The Role of Novel Antipsychotics in Bipolar Disorders

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Patients with bipolar disorder frequently receive antipsychotic agents during both the acute and maintenance phases of treatment. Conventional antipsychotics are effective against mania, but they may induce depressive symptoms and expose patients with bipolar disorder to increased risks of tardive dyskinesia. Recent studies have shown risperidone to be effective for acute mania, both as monotherapy and in combination with mood stabilizers; this agent has also shown efficacy as add-on maintenance therapy in open-label studies as it exhibited both antimanic and antidepressant effects. Olanzapine, another novel antipsychotic, is also effective against both manic and depressive symptoms and in the maintenance treatment as indicated by an open-label study. Data on other novel agents are more limited.
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Antipsychotic medications have a long history of use in bipolar disorders, considerably predating the use of lithium. Chlorpromazine, for example, has been used to control agitation and psychotic symptoms almost since its introduction in the early 1950s.[1] Increasingly, research is focusing on the potential uses of the novel antipsychotics in bipolar disorders. This article reviews some of the most recent results obtained with these agents.

Studies examining prescription rates have suggested that up to 90% of patients with bipolar disorders receive antipsychotic medications at some time during the illness.[2] A survey at a university teaching hospital, whose prevailing philosophy was to discourage the use of unnecessary medications, found that 82% of patients with mania admitted to a hospital were receiving an antipsychotic (L.N.Y., unpublished observation, 1999). The most common reasons for their use included rapid control of psychotic symptoms, agitation or overactivity, violent behavior, and refractoriness to treatment with a mood stabilizer alone. Moreover, the use of antipsychotic medications often extended well beyond the acute treatment phase into the maintenance phase.[3]

Given this high degree of antipsychotic use, which antipsychotic agents are preferable to use in the setting of bipolar illness? Conventional antipsychotics are effective not only in the treatment of the symptoms of acute mania,[4-6] but also may have some usefulness in the prevention of manic episodes.[2,7,8] However, the incidence of tardive dyskinesia associated with these agents is of concern, and there is some evidence that the risk of tardive dyskinesia is higher in patients with bipolar disorders than in those with schizophrenia.[9] Furthermore, conventional antipsychotic medications do not appear to help patients with depressive episodes—in fact, they may even induce depression.[10] Therefore, conventional antipsychotics are unlikely to be the optimal choices for treating patients with bipolar disorder who require antipsychotic medication.

The remainder of this article will review the current evidence for treating bipolar disorder patients with novel antipsychotics. Risperidone and olanzapine are the 2 novel antipsychotics for which the most evidence has accumulated.

RISPERIDONE

There are robust double-blind data on the use of risperidone in acute mania. One small 4-week monotherapy study[11] compared risperidone, 6 mg/day; haloperidol, 10 mg/day; and lithium, 800 to 1200 mg/day, in 45 patients

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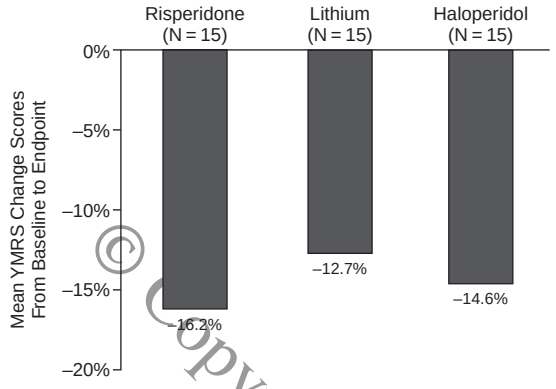
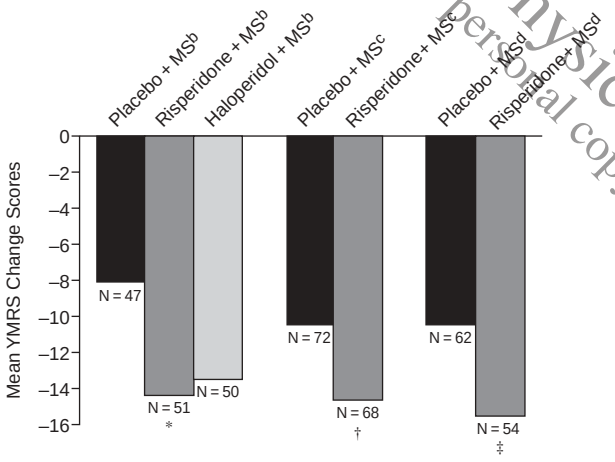
Figure 1. Mean Young Mania Rating Scale (YMRS) Change Scores With Risperidone, Lithium, or Haloperidol[a]



