Efficacy of Olanzapine in Acute Bipolar Mania

A Double-blind, Placebo-Controlled Study

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Background: We compared the efficacy and safety of olanzapine vs placebo for the treatment of acute bipolar mania.

Methods: Four-week, randomized, double-blind, parallel study. A total of 115 patients with a DSM-IV diagnosis of bipolar disorder, manic or mixed, were randomized to olanzapine, 5 to 20 mg/d (n=55), or placebo (n=60). The primary efficacy measure was the Young-Mania Rating Scale (Y-MRS) total score. Response and euthymia were defined, a priori, as at least a 50% improvement from baseline to end point and as a score of no less than 12 at end point in the Y-MRS total score, respectively. Safety was assessed using adverse events, Extrapyramidal Symptom (EPS) rating scales, laboratory values, electrocardiograms, vital signs, and weight change.

Results: Olanzapine-treated patients demonstrated a statistically significant greater mean (± SD) improvement in Y-MRS total score than placebo-treated patients (−14.8±12.5 and −8.1±12.7, respectively; P<.001), which was evident at the first postbaseline observation 1 week after randomization and was maintained throughout the study (last observation carried forward). Olanzapine-treated patients demonstrated a higher rate of response (65% vs 43%, respectively; P=.02) and euthymia (61% vs 36%, respectively; P=.01) than placebo-treated patients. There were no statistically significant differences in EPSs between groups. However, olanzapine-treated patients had a statistically significant greater mean (± SD) weight gain than placebo-treated patients (2.1±2.8 vs 0.45±2.3 kg, respectively) and also experienced more treatment-emergent somnolence (21 patients [38.2%] vs 5 [8.3%], respectively).

Conclusion: Olanzapine demonstrated greater efficacy than placebo in the treatment of acute bipolar mania and was generally well tolerated.

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Although advances have been made in the treatment of bipolar disorder, existing therapies are not always effective or are accompanied by adverse effects that limit their acceptance. The efficacy of lithium and valproate has been established by well-designed clinical trials, however, side effects and treatment failures are present with both drugs. Typical antipsychotics are also used for the treatment of acute mania, although their side effect profiles are far from ideal.

Olanzapine has also been used for the treatment of bipolar disorder. A 21-day, double-blind, placebo-controlled study found olanzapine to be an effective and safe treatment in acute mania. Limitations of that trial included separation of olanzapine from placebo at week 3 of treatment, rather than earlier, as occurred in other similarly designed studies. Olanzapine dosing (ie, acute mania may require more aggressive olanzapine dosing for optimal response) (2) too liberal use of adjunctive lorazepam; (3) inclusion of first-episode patients (who showed a disproportionately high rate of response to placebo); and (4) too short a treatment period. We therefore conducted a second double-blind, placebo-controlled study to further evaluate the efficacy and safety of olanzapine in the treatment of acute bipolar mania, with special attention to the potential methodological limitations of the first trial. Specifically, we conducted a 28-day study of 115 multiple-episode patients from December 1, 1997, through February 28, 1999, that used a more aggressive olanzapine-dosing schedule but permitted less concomitant lorazepam use.
PATIENTS AND METHODS

PATIENTS

Patients, aged 18 through 70 years, with a DSM-IVdiagnosis of bipolar disorder, manic or mixed, with or without psychotic features, were eligible to be enrolled in this study. Investigators recruited patients from private practices (13 sites), inpatient and outpatient services of university-affiliated centers (10 sites), and a Veterans Affairs facility. In addition, some sites recruited patients through colleague referral, and 6 sites advertised the study in local newspapers. Diagnosis was based on clinical assessment and confirmed by results of the Structured Clinical Interview for the DSM-IV, Patient Version (SCID-P), administered by trained clinicians (including principal and subinvestigators [all physicians] and study personnel with appropriate clinical degrees [PhD in psychology or MSW] and experience). After having the protocol explained to them, patients provided written informed consent to participate in the study. A minimum total score of at least 20 on the Young–Mania Rating Scale (Y-MRS) was required at the screening visit and on the day of randomization (baseline). At baseline, patients displayed a clinically severe symptom profile, with a mean Y-MRS score of 29.10 (range, 14-49; 1 patient was enrolled with a baseline Y-MRS total score of 14). Patients were excluded with any of the following criteria: serious, unstable medical illness; DSM-IV substance dependence (except nicotine or caffeine) within the past 3 months; and serious suicidal risk.

