Employing Pharmacologic Treatment of Bipolar Disorder to Greatest Effect

Alan F. Schatzberg, M.D.

Mechanisms of action, onset and duration of action, and interactions with other medications—all of these pharmacokinetic properties of pharmacologic agents affect the efficacy and safety of therapeutic regimens for bipolar disorder. For example, antiglutamatergic agents such as lamotrigine may relieve depression but have no impact on mania. Atypical antipsychotics with the dual effect of blocking dopamine and serotonin receptors in the brain decrease psychosis, mania, and, according to some preliminary indications, possibly depression. The impact of these properties has been borne out in clinical studies. Mood stabilizers such as lithium and valproate stabilize mood by significantly decreasing the manic and hypomanic symptoms of bipolar disorder, although they can have effects on depressive symptoms too. Lamotrigine stabilizes mood by reducing depression. The atypical antipsychotics have been shown to be effective either as monotherapy or in combination with mood stabilizers. *(J Clin Psychiatry 2004;65[suppl 15]:15–20)*

TREATMENT OVERVIEW

Bipolar disorder has diverse clinical manifestations, with wide variance in symptoms, course of disease, severity, and response to treatment. Therefore, implementing a treatment regimen for both acute episodes of bipolar disorder and long-term maintenance therapy requires a thorough consideration of each drug's pharmacologic profile, including its mechanisms and onset of action, its half-life, and its potential for interacting with other pharmaceuticals. For example, a rapid onset of action may be an important factor for patients experiencing a severe acute episode and/or suicidal symptoms.

In addition to considering these properties, clinicians also can consult the American Psychiatric Association (APA) Practice Guideline for the Treatment of Patients With Bipolar Disorder.[1] For severe acute mania, the guideline recommends that therapy be initiated with a combination of lithium or valproate plus an antipsychotic, preferably one of the atypical antipsychotics, which generally have fewer adverse effects than do typical antipsychotics. In less severe cases, lithium, valproate, or an antipsychotic alone are preferred, and a benzodiazepine also may be helpful.[1]

For acute bipolar depressive episodes, the APA Practice Guideline recommends initial treatment with lithium or lamotrigine, with more clinical evidence supporting the former.[1] The U.S. Food and Drug Administration has approved lamotrigine to help lengthen the time between mood episodes for people receiving treatment for bipolar disorder, but not for the treatment of acute bipolar depression. Monotherapy with an antidepressant is not recommended due to the risk for precipitating a switch to mania, and antidepressants usually have been employed as add-on treatments to lithium or valproate. In patients with life-threatening inanition, suicidality, or psychosis, electroconvulsive therapy (ECT) is considered a reasonable alternative. ECT also is a potential treatment for severe depression in pregnant women. If patients fail to respond to optimal doses of a mood stabilizer, the guideline suggests adding lamotrigine, bupropion*, or paroxetine* or another class of antidepressant.[1] However, the APA guideline states that the clinician should make the ultimate decision about treatment regimen based on patient diagnosis and treatment options.

MECHANISMS OF ACTION

The agents used most often for bipolar disorder are mood stabilizers, conventional antipsychotics, atypical antipsychotics, and antiepileptic drugs. The putative mechanisms of action of these agents include interactions with receptors for gamma-aminobutyric acid (GABA), dopamine, serotonin, and other neurotransmitters[2] (Table 1).

Among the mood stabilizers, lithium acts on inositol and related second messenger systems. The mechanisms

From the Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, Calif.

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Corresponding author and reprints: Alan F. Schatzberg, M.D., Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, 401 Quarry Rd., Stanford, CA 94305-6811.

Table 1. Bipolar Disorder Treatment Options and Their Mechanisms of Action

Treatment Option	Drug	Mechanism of Action
Mood stabilizers	Lithium, valproate	Lithium exerts multiple effects, including on inositol activity; valproate is GABAergic
Conventional antipsychotics	Chlorpromazine, haloperidol*	D_2 receptor blockade
Atypical antipsychotics	Clozapine*, olanzapine, risperidone, quetiapine, ziprasidone*, aripiprazole*	Mechanisms differ by agent and include blockade of D_2 receptors and 5-HT_2 receptors; potential GABAergic effects
Antiepileptics	Lamotrigine, carbamazepine*, oxcarbazepine*	Glutamatergic (lamotrigine); GABAergic (carbamazepine, oxcarbazepine)

*These agents have not been approved by the Food and Drug Administration for the treatment of bipolar disorder.
Abbreviations: D_2 = dopamine-2, 5-HT_2 = serotonin-2, GABA = gamma-aminobutyric acid.