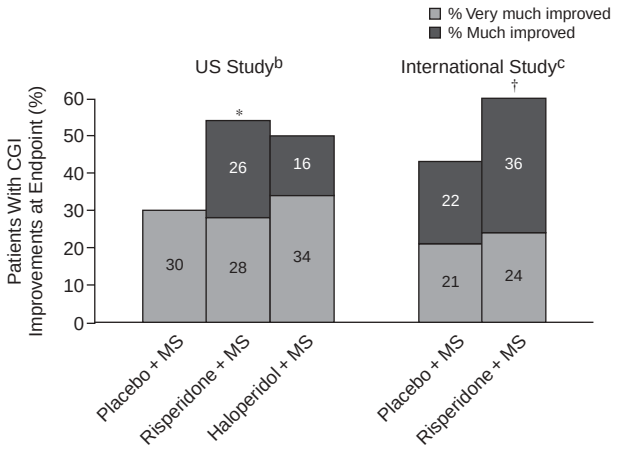
[a]Data from Segal et al.[11]

Figure 2. Young Mania Rating Scale (YMRS) Change Scores From Baseline to Endpoint With Risperidone or Placebo or Haloperidol Add-On to Mood Stabilizers in 2 Double-Blind Studies[a]



[a]Abbreviation: MS = mood stabilizer.
[b]U.S. study. Data from Sachs.[13]
[c]International study. Data from Yatham.[12]
[d]International revised sample excluding carbamazepine.
*p < .01.
†p = .089.
‡p < .047.

Figure 3. Patients With Improvement on Clinical Global Impressions-Improvement (CGI-I) Scale in 2 Double-Blind Studies[a]

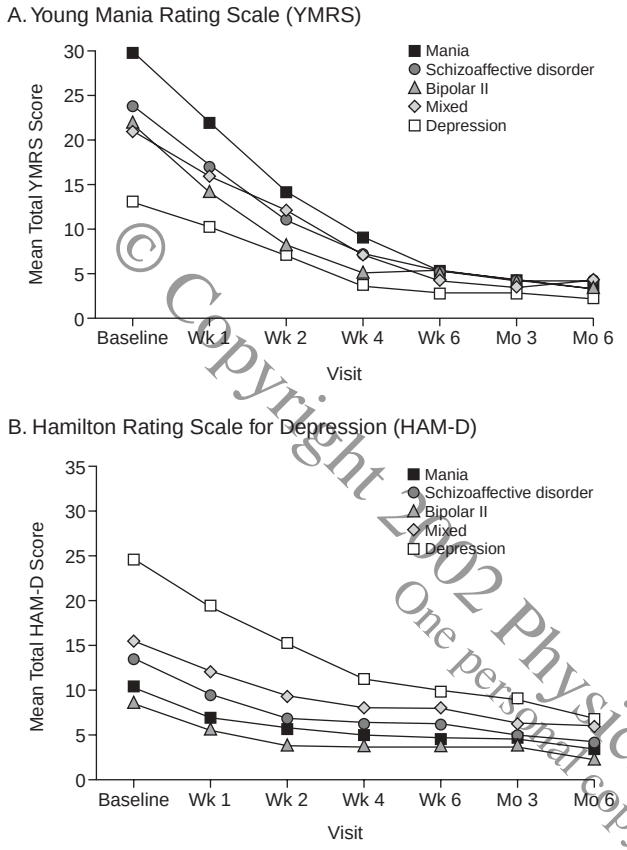


[a]Abbreviation: MS = mood stabilizer.
[b]U.S. study. Data from Sachs.[13]
[c]International study. Data from Yatham.[12]
*p < .01 risperidone vs. placebo.
†p < .05.

with acute mania. Risperidone was found to be as effective as the other 2 agents—the mean Young Mania Rating Scale (YMRS) scores decreased by 16.2 points for the risperidone group, 14.6 points for the haloperidol group, and 12.7 points for the lithium group (Figure 1).