STUDY DESIGN

We conducted a 4-week, randomized, double-blind, parallel study. All psychotropic medication therapy (except benzodiazepines) was tapered during the screening period and discontinued at least 1 day before randomization. Patients were randomized to olanzapine or placebo, in a 1:1 ratio.

RESULTS

PATIENTS

A total of 115 patients were enrolled in the study. Mean age was 39 years; 80.0% were white, and 50.0% were men. Based on DSM-IV criteria using the SCID-P, 42.6% of the patients were in a mixed episode and 55.7% were experiencing psychotic features. Of those 64 patients with psychotic features, 47 (73.4%) were experiencing mood-congruent psychotic features. There were no statistically significant differences in any demographic or illness characteristics between treatment groups. Historical illness characteristics and previous medication use and response are presented in Table 1. A statistically significant greater number of patients randomized to the placebo-treated group had a history of previous response to valproate than in the olanzapine-treated group (P = .02, Fisher exact test). Frequency of recorded medication use at the beginning of the screening period included benzodiazepines and/or hypnotics (68.7%), anticonvulsants (23.5%), typical antipsychotics (16.5%), anticholinergics (14.8%), lithium (9.6%), atypical antipsychotics (7.8%), and antidepressants (4.3%). Study completion and discontinuation summary details are presented in Table 2. Frequency of study completion was significantly greater (P = .04; Fisher exact test) in the olanzapine group (61.8%) compared with the placebo group (41.7%). There were no significant differences between groups regarding reasons for discontinuation.

Efficacy

The primary efficacy measure was the change in Y-MRS score from baseline to end point (LOCF), after up to 4 weeks of acute double-blind treatment. The olanzapine group experienced a 6.65-point greater mean improvement in Y-MRS total score compared with the placebo group (F1,86 = 12.47; P < .001). The impact of initial severity on LOCF change in Y-MRS score was not significantly different between the treatment groups.
Angus scale\(^1\) and akathisia as measured by the Barnes Akathisia scale\(^4\), laboratory values, electrocardiograms (ECGs), vital signs, and weight change. All adverse events reported by patients during the study were recorded and coded using the Clinical Symbol and Thesaurus for Adverse Event Terminology (COSTART) dictionary.

The primary efficacy variable, as defined by the protocol, was the reduction from baseline of the Y-MRS total score after 4 weeks of therapy. Response and euthymia were defined, a priori, as at least a 50% improvement from baseline to end point and as a score of no greater than 12 at end point in the Y-MRS total score, respectively. Inter-rater reliability assessments with the Y-MRS were conducted before study initiation by measuring the correlation of each rater with the groupwise median score of each item. Raters who did not achieve a correlation of at least 0.80 were not allowed to rate patients in this study.

To further investigate the effect of olanzapine on depressive symptoms, additional analyses were performed. The mean change from baseline to end point on the HAMD-21 score was calculated for all randomized patients and for a subset of patients with moderate to severe depressive symptoms (HAMD-21 score \(\geq 20\) at baseline). In addition, the proportion of patients experiencing a clinically detectable worsening in depressive symptoms at any time during acute therapy was assessed. A worsening of at least 3 points on the HAMD-21 score was used as a definition of clinically detectable worsening of depressive symptoms.

**STATISTICAL METHODS**

Patient data were analyzed on an intent-to-treat basis. For analysis of last observation carried forward (LOCF) mean change from baseline to end point, patients with a baseline and at least 1 postbaseline measurement were included in the analysis. Four placebo-treated patients and 1 olanzapine-treated patient did not have a postbaseline measurement and were excluded from all efficacy analyses. Total scores from rating scales were derived from the individual items; if any single item was missing, the total score was treated as missing.

