addition to ongoing treatment with a mood stabilizer (either divalproex or lithium) or placebo. Of the 372 patients randomly assigned to double-blind treatment with divalproex, lithium, or placebo, 82 received adjunctive SSRI therapy for breakthrough depression. Nine (45%) of the 20 patients who received an SSRI and placebo discontinued the study early for worsening of depression, compared with 4 (10%) of the 41 patients who were given an SSRI and divalproex and 6 (29%) of the 21 patients who were given an SSRI and lithium together. Therefore, the combination of an SSRI and a mood stabilizer was substantially more efficacious for bipolar disorder than an SSRI alone.

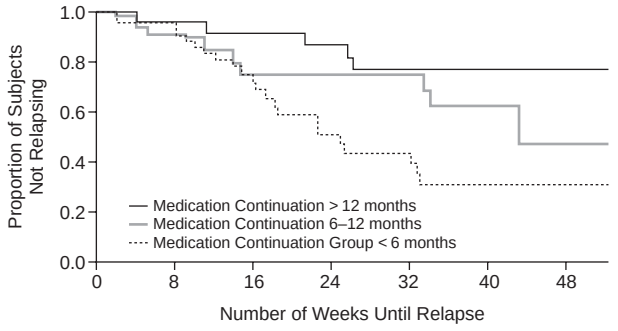
**Table 1. Rates of Induction Into Mania Reported in Untreated Patients and Patients Taking Various Medications**

| Treatment | Rate (%) |
|---|---|
| Tricyclic antidepressants | 11,[11] 21–25,[12] 70[13] |
| Monoamine oxidase inhibitors | 35–50[13] |
| Venlafaxine | 13[15] |
| Lamotrigine | 5[14] |
| Placebo | 4[11] |
| Selective serotonin reuptake inhibitors | 3[11] |
| No treatment | 41[16] |

A study by Nemeroff et al.[10] compared paroxetine and imipramine as adjunctive treatment to lithium. Patients were randomly assigned to 1 of 3 treatment groups: lithium plus paroxetine (N = 35), imipramine (N = 39), or placebo (N = 43). For patients who had a high serum lithium level (> 0.8 mEq/L, N = 52) at study entry, no significant differences in response were found among the 3 treatment groups. In the patients who had a lithium level ≤ 0.8 mEq/L at study entry, those patients given paroxetine and lithium (N = 19) and those patients given imipramine and lithium (N = 19) showed significantly ($p \leq .04$) more improvement than the patients given placebo and lithium (N = 22). Over the 7-week period of this study, Nemeroff et al. also examined the rates of patients switching into mania. In the patients treated with lithium and placebo alone, 1 patient (2.3%) had treatment-emergent mania, and in the patients treated with lithium plus imipramine, 3 patients (7.7%) switched into mania. No patients in the group treated with paroxetine and lithium switched into mania.

Rates of antidepressant-induced mania have varied greatly in other studies[11–16] (Table 1). Tricyclic antidepressants and monoamine oxidase inhibitors are associated with the highest rates of induction of mania. Other medications such as venlafaxine that have noradrenergic augmenting effects in the central nervous system generally have higher rates of induction of mania than the SSRIs. The rates of induction of mania for SSRIs and lamotrigine are similar to the rate seen with placebo. However, exact data on rates of antidepressant-induced mania are hard to find; the reason the rates in the studies in Table 1 range

**Figure 1. Time to Relapse Among Subjects With Bipolar Disorder[a]**




[a]Reprinted with permission from Altshuler et al.[17]

substantially might be because, with a few exceptions, the studies used samples of convenience rather than prospective, randomized data.

The optimal length of time to continue antidepressant treatment in bipolar disorder has been debated. A recent study by Altshuler et al.[17] suggests that, at least for the subset of patients who respond favorably when an antidepressant is added to a mood stabilizer, discontinuing antidepressant medication may be inadvisable. In this study, 84 patients whose depression had remitted within 60 days of the addition of an antidepressant to a mood stabilizer were followed for 1 year after remission of depression. The risk of relapse into depression was significantly ($p = .005$) higher for the patients who discontinued antidepressant medication within 6 months of remission than in the patients who discontinued medication more than 6 months after remission (Figure 1). Of the 43 patients who discontinued antidepressant medication before 6 months, 70% relapsed. Of the 20 patients who discontinued antidepressants between 6 and 12 months, 53% relapsed, and of the 21 patients who continued medication for at least 1 year, 24% relapsed.

### Olanzapine-Fluoxetine Combination

The first treatment approved by the U.S. Food and Drug Administration (FDA) for depressive episodes in bipolar disorder is a combination of olanzapine and fluoxetine. In a study[18] of patients with bipolar I who were experiencing an acute episode of depression, 833 patients were randomly assigned to 1 of 3 treatment groups: olanzapine alone ($N = 370$), the olanzapine-fluoxetine combination ($N = 86$), or placebo ($N = 377$). Of the patients who received olanzapine alone, the response rate was 39.0%, which was significantly ($p = .02$) higher than the percentage of patients receiving placebo who responded (30.4%). Of the patients receiving the olanzapine-fluoxetine combination, the response rate was 56.1%, which was significantly higher than the response rates for both olanzapine alone ($p = .006$) and placebo ($p < .001$). Although the effectiveness of olanzapine alone was statistically significant versus placebo, the olanzapine-fluoxetine combination showed significant improvements in items (such as pessimistic thoughts and inability to feel) on which olanzapine alone was not significantly more effective than placebo.

