# Atypical Antipsychotics: Efficacy Across Bipolar Disorder Subpopulations

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Atypical antipsychotic medications, used as monotherapy or as adjunctive therapy with mood stabilizers, have shown efficacy and tolerability for 4 subpopulations of patients with bipolar disorder: patients with mixed mania, patients with psychotic episodes, children and adolescents, and the elderly. Patients experiencing mixed mania generally respond poorly to lithium therapy and are more difficult to treat than patients with pure mania. Atypical antipsychotics are increasingly being considered for this bipolar subpopulation because of their efficacy as antimanic agents, and because they are less likely to cause as many or as severe adverse events as conventional antipsychotics. Atypical antipsychotics have also demonstrated beneficial effects as monotherapy and adjunctive therapy for bipolar I disorder patients experiencing psychotic states. In addition, they have shown effectiveness and tolerability in small-scale and open-label trials and case studies with pediatric and geriatric bipolar patients. *(J Clin Psychiatry 2005;66[suppl 3]:20–27)*

The treatment of certain subpopulations of bipolar disorder patients presents challenges that are different from those encountered in treating patients experiencing the solely manic, hypomanic, or depressive episodes of bipolar I or II disorders. For example, patients who have mixed manic episodes often do not respond to treatment with lithium[1] and have a shorter time to relapse than patients whose index episode was purely manic or depressive.[2] Patients who experience psychosis with bipolar mania in their index episode have been reported to be more likely to have an unfavorable outcome to treatment and briefer periods of remission.[3] The 2 bipolar subpopulations at opposite ends of the age spectrum—children/adolescents and the elderly—also have specific treatment problems, including greater susceptibility to some side effects.[4]

Atypical antipsychotic medications, used as monotherapy or as augmentation therapy with mood stabilizers, have shown efficacy and relatively well-tolerated side effect profiles in these patient populations. The results of clinical studies with clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole are discussed for these 4 subpopulations of people with bipolar disorder.

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## MIXED MANIA

Although the concept of mixed mania was delineated in the late 19th century by Emil Kraepelin, the term *mixed mania* was not incorporated into the psychiatric nomenclature until 1987.[5,6] Mixed mania meets the criteria for both a manic and a major depressive episode—except for duration—for nearly every day over the course of at least 1 week.[4] Patients experiencing a mixed manic state often have classic manic symptoms, such as racing thoughts and delusions of grandiosity, as well as a depressed mood, sadness, and anxiety.[7] The mood disturbance in a mixed manic episode is sufficiently severe to cause marked impairment in social or occupational functioning and may necessitate hospitalization to prevent harm to self or others; psychotic features may also be present.[4] McElroy et al.[8] monitored 71 patients hospitalized with bipolar I disorder. On follow-up for more than a 1-year period, they found that mixed manic episodes occurred in approximately 33% to 40% of these patients. This result is consistent with other modern studies on rates of mixed bipolar disorder,[8] although in the 1970s mixed mania was much less common.

### Demographics and Severity of Mixed Mania

People experiencing mixed manic episodes have different symptoms than patients having pure manic episodes (Table 1). Patients with mixed episodes are more likely to have experienced more depressive episodes[7] and to be prescribed antidepressants at hospital discharge ($p < .01$),[9] a result that corresponds to findings of Goldberg and colleagues[10] about the use of antidepressants in patients with mixed mania. In 1 study, mixed manic patients were more

**Table 1. Differentiating the Symptoms of Mixed and Pure Mania Bipolar Disorder Episodes[a]**

| Symptoms of Mixed Mania | Symptoms of Pure Mania |
|---|---|
| Manic symptoms | Grandiosity, inflated self-esteem |
| Severe anxiety | Pressured speech, more talkative than usual |
| Agitation | Euphoria |
| Hostility | Decreased need for sleep |
| Somatization | Distractibility |
| Apparent distress | Flight of ideas |
| Cognitive impairment | Excessive involvement in pleasurable activities with a strong potential for painful consequences |
| Irritable mood | |
| Depressive symptoms | |
| Fatigue or loss of energy | |
| Feelings of helplessness, hopelessness | |
| Feelings of worthlessness or excessive or inappropriate guilt | |

[a]Based on McElroy et al.,[8] Goldberg et al.,[10] and the American Psychiatric Association.[4]

likely to be female ($p = .05$) and to have higher Brief Psychiatric Rating Scale (BPRS) scores measuring depression ($p < .001$) and anxiety ($p < .01$) than were patients with mania only.[9] Conversely, pure mania patients had statistically higher BPRS scores on uncooperativeness ($p < .001$), conceptual disorganization ($p < .01$), grandiosity ($p < .01$), suspiciousness ($p < .05$), and excitement ($p < .05$) compared with mixed mania patients.

