Antidepressants and Antipsychotics in the Long-Term Treatment of Bipolar Disorder

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Antidepressants and antipsychotics are frequently used as mood stabilizers in the treatment of bipolar disorder. As common as these agents appear to be in bipolar treatment, the literature contains little research on their efficacy and safety in the long term. Most of the available literature on long-term antidepressant treatment focuses on tricyclic antidepressants, which have been shown to induce mania or hypomania. Rapid cycling is another side effect that is associated with antidepressant treatment in bipolar disorder. Antidepressants do not appear to be any more effective than mood stabilizers in treating bipolar depression. Conventional antipsychotics in depot formulations have been shown to be an effective treatment, but conventional antipsychotics may cause tardive dyskinesia. The novel antipsychotics clozapine, risperidone, and olanzapine appear to be efficacious; however, their side effect profiles include agranulocytosis and weight gain. Given the frequency with which antidepressants and antipsychotics are used in bipolar disorder and that bipolar disorder is a chronic disease requiring maintenance treatment, more research on the use of these types of agents in long-term treatment is needed. Until more evidence is available on the long-term treatment outcomes, clinicians should be aware that the adverse events associated with antidepressants and antipsychotics may outweigh the benefit, if any, of the use of these agents in bipolar disorder.

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Antidepressants and antipsychotics are frequently used as mood stabilizers in the treatment of bipolar disorder. As common as these agents appear to be in bipolar treatment, the literature contains little research on their efficacy and safety in the long term. Existing research indicates that antidepressants do not appear to be more efficacious than traditional mood stabilizers in long-term treatment, whereas antipsychotics, especially novel antipsychotics, have been proven to be effective in the long term. Both classes carry the risk of adverse events, such as inducing mania or rapid cycling (antidepressants) or movement disorders, agranulocytosis, or weight gain (antipsychotics), that may make their use in long-term treatment inappropriate for patients with bipolar disorder.

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ANTIDEPRESSANTS IN LONG-TERM TREATMENT OF BIPOLAR DISORDER

Bipolar disorder is largely a condition of depression. Although diagnosis is often made on the presence of hypomania or mania, in the average patient with bipolar disorder, depressive episodes are more common than manic episodes. The first impairment associated with affective symptoms occurs in the middle of adolescence at approximately age 15 years,[1] so many months or years may go by during which time a person may experience only depressive episodes. Under certain conditions, depressive episodes can predict bipolarity (Table 1); however, full diagnostic criteria for bipolar disorder are frequently not reached until late adolescence or early adulthood when a manic or hypomanic episode occurs. If people receive treatment at all in the years between first episode and diagnosis, the treatment is usually with antidepressants.

Prevalence of Antidepressant Treatment

Once diagnosed with bipolar disorder, many patients continue to be treated with antidepressants. In fact, antidepressants may be more commonly prescribed than mood stabilizers in the treatment of bipolar depressed patients.[2] Fluoxetine, sertraline, and paroxetine have been reported

Table 1. Conditions in Depressed Patients That May Predict Bipolarity

Family history of bipolar disorder especially in first-degree relatives
Young age at the onset of depression
Psychotic symptoms as part of the depression
Agitated depression
Chronic depression or anxiety
Chronic, treatment-resistant depression
Prior pharmacologic-induced mania or hypomania
Reverse vegetative symptoms
Psychomotor retardation

as being among the most prescribed agents for this disorder. In a naturalistic study, Ghaemi et al.[3] reviewed the charts of outpatients diagnosed with affective disorders and found that 78% of patients with bipolar disorder had received antidepressants as treatment. Fifty-six percent of these patients had received mood stabilizers, and only 33% were treated with mood stabilizers alone. Despite the frequent use of antidepressants to treat bipolar disorder, few studies about the long-term treatment outcome of these agents can be found in the literature (Table 2).

