The Evidence for Antidepressant Use in Bipolar Depression

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Mood elevation, which includes mania, hypomania, and mixed states, was previously considered the defining symptom of bipolar disorder, but bipolar depression by comparison is actually a much more substantial challenge to diagnose and treat. Recent studies, including research by the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), found that patients with bipolar disorder spend longer periods of time in depressive episodes and are more likely to relapse to depression compared with mania or hypomania. However, the treatment of bipolar depression is hampered by the limited number and varying quality of available studies of pharmacologic treatments to guide clinical decision making. Clinicians should rely on studies with the highest level of evidence (category A) when prescribing appropriate antidepressant treatments. The standard care pathways outlined by STEP-BD to aid clinicians in treating varying phases of bipolar disorder provide data on the use of various treatments for bipolar depression and their outcomes. While some treatments have the potential to induce mania, others appear to have some efficacy without inducing mania.

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The most pressing challenge facing clinicians in the treatment of bipolar disorder is how to treat bipolar depression. While some studies show that the use of antidepressants appears to have benefits for patients with bipolar depression, the evidence is actually thin and of varying quality. As there are risks associated with antidepressant use and limited evidence of efficacy, clinicians should carefully weigh evidence from antidepressant studies when considering pharmacologic treatments for their patients with bipolar depression.

ANTIDEPRESSANT STUDIES AND LEVELS OF EVIDENCE

Previously, clinicians were trained to consider mood elevation, which includes mania, hypomania, and mixed states, as the defining symptom of bipolar disorder, but bipolar depression is actually a much more significant problem than mood elevation. Recent data suggest that the periods of time that people with bipolar disorder spend with symptoms of mood elevation are relatively short compared with the time people spend in depressed states over the course of their lifetime. Judd et al.[1] conducted a prospective symptomatic follow-up study that looked into the course of bipolar disorder in 135 bipolar I and 71 bipolar II patients for up to 20 years. Both sets of patients were found to spend more time in depressive than manic episodes. Specifically, of the total number of weeks spent with any symptoms of bipolar disorder, patients spent 30.6% of that time with depressive symptoms compared with 9.8% spent with hypomanic symptoms (Figure 1).[1] In addition, bipolar II patients spent more weeks with depression (51.9%) than manic or hypomanic symptoms (1.9%).[1] Overall, the findings suggest that depression is the more substantial problem.

Other research further indicates that bipolar depression has health-related as well as economic implications. Sachs et al.[2] recently presented findings that, among bipolar patients who recover from a mood episode, 5% will relapse each month following their recovery, and 80% of the relapses will be to depression. The findings resulted from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD),[3] a national longitudinal public health initiative funded by the National Institute of Mental Health (NIMH). The rate of psychiatric hospitalization associated with relapse was found to be 14.2 per 100 patient years, and the mortality rate is about 0.11 per 100 patient years, with a small number of those mortalities being due to suicide.[2]

The amount of available evidence to support pharmacologic treatments for bipolar depression is limited and of varying quality. Evidence-based studies are rated by letter (Table 1) in order to allow clinicians to better evaluate levels of evidence and therefore base treatment on the best evidence.[4,5]

Unfortunately, A or B evidence showing efficacy for treatment of bipolar depression is limited, but a recent

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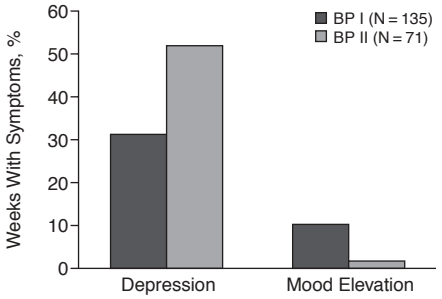
Figure 1. The Number of Weeks Spent With Bipolar Symptoms: Depression Versus Mood Elevation[a]



[a]Data from Judd et al.[1]

Table 1. Levels of Evidence for Evidence-Based Studies[a]