Table 2. Receptor-Binding Characteristics and Effects of Various Antipsychotics[a]

	Drug[a]						
Receptor	Haloperidol	Clozapine	Risperidone	Olanzapine	Quetiapine	Ziprasidone	Effect of Blockade[b]
5-HT_{2A}	+	+++	+++++	++++	+	++++	Negative symptoms decrease, mitigates EPS
D_2	++++	++	++++	+++	++	++++	Positive symptoms decrease, EPS, endocrine effects
α_2	NA	+++	+++	NA	+	NA	Antidepressant (?)
α_1	++	+++	+++	+++	++++	++	Hypotension, dizziness, reflex tachycardia
Histamine H_1	NA	++++	++	++++	++++	+	Sedation, weight gain
Muscarinic M_1	NA	+++++	NA	+++++	+++	NA	Memory dysfunction, anticholinergic effects, mitigates EPS

[a]Adapted with permission from Pickar.[5]
[b]Data from Richelson.[4]
Abbreviations: D_2 = dopamine-2, EPS = extrapyramidal symptoms, 5-HT_{2A} = serotonin-2A, NA = not applicable.

of action of the other mood stabilizers, valproate and oxcarbazepine*, may be related to inhibition of GABA metabolism, stimulation of GABA synthesis and release, or augmentation of the postsynaptic inhibitory effect of GABA. The antiepileptic agent lamotrigine has been found to block glutamate activity. Other antiepileptics—carbamazepine* and topiramate*, specifically—may have GABAergic properties similar to the mood stabilizers.[2]

Conventional antipsychotics such as chlorpromazine and haloperidol* are dopamine antagonists with affinity for both the dopamine-1 (D_1) and D_2 receptors but with a greater affinity for D_2 receptors. Blockade of D_2 receptors in the midbrain is thought to decrease symptoms of psychosis and mania. Atypical antipsychotics block both D_2 and serotonin-2 (5-HT_2) receptors, which could contribute to antimanic and antidepressive effects, respectively. Atypical antipsychotics also increase prefrontal dopamine activity, providing antidepressive and cognitive-enhancing effects. Blockade of 5-HT_2 receptors may increase dopamine release in the striatum, an effect that may lead to fewer extrapyramidal symptoms (EPS). In addition, atypical antipsychotics may have some GABAergic actions.[2]

CLINICAL APPLICATIONS

Antiglutamatergic agents such as lamotrigine decrease the activity of glutamate, an excitatory neurotransmitter. These medications may relieve depression, but do not affect mania in patients with bipolar disorder. Antiglutamatergic agents offer the advantage of causing no weight gain, a side effect of mood stabilizers and antipsychotics, and may even promote weight loss.[2]

The different mechanisms of action of these agents are reflected in the way in which they stabilize mood. For example, double-blind, placebo-controlled studies of lamotrigine have demonstrated the drug's efficacy in bipolar depression, rapid-cycling bipolar disorder, and treatment-resistant rapid-cycling bipolar disorder.[3] According to Ketter and Wang,[2] lamotrigine may "stabilize mood from below" by exerting its greatest effects on the depressive symptoms of bipolar disorder. In contrast, the older mood stabilizers, lithium, carbamazepine, and valproate, act to "stabilize mood from above" by significantly affecting the manic or hypomanic symptoms of bipolar disorder.[2]

In separate studies, Richelson[4] and Pickar[5] delineated the receptor-binding profiles of several antipsychotic agents (Table 2). As demonstrated by in vitro and positron emission tomography studies, the therapeutic and adverse effects of these drugs are related to their activity on various receptor binding sites. For example, the affinity of haloperidol, olanzapine, risperidone, and ziprasidone* for the D_2 receptor partially accounts for the efficacy of these drugs in controlling the positive effects (e.g., hallucinations and delusions) of psychosis.[5]

The results of these studies and continuing clinical trials have led to the definition of an atypical antipsychotic as a drug that, in most cases, is effective against psychosis and causes few EPS and virtually no tardive dyskinesia.

