The Role of Second-Generation Antipsychotic Monotherapy in the Rapid Control of Acute Bipolar Mania

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A key goal of the pharmacologic treatment of acute bipolar mania is rapid symptom improvement. Medications commonly used to attain this goal include lithium, several anticonvulsants, and both first- and second-generation antipsychotics. Second-generation antipsychotics, which are associated with substantially lower rates of extrapyramidal side effects than first-generation agents, are becoming a mainstay in the treatment of acute mania. Although their efficacy appears to be comparable, second-generation antipsychotics may differ in time to onset and in their side effect profiles. Therefore, selecting a second-generation antipsychotic requires consideration of how an agent's efficacy, onset of action, and adverse events profile influence its appropriateness for each patient.

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Mania is characterized by heightened mood, euphoria or irritability, decreased or lack of need for sleep, elevated activity, enhanced sexual drive, and disinhibition. Patients experiencing an acute manic episode are susceptible to extreme optimism, racing thoughts, and impaired judgment. Their customary behavior changes noticeably, and social and occupational functioning is adversely affected. In severe episodes, patients often require hospitalization to ensure their safety and that of others. One episode of mania is adequate for a diagnosis of bipolar I disorder.[1,2]

Acute mania frequently constitutes a medical emergency, requiring prompt intervention to avoid destructive and possibly life-endangering behavior.[1,2] A heterogeneous group of medications—including the mood stabilizer lithium, certain anticonvulsants, and first- and second-generation antipsychotics (also referred to as conventional and atypical antipsychotics, respectively)—is available for the treatment of acute mania. Initial pharmacologic therapy for severe episodes of mania often consists of the mood stabilizer lithium or the anticonvulsant valproate plus a second-generation antipsychotic. Less severe episodes can sometimes be treated with monotherapy consisting of lithium, valproate, or an antipsychotic, preferably a second-generation antipsychotic.[1]

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The selection of antipsychotic treatment requires consideration of individual patient factors as well as evidence supporting a drug's safety and efficacy. This article reviews the expanding body of evidence from randomized controlled trials, which indicates that second-generation antipsychotics are efficacious, may control mania more rapidly than mood stabilizers, and offer a better tolerability profile than first-generation antipsychotics for initial monotherapy of acute mania.[1] (The article in this supplement by McIntyre and Konarski[3] reviews in detail the tolerability of the second-generation antipsychotics.)

TRADITIONAL FIRST-LINE TREATMENTS

The traditional first-line treatments for acute mania are the mood stabilizer lithium and anticonvulsants such as valproate and carbamazepine. Approximately 50 years of experience and evidence from randomized, controlled trials support the antimanic efficacy of lithium, and more than 20 years of evidence support the antimanic efficacy of valproate and carbamazepine.[2] Carbamazepine has been shown to be comparable to lithium and first-generation antipsychotics,[4–6] although it had a slower onset of action than valproate in one study.[5] Table 1 summarizes clinical trial efficacy results and adverse events with lithium, valproate, and carbamazepine.[4–8]

These 3 agents have a number of limitations. Lithium and valproate require blood monitoring to ensure that serum levels are maintained in the therapeutic range.[2] Lithium and valproate are associated with weight gain in some patients.[9] Lithium's other side effects include polyuria, polydipsia, cognitive dysfunction, tremor, lethargy, incoordination, and gastrointestinal distress. Dose-related side effects of valproate are predominantly gastrointestinal and include anorexia, nausea, dyspepsia, vomiting,

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Table 1. Clinical Trial Findings: Lithium, Valproate, and Carbamazepine in Mania

