*Notice of Correction 12/23/09: The vertical axis scale for Figure 2B has been corrected to display 0 to −16.*

*Notice of correction 6/21/2011: Data for the adverse event peripheral edema have been added to Table 3 on page 1545.*

# Olanzapine-Divalproex Combination Versus Divalproex Monotherapy in the Treatment of Bipolar Mixed Episodes: A Double-Blind, Placebo-Controlled Study

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***Objective:*** This 6-week, randomized, double-blind, placebo-controlled trial used simultaneous depression and mania criteria to compare a single mood stabilizer, divalproex, with and without adjunctive olanzapine in patients with bipolar I disorder experiencing acute mixed episodes.

***Method:*** Two hundred two adults, aged 18 to 60 years, who met *DSM-IV-TR* criteria for bipolar disorder with a current mixed episode and had been taking divalproex for ≥ 14 days at levels of 75 to 125 µg/mL with inadequate efficacy (21-item Hamilton Depression Rating Scale [HDRS-21] and Young Mania Rating Scale [YMRS] scores ≥ 16) were randomly assigned to olanzapine 5 to 20 mg/d versus placebo augmentation. HDRS-21, YMRS, Clinical Global Impressions for Bipolar Disorder (CGI-BP), hospitalizations, concomitant medications, and adverse events were assessed. Comparisons included changes in both HDRS-21 and YMRS (primary outcome measure), time to partial response and time to response, CGI-BP improvement, hospitalizations, and safety (secondary outcome measures). The study was conducted from December 2006 to February 2008.

***Results:*** Mean (SD) baseline HDRS-21 and YMRS scores were 22.2 (4.5) and 20.9 (4.4), respectively, with 59% female and 51% white subjects. Mean ± SE score changes from baseline across the 6-week treatment period for adjunctive olanzapine (n = 100) versus adjunctive placebo (n = 101) arms, respectively, were −9.37 ± 0.55 versus −7.69 ± 0.54, $P = .022$, on the HDRS-21 and −10.15 ± 0.44 versus −7.68 ± 0.44 $P < .001$, on the YMRS. Mean ± SE score changes from baseline to last observation carried forward for CGI-BP measures were −1.34 ± 0.11 for adjunctive olanzapine versus −1.06 ± 0.11 for adjunctive placebo, $P = .056$. Time to partial response (≥ 25% HDRS-21 and YMRS decreases, median 7 versus 14 days) and time to response (≥ 50% HDRS-21 and YMRS decreases, median 25 versus 49 days) were significantly shorter with adjunctive olanzapine. Increases in weight (total and ≥ 7%) and fasting blood glucose were significantly greater with adjunctive olanzapine.

***Conclusion:*** Adjunctive olanzapine yielded greater and earlier reduction of manic and depressive symptoms in mixed-episode patients with inadequate response to at least 2 weeks of divalproex.

***Trial Registration:*** clinicaltrials.gov Identifier: NCT00402324

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*See also Commentary on page 1548.*

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Manic and depressive symptoms are characteristic of mixed episodes in bipolar disorder. Mixed episodes are associated with high-risk events (for example, hospitalization or suicide), longer episode duration, more frequent psychosis, and greater risk of experiencing future mixed episodes.[1,2] Time to recovery from mixed versus manic episodes tends to be longer,[3] even in first-episode patients.[4] Although current estimates indicate that up to 40% of patients with bipolar I disorder will experience mixed episodes,[5,6] with a possible higher prevalence in women,[7] no adequately powered clinical trial has reported outcomes in a homogeneous sample of patients with mixed states who are currently on 1 specific mood stabilizer prior to this study.[8] Instead, patients with mixed episodes have either been a subset of those included in studies of heterogeneous (manic and mixed) samples (for example, utilizing divalproex, carbamazepine, olanzapine, aripiprazole, ziprasidone, and risperidone)[1] or have been pooled together in a group taking either 1 or 2 medications plus augmention.[9] However, secondary and pooled analyses support treatment with olanzapine,[10] ziprasidone,[11] and aripiprazole[12] monotherapy. One study demonstrated the efficacy of olanzapine as adjunctive treatment to divalproex or lithium in acute manic or mixed episodes[13]; the study also identified a trend toward the reduction of depressive symptoms.[14]

We report the results of a 6-week, multicenter, randomized, double-blind, placebo-controlled, parallel-treatment

