

# The Efficacy of Atypical Antipsychotics in Bipolar Disorders

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Current treatment options for patients with bipolar spectrum disorders are expanding. New evidence in the treatment of various phases of illness of bipolar disorder is emerging. Atypical antipsychotic medications, used as monotherapy or as adjunctive therapy with mood stabilizers, have shown efficacy as well as well-tolerated side effect profiles, thus becoming valuable new resources in the treatment of bipolar disorder.  
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Over the past several decades, substantial progress has been made in the pharmacologic treatment of bipolar disorder. In 1972, lithium was approved by the U.S. Food and Drug Administration (FDA) for the treatment of manic episodes of bipolar disorder and as maintenance treatment.<sup>1</sup> More than 20 years later, divalproex was approved for the treatment of acute manic episodes in patients with bipolar disorder. In 2000, olanzapine, an atypical antipsychotic, was approved for the acute treatment of mania. In addition to these 3 medications, a number of other compounds have been investigated in the treatment of various phases of bipolar disorder. These have included anticonvulsants, antidepressants, conventional antipsychotics, and, most recently, atypical antipsychotics.

Because of the recency of presentation and publication of the results of these studies, this evidence is not well known. In the spirit of disseminating these new data to clinicians, this article will review important research findings on the efficacy and tolerability of clozapine, olanzapine, and risperidone and 3 of the newer atypical antipsychotics—quetiapine, ziprasidone, and aripiprazole—for acute mania, depression, and maintenance in bipolar disorder.

## CLOZAPINE

Clozapine is the prototype for all the atypical antipsychotics. Its pharmacology differs from conventional antipsychotics.<sup>2</sup> It is a serotonin-2A (5-HT<sub>2A</sub>)-dopamine-2

(D<sub>2</sub>) receptor antagonist that binds to several other neurotransmitter receptors. The success of clozapine for treatment-resistant schizophrenia led to its testing in patients with refractory bipolar disorder, although requirements for regular blood monitoring due to its risk of agranulocytosis restrict its use.

The efficacy of clozapine monotherapy in patients with treatment-resistant bipolar disorder has been reported in 2 open-label studies.<sup>3,4</sup> In a 13-week trial<sup>3</sup> of clozapine in 25 acutely manic, treatment-resistant patients with either bipolar disorder (N = 10) or schizoaffective disorder-bipolar subtype (N = 15) (DSM-III-R criteria for manic phase), 72% of patients showed marked improvement from baseline to endpoint on either Young Mania Rating Scale (YMRS) or Brief Psychiatric Rating Scale (BPRS) scores. A 12-week study<sup>4</sup> of 22 patients with treatment-resistant bipolar disorder with manic and psychotic symptoms reported similar results. For all subjects, the difference in scores from baseline to endpoint on the BPRS, YMRS, and the Clinical Global Impressions (CGI) scale was significant ( $p < .0001$ ). Further, 17 (77%) of the 22 patients experienced at least a 20% improvement on all 3 scales.

In a 3-week open-label augmentation study,<sup>5</sup> 30 patients with bipolar disorder (DSM-IV), acute mania, were randomly assigned to clozapine plus lithium (N = 15) or the conventional antipsychotic chlorpromazine plus lithium (N = 12) (3 dropped out during week 1). Although the administration of both clozapine and chlorpromazine caused a substantial decrease in YMRS scores, clozapine had a highly significant ( $p < .0001$ ) effect over time in decreasing mania.