Reference	Design	Efficacy	Adverse Effects
Lithium			
McElroy and Keck, 2000[7]	Double-blind, placebo-controlled evaluations of lithium monotherapy	Superior to placebo; antimanic effects seen in 1 to 3 weeks of treatment initiation. At least comparable in efficacy to first-generation antipsychotics in acute period	Polyuria, polydipsia, weight gain, cognitive dysfunction, tremor, lethargy, gastrointestinal distress, and intoxication featuring tremor, nausea, blurred vision, delirium
Valproate			
McElroy and Keck, 2000[7]	Double-blind, placebo-controlled evaluations of valproate monotherapy	Half of valproate-treated patients showed ≥ 50% decrease in baseline manic symptoms by 3 weeks in pooled studies	Anorexia, nausea, dyspepsia, vomiting, diarrhea, hair loss, weight gain, tremor, sedation
Carbamazepine			
Immediate-release			
McElroy and Keck, 2000[7]	Randomized controlled	Overall response of 52% in pooled studies. Improved antimanic effects with combination therapy. Slower onset of action with carbamazepine	Diplopia, blurred vision, fatigue, headache, dizziness, nausea, ataxia, skin rashes, nystagmus, ophthalmoplegia, leukopenia, thrombocytopenia[a]
Freeman and Stoll, 1998[8]	Plus adjunctive therapy with first-generation antipsychotic		
Vasudev et al, 2000[5]	Comparison with valproate		
Extended-release			
Weisler et al, 2004[6]	Randomized, double-blind, placebo-controlled	Superior to placebo in improving YMRS, CGI-S, and CGI-I scores	
Ketter et al, 2004[4]	6-month continuation	14% relapse rate	

[a]Adverse effects apply to both immediate- and extended-release formulations.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, YMRS = Young Mania Rating Scale.

and diarrhea. These side effects can be substantially diminished by using divalproex sodium or divalproex sodium extended-release formulations. The most common dose-related side effects of carbamazepine include diplopia, blurred vision, fatigue, nausea, and ataxia. Skin rashes, including a very rare but potentially fatal exfoliative dermatitis, as well as very low incidences of agranulocytosis and aplastic anemia have also been reported.[7–10]

Thus, despite the efficacy of these agents in treating mania, their limitations have provided impetus for the development of other classes of psychotropic medications, such as the second-generation antipsychotics, for the treatment of acute mania.

SECOND-GENERATION ANTIPSYCHOTICS

An antipsychotic plus lithium or valproate is recommended as first-line treatment for severe episodes of bipolar mania.[1] For less severe episodes, monotherapy with an antipsychotic, lithium, or valproate may be adequate. Treatment guidelines recommend the use of second-generation antipsychotics, in preference to first-generation agents, due to their generally more favorable side effect profiles.[1] The U.S. Food and Drug Administration has approved the second-generation antipsychotics risperidone,[11] olanzapine,[12] quetiapine,[13] ziprasidone,[14] and aripiprazole[15] for the treatment of bipolar mania. Olanzapine has been approved for the treatment of acute bipolar manic or mixed episodes and for maintenance therapy; risperidone and quetiapine, for monotherapy and augmentation therapy; and risperidone, ziprasidone, and aripiprazole, for the treatment of manic and mixed episodes.

The second-generation antipsychotics provide acute antimanic efficacy with improved safety compared with first-generation antipsychotics. Evidence from randomized controlled trials supports the role of second-generation antipsychotics (with the exception of clozapine, which is employed primarily in treatment-resistant patients) as first-line agents for the treatment of acute bipolar mania.[7] Compared with first-generation agents, second-generation antipsychotics have a lower potential for acute treatment-emergent side effects, especially extrapyramidal symptoms (EPS), cognitive impairment, and dysphoria.[16,17] Table 2 summarizes the results of several randomized controlled clinical trials with 5 of the second-generation antipsychotics.[18–22]

The results of these and other clinical trials have shown that the second-generation antipsychotics have different times to demonstrating a statistically significant separation from placebo. Ziprasidone differentiated from placebo in 2 days; risperidone, in 3 days in 1 trial and 7 days in 2 studies; aripiprazole, in 4 days; olanzapine, in 7 days; and quetiapine, in 21 days (Figure 1).[18] The clinical significance of time to separation from placebo is not known, and the differences in first time to separation have not been directly compared in controlled clinical trials.