Continuous efficacy and safety parameters were evaluated using analysis of variance. The models generally included terms for the fixed effects of treatment, investigator, and treatment \(\times\) investigator interaction. Investigators with fewer than 2 patients per treatment group were pooled as specified in the protocol. Analyses of subgroups included a term for treatment only, owing to sparse data. The LOCF change in the Y-MRS total score was also compared between treatment groups using the baseline Y-MRS score as a covariate to examine change in relation to initial severity; investigator was not included in this model. An examination of the effect of treatment over time was conducted on the Y-MRS total score using a likelihood-based repeated-measures analysis. The Y-MRS total score at each postbaseline visit was used as the response variable, and the baseline Y-MRS total score was used as a covariate. This analysis evaluated treatment and investigator effects along with the treatment \(\times\) investigator and treatment \(\times\) visit interactions using an unstructured covariance matrix for the within-patient error as specified in the protocol. In addition, an examination of the therapy difference stratified by time for the Y-MRS total score was performed using a pattern-mixture analysis.\(^3\) A mixed-effects model was used, including the main effects for therapy, visit, treatment time, investigator, and the interaction effects for therapy \(\times\) investigator, therapy \(\times\) treatment time, therapy \(\times\) visit, investigator \(\times\) visit, and therapy \(\times\) treatment time \(\times\) visit. Visit and dropout time were random effects; therapy and investigator were fixed effects in the model. The Kruskal-Wallis test was used to compare treatments for each of the individual items of the Y-MRS. The Fisher exact test was used to analyze treatment effects for categorical efficacy and safety parameters. All cited P values are 2-tailed, with a significance level of .05 as specified in the protocol. Unless otherwise indicated, data are given as mean \(\pm\) SD.

(\(F_{1,109}=2.19; P = .14\); **Figure 1**). In addition, olanzapine-treated patients demonstrated a statistically significant greater mean improvement on the CGI-BP severity of mania, CGI-BP severity of overall bipolar illness, and PANSS total and positive scores compared with placebo-treated patients (Table 3). Efficacy subgroup analyses were also performed based on the presence or absence of psychotic features and between patients in a manic or a mixed episode. Olanzapine-treated patients exhibited no statistically significant difference in the mean change in Y-MRS scores for any of these subtypes. For olanzapine-treated patients, the antimanic effect in patients with and without psychotic features was similar.

**WEEKLY ANALYSIS**

The olanzapine group consistently showed greater LOCF mean improvement on Y-MRS total score; HAMD-21 total score; CGI-BP mania, depression, and overall bipolar illness scores; and PANSS total, positive, and negative scores compared with the placebo group at each week. Olanzapine-treated patients demonstrated a statistically significant greater improvement in the mean change from baseline in the Y-MRS total score at the first postbaseline observation at week 1 (\(F_{1,36}=4.78; P = .03\); **Figure 2**). This statistically significant separation from the placebo group was maintained during the 4-week study. In addition, treatment differences were statistically significant at each week for CGI-BP severity of mania and overall bipolar illness scores and PANSS total and positive scores.

An examination of treatment effect over time using a repeated-measures analysis was conducted on the Y-MRS total score as specified in the protocol. Olanzapine demonstrated a statistically significant greater treatment effect compared with placebo (\(F_{1,207}=10.47; P = .002\)). The superior treatment effect of olanzapine was evident at week 1, and the superiority was maintained over time (Table 4).

A post hoc examination of the effect of dropout time on treatment result was performed. Patients who dropped...
out at week 1 had a similar response regardless of therapy. Placebo-treated patients who dropped out at weeks 2 or 3 had minimal response. On the other hand, olanzapine-treated patients who dropped out at week 2 or 3 did have some improvement (Table 5). To estimate the therapy difference stratified by treatment time, a pattern-mixture analysis\(^1\) was performed. The results of this analysis were similar to the results of the LOCF and repeated-measures visitwise analyses. The main difference was that in this analysis, there was no statistical separation at week 1 (Table 6).

In the analysis of the individual items of the Y-MRS, olanzapine-treated patients exhibited a statistically significant greater mean improvement than placebo-treated patients on the following items: elevated mood (\( \chi^2 = 9.11; \ P = .003 \)), sleep (\( \chi^2 = 12.33; \ P < .001 \)), language-thought disorder (\( \chi^2 = 4.66; \ P = .03 \)), content (\( \chi^2 = 8.48; \ P = .004 \)), and disruptive-aggressive behavior (\( \chi^2 = 6.64; \ P = .01 \)).

