Olanzapine Versus Divalproex Versus Placebo in the Treatment of Mild to Moderate Mania: A Randomized, 12-Week, Double-Blind Study

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Objective: To evaluate the efficacy and safety of olanzapine, divalproex, and placebo in a randomized, double-blind trial in mild to moderate mania (DSM-IV-TR criteria).

Method: The study was conducted from October 2004 to December 2006. A total of 521 patients from private practices, hospitals, and university clinics were randomly assigned to olanzapine (5–20 mg/day), divalproex (500–2500 mg/day), or placebo for 3 weeks; those completing continued with a 9-week double-blind extension. Efficacy (mean change in Young Mania Rating Scale [YMRS] total score was the primary outcome) and safety were assessed.

Results: After 3 weeks of treatment, olanzapine-treated (N = 215) and placebo-treated (N = 105) patients significantly differed in YMRS baseline-to-endpoint total score change (p = .034; least squares [LS] mean: –9.4 and –7.4, respectively). Such changes were not significantly different between olanzapine vs. divalproex (N = 201) or divalproex vs. placebo. After 12 weeks of treatment, olanzapine- and divalproex-treated patients significantly differed in YMRS baseline-to-endpoint changes (p = .004; LS mean: –13.3 and –10.7, respectively). Of observed cases, 35.4% (35/99; 3 weeks) to 57.1% (28/49; 12 weeks) had valproate plasma concentrations lower than the recommended valproate therapeutic range, but these patients' YMRS scores were lower than those of patients with valproate concentrations above/within range. Compared with divalproex, after 12 weeks, olanzapine-treated patients had significant increases in weight (p < .001) and in glucose (p < .001), triglyceride (p = .003), cholesterol (p = .024), uric acid (p = .027), and prolactin (p < .001) levels. Divalproex-treated patients had significant decreases in leukocytes (p = .044) and platelets (p < .001) compared with olanzapine after 12 weeks of treatment. The incidence of potentially clinically significant weight gain (≥ 7% from baseline) was higher with olanzapine than with divalproex (3-week: p = .064, 6.4% vs. 2.7%; 12-week: p = .002, 18.8% vs. 8.5%; respectively).

Conclusion: Olanzapine was significantly more efficacious than placebo but not divalproex at 3 weeks and significantly more efficacious than divalproex at 12 weeks. Olanzapine-treated patients had significantly greater increases in weight and in glucose, cholesterol, triglyceride, uric acid, and prolactin levels than divalproex-treated patients.

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The efficacy of olanzapine and divalproex for the treatment of moderate to severe episodes of bipolar mania has been established in placebo-controlled studies.[1–4] Two head-to-head comparison studies addressing the risks and benefits of these 2 treatments have also been conducted in patients with a moderate to severe manic episode.[5–7] In contrast to the breadth of studies evaluating

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moderate to severe patients, only 1 study could be located that has examined the efficacy and safety of olanzapine in patients with mild to moderate mania.[8] To our knowledge, no such studies of divalproex have been published. In discussion with the European regulatory agency (European Medicines Agency), the lead author agreed that there was a need to study less severely ill populations because (1) many patients present with mild to moderate mania and (2) these patients are treated similarly to those with severe mania because of an absence of empirical data and the assumption that the response will be the same. The purpose of the present study was to evaluate the efficacy and safety of olanzapine versus divalproex (primary objective) in a multicenter, randomized, double-blind, parallel trial of patients with mild to moderate manic or mixed episodes without psychotic features. Importantly, this is the first study in bipolar disorder to compare olanzapine and placebo (secondary objective) in a randomized, controlled design including a third active-control arm. Three-arm trials, including the drug to be studied, placebo, and active control, are optimal for assay sensitivity.[9]

METHOD

Study Design

The study (ClinicalTrials.gov identifier: NCT-00094549; Lilly Study Code: F1D-MC-HGKQ) was a double-blind, placebo-controlled, parallel-design trial with patients randomly allocated to olanzapine (5–20 mg/day), divalproex (500–2500 mg/day), or placebo in a 2:2:1 ratio. A computer-generated random sequence randomly assigned patients to treatment groups within each study site. The study was composed of 3 phases: study period I was a 2- to 14-day screening period; study period II was a 3-week, double-blind, acute therapy period; study period III was a 9-week, double-blind extension period (patients who had received placebo in study period II were switched under double-blind conditions to olanzapine 5 to 20 mg/day, while other patients remained on their current treatment). The study was conducted following the principles of the Declaration of Helsinki, good clinical practices guidelines, and all applicable laws and regulations. All patients gave written informed consent after the procedures and possible adverse events were fully explained.

Patients

Patients were men or women (inpatient or outpatient), aged 18 to 65 years, with a diagnosis of DSM-IV-TR[10] acute bipolar manic or mixed episode without psychotic features, based on clinical assessment and confirmed by the Structured Clinical Interview for the DSM-IV Axis I Disorders (SCID-I), Clinical Version[11] plus the rapid cycling item from the bipolar specifiers obtained from the SCID-I. Patients were required to have had a Young Mania Rating Scale (YMRS)[12] total score of ≥ 20 and ≤ 30 (mild to moderate) and a Clinical Global Impressions for Bipolar Disorder-Severity of Illness scale (CGI-BP)[13] mania subscore of 3 (mild) or 4 (moderate) at screening (week –1) and at randomization (week 0). Female patients were required to test negative for pregnancy and to be using medically accepted contraception. Exclusion criteria included a rapid-cycling course or presence of psychotic features as defined in DSM-IV-TR. A limited dose of benzodiazepines (lorazepam ≤ 2 mg/day or equivalents, administered > 8 hours before psychiatric evaluation), anticholinergics (benztropine mesylate or biperiden ≤ 6 mg/day), and ongoing thyroid supplement therapy were permitted.

Treatments

Olanzapine (5–20 mg) was administered orally once daily in the evening, divalproex (500–2500 mg) was administered orally twice daily (for the 500-mg dose) or 3 times daily (for the 750-mg to 2500-mg doses), and placebo was administered orally 3 times daily. To maintain blinding, placebo capsules were used to balance out the daily treatment regimen into 3 divided doses for all patients, thereby ensuring that all patients had an identical 3-times–daily dosing regimen irrespective of treatment group and dose level. All study medications appeared identical. The daily dose was adjusted upward or downward by each site investigator on the basis of the following criteria: (1) as clinically indicated (taking into account efficacy and tolerability), (2) to maintain valproate plasma concentrations within the recommended range of 50 to 125 μg/mL,[14] and (3) to maintain medication dose within approved labeling dosages.[14,15] To keep investigators blind to treatment assignment, all study drugs were dispensed by an interactive voice response/web/fax tool (Fisher Automated Clinical Trials Services; Fisher Scientific International Inc., Pittsburgh, Pa.), and dose adjustments were conducted via the interactive voice response/web/fax tool. To maintain blinding, every time the voice/fax/web-based interface tool sent a message to alter the dose of a divalproex-treated patient, a dummy message was sent to alter the dose of an olanzapine- or placebo-treated patient. Valproate oral loading was not permitted.