A.	More than 1 double-blind, placebo-controlled trial with an adequate sample size*
B.	Single double-blind comparison study with an adequate sample size*
C.	Open comparison trials with an adequate sample size*
D.	Uncontrolled observation or a controlled study with an ambiguous result
E.	No published evidence
F.	Available evidence negative

[a]Data from Sachs.[5]
*Statistical power ≥ 0.8 to detect meaningful differences at $p < .05$.

literature review[5] lists which studies are available. Studies with an A rating include research on lamotrigine,[6] olanzapine and the combination of olanzapine and fluoxetine,[7] and quetiapine.[8] While older research into imipramine[9] was rated as a B study,[5] more recent research of imipramine versus paroxetine[10] was rated as a negative or failed trial of adequate size (category F).[5]

THE USE OF ANTIDEPRESSANTS FOR BIPOLAR DEPRESSION

The use of antidepressants for bipolar depression is problematic given that available data suggest either limited or no efficacy for those drugs. While many studies[5,11–14] highlight the increased likelihood of manic switch, Altshuler et al.[15] found that of a total of 1078 subjects enrolled in the Stanley Foundation Bipolar Network, 189 developed depression and received adjunctive antidepressants. Of those, 84 subjects (44%) achieved remission. Forty-three of the 84 subjects discontinued antidepressant therapy at the point of remission, while the other 41 subjects continued with antidepressant therapy. Both groups were then monitored for a year. What Altshuler et al. discovered was that 19% of the 84 subjects (N = 15) switched to mania at the end of the yearlong follow-up. Only 6 of the 15 subjects were taking antidepressants when the switch occurred. Decreasing the time of antidepressant use was associated with a decreased time to relapse, and the authors concluded that if patients did well on antidepressant therapy, their antidepressants should be continued. However, the findings are too limiting to suggest that antidepressants have either short-term or long-term efficacy.

Treatment-Emergent Mania

In addition to the limited evidence for antidepressant efficacy, antidepressant treatment is associated with a high risk of treatment-emergent switch to mania in bipolar patients. For example, of the patients in the STEP-BD sample, 19.5% of bipolar patients reported a switch to mania during 1 of their antidepressant trials.[5,11,14] The highest rates of switch were associated with selective serotonin reuptake inhibitors (SSRIs): 33% of 353 patients taking 1 SSRI or more experienced switch, and 22% of 706 patients from all SSRI trials that STEP-BD investigated experienced a switch.[14] And of the patients who experienced a switch to mania with one or more SSRIs, 67 patients (58%) switched to mania again when given a different SSRI.[14]

Heterocyclic antidepressants, which include tricyclics, have been considered the riskiest medications for patients with bipolar disorder because they are thought to cause the most switches to mania. According to STEP-BD findings, 19 (23%) of 83 patients reported switch, and of the patients who switched, 38% developed mania again when later given different heterocyclic antidepressants.[14] While the percentage of repeated treatment-associated switches was higher among patients taking SSRIs compared with patients taking heterocyclic antidepressants, the STEP-BD findings do not necessarily suggest that SSRIs are more dangerous than heterocyclic or other antidepressants. The data do suggest, however, that there may be patient-specific factors that are more important than drug-specific factors in determining whether or not patients develop treatment-emergent mania.

Standard Antidepressants for Bipolar Depression

The limited evidence illustrates that the efficacy of standard antidepressants for bipolar depression is unproven and that the risk of switch to mania makes standard antidepressant use problematic. Despite the overall lack of adequately powered placebo-controlled studies, meta-analysis[16] of randomized controlled trials suggests that there is some efficacy with short-term use of antidepressants for bipolar depression, but more research is needed. Since there is no proven advantage of any antidepressant medication over lithium or drugs considered to be mood stabilizers, the risk-to-benefit ratio can be understood as the risk being greater than 0 with a yet unproven benefit for the medications.[1,13,14,16] This necessitates extremely cautious antidepressant use.