Clozapine

Clozapine has been shown to be effective as acute therapy for mania (with or without psychotic features), as well as for intractable and refractory cases.[7,23] Despite

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Table 2. Randomized, Double-Blind, Controlled Clinical Studies With Atypical Antipsychotics in Acute Mania

Antipsychotic	Control	Dosage	Patients	Results	Adverse Events
Risperidone[18]	Placebo	Mean modal dose of 4.1 mg/d	Acute mania (N = 259)	Significant ($p < .001$) improvement in mean YMRS total score	Somnolence, headache, hyperkinesia, dizziness, dyspepsia, nausea
Olanzapine[19]	Divalproex	Mean modal dose of 17.4 mg/d	Manic and mixed episodes (N = 248)	Significantly ($p < .03$) greater improvement in mean YMRS with olanzapine; responders had more rapid time to response with olanzapine	Somnolence, dry mouth, headache, asthenia, dizziness, nausea, nervousness; significantly ($p < .001$) more weight gain in olanzapine group
Quetiapine[20]	Placebo	Average dose in responders of 600 mg/d	Bipolar mania; data combined from 2 clinical trials (N = 405)	Significantly ($p \leq .007$) more effective than placebo at 21-day endpoint in 11 YMRS items; statistical significance ($p < .05$) at day 4	Somnolence, dry mouth, dizziness, constipation, asthenia, abdominal pain, postural hypotension, weight gain
Ziprasidone[21]	Placebo	Flexibly dosed: mean = 81.3 mg/d day 1; mean = 147.1 mg/d day 2; average = 139.1 mg/d days 8–14; average = 130.1 mg/d days 15–21	Manic and mixed episodes (N = 210)	Significantly ($p < .003$) greater improvement on MRS beginning on day 2; significantly ($p < .05$) greater response in ziprasidone group	Somnolence, dizziness, headache, hypertonia, nausea, akathisia
Aripiprazole[22]	Placebo	Mean dose of 27.9 mg/d at endpoint	Manic episodes (N = 262)	Significantly ($p = .002$) greater mean improvements on YMRS beginning at day 4; significantly ($p \leq .005$) higher response rate	Headache, nausea, dyspepsia, somnolence, agitation, anxiety, vomiting, insomnia, light-headedness, constipation

Abbreviations: MRS = Mania Rating Scale, YMRS = Young Mania Rating Scale.

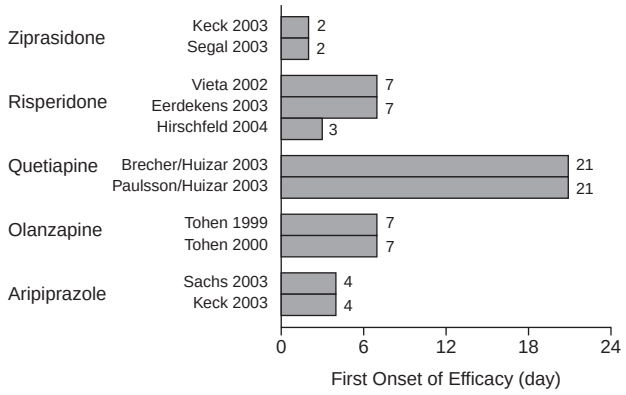
its efficacy, clozapine's use has been limited by its risks for serious adverse events, including agranulocytosis and seizures. Consequently, interest has shifted to other second-generation agents.[16,24]

Risperidone

The efficacy of risperidone in the treatment of bipolar mania has been shown in a double-blind, placebo-controlled monotherapy study[18] and in controlled comparisons with first-generation antipsychotics and mood stabilizers.[7,25–27]

In a 3-week, multicenter, double-blind, placebo-controlled trial in acute bipolar mania, risperidone monotherapy was superior to placebo.[18] Patients experiencing an acute manic episode (baseline Young Mania Rating Scale [YMRS] score ≥ 20) were randomly assigned to risperidone (N = 134; 1–6 mg/day) or placebo (N = 125). Improvement in mean YMRS total score was significantly ($p < .001$) greater for risperidone compared with placebo (mean change = –10.6 [SD = 9.5] vs. –4.8 [SD = 9.5], respectively). Significant between-drug differences ($p < .001$) were seen beginning at day 3 of treatment. These differences were sustained through subsequent time points. Significantly greater improvements in secondary outcome measures were also documented among patients receiving risperidone. Subgroup analyses did not show differences in response based on age, sex, race, or YMRS scores.