Valproate Plasma Concentrations

Valproate plasma concentrations were monitored weekly during study period II and approximately monthly during study period III, with additional monitoring at the discretion of each site's investigator. To maintain the blinding, all patients had blood collected for assessing valproate concentration, irrespective of whether they received divalproex. Blood samples were obtained at a time that reflected the trough level of valproate (8–12 hours after the last dose of divalproex). Times outside this window were considered to provide inaccurate valproate

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concentration data and were not taken into account for dose adjustment. If a concentration was found to be above the upper limit of the therapeutic range (50–125 μg/mL[14]), it was recommended that the dose of divalproex should be decreased to bring the concentration into therapeutic range. If a concentration was below the lower limit of the therapeutic range, the dose could be increased at the investigator's discretion on the basis of the patient's clinical status and taking into account efficacy and tolerability considerations.

Efficacy Measures

The primary efficacy measure was the baseline-to-endpoint (study period II, week 3) mean change in the YMRS total score between olanzapine and divalproex. Both the Montgomery-Asberg Depression Rating Scale (MADRS)[16] and the CGI-BP were secondary efficacy measures. Other secondary efficacy measures included an item-wise analysis of the YMRS, rates of and time to response, and rates of remission. Response was defined as a ≥ 50% reduction in the total YMRS score at the endpoint of study period II and study period II/III. Time to response was defined as the days from first dose at which a reduction of ≥ 50% in the YMRS total score was first observed. Remission was defined as a score of ≤ 12 on the YMRS at endpoint of study period II.

Safety Measures

Safety was monitored by assessing adverse events (AEs), laboratory values, electrocardiograms, vital signs, and extrapyramidal symptoms. Extrapyramidal symptoms were measured with the Simpson-Angus Scale,[17] the Barnes Akathisia Scale,[18] and the Abnormal Involuntary Movement Scale.[19] Clinical analysis of blood samples was done by Covance Central Laboratory Services, Inc. (Indianapolis, Ind., and Geneva, Switzerland). The criteria for clinically significant treatment-emergent changes in lipids and glucose were based on guidelines from the National Cholesterol Education Program[20] and the American Diabetes Association.[21] Potentially clinically significant changes for all laboratory values were defined as any changes that could be considered potentially serious or clinically significant by a clinician. Criteria for identifying patients with potentially clinically significant changes were determined before unblinding and data lock.

Statistical Analysis

As specified in the protocol, 500 patients were to be randomly assigned in a ratio of 2:2:1 allocated across the 3 treatment groups: olanzapine (N = 200), divalproex (N = 200), and placebo (N = 100). This sample size was estimated to provide 80% power of detecting a 3.4 point difference in the mean YMRS scores between olanzapine and divalproex at 3 weeks. For the active treatments versus placebo, this sample size was estimated to provide 80% power of detecting a 4.2 point difference in the mean YMRS scores. These estimates were based on a significance level of .05, 2-tailed, with an estimated standard deviation of 12.0.

The primary endpoint analysis was change from baseline to endpoint in YMRS total scores at the end of the 3-week treatment period, estimated via the last observation carried forward (LOCF). For the primary variable and continuous secondary efficacy and safety variables, analyses of covariance (ANCOVA; with terms of investigator, treatment, and baseline value as a covariate) were performed to compare treatments based on the intent-to-treat (ITT) sample. The ITT sample included all randomly assigned patients who received at least 1 dose of treatment and had at least a baseline and a postbaseline value. Analyses were performed for study period II and for combined periods (study period II and III) separately. The efficacy analysis for study period II (3-week treatment) included all ITT patients. The efficacy analysis for study period II/III (12 weeks of treatment) did not include patients who were randomly assigned to placebo in study period II. Main treatment effects and pair-wise treatment comparison were both analyzed for the 3 treatment groups during study period II.

Additional analyses using a mixed-effects model repeated-measures (MMRM) analysis of variance for the primary efficacy variable were conducted and included terms for investigator, treatment, visit, and visit-by-investigator interaction in the model, with baseline score as a covariate, and with an unstructured covariance structure. Subgroup analyses stratified by patients with manic or mixed episodes were also conducted. Time to response was compared among treatment groups using the Kaplan-Meier product limit estimates and the log-rank test for pairwise comparisons. The same method was applied to analyzing time to response in subgroups (manic and mixed). An additional exploratory analysis for the primary endpoint was performed to examine region (geographic) and region-by-treatment interaction (ANCOVA; with terms of region, treatment, region-by-treatment interaction, and baseline value as a covariate). The country was not chosen in the model because the sample size varied greatly from country to country. The regions were classified as United States (including Puerto Rico) or Eastern Europe. For statistical purposes, the 4 patients from 2 Western European countries were included in the U.S. region. Effect size (Cohen's d) was calculated as the difference of 2 treatment least squares (LS) means divided by the standard deviation. For categorical variables, such as response rate and adverse event rate, Cochran-Mantel-Haenszel tests stratified by investigator were used to compare treatment difference. Post hoc analyses using methods as described above were performed to explore the relationship between efficacy outcomes and valproic acid concentrations.

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Number needed to treat (NNT) and number needed to harm (NNH) were calculated when appropriate. The NNT is the number of patients who need to be treated with the first treatment rather than with the second treatment of the given treatment contrast in order for 1 additional patient (for example, 1 additional responder or remitter) to benefit from treatment. This was calculated as NNT = 1/(Pt-Pc). *Pt* is the probability of benefit of the study treatment, and *Pc* is the probability of benefit of a comparator. The NNH is the number of patients who need to be treated with the first treatment rather than with the second treatment of the given treatment contrast in order for 1 additional patient to be harmed (that is, suffer the indicated adverse outcome). The NNH was calculated as NNH = 1/(Pc-Pt). *Pc* is the probability of risk of the comparator, and *Pt* is the probability risk of the study treatment.

All p values were based on 2-tailed tests with a significance level of .05. Statistical Analysis System (SAS) software version 8.2 (SAS Institute, Inc., Cary, N.C.) was used for all statistical analyses.

RESULTS

Patient Characteristics

The study was conducted from October 2004 to December 2006. Patients were recruited in France, Germany, Lithuania, Puerto Rico, Romania, Russia, and the United States from private practices, hospital clinics, and university clinics. A total of 521 patients were randomly assigned to olanzapine (N = 215), divalproex (N = 201), or placebo (N = 105). Study phase II was completed by 74.3% (387/521) of the patients, 99.7% (386/387) of these patients entered phase III, and 62.2% (240/386) completed study phase III (Figure 1). The proportions of patients who discontinued due to any particular reason were not significantly different between treatment groups (Figure 1).

