

# Atypical Antipsychotic Augmentation of Mood Stabilizer Therapy in Bipolar Disorder

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Although monotherapy with lithium or divalproex is the recommended initial therapy for bipolar disorder, these agents are associated with prolonged favorable outcomes in only 30% of patients. Increasingly, the medical literature is demonstrating that augmentation of mood stabilizers with atypical antipsychotics is a more effective therapy. This form of combination therapy is recommended as first-line treatment for severe bipolar mania. Recent clinical studies have shown that augmentation therapy with the atypical antipsychotics risperidone, olanzapine, quetiapine, and ziprasidone is effective in long-term maintenance treatment, and preliminary evidence is emerging that use of atypicals with mood stabilizers can help control the depressive phase of bipolar disorder. The atypical antipsychotics also have relatively mild side effect profiles, although augmentation therapy with some antipsychotics and mood stabilizers has been associated with excessive weight gain.

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The mood stabilizers lithium and divalproex are the recommended first-line treatments for bipolar disorder.<sup>1,2</sup> However, various shortcomings prevent them from being a monotherapy panacea for this disease. For example, lithium is ineffective or poorly tolerated in about one third of patients<sup>3</sup> and has a relatively slow onset of action, often requiring weeks to produce maximum therapeutic effects.<sup>1</sup> Further, monotherapy is not recommended as initial therapy for severe cases of bipolar disorder.<sup>1</sup>

Augmentation therapy is used to improve efficacy in patients who are unresponsive or who respond partially to monotherapy with a mood stabilizer and to achieve more rapid control of manic symptoms. The 2 types of augmentation therapy are cotherapy, in which 2 or more agents are initiated concurrently, and add-on therapy, in which a second or third drug is added to a continuing regimen. Most clinical studies of mood stabilizer and antipsychotic combinations have shown that the severity of adverse events decreases with augmentation therapy due to the lower doses used for the antipsychotic.

Augmentation treatment with a mood stabilizer and an antipsychotic is becoming a common therapy for patients

with mania,<sup>4</sup> with as many as 90% of subjects with acute mania receiving mood stabilizer/antipsychotic combinations.<sup>5</sup> The treatment guidelines of the American Psychiatric Association (APA) endorse the use of such combinations as first-line management in subjects with severe bipolar mania or with rapid-cycling disease.<sup>1</sup> Augmentation therapy with atypical antipsychotics also has been investigated in both acute and long-term treatment of bipolar disorder with psychosis.<sup>6,7</sup>

## CONVENTIONAL AND ATYPICAL ANTIPSYCHOTICS IN COMBINATION THERAPY

Both conventional and atypical antipsychotics have been shown to have antimanic properties and to be useful in the treatment of bipolar disorder. However, only a limited amount of published clinical data is available about the use of conventional antipsychotics such as haloperidol, perazine, perphenazine, and chlorpromazine in combination with mood stabilizers. Muller-Oerlinghausen and colleagues<sup>8</sup> conducted a 21-day, double-blind, placebo-controlled study comparing the use of a conventional antipsychotic (haloperidol or perazine) alone or in combination with a mood stabilizer (valproate) in patients (N = 136) with bipolar mania. The combination of an antipsychotic plus valproate was associated with a significantly higher response rate compared with antipsychotic monotherapy (70% vs. 46%;  $p = .005$ ). The combination regimen also had a continuous down-titration of antipsychotic dose, while the antipsychotic dose in the monotherapy group varied only slightly throughout the trial.<sup>8</sup> In another published trial,<sup>9</sup> the conventional antipsychotic perphenazine (dose of 4-64 mg/day), used in combination with

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a mood stabilizer for maintenance therapy in remitted manic patients ( $N = 37$ ), was associated with a shorter time to relapse and higher rates of treatment discontinuation, dysphoria, depression, and extrapyramidal symptoms (EPS).

