Antidepressants for Bipolar Disorder

June 01, 2008 | Bipolar Disorder [1], Bipolar Disorder [2], Bipolar II Disorder [3], Depression [4], Major Depressive Disorder [5], Mania [6], Mood Disorders [7]
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What is the effectiveness (if any) of antidepressants in bipolar depression? What is the risk of manic switching? How effective are antidepressants in preventing relapse of bipolar depression? Insights here.

According to DSM-IV diagnostic criteria, bipolar disorder (bipolar affective disorder, manic-depressive disorder) is characterized by marked mood swings between mania (mood elevation) and depression. The essential feature of bipolar I disorder (BDI) is a clinical course that is defined by the occurrence of 1 or more manic or mixed episodes; the essential feature of bipolar II disorder (BDII) is a clinical course that is defined by the occurrence of 1 or more major depressive episodes accompanied by at least 1 hypomanic episode. As such, bipolar disorder can cause significant personal distress and social dysfunction.

Bipolar disorder has been subdivided in several ways, but classically there are 2 clinical categories of the disorder. BDI is characterized by the occurrence of 1 or more manic or mixed episodes (mixed episode means that symptoms of mania and depression are present at the same time). Often individuals with BDI have also had 1 or more major depressive episodes. Episodes of substance-induced mood disorder (caused by the direct effects of a medication, other somatic treatments for depression, drug abuse, or toxin exposure) or of mood disorder caused by a general medical condition are not considered when making a diagnosis of bipolar disorder. By contrast, BDII is diagnosed when depression is interspersed with less severe episodes of elevated mood that do not lead to dysfunction or disability (hypomania).

Although individuals with BDI can return to a fully functional level between episodes, some continue to display mood lability and interpersonal or occupational difficulties. Manic symptoms are the hallmark of the illness and can represent a real medical emergency. However, bipolar depression is often much more clinically significant. Depression was the third leading cause of burden among all diseases in 2002, and it is expected to rise in the next 20 years. Evidence suggests that depressive episodes and symptoms are equal to or more disabling than corresponding levels of manic or hypomanic symptoms and that only subsyndromal depressive symptoms (and not subsyndromal manic or hypomanic symptoms) are associated with significant impairment in patients with bipolar disorder. This scenario highlights the need for effectively treating bipolar depression.

Although antidepressant drugs remain the mainstay of treatment for unipolar major depression in both primary and secondary care settings, the evidence to support antidepressant treatment for bipolar depression is limited and increasingly controversial—especially now that evidence is available for alternative medications, including quetiapine and lamotrigine.

Apart from the limited evidence, a key problem with antidepressants is the potential for increasing the risk of iatrogenic episodes of elevated mood. This is the reason many reviews and guidelines for bipolar depression have recommended the use of a mood stabilizer (usually lithium or valproate) rather than an antidepressant as the first-line treatment for bipolar depression. Antidepressants are advised only as second-line treatment and always with a concurrent mood stabilizer to prevent switching to mania. However, in real-world clinical practice, antidepressants are still frequently
prescribed for bipolar disorder. Thus, 3 important clinical questions arise: (1) What is the effectiveness (if any) of antidepressants in bipolar depression? (2) What is the risk of manic switching? (3) How effective are antidepressants in preventing relapse of bipolar depression?

Efficacy of antidepressants and risk of manic switching

In 2004, the efficacy and safety of antidepressants for the short-term treatment of bipolar depression were studied and the results were analyzed. The main aims of the study were to shed light on the effectiveness of antidepressants using a methodologically sound approach, to quantify the increased risk of a manic switch, and to see whether there were antidepressants that were more effective or less likely to produce a switch. Using various electronic databases, the authors performed a systematic review and meta-analysis of randomized controlled trials. Twelve studies were included and 1088 participants were analyzed. Participants were adults aged up to 70 years of whom approximately 60% to 70% were women; patients with a diagnosis of serious physical illness or substance abuse were excluded. The review found that antidepressants significantly increased treatment response at 4 to 10 weeks. Comparing 1 or more antidepressants with placebo, patients taking an antidepressant (paroxetine, imipramine, fluoxetine, tranylcypromine, or selegiline) were more likely to respond (risk ratio [RR], 1.9; 95% confidence interval [CI], 1.5 to 2.3). The number needed to treat (NNT) with antidepressants was 5 (95% CI, 4 to 7). (The NNT is a measure of treatment effectiveness and the average number of people who need to be treated with a specific intervention [for a given period] to achieve 1 additional beneficial outcome.)