Tricyclic Antidepressants

Much of the existing research on antidepressant use in the long-term treatment of bipolar disorder focuses on tricyclic antidepressants. A study from the early 1970s by Prien et al.[4] compared 44 patients with bipolar disorder taking imipramine, lithium, and placebo for 2 years. Lithium was the most effective of the 3 in preventing both mania and depression. Further, imipramine was no better than placebo in preventing depression. Several years later, Wehr and Goodwin[5] found that the 5 female patients in their study cycled nearly 4 times more rapidly while being treated with tricyclic antidepressants than when they were not receiving these agents. The patients, who had been diagnosed with Research Diagnostic Criteria (RDC) for major depressive type, bipolar type, were treated with tricyclics for several months to more than a year. The authors noted that although many patients received combination treatment, rapid cycling did not occur when tricyclics were absent.

Quitkin et al.[6] researched whether adding imipramine to lithium treatment would reduce the risk of depression in patients with bipolar I disorder. The study included 75 patients who met RDC for bipolar I illness and who were randomly assigned to either lithium-imipramine treatment (N = 37) or lithium-placebo treatment (N = 38). Patients spent an average of 19 months in the study. Of the 37 patients treated with adjunctive imipramine, 24% experienced manic relapses and 8% experienced depressive relapses. Among those patients receiving lithium and placebo, 10.5% had manic relapses and 10.5% had depressive relapses. Although these differences were not statistically significant, the authors concluded that imipramine may increase the risk for manic relapses. The low depressive relapse rates of both study groups prevented the authors from making any conclusions about the advantage of adding imipramine to lithium treatment. Later, the same research group[7] compared lithium, imipramine, their combination, and placebo in patients with unipolar or bipolar II illness. Forty-nine patients meeting RDC for unipolar illness (N = 27) and bipolar II illness (N = 22) spent a mean of 11 months in the study. Depressive relapses occurred in 8 of the patients with bipolar II disorder: 1 treated with lithium and imipramine, 1 treated with lithium, 2 treated with imipramine, and 4 treated with placebo. Mania occurred in 1 imipramine-treated patient and hypomania occurred in 1 placebo-treated patient.

In a double-blind study with a 2-year maintenance phase by Prien et al.,[8] 117 patients with RDC bipolar disorder were treated with lithium, imipramine, or both agents. Lithium was significantly more effective than imipramine in protecting against mania and was equally effective as imipramine in protecting against depression. Patients taking lithium experienced manic episodes at a rate of 26%, whereas 53% of patients taking imipramine experienced manic episodes, causing the authors to recommend that imipramine not be used for the long-term preventative treatment of bipolar disorder. The combination of lithium and imipramine provided no advantage over monotherapy.

Other Antidepressants

Sachs et al.[9] conducted a prospective double-blind study with bupropion, a norepinephrine dopamine reuptake inhibitor, and desipramine, a tricyclic, to assess efficacy and rate of treatment-emergent mania of these agents when they were added to lithium or anticonvulsant therapy. Results for 15 patients meeting DSM-III-R criteria for bipolar disorder, current episode of major depression, and a Hamilton Rating Scale for Depression (HAM-D) score ≥ 20 were determined after 8 weeks of acute treatment and during maintenance treatment of up to a year. Of the 15 patients, 4 crossed over to a second trial. In the first trial, 5 of 7 desipramine-treated and 5 of 8 bupropion-treated patients met criteria for antidepressant response. None of the patients crossed over to the second trial had a response. In the acute treatment phase, mania or hypomania occurred in 3 desipramine-treated patients and 1 bupropion-treated patient. In the maintenance phase, mania or hypomania occurred in 2 desipramine-treated patients but no bupropion-treated patients. Although the 2 agents had similar antidepressant efficacy, bupropion appeared less likely to induce mood elevation than desipramine.

Amsterdam et al.[10] studied the efficacy and safety of fluoxetine, a selective serotonin reuptake inhibitor, in the treatment of bipolar II depression. Eighty-nine patients with DSM-IV bipolar II disorder major depression were compared with 750 patients (N = 89 matched for age and gender, N = 661 unmatched) with unipolar major depression. All patients received fluoxetine therapy for up to 12 weeks.