The treatment groups did not significantly differ with respect to demographic and illness characteristics (Table 1). Approximately half (52.3% [254/486]) of the sample were women, 81.1% of the sample was white, and the mean age was 39.6 years. The mean ± SD baseline YMRS total score was 23.8 ± 2.7, with 21.5% (104/484) having mild mania and 78.2% (380/486) having moderate mania. In study period II, the use of any concomitant medications was not significantly different between the groups. In study period II/III, significantly more olanzapine-treated patients than divalproex-treated patients used any anticholinergic (p = .023; 9/201 and 1/186, respectively).

The mean ± SD dose of olanzapine was 11.4 ± 2.49 mg/day in study period II and 12.5 ± 3.84 mg/day in study period II/III. The mean ± SD dose of divalproex was 848.4 ± 135.62 mg/day in study period II and 986.4 ± 297.14 mg/day in study period II/III. The mean ± SD plasma levels of valproate were 61.3 ± 32.04 µg/mL at the end of study period II, 53.1 ± 27.11 µg/mL during study period II/III (II + III), and 45.7 ± 34.23 µg/mL at the end of study period III. For both study periods, the percentage of days compliant was not significantly different between the olanzapine-treated and divalproex-treated patients (study period II: 88.3% and 85.5%, respectively, and study period II/III: 88.1% and 85.6%, respectively).

Primary Efficacy Outcomes

Study period II. After 3 weeks of treatment, there were no significant differences in baseline-to-endpoint changes in YMRS total score (primary efficacy measure) between patients treated with olanzapine compared with those treated with divalproex (Table 2). For olanzapine compared with placebo, the change from baseline to endpoint (study period II, LOCF) in the YMRS total score was significantly greater in olanzapine-treated patients than in placebo-treated patients (p = .034; LS mean change: –9.4 and –7.4, respectively; effect size: –0.26); however, no significant differences were found between divalproex and placebo (Table 2). An item-wise analysis of the YMRS revealed that olanzapine-treated patients showed a significantly greater improvement at endpoint (study period II) compared with placebo on the item speech (rate and amount; p = .021; LS mean change: –1.6 and –1.1, respectively; effect size: –0.28). No other items significantly differed between treatments.

Study period II/III. After 12 weeks of treatment, the change from baseline to endpoint (study period II/III, LOCF) in the YMRS total score was significantly greater in olanzapine-treated patients than in divalproex-treated patients (p = .004; LS mean change: –13.3 and –10.7, respectively; effect size: –0.29; Table 2). An item-wise analysis of the YMRS revealed that olanzapine-treated patients showed a significantly greater improvement than divalproex-treated patients at endpoint (study period II/III) on the following 4 items: speech (rate and amount; p = .042; LS mean change: –2.4 and –2.0, respectively; effect size: –0.21), sexual interest (p = .015; LS mean change: –0.8 and –0.6, respectively; effect size: –0.25), sleep (p = .004; LS mean change: –1.2 and –0.9, respectively; effect size: –0.29), disruptive-aggressive behavior (p = .035; LS mean change: –1.1 and –0.8, respectively; effect size: –0.22). No other items significantly differed between treatments.

The visitwise changes in YMRS total score from baseline are shown in Figure 2. During the course of the study, the results of the LOCF ANCOVA and MMRM analyses of such changes in YMRS total score were generally consistent with regard to statistical significance of the difference between olanzapine and divalproex, olanzapine and placebo, and divalproex and placebo. The only difference was at week 2, when the LOCF ANCOVA revealed a significant difference (p = .034) between olanzapine and placebo and the MMRM analysis approached significance (p = .051).

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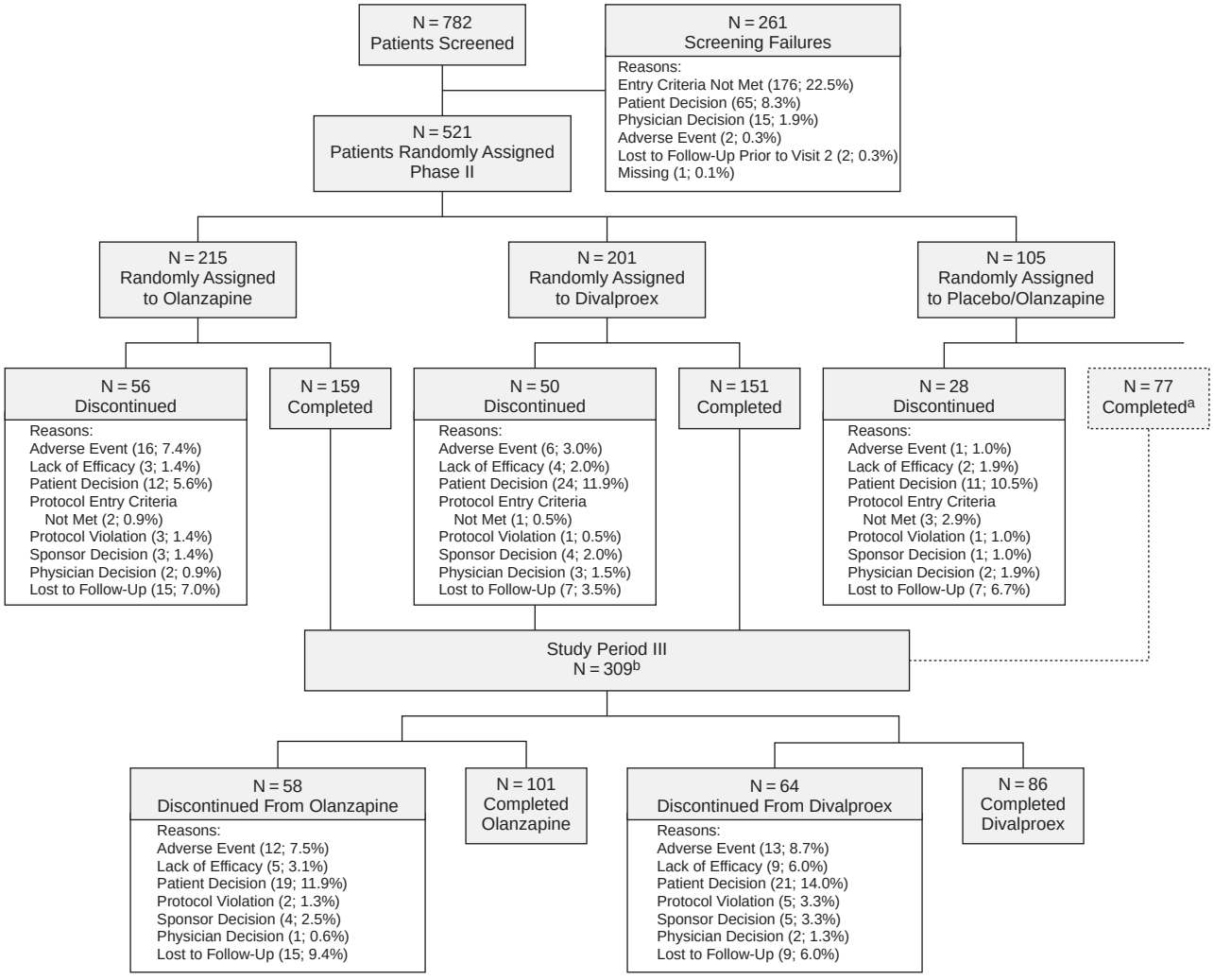
Figure 1. CONSORT Diagram Showing Progress of the Participants Through the Trial



[a]Patients switched to olanzapine but not included in the olanzapine analyses due to the delayed start.
[b]Does not include patients who were randomly assigned to placebo in study period II. One patient (divalproex group) completed study period II, but did not enter study period III; thus, N = 309 (not 310).