MONOTHERAPY CLINICAL TRIALS

Clinical studies of atypical antipsychotic agents such as olanzapine, risperidone, and ziprasidone have shown them to be effective as monotherapy for acute mania and in the long-term management of mania. Atypical antipsychotics have been found to be effective for patients with pure and mixed features, in rapid and nonrapid cycling, and in patients with or without psychotic features. Atypical antipsychotics also appear to be effective in patients who are refractory to mood stabilizers and conventional antipsychotics.

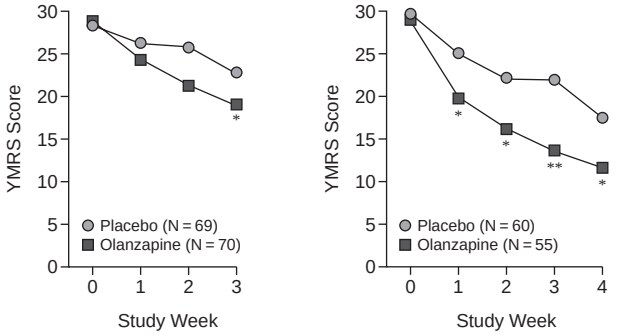
Olanzapine[6–11] and risperidone[12,13] have demonstrated efficacy in monotherapy and combination trials. Other atypical antipsychotics that have had successful clinical trials for the treatment of mania are aripiprazole*,[14] ziprasidone*,[15] and quetiapine.[16]

In 2 separate studies by Tohen and colleagues[6,7] of olanzapine in bipolar manic or mixed episodes, statistically significant reductions in Young Mania Rating Scale (YMRS) scores were observed in patients taking olanzapine as compared with placebo (Figure 1). Olanzapine was equally effective in treating mania with or without psychotic features. Dizziness, dry mouth, weight gain, and treatment-emergent somnolence were seen significantly more often in patients treated with olanzapine than in those receiving placebo. Olanzapine and haloperidol given as monotherapy produced similar remission rates for acute mania.[8]

Olanzapine demonstrated efficacy in treating patients with a history of rapid-cycling bipolar disorder in a relatively small (N = 45), placebo-controlled, 3-week study.[9] Olanzapine reduced YMRS total scores significantly ($p = .011$) more than did placebo. A higher percentage of patients treated with olanzapine achieved clinical responses (defined as an improvement in YMRS scores of ≥ 50%), but the difference was not significantly ($p = .06$) greater than with placebo.

Long-term studies with olanzapine have investigated the drug's use in maintenance therapy for up to 1 year. In a 47-week comparative study with divalproex,[10] olanzapine was associated with faster symptomatic remission and greater overall improvement in mania than was divalproex in 251 patients experiencing manic and mixed episodes of bipolar disorder. Median time to symptomatic mania remission was 14 days for olanzapine, compared with 62 days for divalproex. Patients treated with olanzapine also had significantly ($p = .002$) greater improvements in YMRS scores between weeks 2 and 23. However, no significant differences between the 2 treatments were found in symptom management from week 30 to the end of the study or in rates of subsequent relapses into mania or depression. Treatment-emergent adverse events occurring more frequently with olanzapine than divalproex were somnolence, dry mouth, weight gain, akathisia, and high alanine aminotransferase levels; more frequent side effects with divalproex were nausea and nervousness.

Figure 1. Change From Baseline in Young Mania Rating Scale (YMRS) Scores for Patients Taking Olanzapine Monotherapy or Placebo for Acute Mania[a]