Patients who remitted were then randomly assigned to receive one of the following treatments: (1) 52 weeks of fluoxetine, (2) 38 weeks of fluoxetine and 14 weeks of placebo, (3) 14 weeks of fluoxetine and 38 weeks of placebo, or (4) 52 weeks of placebo. Relapse rates were similar for the bipolar II and unipolar groups during long-term treatment. In short-term treatment, 3.8% of the bipolar II group, 0.3% of the unmatched unipolar group, and none of the matched unipolar group had a manic episode; in long-term treatment, 2% of the bipolar II group and 1% of the unmatched unipolar group had a manic episode. The authors concluded that fluoxetine was a safe and effective treatment with a relatively low manic switch rate for bipolar II depression.

Table 2. Research Outcomes in Long-Term Antidepressant Treatment

Study	Agents	Outcome
Prien et al[4]	Imipramine, lithium, placebo	Lithium most effective in preventing mania and depression; imipramine no better than placebo for depression
Wehr and Goodwin[5]	Amitriptyline, chlorpromazine, desipramine, imipramine, lithium, nortriptyline, phenelzine	Tricyclics induced rapid cycling
Quitkin et al[6]	Imipramine, lithium, placebo	Imipramine added to lithium increased risk for manic relapses
Kane et al[7]	Imipramine, lithium, placebo	Depression and mania occurred more frequently with imipramine and placebo
Prien et al[8]	Imipramine, lithium, placebo	Lithium significantly more effective than imipramine for mania and equally as effective for depression
Sachs et al[9]	Bupropion, desipramine	Mania occurred more frequently with desipramine
Amsterdam et al[10]	Fluoxetine, placebo	Mania occurred at a rate of 2% in bipolar disorder with fluoxetine

Adverse Events Associated With Antidepressant Treatment

As indicated by the research, antidepressants, especially tricyclics, carry a risk of inducing mania or hypomania. Although new antidepressants appear to have a low risk of causing a switch to mania or hypomania, only a few studies exist to support this hypothesis. Another adverse event associated with antidepressant treatment is the acceleration of the cycles of bipolar disorder.[5] Altshuler et al.[11] assessed the effect of antidepressants on cycle length by evaluating the life charts of 35 treatment-refractory patients with bipolar I and II disorder who had received heterocyclic antidepressants for at least 6 months. Of this group, 9 patients—5 from the bipolar I group and 4 from the bipolar II group—were judged to have antidepressant-induced cycle acceleration.

Without question, treating bipolar depression is imperative in maintaining the quality of life of patients with bipolar disorder, especially since repetitive or prolonged depressive episodes can have devastating effects on the brain and brain functioning. In the long-term treatment of bipolar depression, the literature suggests that not only do antidepressants increase the risk of mania, hypomania, and cycle acceleration, but they are also no more effective than mood stabilizers.

ANTIPSYCHOTICS IN LONG-TERM TREATMENT OF BIPOLAR DISORDER

Prevalence of Antipsychotic Treatment

Like antidepressants, antipsychotics are commonly used in the treatment of bipolar disorder. Many patients who enter an inpatient unit with mania continue to take antipsychotic medication for months after being discharged.[12–16] Verdoux et al.[15] surveyed a group of French psychiatrists and collected data on the maintenance treatment of 222 manic-depressive outpatients. Over two thirds of these patients were being treated with at least one antipsychotic, and 17% had been prescribed depot antipsychotics. A study by Keck et al.[14] found that 68% of patients in their study continued to receive antipsychotics 6 months after discharge. Research by Sernyak and colleagues[13] showed that, at the end of 6 months, patients who had been treated with adjunctive antipsychotic treatment in acute mania at index hospitalization were still receiving antipsychotics, although the decrease in mean daily dose at 6 months was statistically significant. Despite the frequency with which bipolar disorder is treated with antipsychotics, few studies exist on the efficacy and safety of these agents in the long-term treatment of bipolar disorder.