At endpoint of study period II, there was a significant region effect on YMRS total score ($p < .0001$). Patients in the U.S. region had a significantly greater reduction in YMRS total score compared with patients in the Eastern European region. However, there was no significant treatment-by-region interaction ($p = .309$). At endpoint of study period II/III, no significant differences were found in either region effect ($p = .813$) or treatment-by-region interaction ($p = .933$).

Secondary Efficacy Outcomes

As shown in Table 2, at study period II endpoint, olanzapine-treated patients (compared with divalproex-treated patients) had a statistically significantly greater improvement in CGI-BP mania, CGI-BP depression, overall CGI-BP, and MADRS total scores. At study period II/III endpoint, olanzapine-treated patients had statistically significantly greater improvements in overall CGI-BP and CGI-BP mania scores than divalproex-treated patients.

Clinical response at the end of study period II was reported in 40.8% (82/201) of the olanzapine-treated patients, 40.3% (75/186) of the divalproex-treated patients, and 31.3% (31/99) of the placebo-treated patients. Treatment groups did not significantly differ in the rates of response (olanzapine vs. divalproex: $p = .653$, NNT = 212; olanzapine vs. placebo: $p = .063$, NNT = 11; divalproex vs. placebo: $p = .140$, NNT = 12). The time to response did not significantly differ either. Clinical response at the end of study period II/III was reported in significantly more olanzapine-treated patients (66.2% [133/201]) than

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Table 1. Demographic and Baseline Characteristics of Patients With Mild to Moderate Mania

Characteristic	Olanzapine[a] (N = 215)[b]	Divalproex (N = 201)[b]	Placebo (N = 105)[b]
Age, mean ± SD, y	39.5 ± 11.9	39.2 ± 11.7	40.6 ± 12.8
Sex, N (%)[c]			
Female	109 (54.2)	99 (53.2)	46 (46.5)
Male	92 (45.8)	87 (46.8)	53 (53.5)
Weight, mean ± SD, kg	82.5 ± 21.6	81.3 ± 20.5	79.9 ± 19.3
Current episode, N (%)[d]			
Bipolar mixed	57 (28.4)	54 (29.0)	30 (30.3)
Bipolar manic	132 (65.7)	126 (67.7)	65 (65.7)
Current episode severity, N (%)[d]			
Mild	46 (22.9)	32 (17.2)	21 (21.2)
Moderate	143 (71.1)	148 (79.6)	74 (74.7)
Severe	0 (0.0)	0 (0.0)	1 (1.0)
Single manic episode severity, N (%)[c]			
Mild	1 (0.5)	2 (1.1)	2 (2.0)
Moderate	10 (5.0)	4 (2.2)	1 (1.0)
YMRS total score, mean ± SD	23.8 ± 2.8	23.9 ± 2.8	23.5 ± 2.5
CGI-BP overall score, mean ± SD	3.6 ± 0.6	3.7 ± 0.5	3.6 ± 0.7
CGI-BP mania score, mean ± SD	3.7 ± 0.5	3.7 ± 0.5	3.7 ± 0.5
CGI-BP depression score, mean ± SD	1.9 ± 1.1	2.0 ± 1.2	2.0 ± 1.2
MADRS total score, mean ± SD	10.6 ± 7.8	10.6 ± 7.1	11.3 ± 7.8

[a]None of the between-group differences were statistically significant.
[b]Number of patients (olanzapine = 215, divalproex = 201, and placebo = 105) corresponds to the safety sample, which includes patients who did not provide any efficacy data during treatment.
[c]Includes only the intent-to-treat sample: olanzapine, N = 201; divalproex, N = 186; and placebo, N = 99.
[d]Includes only the patients whose current episode is defined as recent episode manic or mixed, calculations based on the intent-to-treat sample: olanzapine, N = 201; divalproex, N = 186; and placebo, N = 99.
Abbreviations: CGI-BP = Clinical Global Impressions for Bipolar Disorder-Severity of Illness scale, MADRS = Montgomery-Asberg Depression Rating Scale, YMRS = Young Mania Rating Scale.

Table 2. Change From Baseline to Endpoint (study period II and study period II/III) in Efficacy Scores (LOCF)

Measure	Olanzapine, LS Mean Change (SE)	Divalproex, LS Mean Change (SE)	Placebo, LS Mean Change (SE)	Olanzapine vs Divalproex, p Value[a] (effect size)[b]	Olanzapine vs Placebo, p Value[a] (effect size)[b]	Divalproex vs Placebo, p Value[a]
Study period II[c]						
YMRS total score	–9.4 (0.60)	–8.2 (0.62)	–7.4 (0.80)	.143	.034 (–0.26)	.373
CGI-BP overall score	–0.8 (0.07)	–0.6 (0.08)	–0.5 (0.10)	.014 (–0.25)	.005 (–0.34)	.461
CGI-BP mania score	–1.0 (0.08)	–0.8 (0.08)	–0.7 (0.11)	.038 (–0.21)	.031 (–0.27)	.665
CGI-BP depression score	–0.3 (0.07)	–0.2 (0.07)	–0.1 (0.09)	.040 (–0.21)	.036 (–0.26)	.700
MADRS total score	–3.3 (0.46)	–2.1 (0.47)	–2.4 (0.61)	.045 (–0.20)	.209	.686
Study period II/III[d]						
YMRS total score	–13.3 (0.69)	–10.7 (0.72)	…	.004 (–0.29)	…	…
CGI-BP overall score	–1.2 (0.09)	–0.9 (0.10)	…	.023 (–0.23)	…	…
CGI-BP mania score	–1.5 (0.10)	–1.2 (0.10)	…	.008 (–0.27)	…	…
CGI-BP depression score	–0.2 (0.07)	–0.2 (0.08)	…	.910	…	…
MADRS total score	–2.3 (0.57)	–2.2 (0.59)	…	.883	…	…

