

# Use of Antidepressants to Treat Depression in Bipolar Disorder

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**For decades, clinicians and researchers did not distinguish between bipolar and unipolar depression. The safety and efficacy of antidepressants for the treatment of unipolar depression were studied, and the data were applied to the treatment of bipolar depression without validation. As evidence has accumulated that antidepressants may adversely affect the course of bipolar illness, more research has been focused on that problem. Current evidence suggests that although antidepressants are clearly effective in the acute treatment of type I and type II bipolar depression, they are also associated with a variety of adverse outcomes. They may induce a switch to mania or hypomania at a rate two or three times the spontaneous rate. Long-term use may destabilize the illness, leading to an increase in the number of both manic and depressed episodes; induce rapid cycling (at least four episodes a year); and increase the likelihood of a mixed state. Antidepressants should be used with caution in the treatment of bipolar depression. (*Psychiatric Services* 53:580–584, 2002)**

**B**ipolar disorder, or manic-depression, is challenging to manage. The primary goal of pharmacotherapy is to prevent recurrence of mania and depression. However, although mood stabilizers are generally effective in treating and preventing mania (1–5), their efficacy in treating depression is suboptimal (1,6–9). This is unfortunate, because people with bipolar disorder seem to have greater problems with depression than with mania.

Cross-sectionally, outpatients with bipolar disorder are significantly more likely to be depressed than those with mania or hypomania (29.8 percent compared with 7.9 percent) (10) and less likely to respond to treatment with either a mood stabilizer or an antidepressant (10,11). Persons with bipolar disorder spend much more time depressed than in a

manic or hypomanic state (49 percent compared with 12 percent), as demonstrated in a study of 27 patients with type I bipolar disorder, 11 patients with type II bipolar disorder, and six patients with bipolar disorder not otherwise specified (12).

Frequently, persons with bipolar disorder initially receive a diagnosis of unipolar depression (13) along with a prescription for an antidepressant (12,14). Although antidepressants appear to be effective, they are now also believed to be not infrequently associated with adverse consequences for the course of bipolar illness. Thus it is important to carefully diagnose mood disturbances, to closely monitor treatment, and to keep informed about the most recent data. In this article we review the most recent data on the use of antidepressants for bipolar disorders.

## Diagnosis of bipolar illness

For the purposes of diagnosis, the key feature of bipolar illness is a manic or hypomanic episode. When an episode is actually witnessed by a clinician, the diagnosis is usually straightforward. In a community sample of 1,709 adolescents with bipolar disorder, Lewinsohn and colleagues (15) found that 61 percent presented with an initial episode of depression. Such an episode can often result in a diagnosis of unipolar depression. Thus when Geller and associates (16) conducted a ten-year follow-up study of 72 prepubertal children with major depression, they found that 33.3 percent met criteria for type I bipolar disorder and 15.3 percent met criteria for type II bipolar disorder (16).

The rate of misdiagnosis is also high among adults. In a study in which the Structured Clinical Interview for DSM-IV (SCID) was administered to patients who presented with a major depressive episode, more than half (55 percent) were found to have bipolar disorder (17). In a survey of 400 members of the National Depressive and Manic-Depressive Association, 60 percent of the patients who identified their illness as bipolar disorder reported that their initial diagnosis was depression (11).

Ghaemi and associates (12,18) used a modified version of the SCID to provide prospective diagnoses for consecutively referred patients with bipolar illness. Forty percent in one sample (18) and more than half (54 percent) in another (12) had previously received misdiagnoses. The mean duration between the first contact with the mental health system and the correct diagnosis among patients with type I bipolar disorder was

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5.9 years. The mean delay for type II illness was much longer at 11.6 years. These delays are significantly longer than the lag of 3.3 years in the diagnosis of unipolar depression (12).

Even when the initial diagnosis is made carefully and systematically, the rate of missed bipolar illness can be high. In an 11-year follow-up study of 559 patients with unipolar depression initially diagnosed with the SCID, 3.9 percent were subsequently found to have type I bipolar disorder and 8.6 percent to have type II bipolar disorder (19).

When the initial presentation is depression and there is no clear history of mania or hypomania, certain clues can raise the index of suspicion. One of the most important clues for children is a family history of manic-depression (20). In addition, a psychotic illness, prepubertal or postpartum onset of depression, and a severe vegetative depression are more frequently associated with subsequent development of bipolar illness (16,20). Akiskal and colleagues (21) found that the mean duration between the index depressive episode and the appearance of the first manic or hypomanic episode among adults was 6.4 years. They observed predisposing characteristics among their subjects similar to those noted in the other studies, particularly a family history of bipolar disorder, early onset (before the age of 25 years), postpartum onset, and a severe vegetative depression (21). Among both adults and children, antidepressant-induced mania or hypomania was a good predictor of the presence or subsequent development of bipolar disorder (20, 21), although *DSM-IV* defines this type of disorder as substance-induced mania (22). If any three of the predisposing characteristics were present, the likelihood was 98 percent that the ultimate diagnosis would be manic depression (21).