Open-label clinical trials of clozapine as a potential mood stabilizer in bipolar disorder suggest that clozapine has greater antimanic than antidepressant properties.<sup>2</sup> Data from prospective studies suggest that clozapine monotherapy is effective for acute affective episodes (particularly mania), and a retrospective review of the literature sug-

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Table 1. Efficacy of Olanzapine in Double-Blind Trials in Bipolar Disorder

Study Phase	Total N	Dose (range)	Duration	Primary Outcome Measures	Results
<b>Mania</b>					
<b>Monotherapy</b>					
Tohen et al <sup>6</sup>	139	Olanzapine 10 mg/d <sup>a</sup> (5–20 mg/d) + lorazepam ≤ 4 mg/d	3 wk	YMRS	Olanzapine + lorazepam > placebo
Tohen et al <sup>7</sup>	115	Olanzapine 15 mg/d <sup>a</sup> (5–20 mg/d) + lorazepam ≤ 2 mg/d	4 wk	YMRS	Olanzapine + lorazepam > placebo
Tohen et al <sup>8</sup>	251	Olanzapine 15 mg/d <sup>a</sup> (5–20 mg/d) vs divalproex 750 mg/d <sup>a</sup> (500–2500 mg/d)	3 wk	YMRS	Olanzapine > divalproex
Zajecka et al <sup>9</sup>	120	Olanzapine 14.7 mg/d <sup>b</sup> (5–25 mg) vs divalproex 2115 mg/d <sup>b</sup> (750–3250 mg)	12 wk	SADS-C MRS, BPRS, HAM-D, CGI-S	Olanzapine = divalproex
Tohen et al <sup>10</sup>	453	Olanzapine (5–20 mg/d) vs haloperidol (3–15 mg/d)	6 wk	YMRS, MADRS	Olanzapine > haloperidol
<b>Combination</b>					
Tohen et al <sup>11</sup>	344	Olanzapine (5–20 mg/d) + mood stabilizer vs placebo + mood stabilizer	6 wk	YMRS, HAM-D	Olanzapine + mood stabilizer > placebo + mood stabilizer
<b>Depression</b>					
Tohen et al <sup>14</sup>	733	Olanzapine (5–20 mg/d) vs olanzapine (6 or 12 mg/d) + fluoxetine (25 or 50 mg/d)	8 wk	MADRS	Olanzapine, olanzapine + fluoxetine > placebo; olanzapine + fluoxetine > olanzapine

<sup>a</sup>Initial dose.<sup>b</sup>Mean maximum daily dose.

Abbreviations: BPRS = Brief Psychiatric Rating Scale; CGI-S = Clinical Global Impressions scale, Severity subscale; HAM-D = Hamilton Rating Scale for Depression; MADRS = Montgomery-Asberg Depression Rating Scale; SADS-C MRS = Schedule for Affective Disorders and Schizophrenia-Change version, Mania Rating Scale; YMRS = Young Mania Rating Scale.

gests better clozapine responses in schizoaffective or bipolar patients compared with patients with schizophrenia.<sup>2</sup> Although there are no double-blind, controlled trials of clozapine in the treatment of acute mania, clozapine has shown promise as an antimanic drug for patients who do not respond to first-line agents.<sup>2</sup>

## OLANZAPINE

Olanzapine has shown efficacy in the treatment of both the manic and depressive phases of bipolar disorder (Table 1).

### Mania

**Monotherapy.** Several studies in mania have investigated the efficacy and safety of olanzapine monotherapy and found that olanzapine is superior to placebo<sup>6,7</sup> and superior to or equally efficacious as divalproex<sup>8,9</sup> in treating acute mania.

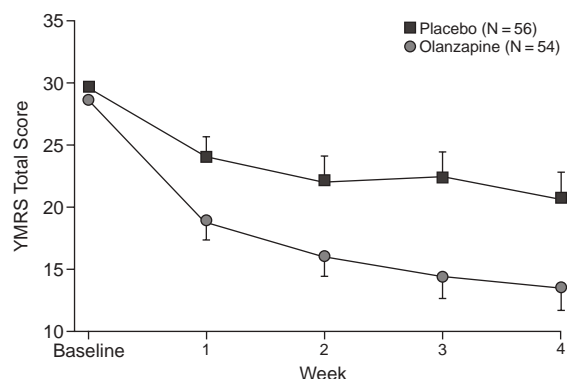
Tohen et al. conducted 2 separate randomized, double-blind, placebo-controlled studies comparing the efficacy and safety of olanzapine with placebo in patients diagnosed with DSM-IV bipolar disorder (manic or mixed).<sup>6,7</sup> Differences between the 2 study designs included olanzapine dose, dose of concomitant lorazepam, and study duration. In the first study, olanzapine-treated patients received an initial dose of 10 mg/day, liberal use of lorazepam was allowed, and study duration was 3 weeks.<sup>6</sup> The initial olanzapine dose in the second study was in-