[a]ANCOVA: model = treatment, investigator, and baseline score as covariate.
[b]Effect size (Cohen's d) was calculated as the difference of 2 treatment least squares means divided by the square root of the mean square error. Effect sizes are provided only for significant p values.
[c]Data are based on patients who had both a baseline and a postbaseline measure: N = 201 for olanzapine, N = 186 for divalproex, and N = 99 for placebo.
[d]Data are based on patients who had both a baseline and a postbaseline measure: N = 201 for olanzapine and N = 186 for divalproex.
Abbreviations: ANCOVA = analysis of covariance, CGI-BP = Clinical Global Impressions for Bipolar Disorder-Severity of Illness scale, LOCF = last observation carried forward, LS = least-squares, MADRS = Montgomery-Asberg Depression Rating Scale, YMRS = Young Mania Rating Scale.
Symbol: … = not applicable.

divalproex-treated patients (57.0% [106/186]; p = .044, NNT = 11). At the end of study period II, the treatment groups did not significantly differ in the proportion of patients who reached remission (LOCF), with 42.8% (86/201) of olanzapine-treated patients, 40.3% (75/186) of divalproex-treated patients, and 35.4% (35/99) of placebo-treated patients entering remission (olanzapine vs. divalproex: p = .360, NNT = 41; olanzapine vs. placebo: p = .175, NNT = 14; divalproex vs. placebo: p = .519, NNT = 21).

At endpoint of study period II, a subgroup analysis of patients with manic or mixed episode revealed no statistically significant difference between treatments in YMRS total score change from baseline. At endpoint of study

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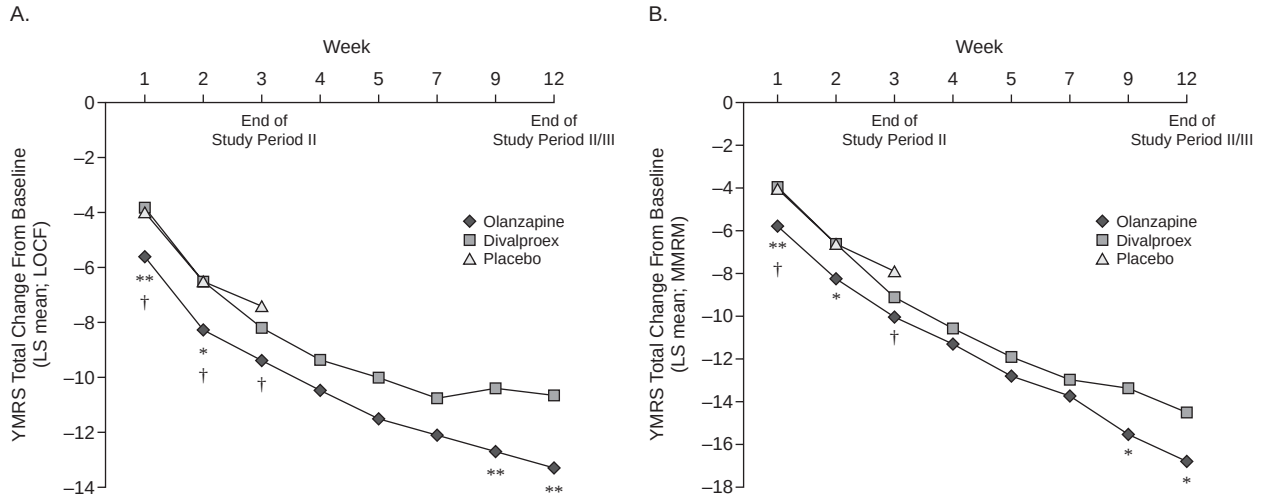
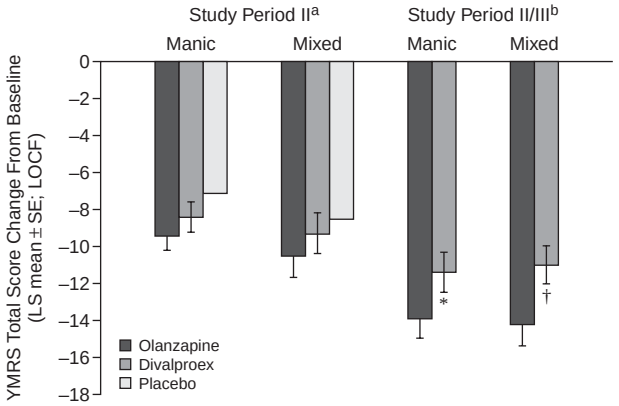
Figure 2. Visitwise Change From Baseline in YMRS Total Score: LOCF ANCOVA Analysis (A)[a] and MMRM Analysis (B)[b]



[a]ANCOVA with missing data imputed by the LOCF (ANCOVA: model = treatment, investigator, and baseline as covariate); olanzapine (5–20 mg/day), N = 201; divalproex (500–2500 mg/day), N = 186; placebo N = 99.
[b]MMRM analysis (terms of treatment, investigator, visit, treatment × visit, and baseline value as covariate, and with unstructured covariance structure); olanzapine, N = 104 to 201; divalproex, N = 89 to 186; placebo, N = 80 to 99.
*p < .05 (olanzapine vs. divalproex).
**p < .01 (olanzapine vs. divalproex).
†p < .05 (olanzapine vs. placebo).
Abbreviations: ANCOVA = analysis of covariance, LOCF = last observation carried forward, LS = least-squares, MMRM = mixed-effects model repeated measures, YMRS = Young Mania Rating Scale.

Figure 3. YMRS Total Score Change from Baseline (LOCF): Mixed/Manic Subgroup Analysis



[a]Study period II—manic: olanzapine, N = 143; divalproex, N = 132; placebo, N = 68; mixed: olanzapine, N = 57; divalproex, N = 54; placebo, N = 30.
[b]Study period II/III—manic: olanzapine, N = 143; divalproex, N = 132; mixed: olanzapine, N = 57; divalproex, N = 54.
*p = .034, effect size: –0.26, olanzapine versus divalproex. ANCOVA: model = treatment, investigator, and baseline as covariate for each subgroup.
†p = .020, effect size: –0.45, olanzapine versus divalproex. ANCOVA: model = treatment, investigator, and baseline as covariate for each subgroup.
Abbreviations: ANCOVA = analysis of covariance, LOCF = last observation carried forward, LS = least-squares, YMRS = Young Mania Rating Scale.

period II/III, olanzapine-treated patients experienced a significantly greater improvement in YMRS total score than divalproex-treated patients in both subgroups (Figure 3).