Figure 1. First Onset of Efficacy in Placebo-Controlled Trials of Atypical Antipsychotic Monotherapy for Acute Bipolar Mania[a]



[a]Data from Hirschfeld et al.[18]

Adverse events occurring in > 10% of risperidone-treated patients and to a greater degree than with placebo included somnolence, headache, hyperkinesia, dizziness, dyspepsia, and nausea.[18] Extrapyramidal symptom scores were slightly but significantly higher with risperidone. This study was the first large, controlled trial to show that monotherapy with risperidone significantly improved the manic symptoms of bipolar I disorder.

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Risperidone may elevate prolactin through modulation of dopamine-related tracts in the anterior pituitary, which in turn may result in side effects such as menstrual disorders, sexual dysfunction, galactorrhea and other breast complaints, and osteoporosis. In one clinical study, men given risperidone experienced an increase in prolactin levels from 13.7 ng/mL to 43.5 ng/mL; in women, prolactin increased from 19.4 ng/mL to 96.1 ng/mL.[18] The other second-generation antipsychotics display variable effects on serum prolactin. Olanzapine, quetiapine, and ziprasidone have little effect on prolactin; clozapine and aripiprazole appear to promote reductions.[28]

Olanzapine

Olanzapine has shown efficacy for acute mania in trials versus placebo, lithium, divalproex, haloperidol, and risperidone.[24,29–33] In controlled and open-label studies, olanzapine achieved clinically relevant improvements in bipolar mania when administered alone or in combination with lithium and valproate.[7,34] Olanzapine has been an effective treatment for severe or intractable forms of bipolar disorder, including mixed, psychotic, and rapid-cycling states, and was significantly ($p = .04$) more effective than haloperidol in treating patients without psychotic features.[7,30,35,36]

Two trials comparing olanzapine and divalproex had contrasting results.[19,37] A 3-week, double-blind, randomized trial included 248 patients with manic or mixed episodes of bipolar disorder who were hospitalized at baseline and for the first week of double-blind treatment.[19] The mean improvement in YMRS scores of 13.4 in the olanzapine group ($N = 125$; mean modal dose = 17.4 mg/day) was significantly ($p < .03$) greater than the mean improvement of 10.4 in the divalproex group ($N = 123$; mean modal dose = 1401.2 mg/day). Clinical response, defined as ≥ 50% improvement in YMRS score at endpoint, was attained by 54.4% of patients receiving olanzapine and 42.3% of patients receiving divalproex. The response rate between treatment groups was not statistically different, but, among responders, the olanzapine group had a significantly ($p < .05$) more rapid time to response than patients in the divalproex group. Improvement from baseline to endpoint in the YMRS total score (last observation carried forward) was significantly greater in the olanzapine group at day 1, but not at day 2 or at days 3 through 7.[19]

A 44-week continuation of this trial found that olanzapine yielded significantly superior improvement in mean YMRS scores between weeks 2 and 15 but that olanzapine and divalproex achieved comparable rates of remission from symptomatic manic episodes (56.8% for olanzapine; 45.5% for divalproex) at 47 weeks.[32]

Adverse events in the 3-week trial occurring in > 10% of olanzapine-treated patients and to a greater extent than with placebo included somnolence, dry mouth, headache, asthenia, dizziness, constipation, dyspepsia, pain, increased appetite, weight gain, nausea, and nervousness.[19] Patients who received olanzapine gained significantly more weight (mean = 2.5 kg) than those treated with divalproex ($p < .001$ vs. divalproex).