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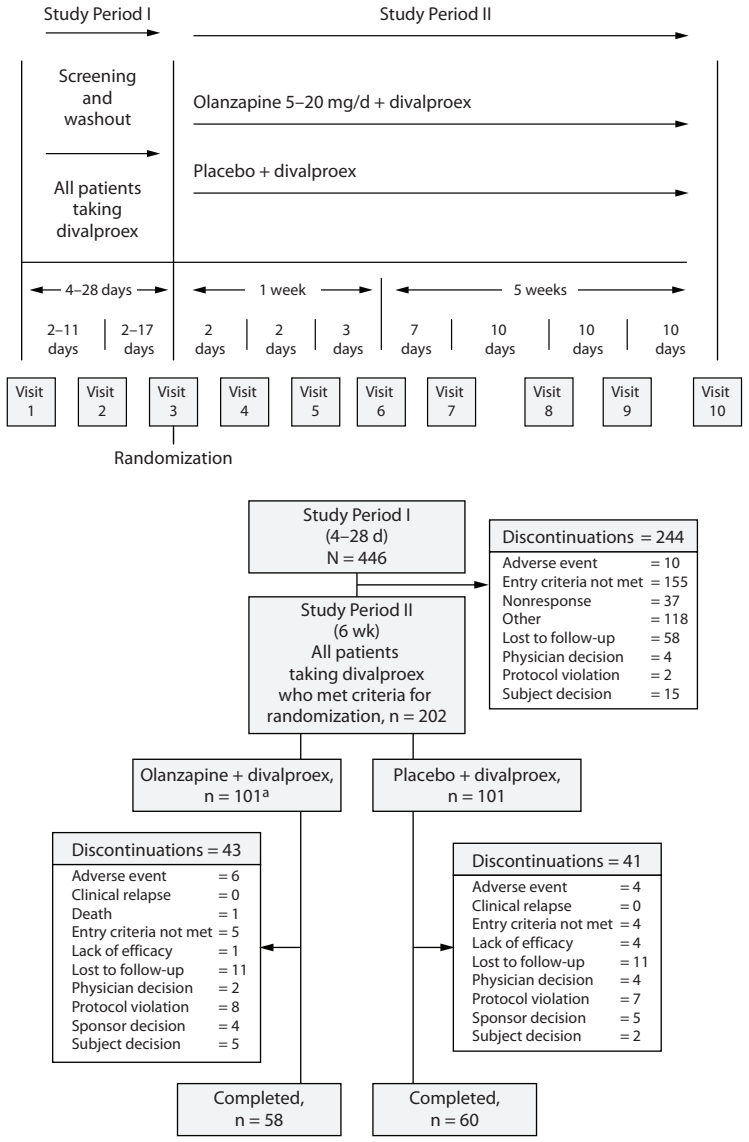
Figure 1. Study Characteristics: Study Diagram and Patient Disposition




[a]One patient provided no postbaseline data due to lost to follow-up status immediately after randomization.

augmentation study of 202 outpatients who demonstrated inadequate response to divalproex monotherapy. All participants were taking divalproex during the entire study. Coprimary measures of response in manic and depressive symptoms included clinical assessments as early as day 2 of treatment. The study was conducted at 24 centers in the United States, including Puerto Rico, between December 6, 2006, and February 13, 2008, in participants with bipolar disorder meeting criteria for a current mixed episode.

The design of this study represents a number of improvements over some previous studies of mood stabilizer augmentation with antipsychotics. These include increased divalproex minimum levels of 75 μg/mL rather than 50 μg/mL[9,13] in order to diminish the issue of patients being on suboptimal doses of divalproex at randomization and augmentation of a single mood stabilizer (divalproex) rather than augmentation of 2 nonrandomized treatments (lithium or divalproex).[9,13] A patient population of exclusively mixed-state bipolar patients with both depression and mania response criteria, rather than a patient population including manic and mixed states together and earlier clinical assessments at 2 and 4 days' postrandomization, also adds to the uniqueness of this study.

## METHOD

### Patients

For study period I (Figure 1), all patients were 18–60 years old and met diagnostic criteria for bipolar disorder with a current mixed episode (with or without psychotic features; *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision [*DSM-IV-TR*] 296.60 to 296.66).[15] Inadequate response to divalproex for at least 14 days, as defined by the 21-item Hamilton Depression Rating Scale (HDRS-21)[16] and Young Mania Rating Scale (YMRS)[17] total scores ≥ 16 at visits 2 and 3, with a blood level of divalproex between 75 to 125 μg/mL, was required for randomization to study period II. This study was reviewed and approved by the institutional review board at each site and was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines. Verbal and written informed consent was obtained from all subjects prior to participation. The study was conducted from December 2006 to February 2008.

### Study Design

Divalproex dose adjustments were permitted during study period I in efforts to obtain target blood divalproex levels of 75 to 125 μg/mL. Participants who met study period II entry criteria were randomly assigned 1:1 in a double-blind fashion to either adjunctive olanzapine therapy (olanzapine + divalproex: olanzapine 15 mg/d initially, followed by flexible dosing of olanzapine 5, 10, 15, or 20 mg/d) or adjunctive placebo (divalproex monotherapy). The level of divalproex was maintained following randomization and throughout the study.

Concomitant benzodiazepine therapy was permitted for ≤ 15 cumulative days or ≤ 5 consecutive days, with a

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maximum daily dose of 2 mg of lorazepam or lorazepam equivalents (temazepam 30 mg, diazepam 10 mg, oxazepam 30 mg, or chlordiazepoxide 20 mg) and no more than 1 mg of lorazepam equivalent per single dose. Thyroid hormone supplements for hypothyroidism were permitted only if the participant had been on a stable dose of such medication for at least 2 months prior to visit 3 and had serum thyroid stimulating hormone levels within the normal range at screening. Other concomitant medications with primarily central nervous system activity were not allowed.