Conventional Antipsychotics

Conventional antipsychotics have been shown to prevent mania and to have a more rapid onset of action than lithium, but these agents appear to be less effective than lithium, valproate, and carbamazepine for long-term treatment of bipolar disorder.[17] Depot antipsychotics in the maintenance treatment of bipolar disorder have been reported to decrease mania but increase depressive episodes.[18] However, in a study with 18 patients who had been treated with depot antipsychotics for a mean of 8.2 years, Littlejohn et al.[19] found that patients spent less time in the hospital with manic ($p < .001$), depressed ($p < .05$), and mixed affective illness ($p < .01$) when being treated with depot antipsychotics.

Novel Antipsychotics

Novel antipsychotics have a more favorable side effect profile and effect on overall functioning than conventional

antipsychotics. Clozapine, the oldest of the novel antipsychotics, has been shown to be effective in the treatment of patients with schizoaffective and bipolar disorder who responded poorly to or were unable to tolerate mood stabilizers or conventional antipsychotics, but its use is limited by requirements for regular blood monitoring to avoid agranulocytosis. The efficacy of clozapine in affective disorders is reviewed by Zarate et al.[20] and Frye et al.[21] In their study, Zarate et al.[22] followed up with 17 patients with a DSM-III-R diagnosis of bipolar disorder for 16.1 ± 5.6 months after beginning clozapine treatment. Many of these patients had unsuccessful trials with valproate, lithium, carbamazepine, neuroleptics, combinations of these agents, or electroconvulsive therapy. Criteria for the effectiveness of clozapine were the number of hospitalizations before and during clozapine therapy, number of subsequent affective episodes, clinical response determined by the Clinical Global Impressions-Improvement scale (CGI-I), and absence of adding medications after discharge. At follow-up, 65% of patients continued to take only clozapine without any hospitalizations or affective episodes. Further, 88% of patients were considered responders to clozapine at follow-up, with response being defined as a CGI-I score of 1 or 2 (very much or much improved), whereas only 65% of patients had been considered responders at discharge.

In another study by Suppes et al.,[23] 38 treatment-resistant patients meeting DSM-IV criteria for schizoaffective or bipolar disorder were randomly assigned either to be treated with clozapine in addition to their usual treatment or to continue with their usual treatment for 1 year. Patients were assessed monthly using rating scales such as the Brief Psychiatric Rating Scale, the Clinical Global Impressions scale (CGI), and the HAM-D. Results showed that patients receiving clozapine therapy had statistically significant clinical improvement compared with patients receiving usual treatment.

More recently, Ciapparelli et al.[24] evaluated the efficacy of clozapine over a 24-month period in 91 patients with a principal DSM-III-R diagnosis of schizophrenia (N = 31), schizoaffective disorder (N = 26), or psychotic bipolar disorder (N = 34). All the patients had significantly improved after 24 months of clozapine therapy, with the greatest improvement appearing in the schizoaffective and bipolar groups. The authors concluded that clozapine was effective and relatively well tolerated in the long-term treatment of these patient populations.

To date there appears to be no evidence to support the long-term use of risperidone monotherapy in bipolar disorder; however, in clinical practice, patients with bipolar disorder are frequently treated with combinations of antipsychotics and other mood-stabilizing agents. The safety and efficacy of risperidone were researched in a 6-month, multicenter, open study conducted by Vieta et al.[25] Over 400 patients with DSM-IV bipolar and schizoaffective disorders had risperidone added to their mood-stabilizing treatment. Efficacy was assessed using the Young Mania Rating Scale (YMRS), the HAM-D, the Positive and Negative Syndrome Scale (PANSS), and the CGI. The addition of risperidone to treatment produced highly significant improvements ($p < .0001$) on the YMRS, HAM-D, CGI, and PANSS at 6 months. The authors concluded that risperidone is clinically effective when combined with conventional mood stabilizers for the treatment of bipolar and schizoaffective disorders.

Ghaemi and Sachs[26] studied the outcome of adding risperidone to the treatment regimen of 12 outpatients with bipolar I disorder who suffered breakthrough episodes, which are episodes of mania or depression that occur despite adequate treatment, for a mean of 6 months. Two patients stopped taking risperidone for lack of efficacy and 2 for adverse events. Of the 8 patients remaining, half showed improved scores on the Global Assessment of Functioning (GAF) scale and were rated much better on the CGI-I.