Research shows that all antidepressants appear to carry a risk of switch to mania,[13] and many carry a risk of switch to depression,[1] but the evidence as to which antidepres-

sants are the most dangerous for patients to use remains weak, and the risk of switch may in fact be limited. Because of the lack of evidence, the clinician's best guide for understanding patient risk for switch may be the patient's prior history. Certainly, patients who responded well to antidepressants in the past may respond well in the future, but those who have had switch in their past probably should not be treated with antidepressants.

STEP-BD STANDARD CARE PATHWAYS RESEARCH

The standard care pathways outlined by STEP-BD[3] to aid clinicians in treating varying phases of bipolar disorder provide data that emphasize the increased prevalence of bipolar depression over bipolar mania. Prospective open data collected with formal rating scales illustrate the number of new episodes of major depression that developed after patients had entered STEP-BD. Of the 809 patients who entered the standard care pathways for any episode, 368 (45.4%) entered for a recurrent episode of depression, and 93 patients entered the depression pathway for the first time in STEP-BD. Of the 93 patients, 49 were started on any antidepressant within 3 weeks of the onset of their depression, whereas 44 were not, which raises the possibility that clinicians decided whether patients were given an antidepressant or a nonstandard antidepressant treatment for their mood episode on the basis of the severity of their depression or perceived risk of switch to mania. The Clinical Monitoring Form (CMF) subscale scores—used as progress notes for the medical records of STEP-BD patients—for depression were not different between the 2 groups of patients. The CMF subscale scores for patients who were given antidepressants had a depression score of 7.2 (SD = 1.8), and those who were not given antidepressants had a CMF subscale depression score of 7.2 (SD = 1.9). Neither of the groups had any significant mood elevation.

Recovery and Remission With Antidepressants

The STEP-BD naturalistic trial[3] showed that by the time to first recovery, defined as having 2 or fewer symptoms of a major depressive episode according to DSM-IV criteria, patients treated with antidepressant medication appeared to reach recovery quicker than those who were not given antidepressants. After 42 days, half the patients given antidepressants had recovered (N = 25), while it took more than 60 days for those who had not taken antidepressants to reach first recovery. Of those patients who maintained recovery for 8 continuous weeks and met both STEP-BD and DSM-IV criteria for recovery from a major depressive episode, there appeared to be no difference between those who did and did not take antidepressants: 26% of those given an antidepressant and 25% not given an antidepressant remained recovered. The number of recovered patients is small, which underscores how difficult the treatment of bipolar depression is and suggests that antidepressants do not have a benefit in helping patients completely recover from their episode. However, 18% of the patients who used standard antidepressants switched to mania, hypomania, or mixed states compared with 11% in the group treated without antidepressants. In addition, there was little difference between groups that did or did not take antidepressants in the time to onset of remission in those who met criteria for remaining recovered. The time to onset of remission was 45.4 days (SD = 38.1) for patients who took antidepressants compared with 49.3 days (SD = 42.7) for patients who did not take antidepressants.

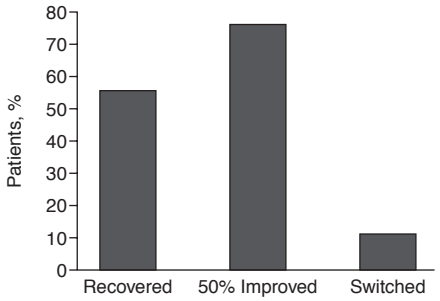
Treatment With Lamotrigine

Lamotrigine, an antiepileptic compound, was previously found to be effective in patients with bipolar I depression.[6] Patients with bipolar disorder who entered the STEP-BD standard care pathway for depression were given an antidepressant (N = 152), lamotrigine (N = 57), an antidepressant plus lamotrigine (N = 41), or neither (N = 103) in addition to their mood stabilizers. The baseline severity of depression and mood elevation were not differentiated between the groups. The CMF depression subscale scores at baseline were 8.1 for the antidepressant group, 8.2 for the lamotrigine group, 8.0 for the combined group, and 8.4 for those who received neither drug (with standard deviations of 1.8, 2.6, 1.6, and 1.9, respectively). The baseline CMF subscale scores for elevation were 1.1 for antidepressant, 1.5 for lamotrigine, 1.5 for both, and 1.2 for neither (with standard deviations of 0.9, 1.2, 1.3, and 1.1, respectively).