**RESPONSE AND EUTHYMICITY**

Responders were classified as patients with an improvement of 50% or more in Y-MRS total score from baseline to end point (LOCF). The olanzapine group demonstrated a significantly greater mean improvement than placebo-treated patients on the following items: elevated mood (\( \chi^2 = 9.11; \ P = .003 \)), sleep (\( \chi^2 = 12.33; \ P < .001 \)), language-thought disorder (\( \chi^2 = 4.66; \ P = .03 \)), content (\( \chi^2 = 8.48; \ P = .004 \)), and disruptive-aggressive behavior (\( \chi^2 = 6.64; \ P = .01 \)).

### Table 1. Patient and Illness Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo Group</th>
<th>Olanzapine Group</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60</td>
<td>55</td>
<td>0.52*</td>
</tr>
<tr>
<td>Current episode, d</td>
<td>60</td>
<td>55</td>
<td>0.74*</td>
</tr>
<tr>
<td>Age at onset of illness, y</td>
<td>60</td>
<td>55</td>
<td>0.75*</td>
</tr>
<tr>
<td>No. of previous episodes of mania, lifetime</td>
<td>49</td>
<td>44</td>
<td>0.35*</td>
</tr>
<tr>
<td>No. of previous episodes of mania, previous 12 mo</td>
<td>60</td>
<td>55</td>
<td>0.24*</td>
</tr>
<tr>
<td>No. of previous episodes of depression, lifetime</td>
<td>49</td>
<td>43</td>
<td>0.08*</td>
</tr>
<tr>
<td>No. of previous episodes of depression, previous 12 mo</td>
<td>59</td>
<td>55</td>
<td>0.43*</td>
</tr>
<tr>
<td>No. of previous mixed episodes, lifetime</td>
<td>49</td>
<td>43</td>
<td>0.51*</td>
</tr>
<tr>
<td>No. of previous mixed episodes, previous 12 mo</td>
<td>59</td>
<td>54</td>
<td>0.69*</td>
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### Table 2. Patient Disposition

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n = 60)</th>
<th>Olanzapine (n = 55)</th>
<th>( P ) *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed</td>
<td>25 (41.7)</td>
<td>34 (61.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>Discontinued</td>
<td>35 (58.3)</td>
<td>21 (38.2)</td>
<td></td>
</tr>
<tr>
<td>Adverse event</td>
<td>1 (1.7)</td>
<td>2 (3.6)</td>
<td>0.61</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>23 (38.3)</td>
<td>15 (27.3)</td>
<td>0.24</td>
</tr>
<tr>
<td>Unavailable for follow-up</td>
<td>3 (5.0)</td>
<td>1 (1.8)</td>
<td>0.62</td>
</tr>
<tr>
<td>Patient decision</td>
<td>5 (8.3)</td>
<td>3 (5.5)</td>
<td>0.72</td>
</tr>
<tr>
<td>Physician decision</td>
<td>3 (5.0)</td>
<td>0</td>
<td>0.25</td>
</tr>
</tbody>
</table>

*Frequencies analyzed using Fisher exact test.

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IMPROVEMENT IN DEPRESSIVE SYMPTOMS AND LACK OF DEPRESSOGENIC EFFECTS

The analysis of change in HAMD-21 score from baseline to end point for all randomized patients showed a similar improvement in olanzapine- and placebo-treated patients (−7.83±7.79 vs −4.45±6.95, respectively; F1,86=2.91; P=.09). In patients who presented with moderate to severe depressive symptoms (HAMD-21 score, ≥20 at baseline), a statistically significant greater improvement in olanzapine- compared with placebo-treated patients was observed on the change in HAMD-21 score from baseline to end point (−12.29±8.79 vs −7.83±7.79, respectively; F1,40=4.24; P=.05) (Figure 3).

Using a 6-item subscale score of the HAMD-21 to reflect moderate to severe depressive symptoms (HAMD-21 score, ≥7 at baseline), a statistically significant greater improvement in olanzapine- compared with placebo-treated patients (−3.06±4.24 vs −2.04±3.69, respectively; F1,86=2.91; P=.09) was observed on the change in HAMD-21 score from baseline to end point when comparing all olanzapine- and placebo-treated patients. A total of 4 placebo-treated patients and 1 olanzapine-treated patient had no postbaseline scores for any of the efficacy measures and were excluded from all analyses.

The effect of olanzapine on induction of depressive symptoms was also investigated. A worsening in the HAMD-21 score of at least 3 points was used as a definition of a clinically detectable worsening. The percentage of olanzapine-treated patients who experienced a clinically detectable worsening in depressive symptoms at any time during double-blind therapy was similar to that seen in placebo-treated patients (11.1% vs 17.9%, respectively; F1,46=2.78; P=.10).