In contrast, a 12-week, randomized, double-blind comparison showed no statistically significant differences in efficacy between olanzapine and divalproex.[37] The study included 120 patients (divalproex [$N = 63$] mean maximal dose = 2115 mg/day; olanzapine [$N = 57$] mean maximal dose = 14.7 mg/day) hospitalized for acute mania for up to 21 days and then followed as outpatients. No significant differences were found between the 2 groups on the Mania Rating Scale (MRS), Brief Psychiatric Rating Scale (BPRS) total scores, BPRS positive scores in patients with psychotic symptoms, Clinical Global Impressions-Severity of Illness scale (CGI-S), or the Hamilton Rating Scale for Depression (HAM-D) from baseline to day 84.

The mean increase in body weight from baseline to endpoint was significantly ($p = .05$) greater in the olanzapine group at 8.8 lb compared with the 5.5-lb mean increase in the divalproex group.[37] Somnolence, edema, and slurred speech also occurred in a significantly larger percentage of patients receiving olanzapine than divalproex ($p \leq .05$). No adverse event occurred significantly more often in divalproex patients.

Different doses of divalproex were given in these 2 studies; the mean modal dose was 1401 mg/day in the 3-week trial and 2115 mg/day in the 12-week study. Differences in the agent's efficacy between the 2 studies may be due to either the different doses or the limitations in statistical power in the second trial.[37]

The weight gain associated with olanzapine and other agents for bipolar disorder has emerged as an important side effect of psychotropic drug treatment, with significant implications for morbidity and treatment adherence. Substantial weight gain is associated with coronary artery disease, hypertension, dyslipidemia, and diabetes mellitus and is a predictor of nonadherence to treatment.[38,39] In addition to olanzapine, the mood-stabilizing and antipsychotic drugs associated with weight gain include lithium, valproate, chlorpromazine, clozapine, risperidone, and quetiapine.[9,40–43]

Quetiapine

Quetiapine was found to be efficacious as monotherapy and as adjunctive therapy in open-label studies and randomized controlled clinical trials for acute mania. This atypical antipsychotic has been investigated in acute mania, treatment-refractory bipolar I disorder, mixed episode bipolar disorder, bipolar disorder comorbid with cocaine dependency, and rapid-cycling bipolar disorder.[44] In 2 double-blind, placebo-controlled studies, quetiapine combined with a mood stabilizer was shown to be effective in the treatment of bipolar disorder in children and adolescents[45] as well as in adults.[46]

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In a 12-week study, quetiapine monotherapy for acute mania was compared with placebo and haloperidol in randomized, double-blind fashion.[47] Brecher and Huizar evaluated 302 patients and found that significantly more patients (61.4%) receiving quetiapine (up to 800 mg/day) achieved the clinical endpoint of ≥ 50% decrease in YMRS by day 21 than patients given placebo (39%); this result was sustained at study end (day 84). Quetiapine and haloperidol demonstrated similar efficacy for mania. Patients treated with haloperidol experienced a significantly higher rate of EPS compared with patients receiving quetiapine or placebo. Quetiapine monotherapy was well tolerated.

Pooled data from 604 patients enrolled in randomized, double-blind, placebo-controlled quetiapine monotherapy trials were evaluated, using data from lithium and haloperidol treatment groups as controls.[48] Quetiapine was similar to lithium and haloperidol in efficacy versus placebo. Finally, quetiapine (up to 800 mg/day) as an adjunctive therapy for acute mania was evaluated in 191 patients randomly assigned to receive it or placebo with either lithium or divalproex for 21 days.[49] Quetiapine plus a mood stabilizer demonstrated significantly greater reduction in mania scores than placebo plus a mood stabilizer. Somnolence, dry mouth, and postural hypotension were the most common side effects experienced with quetiapine.