Miller and colleagues<sup>5</sup> conducted a retrospective chart review of 155 patients treated for bipolar mania in a university hospital over 30 months. The analysis compared the efficacy of conventional and atypical antipsychotics when used as add-on therapy with mood stabilizers. Discharge records indicated significantly greater improvement in patients treated with atypical antipsychotics relative to typical antipsychotics as measured by Clinical Global Impressions-Improvement (CGI-I) scores ( $p < .005$ ). The incidence of EPS was significantly lower among patients receiving the atypical agents risperidone ( $p < .01$ ) and olanzapine ( $p < .001$ ).<sup>5</sup>

The use of conventional antipsychotics such as haloperidol and chlorpromazine poses safety risks, most notably EPS, dysphoria, tardive dyskinesia, and neuroleptic malignant syndrome.<sup>8</sup> The risk for EPS is of particular concern in patients with bipolar disorder, who appear to be more susceptible to motor side effects, including tardive dyskinesia, than are people with schizophrenia.<sup>10</sup> Atypical antipsychotics have substantially lower risks for such adverse events.<sup>1</sup> In addition, conventional antipsychotics may worsen depression in some bipolar patients, while recent data indicate that atypical agents may have clinically relevant antidepressant activity.<sup>5</sup> Therefore, atypical antipsychotics have become the agents of choice when augmentation of a mood stabilizer with an antipsychotic is warranted.<sup>1</sup>

Growing interest in the use of atypical antipsychotic agents as augmentation therapy in bipolar disorder has been evidenced by the number of clinical trials appearing in the medical literature. This article reviews the accumulating clinical evidence, consisting of published and presented data, for combination regimens of mood stabilizers and atypical antipsychotics in both acute and maintenance therapy. The one exception to this trend is the most recently introduced atypical antipsychotic, aripiprazole, for which no published clinical studies of combination therapy for bipolar disorder could be found as of this writing.

## MANAGEMENT OF ACUTE BIPOLAR MANIA WITH AUGMENTATION THERAPY

### Risperidone

Beginning in 2002, an increasing amount of controlled clinical research began to appear in the medical literature examining the use of adjunctive risperidone in bipolar disorder. Sachs and colleagues<sup>11</sup> published the results of a 3-week, randomized, double-blind, placebo-controlled study in which lithium or divalproex was given in com-

**Table 1. Mean Scores on the YMRS at Baseline and Declines in Mean Scores at Each Week and Endpoint of a 3-Week Comparison Study of Augmentation Therapy With a Mood Stabilizer Alone or With Haloperidol or Risperidone<sup>a</sup>**

Mean YMRS Score	Placebo/ Mood Stabilizer	Haloperidol/ Mood Stabilizer	Risperidone/ Mood Stabilizer
Baseline	28.0	27.3	28.0
Decrease from baseline			
Week 1	-6.1	-9.4	-9.7
Week 2	-8.4	-11.5	-13.7
Week 3	-13.4	-15.4	-16.6
Endpoint	-8.2	-13.4	-14.3

<sup>a</sup>Adapted with permission from Sachs et al.<sup>11</sup>

Abbreviation: YMRS = Young Mania Rating Scale.

bination with placebo, risperidone, or haloperidol to 156 subjects with a diagnosis of manic or mixed bipolar disorder according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV). This was the first published study comparing an atypical antipsychotic with a conventional antipsychotic in adjunctive therapy for mania. During the trial's double-blind phase, the mean modal doses were 3.8 mg/day ( $SD = 1.8$ ) for risperidone and 6.2 mg/day ( $SD = 2.9$ ) for haloperidol.

Significantly greater reductions in Young Mania Rating Scale (YMRS) scores were observed in both the risperidone and haloperidol groups than with placebo at each week of treatment and at study endpoint ( $-14.3$  vs.  $-13.4$  vs.  $-8.2$ , respectively) (Table 1). Notable differences were observed with regard to safety and tolerability between the risperidone and haloperidol regimens. The mean change in Extrapyramidal Symptom Rating Scale (ESRS) score and the mean change in maximum ESRS score were significantly greater among subjects receiving haloperidol than among subjects receiving risperidone or placebo. The adverse events of headache, extrapyramidal disorder, and tremor were reported with greater frequency in subjects receiving adjunctive haloperidol than in the other 2 treatment groups.<sup>11</sup>

Vieta and colleagues<sup>12</sup> studied the use of adjunctive risperidone with a mood stabilizer in an open-label trial involving 174 subjects with manic, hypomanic, or mixed symptoms. Only 10% of subjects in this trial were treated with risperidone alone. Concomitant medications used in the other subjects included lithium alone (42%), lithium with another mood stabilizer (16%), carbamazepine (23%), and valproate (12%). At study endpoint, the mean YMRS score in subjects receiving risperidone plus a mood stabilizer had declined from 26.3 at baseline to 5.7 ( $p < .0001$ ). Highly significant ( $p < .0001$  for all) improvements for this group were also observed in mean scores on the Positive and Negative Syndrome Scale (PANSS), Hamilton Rating Scale for Depression (HAM-D), CGI-I, and CGI-Severity of Illness (CGI-S). As demonstrated by scores on the Udvalg for Kliniske Undersøgelser (UKU), a scale for EPS side effects, there was no significant change in EPS severity.<sup>12</sup>