### Efficacy and Safety Assessments

The primary efficacy endpoint was a between-treatment comparison of the change from baseline across the 6-week treatment period in both the YMRS and the HDRS-21. Secondary endpoints, in the following order, were between-treatment comparisons of time to partial response in the mixed episode (at least 25% reduction from baseline on both HDRS-21 and YMRS total scores), time to response in the mixed episode (at least 50% reduction from baseline on both HDRS-21 and YMRS total scores), mean change from baseline to endpoint in overall illness severity on the Clinical Global Impressions for Bipolar Disorder (CGI-BP,[18] composite overall rating for CGI-BP), and time to and rates of hospitalization due to mania or depression. Safety and tolerability, as measured by treatment-emergent adverse events and statistically significant changes in laboratory values and vital signs (weight, standing and supine heart rate, and blood pressure), were the remaining secondary measures. Clinical laboratory tests included clinical chemistry, serum and urine pregnancy tests, lipid panel, and divalproex serum level values.

### Statistical Analyses

All analyses were conducted on an intent-to-treat basis and were performed using Statistical Application Software (SAS Institute Inc, Cary, North Carolina). Tests were done at a 2-sided significance level of $P < .05$.

Potential between-group differences on the demographic variables and baseline disease characteristics were examined by Fisher exact test for categorical variables and by analysis-of-variance (ANOVA) methods for continuous variables with the treatment and investigator in the model. Patients who reported YMRS item scores consistent with psychosis, either a score of 4 ("incoherent; communication impossible") on item 7 (language-thought disorder) or a score of 8 ("delusions; hallucinations") on item 8 (content), were classified as psychotic. Patients with 4 or more total episodes of mania, mixed mania, and depression in the previous year (hypomania not captured) were classified as rapid cyclers.

The primary study objective was assessed using a mixed-effects model repeated-measures (MMRM) analysis with categorical effects of treatment, investigator, duration of treatment, treatment-by-time interaction, continuous baseline score, and baseline score-by-time interaction. Correlation in repeated measures was modeled with unstructured covariance.

Treatment differences in efficacy measures such as YMRS, HDRS-21, and CGI-BP were also evaluated with analysis of covariance (ANCOVA) methods, which were used on the changes from baseline to last-observation-carried-forward (LOCF) endpoints, with terms for categorical effects of treatment, investigator, and continuous baseline score in the model.

Time to partial response, time to response, and time to study discontinuation were analyzed using the Kaplan-Meier method for between-group differences. Rates of partial response, response, remission, and study discontinuation by treatment group were compared using Fisher exact test.

Numbers needed to treat (NNTs) or numbers needed to harm (NNHs) were calculated using the formula NNT or NNH = 1/ absolute risk reduction (ARR) = $1/(P_{arm1} - P_{arm2})$, where *P* represents the event rate in each treatment group. The 95% confidence interval (CI) for NNT or NNH was calculated as 1/[95% CI for ARR], where 95% CI for

$$\mathrm{ARR} = (P_{arm1} - P_{arm2}) \pm 1.96\sqrt{\frac{P_{arm1}(1-P_{arm1})}{N_{arm1}} + \frac{P_{arm2}(1-P_{arm2})}{N_{arm2}}}.$$

By convention, calculations were structured so that olanzapine augmentation was superior when the NNT or NNH was positive and the placebo augmentation was superior when the NNT or NNH was negative.

Treatment-emergent adverse events, serious adverse events, and rates of clinically significant changes in weight (≥ 7%) were evaluated using Fisher exact test.

Changes from baseline to endpoint (using LOCF) in laboratory values were compared between treatment groups with ANOVA for ranks of change with treatment and investigator effects in the model. Change from baseline to endpoint (using LOCF) in weight was compared with ANCOVA with treatment and investigator in the model and also adjusted by the baseline weight.

*Partial response* and *response* were defined as a total score reduction from baseline in both YMRS (mania and HDRS-21 (depression) of ≥ 25% and ≥ 50%, respectively, and *remission* was defined as a YMRS score ≤ 12 and an HDRS-21 score ≤ 8.

Additionally, the potential impact of serum divalproex concentration on measures of depression and mania was assessed. Using a mean serum divalproex level of ≥ 90 μg/mL as the definition of high serum divalproex concentration for any given patient, we performed MMRM analyses. A higher cutoff concentration would have resulted in too few patients in the high serum divalproex group.

## RESULTS

All results reported were specified a priori unless indicated otherwise.

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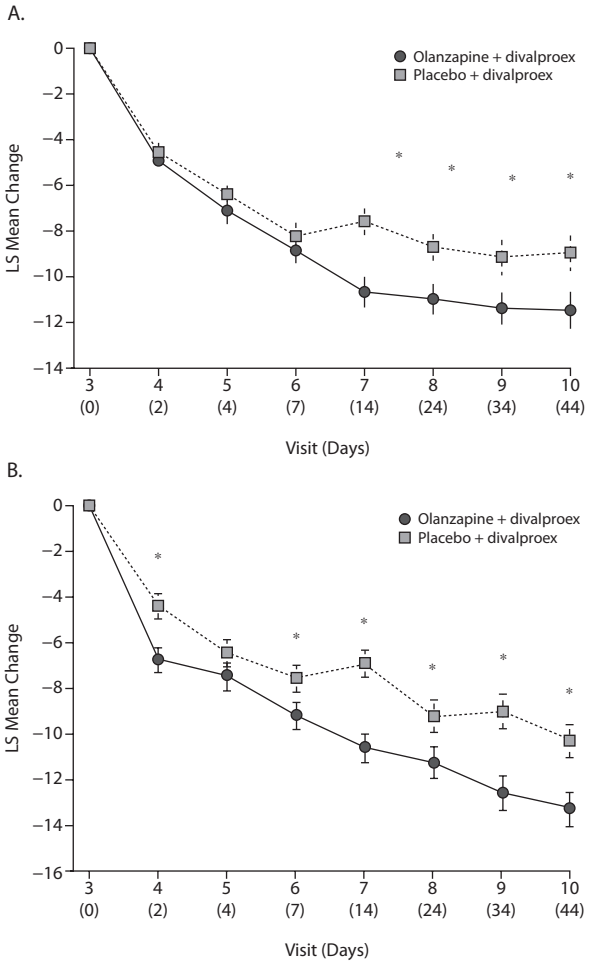
Table 1. Subject Demographics and Baseline Characteristics