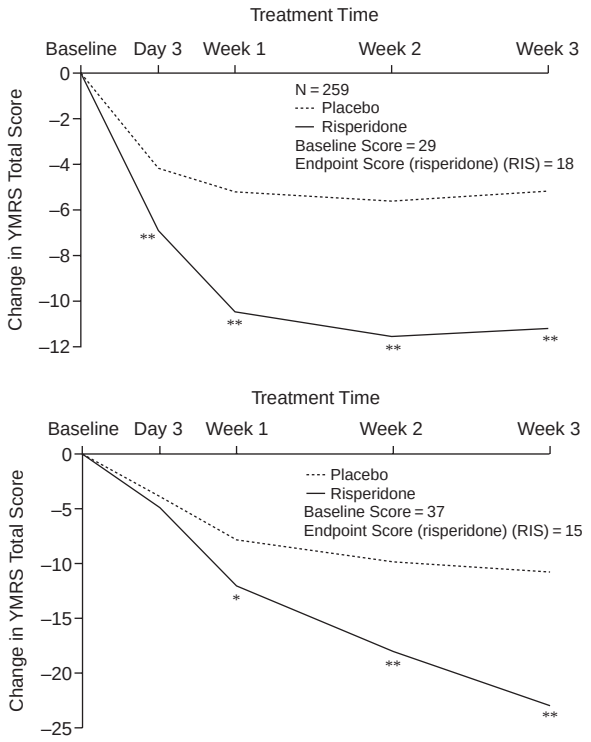
[a]From Tohen et al.[6] (left) and Tohen et al.[7] (right), with permission.
*$p < .05$.
**$p < .01$ vs. placebo.

Olanzapine was significantly more effective than lithium in preventing relapse to mania but not depression in a 52-week study.[11] In the first acute phase of the study, a combination of the 2 agents was used for 6 to 12 weeks. Of the 543 patients with manic or mixed type bipolar I disorder who entered the clinical study, 431 fulfilled the symptomatic remission criteria of a YMRS score of ≤ 12 and a 21-item Hamilton Rating Scale for Depression (HAM-D-21) score of ≤ 8 after the acute phase. Patients treated with olanzapine had a significantly ($p < .001$) lower rate of relapse to mania after 52 weeks of therapy than did patients receiving lithium. However, the differences between the 2 groups were not statistically significant in preventing relapse to an affective episode, and the 2 drugs were equally effective in preventing relapse to a depressive episode. A statistically significant ($p < .001$) weight gain of 1.8 kg occurred among patients receiving olanzapine during the maintenance phase, compared with a weight loss of 1.4 kg among those treated with lithium.

Hirschfeld et al.[12] and Vieta et al.[13] presented data from 2 separate clinical trials that showed risperidone's effectiveness in reducing YMRS scores (Figure 2). Patients receiving risperidone experienced significantly greater improvements in symptoms by 3 or 7 days after starting therapy than did patients given placebo. Risperidone therapy led to a statistically significant ($p < .001$ in both studies) greater reduction in endpoint YMRS scores compared with placebo. The side effects associated with risperidone have included weight gain, drowsiness, a risk for elevated prolactin levels, and, at higher doses, EPS.

In a 3-week placebo-controlled trial,[14] aripiprazole-treated patients with acute bipolar mania had greater reductions in score on the YMRS than did those in the group

Figure 2. Risperidone Monotherapy for Acute Mania[a]



[a]From Hirschfeld et al.[12] (top) and Vieta et al.[13] (bottom), with permission.
*p < .01 vs. placebo; last-observation-carried-forward analysis.
**p < .001 vs. placebo; last-observation-carried-forward analysis.
Abbreviation: YMRS = Young Mania Rating Scale.

receiving placebo. Forty percent of patients receiving aripiprazole were rated as responders (≥ 50% reduction in manic symptoms), compared with 19% given placebo. Adverse effects of aripiprazole included headache, nausea, dyspepsia, somnolence, and agitation; discontinuation rates were comparable between the study groups, and little variation in body weight was observed.

A 3-week, placebo-controlled study[15] evaluated ziprasidone versus placebo in adult patients with acute bipolar mania. Treatment with ziprasidone produced a 12.4-point reduction in the Mania Rating Scale score, compared with a reduction of 7.8 points for the placebo group. Improvement began at day 2 and was maintained through day 21. Somnolence was the most common side effect, followed by dizziness and headache. Rates of EPS were low, and no weight gain was found in the ziprasidone group.

