(SD=0.7) points in the olanzapine group, and 18.6 (SD=1.3) points in the olanzapine-fluoxetine group. These differences were statistically significant, but it is at least questionable whether these differences should be considered clinically meaningful. This 3-point difference between placebo and olanzapine represents only about 10% of the baseline Montgomery-Asberg Depression Rating Scale score.

The conclusions of the study by Tohen and colleagues become even more doubtful if we consider that 20% of the overall score of the Montgomery-Asberg Depression Rating Scale is given by items that can represent an improvement in depressive symptoms as well as a side effect associated with olanzapine. Namely, the two most frequent side effects of olanzapine described in this study were somnolence (28.1% in intervention versus 12.5% in control) and weight gain (17.3% versus 2.7%), when in fact the Montgomery-Asberg Depression Rating Scale consists of 10 items, two of them being "reduced sleep" and "reduced appetite" as symptoms of depression. Both items were among the only three items in which the olanzapine group had a statistically significant higher decrease than the placebo group; the other item was "inner tension." None of these items are core depressive symptoms, and all of them could be reduced by the well known sedative and increased appetite side effects of olanzapine.

These facts above raise suspicion as to whether these differences in Montgomery-Asberg Depression Rating Scale scores can be truly attributed to an actual antidepressant property of olanzapine and whether they have any clinical significance.

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Drs. Tohen and Lin Reply

TO THE EDITOR: We would like to thank Drs. Moreira-Almeida and Pietrobon for their comments. We feel extremely gratified that our study has generated interest in the field of pharmacotherapy for bipolar depression, and hopefully this interest will translate into better outcomes for patients. The depressive phase of bipolar disorder is associated with a high degree of mortality and morbidity, and patients who suffer from this condition are in need of more effective and safer treatments. It should be noted that the most important clinical finding of our study was the greater efficacy of the olanzapine-fluoxetine combination relative to both placebo and olanzapine monotherapy for the acute treatment of bipolar depression in patients with bipolar disorder. Furthermore, it was the olanzapine-fluoxetine combination but not olanzapine monotherapy that received approval from the Food and Drug Administration for the treatment of acute bipolar depression.

We concur with the observations of Drs. Moreira-Almeida and Pietrobon regarding the effectiveness of olanzapine monotherapy on a subset of depressive symptoms. In the primary publication, it was noted that analysis of individual items on the Montgomery-Asberg Depression Rating Scale indicated that the olanzapine-fluoxetine combination, but not olanzapine monotherapy, was effective at reducing core mood symptoms of depression (depressed mood/apparent sadness, diminished interest or pleasure in activities). Differences between olanzapine monotherapy and placebo in baseline-to-endpoint changes on the "apparent sadness" and "suicidal thoughts" items of the Montgomery-Asberg Depression Rating Scale approached but did not achieve statistical significance. Mean baseline-to-endpoint change in the Montgomery-Asberg Depression Rating Scale total score was significantly greater for olanzapine monotherapy relative to placebo, which suggests that there may be a "signal," albeit modest relative to the olanzapine-fluoxetine combination (effect sizes: 0.32 and 0.68, respectively). Further studies are needed to determine if this signal translates into a true effect of olanzapine monotherapy on core depressive symptoms. As additional controlled studies evaluate the relative benefits of combined antidepressant treatment with atypical antipsychotics, lithium, or anticonvulsants, we hope to gain a greater understanding of how best to treat bipolar depression in order to improve the outcomes of patients who suffer from this devastating condition.

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Dr. Hirschfeld Replies

TO THE EDITOR: The letter by Drs. Moreira-Almeida and Pietrobon casts doubt on whether olanzapine monotherapy is efficacious for treatment of bipolar depression. The authors acknowledge that olanzapine monotherapy was associated with a statistically significant drop in the Montgomery-Asberg Depression Rating Scale score over 8 weeks compared with placebo. Most of this drug/placebo difference was due to improvement in sleep and increased appetite, which are known side effects of olanzapine. Olanzapine monotherapy was not associated with improvement in core symptoms of depression, including depressed mood.

My professional opinion is in agreement with the position that olanzapine monotherapy is of limited utility in treating bipolar depression. I believe the efficacy of olanzapine-fluoxetine combination is well established and is reflected in the fact that eight of the 10 Montgomery-Asberg Depression Rating Scale items showed improvement over placebo.

I do take issue with the assertion that the APA Guideline Watch for the Treatment of Patients with Bipolar Disorder claimed "the efficacy associated with olanzapine or olanzapine plus fluoxetine in the treatment of bipolar depression." In the Guideline Watch, the results of the study were presented, but no claim to efficacy was made.

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