Valproate Plasma Concentration

A post hoc analysis of the mean divalproex dose and plasma concentration revealed that throughout the study, a large proportion of patients (observed cases) received less than the recommended therapeutic range of valproate (Figure 4A). At the end of study period II (observed cases), 35.4% (35/99) of the divalproex-treated patients had valproate plasma concentrations below the recommended range (mean ± SD dose: 864.3 ± 229.63 mg/day), although significantly more patients had valproate plasma concentrations above/within range (p = .009, 64.6% [64/99], mean ± SD dosage: 1070.3 ± 257.69 mg/day). At the end of study period II/III (observed cases), 57.1% (28/49) of the divalproex-treated patients had valproate plasma concentrations below the therapeutic range (mean ± SD dosage: 1098.2 ± 487.53 mg/day) and fewer patients had valproate plasma concentrations above/within range (p = .547, 42.9% [21/49], mean ± SD dosage: 1272.4 ± 454.46 mg/day; Figure 4A).

At the end of study period II, there were no significant differences in the YMRS total score change from baseline between placebo-treated patients or divalproex-treated patients (observed cases) who had valproate plasma concentrations above/within or below range (post hoc

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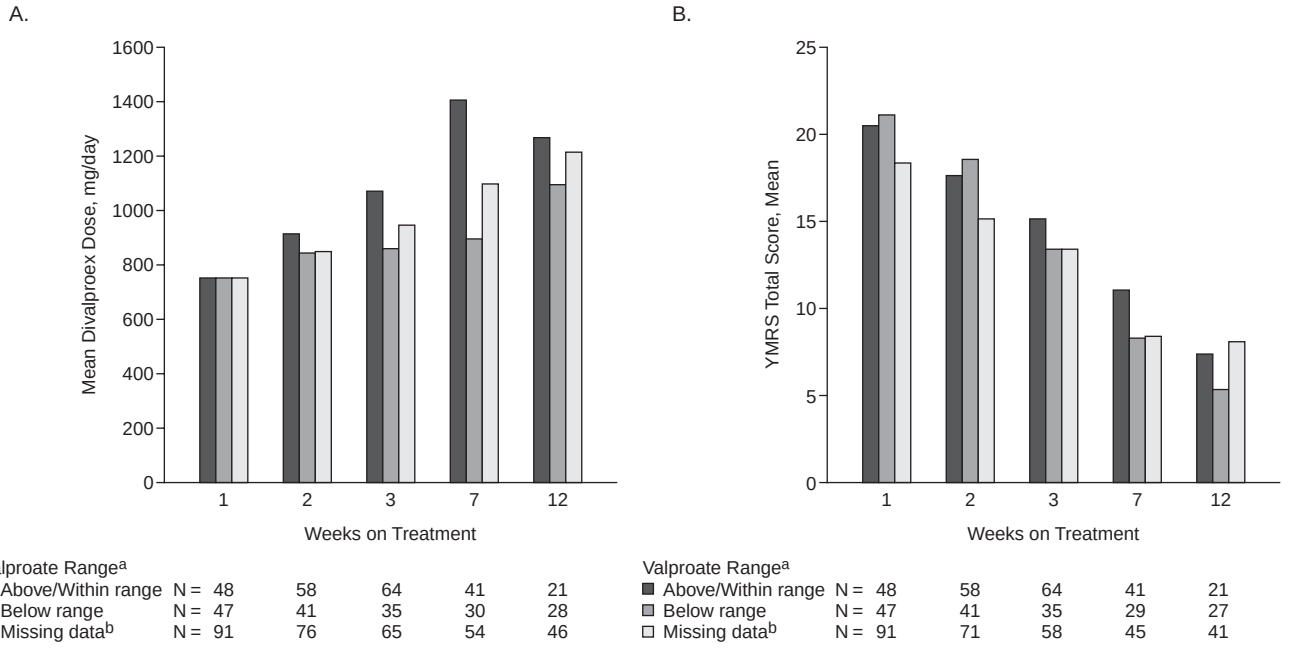
Figure 4. Divalproex Mean Dose (A) and Mean Young Mania Rating Scale (YMRS) Total Score (B) Subgrouped by Valproate Concentration and by Visit (post hoc analysis)



Valproate Range[a]						
Above/Within range	N =	48	58	64	41	21
Below range	N =	47	41	35	30	28
Missing data[b]	N =	91	76	65	54	46

Valproate Range[a]						
Above/Within range	N =	48	58	64	41	21
Below range	N =	47	41	35	29	27
Missing data[b]	N =	91	71	58	45	41

[a]Valproate concentration therapeutic range: 50 to 125 μg/mL.[14]
[b]Missing data refer to blood drawn outside the specified window (8–12 hours after the last dose of divalproex).

analysis, LS mean ± SE: placebo-treated, –7.5 ± 0.83; divalproex-treated, –9.1 ± 1.03 and –9.7 ± 1.36, respectively). Importantly, by the end of study period II/III, patients with valproate concentrations below the therapeutic range had lower YMRS scores than patients with concentrations above/within range, although the difference between groups was not statistically significant (Figure 4B). Accordingly, at the end of study period II/III, YMRS total score change from baseline for divalproex-treated patients with valproate concentrations below range (observed cases) was comparable with that of olanzapine-treated patients (LS mean ± SE: –13.8 ± 1.53 and –13.5 ± 0.75, respectively). At the end of study period II/III, olanzapine-treated patients had a statistically significantly greater change in YMRS total score from baseline compared with divalproex-treated patients (observed cases) with valproate concentrations above/within range (p = .048, LS mean ± SE: –13.5 ± 0.75 and –10.4 ± 1.51, respectively).

At the end of study period II, there was no significant difference in the mean divalproex dose or valproate concentration between the responders and nonresponders or the remitters and nonremitters (post hoc analysis). Likewise, at the end of study period II/III, there was no significant difference in the mean divalproex dose or valproate concentration between the responders and nonresponders. Remitters had a significantly greater mean divalproex dosage than nonremitters at the end of study period II/III (p = .043, mean ± SD: 1165.5 ± 449.7 mg/day and 1054.2 ± 413.6 mg/day, respectively), but the mean valproate concentration did not significantly differ.

Safety

Adverse events. In study period II, 7.4% (16/215) of olanzapine-treated patients, 3.0% (6/201) of divalproex-treated patients, and 1.0% (1/105) of placebo-treated patients discontinued the study because of AEs. In study period II/III, 13.0% (28/215) of olanzapine-treated patients and 9.5% (19/201) of divalproex-treated patients discontinued the study because of AEs. In both study periods, none of the AEs contributed to discontinuations for more than 1 to 2 patients within each treatment group. The treatment groups did not significantly differ in the incidence of AEs that led to discontinuations.