creased to 15 mg/day, the use of lorazepam was cut approximately in half, and study duration was increased to 4 weeks.<sup>7</sup> The primary efficacy measure for both studies was a change from baseline to endpoint in the YMRS total score. Similar mean differences in YMRS total scores between the olanzapine and placebo groups were reported in both studies (–5.4 points [ $p = .02$ ] and –6.7 points [ $p < .001$ ], respectively), but a larger percentage of patients responded in the second study (34/70 [49%] vs. 35/54 [65%], respectively).

In the 4-week study,<sup>7</sup> olanzapine-treated patients demonstrated a statistically significant greater improvement in the mean change from baseline in the YMRS total score at the first postbaseline observation at week 1 ( $F = 4.78$ ,  $df = 1,86$ ;  $p = .03$ ; Figure 1), which may be attributed to the higher initial dose.

Treatment-emergent adverse events with olanzapine compared with placebo reported by at least 10% of patients in the first study included somnolence, dry mouth, dizziness, and weight gain.<sup>6</sup> The only treatment-emergent adverse event reported in the second study as occurring in at least 10% of patients was somnolence.<sup>7</sup> Results from these 2 studies indicated that olanzapine was an effective, safe, and tolerable treatment for bipolar mania and did not exacerbate depressive symptoms.

In a double-blind study ( $N = 251$ ) comparing the use of olanzapine versus divalproex in acute mania, Tohen et al.<sup>8</sup> reported the efficacy of olanzapine as statistically significant ( $F = 4.92$ ,  $df = 1,190$ ;  $p < .03$ ) over that of dival-

Figure 1. Young Mania Rating Scale (YMRS) Weekly Analysis<sup>a</sup>

<sup>a</sup>Reprinted with permission from Tohen et al.<sup>7</sup> Change from baseline (mean  $\pm$  SD), last observation carried forward: week 1,  $F = 4.78$ ,  $df = 1,86$  ( $p = .03$ ); week 2,  $F = 8.87$ ,  $df = 1,86$  ( $p = .004$ ); week 3,  $F = 16.13$ ,  $df = 1,86$  ( $p < .001$ ); and week 4,  $F = 12.47$ ,  $df = 1,86$  ( $p < .001$ ).

proex. Patients diagnosed with bipolar I disorder, manic or mixed episode (DSM-IV), randomly assigned to the olanzapine-treated group, had significantly greater mean reductions in mania ratings as early as day 2. In a similar study of about half the number of subjects meeting the same criteria, Zajecka et al.<sup>9</sup> found no statistical significance in efficacy between divalproex and olanzapine but substantial differences in tolerability. Zajecka et al.<sup>9</sup> reported somnolence, weight gain, edema, and rhinitis in patients in the olanzapine group.