A 3-week, double-blind, placebo-controlled study compared the effects of risperidone (mean doses from 0.5 to 6 mg/day) to placebo in 151 acutely manic bipolar subjects already receiving a mood stabilizer (lithium, divalproex, or carbamazepine).<sup>13</sup> The reduction in YMRS scores was more rapid in the group receiving adjunctive risperidone; reductions from baseline at week 1 were  $-10.2$  in the risperidone/mood stabilizer group and  $-6.7$  in the placebo/mood stabilizer group ( $p = .029$ ). At study endpoint, mean decreases in YMRS scores were numerically, but not significantly, greater with adjunctive risperidone than with placebo ( $-14.5$  vs.  $-10.3$ ).<sup>13</sup> A separate study<sup>4</sup> comparing risperidone/mood stabilizer ( $N = 75$ ) with mood stabilizer/placebo ( $N = 76$ ) found that the overall incidence of adverse events was similar between treatment groups. However, EPS-related events were more frequent in the risperidone/mood stabilizer group than in the placebo/mood stabilizer group (16 cases vs. 6 cases;  $p = .013$ ).<sup>4</sup>

The efficacy of risperidone (dosed between 2 and 6 mg/day) cotherapy with mood stabilizers for acute mania with psychotic features was evaluated in an open-label pilot study with 15 subjects.<sup>7</sup> Of the 13 subjects who completed 2 weeks of therapy, 8 had a 50% improvement from baseline on the Brief Psychiatric Rating Scale (BPRS), and all 13 had at least a 25% improvement ( $p = .002$ , 95% confidence interval [CI] = 46.0 to 57.8). By 6 weeks, 7 of the 8 subjects remaining in the study had a 50% improvement on the BPRS, and all 8 had a  $\geq 25\%$  improvement ( $p = .012$ , 95% CI = 55.1 to 89.9). No case worsened, and the cotherapy was well tolerated.<sup>7</sup>

### Olanzapine

Olanzapine's use in augmentation therapy has been studied extensively. A 6-week, randomized, double-blind trial by Tohen and colleagues<sup>14</sup> compared the effects of combined therapy with olanzapine and either valproate or lithium with either mood stabilizer alone in patients having an acute bipolar manic or mixed episode. Patients were required to have a history of at least 2 previous depressed, manic, or mixed episodes; a YMRS score  $\geq 16$ ; and an inadequate response to lithium or valproate monotherapy for a minimum of 2 weeks. A total of 344 patients were randomly assigned 2:1 to receive olanzapine (dose adjusted from 5–20 mg/day with a mean modal dose of 10.4 [4.9] mg/day) or placebo in addition to the mood stabilizer.<sup>14</sup>

After 6 weeks of double-blind treatment, patients in both groups demonstrated improvement from baseline in YMRS total score.<sup>14</sup> However, the group receiving adjunctive olanzapine experienced a significantly greater reduction compared with those receiving mood stabilizer therapy alone ( $-13.1$  vs.  $-9.1$ ;  $p = .003$ ). Significantly greater improvements were also noted in the YMRS items of irritability, speech, language/thought disorder, and disruptive/aggressive behavior. More patients were categorized as clinical responders (improvement of  $\geq 50\%$

from baseline in YMRS total score) in the group receiving adjunctive olanzapine compared with those receiving mood stabilizer monotherapy (67.7% vs. 44.7%;  $p < .001$ ). The median time to response was also significantly shorter in the group receiving olanzapine cotherapy (18 vs. 28 days;  $p = .002$ ).<sup>14</sup>

Olanzapine cotherapy improved scores on the 21-item HAM-D (HAM-D-21) by 4.98 points, a significantly greater improvement than the 0.89-point decrease observed in the mood stabilizer monotherapy group ( $p < .001$ ).<sup>14</sup> In a subgroup analysis of patients experiencing mixed bipolar episodes with moderate-to-severe depression, olanzapine/mood stabilizer therapy was associated with a mean 10.31-point improvement in HAM-D-21 score, compared with a 1.57-point improvement in the placebo/mood stabilizer group ( $p < .001$ ).