### Efficacy of antidepressants for bipolar depression

Several lines of evidence suggest that antidepressants are effective in the treatment of bipolar depression (23–33). In double-blind placebo-controlled or randomized studies of anergic depression, Himmelhoch and col-

**Editor's Note:** This paper is part of an occasional series on the treatment of depression edited by Charles L. Bowden, M.D. Contributions are invited that address major depression, bipolar depression, dysthymia, and dysphoric mania. Papers should focus on integrating new information for the purpose of improving some aspect of diagnosis or treatment. For more information, please contact Dr. Bowden at the Department of Psychiatry, Mail Code 7792, University of Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, Texas 78229-3900; 210-567-6941; bowdenc@uthscsa.edu.

leagues (23,24) found that the monoamine oxidase inhibitor (MAOI) tranylcypromine was superior to placebo in the treatment of 29 patients with type I or type II bipolar depression and superior to imipramine among 56 patients with bipolar depression. In a study by Thase and associates (27), nine of the 12 patients who did not respond to imipramine responded to tranylcypromine, whereas only one of the four who did not respond to tranylcypromine responded to imipramine.

Imipramine was equivalent to paroxetine in the treatment of 60 patients with bipolar depression who were already taking either lithium alone or lithium plus another mood stabilizer and who had either of the two antidepressants (19 subjects in each treatment group) or placebo (22 subjects) added to their regimen (32). However, among patients for whom lithium was used aggressively—serum concentrations above .8 mEq/L—the antidepressants did not provide additional efficacy in treating the depression (32).

On the other hand, fluoxetine was found to be more effective than imipramine in a small double-blind, placebo-controlled comparison of patients with bipolar depression who were also taking lithium (25). Either ac-

tive medication was superior to placebo, and fluoxetine was associated with a higher response rate than imipramine (86 percent and 57 percent, respectively) (25). Desipramine and bupropion were found to be equivalent in a double-blind study of 15 patients with bipolar depression who received mood stabilizers as maintenance therapy (33). About 71 percent of the patients who received desipramine and 63 percent of those who received bupropion experienced improvement of more than 50 percent (33).

In an open-label study, the first author administered methylphenidate for 12 weeks to 14 patients with mild to moderate bipolar depression—ten with type I bipolar disorder, two with type II bipolar disorder, and two with secondary mania—who were also taking mood stabilizers (31). A last-observation-carried-forward (LOCF) intention-to-treat analysis showed a significant improvement in depressive symptoms as indicated by mean scores on the 21-item Hamilton Depression Rating Scale (HDRS) (from 16.9 at baseline to 9.8 on the LOCF). (Possible scores on the HDRS range from 0 to 62, with a score of 15 indicating depression and higher scores representing more severe depression.) The response by the end of the first week was an excellent predictor of response at the end of the study.

Placebo-controlled studies have not been conducted among children with bipolar depression. Biederman and colleagues (30) reviewed the charts of 59 youths with a mean age of 10.8 years (range, 3.5 to 17 years), 83 percent of whom were male, who had *DSM-III-R* diagnoses of bipolar disorder and who were studied for up to four years. They found that selective serotonin reuptake inhibitors (SSRIs) were significantly associated with improvement in depressive symptoms between visits. Antidepressants also may be effective for type II bipolar depression. Amsterdam and colleagues (29) retrospectively examined participants in a long-term study of fluoxetine for *DSM-III-R* major depression in which hypomania (type II bipolar disorder) was not exclusionary. They identified 89 patients with type II bipolar disorder among 839 patients studied. They compared

these patients with 89 age- and sex-matched patients with unipolar depression and 661 unmatched patients with unipolar depression. No differences were found between groups in the efficacy of fluoxetine for the treatment or prevention of depression.

The same researchers also studied monotherapy with venlafaxine 225 mg a day among 17 patients with type II bipolar depression. Reductions in mean scores on the HDRS (from 22 to 9) and the Montgomery Asberg Depression Rating Scale (MADRS) (from 22 to 9) were significant and were equivalent to those seen among 26 patients with unipolar disorder over the six weeks of the study (28). (Possible scores on the MADRS range from 0 to 60, with higher scores indicating more severe depression.)

The prophylactic efficacy of antidepressants has not been as well studied. Quitkin and associates (34) conducted a 30-month double-blind study of the efficacy of imipramine compared with placebo added to lithium in the prevention of depressive relapse among 75 patients with type I bipolar disorder and found that imipramine was ineffective in preventing bipolar depression. Three (8 percent) of 37 patients who received imipramine and four (10.5 percent) of 38 who received placebo experienced depressive relapse (34).