Data from a study<sup>10</sup> of ongoing olanzapine therapy following treatment for acute mania further supports the efficacy and safety of olanzapine therapy in extension studies. In this large, double-blind study, patients with bipolar I disorder were randomly assigned to olanzapine (5–20 mg/day,  $N = 234$ ) or haloperidol (3–15 mg/day,  $N = 219$ ) for 6 weeks, followed by a 6-week double-blind extension study at the same dose. No significant difference in rates of remission (defined a priori as YMRS  $\leq 12$  and 21-item Hamilton Rating Scale for Depression [HAM-D-21]  $\leq 8$ ) between the 2 drugs was seen at 6 weeks; however, scores on the Montgomery-Asberg Depression Rating Scale (MADRS) improved more among nonpsychotic patients in the olanzapine-treated group than in the haloperidol-treated group. Importantly, more olanzapine-treated patients remitted at the end of the 6-week extension phase than did haloperidol-treated patients. Olanzapine-treated patients showed improvement in motor side effects, whereas haloperidol patients showed a worsening in motor side effects. The only adverse event reported in the olanzapine group was weight gain, which was significant ( $p < .001$ ) compared with haloperidol (+3.55 kg vs. +0.72 kg, respectively). Results indicated that olanzapine may be at least as effective as haloperidol in achieving remission of bipolar mania and,

because of fewer motor side effects, may be associated with a more favorable safety profile in extended use.

**Combination therapy.** Olanzapine also demonstrated superior efficacy when added to lithium or valproate over those agents alone.<sup>11</sup> The addition of olanzapine after an inadequate response to at least 2 weeks of lithium or valproate monotherapy resulted in superior efficacy in a double-blind, placebo-controlled study of acute mania. In this study, patients diagnosed with bipolar disorder, manic or mixed episode (DSM-IV) ( $N = 344$ ) were randomly assigned to receive cotherapy (olanzapine + mood stabilizer) or monotherapy (placebo + mood stabilizer).

YMRS total scores were significantly reduced ( $p = .003$ ) and clinical response was significantly higher ( $p < .001$ ) with cotherapy.<sup>11</sup> Total scores on the HAM-D-21 also improved significantly more in the group on olanzapine cotherapy than monotherapy (4.98 vs. 0.89 points, respectively;  $p < .001$ ), suggesting that patients with bipolar disorder with depressive symptoms may benefit from the addition of olanzapine.

Although patients treated with combination therapy experienced more adverse events than the group receiving monotherapy, none were severe or life-threatening. Adverse events reported by at least 10% of patients in the olanzapine cotherapy group included somnolence, dry mouth, weight gain, increased appetite, tremor, asthenia, depression, headache, dizziness, diarrhea, nervousness, and thirst.<sup>11</sup>

### Maintenance

Olanzapine has shown promise as maintenance therapy compared with placebo<sup>12</sup> or haloperidol<sup>13</sup> in double-blind studies of patients with schizophrenia and related psychoses, but no double-blind studies of its use as maintenance therapy in patients with bipolar disorder have been reported.

### Depression

Results from a large, double-blind, placebo-controlled study<sup>14</sup> demonstrated that olanzapine is superior to placebo, and, further, olanzapine plus fluoxetine is superior to placebo and to olanzapine monotherapy in the treatment of depression in bipolar disorder. Improvement with the combination of olanzapine plus fluoxetine on the MADRS was significantly greater than olanzapine therapy alone ( $p = .002$ ) in patients with bipolar disorder starting at week 1 and continuing throughout the 8-week study. Common side effects reported in the olanzapine group included somnolence, weight gain, increased appetite, and dry mouth.

### RISPERIDONE

Risperidone, another atypical antipsychotic with  $D_2$ ,  $5-HT_{2A}$ , and  $\alpha_2$ -adrenergic antagonistic properties, has