Goldberg et al.[10] showed that the baseline Clinical Global Impressions (CGI) scale scores of patients with pure mania indicated that they had more severe illness than mixed manic patients. Compared with manic bipolar patients, mixed manic patients experienced greater irritability ($p < .001$) but less grandiosity ($p < .001$), less euphoria ($p < .03$), and an increased need for sleep ($p < .01$).

Patients with mixed mania tend to have a slower recovery from each episode and a shorter time to relapse after recovery from the index episode than patients who have either manic or depressive index episodes. A review[2] of 172 subjects with bipolar I disorder who were monitored for 5 years concluded that patients with mixed mania or rapid cycling episodes recovered from their index episode in a median of 17 weeks, compared with a median of 6 weeks for patients who had a pure manic episode and a median of 11 weeks for subjects with a pure depressive episode. At 6 months after the first episode, the cumulative probability of relapse was 20% for patients whose last episode was manic, 33% for those with a depressive episode, and 36% for patients with a mixed/cycling episode.[2]

Suicide attempts and suicidal ideation are more common in patients experiencing mixed episodes than in patients with pure mania. In a pooled sample of 504 patients with bipolar or other major affective disorders who had been hospitalized at least once, a recent suicide attempt was identified in 29.2% of patients (28/96) with mixed mania.[11] In contrast, 20.3% (32/158) of patients with a depressive episode and 2.0% (5/250) with a manic episode had recently attempted suicide ($p < .0001$). The overall rate for suicide attempts per year among all patients in the study was 74 times greater in patients with mixed mania as their index episode than among patients who were manic; patients with acute depression had 62 times more suicide attempts per year.[11]

Suicide attempts correlate with substance abuse. A substance use comorbidity (e.g., polysubstance, alcohol, heroin, cocaine) was found in 38.2% of mixed manic patients compared with 32.6% of all bipolar I patients evaluated and 30.3% of patients not having mixed episodes.[11] Strakowski and colleagues[12] also reported a significantly higher prevalence of suicidality or suicidal ideation among mixed manic than among manic patients with bipolar disorder.

## Treatment of Mixed Mania

The combination of severe depressive and manic symptoms increases the difficulty of treating mixed manic episodes.[7] Monotherapy or adjunctive therapy with lithium is recommended as first-line treatment for acute mania,[4] but mixed mania generally responds poorly to lithium therapy.[1] Long-term lithium-based therapy is less effective in patients experiencing mixed manic episodes than in patients with pure manic or depressive episodes.[2] Divalproex was reported to be more effective than lithium in patients with mixed mania.[1]

Atypical antipsychotics are increasingly being considered for mixed manic states because of their efficacy as antimanic agents and because their adverse event profiles are milder than those of conventional antipsychotics.[13] Not all of the large, randomized, controlled clinical trials[14–19] that demonstrated the efficacy of atypical antipsychotics in bipolar disorder reported results separately for patients with mixed mania. Further, several studies[14,15,17,20] of atypical antipsychotics with only mixed bipolar patients were open-label trials with a small number of patients. However, enough data have emerged from all of these trials to support the efficacy of atypical antipsychotics in patients with mixed manic episodes.