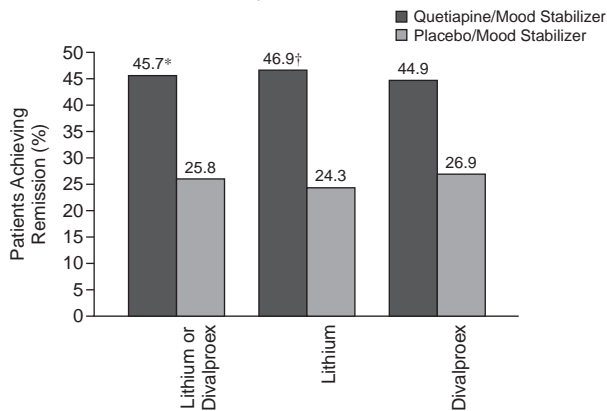
No significant change was observed from baseline in either group in ratings of EPS.<sup>14</sup> Adverse events reported with significantly greater frequency in the olanzapine cotherapy group included somnolence (51.5% with olanzapine/mood stabilizer vs. 27.0% with placebo/mood stabilizer), dry mouth (31.9% vs. 7.8%), weight gain (26.2% vs. 7.0%), increased appetite (23.6% vs. 7.8%), tremor (23.1% vs. 13.0%), and speech disorder (6.6% vs. 0.9%).<sup>14</sup>

### Quetiapine

The efficacy and tolerability of quetiapine in augmentation therapy have been investigated in both adult and adolescent inpatients.

A double-blind, placebo-controlled, multicenter study<sup>15</sup> investigated the use of quetiapine in combination with lithium or divalproex in 191 subjects hospitalized for acute bipolar mania. All participants had been treated with a mood stabilizer (lithium or divalproex) for at least 7 of 28 days before being randomly assigned to receive adjunctive quetiapine ( $N = 91$ ) or placebo ( $N = 100$ ) for 21 days. The mean daily dose of quetiapine at study endpoint was 504 mg. The reduction in mean YMRS score from baseline to day 21 was significantly greater in the group treated with adjunctive quetiapine than in the group treated with mood stabilizer alone ( $-13.76$  vs.  $-9.93$ ;  $p = .021$ ). The percentage of responders ( $\geq 50\%$  improvement in YMRS score) among patients receiving quetiapine/lithium or quetiapine/divalproex was significantly higher than in those receiving lithium or divalproex monotherapy (54.3% vs. 32.6%;  $p = .005$ ), as was the rate of clinical remission, defined as a YMRS score  $< 12$  (45.7% vs. 25.8%;  $p = .007$ ) (Figure 1). Adjunctive quetiapine treatment was associated with a significantly greater effect on the PANSS supplemental aggression risk subscale at day 21. Treatment withdrawal rates secondary to adverse events were similar between the groups. Somnolence and dry mouth were the only adverse events that occurred with a statistically greater frequency in the quetiapine/mood stabilizer group compared with the

**Figure 1. Percentage of Patients Achieving Clinical Remission on YMRS on Quetiapine/Mood Stabilizer vs. Mood Stabilizer/Placebo by Baseline Medication<sup>a</sup>**



<sup>a</sup>Data from Sachs et al.<sup>15</sup>

\* $p = .007$ .

† $p$  value not provided.

Abbreviation: YMRS = Young Mania Rating Scale.

placebo/mood stabilizer group. A modest weight increase of 3.53 lb was observed in the quetiapine/mood stabilizer group, compared with 0.79 lb in the placebo/mood stabilizer group. Both treatment groups experienced similarly low levels of EPS.<sup>15</sup>