Research into the use of quetiapine for the treatment of bipolar disorder has been limited. No systematic studies with large patient populations on the efficacy of quetiapine in the prevention of bipolar disorder have been conducted. An open-label study[16] compared the efficacy of quetiapine and a mood stabilizer in maintenance treatment of 28 outpatients who were randomized to receive either agent at flexible doses for 12 months. The patients were evaluated with the Brief Psychiatric Rating Scale (BPRS), Clinical Global Impressions scale (CGI), YMRS, and HAM-D at baseline and every 2 months until the end of the study. All patients treated with quetiapine experienced significant improvements in BPRS, CGI, and HAM-D scores, with no significant side effects and good compliance. This study should be considered preliminary, given the small patient population and the open-label design.

Calabrese and colleagues[17] reported a significant improvement in Montgomery-Asberg Depression Rating Scale scores for patients with bipolar depression treated with lamotrigine at 50 mg/day or 200 mg/day compared with placebo beginning at 3 weeks and continuing to the end of the 7-week study. However, the mean observed score on the 31-item HAM-D was significantly reduced only for patients receiving 200 mg of lamotrigine compared with placebo and only at week 4. The HAM-D scores at the last observation carried forward were not significantly different from placebo with either dose of lamotrigine.[17]

Lamotrigine also has been found to be effective as a maintenance therapy in prolonging the time to recurrence, particularly for bipolar depression.[3] Lamotrigine has not demonstrated efficacy in the treatment of acute mania.[18] The most common adverse events in studies with lamotrigine have been headache, nausea, infection, and insomnia. The dosage of lamotrigine must be titrated over a 6-week period to minimize the incidence of serious rash, including Stevens-Johnson syndrome.[18]

Table 3 lists the onset and duration of action and other pharmacologic characteristics of atypical antipsychotics when used as monotherapy in bipolar disorder.[6,7,12,13,19,20] Onset of action for all atypical antipsychotics appears to be relatively rapid (2 to 7 days), and duration of action, at least 4 weeks. For many of the agents, separation from placebo occurs at week 1 with reasonable effect sizes.

COMBINATION THERAPY CLINICAL TRIALS

As many as 40% of patients with bipolar disorder respond poorly to monotherapy with lithium or valproate,[21] and, at some point, the vast majority of patients with bipolar disorder require combination therapy for long-term maintenance.

Combination regimens of a mood stabilizer plus an antipsychotic have provided a greater degree of efficacy than has either agent used alone. Controlled trials of lithium or divalproex sodium plus an antipsychotic have reported increased overall efficacy and a quicker onset of action than when these agents are used alone.[21–23] In addition, antipsychotic doses can be kept relatively low in combination therapy, thereby helping to reduce the risk for side effects.

Table 3. Atypical Antipsychotics as Monotherapy in Mania: Efficacy and Onset of Action

Study	Atypical Antipsychotic	Study Duration, wk	Mean Change From Baseline[a]	Relative Effect[b]	Measured Onset of Action Day[c]
Tohen et al[6]	Olanzapine	3	–10.3	5.4	7
Tohen et al[7]	Olanzapine	4	–14.8	6.7	7
Keck et al[19]	Ziprasidone	3	–12.4[d]	4.7[d]	2
Keck et al[20]	Aripiprazole	3	–8.2	4.8	4
Hirschfeld et al[12]	Risperidone	3	–11.1	6.1	3
Vieta et al[13]	Risperidone	3	–22.7	12.2	7

[a]Mean change from baseline to endpoint in Young Mania Rating Scale total score.
[b]Difference in change from baseline between active and placebo groups.
[c]First timepoint with significant difference from placebo.
[d]Mania Rating Scale.

For example, olanzapine combined with a mood stabilizer was significantly more effective than monotherapy with a mood stabilizer in a 6-week double-blind, placebo-controlled study with 344 patients with manic or mixed episodes of bipolar disorder who had shown inadequate responses to a mood stabilizer.[21] Olanzapine cotherapy produced statistically significant ($p < .001$) improvements in clinical responses on the YMRS and the HAM-D. The most common side effects were somnolence, dry mouth, weight gain, increased appetite, tremor, and slurred speech.[22]