Clozapine, which is used primarily for treatment-resistant bipolar disorder patients, has shown some efficacy in patients with mixed manic episodes. A MEDLINE search identified 30 studies that reviewed the use of clozapine in severe or psychotic bipolar or schizoaffective disorders. In 1 study,[21] clozapine was effective for 20 of 29 patients with mixed mania. The most common side effects seen in all patients with mood disorders ($N = 138$) were sedation ($N = 43$), hypersalivation ($N = 21$), and weight gain ($N = 15$).[21] A review[22] of hospital discharge records of 193 patients with treatment-resistant bipolar disorder, schizophrenia, or other disorders identified 5 patients with mixed manic disorder who were treated for at least 6 months with clozapine. The patients showed slight improvement on the CGI-Improvement (CGI-I) scale, but

more than 60% discontinued treatment because of side effects.[22]

Risperidone, used in augmentation therapy with a mood stabilizer, has shown efficacy in several clinical studies for the treatment of mixed mania. An open-label, 6-month trial[23] of 31 patients with mixed mania who had been previously treated with a mood stabilizer alone examined the efficacy of risperidone plus a mood stabilizer as assessed by the Young Mania Rating Scale (YMRS), the CGI, and the Positive and Negative Syndrome Scale (PANSS). Among the 24 patients who completed the study (the authors did not explain the reasons for discontinuations), significant improvements were seen in YMRS scores at week 1 and in both CGI and PANSS scores at week 4, with improvements continuing until endpoint. No worsening of extrapyramidal symptoms (EPS) was observed during the study.[23] Similar improvements were observed in a prospective study[24] of 17 subjects with mixed mania who received risperidone plus a mood stabilizer for the acute and continuation treatment of mania for 12 weeks. In an open-label study[25] with manic (N = 137), hypomanic (N = 21), or mixed (N = 16) bipolar patients, risperidone plus a mood stabilizer effectively treated depressive symptoms of mixed episodes as measured by improvements on the Hamilton Rating Scale for Depression (HAM-D).

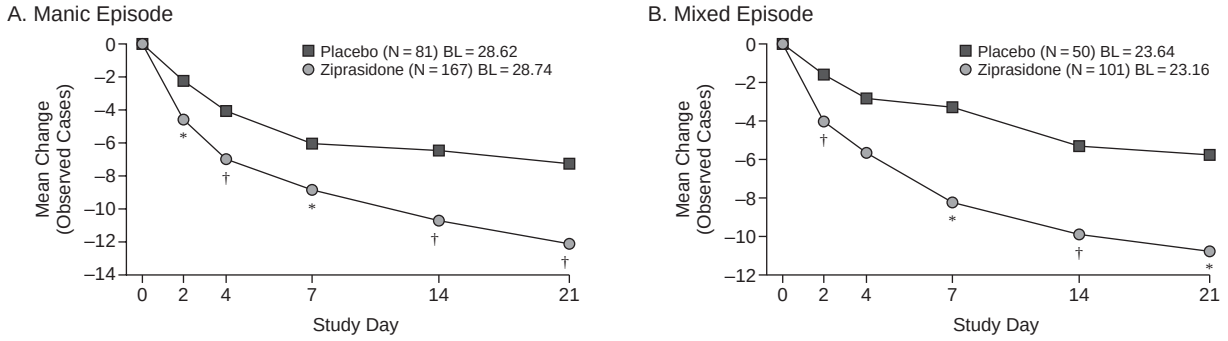
Olanzapine has been found to effectively treat bipolar disorder patients with mixed manic episodes as both monotherapy and combination therapy. A pooled analysis[26] of data from 2 clinical studies comparing the efficacy of olanzapine (N = 125) and placebo (N = 129) in 10 subpopulations of patients with bipolar disorder found that 66.7% of olanzapine-treated patients (24 of 36) who experienced a mixed episode achieved an antimanic response (defined as ≥ 50% decrease from baseline in YMRS total scores). In comparison, 48.6% (18 of 37) of patients with mixed episodes who received a placebo attained an antimanic response. For the whole study, 64.0% (80 of 125) of patients in the olanzapine group and 39.5% (51 of 129) in the placebo group met the antimanic response criteria.[26]