There were fewer data available for analysis of remission, but the results were consistent. Patients treated with an antidepressant (paroxetine, imipramine, or fluoxetine) were more likely to achieve remission than those who were not taking an antidepressant (RR, 1.41; 95% CI, 1.11 to 1.80). NNT was 9 (95% CI, 5 to 33). In the studies comparing antidepressants with placebo, about 75% of patients received a concurrent mood stabilizer or an atypical antipsychotic (this point should be taken into account in order to draw clinically meaningful conclusions).

The review data did not suggest that switching to mania is a common early complication of treatment with antidepressants. In the review by Gijsman and colleagues, there was no evidence of an increased risk for switching to a manic episode in the included trials. The event rate for antidepressants was 3.8% and for placebo it was 4.7%. This difference was not statistically significant. Gijsman and colleagues also looked at whether some antidepressants are less likely to produce a manic switch. They found 3 trials that allowed comparison between 2 important classes of antidepressants, tri-cyclic antidepressants (TCAs), and SSRIs. Findings from this study show that switching occurred in 8% of patients taking TCAs versus 0% of those taking SSRIs (although the difference is not statistically significant), and suggest that TCAs may be more likely to induce mania than SSRIs. The main limitation of these analyses is that there were few manic events overall, limiting the power to detect a clinically important difference between compounds.

Recently, Sachs and colleagues reported the results of a large (N = 366) randomized trial comparing mood stabilizers alone (valproate, lithium, carbamazepine) with combination therapy with an antidepressant (paroxetine or bupropion) plus a mood stabilizer in patients with bipolar depression. At 26 weeks, there was no significant difference in the proportion of patients who achieved a durable recovery (27.3% vs 23.5% respectively), nor was there any difference in the pro-portion of patients who experienced a manic episode (10.7% vs 10.1%).

Other studies have examined the relative risk of switching into hypomania or mania associated with second-generation antidepressants in patients with bipolar depression. Results conflicted somewhat with the findings reported by Gijsman and colleagues. Examining the comparative risks of switching into hypomania/mania during acute and continuation trials of adjunctive antidepressant treatment for bipolar depression, one study found that adjunctive treatment with antidepressants for bipolar depression was associated with substantial risks of threshold switches to full-duration hypomania or mania even during short-term treatment.

This 10-week trial examined the relative acute effects of 3 second-generation antidepressants (bupropion, sertraline, and venlafaxine) as add-on treatments to mood stabilizers. In this study, 174 outpatients with BDI or BDII (stratified for rapid cycling) and in the depressed phase were randomly treated with a flexible therapeutic dose of an antidepressant. All 3 antidepressants were associated with a similar range of acute response (49% to 53%) and remission (34% to 41%); however, a significantly increased risk of switches into hypomania or mania in participants treated with venlafaxine compared with bupropion or sertraline was found: standardized rating scale scores showed that switching occurred in 10% of patients taking bupropion, 9% taking sertraline, and 29% taking venlafaxine.
Interestingly, this trial also found a strong interaction between the rapid-cycling status of patients and the relative risk of switching for all 3 medication groups. In participants without rapid cycling disorder, the risk of switching was identical for all 3 medication groups. It could be that the dual actions of venlafaxine on serotonin and noradrenaline reuptake, which may account for its greater efficacy in patients with unipolar depression,14,15 may have contributed to the higher rate of switching with this agent than with the other 2 agents. These findings may also be consistent with the higher switch rates for the TCAs, which represent combined serotonin and noradrenaline reuptake inhibitors.9

The results from the study by Post and colleagues11 were confirmed in a long-term continuation treatment follow-up phase lasting up to 1 year.13 Hence, more caution appears indicated for patients with bipolar depression for use of venlafaxine than use of bupropion or sertraline as adjunctive treatment to a mood stabilizer, especially if there is a history of rapid cycling. It should be noted that all of these antidepressants are FDA-approved for the treatment of major depression but are not FDA-approved for use in bipolar depression.