The categorical rates of patients who received at least 1 dose of benzodiazepine were 36 (65.5%) of 55 patients and 44 (73.3%) of 60 patients in the olanzapine and placebo groups, respectively. The between-treatment group difference in categorical use was not statistically significant (F1,106=0.30; P=.59), or in the subset of patients who presented with moderate to severe depressive symptoms at baseline (−5.52±4.72 vs −3.19±4.34, respectively; F1,46=2.78; P=.10).

SAFETY

Adverse Events

Adverse events that originally occurred or worsened in severity during double-blind therapy were considered treatment emergent. One patient in the placebo group (agitation) and 2 patients in the olanzapine group (unintended pregnancy and rash) discontinued treatment because of an adverse event. The only treatment-emergent event with a statistically significant more frequent occurrence in the olanzapine group compared with the placebo group was somnolence (P<.001, Fisher exact test) (Table 7). The only treatment-emergent event with a statistically significant more frequent occurrence in the placebo group was agitation (P=.03, Fisher exact test).

Table 3. Change in the Severity-of-Illness Scores From Baseline to End Point*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Placebo Group (n = 56)</th>
<th>Olanzapine Group (n = 54)</th>
<th>Change From Baseline</th>
<th>F1,86</th>
<th>P†</th>
<th>Change From Baseline</th>
<th>F1,90</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y-MRS total</td>
<td>29.43 (6.77)</td>
<td>28.76 (6.72)</td>
<td>−8.13 (12.72)</td>
<td>17.33</td>
<td>.09</td>
<td>−14.78 (12.49)</td>
<td>12.47</td>
<td>.001</td>
</tr>
<tr>
<td>HAMD-21 total</td>
<td>16.16 (5.49)</td>
<td>17.33 (9.24)</td>
<td>−4.54 (6.95)</td>
<td>17.33</td>
<td>.09</td>
<td>−7.83 (7.79)</td>
<td>2.91</td>
<td>.10</td>
</tr>
<tr>
<td>PANSS total</td>
<td>72.61 (21.68)</td>
<td>76.74 (25.72)</td>
<td>−7.43 (19.73)</td>
<td>21.72</td>
<td>.001</td>
<td>−21.19 (23.73)</td>
<td>13.25</td>
<td>.001</td>
</tr>
<tr>
<td>PANSS positive</td>
<td>20.54 (6.38)</td>
<td>14.46 (7.32)</td>
<td>−2.96 (6.61)</td>
<td>21.72</td>
<td>.001</td>
<td>−7.76 (7.59)</td>
<td>15.94</td>
<td>.001</td>
</tr>
<tr>
<td>PANSS negative</td>
<td>13.29 (6.15)</td>
<td>14.46 (7.32)</td>
<td>−0.63 (4.41)</td>
<td>14.46</td>
<td>.03</td>
<td>−2.78 (6.50)</td>
<td>3.21</td>
<td>.06</td>
</tr>
<tr>
<td>CGI-BP severity of mania</td>
<td>4.80 (0.82)</td>
<td>4.78 (0.77)</td>
<td>−0.08 (1.54)</td>
<td>4.78</td>
<td>.12</td>
<td>−1.83 (1.45)</td>
<td>15.02</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CGI-BP severity of depression</td>
<td>2.61 (1.57)</td>
<td>2.89 (1.53)</td>
<td>−0.45 (1.26)</td>
<td>2.89</td>
<td>.37</td>
<td>−0.74 (1.32)</td>
<td>0.82</td>
<td>.68</td>
</tr>
<tr>
<td>CGI severity of overall bipolar illness</td>
<td>4.77 (0.89)</td>
<td>4.78 (0.77)</td>
<td>−0.73 (1.43)</td>
<td>4.78 (0.77)</td>
<td>−1.72 (1.46)</td>
<td>16.20</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

* A total of 4 placebo-treated patients and 1 olanzapine-treated patient had no postbaseline scores for any of the efficacy measures and were excluded from all efficacy analyses. No statistically significant differences were observed between baseline values for any measure. Y-MRS indicates Young–Mania Rating Scale; HAMD-21, Hamilton Psychiatric Rating Scale for Depression–21 Item; PANSS, Positive and Negative Symptoms Scale; and CGI-BP, Clinical Global Impressions–Bipolar Version of Severity of Illness. Data are given as mean (SD).