This study was suggestive of the efficacy of risperidone monotherapy in acute mania. However, in clinical practice, the combination of an antipsychotic medication with a mood-stabilizing agent is far more common. Accordingly, 2 similarly designed double-blind combination studies in acute mania examined the addition of risperidone or placebo to a mood stabilizer.[12,13] One study was an international trial[12] that enrolled 150 patients and included lithium, valproate, or carbamazepine as the mood stabilizers. The other was a U.S. trial[13] that included an additional haloperidol treatment arm, but in this study only lithium or valproate were permitted as mood stabilizers. Both studies were double blind and were of 3 weeks' duration followed by a 10-week open-label extension period. In the U.S. study, both risperidone and haloperidol reduced YMRS scores by approximately 6 points compared with placebo; this difference was both statistically and clinically significant (Figure 2). In the international study,[12] initial analysis of data showed a difference of about 4.5 points on YMRS scores between the risperidone plus mood stabilizer and placebo plus mood stabilizer groups, which was clinically but not statistically significant. However, patients in this study who received both risperidone and carbamazepine had mean serum risperidone concentrations 1.7 times lower than those who received risperidone with valproic acid or lithium. The lower serum concentrations were most likely caused by the induction of risperidone metabolism by carbamazepine. Exclusion of the patients taking carbamazepine yielded a statistically significant difference ($p < .05$; Figure 2) between the 2 groups. Moreover, in both studies, the proportion of patients who were "much improved" or "very much improved" was significantly greater in the risperidone group than in the placebo group (Figure 3). In addition, the improvement in the risperi-

Figure 4. Scores of 541 Bipolar Patients According to Subtype Treated With Add-On Risperidone in an Open-Label Study[a]

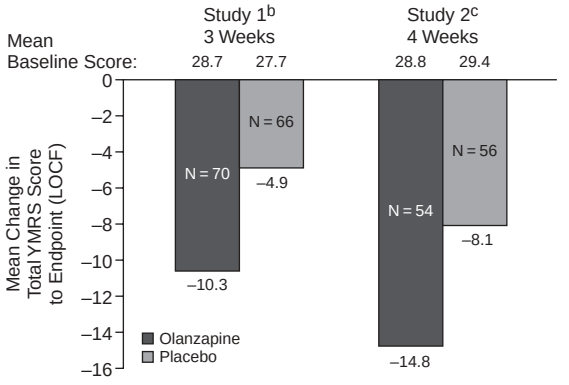


[a]Data from Vieta et al.[14] There was a highly statistically significant trend toward reduction in YMRS scores and HAM-D scores across all groups ($p < .0001$).

done-treated patients was seen within the first week. This improvement in manic symptoms was evident in patients both with and without psychosis, suggesting that risperidone is not simply an antipsychotic agent but also an effective antimanic agent.

A 6-month open-maintenance trial[14] involving 541 patients found that risperidone, used as an add-on therapy, was effective in treating both manic (as measured by YMRS scores) and depressive symptoms (as measured by the Hamilton Rating Scale for Depression [HAM-D]), and maintaining the improvement throughout the study period (Figure 4, A and B). Only 7% of the patients subsequently relapsed. None of the patients developed tardive dyskinesia during the 6-month study period; if these patients had been taking haloperidol, 15 to 20 new cases of tardive dyskinesia would have been expected to emerge. Open data such as these will require confirmation with double-blind studies, but the results of this study suggest that risperidone does not induce depressive symptoms, and it may be useful in preventing both depressive and manic episodes.

Figure 5. Olanzapine Versus Placebo in Acute Mania[a]



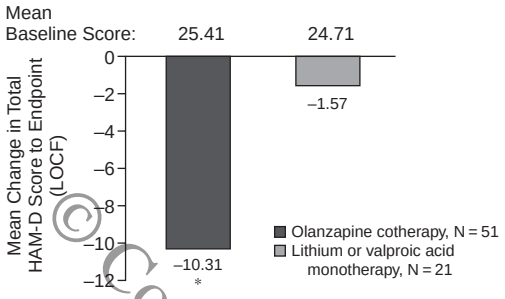
[a]Abbreviation: LOCF = last observation carried forward.
[b]Data from Tohen et al.[15]
[c]Data from Tohen et al.[16]