Several studies have shown that olanzapine administered in combination with a mood stabilizer is effective against the manic and depressive symptoms of mixed episodes.[20,27,28] In one of the larger augmentation therapy trials, olanzapine plus valproate reduced mild-to-moderate symptoms of depression (score ≥ 20 at baseline on the 21-item HAM-D [HAM-D-21]) and YMRS scores in patients with mixed episodes.[20] The 6-week, double-blind, randomized trial compared the efficacy of olanzapine in combination with lithium or valproate to monotherapy with lithium or valproate in patients with a manic (N = 179) or mixed (N = 165) episode of bipolar I disorder. Patients included in the study previously had an inadequate response (YMRS total score ≥ 16) to lithium or valproate monotherapy. The HAM-D-21 scores of mixed episode patients receiving combination therapy improved by 10.31 points, a statistically significant difference from the improvement of 1.57 points in the monotherapy group. Of mixed-episode patients, 43.1% who received combination therapy experienced ≥ 50% improvement in depressive symptoms compared with 9.5% in the monotherapy group. Combination therapy was associated with a significantly greater improvement in YMRS scores—a decline of 12.92 compared with a decrease of 7.46 for monotherapy—among patients who experienced mixed episodes. Olanzapine combination therapy was superior to monotherapy only in mixed episode patients who received valproate. Patients with mixed episodes did not respond as well to monotherapy with either lithium or valproate as did patients with purely manic episodes. Olanzapine therapy was not associated with an increase in EPS; adverse effects that occurred more frequently in the combination therapy group included somnolence, dry mouth, weight gain (3.6% increase in body weight, significantly higher than in the monotherapy group), increased appetite, tremor, and speech disorder.[20]

The efficacy and tolerability of ziprasidone in patients with mixed mania were assessed in studies that evaluated ziprasidone in several bipolar disorder subpopulations. Keck et al.[29] reported a 3-week, placebo-controlled, double-blind, randomized trial of the efficacy and tolerability of ziprasidone in the treatment of adults with acute bipolar mania. Of the patients evaluated for efficacy, 133, including 46 (35%) with mixed mania, were randomly assigned to ziprasidone, and 66 patients, including 24 (37%) with mixed mania, were randomly assigned to placebo. Primary efficacy analyses were changes from baseline in Mania Rating Scale (MRS) and CGI-Severity (CGI-S) scale scores. Patients with mixed mania who received ziprasidone had mean decreases from baseline of 11.2 (SD = 10.6) in MRS scores and 1.17 (SD = 1.43) in CGI-S scores. The study did not report responses for patients with mixed mania in the placebo group, but improvements among all ziprasidone patients in MRS and CGI-S scores were significantly better than in the entire placebo group. The difference in MRS scores between the ziprasidone and placebo groups was evident by day 2 of treatment. Ziprasidone was well tolerated, with a low rate of EPS and no weight gain or clinically significant changes in vital signs.[29]

The efficacy of ziprasidone for mixed mania was also assessed in a pooled analysis[30] of 2 randomized, 21-day, double-blind trials that compared flexible-dose ziprasidone (N = 268) with placebo (N = 131); 101 (37.7%) patients in the ziprasidone group and 50 (38.2%) patients in the placebo group had mixed mania. At endpoint, the mean decrease in the MRS score for patients with mixed mania treated with ziprasidone was significantly better than for mixed mania patients receiving a placebo (Figure 1). Movement disorder assessments were comparable between the ziprasidone and placebo groups.

**Figure 1. Change in Mania Rating Scale Score in Subjects Receiving Ziprasidone or Placebo, Manic and Mixed Episodes[a]**




[a]Adapted with permission from Potkin et al.[30]
*p < .05 vs. placebo.
†p < .01 vs. placebo.
Abbreviation: BL = baseline.

Aripiprazole's efficacy in bipolar I disorder was assessed in a 3-week, multicenter, double-blind, placebo-controlled study[14] with 262 patients, including 37 patients in the treatment group and 49 patients in the placebo group who had experienced a mixed manic episode. The researchers did not provide separate results for patient subpopulations. However, treatment with aripiprazole led to statistically significant improvements on the CGI-Bipolar Version (CGI-BP) scale for depression and overall bipolar illness among patients with manic or depressive episodes, indicating symptom improvement in patients experiencing mixed episodes. Aripiprazole produced significant improvements compared with placebo on the YMRS from baseline to endpoint, with a significant difference from day 4 onward. Discontinuations due to adverse events did not differ significantly between the aripiprazole and placebo groups.[14]