† Change from baseline to end point means were analyzed using an F test from analysis of variance model, which included terms for treatment, investigator, and interaction.

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EPS Rating Scales

Emergence of EPSs was low, and anticholinergic use was negligible for both groups (mean, 0.33 ± 0.26 vs 0.22 ± 0.17 mg/d for olanzapine- vs placebo-treated patients, respectively; F1,3 = 2.28; P = .23). Olanzapine-treated patients experienced an improvement in parkinsonism (Simpson-Angus) and akathisia (Barnes) from baseline to end point, whereas placebo-treated patients experienced a worsening in parkinsonism and an improvement in akathisia. The difference in mean change at end point between olanzapine- and placebo-treated patients was not statistically significant for parkinsonism (−0.27 ± 1.16 vs 0.13 ± 1.61, respectively; F1,86 = 1.81; P = .18) or akathisia (−0.40 ± 0.83 vs −0.16 ± 0.76, respectively; F1,87 = 2.07; P = .16).

Vital Signs and Weight

Significant differences between groups were observed for mean change in supine systolic blood pressure from baseline to end point (5.04 ± 15.98 vs −3.86 ± 17.92 mm Hg for olanzapine- vs placebo-treated patients, respectively; F1,86 = 9.84; P = .04). Patients in the olanzapine group had a statistically significant larger mean weight gain compared with the placebo group (2.11 ± 2.83 vs 0.45 ± 2.31 kg, respectively; F1,88 = 4.22; P = .002).

Laboratory Values

The only statistically significant difference in laboratory values between treatment groups occurred in alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Patients in the olanzapine group had a statistically significant higher incidence of increased ALT and AST levels than patients in the placebo group (ALT, 21.6% vs 3.9%; P = .02, Fisher exact test; AST, 17.3% vs 0%; P = .003, Fisher exact test). High and low limits that are of potential clinical concern were determined a priori for each laboratory test. Patients who met these criteria at end point or for 2 consecutive observations were defined to have a potentially clinically significant abnormality. One olanzapine-treated patient met this definition for ALT ($165 \text{ U/L}$) and AST levels ($150 \text{ U/L}$). No patients displayed clinical symptoms of hepatic dysfunction at any time during the study, and none were discontinued because of abnormal results of liver function tests.

Electrocardiogram

There were no statistically significant differences in ECGs between treatment groups, although fewer olanzapine- than placebo-treated patients experienced a treatment-emergent ECG abnormality (13.3% vs 33.3%, respectively; P = .11, Fisher exact test). No statistically-
This 4-week, double-blind, placebo-controlled trial suggests that olanzapine is an effective and safe treatment in acute bipolar mania. Olanzapine demonstrated an improvement of 14.8 points from baseline to end point in acute bipolar mania. Olanzapine demonstrated an antimanic effect of olanzapine was evident at the first visit, investigator \( \times \) treatment modeled as random effects, whereas treatment and investigator were modeled as fixed effects. The within-patient error was estimated using an unstructured covariance structure.

**Table 6. Pattern Mixture Analysis for Y-MRS Total Score**

<table>
<thead>
<tr>
<th>Week</th>
<th>Placebo Group, LS Mean (SE)</th>
<th>Olanzapine Group, LS MEAN (SE)</th>
<th>t</th>
<th>df</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>28.0 (1.4)</td>
<td>26.4 (1.7)</td>
<td>0.77</td>
<td>196</td>
<td>.44</td>
</tr>
<tr>
<td>1</td>
<td>27.4 (1.2)</td>
<td>23.8 (1.5)</td>
<td>1.86</td>
<td>128</td>
<td>.07</td>
</tr>
<tr>
<td>2</td>
<td>26.7 (1.5)</td>
<td>21.2 (1.9)</td>
<td>2.32</td>
<td>263</td>
<td>.02</td>
</tr>
<tr>
<td>3</td>
<td>26.1 (2.1)</td>
<td>18.6 (2.6)</td>
<td>2.30</td>
<td>423</td>
<td>.02</td>
</tr>
<tr>
<td>4</td>
<td>25.4 (2.7)</td>
<td>16.0 (3.4)</td>
<td>2.19</td>
<td>421</td>
<td>.03</td>
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</table>