OLANZAPINE

Two double-blind trials[15,16] lasting 3 and 4 weeks, respectively, compared olanzapine monotherapy with placebo in the treatment of acute mania. In both studies, olanzapine produced at least a 5-point improvement on the YMRS score compared with placebo (Figure 5). Olanzapine was effective in treating manic symptoms in both psychotic and nonpsychotic mania as well as in those with mixed episodes. Of the 139 patients in the 3-week double-blind study,[15] 113 entered a 49-week, open-label extension phase. Forty-one percent of patients received olanzapine monotherapy during this phase. The YMRS scores decreased 18 points, and 88% of patients experienced remission of manic symptoms; 25% subsequently relapsed. HAM-D scores also decreased by a mean of 5.77 points ($p < .001$), which suggests that olanzapine does not induce depressive symptoms and that it may be effective in preventing both depressive and manic episodes.[17] No cases of tardive dyskinesia were seen.

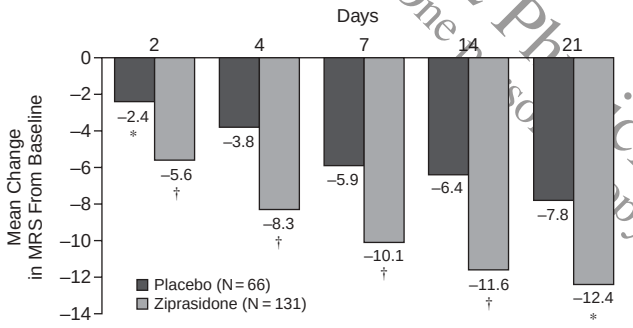
Olanzapine monotherapy has also been found to be at least as effective as lithium[18] or divalproex sodium[19] for treating patients with acute mania. In a 6-week augmentation study,[20] 334 patients with mania who took mood stabilizers (lithium or valproic acid) received olanzapine or placebo add-on therapy. The YMRS scores decreased by a mean of 13.11 in the olanzapine group and 9.10 in the placebo group ($p = .003$). Moreover, significantly more patients receiving olanzapine achieved at least a 50% decrease in YMRS scores (67.7% vs. 44.7%; $p = .023$). Among the 72 patients in this study who also had substantial depressive symptoms, scores on the 21-item HAM-D scale decreased by 10.31 with olanzapine vs. 1.57 with placebo ($p < .001$), again consistent with the hypothesis that olanzapine has antidepressant properties (Figure 6).

Figure 6. 21-Item Hamilton Rating Scale for Depression (HAM-D-21) Total Scores in Patients With Moderate-to-Severe Depressive Symptoms[a]



[a]Data from Tohen et al.[20] A priori definition of DSM-IV mixed episode diagnosis and HAM-D-21 total score ≥ 20 at baseline.
*p < .001.

Figure 7. Mania Rating Scale (MRS) Score Changes in Ziprasidone and Placebo Groups[a]



[a]Data from Keck and Ice.[21]
*p < .01.
†p < .001.

OTHER NOVEL ANTIPSYCHOTICS

The available data on the efficacy of other novel antipsychotics in bipolar disorders are more limited. A 3-week double-blind, placebo-controlled study[21] of ziprasidone monotherapy in 195 acutely manic patients found that ziprasidone significantly improved Mania Rating Scale scores (Figure 7); data about the utility of ziprasidone as an add-on therapy are likely to be available in the near future. Two published uncontrolled open trials of quetiapine[22,23] suggest that it is antimanic and may be mood stabilizing, but these data await confirmation with double-blind studies. Finally, clozapine has also shown promise in open trials as an antimanic drug and mood stabilizer,[2,24,25] but it is not considered a first-line treatment because of concerns about agranulocytosis, sedation, seizures, and other side effects.

In summary, a variety of novel antipsychotics have been used for treating patients with bipolar disorder. Mounting evidence supports their efficacy, their low incidence of extrapyramidal side effects and tardive dyskinesia, and the suggestion that they may also have mood-stabilizing properties in their own right.

Drug names: carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), clozapine (Clozaril and others), divalproex sodium (Depakote), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), valproic acid (Depakene and others), ziprasidone (Geodon).

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