## PSYCHOTIC BIPOLAR STATES

Estimates of the percentages of patients with bipolar I disorder who experience psychotic episodes vary from as low as 20% to nearly 60%. One review[31] of 18 phenomenological studies of bipolar disorder found that psychosis occurred in 20% to 50% of patients. A review of 26 studies of bipolar I disorder with psychotic features concluded that 58% of patients with bipolar disorder had at least 1 psychotic episode in a lifetime,[31] with 48% reporting at least 1 delusion, 15% at least 1 hallucination, and 19% at least 1 "formal thought disorder" (in manic patients, this has been defined as overinclusive or combinatory thinking characterized by pressure of speech, racing thoughts, derailment, loss of goal, tangentiality, and distractibility[3]). The mood-congruent psychotic symptoms that are more characteristic of mania than schizophrenia include grandiose delusions and persecutory delusions related to grandiose themes.[3] Table 2 lists the psychotic symptoms found in patients with bipolar mania.

**Table 2. Psychotic Symptoms Characteristic of Bipolar Mania[a]**

| |
|---|
| Mood-congruent features |
| Grandiose delusions: inflated worth, power, knowledge, identity, special relationship to deity or famous person |
| Depressive delusions: personal inadequacy, guilt, disease, death, nihilism, deserved punishment |
| Persecutory delusions related to delusions |
| Auditory hallucinations |
| Paranoid and bizarre delusions |
| Positive thought disorder: pressure of speech, racing thoughts, derailment, tangentiality, distractibility, overinclusive thinking |
| Negative thought disorder: poverty of speech and content of speech, neologisms, disorganized or confused speech, underinclusive thinking |
| Catatonia |

[a]Based on McElroy et al.[3] and the American Psychiatric Association.[5]

### Atypical Antipsychotics for Psychotic Symptoms

Overall, atypical antipsychotics as adjunctive therapy and as monotherapy have demonstrated beneficial effects for psychotic patients with bipolar disorder. For patients experiencing acute agitation with psychosis, intramuscular formulations of olanzapine and ziprasidone have been shown to be efficacious in randomized, controlled clinical trials.[32,33]

The efficacy of clozapine for psychotic bipolar disorder was evaluated in 22 patients with treatment-refractory psychotic features in a 12-week open-label trial.[34] Of the 14 subjects who received clozapine for at least 10 of the 12 weeks, mean improvements from baseline on the BPRS, YMRS, and CGI were –44.4, –24.4, and –2.8, respectively ($p < .0001$ for all). Of the 19 subjects evaluated for safety, the most common side effect was sedation (N = 14).[34] Ciapparelli et al.[35] evaluated treatment with clozapine for 48 months in 101 patients with a diagnosis of schizophrenia; schizoaffective disorder, bipolar type; or bipolar dis-

order with psychotic features. After 48 months, 83.8% of patients in the bipolar disorder group who did not discontinue treatment satisfied the criterion (50% reduction in BPRS score) for a response. Of the 3 patient groups treated, patients with bipolar disorder had the most rapid improvement on BPRS scores and the highest percentage of improvements within 18 months. However, 34 (62.2%) of the patients with bipolar disorder discontinued clozapine therapy.[35]

Risperidone, in combination with a mood stabilizer, has been shown to control psychotic bipolar mania. In a 3-week, randomized, double-blind, placebo-controlled study,[36] 156 patients from various bipolar disorder subpopulations received a mood stabilizer (lithium or divalproex) and placebo, a mood stabilizer and risperidone, or a mood stabilizer and haloperidol. Of the study's patients with psychosis, 22 were randomly assigned to a mood stabilizer and placebo, 21 to a mood stabilizer and risperidone, and 18 to a mood stabilizer and haloperidol. The mean reductions in YMRS scores, the primary efficacy measure, for patients with psychosis were –9.3, –15.4, and –16.8 for the placebo, risperidone, and haloperidol combination groups, respectively.[36] The mean weight gains in the mood stabilizer/placebo, haloperidol/mood stabilizer, and risperidone/mood stabilizer groups were 1.1 lb, 0.3 lb, and 5.3 lb, respectively; the difference in weight gain between the mood stabilizer/placebo and risperidone/mood stabilizer groups reached statistical significance.[36]