### Antidepressants and mania

Antidepressant medications appear to induce mania or rapid cycling—that is, at least four episodes a year—among some patients with bipolar disorder (12,35–37). The absolute rate of manic induction is quite varied among studies. However, when spontaneous switch rates were also presented in the studies, the rate of antidepressant-induced mania was consistently two or three times the spontaneous rate (29,34,36–40).

In type I bipolar disorder, antidepressant-induced mania is generally mixed or has a significant irritable mood component, and it resolves relatively quickly when the antidepressant is discontinued (36). Persons with type II bipolar disorder may show a similar pattern. Patients with cyclothymia may switch to type II illness when treated with antidepressants (41).

One of the earliest reports of anti-

depressant-induced mania was presented by Wehr and Goodwin (35). In the study by Nemeroff and colleagues (32) in which imipramine, paroxetine, and placebo added to lithium with or without another mood stabilizer were compared, a switch to mania occurred more frequently among patients who had serum lithium concentrations below .8 mEq/L. At these concentrations, 11 percent of the patients who received imipramine and 5 percent of those who were treated with mood stabilizers alone (spontaneous rate) became manic or hypomanic. At lithium concentrations above .8 mEq/L, none of the patients who received mood stabilizers alone switched, compared with 8 percent of the patients who were treated with imipramine. In the study by Wehr and Goodwin, none of the 33 patients who received paroxetine experienced a switch to mania or hypomania (35).

Similar results were reported in the 30-month relapse study by Quitkin and colleagues (34). The risk of manic relapse was twice as high for patients treated with imipramine (nine of 37 patients, or 24 percent) as for those who received placebo (four of 38 patients, or 10.5 percent), although this effect was not significant.

However, manic induction is not exclusively related to tricyclic antidepressants. Altshuler and colleagues (37) retrospectively reviewed the life charts of 51 patients with treatment-refractory bipolar illness. More than a third of the patients (35 percent) had antidepressant-associated manic episodes. Patients with antidepressant-induced mania had a greater risk of rapid cycling than those who did not (46 percent and 14 percent, respectively). Ghaemi and associates (12) reviewed the charts of 27 patients with type I bipolar disorder, 11 patients with type II bipolar disorder, and 16 patients with bipolar disorder not otherwise specified whose diagnoses had been made on the basis of a modified SCID. A total of 42 patients had received antidepressant treatment at some point, but sufficient data for analyses were available for only 38 patients. Fifty-five percent had experienced an antidepressant-related mania or hypomania. In both studies, the

patients had received either SSRI or non-SSRI antidepressants.

Longer duration of antidepressant treatment may increase the risk of a manic switch. The Stanley Foundation Bipolar Network is currently conducting a comparative study of antidepressants for breakthrough depression among patients with bipolar disorder (42,43). During a ten-week acute phase, 18.2 percent of 1,035 patients experienced either mania or hypomania (43). At a one-year follow-up, 16.4 percent had experienced a switch to mania and 19.2 percent to hypomania (43).

In a double-blind comparative study, desipramine induced mania or hypomania during the first eight weeks of treatment among 30 percent of patients, compared with only 11 percent of patients treated with bupropion—a significant difference (33).

In a study of 49 consecutively admitted patients with antidepressant-induced mania and 49 matched control patients with spontaneous mania, the antidepressant-induced mania was consistently less severe than the spontaneous mania (36). Overall severity of mania at admission was lower among the patients who received bupropion or an MAOI than among those who received a tricyclic agent or fluoxetine (36).

Kupfer and associates (40) examined the incidence of imipramine-induced mania among 33 patients with type II bipolar disorder and 197 patients with unipolar depression. All the patients received imipramine at a target dosage of 200 mg a day as well as interpersonal psychotherapy for 40 weeks. Six patients developed hypomania, and none developed mania. Of the six, four developed hypomania after more than 20 weeks of treatment, and the other two after 16 weeks or less (40).

Antidepressant-induced mania may also occur among children. Biederman and colleagues (30) found that SSRIs were associated with a significantly greater probability of manic symptoms than no antidepressant treatment. Cicero and associates (44) have noted that children who were treated with stimulants or antidepressants were given a bipolar diagnosis two years earlier than children who

had not received those medications, although the difference was not significant. In a similar study, DelBello and colleagues (45) found that the mean time to onset of bipolar disorder was more than three years less for 21 children who had received stimulants than for 13 children who had not (10.7 years and 13.9 years, respectively).