**Effect of antidepressants in preventing relapse**

The other compelling clinical issue in bipolar depression is the risk of recurrence and prevention of relapse. Bipolar disorder is known to be a recurrent disorder, and more than 90% of patients with bipolar disorder experience recurrences.16

However, available data are scarce on the clinical features associated with the risk of recurrence. Interesting findings resulted from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), a national longitudinal public health initiative funded by NIMH.17 One of the main aims of the trial was to look for the features associated with risk of recurrence.18 The study prospectively enrolled patients with bipolar disorder who were receiving treatment according to contemporary practice guidelines and observed them for up to 24 months.

Of the 1469 participants who were symptomatic at study entry, 858 subsequently achieved recovery (58.4%). During the 24-month follow-up period, 48.5% of patients experienced recurrences, and depressive episodes developed in more than 34.7%, compared with manic/hypomanic/mixed episodes in 13.8%. Furthermore, in this study, residual depressive or manic symptoms at recovery and proportion of days depressed or anxious in the preceding year were significantly associated with shorter time to depressive recurrence.

Unfortunately, we found just one systematic review investigating the effectiveness of long-term use of antidepressants, which did not provide sufficient evidence to assess the ability of antidepressants to prevent relapse of bipolar disorder.19 The review found 7 randomized controlled trials that enrolled 363 people with BDI or BDII. Data were found only for imipramine, desipramine, bupropion, and fluoxetine (antidepressants) and lithium (a mood stabilizer).

The review provided a narrative overview of the studies, because the variety of comparisons did not allow researchers to perform a meta-analysis or to quantify reliable conclusions. The available evidence suggested that there was no clear benefit for routinely adding long-term antidepressants to ongoing treatment with lithium. Moreover, the same review found that antidepressants may be less effective in preventing relapse when they are prescribed without a mood stabilizer (in this case, lithium).19

**Clinical implications**

There is some evidence20 that antidepressants are effective in the short-term treatment of bipolar depression, but a large recent trial reported no benefit10 and caution should be paid to the risk of manic switching. Alternative agents, such as quetiapine or lamotrigine, should be considered. When using an antidepressant, it may be prudent to use an SSRI or bupropion rather than a TCA or venlafaxine as first-line treatment. However, the patient history (ie, response to antidepressant treatment without adverse effects, including treatment-emerging manic switch) should be the best guide for choosing the individual treatment strategy.

Looking at the randomized evidence, there is no support for the addition of long-term antidepressants to ongoing treatment with a mood stabilizer for maintenance treatment in persons with bipolar depression. Early discontinuation following resolution of the acute episode should be consi-dered. Recurrence is frequent and associated with the presence of residual mood symptoms at initial recovery. Targeting residual symptoms in maintenance treatment may represent an opportunity to reduce the risk of recurrence. Given the limited evidence, there is a compelling need for further studies with longer follow-up and careful definition of the risk/benefit profile in terms of efficacy and tolerability.

Recent evidence found conflicting results about possible correlates between suicidality and antidepressant exposure.21,22 This aspect is of crucial importance when using antidepressants not
only for bipolar disorder but also for unipolar disorder, and it indicates important directions for further research. New pharmacological strategies with agents different from antidepressants are under investigation (quetiapine, lamotrigine, olanzapine, olanzapine plus fluoxetine) and need to be carefully evaluated to improve our therapeutic skills for treating bipolar depression.

References:


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