A prospective study examined the efficacy of risperidone added to mood stabilizers in the acute and continuation treatment of mania over a 12-week period in 108 patients, 35 of whom had psychotic features.[24] All patients were receiving 1 or 2 mood stabilizers at the time of risperidone initiation, but no other antipsychotic medication or benzodiazepine therapy was allowed. The investigators evaluated the patients according to YMRS from baseline through week 12. At weeks 1, 3, and 12, the patients with psychotic features had a mean YMRS score reduction of –14.9, –22.2, and –27.4, respectively ($p < .0001$).

Olanzapine has been shown to improve psychosis in bipolar disorder with the same degree of efficacy as haloperidol. Of 150 patients with psychosis evaluated in a retrospective chart review,[37] 47 (31%) were diagnosed with bipolar disorder with psychotic features. Thirty-nine of the patients with psychotic symptoms had a moderate-to-marked improvement with olanzapine, and 8 had either no or minimal response ($p = .03$).

Olanzapine also produced a treatment response similar to that of haloperidol in a 12-week, randomized, controlled trial[38] with 453 patients with bipolar mania; 130 patients in each treatment group had psychotic features. With remission defined as scores of ≤ 12 on the YMRS scale and ≤ 8 on the HAM-D, remission rates were 48.5% and 49.2% for patients with psychotic features treated with olanzapine and haloperidol, respectively ($p$ = not significant). Patients in the olanzapine group gained significantly more weight than those in the haloperidol group (2.82 vs. 0.02 kg), although haloperidol was associated with a higher rate of EPS.

Quetiapine's efficacy in treating the psychotic symptoms accompanying bipolar disorder was investigated in a small-scale (N = 7), retrospective chart review of acutely ill mixed or manic patients.[39] The study found that 5 of the patients were "much improved" or "very much improved" on the CGI-BP scale. Quetiapine treatment led to significant improvements in YMRS and CGI-BP scores at endpoint from baseline.

The efficacy of ziprasidone for psychotic symptoms of bipolar disorder was demonstrated in a 21-day trial.[30] Patients who exhibited psychotic symptoms and were treated with ziprasidone (N = 116) had a decrease in their MRS scores of approximately 13 points, compared with a decline of about 7 points in patients who received a placebo (N = 52), at endpoint. The difference reached statistical significance at day 4. A significantly higher percentage, 53% (62/116), of patients with psychosis who received ziprasidone were classified as responders (defined as a decrease in MRS scores ≥ 50% from baseline) compared with 31% (16/52) of psychotic patients who received a placebo.[30] Similarly, an unpublished analysis of data (data on file, Pfizer Inc, New York, N.Y.) from a clinical study[29] found that patients treated with ziprasidone (N = 125) had a significantly greater reduction in the psychotic symptoms of acute bipolar mania, as measured by improvement on the PANSS positive subscale, from baseline through day 21 than patients (N = 64) receiving placebo.

## ATYPICAL ANTIPSYCHOTICS FOR CHILDREN AND ADOLESCENTS

Lewinsohn et al.[40] estimated the lifetime prevalence of bipolar disorder among adolescents at approximately 1%. Children who have had at least 1 manic episode are classified as having bipolar I disorder, and those who have had at least 1 episode of both hypomania and major depressive disorder are considered to have bipolar II disorder. The criteria for manic disorders are the same for children and adolescents as for adults. However, some investigators recognize a chronic mood-labile state as childhood mania, whereas others require a true episode to make this diagnosis.[41,42] Some symptoms of bipolar disorder are different in children and adolescents than in adults, with irritability, ultrarapid cycling, and mixed mania much more common in younger age groups (Table 3). The 2 most common comorbidities among children and adolescents with bipolar disorder are disruptive behavior disorder and attention-deficit/hyperactivity disorder.[43]

A literature review[44] of studies in which antipsychotics were used to treat children and adolescents concluded that more EPS occurred in younger than in older subjects.