| Variable | Olanzapine + Divalproex (n = 101) | Placebo + Divalproex (n = 101) |
|---|---|---|
| Male gender, n (%) | 40 (39.6) | 43 (42.6) |
| Age, mean (SD), y | 38.6 (11.2) | 38.5 (11.1) |
| BMI, mean (SD) | 30.73 (9.0) | 31.72 (8.3) |
| Ethnicity, n (%) | | |
| White | 46 (45.5) | 56 (55.4) |
| African American | 38 (37.6) | 29 (28.7) |
| Hispanic | 15 (14.9) | 13 (12.9) |
| Other | 2 (2.0) | 3 (3.0) |
| Illness severity | | |
| HDRS-21 score, mean (SD) | 22.45 (4.2) | 21.87 (4.9) |
| YMRS score, mean (SD) | 21.42 (4.8) | 20.40 (4.0) |
| CGI-S score, mean (SD) | 4.33 (0.55) | 4.26 (0.52) |
| Clinical history[a] | | |
| Hospitalized, n (%) | 14 (13.9) | 16 (15.8) |
| No. of manic episodes, mean (SD)[b] | 0.65 (0.87)[c] | 0.85 (1.65)[c] |
| No. of depressive episodes, mean (SD)[b] | 0.91 (0.62)[d] | 1.14 (2.31)[c] |
| No. of mixed episodes, mean (SD)[b] | 1.82 (1.64)[c] | 1.61 (1.71)[c] |
| Psychosis, n (%)[e] | 4 (4.0) | 1 (1.0) |
| Rapid cycling, n (%)[f] | 27 (26.7) | 22 (21.8) |

[a]In past 12 months, not including current episode.
[b]Excludes those categorized as having a high, undetermined number of manic, depressive, or mixed episodes.
[c]n = 99.
[d]n = 100.
[e]YMRS item 7 (language/thought disorder) score of 4 or YMRS item 8 (content) score of 8.
[f]Minimum of 4 total episodes of mania, mixed mania, and depression over the last year (hypomania not assessed).
Abbreviations: BMI = body mass index, CGI-BP = Clinical Global Impressions for Bipolar Disorder, HDRS-21 = 21-item Hamilton Depression Rating Scale, YMRS = Young Mania Rating Scale.

Figure 2. Primary Efficacy Measures: Change From Baseline Across the 6-Week Treatment Period in 21-Item Hamilton Depression Rating Scale (A) and Young Mania Rating Scale (B) Scores[a]




[a]Olanzapine + divalproex, n = 100; placebo + divalproex, n = 101.
*$P < .05$.

## Patient Characteristics

Of the 446 patients who entered the screening and washout study period I, 202 patients met criteria for randomization in study period II (Figure 1). Enrolled participants were 59% female, 51% white, 33% African American, and 14% Hispanic, with mean (SD) scores of 22.2 (4.5) on the HDRS-21, 20.9 (4.4) on the YMRS, and 4.3 (0.5) on the CGI-BP. Table 1 provides patient information by treatment arm. Few patients had psychosis, and about a quarter of patients were rapid cyclers. There were no statistically significant differences between treatment arms at randomization.

## Patient Disposition

Study completion rates and reasons for discontinuation were similar for both treatment arms (Figure 1). In study period II, mean (SD) modal daily dose for olanzapine was 14.6 (8.9) mg. Median blood levels of divalproex measured at randomization, day 7, day 24, and day 44 after randomization were generally within the protocol-specified range (75 to 125 μg/mL) during study period II: for the olanzapine + divalproex–treated patients, the levels were 92, 79, 71, and 69 μg/mL, respectively; for divalproex-treated patients, they were 95, 86, 86, and 80 μg/mL, respectively. During study period II, median time to study discontinuation was similar for both study groups (57 days for olanzapine + divalproex–treated patients [discontinuation, n = 43]; 55 days for divalproex-treated patients [discontinuation, n = 41]).