Risperidone plus a mood stabilizer given for 6 months in a large ($N = 541$) open-label study produced highly significant ($p < .0001$) improvements in both mania and depression.[22] Adverse events, the most frequent of which were EPS and weight gain, were classified as mild. The study by Vieta et al.[22] is one of the few trials to demonstrate the efficacy of an atypical antipsychotic in treating bipolar depression. Overall mean scores on the HAM-D decreased significantly ($p < .0001$) from 12.8 at baseline to 4.1 after 6 months of therapy with risperidone. The potential effectiveness of risperidone in treating depression had been demonstrated previously in an analysis of combined data from 2 clinical studies of 513 patients with schizophrenia.[23] Risperidone produced considerable improvement in treating depression compared with haloperidol and placebo. The authors postulated that atypical antipsychotics that are 5-HT_2 and D_2 antagonists have qualitatively different effects than do conventional antipsychotics.

In a 3-week randomized, double-blind, placebo-controlled study in patients with acute mania,[24] risperidone plus a mood stabilizer was compared with haloperidol plus a mood stabilizer and with placebo plus a mood stabilizer. The addition of risperidone to lithium or divalproex was as efficacious as haloperidol, and both were superior to a mood stabilizer plus placebo for the rapid reduction of manic symptoms. Risperidone produced significantly greater mean improvements (–16.6) on the YMRS than did placebo (–13.4), as did haloperidol (–15.4). Adjunctive risperidone was more effective than a mood stabilizer alone in patients with and without psychosis, as well as in those with pure manic episodes. Risperidone appeared to be well tolerated; however, the mean weight gain for patients receiving risperidone was significant compared with that for placebo. Other adverse effects associated with risperidone and haloperidol were somnolence, headache, dizziness, and dyspepsia.

A prospective study examined the efficacy of risperidone plus a mood stabilizer in the treatment of mania for 12 weeks in 108 patients with manic or mixed bipolar disorder.[25] The combination therapy produced a significant (–22.6, $p < .0001$) decrease by week 12 in mean ± SD YMRS scores from a baseline score of 27.5 ± 7.5. The risperidone and mood stabilizer combination also led to a significant reduction (–5.7, $p < .0001$) by week 12 in mean 21-item HAM-D scores from a baseline score of 12.2 ± 7.7.

Preliminary, small open-label trials suggest a potential adjunctive role for quetiapine in patients who are suboptimally responsive to mood stabilizers[26] or as an alternative maintenance therapy.[16] Quetiapine may also have a role in the treatment of younger patients. Adolescents with manic or mixed bipolar I disorder given quetiapine plus divalproex had significantly greater reductions in YMRS scores than did the divalproex plus placebo group (87% vs. 53%, respectively).[27] Sedation was the most notable adverse effect of treatment and was significantly more common in the quetiapine plus divalproex group, occurring in 12 of the 15 patients receiving quetiapine.

Problems can arise from the pharmacokinetics of combination therapy. For example, the antiepileptic carbamazepine reduces the blood levels of atypical antipsychotics if the 2 types of agents are used in cotherapy.[28]

SUMMARY

Most clinical trials have demonstrated that the medications for bipolar disorder are effective for treating only 1 pole of bipolar disorder. Atypical antipsychotics should be considered for rapid control of acute mania and for maintenance. However, a few clinical trials indicate that the atypical antipsychotics may have a role in the treatment of bipolar depression. The effects of the mood stabilizers on

GABA metabolism account for their ability to control mania, while antiglutamatergic agents such as lamotrigine are effective for bipolar depression. Unlike both atypical antipsychotics and mood stabilizers, lamotrigine does not cause weight gain.

When selecting initial and maintenance therapies, clinicians should balance efficacy with the prevalence and severity of side effects such as weight gain, sedation, and EPS that can prompt patients to discontinue therapy.

*These agents have not been approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder.

Drug names: aripiprazole (Abilify), bupropion (Wellbutrin and others), carbamazepine (Carbatrol, Tegretol, and, others), chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril and others), divalproex sodium (Depakote), haloperidol (Haldol and others), lamotrigine (Lamictal), lithium (Lithobid, Eskalith, and others), olanzapine (Zyprexa), oxcarbazapine (Trileptal), paroxetine (Paxil and others), quetiapine (Seroquel), risperidone (Risperdal), topiramate (Topamax), ziprasidone (Geodon).

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