Olanzapine has been approved by the U.S. Food and Drug Administration for the treatment of acute mania in bipolar disorder, but, like clozapine and risperidone, little research explores its efficacy and safety in the long-term treatment of this disorder. In a 49-week extension of a 3-week double-blind study, 113 patients with DSM-IV bipolar disorder were treated with olanzapine.[27] Patients were allowed to take adjunctive lithium and fluoxetine during this extension. Efficacy was measured by the YMRS, the 21-item HAM-D, the CGI-Bipolar Version, and the PANSS. During treatment with olanzapine, 88.3% of patients experienced a remission of mania and significant improvement in 21-item HAM-D scores was observed ($p \leq .001$). Of the 113 patients in the extension, 41% were treated with olanzapine monotherapy. The authors concluded that olanzapine treatment, either alone or in combination with lithium and/or fluoxetine, improved mania and depressive symptoms in patients with bipolar disorder.

Narendran et al.[28] conducted a naturalistic study to determine the long-term effectiveness and tolerability of olanzapine therapy in psychotic mood disorders. Hospital records were reviewed for inpatients with a DSM-IV discharge or most recent chart diagnosis for schizophrenia (bipolar depressed type), bipolar disorder (I, II, and NOS) with psychotic features, or major depression with psychotic features. The control group was made up of patients with schizophrenia. Information on patients was obtained from a follow-up a minimum of 6 months after the initiation of olanzapine therapy. Follow-up information was available for 102 patients (N = 61 [psychotic mood disorders] and N = 41 [schizophrenia]), with a mean follow-up of 15 months. At follow-up, 50 of the 102 patients continued on olanzapine treatment, with the primary reason for discontinuation being lack of response for both

Table 3. Adverse Events Associated With Antipsychotic Treatment

Type of Agent	Adverse Event
Conventional antipsychotics	Extrapyramidal symptoms, tardive dyskinesia, tremor, hypokinetic parkinsonism, akathisia, dystonia, dysphoria, depression
Novel antipsychotics	
Clozapine	Agranulocytosis, seizure, orthostatic hypotension, weight gain
Risperidone	Mania, extrapyramidal symptoms, weight gain, depression
Olanzapine	Weight gain

patient groups. The patients with psychotic mood disorders (N = 32) and the patients with schizophrenia (N = 18) who continued with olanzapine treatment showed a statistically significant change toward improvement on the CGI and the GAF-Equivalent.

Vieta et al.[29] tested the long-term effectiveness of adjunctive olanzapine therapy in patients with treatment-resistant bipolar disorder. Patients (N = 23) meeting RDC for bipolar I and II disorder received open-label olanzapine. Prior to the study, all patients had frequent relapses, residual subsyndromal symptoms, and inadequate responses to drugs such as lithium, valproate, and carbamazepine. While taking olanzapine, patients continued their other medications. Patients were assessed throughout the study with the CGI. A significant reduction in CGI scores was noted after the introduction of olanzapine in the following areas: manic symptoms (p = .0015), depressive symptoms (p = .0063), or global symptoms (p = .0003).

However, the evidence for the efficacy of olanzapine for depressive symptoms, which are more common in many patients with bipolar disorder, is less clear than the evidence for its efficacy in mania. An unpublished 18-month study that compares the efficacy of adjunctive olanzapine therapy to lithium or valproate with placebo found that although olanzapine prevented manic recurrences, olanzapine was no better than placebo for preventing depressive recurrences.[30]