## Efficacy Measures

The primary objective of this study was to compare the MMRM mean ± SE total score changes from baseline across the 6-week treatment period for the olanzapine + divalproex treatment group (n = 100) versus the divalproex monotherapy treatment group (n = 101): on the HDRS-21, −9.37 ± 0.55 versus −7.69 ± 0.54, $P = .022$, respectively; on the YMRS, −10.15 ± 0.44 versus −7.68 ± 0.44, $P < .001$, respectively (Figure 2). The overall treatment effect for both YMRS and HDRS-21 total scores was statistically significant for olanzapine + divalproex treatment versus divalproex monotherapy. Considering the data on a visit-by-visit basis beginning with the first week of study period

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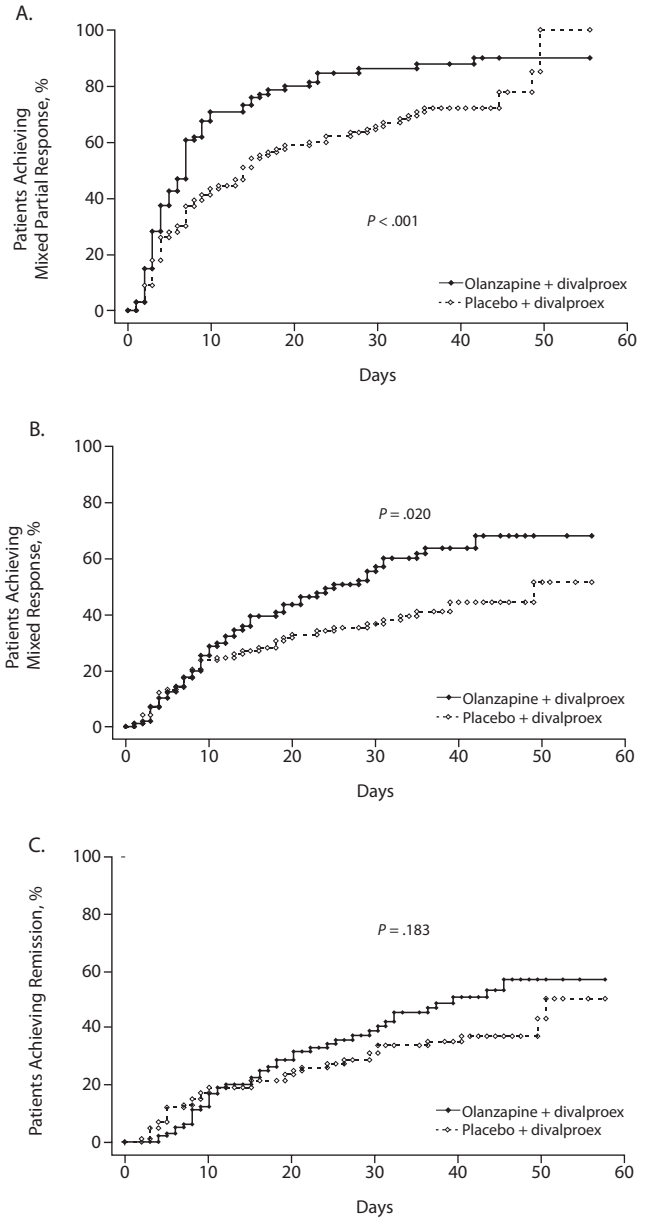
Figure 3. Secondary Efficacy Measures: Kaplan-Meier Curves Showing Time to Partial Response (A), Time to Response (B), and Time to Remission (C) as Determined by Meeting Combined 21-Item Hamilton Depression Rating Scale and Young Mania Rating Scale Criteria[a]




[a]Olanzapine + divalproex, n = 100; placebo + divalproex, n = 101.

II, significant improvement in mania occurred much more rapidly than significant improvement in depression, and these improvements were sustained for the remainder of the study (Figure 2). Using LOCF analyses, the mean ± SE changes for patients receiving olanzapine + divalproex treatment versus those receiving divalproex monotherapy were also statistically significant (HDRS-21, −10.59 ± 0.76 versus −8.51 ± 0.75, $P = .038$; YMRS, −11.71 ± 0.7 versus −8.97 ± 0.69, $P = .004$). Significant improvement in mania symptoms in the olanzapine + divalproex treatment arm over the divalproex monotherapy arm was seen at every visit from 2 days after randomization onward, with the exception of the visit at 4 days ($P = .214$). Depression symptoms were significantly improved in the olanzapine + divalproex treatment arm from day 14 onward (Figure 2). At visit 10, 32 of 58 olanzapine + divalproex patients (55.2%) and 24 of 61 placebo + divalproex patients (39.3%) achieved at least a 50% reduction from baseline on the HDRS-21 ($P = .100$). Similarly, at visit 10, 40 of 58 olanzapine + divalproex patients (69.0%) and 30 of 61 placebo + divalproex patients (49.2%) had at least a 50% score reduction from baseline on the YMRS ($P = .040$). Between-treatment effect sizes[19] were 0.298 for HDRS-21 and 0.423 for YMRS.

## Secondary Objectives

The time to partial response and time to response were statistically significantly shorter with olanzapine augmentation versus divalproex monotherapy ($P < .001$ and $P = .020$, respectively; Figure 3). For the olanzapine augmentation versus divalproex monotherapy group, the median time to partial response was 7 days (uncensored n [in other words, number achieving partial response] = 81) versus 14 days (uncensored n = 71), and median time to response was 25 days (uncensored n = 54) versus 49 days (uncensored n = 40). The LOCF mean ± SE change from baseline to endpoint on the CGI-BP was −1.34 ± 0.11 and −1.06 ± 0.11, $P = .056$, for olanzapine + divalproex treatment and divalproex monotherapy, respectively. There was only 1 hospitalization due to mania or depression during the study (patient in adjunctive olanzapine treatment arm).

For olanzapine + divalproex treatment versus divalproex monotherapy at endpoint, partial response rates were 65% versus 47% ($P = .011$), response rates were 41% versus 28% ($P = .054$), and remission rates were 31% versus 26%, ($P = .437$).