*Explanation of the abbreviations are given in the footnote to Table 4. Y-MRS total score means are analyzed with a repeated-measures, mixed-effects model incorporating a drop out pattern term (a pattern mixture model), also including terms for treatment investigator, visit, and interaction terms for treatment \( \times \) investigator, treatment \( \times \) visit, investigator \( \times \) visit, therapy \( \times \) dropout, and therapy \( \times \) visit \( \times \) dropout. Visit and dropout were modeled as random effects, whereas treatment and investigator were modeled as fixed effects. The within-patient error was estimated using an unstructured covariance structure.*

**Table 7. Treatment-Emergent Adverse Events**

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo Group (n = 60)</th>
<th>Olanzapine Group (n = 55)</th>
<th>P †</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>5 (8.3)</td>
<td>21 (38.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Agitation</td>
<td>15 (25.0)</td>
<td>5 (9.1)</td>
<td>.03</td>
</tr>
<tr>
<td>Anxiety</td>
<td>9 (15.0)</td>
<td>2 (3.6)</td>
<td>.06</td>
</tr>
<tr>
<td>Personality disorder</td>
<td>7 (11.7)</td>
<td>1 (1.8)</td>
<td>.06</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>3 (5.0)</td>
<td>9 (16.4)</td>
<td>.07</td>
</tr>
<tr>
<td>Hostility</td>
<td>6 (10.0)</td>
<td>1 (1.8)</td>
<td>.12</td>
</tr>
<tr>
<td>Nervousness</td>
<td>12 (20.0)</td>
<td>5 (9.1)</td>
<td>.12</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>3 (5.0)</td>
<td>7 (12.7)</td>
<td>.19</td>
</tr>
<tr>
<td>Asthenia</td>
<td>3 (5.0)</td>
<td>6 (10.9)</td>
<td>.31</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4 (6.7)</td>
<td>7 (12.7)</td>
<td>.35</td>
</tr>
<tr>
<td>Constipation</td>
<td>5 (8.3)</td>
<td>6 (10.9)</td>
<td>.76</td>
</tr>
<tr>
<td>Headache</td>
<td>13 (21.7)</td>
<td>10 (18.2)</td>
<td>.82</td>
</tr>
</tbody>
</table>

*Treatment-emergent adverse events are events that first occurred or worsened in severity during double-blind therapy in at least 10% of any treatment group or statistically significant between-group difference. †Frequencies are analyzed using the Fisher exact test.*

Some differences emerge with the results of this study compared with the only other placebo-controlled study of olanzapine in acute mania. Differences in the study design include a starting dose of 15 instead of 10 mg, duration of 4 weeks rather than 3 weeks, and approximately half of the allowed dose of lorazepam. In terms of efficacy, our present study achieved a similar mean difference as the previous study between the olanzapine and placebo groups in the Y-MRS study (−6.7 points \( P<.001 \) vs −5.4 points \( P=.02 \), respectively). A larger percentage of olanzapine-treated patients in our study were classified as responders (35 [64.8%] of 54 patients vs 34 [48.6%] of 70 patients). In addition, in our study, a statistically significant difference was first observed at week 1 as opposed to week 3 for the previous study. The more robust results in our study could be explained by the higher starting dose (15 vs 10 mg) or by patient variability.

In our study, 43% of placebo-treated patients responded (improved ≥50% in Y-MRS score), which was higher compared with our previous study and any other modern, similarly designed trials in mania, which found placebo response rates of 24%, 19% 11%, and 25%. Nonetheless, despite the high placebo response, the difference between placebo- and olanzapine-treated patients was statistically significant. The higher proportion of patients with a history of previous response to valproate in the placebo group may have contributed to the high placebo response, as has been suggested by Keck and colleagues, being higher in non–treatment-resistant patients. The longer trial duration may have allowed more
placebo-treated patients to achieve responder status. Analysis of the data from baseline to week 3 revealed a much smaller placebo effect than the data from baseline to week 4. In contrast, a much smaller difference between the week-3 and week-4 results were observed among olanzapine-treated patients. Beyond the increased duration of study in this clinical trial, it is difficult to speculate why the placebo response was so high. However, it is important to note that placebo response is not the same as spontaneous remission. In patients with major depression, placebo response has been reported to be as high as 70%; however, improvement of patients assigned to a waiting list is minimal. To our knowledge, similar studies have not been conducted in patients with bipolar disorder. Brown suggested that the benefits of placebo in psychiatric disorders to some extent have similarities with the benefits of psychotherapy, ie, they both provide “expectation of improvement, support, and mobilization of hope.” In addition, the large percentage of patients with rapid-cycling illness (45 [39.1%] of 115 patients) combined with the longer trial duration could have accounted for the placebo response at the time of the rating. Keck and colleagues recently concluded that a number of variables can contribute to placebo response in acute mania, including the presence of patients with a rapid-cycling course and spontaneous remissions, the latter more likely to happen in trials of longer duration. They also concluded that a higher placebo response is likely to be observed in large multicenter trials like the present one, because of the potentially larger variance in interrater reliability across the many study sites.