The time to 50% decrease in the CMF subscale score for depression was no different among patients taking a mood stabilizer only, a mood stabilizer plus an antidepressant, a mood stabilizer plus lamotrigine, or a mood stabilizer plus an antidepressant plus lamotrigine. All patients took approximately the same amount of time to reach recovery, which, in a 2-year follow-up of the 377 patients, revealed much better results than expected. Fifty-six percent of patients (N = 213) ultimately recovered during the trial (Figure 2). In addition, 76% (N = 286) of the total group of patients had at least a 50% improvement in their depression scale scores.

Approximately 11% of patients switched to episodes of mania, hypomania, or mixed states, and of this 11%, antidepressants alone were associated with an 8.6% (N = 13/152) rate of switch, and lamotrigine with an 8.8% (N = 5/57) rate of switch. The highest rates of switch were associated with patients who received either an antidepressant and lamotrigine, with a rate of 14.6% (N = 6/41), or neither, with a rate of 14.6% (N = 15/103). The rate of switch to episodes of mood elevation was higher in these groups, most likely because clinicians generally took into account whether or not their patients had episodes of mood elevation in the past or whether or not they felt patients might be at risk for

Figure 2. STEP-BD Patient Outcome After Antidepressant, Lamotrigine, or the Combination Added to Mood Stabilizers for Bipolar Depression (N = 377)[a]



[a]Data from Sachs.[5]

future episodes of mood elevation. Clinicians were probably less likely to prescribe standard antidepressants for their patients who, based on their history, were more likely to experience a switch.

CONCLUSION

With the currently available data for the treatment of bipolar depression, several recommendations can be made to aid clinicians. First, knowing the patient is important. The patient history is the best guide in the absence of data that confirm the benefit of the use of antidepressants. If, for example, patients have had antidepressant treatment in the past and have responded favorably to it without adverse effects, including treatment-emergent switch to mood elevation, then future treatment with antidepressants is probably safe for those patients. Second, clinicians should weigh benefit with risk. Because data are limited and sometimes questionable, clinicians need to carefully consider data from category A studies. Categories D, E, and F studies are difficult to interpret and may provide limited or inaccurate data. Third, clinicians need to assess the severity of bipolar depression in order to monitor risk of suicide, hospitalization, or the need for electroconvulsive therapy.

Ultimately, clinicians will be faced with the issue of whether or not to treat their bipolar patients with antidepressants. Patients may not feel comfortable with treatment with the few agents that do currently have efficacy for the treatment of bipolar disorder. Quetiapine,[8] olanzapine,[7] and olanzapine plus fluoxetine[7] have associated adverse metabolic effects and may not be treatments that patients wish to choose (even compared with treatments for which there is limited data). The use of lamotrigine, while increasing, may still be frightening to some patients who do not wish to put themselves at risk of any life-threatening rash, even if the risk of developing that rash is quite small.

The best recommendation is for clinicians to approach their patients with the treatments that have the most data to support their use: for new-onset depression, that means lamotrigine, quetiapine, olanzapine, and the combination of olanzapine plus fluoxetine. Of course, patient choice will dictate in large part how clinicians prescribe. Until solid data are available to support the use of standard antidepressants in bipolar disorder, clinicians need to be careful and circumspect about their use.

Drug names: imipramine (Tofranil and others), lamotrigine (Lamictal), olanzapine (Zyprexa), olanzapine/fluoxetine combination (Symbyax), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, imipramine, lamotrigine, olanzapine, paroxetine, and quetiapine are not approved by the U.S. Food and Drug Administration for the treatment of bipolar depression.

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