Numbers needed to treat were calculated for response and remission at any time during the study or at study endpoint in an a priori–specified analysis. The NNTs (95% CI) observed for response at any time during the study or at endpoint were 7 (4–135) and 8 (4–368), respectively. The NNTs (95% CI) for remission at any time during the study or at endpoint were 14 (−17 to 5) and 20 (−14 to 6), respectively. (CIs that contain both a negative number and a positive number indicate a nonsignificant difference). Hence, NNTs were favorable for the olanzapine + divalproex treatment group.

No significant differences were found in manic and depression symptom changes in high versus low serum divalproex groups. There were 22 and 37 patients in the olanzapine + divalproex and placebo + divalproex arms for high serum divalproex, respectively, and 78 and 64 patients in the olanzapine + divalproex and placebo + divalproex arms for low serum divalproex, respectively. Overall least squares mean ± SE changes by divalproex level were

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**Table 2. Baseline-to-Endpoint Laboratory, BMI, and Weight Values**

| Measure | Olanzapine + Divalproex | | | Placebo + Divalproex | | | |
|---|---|---|---|---|---|---|---|
| | Baseline, Mean (SD) | Change, Mean (SD) | *P* Value (within therapy) | Baseline, Mean (SD) | Change, Mean (SD) | *P* Value (within therapy) | *P* Value (between therapy) |
| Cholesterol, mg/dL[a] | | | | | | | |
| Total | 191.37 (41.23) | −7.8 (31.77) | .035 | 192.25 (44.45) | −8.72 (28.80) | .011 | .657 |
| LDL | 115.32 (38.82) | −9.22 (27.31) | .011 | 111.01 (36.74) | −9.77 (28.05) | .001 | .924 |
| HDL-Dextra | 53.76 (12.03) | −3.24 (10.02) | .012 | 51.48 (11.64) | −1.22 (8.90) | .286 | .122 |
| Total triglycerides, mg/dL[a] | 111.46 (61.54) | 22.91 (67.70) | < .001 | 139.75 (77.22) | 16.8 (73.25) | .099 | .293 |
| Fasting glucose, mg/dL[b] | 91.81 (11.98) | 6.93 (23.72) | .013 | 91.9 (10.13) | −0.55 (14.00) | .362 | .007 |
| Bilirubin total mg/dL[c] | 6.50 (3.46) | −1.56 (2.99) | < .001 | 6.65 (3.43) | −0.74 (3.03) | .024 | .046 |
| | Baseline, Mean (SD) | Change, LS Mean ± SE | *P* Value (within therapy) | Baseline, Mean (SD) | Change, LS Mean ± SE | *P* Value (within therapy) | *P* Value (between therapy) |
| BMI, kg/m$^2$[d] | 30.72 (9.04) | 1.18 ± 0.12 | < .001 | 31.72 (8.29) | 0.26 ± 0.12 | .004 | < .001 |
| Weight, kg[d] | 87.35 (24.29) | 3.34 ± 0.34 | < .001 | 90.75 (23.7) | 0.7 ± 0.34 | .004 | < .001 |

[a]Olanzapine + divalproex, n = 62; placebo + divalproex, n = 69.
[b]Olanzapine + divalproex, n = 77; placebo + divalproex, n = 82.
[c]Olanzapine + divalproex, n = 82; placebo + divalproex, n = 84.
[d]Olanzapine + divalproex, n = 100; placebo + divalproex, n = 101.
Abbreviations: BMI = body mass index, HDL = high-density lipoprotein, LDL = low-density lipoprotein, LS = least squares, SE = standard error.

**Table 3. Treatment-Emergent Adverse Events (frequency ≥ 5% or statistically significant)**

| Event | Frequency, n (%) | | *P* Value |
|---|---|---|---|
| | Olanzapine + Divalproex (n = 101) | Placebo + Divalproex (n = 101) | |
| Sedation | 24 (23.8) | 4 (4.0) | < .001 |
| Somnolence | 21 (20.8) | 6 (5.9) | .003 |
| Weight increased | 21 (20.8) | 4 (4.0) | < .001 |
| Dry mouth | 13 (12.9) | 3 (3.0) | .017 |
| Increased appetite | 13 (12.9) | 5 (5.0) | .081 |
| Fatigue | 10 (9.9) | 4 (4.0) | .164 |
| Tremor | 9 (8.9) | 0 (0.0) | .003 |
| Peripheral edema | 6 (5.9) | 1 (1.0) | .118 |
| Headache | 5 (5.0) | 7 (6.9) | .767 |
| Nasopharyngitis | 4 (4.0) | 7 (6.9) | .537 |
| Insomnia | 2 (2.0) | 6 (5.9) | .279 |

- −9.67 ± 1.54 ≥ 90 µg/mL and −9.46 ± 0.6 < 90 µg/mL in the olanzapine + divalproex group (HDRS),
- −7.47 ± 1.33 ≥ 90 µg/mL and −7.42 ± 0.67 < 90 µg/mL in the placebo + divalproex group (HDRS),
- −10.47 ± 0.99 ≥ 90 µg/mL and −10.19 ± 0.53 < 90 µg/mL in the olanzapine + divalproex group (YMRS), and
- −8.00 ± 0.87 ≥ 90 µg/mL and −7.67 ± 0.60 < 90 µg/mL in the placebo + divalproex group (YMRS).