Ziprasidone

Ziprasidone's efficacy as monotherapy has been demonstrated in 2 double-blind trials for acute bipolar mania[21,50] and in an open-label trial for the long-term treatment of bipolar disorder.[51]

Ziprasidone demonstrated an antimanic effect significantly superior to placebo by day 2 in a randomized, placebo-controlled, double-blind, parallel-group study in patients with bipolar manic or mixed episodes.[21] Patients were assigned to 3 weeks of double-blind treatment with twice-daily ziprasidone (N = 140) or placebo (N = 70). The ziprasidone dosage began at 80 mg/day on day 1, increased to 160 mg/day on day 2, and was flexibly dosed from 80 to 160 mg/day over the remainder of the trial. Primary efficacy outcome variables were measured by changes from baseline to endpoint in the mean MRS and CGI-S scores, while secondary measures were obtained using the Positive and Negative Syndrome Scale (PANSS), CGI-Improvement (CGI-I), and the Global Assessment of Functioning (GAF). Ziprasidone improved mood and other symptoms of acute bipolar mania for all primary and secondary outcome variables. Ziprasidone was statistically superior to placebo on the MRS at all time points beginning on day 2 ($p < .003$), and 50% of 131 patients randomly assigned to ziprasidone displayed a response, versus 35% of 66 patients given placebo ($p < .05$). At day 7, ziprasidone-treated patients showed significant improvement versus the placebo group on all evaluation scales, and intergroup differences increased throughout the study.[21] Ziprasidone was well tolerated overall and was associated with a low rate of EPS and no significant weight gain. Adverse events occurring more frequently with ziprasidone than placebo were somnolence, headache, dizziness, hypertonia, nausea, and akathisia.

In a similarly designed 21-day study, treatment with ziprasidone (N = 137) led to significant ($p = .001$) improvement compared with placebo (N = 65) on the MRS, the primary efficacy variable, beginning on day 2 and continuing through the end of the study.[52] The mean reductions in MRS scores from baseline to endpoint were –11.12 with ziprasidone and –5.62 with placebo, and the percentage of MRS responders was significantly greater with ziprasidone than with placebo (46% vs. 29%; $p < .05$). Statistically significant improvements were observed at endpoint for the secondary variables: CGI-S, CGI-I, and behavior and ideation subscale of the MRS ($p < .001$ for all); manic syndrome subscale of the MRS ($p < .01$); PANSS positive subscale ($p < .001$); PANSS total score ($p = .005$); and GAF ($p = .001$). Ziprasidone was well tolerated, with few discontinuations due to adverse events and no clinically relevant differences from placebo in clinical laboratory abnormalities.

In a pooled evaluation of these 2 trials, ziprasidone was significantly more efficacious than placebo.[50] Ziprasidone (mean dose = 122 mg/day) significantly improved MRS scores at day 2 ($p < .0001$ vs. placebo), and this difference was maintained at all time points after separation from placebo on day 2. Patients treated with ziprasidone (N = 268) also had significantly greater improvements on the CGI-S ($p < .001$) at endpoint than patients receiving placebo (N = 131).

Subgroup analyses were performed in patients with manic or mixed episodes and with or without psychotic symptoms.[50] Patients treated with ziprasidone who had mixed (N = 101) or manic (N = 167) episodes showed significantly greater improvement on the MRS ($p < .01$ and $p < .05$ vs. placebo, N = 50 and N = 61, respectively) at day 2 and in CGI-S scores at day 4 ($p \leq .01$). These differences were maintained through endpoint. For patients with and without psychotic symptoms, ziprasidone treatment significantly improved MRS scores. According to last-observation-carried-forward analysis, treatment with ziprasidone produced significant improvements in MRS scores from day 2 for patients (N = 152) without psychotic symptoms and from day 4 through endpoint in patients (N = 116) with psychotic symptoms ($p < .01$ for both, compared with placebo). Among patients with symptoms of depression, treatment with ziprasidone was associated with statistically significant improvements compared with placebo on the HAM-D at day 4 ($p < .05$) and day 7 ($p < .01$). Another study found that among mixed manic patients (N = 18) with a HAM-D ≥ 14 at baseline, patients receiving ziprasidone experienced a significant ($p < .05$)

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improvement compared with placebo in HAM-D-17 scores from day 2 through day 21.[53] Numeric improvements on the HAM-D were observed at all time points. Overall, ziprasidone was well tolerated; somnolence, which had a mean duration of 7 days among ziprasidone-treated patients and 5 days among those receiving placebo, was the most commonly reported adverse event.