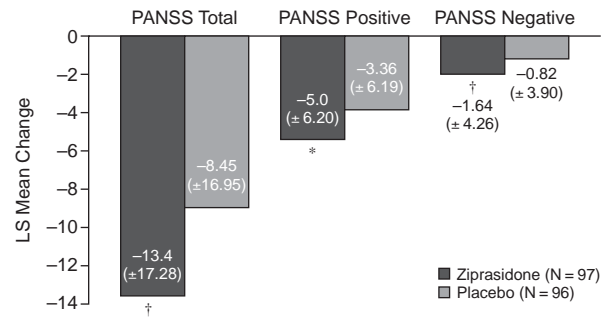
The combination of quetiapine (mean dose of 432 mg/day) and divalproex was evaluated in a randomized, double-blind, placebo-controlled study involving 30 adolescents hospitalized for a manic or mixed episode of bipolar disorder.<sup>16</sup> After patients had been treated for 6 weeks, reductions in YMRS scores from baseline and response rates were significantly ( $p = .03$  and  $p = .05$ , respectively) greater in the group treated with quetiapine and divalproex than in the group treated with divalproex and placebo. Other than sedation, which was statistically more frequent in the group receiving adjunctive quetiapine, no differences in safety or tolerability were noted between the treatment groups. Although somnolence can be a desirable effect in manic adolescents, analysis confirmed that the antimanic effects of quetiapine were not associated solely with excessive sedation.<sup>16</sup>

### Ziprasidone

Ziprasidone has been shown to have rapid efficacy as monotherapy in subjects with bipolar mania, with significant improvements evident within 2 days of therapy initiation.<sup>17</sup> Ziprasidone also has been shown not to change steady-state serum concentrations or renal clearance of lithium in healthy subjects with stable serum lithium levels.<sup>18</sup>

Weisler and colleagues<sup>19</sup> conducted a randomized, double-blind, placebo-controlled trial of ziprasidone in combination with lithium in subjects with bipolar mania to assess whether the addition of ziprasidone to a lithium

**Figure 2. LS Mean Change ( $\pm$  SD) From Baseline to Day 21 (or termination) in PANSS Total and Positive and Negative Subscale Scores (all patients, LOCF) With Ziprasidone/Lithium vs. Placebo/Lithium<sup>a</sup>**



<sup>a</sup>Reprinted with permission from Weisler et al.<sup>19</sup>

\* $p < .05$  vs. placebo.

† $p < .01$  vs. placebo.

Abbreviations: LOCF = last observation carried forward, LS = least squares, PANSS = Positive and Negative Syndrome Scale.

regimen could reduce the time to improvement. A total of 205 subjects were randomly assigned to treatment with open-label lithium plus a placebo ( $N = 103$ ) or double-blind ziprasidone plus lithium ( $N = 102$ ) for 21 days. Ziprasidone dosage was 80 mg on day 1, 160 mg on day 2, and adjusted from days 3 through 21 within a range of 80 to 160 mg/day. Lithium dosage was titrated to maintain serum levels of 0.8 to 1.2 mEq/L.<sup>19</sup>

From baseline to day 4, improvement (rate of change) was significantly greater for the Mania Rating Scale (MRS) ( $p < .05$ ), CGI-S ( $p < .01$ ), CGI-I ( $p < .01$ ), behavior and ideation subscale of the MRS ( $p < .01$ ), extracted HAM-D ( $p < .05$ ), and PANSS total ( $p < .01$ ) scores in the group receiving adjunctive ziprasidone.<sup>19</sup> By day 14, improvement in primary and secondary efficacy variables was comparable between the 2 treatment groups. However, the least-squares mean changes from baseline were significantly greater for CGI-S ( $p < .05$ ) and CGI-I ( $p < .02$ ) and numerically greater for MRS ( $-6.50$  vs.  $-5.51$ ) in the ziprasidone/lithium group than in the lithium/placebo group. The ziprasidone/lithium group was superior to the lithium/placebo group at day 21 with regard to least-squares mean changes from baseline in PANSS total ( $p < .01$ ), PANSS positive ( $p < .05$ ), and PANSS negative ( $p < .01$ ) scores (Figure 2). The ziprasidone/lithium group also had a numerically greater improvement in CGI-S at endpoint ( $-1.39$  vs.  $-1.21$ ). The authors concluded that augmentation treatment with ziprasidone/lithium was associated with earlier improvement in manic symptoms and overall psychopathology compared with lithium therapy alone.<sup>19,20</sup>

No clinically relevant differences were seen between the 2 treatment groups in clinical laboratory abnormalities, vital signs (including weight), or corrected QT interval changes from baseline to endpoint.<sup>19</sup> Adverse events noted



more frequently in the group receiving ziprasidone/lithium compared with placebo/lithium included somnolence (34% vs. 12%), EPS (22% vs. 4%), dizziness (13% vs. 6%), and agitation (11% vs. 2%).