Table 2. Efficacy of Risperidone in Trials in Bipolar Disorder

Study Phase	Total N	Study Design	Dose (range)	Duration	Primary Outcome Measures	Results
<b>Mania</b>						
<b>Monotherapy</b>						
Segal et al <sup>15</sup>	45	Double-blind	Risperidone (6 mg/d) vs haloperidol (10 mg/d) vs lithium (800–1200 mg/d)	28 d	YMRS	Risperidone = haloperidol = lithium
Hirschfeld et al <sup>16</sup>	259	Double-blind	Risperidone (1–6 mg/d); mean $\pm$ SE dose = 4.1 $\pm$ 0.1 mg/d	3 wk	YMRS	Risperidone > placebo
Vieta et al <sup>17</sup>	291	Double-blind	Risperidone (1–6 mg/d); mean modal $\pm$ SE dose = 5.6 $\pm$ 0.8 mg/d	3 wk	YMRS	Risperidone > placebo
<b>Combination</b>						
Sachs et al <sup>18</sup>	156	Double-blind	Risperidone (3.8 $\pm$ 1.8 mg/d <sup>a</sup> ) + mood stabilizer vs haloperidol (6.2 $\pm$ 2.9 mg/d <sup>a</sup> ) + mood stabilizer	3 wk	YMRS	Risperidone, haloperidol > placebo
Yatham et al <sup>19</sup>	151	Double-blind	Risperidone (median dose = 4.0 mg/d) added to ongoing mood stabilizer	3 wk	YMRS	Risperidone + mood stabilizer > mood stabilizer alone or mood stabilizer + placebo
<b>Maintenance</b>						
Vieta et al <sup>20</sup>	541	Open-label	Risperidone (3.9 mg/d) + mood stabilizer	6 mo	YMRS, HAM-D, PANSS, CGI	Risperidone was effective
<b>Depression</b>						
Ostroff and Nelson <sup>21</sup>	8	Open-label	SSRI + risperidone (0.5–1.0 mg/d)	1 wk	HAM-D	SSRI + risperidone > SSRI monotherapy
Stahl and Shelton <sup>22</sup>	30	Double-blind	Risperidone (1–4 mg/d) + placebo vs paroxetine (10–40 mg/d) + placebo vs risperidone + paroxetine	12 wk	MADRS	Added to ongoing mood stabilizer risperidone = paroxetine; risperidone + paroxetine > risperidone alone or paroxetine alone

<sup>a</sup>Mean modal doses  $\pm$  SD.

Abbreviations: BDI = Beck Depression Inventory, CGI = Clinical Global Impressions scale, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale, SSRI = selective serotonin reuptake inhibitor, YMRS = Young Mania Rating Scale.

shown robust efficacy in controlled trials against psychotic symptoms and is well tolerated in the treatment of the manic phase of bipolar disorder.<sup>15–19</sup> Other studies have suggested that risperidone may be useful as maintenance treatment<sup>20</sup> and in bipolar depression<sup>21,22</sup> (Table 2).

### Mania

**Monotherapy.** Clinical trials<sup>15–17</sup> of risperidone monotherapy have indicated rapid and significant improvement in acute mania and reduction of symptoms. In a 28-day double-blind trial of inpatients diagnosed with mania (DSM-IV criteria; N = 45),<sup>15</sup> risperidone was as efficacious as either haloperidol or lithium. YMRS total scores at the end of the trial showed significant improvement for patients in all 3 groups ( $p < .001$ ).

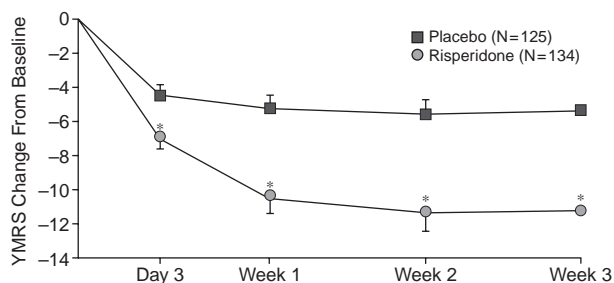
Two large, 3-week, double-blind, placebo-controlled studies of risperidone monotherapy in patients voluntarily hospitalized with a primary diagnosis of mania (DSM-IV bipolar I disorder) were conducted.<sup>16,17</sup> Risperidone was flexibly dosed up to 6 mg/day in both studies. Symptom improvement was prompt and substantial, and manic

symptoms improved even in patients with high YMRS baseline scores. In our study,<sup>16</sup> risperidone-treated patients (N = 134) showed significantly greater reduction in YMRS total scores than placebo-treated patients (N = 125) at day 3 and sustained symptom reductions for 3 weeks ( $p < .001$ ; Figure 2).