Ziprasidone and aripiprazole have not been associated with significant weight gain[42,54] or a significant adverse impact on serum lipid profiles.[55,56] The effects of weight gain on metabolic and lipid profiles were illustrated in an open-label switch study in which patients with schizophrenia who had received conventional antipsychotics (N = 71), risperidone (N = 43), or olanzapine (N = 71) were switched to ziprasidone and followed for 58 weeks.[57] Patients receiving ziprasidone after therapy with risperidone lost a mean of 15.2 lb ($p < .005$) and had a significant reduction ($p < .0005$) in total cholesterol. Patients switched from olanzapine experienced a weight loss of 21.6 lb ($p < .0001$) and significant decreases in mean total cholesterol ($p < .0001$) and triglycerides ($p = .0005$). No significant change in weight was observed for patients who had been receiving a conventional antipsychotic.

Aripiprazole

Aripiprazole has demonstrated consistent efficacy in bipolar mania in double-blind, placebo-controlled, randomized studies.[22,58] As with ziprasidone, therapeutic efficacy was achieved with a low likelihood of EPS and without significant weight gain.[22] A pooled analysis of data from 3 double-blind, multicenter, 3-week trials in patients with acute mania found significantly greater improvements in YMRS total score ($p < .001$), response rate ($p = .001$), and remission rate ($p = .001$) at endpoint among patients receiving aripiprazole (N = 515) than in those receiving placebo (N = 384).[59] The decrease in YMRS total score reached statistical significance ($p < .001$) at day 4.

In a 3-week, multicenter, double-blind study of aripiprazole with 262 manic patients, aripiprazole (N = 130) at a starting dose of 30 mg/day produced statistically significant ($p = .002$) mean improvements on the YMRS total score compared with placebo (–8.2 vs. –3.4, respectively) and a significantly ($p \leq .005$) higher response rate (40% vs. 19%).[22] Aripiprazole separated from placebo by day 4 on several key efficacy variables, and aripiprazole patients had a significantly ($p < .001$) higher completion rate versus placebo (42% vs. 21% at endpoint). Treatment with aripiprazole also led to significantly greater improvements than placebo in severity of illness as evaluated by efficacy assessments of mania ($p = .001$), depression ($p = .03$), and overall bipolar disorder ($p = .001$). Discontinuations due to adverse events were comparable between groups. The most common adverse events in patients treated with aripiprazole were headache, nausea, dyspepsia, somnolence, agitation, anxiety, vomiting, insomnia, light-headedness, and constipation. No significant changes in body weight were observed versus placebo.[22]

Monotherapy with aripiprazole was compared with haloperidol in a randomized, double-blind, 12-week study with 347 patients presenting with acute manic or mixed episodes.[58] Significantly more aripiprazole patients responded to treatment. Approximately 29% of patients in the haloperidol group completed the study, with discontinuations due mainly to adverse effects, compared with almost 51% of the aripiprazole group. Extrapyramidal side effects were reported in 36% of the haloperidol group, in contrast to only 9% of patients receiving aripiprazole.

CONCLUSION

In the recent past, monotherapy with lithium, valproate, or carbamazepine represented common first-line treatment for bipolar mania. The advent of newer medications, especially the second-generation antipsychotics, is leading to an expansion of first-line treatments for acute mania.[60] These agents have an improved tolerability and safety profile compared with first-generation antipsychotics, and mounting evidence from well-designed clinical trials supports their use as monotherapy or in augmentation therapy in acute mania and acute mixed episodes. These trials demonstrated that treatment with second-generation antipsychotics can lead to a rapid and significant response in bipolar mania. Clinical studies also have shown the varying propensities of these agents to induce weight gain, lipid elevations, hyperprolactinemia, and other adverse events. Second-generation antipsychotics are likely to have an increasingly prominent role in the pharmacologic management of mania in bipolar disorder patients.

Drug names: aripiprazole (Abilify), carbamazepine (Carbatrol, Tegretol, and others), chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril, Fazaclo, and others), divalproex (Depakote), haloperidol (Haldol and others), 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, carbamazepine, clozapine, and haloperidol are not approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder.

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