### MAINTENANCE THERAPY

Less controlled data have been published about the combined use of mood stabilizers and antipsychotics in the maintenance treatment of bipolar disorder than in acute treatment. The majority of data are from open-label continuation phases of short-term, double-blind trials, with the exception of an 18-month double-blind assessment of olanzapine augmentation therapy.<sup>21</sup> Maintenance of remission from bipolar disorder is a critical phase of treatment, but about half of all patients experience a second episode within 1 year of recovering from the first one.<sup>22,23</sup> The APA treatment guidelines<sup>1</sup> acknowledge that continued use of an antipsychotic may be necessary to control persistent psychosis or provide prophylaxis against recurrence.

#### Risperidone

In an open-label study reported in 2001,<sup>24</sup> adjunctive risperidone was administered to 541 subjects with bipolar disorder or schizoaffective disorder for up to 6 months. Subjects were experiencing a manic, hypomanic, depressive, or mixed episode at enrollment. Medications used in combination with risperidone included lithium, anti-convulsants, and antidepressants. The mean dose of risperidone at 6 months was 3.9 mg/day. Among 430 subjects who completed the study, risperidone combination treatment was associated with significant improvements in YMRS, HAM-D, CGI, and PANSS scores ( $p < .001$  for all). Seventy-six percent of subjects were considered responders at endpoint ( $\geq 50\%$  reduction in YMRS score and at least a 2-point reduction in CGI score). A  $\geq 50\%$  reduction in HAM-D score was noted in 69% of subjects with baseline depression. Relapse into a mood state different from that at baseline was observed in 25.1% of subjects. There were no cases of treatment-emergent tardive dyskinesia, and there was a very low incidence at a 6-week cutoff of mania exacerbation (1.8%) or early switch into depression (3.0%). A significant ( $p < .0001$ ) reduction in UKU total and subscale scores was observed at 6 months, suggesting an improvement in EPS compared to baseline.<sup>24</sup>

Yatham and colleagues<sup>13</sup> conducted a prospective, open-label, 12-week study of risperidone added to mood stabilizer therapy in 108 bipolar subjects with a DSM-IV diagnosis of bipolar disorder, manic or mixed episode. All subjects were receiving at least 1 mood stabilizer (lithium, valproate, or carbamazepine) when risperidone was added. Risperidone was initiated at a dosage of 0.5 to 2.0 mg/day and titrated to a maximum dosage of 4.0 mg/day as necessary. The average daily dosage of risperidone at the end of the study was 2.0 mg. Significant changes from baseline in

mean YMRS score were seen as early as week 1 ( $-10.8$ ;  $p < .0001$ ) and continued to improve through week 12 ( $-22.6$ ;  $p < .0001$ ). Response, defined as  $\geq 50\%$  decrease in YMRS score from baseline, was evident in 90% of subjects at week 12. Remission (YMRS score  $\leq 8$ ) was achieved by 88% of subjects at week 12. No cases of tardive dyskinesia and no changes in EPS were reported. A subsequent reanalysis of the data according to mood stabilizer used did not identify any meaningful differences in safety or efficacy whether risperidone was combined with lithium or valproate.<sup>13</sup>

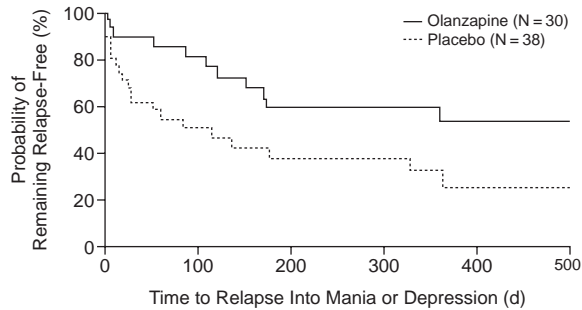
#### Olanzapine

Tohen and colleagues<sup>21</sup> published in 2004 a follow-up study to a previously reported trial of adjunctive olanzapine for the control of acute bipolar mania. This study involved 99 subjects who had achieved remission using a combination of olanzapine and either lithium or valproate. The subjects were randomly assigned to continue double-blind maintenance therapy with lithium or valproate and a placebo ( $N = 48$ ) or a combination of lithium or valproate and olanzapine ( $N = 51$ ) (mean modal dose of 8.6 mg/day) for 18 months. Relapse was defined as syndromic if subjects experienced symptoms meeting DSM-IV criteria for a manic, mixed, or depressive episode. Symptomatic relapse was defined as a total score on both the YMRS and the HAM-D-21  $\geq 15$ .