Baseline YMRS scores in the study by Vieta et al.,<sup>17</sup> although similar in size (total N = 291) to our study, were more severe (an average 10 points greater on the YMRS) than those observed in our trial. Significant reductions in YMRS scores were seen at the end of week 1 ( $p < .001$ ) and were sustained through endpoint. Regardless of the severity of the mania at baseline in either study, overall reduction in mania was the same, and significantly greater reductions in YMRS scores were seen in the risperidone group than the placebo group in both studies.<sup>16,17</sup>

Treatment was safe and well tolerated in all 3 trials. Adverse events with risperidone monotherapy reported in at least 10% of patients in our study<sup>16</sup> included somnolence, hyperkinesia, headache, dizziness, dyspepsia, and nausea, whereas adverse events reported in at least 10% of

Figure 2. Change From Baseline in Mean (SE) Total Young Mania Rating Scale (YMRS) Scores<sup>a</sup>



<sup>a</sup>Data from Hirschfeld et al.<sup>16</sup>

\* $p < .001$  vs. placebo.

patients in the study by Vieta et al.<sup>17</sup> included motor side effects and tremor. In our study,<sup>16</sup> 3.9% of patients gained weight as measured by a  $> 7\%$  increase in body mass index.

**Combination therapy.** Risperidone is effective and well tolerated in combination with a mood stabilizer in the treatment of acute mania in bipolar disorder.<sup>18,19</sup> In a 3-week, double-blind, placebo-controlled study of risperidone combined with a mood stabilizer that included a haloperidol arm as an active control, Sachs et al.<sup>18</sup> reported significantly greater reductions in the mean total score on the YMRS in both the risperidone plus mood stabilizer ( $-14.3$ ) and haloperidol plus mood stabilizer ( $-13.4$ ) groups than in the placebo plus mood stabilizer ( $-8.2$ ) group at endpoint and over time ( $p < .009$  and  $p < .04$ , respectively). Significant differences in CGI-change scores were reported in the risperidone and haloperidol groups compared with placebo (Cochran-Mantel-Haenszel  $\chi^2 = 9.7$ ,  $df = 1$ ,  $p = .002$ ;  $\chi^2 = 8.9$ ,  $df = 1$ ,  $p = .003$ , respectively). Ratings of “much improved” and “very much improved” were reported in 25% (13/51) of the risperidone plus mood stabilizer group, in 16% (8/50) of the haloperidol plus mood stabilizer group, and none in the placebo group. These results demonstrate that risperidone plus a mood stabilizer is as efficacious as haloperidol plus a mood stabilizer and both are superior to mood stabilizer alone or in combination with placebo.

In a double-blind, 3-week trial, Yatham et al.<sup>19</sup> added risperidone or placebo therapy to a mood stabilizer (either lithium or divalproex) in patients with a diagnosis of DSM-IV bipolar disorder (mixed or manic episode). More rapid reductions in YMRS scores were noted at week 1 in the risperidone plus mood stabilizer group but not in the placebo plus mood stabilizer group ( $p = .029$ ). At endpoint, YMRS scores had decreased by 14.5 and 10.3 points in the risperidone plus mood stabilizer and placebo plus mood stabilizer groups, respectively, indicating that risperidone was more effective than placebo but to a lesser degree than during the first week of treatment. Rapid and

greater improvements in CGI and BPRS measures were noted in the risperidone plus mood stabilizer group compared with the placebo plus mood stabilizer group. At the end of week 1 and at endpoint, the distribution of CGI improvement scores for the risperidone plus placebo group was more concentrated on the “very much improved” and “much improved” categories compared with the placebo group ( $p = .013$  at week 1 and  $p = .022$  at endpoint). Likewise, significant improvement on total BPRS scores was reported between groups at week 1 and endpoint ( $p = .012$  and  $p = .006$ , respectively). The results of this study<sup>19</sup> indicate that risperidone, at a median modal dose of 4 mg/day, is more efficacious than placebo when combined with mood-stabilizing therapy in the treatment of manic episodes associated with bipolar disorder.