Adverse Events Associated With Antipsychotic Treatment

Several adverse events associated with conventional and novel antipsychotics may prevent them from being safe, tolerable treatments for bipolar disorder (Table 3). Side effects such as extrapyramidal symptoms (EPS) and tardive dyskinesia may occur with the long-term use of conventional antipsychotics. Further, patients with affective disorders may be at greater risk for developing tardive dyskinesia when compared with patients with schizophrenia.[31] Mukherjee at al.[32] studied the prevalence and outcome of persistent tardive dyskinesia in 131 bipolar patients. The patients were divided into 2 groups: those who had received neuroleptic treatment (N = 96) and those who had not (N = 35). Thirty-four patients previously treated with neuroleptics were diagnosed as having persistent tardive dyskinesia at some point during the study. Despite being treated with only lithium for a medium duration of 15 months, 14 patients continued to be classified as having persistent tardive dyskinesia. In another study,[33] the combination treatment of lithium and neuroleptics was associated with a high prevalence of EPS. The study sample included 110 patients with bipolar disorder, 18 with unipolar (major) depression, and 2 with atypical affective disorder. Patients were being treated as follows: 110 with only lithium, 37 with lithium and antidepressants, and 19 with lithium and neuroleptics. Forty patients had been treated with neuroleptics during the previous 6 months. Tremor was prevalent in 20.8% of the patients; hypokinetic parkinsonism, 7.7%; akathisia, 4.6%; dystonia, 3.8%; and tardive dyskinesia, 9.2%. Of 51 patients taking lithium with no neuroleptic treatment in the previous 6 months, 7 had symptoms of tardive dyskinesia. Finally, in addition to being associated with adverse events such as movement disorders, conventional antipsychotics used as long-term treatment may also worsen the course of illness by causing dysphoria or increasing the frequency of depressive episodes.[34]

Although clozapine appears to be an effective long-term treatment for bipolar disorder, this agent carries with it several adverse events such as agranulocytosis, seizure, and orthostatic hypotension. Because agranulocytosis is potentially deadly, weekly white blood cell counts are required for the first 6 months of clozapine treatment. If the counts stay within normal range during that time, they may be measured every 2 weeks thereafter. Such frequent blood monitoring may interfere with compliance, so clozapine is recommended only for treatment-resistant patients.

Several cases of risperidone-induced mania have been reported in the literature.[21] Vieta et al.[25] reported mania being exacerbated in 2% of patients in the first 6 weeks of their study, with the most common adverse events being extrapyramidal symptoms and weight gain. No patient's mania worsened while taking risperidone in the study by Ghaemi and Sachs,[26] but 1 patient was reported as having a major depressive episode during week 22.

Weight gain is frequently cited as a side effect of olanzapine treatment,[27–29] but clozapine[35] and risperidone[25] have also been associated with weight gain. Allison et al.[35] conducted a study that compared the effects of antipsychotics on body weight and found that the mean weight increase after 10 weeks of treatment was 4.45 kg (9.89 lb) for clozapine, 4.15 kg (9.22 lb) for olanzapine, and 2.92 kg (6.49 lb) for risperidone. Increased weight may lead to the development of diabetes, which raises concern about the safety of these novel antipsychotics for long-term treatment. Treatment with novel antipsychotics must include an assessment, at baseline, of patients' family history of obesity, diabetes, and cardiovascular disease; body mass index; lipid and triglyceride levels; and fasting blood

glucose or hemoglobin A_{1c}. Body mass index and blood levels should then be monitored every 6 months or annually during antipsychotic treatment.

CONCLUSION

Despite the paucity of research on antidepressants and antipsychotics in the long-term treatment of bipolar disorder, patients are commonly treated with these agents for months or years. Given the frequency with which antidepressants and antipsychotics are used in bipolar disorder and that bipolar disorder is a chronic disease requiring maintenance treatment, more research on the use of these types of agents in long-term treatment are needed. Until more evidence is available on the long-term treatment outcomes, clinicians should be aware that adverse events such as mania, rapid cycling, movement disorders, agranulocytosis, and weight gain may outweigh the benefit, if any, of the use of antidepressants and antipsychotics in bipolar disorder.

Drug names: amitriptyline (Elavil and others), bupropion (Wellbutrin and others), carbamazepine (Epitol, Tegretol, and others), chlorpromazine (Sonazine, Thorazine, and others), clozapine (Clozaril and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), nortriptyline (Aventyl, Pamelor, and others), olanzapine (Zyprexa), paroxetine (Paxil), phenelzine (Nardil), risperidone (Risperdal), sertraline (Zoloft).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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