### Safety

Baseline-to-endpoint changes in laboratory values, weight, and body mass index (BMI) were assessed (Table 2). Fasting blood glucose, BMI, and weight were significantly increased in the olanzapine augmentation versus the monotherapy group. Changes in cholesterol and total triglycerides levels were similar between treatment groups (Table 2). Reductions in baseline-to-endpoint total bilirubin levels were statistically greater for the olanzapine + divalproex treatment arm (Table 2).

Serious adverse events for olanzapine + divalproex–treated patients (n = 1 for each event term) were a head injury from a road traffic accident (resulting in death) and an acute hepatic failure. Serious adverse events for divalproex monotherapy–treated patients (n = 1 for each event term) were spontaneous abortion, asthenia, chest pain, hypoesthesia, and overdose. A worsening of current bipolar I disorder mood episode occurred once in each treatment arm. Differences between study arms were not statistically significant.

Table 3 shows rates of treatment-emergent adverse events. The rates of baseline-to-endpoint weight increase of at least 7% were 22% and 3% for the olanzapine + divalproex and divalproex monotherapy treatment groups, respectively (*P* < .001).

While prospectively defined NNHs at any time and at endpoint were calculated for subjects with ≥ 7% weight gain, high fasting glucose (≥ 126 mg/dL), high total cholesterol (≥ 200 mg/dL), high low-density lipoprotein cholesterol (≥ 100 mg/dL), low high-density lipoprotein cholesterol (< 40 mg/dL), and high fasting triglycerides (≥ 150 mg/dL), only the NNH (95% CI) for ≥ 7% weight gain was significantly different for olanzapine + divalproex compared to divalproex monotherapy groups: −6 (−10 to −4) at endpoint and −5 (−7 to −3) at any time postbaseline.

## DISCUSSION

To our knowledge, this study represents the first adequately powered clinical trial of combination treatment with an atypical antipsychotic and divalproex in patients with mixed bipolar episodes, including improvement of both depressive and manic symptoms as the primary outcome.

Results of this study show that 6-week olanzapine treatment compared to placebo augmentation of divalproex (in

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other words, combination treatment versus monotherapy) in patients with inadequate responses to divalproex monotherapy yielded statistically significant improvement in both depressive and manic symptoms, as measured by the mean change from baseline across the 6-week treatment period in HDRS-21 and YMRS scores, respectively. Time to partial response and time to response were also shorter with olanzapine treatment compared to placebo augmentation of divalproex. Also of interest was the very early statistical separation of outcomes in patients with combination treatment compared to monotherapy treatment for relief of manic symptoms (from day 2 onward, with the exception of day 4) but later separation for relief of depressive symptoms (from day 14 onward). However, at LOCF endpoint, there were still substantial proportions of patients whose depressive symptoms had not responded (51% in the olanzapine + divalproex treatment arm versus 62% in the divalproex monotherapy arm, $P = .156$). While these data support more rapid symptom improvement of manic symptoms than depressive symptoms with combination treatment, manic symptom improvement is also more robust (38% nonresponse in the olanzapine + divalproex treatment arm versus 58% in the divalproex monotherapy arm, $P = .005$). The low NNTs calculated for this study at endpoint also support combination treatment in patients with mixed bipolar episodes who have demonstrated inadequate responses to divalproex monotherapy. However, the efficacy benefits of olanzapine augmentation (NNT) need to be considered in relationship to the increased potential risk for weight gain (NNH). The effect sizes calculated between the 2 active treatment groups in our study were similar to the weighted means previously reported in studies of both bipolar mania (0.40 [95% CI, 0.28–0.53])[20] and depression (0.37 [95% CI, 0.33–0.41])[21] for active medications versus placebo.

The overall study period II outcomes were similar for HDRS-21 and YMRS measures by therapy when patients were divided into high or low serum divalproex levels, suggesting that the efficacy differences noted between treatment groups was independent of divalproex serum levels.

The treatment-emergent adverse event profiles for both study arms were similar to those reported in prior literature.[14] Our results were consistent with another subset analysis of 85 nonresponsive dysphoric mania patients also taking divalproex (or lithium) monotherapy for at least 2 weeks prior to therapy.[14] Although study duration, participant illness (dysphoric mania versus mixed episode), and baseline HDRS-21 and YMRS scores were broadly similar to this study, the lower limit of permissible serum divalproex concentration was slightly lower (50 μg/mL). Baseline-to-endpoint (6 weeks) mean HDRS-21 and YMRS scores for the olanzapine + divalproex versus divalproex monotherapy groups were −8.8 and −1.4 ($P < .001$) versus −11.8 and −4.7 ($P < .001$), respectively.[14]

The mean baseline-to-endpoint increases in fasting blood glucose (+6.9 versus −0.6 mg/dL, $P = .007$; Table 2) and weight (+3.4 versus +0.7 kg, $P < .001$) were greater in the olanzapine + divalproex treatment group versus the divalproex monotherapy treatment group. A similar study found no significant increase in fasting blood glucose levels with olanzapine cotherapy, and it found similar weight gain (+3.08 kg [cotherapy] versus +0.23 kg [monotherapy], $P < .001$).[13] It is unclear whether these increases suggest any pharmacologic synergy between olanzapine and the slightly higher levels of divalproex. However, the presence of a high mean baseline BMI has been associated with less subsequent weight gain and potentially less increase in lipids.[22] The mean (SD) decrease in total bilirubin levels, statistically greater for the olanzapine + divalproex treatment arm (−1.56 [2.99] μmol/L versus −0.74 [3.03] μmol/L, $P = .046$), is of unclear significance, although it may suggest that combined therapies did not increase adverse hepatic effects.