### Maintenance

Risperidone may be useful in preventing both depressive and manic episodes. Five hundred forty-one patients with a diagnosis of bipolar disorder or schizoaffective disorder, bipolar type (DSM-IV), entered an open, multicenter, 6-month study<sup>20</sup> during a manic, hypomanic, mixed, or depressive episode. Risperidone was added to any previous mood-stabilizing medication, and efficacy was assessed with the YMRS, the HAM-D, the Positive and Negative Syndrome Scale (PANSS), and the CGI scale. The addition of risperidone produced highly significant improvements ( $p < .0001$ ) on the YMRS and HAM-D at both 6 weeks and 6 months and on the CGI scale and the PANSS at both 4 weeks and 6 months. Adverse events were rated as generally mild to moderate, and the most frequently reported were motor side effects and weight gain. Controlled, double-blind studies are needed to confirm these findings.

### Depression

Augmentation with risperidone may be effective in treating depressive symptoms in patients with bipolar disorder and in patients with depression who have not responded to selective serotonin reuptake inhibitor (SSRI) therapy alone.<sup>21</sup> In a double-blind, placebo-controlled pilot study, Stahl and Shelton<sup>22</sup> compared the efficacy of risperidone plus placebo, paroxetine plus placebo, and risperidone plus paroxetine in 30 patients with bipolar depression (DSM-IV) who were taking ongoing mood stabilizers. Results were similar between treatments on primary (MADRS) and secondary (HAM-D, YMRS, and CGI-Improvement scale) measures at weeks 6 and 12. Substantial reductions in Beck Depression Inventory scores were reported in the risperidone plus paroxetine group with low doses of risperidone (range, 1–4 mg/day) compared with the paroxetine alone group ( $p < .10$ ). The combination of risperidone and paroxetine was generally safe and well tolerated, but further studies of risperidone in combination with SSRIs are needed.



## OTHER ATYPICAL ANTIPSYCHOTICS

Data evaluating the efficacy of quetiapine, ziprasidone, and aripiprazole in bipolar disorder are more limited. Early evidence suggests efficacy in acute mania.

Quetiapine, for example, was effective and well tolerated as adjunctive therapy to mood stabilizers for the treatment of acute bipolar mania in a 3-week, double-blind, placebo-controlled trial.<sup>23</sup> Patients diagnosed with bipolar I disorder and experiencing a manic episode ( $N = 191$ ) were titrated to therapeutic levels with lithium or divalproex and were randomly assigned to adjunctive quetiapine (500 mg/day) or placebo. The quetiapine group did significantly better than the placebo group on the basis of YMRS scores (54% vs. 33%,  $p = .003$ ), and more patients treated with quetiapine experienced a full remission of their manic symptoms compared with patients taking mood stabilizers alone. Reported adverse events in the group taking quetiapine included somnolence, headache, dry mouth, asthenia, orthostatic hypotension, and dizziness.

Ziprasidone is a new atypical antipsychotic with combined  $D_2$  and 5-HT<sub>2A</sub> receptor antagonist activity. Efficacy and safety data support the use of ziprasidone as first-line treatment for schizophrenia with the possibility of beneficial effects on the negative symptoms of depression. A single, double-blind, placebo-controlled study<sup>24</sup> was conducted with ziprasidone therapy in the acute treatment of mania. Patients with bipolar disorder, acute mania, were randomly assigned to ziprasidone ( $N = 131$ ) or placebo ( $N = 64$ ). Ziprasidone was more effective than placebo as measured by the Schedule for Affective Disorders and Schizophrenia-Change version (SADS-C), Mania Rating Scale (MRS), PANSS, and CGI-Severity scale. Ziprasidone was well tolerated.