Not all studies have shown such associations between antidepressants and mania. Lewis and Winokur (46) retrospectively examined the charts of 87 patients who at admission were neither manic nor receiving antidepressants. The switch rates were 26.7 percent for those who were treated with antidepressants (tricyclics or MAOIs), 15 percent for those who were treated with lithium or neuroleptics, and 41 percent for those who received no pharmacologic treatment. Lithium or neuroleptic treatment protected against mania. Antidepressants were associated with a nonsignificantly higher switch rate than mood stabilizers but did not induce mania at a rate higher than the spontaneous rate. The difference might have been statistically significant if the sample had been larger.

Evidence is emerging that administration of an antidepressant during euthymia may be more problematic, although the mechanisms for this effect are not known. A recent case report describes a patient with bipolar disorder who responded well when given bupropion during a depressive episode but experienced a manic episode when the drug was readministered at a lower dosage during euthymia (47).

### Antidepressants and rapid cycling

In the preantidepressant era—that is, before the 1950s—rapid cycling among persons with bipolar disorder was rare; it is now more than five times as common (38). A wealth of data associates antidepressant treatment with the induction of rapid cycling among patients with bipolar disorder.

In a study of 51 patients who experienced rapid cycling, Wehr and colleagues (48) found an association between tricyclics and a shortened duration of the cycle. When the drug was discontinued, nearly a third of the patients stopped experiencing rapid cycling. In a retrospective chart

review of 109 patients with bipolar disorder who were experiencing rapid cycling, Kukopulos and colleagues (38) found that among 80 patients (73.4 percent) the onset of rapid cycling was associated with antidepressant treatment; for the patients who continued to receive antidepressants, rapid cycling continued through euthymic periods in the case of 17 patients, persisted for at least a year in the case of 33 patients, for two years in the case of 14 patients, and for a longer period in the case of five patients (38). The types of antidepressants used were not specified.

When Altshuler and colleagues (37) retrospectively reviewed the life charts of 51 patients with treatment-refractory bipolar illness, they found that 26 percent experienced antidepressant-associated cycle acceleration. The risk of cycle acceleration was significantly higher for the 35 percent of patients who had previously experienced an antidepressant-induced mania than for those who had not (46 percent and 14 percent, respectively). Younger age at first treatment also predicted cycle acceleration (37). No specific association with antidepressant class was found.

In the study by Ghaemi and colleagues (12), 23 percent of the 54 patients with bipolar disorder experienced cycle acceleration associated with antidepressant treatment. Most of these patients had received SSRIs. Interestingly, although the mean number of episodes per year increased from 3.9 to 9.8, the episodes were sufficiently brief that the absolute duration of illness dropped from 60 percent to 45 percent.

Rapid cycling faded quickly among 29 percent of the 51 patients studied by Wehr and colleagues (47). Similarly, for eight of nine patients studied by Altshuler and colleagues (37), rapid cycling stopped within two months after antidepressant treatment was ended. One patient experienced cycling for five months before stabilizing after antidepressant treatment was discontinued (37).

These reports suggest that rapid cycling of manic and depressive episodes can both be induced by antidepressants and fade after discontinuation of antidepressants. The duration

of antidepressant treatment before the onset of complications is variable, but rapid cycling appears to be associated with longer treatment periods and with treatment through euthymic periods. Similarly, recovery time after discontinuation of the drug may mirror the time required for episode induction, so that in some cases rapid cycling may resolve months after the patient has stopped taking antidepressants. Both SSRIs and tricyclic antidepressants have been implicated, although the relative risk is not clear. Data on bupropion are lacking.

### Conclusions

Although antidepressants appear to be effective in the treatment of acute bipolar depression, their use is not without risk. Patients with bipolar disorder who are treated with antidepressants may have an elevated risk of mania, cycle acceleration, or induction of a chronic irritable dysphoric state. There is preliminary evidence that specific risk factors may be associated with these complications, notably long-term use of an antidepressant or administration of the drug during euthymic periods. Previous antidepressant-associated mania appears to predict subsequent rapid cycling.

In general, tricyclic antidepressants are the most notorious, while SSRIs and bupropion appear to be safer. However, all antidepressant agents have been associated with these undesirable outcomes. It has been suggested that stimulants may be safer in short-term treatment of bipolar depression, but this needs to be investigated further.

A clinician confronted with a patient who has bipolar depression should first try treatment with a mood stabilizer. If an antidepressant is required, brief treatment—one to six months—with subsequent tapering is desirable. Occasionally, chronic treatment will be needed, but this should not be the norm. Treatment of chronic conditions, such as an anxiety disturbance, is more problematic. Use of an alternative agent, such as gabapentin or an atypical antipsychotic, may be appropriate. Antidepressants clearly have a role in reducing the suffering of persons with bipolar depression but must be used judiciously and cautiously. ♦

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