These results are consistent with those of a similar study[13] that assessed efficacy of divalproex or lithium monotherapy compared with olanzapine augmentation in acute manic or mixed bipolar episodes; a subset analysis of patients with mixed bipolar episodes who were randomly assigned to olanzapine plus either divalproex (mean blood levels were lower than in the present study: 64 μg/mL [cotherapy] and 75 μg/mL [monotherapy]) or lithium compared to those taking mood stabilizer monotherapy had YMRS score reductions of −12.9 versus −7.5 ($P < .001$). This advantage for adjunctive olanzapine treatment was also seen in time to mania response.[13]

There were several limitations to this study. First, our findings can be generalized only to patients with inadequate responses to divalproex. Second, while the comparison of treatment phase (study period II) of the study was blinded, the open-label phase of divalproex (study period I) may have yielded bias related to investigator and participant speculation regarding treatment group, based on emergent side effects observed during the randomization phase (study period II). Third, results from our outpatient study cannot be extrapolated to hospitalized bipolar I disorder patients or to bipolar II disorder patients with concomitant hypomanic and depressive features (*DSM-IV* mixed episodes pertain only to bipolar I disorder).

## CONCLUSIONS

Six weeks of olanzapine treatment augmentation was associated with greater and earlier reduction of both manic and depressive symptoms in patients with bipolar mixed episodes already on at least 2 weeks of stable divalproex monotherapy treatment but without adequate response to this monotherapy prior to treatment augmentation. Mean baseline-to-endpoint increases in fasting blood glucose and weight were statistically significantly greater in the olanzapine + divalproex treatment group, but lipid changes were not significantly different between treatment groups.

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***Drug names:*** aripiprazole (Abilify), carbamazepine (Carbatrol, Equetro, and others), chlordiazepoxide (Librium and others), diazepam (Diastat, Valium, and others), divalproex (Depakote and others), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), risperidone (Risperdal and others), temazepam (Restoril and others), ziprasidone (Geodon).

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***Study participants:*** This study involved the participation of the following investigators and sites: Roberta Ball, DO, CRI Worldwide-Philadelphia Division, Philadelphia, Pennsylvania; Grant Belnap, MD, Mountain West Clinical Trials, Eagle, Idaho; Matthew Brams, MD, Bayou City Research Corporation, Inc., Houston, Texas; Ronald Brenner, MD, Neurobehavioral Research, Inc., Cedarhurst, New York; Barbara Diaz, MD, San Juan Capestrano Hospital, Rio Piedras, Puerto Rico; Michael Downing, MD, Future Search Trials of Dallas, L.P., Dallas, Texas; Nizar El-Khalili, MD, Alpine Clinic, Lafayette, Indiana; Judith Engelman, MD, Dedicated Phase I, Phoenix, Arizona; Miguel Flores, MD, Berma Research Group, Hialeah, Florida; Thomas Gualtieri, MD, North Carolina Neuropsychiatry PA, Chapel Hill, North Carolina; Angel Guerra MD, Servicios de Salud del Valle de Lajas, Lajas, Puerto Rico; Howard Hassman, MD, CNS Research Institute, Clementon, New Jersey; Robert Horne, MD, Horne Research, Las Vegas, Nevada; Richard Jaffe, MD, Belmont Center for Comprehensive Research, Philadelphia, Pennsylvania; Rakesh Jain, MD, R/D Clinical Research, Inc., Lake Jackson, Texas; Arif Khan, MD, Northwest Clinical Research Center, Bellevue, Washington; Veena Luthra, MD, Suburban Research Associates, Media, Pennsylvania; Vikram Mehra, MD, R/D Clinical Research, Inc., Houston, Texas; Robert Riesenberg, MD, Atlanta Center for Medical Research, Atlanta, Georgia; Jose Schuster, MD, Schuster Medical Research Institute, Sherman Oaks, California; Ward Smith, MD, Summit Research Network (Oregon), Inc., Portland, Oregon.

***Financial disclosure:*** **Dr Houston**, **Ms Degenhardt**, and **Mr Jamal** are employees of Lilly USA and stock shareholders in Eli Lilly. **Dr Tohen** is a former employee of Eli Lilly (1996–2008); is a consultant to Eli Lilly and Johnson & Johnson; and serves on speakers or advisory boards of AstraZeneca and Bristol-Myers Squibb. His wife is an employee of and stock shareholder in Eli Lilly. **Dr Liu** was an employee of Lilly USA at the time this study was conducted. **Dr Ketter** has received grant/research support from Abbot, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, GlaxoSmithKline, Pfizer, Repligen, and Wyeth; has been a consultant to Abbott, AstraZeneca, Bristol-Myers Squibb, Dainippon Sumitomo Pharma, Eli Lilly, GlaxoSmithKline, Janssen, Jazz, Novartis, Organon, Solvay, Valeant, Vanda, Wyeth, and XenoPort; and has received lecture honoraria from Abbott, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Noven, Otsuka, and Pfizer. His spouse (Nzera Ketter, MD) is an employee of Johnson & Johnson.

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