Time to relapse and rate of relapse into a syndromic episode of mania or depression were similar between treatment groups.<sup>21</sup> With regard to symptomatic assessments, however, the time to symptomatic relapse was significantly longer with combination therapy than with monotherapy (163 days vs. 42 days;  $p = .023$ ) (Figure 3). The significant difference favoring combination therapy was limited to the subset of patients randomly assigned to maintenance treatment who achieved both syndromic and symptomatic remission during the acute phase. During the 18-month study, 37% of subjects receiving combination therapy experienced symptomatic relapse compared with 55% of subjects receiving monotherapy ( $p = \text{NS}$ ). The incidence of side effects was generally similar between the 2 treatment groups, except for insomnia and weight gain, both of which were more frequent in the combination therapy group.<sup>21</sup>

However, a study initiated with 125 inpatients at a psychiatric hospital concluded that augmentation therapy with olanzapine (mean dose at follow-up of  $22.4 \pm 6.5$  mg/day) and mood stabilizers had a sustained, clinically meaningful mood-stabilizing effect in only 26% of the 27 subjects who were followed for a mean of 15 months.<sup>6</sup> The subjects were treated for psychotic mood disorders accompanying bipolar disorders I, II, and not otherwise specified; schizoaffective disorders, bipolar and depressive types; and major depressive disorder. The control group consisted of 50 patients with schizophrenia. The

Figure 3. Time to Symptomatic Relapse (mania or depression) in Patients Receiving Olanzapine/Mood Stabilizer Combination Therapy (N = 30) or Mood Stabilizer/Placebo (N = 38) for 18 Months<sup>a</sup>



<sup>a</sup>Reprinted with permission from Tohen et al.<sup>21</sup>

discontinuation rate for these subjects was 48%, with most of the discontinuations caused by ineffectiveness. Augmentation treatment led to statistically significant improvements in the psychological impairment and social skill subscale scores ( $p < .01$ ) and the violence subscale score ( $p < .02$ ), compared with the control group, among subjects with psychotic mood disorders.<sup>6</sup>

### Quetiapine

A small, open-label study published in 2001<sup>25</sup> described the adjunctive use of quetiapine for 12 weeks in 10 subjects with bipolar disorder and 10 with schizoaffective disorder who were not responding adequately to mood stabilizers alone. All subjects had received conventional antipsychotics for at least 6 months and were unable to be weaned from them without clinical deterioration. Conventional antipsychotics were gradually discontinued over the first 4 weeks of quetiapine administration, which was continued for 12 weeks, either alone or in combination with a mood stabilizer. After 12 weeks of quetiapine therapy (mean dose of  $202.9 \pm 124.3$  mg/day for patients who completed the study), significant improvements were noted in BPRS score ( $p < .001$ ), YMRS score ( $p = .043$ ), and HAM-D score ( $p = .002$ ). No significant difference in treatment response was seen between subjects using quetiapine alone and those using a quetiapine/mood stabilizer combination. A mean weight gain of 10.9 lb noted over the course of the study was higher than expected and could have been a combined effect of quetiapine and mood stabilizer, both of which may cause weight gain.<sup>25</sup>

### Ziprasidone

During an open-label extension of a 21-day double-blind trial,<sup>26</sup> 89 subjects continued to receive ziprasidone (40 to 160 mg/day) with concomitant mood stabilizers and/or antidepressants permitted for up to 52 weeks. The mean daily dosage of ziprasidone at week 52 was

92.6 mg. Mania Rating Scale scores improved successively throughout the 52 weeks and were significantly better than baseline score at all study visits ( $p < .01$  at endpoint). Significant improvements in CGI-S and extracted HAM-D scores were noted at each study visit and at the 52-week endpoint.

Of the patients receiving ziprasidone, 11 (12.4%) discontinued due to adverse events, and nearly the same rate of discontinuation was related to the study drug (29.2%) as was not related to the drug (25.8%).<sup>26</sup> The most frequent adverse events were somnolence (55.1%), abnormal vision (23.6%), tremor (22.5%), EPS (21.3%), and dizziness (20.2%). Scores on movement disorder rating scales with the augmentation therapy had minimal changes. This study indicates that ziprasidone is efficacious and generally well tolerated in the long-term treatment of acute mania, although controlled trials are needed to confirm this result.