Table 3. Symptoms of Bipolar Disorder Unique to Children and Adolescents[a]

| Children | Adolescents | Both |
|---|---|---|
| Happiness not connected to a specific cause | Extremely oppositional or defiant behavior | Abnormal grandiosity unrelated to reality or stage of development |
| Irritability with prolonged temper tantrums | Promiscuous sexual behavior | |
| Hypersexuality manifested by inappropriately touching dolls, peers, or adults | Binges of drinking, drug use, or shopping | |

[a]Based on DelBello and Grcevich.[43]

Atypical antipsychotics cause less EPS in children and adolescents than conventional antipsychotics. Therefore, atypical antipsychotics may be particularly useful for treating bipolar disorder in children and adolescents.[45] None of these agents are approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder in children or adolescents.

Small-scale studies and case reports have indicated that the atypical antipsychotics clozapine, olanzapine, quetiapine, and ziprasidone are effective in treating bipolar disorder in children and adolescents. Case reports of 5 children with bipolar disorder showed that treatment with clozapine led to significant improvements in CGI-S scores.[45] In an open-label study with 23 children 5 to 14 years old, 8 weeks of treatment with olanzapine reduced YMRS scores by 62%.[45] A study of ziprasidone in 4 children, aged 7 to 16 years, with bipolar disorder found that all responded to treatment within 3 days and that side effects were mild and transient.[46]

A randomized, double-blind, placebo-controlled trial evaluated quetiapine in combination with divalproex for acute mania in 30 adolescents 12 to 18 years old.[16] All subjects received an initial dose of divalproex 20 mg/kg before randomization to placebo or quetiapine (titrated up to 450 mg/day). Subjects in the quetiapine group (N = 15) demonstrated a statistically significant reduction in YMRS scores from baseline to endpoint versus the placebo group ($p = .03$). Sedation was significantly more common in those patients receiving quetiapine, although both subjects and caregivers rated all side effects as mild to moderate. The trial was the first parallel-group, placebo-controlled study to compare mood stabilizer monotherapy with augmentation therapy of a mood stabilizer plus antipsychotic in adolescents.

Long-term (88 weeks) quetiapine monotherapy was effective in a single-site, open-label trial with 10 adolescents (aged 12.3 to 15.9 years) with schizoaffective or bipolar disorders.[47] The subjects had significant improvements in their mean scores on the BPRS, CGI, and modified Scale for the Assessment of Negative Symptoms. No EPS or evidence of tardive dyskinesia was observed.

## ATYPICAL ANTIPSYCHOTICS FOR THE ELDERLY

The prevalence of bipolar disorder is estimated at between 0.1% and 0.4% in people older than 65 years of age,[4] but large-scale community surveys of the prevalence of mania and bipolar disorder in the elderly have not been conducted.[48] Between 5% and 10% of elderly patients referred for treatment of mood disorders have been diagnosed with mania or hypomania.[49] Geriatric mania is twice as prevalent in women as in men and is associated with partially or totally irreversible cognitive dysfunction.[48]

Comorbidities frequently complicate the treatment of elderly patients with bipolar disorder. A 10-year retrospective study of elderly patients with bipolar disorder found that they had a mean of 2.1 medical illnesses and were receiving a mean of 1.5 nonpsychiatric medications.[48] Moreover, a broad range of medications, including steroids, anxiolytics, antidepressants, and anti-infectives, have been implicated in the inducement of mania. Clinical studies have also found a correlation between organic cerebral pathologies—such as stroke, traumatic brain injury, and lesions—and the occurrence of mania in geriatric patients.[48]

The elderly are more prone to side effects, particularly from lithium, because of their increased end-organ sensitivity, decreased circulation, and impaired renal function.[13] In general, their medication doses for psychiatric disorders should be lower than those used in younger adults, and the dosages should be carefully titrated. Traditional antipsychotics pose special risks for the elderly because the likelihood of developing medication-induced EPS and tardive dyskinesia has been found to increase with age.[48] The risks posed by benzodiazepines for the elderly include sedation, dizziness, ataxia, and cognitive impairment.