### Lamotrigine

Lamotrigine, which has been used as an anticonvulsant for several years, was approved by the FDA for the maintenance treatment of bipolar I disorder in 2003. Although indicated for delaying time to any mood episode, the approval of lamotrigine as a maintenance treatment for bipolar disorder is principally based on its robust effect of delaying time to depression. In a double-blind study by Calabrese et al.,[15] 195 patients were given 1 of 2 fixed doses of lamotrigine, 50 mg/day and 200 mg/day, for 7 weeks. On the primary outcome measure, the Hamilton Rating Scale for Depression, the 50-mg/day dose of lamotrigine did not have a significant advantage over placebo, but the 200-mg/day dose did. However, on the more sensitive Montgomery-Asberg Depression Rating Scale, both the 50-mg/day and 200-mg/day doses of lamotrigine showed significantly higher response rates than placebo. Doses of lamotrigine higher than 200 mg/day are not recommended because the incidence of serious rash associated with lamotrigine has been reported to increase above that dose.[19]

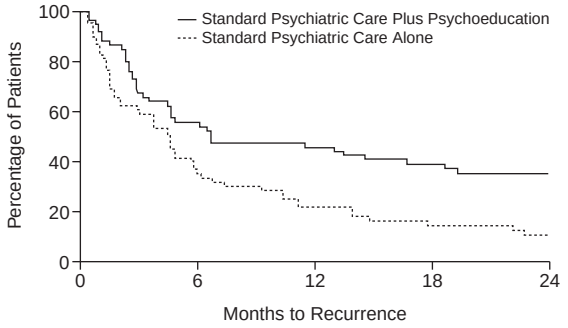
The study by Calabrese et al.[15] led to 2 long-term studies with lamotrigine. In the first study,[20] with patients who were or had recently been in a manic episode, participants were randomly assigned to receive either lamotrigine ($N = 59$), lithium ($N = 46$), or placebo ($N = 70$) for 18 months. When time to any mood episode was measured, both lithium and lamotrigine had a significant ($p = .02$ and $p = .003$, respectively) advantage compared with placebo, but neither medication had a significant advantage over the other. However, when time to a depressive episode was measured, lithium did not differ significantly from placebo, but lamotrigine did ($p = .02$). The second study,[21] which enrolled patients who were or had recently been in a depressive episode, showed a similar advantage for lamotrigine over placebo in time to a depressive episode, although the effect size was not as high. As in the first study,[20] lithium did not significantly differ from placebo in time to a depressive episode.

Of the 2 studies, the one that showed the greater difference between lamotrigine and placebo in rates of relapse into depression was the one in patients who had recently been manic. Although some clinicians believe that they do not need to be concerned about relapse into depression in manic patients, in fact, it is an area in which clinicians have the opportunity to improve course of illness.

### Psychoeducation

Psychoeducation has also been examined as a possible treatment for depression in bipolar disorder. In a study by

**Figure 2. Survival Curves for Recurrence With Mania, Depression, or Mixed Episode[a]**




[a]Adapted with permission from Colom et al.[22] $p < .003$ for between-group difference.

Colom et al.,[22] one group of patients (N = 60) was given standard psychiatric care (including medications) and psychoeducation, while another group of patients (N = 60) was given standard psychiatric care (including medications) alone. At the 2-year follow up, of the patients who received standard psychiatric care alone, 55 (92%) had a recurrence of a mood episode, but only 40 (67%) of the patients who received psychoeducation in addition to standard psychiatric care had a recurrence of a mood episode. The patients given standard psychiatric care and psychoeducation also had a significantly ($p < .003$) longer time to relapse into depression and mania than the patients given standard psychiatric care alone (Figure 2). For a more thorough discussion of the use of psychoeducation in bipolar depression, see the article in this supplement by Vieta.[23]

## CONCLUSION

Although patients with bipolar disorder experience depression more commonly than mania, there is not yet a consensus as to the best treatment for bipolar depression. The controlled data on conventional antidepressant (monoamine oxidase inhibitors, tricyclic antidepressants, and SSRIs) as treatments for depression in bipolar disorder are sparse, and at best suggest modest efficacy with a risk of induction of mania. Atypical antipsychotics, including a combined antipsychotic-antidepressant, appear promising in the treatment of bipolar depression, as does lamotrigine. Data also support the use of psychosocial approaches along with medication treatment. More research is needed to produce an evidence-based standard of care for patients with bipolar disorder who experience depression.

*Drug names:* carbamazepine (Tegretol, Carbatrol, and others), divalproex (Depakote), imipramine (Tofranil, Surmontil, and others), lamotrigine (Lamictal), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), olanzapine-fluoxetine combination (Symbyax), paroxetine (Paxil and others), sertraline (Zoloft), venlafaxine (Effexor).

*Disclosure of off-label usage:* The author has determined that, to the best of his knowledge, carbamazepine, imipramine, paroxetine, sertraline, and venlafaxine are not approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder.

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