Treatment-emergent AEs that occurred in ≥ 5% of the sample during study period II and study period II/III are listed in Table 3. In study period II, significantly more olanzapine-treated patients than divalproex-treated or placebo-treated patients reported weight increase (vs. divalproex: p = .016, NNH [95% CI] = 21 [10 to 503]; vs. placebo: p = .049, NNH [95% CI] = 17 [9 to 98]) and somnolence (vs. divalproex: p = .004, NNH [95% CI] = 16 [9 to 51]; vs. placebo: p = .045, NNH [95% CI] = 17 [9 to 98]). However, significantly more divalproex-treated

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Table 3. Summary of Treatment-Emergent Adverse Events That Occurred in ≥ 5% of Patients in Either Treatment Group: Study Period II and Study Period II/III

Adverse Event	Olanzapine (N = 215), n (%)	Divalproex (N = 201), n (%)	Placebo (N = 105), n (%)	Olanzapine vs Divalproex, p Value[a]	Olanzapine vs Placebo, p Value[a]	Divalproex vs Placebo, p Value[a]
Study period II						
Dry mouth	12 (5.6)	5 (2.5)	3 (2.9)	.092	.224	.895
Nausea	2 (0.9)	17 (8.5)	3 (2.9)	< .001	.173	.063
Weight increase	19 (8.8)	8 (4.0)	3 (2.9)	.016	.049	.663
Increased appetite	12 (5.6)	11 (5.5)	2 (1.9)	.820	.110	.135
Somnolence	19 (8.8)	5 (2.5)	3 (2.9)	.004	.045	.793
Sedation	12 (5.6)	7 (3.5)	5 (4.8)	.260	.849	.525
Headache	9 (4.2)	18 (9.0)	9 (8.6)	.071	.114	.903
Insomnia	2 (0.9)	11 (5.5)	4 (3.8)	.008	.116	.451
Study period II/III[b]						
Dry mouth	14 (6.5)	7 (3.5)	…	.116	…	…
Diarrhea	4 (1.9)	11 (5.5)	…	.057	…	…
Nausea	3 (1.4)	21 (10.4)	…	< .001	…	…
Vomiting	2 (0.9)	10 (5.0)	…	.022	…	…
Fatigue	13 (6.0)	6 (3.0)	…	.101	…	…
Weight increase	28 (13.0)	12 (6.0)	…	.003	…	…
Increased appetite	17 (7.9)	14 (7.0)	…	.581	…	…
Somnolence	24 (11.2)	8 (4.0)	…	.004	…	…
Sedation	14 (6.5)	8 (4.0)	…	.208	…	…
Headache	16 (7.4)	23 (11.4)	…	.249	…	…
Tremor	4 (1.9)	10 (5.0)	…	.103	…	…
Insomnia	5 (2.3)	13 (6.5)	…	.053	…	…

[a]Cochran-Mantel-Haenszel test by investigator.
[b]Does not include patients randomly assigned to placebo during study period II.
Symbol: … = not applicable.

patients reported nausea and insomnia than olanzapine-treated patients (nausea: p < .001, NNH [95% CI] = 14 [8 to 29]; insomnia: p = .008, NNH [95% CI] = 23 [12 to 88]). In addition to these incidences of significant between-group differences that were also observed into study period II/III, significantly more divalproex-treated patients reported vomiting in study period II/III (p = .022, NNH [95% CI] = 25 [13 to 129]; Table 3). There was no statistically significant between-group difference in the incidence of insomnia in study period II/III.

The incidences of serious AEs for either study period did not statistically differ between treatment groups. In study period II, 5 patients in the olanzapine treatment group (2.3%, 5/215) experienced serious AEs (mania, N = 2; ectopic pregnancy, N = 1; pneumonia, N = 1; suicidal ideation, N = 1), 1 patient in the divalproex group (0.5%, 1/201) reported a serious AE (back pain), and 1 patient in the placebo group (1.0%, 1/105) reported a serious AE (breast cancer). In study period II/III, 7 patients in the olanzapine treatment group (3.3%, 7/215) reported the following serious AEs: mania, N = 2; suicidal ideation, N = 2; bipolar I disorder, N = 1; ectopic pregnancy, N = 1; and pneumonia, N = 1. In the divalproex group, 7 patients (3.5%, 7/201) reported the following serious AEs: mania, N = 2; suicidal ideation, N = 1; alanine aminotransferase increased, N = 1; aspartate aminotransferase increased, N = 1; back pain, N = 1; diarrhea, N = 1; hepatitis toxic, N = 1; sepsis, N = 1; transfusion, N = 1; and vomiting, N = 1.

Metabolic and prolactin changes. From baseline to endpoint of study period II, olanzapine-treated patients had a significantly greater mean weight gain than divalproex-treated patients and placebo-treated patients (both p < .001, olanzapine: 1.3 ± 2.4 kg, divalproex: 0.3 ± 1.9 kg, placebo: 0.4 ± 1.6 kg; Table 4). The incidence of potentially clinically significant weight gain (≥ 7%) from baseline to study period II endpoint was greater in the olanzapine treatment group (olanzapine: 6.4% [13/202]; divalproex: 2.7% [5/188]; placebo: 1.0% [1/100]), but the difference between groups did not reach statistical significance (olanzapine vs. divalproex: p = .064, NNH [95% CI] = 27 [N/A]; olanzapine vs. placebo: p = .056, NNH [95% CI] = 19 [11 to 66]; divalproex vs. placebo: p = .378, NNH [95% CI] = 61 [N/A]). Similarly, from baseline to endpoint of study period II/III, olanzapine-treated patients had a statistically significantly greater mean ± SD weight gain than divalproex-treated patients (p < .001, olanzapine: 2.3 ± 3.8 kg, divalproex: 0.5 ± 2.9 kg; Table 4). The incidence of potentially clinically significant weight gain (≥ 7%) from baseline to study period II/III endpoint was statistically greater in olanzapine-treated patients than divalproex-treated patients (p = .002, NNH [95% CI] = 10 [6 to 28]; 18.8% [38/202] and 8.5% [16/188], respectively).

Statistically significant differences in mean changes at endpoint of study period II were observed between treatment groups for several laboratory measures (Table 4). Particularly, there was a significantly greater increase in

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Table 4. Weight and Laboratory Parameters With a Statistically Significant Change From Baseline to Endpoint: Study Period II and Study Period II/III