Depressogenic effects of antipsychotics in bipolar disorder are of great concern. Lack of depressogenic effect was suggested by the percentage of patients who experienced a worsening in depressive symptoms (worsening in HAMD-21 score of ≥3 at any time), ie, 6 (11.1%) of 54 olanzapine- and 10 (17.9%) of 56 placebo-treated patients (P = .42, Fisher exact test). In addition, the analysis of the change in HAMD-21 score from baseline to end point for all randomized patients revealed no statistically significant difference between olanzapine- and placebo-treated patients (−7.8 vs −4.5, respectively; F[1,96] = 2.91; P = .09). Furthermore, in patients with moderate to severe depressive symptoms (HAMD-21 score, ≥20 at baseline), a statistically significant improvement in olanzapine- compared with placebo-treated patients was observed on the change in HAMD-21 score from baseline to end point (F[5,90] = 4.24; P = .05). These results are in contrast to those of the first trial, where depressive symptoms improved by the same amount in both groups (−3.0 vs −2.9 for the olanzapine- vs placebo-treated patients, respectively; F[1,103] = 0.03; P = .87).7 The apparent efficacy of olanzapine in moderate to severe depressive symptoms in mania in our present study, but not in the first study, may be partly explained by a higher rate of mixed episodes and higher mean HAMD-21 score at baseline (17.3 vs 9.2 in our present study vs 12.6 ± 7.2 in the first study). However, the first and present study results suggest that olanzapine does not induce depression during acute therapy, and the results from our present study suggest that for patients with more severe depression, olanzapine may improve symptoms of depression in patients with acute manic or mixed illmcss.

There were no statistically significant differences between treatment groups in these measures of EPSs (aka-thisia and parkinsonism as measured by the Barnes Akathisia scale and Simpson-Angus scale, respectively). In addition, very few EPSs emerged, and anticholinergic medication use was negligible for both treatment groups. The mild worsening of parkinsonian symptoms experienced by patients randomized to placebo was not statistically significant. However, it may have resulted from withdrawal effects of previous antipsychotic and anticholinergic treatments. Olanzapine-treated patients may not have exhibited this mild worsening of parkinsonian symptoms because of the affinity of olanzapine to different neurochemical receptors.

In regard to other safety measures, 2 patients receiving olanzapine discontinued its use because of an adverse event (unintended pregnancy and rash). Somnolence was the only treatment-emergent adverse event that occurred in a statistically significant higher percentage of olanzapine-treated patients compared with placebo-treated patients (38.2% vs 8.3%, respectively; P < .001, Fisher exact test). In addition, there were no clinically significant changes in vital signs, laboratory values, or ECGs. Although no patients in this study discontinued treatment with olanzapine secondary to weight gain, a mean weight gain of 2.1 kg was observed in a 4-week period. Although this amount of weight gain should not be a safety concern, it may lead to treatment noncompliance in some cases.

A possible limitation of this study is the lack of an active comparator, which has been advocated as a tool in aiding the validity of placebo-controlled studies. Further comparator studies need to be completed.

In our clinical trial, olanzapine demonstrated statistically significant greater efficacy in the treatment of acute bipolar mania compared with placebo. Antimanic effect was observed in patients with or without psychotic features and in patients in manic or mixed episodes. Further studies in maintenance treatment and bipolar depression need to be conducted to determine the mood stabilizing properties of olanzapine. In addition, studies comparing olanzapine with current mood stabilizers, such as lithium and valproate, will help to further define olanzapine’s role in bipolar mania.

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