Valproate and carbamazepine have shown safety and efficacy in elderly patients with bipolar disorder.[48] Gabapentin, lamotrigine, and the atypical antipsychotics have also been effective for elderly patients with bipolar disorder, but only a few studies[50–53] have been conducted with those agents in this subpopulation. The atypical antipsychotics may be of particular benefit to the elderly because they have lower rates of EPS and tardive dyskinesia than conventional antipsychotics.[48]

Many of the clinical studies with atypical antipsychotics in the psychotic geriatric bipolar subpopulation have had small patient populations and included patients with several psychiatric disorders in addition to bipolar disorder. Shulman and colleagues[50] assessed the efficacy and safety of clozapine in 3 institutionalized elderly men (mean age of 72 years) with bipolar I disorder whose most recent manic episode included psychotic features. The

patients were refractory or intolerant to treatment with lithium, valproate, benzodiazepines, and traditional neuroleptics both alone and in combination. CGI scores improved from a mean of 6.3 before treatment with clozapine to a mean of 2.0 after treatment ($p < .01$). Significant decreases in granulocyte counts were not observed, and monitoring after 11 months revealed sustained improvement.[50]

Risperidone, quetiapine, and ziprasidone have all been shown to be effective and well tolerated in elderly patients. A computer search at the Veterans Affairs Medical Center in Cleveland, Ohio, for all patients aged 65 years or older who had been treated with risperidone identified 18 psychotic patients with schizophrenia, 2 with schizoaffective disorder, 2 with bipolar disorder, and 4 with other psychotic disorders.[51] Risperidone therapy led to clinical improvement in 22 of these patients and was well tolerated. Quetiapine produced a treatment response in 4 of 7 elderly hospitalized patients (61 to 72 years of age) who manifested symptoms of psychosis related to schizophrenia, schizoaffective disorder, or bipolar disorder.[52] Response was assessed by observation of patients' behavior. Preexisting EPS diminished in 3 patients, but transient hypotension, dizziness, and somnolence occurred in 2 patients.

Loebel et al.[53] evaluated the tolerability of ziprasidone in 471 schizophrenic or schizoaffective patients aged 55 years or older who had participated in phase 2 and 3 clinical studies. Ziprasidone was associated with a mean improvement in the BPRS score as well as lower incidences of EPS and akathisia than risperidone and haloperidol.

## OTHER POPULATIONS

Women generally have similar response rates as men when treated with atypical antipsychotic medication for manic episodes. One study[54] showed a longer time to relapse/recurrence for women who received olanzapine plus either valproate or lithium than women who received olanzapine alone. No such differences were demonstrated for men.

Patients with bipolar II disorder have not been the focus of double-blind, placebo-controlled trials of the atypical antipsychotics. The antidepressant effect of some atypical antipsychotics in patients with bipolar I depression should encourage the study of these compounds in bipolar II patients.[20,55]

## CONCLUSION

People experiencing mixed manic episodes are often difficult to treat. Many patients respond poorly to therapy with lithium, and their treatment can be further complicated by the presence of comorbidities and a high risk for suicide. Still, approximately 40% to 50% of patients with mixed mania have a clinical response to atypical antipsychotics. Similarly, atypical antipsychotics produced significant reductions in BPRS and YMRS scores in bipolar disorder patients with psychotic features.

Atypical antipsychotics have the potential to benefit children and adolescents and the elderly. These subpopulations are prone to the side effects of conventional antipsychotics, such as EPS, with the elderly especially susceptible to tardive dyskinesia. Moreover, comorbidities frequently complicate treatment of elderly patients with bipolar disorder. Atypical antipsychotics have shown effectiveness and tolerability in several small and open-label trials and case studies[45–47,51,52] of pediatric and geriatric patients with bipolar disorder.

*Drug names:* aripiprazole (Abilify), carbamazepine (Carbatrol, Tegretol, and others), clozapine (Clozaril, Fazaclo, and others), divalproex (Depakote), gabapentin (Neurontin and others), haloperidol (Haldol and others), lamotrigine (Lamictal), lithium (Lithobid, Eskalith, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

*Disclosure of off-label usage:* The author has determined that, to the best of his knowledge, aripiprazole, divalproex, olanzapine, quetiapine, risperidone, and ziprasidone are not approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder in children; and carbamazepine, clozapine, gabapentin, and haloperidol are not approved for the treatment of bipolar disorder.

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