Letters to the Editor

Olanzapine for the Treatment of Bipolar Disorder

Sir: In a recent issue of the *Companion*, Masand and colleagues[1] report a retrospective analysis of 36 outpatients with bipolar or schizoaffective disorder in which risperidone and olanzapine were comparable in efficacy and safety, but treatment costs were lower for risperidone-treated patients. Although the acquisition costs of risperidone are lower than those of olanzapine, when other factors are taken into account, the costs of the 2 agents do not differ appreciably. As the authors point out in their article, atypical antipsychotics are becoming commonly prescribed agents in primary care settings. At the same time, primary care providers are assuming the responsibility of managing bipolar disorders. It is sometimes tempting to categorize newer antipsychotic agents into one class for the management of these conditions. However, at the moment there is considerably more evidence supporting the use of olanzapine in bipolar illness than for any other atypical antipsychotic agent, and much more than the "preliminary" evidence to which the authors allude.

On the strength of 2 placebo-controlled studies that tested its efficacy as monotherapy for acute mania in 139 and 115 patients, respectively,[2,3] olanzapine is currently the only atypical antipsychotic that has been approved by the U.S. Food and Drug Administration for this indication. The strength of these data is one reason olanzapine is more prominent than other atypical antipsychotics in recently published treatment guidelines.[4,5] Although a well-controlled study recently demonstrated that risperidone in combination with lithium or divalproex was efficacious as an adjunctive agent for the treatment of mania,[6] no clinical trial demonstrating risperidone's efficacy as a monotherapeutic agent has ever been reported.

Three head-to-head monotherapy studies[7–9] of olanzapine versus FDA-approved mood stabilizers have been conducted in acute mania, with a total of 398 randomized patients. In one study, olanzapine was superior to divalproex in the primary and several secondary outcome measures at 3 weeks[7] and at 47 weeks,[8] and in the second study, these 2 agents had comparable efficacy at 3 weeks.[9] In the third study, the efficacy of olanzapine was similar to lithium on all reported outcome measures.[10] Direct comparisons of this sort between other atypical antipsychotics and established mood stabilizers for the treatment of mania are not yet available.

Treatment of mania is only one aspect of the comprehensive management of bipolar disorder. Treatment of bipolar depression and long-term prevention of acute mood episodes are important goals, and in these areas olanzapine's efficacy is more firmly established than any other atypical antipsychotic agent. In the only placebo-controlled study of an atypical antipsychotic in bipolar depression, the efficacy of olanzapine statistically separated from placebo after 1 week of treatment, and this effect was sustained throughout the 8 weeks of double-blind treatment.[11]

Finally, 2 studies[12,13] evaluating long-term efficacy have been reported. Open-label therapy with olanzapine was continued for up to 1 year in 113 patients who entered one placebo-controlled registration study.[12] In this study, patients demonstrated improvement in mania and depressive symptoms; 88% ultimately achieved protocol-defined remission of symptoms, with only a 25% rate of subsequent relapse. In the second longer-term study, blinded placebo-controlled olanzapine added to lithium or divalproex in 99 patients was much more effective in preventing both depressive and manic relapses than either mood stabilizer alone over a period of 18 months.[13] Two other 1-year studies of olanzapine, one versus placebo and the other versus lithium, will be completed this year.

In summary, among atypical antipsychotic agents, olanzapine has the most supportive data for the treatment of bipolar disorder. Therefore, it is premature to place these agents into a single category. In addition to acquisition costs, which favor risperidone, available clinical trial data on olanzapine should be considered in treatment choice.

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Dr. Masand Replies

Sir: I read with interest the letter to the editor by Dr. Ahmed and colleagues at the Lilly Research Laboratories in Indianapolis, Indiana, regarding our article[1] in the last issue of the journal. I agree with the authors that olanzapine has the best available data for efficacy in bipolar disorder, which is the reason, as they point out, that it has approval from the U.S. Food and Drug Administration (FDA) for the treatment of acute mania. However, the authors are incorrect in stating that there is no clinical trial demonstrating risperidone's efficacy as a monotherapeutic agent in bipolar disorder. In fact, there is a randomized, double-blind, controlled trial comparing risperidone, lithium, and haloperidol in the treatment of acute mania, which found equal efficacy of all 3 active groups.[2] There is also a double-blind, randomized, placebo-controlled trial of ziprasidone in acute mania showing efficacy superior to placebo.[3] There are ongoing double-blind, randomized, placebo-controlled trials of risperidone monotherapy in the treatment of acute mania.

The authors describe 3 head-to-head monotherapy studies of olanzapine versus FDA-approved mood stabilizers in acute mania showing either equal or superior efficacy to lithium or divalproex sodium. Conveniently, however, the authors fail to mention that weight gain with olanzapine was twice as much as with divalproex. One of the very important considerations in choosing a novel antipsychotic, in any psychiatric illness—including bipolar illness—is not just efficacy but tolerability and safety. Olanzapine is the novel antipsychotic most likely to be associated with weight gain.[4] In fact, in a recent study, comparing olanzapine and risperidone, the average weight gain with olanzapine at the end of 12 weeks was 24 lb (11 kg) versus 4 lb (2 kg) with risperidone.[5] Weight gain is a particularly problematic side effect of olanzapine in bipolar disorder since these patients are usually on mood stabilizers like divalproex sodium or lithium, which, in and of themselves, can cause significant weight gain.

Among the mood stabilizers, topiramate is perhaps the least likely to cause weight gain.[6] In addition, there are now data accumulating from several large epidemiologic studies,[7–10] double-blind, randomized, head-to-head, comparison trials,[11] and the FDA MedWatch database[12] showing that olanzapine, among the atypical antipsychotics, is among the most likely to be associated with diabetes mellitus, which can be potentially life threatening. In a recent article published in the journal *Pharmacotherapy*, Koller and Doraiswamy[13] reported on 237 cases of diabetes mellitus associated with olanzapine, including 80 patients with diabetic ketoacidosis and 15 deaths.

Hence, while I agree with the authors that the published efficacy data for olanzapine in bipolar disorder are more extensive than they are for the other atypical antipsychotics, in my experience, the other atypical antipsychotics are as efficacious but safer and better tolerated than olanzapine, particularly with respect to weight gain and diabetes mellitus, which are perhaps the most problematic side effects of some novel antipsychotic medications. Since clinicians now have a choice of 4 first-line novel antipsychotics and a fifth one, aripiprazole, which also showed superiority to placebo in acute mania[14] and will be available in the very near future, clinicians need to weigh the risk-benefit ratio of these agents, not just the benefits that the authors have alluded to. In fact, I agree with the authors that it is premature to place these agents into a single category particularly with respect to safety and tolerability since olanzapine appears to be the most problematic.

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