### Tolerability in Maintenance Therapy

The tolerability of augmentation therapy with atypical antipsychotics assumes greater importance during maintenance treatment than during short-term acute use simply because patients are exposed to the agents for prolonged periods. The atypical antipsychotics differ substantially in their side effects, although many of the long-term studies of the adverse events of these agents have been conducted in patients with schizophrenia. Therefore, subjectively well tolerated and medically safe regimens drive therapeutic selection as much as efficacy data.

Olanzapine, for example, has been associated with a greater incidence of weight gain, increased cholesterol and lipid levels, and risk for diabetes. In a 58-week switch study,<sup>20</sup> patients (N = 71) whose treatment was changed to ziprasidone after therapy with olanzapine had significant reductions in weight and total cholesterol and triglyceride levels. Further, studies have consistently shown that patients treated with clozapine or olanzapine have a greater risk for diabetes than those who received ziprasidone or aripiprazole.<sup>27</sup>

In the 18-month study cited above in which adjunctive olanzapine was compared with mood stabilizer monotherapy,<sup>21</sup> 20% of patients in the olanzapine/mood stabilizer group experienced a weight gain, compared with 6% of patients in the monotherapy group. The mean change in body weight was 3.8 kg more with combination therapy than with monotherapy, and 27% of the combination therapy group had a clinically relevant weight increase ( $\geq 7\%$  change from baseline), compared with 6% of the monotherapy group.<sup>21</sup>

Weight change was not an adverse effect of combination ziprasidone/lithium treatment in the 52-week clinical study.<sup>26</sup> No significant increase was observed in serum lipid levels, while a significant ( $p = .01$ ) decrease occurred in serum triglyceride levels at endpoint with ziprasidone combination therapy.

## TREATMENT OF BIPOLAR DEPRESSION

Managing the depressive pole of bipolar illness represents an ongoing therapeutic challenge. Recommended first-line treatment for this phase is monotherapy with either lithium or lamotrigine.<sup>1</sup> The concomitant use of antidepressants, while often necessary for acute control, can destabilize the disorder, possibly precipitating mania and cycle acceleration.<sup>28</sup> Although there are insufficient clinical data to recommend or discourage the use of antipsychotics in bipolar depression, APA guidelines support use of these medications in subjects having depression with psychotic features.<sup>1</sup>

No clinical studies of antipsychotics used in combination with mood stabilizers to treat bipolar depression have been published, but many of the studies in subjects with manic or mixed episodes included some measure of depressive symptomatology as an endpoint. Among the studies that evaluated depression scale scores, significant improvements with atypical antipsychotic augmentation therapy, often superior to those with mood stabilizer therapy alone, were reported consistently.<sup>13,22,24,26,29,30</sup> Equally important, these studies did not demonstrate a potential for atypical antipsychotics to trigger a switch from depression to mania.

## CONCLUSIONS

This review of clinical trial data highlights the growing body of evidence supporting the benefit of combining an atypical antipsychotic with a mood stabilizer in the management of bipolar disorder. At least 6 double-blind, placebo-controlled trials have consistently found significantly more favorable outcomes in subjects with acute bipolar mania treated with adjunctive atypical antipsychotics compared with mood stabilizer monotherapy. In addition, open-label trials suggest that longer-term maintenance therapy with adjunctive atypical antipsychotics is safe and provides an added measure of effectiveness. The majority of placebo-controlled studies in acute mania indicate that lower doses of an atypical antipsychotic are effective in augmentation therapy than have been reported necessary for significant benefits in trials of these agents as monotherapy, further underscoring the potential tolerability advantages for combination treatment. The incremental benefits realized in acute and maintenance treatment have come with little increase in overall incidence of side effects and without severe movement disorders.

Additional studies with atypical antipsychotics as both monotherapy and augmentation therapy are needed to determine which types of patients with bipolar disorder will benefit the most from these therapies.

*Drug names:* aripiprazole (Abilify), carbamazepine (Carbatrol, Tegretol, and others), chlorpromazine (Thorazine, Sonazine, and others), divalproex (Depakote), haloperidol (Haldol and others), lamo-

trigine (Lamictal), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), perphenazine (Trilafon and others), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

*Disclosure of off-label usage:* The author has determined that, to the best of his knowledge, carbamazepine, haloperidol, and perphenazine are not approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder.

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