The most recent addition to the new class of atypical antipsychotics is aripiprazole, which has shown efficacy in schizophrenia and schizoaffective disorder.<sup>25,26</sup> The receptor binding of aripiprazole combines partial agonist activity at  $D_2$  and 5-HT<sub>1A</sub> receptors with potent antagonism at 5-HT<sub>2A</sub> receptors.<sup>27</sup>

Recently, 3 studies of aripiprazole in bipolar mania have been reported (references 28 and 29 and unpublished data). In the first study,<sup>28</sup> inpatients with bipolar disorder ( $N = 262$ ) were randomly assigned to either placebo or a starting dose of 30 mg/day of aripiprazole in a 3-week, double-blind trial. By day 4, aripiprazole separated from placebo on all efficacy measures. This separation increased throughout the study, and at endpoint, significantly more patients had responded to aripiprazole treatment than to placebo (40% vs. 19%;  $p < .01$ ). Similar percentages of patients in either treatment group experienced clinically significant weight gain. The most common reported adverse events were akathisia, dyspepsia, and constipation.<sup>28</sup> A second placebo-controlled study did not show separation of aripiprazole from placebo (P. E. Keck, Jr., M.D., oral

communication, May 2003). In this study, response to aripiprazole was similar to that in the first study, but the placebo response was unusually high. The third study,<sup>29</sup> a 12-week, multicenter, double-blind study of 347 patients with acute mania, compared aripiprazole and haloperidol. Comparable efficacy was found for both agents at week 3, but the response rate to aripiprazole was significantly higher at week 12 (50%) than to haloperidol (28%,  $p < .001$ ). Significantly more patients continued in treatment in the aripiprazole group (51%) than in the haloperidol group (29%). Weight change associated with aripiprazole and haloperidol was +0.27 kg and -0.10 kg, respectively. Side effects on aripiprazole treatment were considerably less severe than on haloperidol treatment.

These findings support the use of aripiprazole in acute bipolar mania, but further placebo-controlled studies are warranted.

## DISCUSSION

The atypical antipsychotics have been found effective as both monotherapy and adjunct therapy with mood stabilizers in the treatment of acute mania. Risperidone and olanzapine have demonstrated rapid onset of action, raising their suitability as first-line agents in the treatment of acute mania. In addition, olanzapine has shown efficacy for bipolar depression and for maintenance.

As a class of drugs, atypical antipsychotics are associated with much lower risk of treatment-emergent motor side effects than conventional antipsychotics. Patients treated with atypical agents at clinically effective doses that do not cause motor side effects benefit from less dysphoria, less impaired cognition, and lower risk of tardive dyskinesia.

Clozapine-treated and olanzapine-treated patients often experience weight gain. In general, the longer the duration of treatment and symptom improvement, the greater the weight gain. Weight gain was reported in studies of patients treated with olanzapine alone and olanzapine augmented with valproate or lithium.<sup>11</sup> Greater weight gain was reported with olanzapine compared with divalproex<sup>9</sup> or haloperidol.<sup>10</sup> Aripiprazole has demonstrated a low incidence of weight gain, while ziprasidone appears to have a neutral effect on weight.

On the basis of these studies, atypical antipsychotics may play a key role in the treatment of acute mania and manic depression and in continuation therapy for bipolar patients. More double-blind studies of newer atypical agents in patients with bipolar spectrum disorders are needed to confirm efficacy and safety.

*Drug names:* aripiprazole (Abilify), chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril and others), divalproex (Depakote), fluoxetine (Prozac), haloperidol (Haldol and others), lorazepam (Ativan and others), olanzapine (Zyprexa), paroxetine (Paxil), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

*Disclosure of off-label usage:* The author of this article has determined that, to the best of his knowledge, aripiprazole, chlorpromazine, clozapine, fluoxetine, haloperidol, lorazepam, paroxetine, quetiapine, risperidone, and ziprasidone are not approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder.

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