Measure	Olanzapine, Mean Change ± SD	Divalproex, Mean Change ± SD	Placebo, Mean Change ± SD	Olanzapine vs Divalproex, p Value[a]	Olanzapine vs Placebo, p Value[a]	Divalproex vs Placebo, p Value[a]
Study Period II[b]						
Weight, kg[c]	1.3 ± 2.4	0.3 ± 1.9	0.4 ± 1.6	< .001	< .001	.776
Fasting GGPT/SGGT/YGGT, U/L	5.3 ± 40.9	–3.4 ± 13.6	–3.2 ± 12.3	.001	.024	.709
Fasting ALT/SGPT, U/L	9.2 ± 30.4	–5.0 ± 16.8	–0.8 ± 13.8	< .001	.001	.052
Fasting AST/SGOT, U/L	4.0 ± 12.1	–2.2 ± 9.8	–1.6 ± 10.5	< .001	< .001	.076
Fasting uric acid, µmol/L	20.4 ± 53.7	8.3 ± 55.4	–1.4 ± 43.4	.022	.001	.193
Fasting glucose, mmol/L	0.1 ± 1.0	–0.2 ± 0.9	–0.1 ± 0.8	< .001	.028	.349
Fasting triglycerides, mmol/L	0.2 ± 1.2	–0.1 ± 0.8	–0.2 ± 0.7	.002	.001	.531
Fasting cholesterol, mmol/L	0.1 ± 0.7	–0.2 ± 0.7	–0.2 ± 0.8	< .001	.009	.174
Prolactin, µg/L	6.5 ± 20.8	–5.7 ± 22.3	–1.8 ± 23.6	< .001	< .001	.211
Fasting total bilirubin, µmol/L	–0.4 ± 3.5	–0.8 ± 3.5	–0.3 ± 3.4	.617	.042	.015
Fasting direct bilirubin, µmol/L	–0.1 ± 0.8	–0.2 ± 0.8	0.0 ± 0.8	.551	.014	.003
Fasting alkaline phosphatase, U/L	1.0 ± 17.3	–6.3 ± 13.7	1.3 ± 16.0	< .001	.632	< .001
Fasting creatinine, µmol/L	–2.0 ± 8.9	–1.8 ± 9.5	0.2 ± 8.9	.916	.026	.033
Fasting calcium, mmol/L	–0.02 ± 0.1	–0.02 ± 0.1	0.01 ± 0.1	.236	.007	< .001
Fasting albumin, g/L	–1.2 ± 3.4	–1.3 ± 2.9	0.3 ± 2.9	.735	< .001	< .001
Hemoglobin, mmol/L (Fe)	–0.2 ± 0.4	–0.1 ± 0.5	–0.1 ± 0.5	.010	.020	.864
Leukocytes (WBC) × 10^9/L	0.1 ± 2.2	–0.1 ± 1.9	–0.1 ± 1.5	.216	.154	.694
Platelets × 10^9/L	4.0 ± 43.2	–26.4 ± 51.6	–3.2 ± 55.7	< .001	.174	< .001
Study Period II/III[d]						
Weight, kg[e]	2.3 ± 3.8	0.5 ± 2.9	…	< .001	…	…
Fasting GGPT/SGGT/YGGT, U/L	3.3 ± 43.7	–0.7 ± 35.1	…	.184	…	…
Fasting ALT/SGPT, U/L	6.1 ± 32.5	17.4 ± 173.5	…	.273	…	…
Fasting uric acid, µmol/L	20.7 ± 62.3	7.7 ± 47.7	…	.027	…	…
Fasting glucose, mmol/L	0.3 ± 1.1	–0.1 ± 0.9	…	< .001	…	…
Fasting triglycerides, mmol/L	0.3 ± 1.4	–0.1 ± 0.9	…	.003	…	…
Fasting cholesterol, mmol/L	–0.02 ± 0.9	–0.2 ± 0.8	…	.024	…	…
Prolactin, µg/L	2.8 ± 23.5	–5.3 ± 23.9	…	< .001	…	…
Fasting potassium, mmol/L	–0.1 ± 0.4	0.02 ± 0.6	…	.016	…	…
Fasting alkaline phosphatase, U/L	1.0 ± 19.0	–5.9 ± 24.4	…	< .001	…	…
Hemoglobin, mmol/L (Fe)	–0.1 ± 0.5	–0.04 ± 0.6	…	.687	…	…
Leukocytes (WBC) × 10^9/L	0.002 ± 2.0	–0.3 ± 2.0	…	.044	…	…
Platelets × 10^9/L	–5.5 ± 47.0	–26.6 ± 58.2	…	< .001	…	…

[a]ANCOVA: model = treatment, investigator, and baseline as covariate.
[b]Unless otherwise noted, numbers of patients are as follows: olanzapine, N = 196; divalproex, N = 185; placebo, N = 95.
[c]Olanzapine, N = 202; divalproex, N = 188; placebo, N = 100.
[d]Does not include patients randomly assigned to placebo during study period II; unless otherwise noted, numbers are as follows: olanzapine, N = 196; divalproex, N = 187 (includes 2 patients who were missing fasting chemistry laboratory values during study period II).
[e]Olanzapine, N = 202; divalproex, N = 188.
Abbreviations: ALT/SGPT = alanine transaminase/serum glutamic pyruvic transaminase, ANCOVA = analysis of covariance, AST/SGOT = aspartate transaminase/serum glutamic oxaloacetic transaminase, GGPT/SGGT/YGGT = γ-glutamyltransferase, WBC = white blood cell.
Symbol: … = not applicable.

fasting uric acid, fasting glucose, fasting triglycerides, fasting cholesterol, and prolactin in olanzapine-treated patients compared with divalproex- and placebo-treated patients ($p < .001$ to $p = .028$). Also as shown in Table 4, there were statistically significant mean changes in bilirubin, alkaline phosphatase, creatinine, calcium, albumin, and potassium. Compared with divalproex-treated patients, olanzapine-treated patients had a significantly greater incidence of potentially clinically significant changes in fasting triglycerides from normal to high ($p = .019$, NNH [95% CI] = 13 [7 to 85]). For other metabolic parameters, there were no significant differences in the incidence of patients with treatment-emergent increases that changed from normal or borderline to high values (Table 5).

Likewise, in study period II/III, olanzapine-treated patients compared with divalproex-treated patients had a significantly greater increase in fasting uric acid, fasting glucose, fasting triglycerides, and prolactin ($p < .001$ to $p = .027$; Table 4). Compared with divalproex-treated patients, olanzapine-treated patients had a significantly greater incidence of changes in fasting glucose from normal to high ($p = .040$, NNH [95% CI] = 22 [12 to 266]), impaired to high ($p = .029$, NNH [95% CI] = 10 [N/A]), and normal/impaired to high ($p = .022$, NNH [95% CI] = 16 [9 to 87]; Table 5). The groups also significantly differed in the incidence of treatment-emergent changes from normal to high cholesterol ($p = .011$, NNH [95% CI] = 19 [10 to 125]), borderline to high cholesterol ($p = .022$, NNH [95% CI] = 5 [3 to 13]), normal to high triglycerides ($p = .001$, NNH [95% CI] = 7 [5 to 15]), and borderline to high triglycerides ($p = .038$, NNH [95% CI] = 4 [2 to 23]); the higher incidents were with the olanzapine treatment (Table 5).

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Table 5. Summary of Treatment-Emergent Potentially Clinically Significant Changes in Weight Gain, Fasting Blood Glucose, and Lipids[a]: Study Period II and Study Period II/III[b]

	Study Period II						Study Period II/III				
	Olanzapine		Divalproex		Placebo		Olanzapine		Divalproex		
Variable	N[c]	n (%)	N[c]	n (%)	N[c]	n (%)	N[c]	n (%)	N[c]	n (%)	p Value[d]
Weight gain ≥ 7% from baseline	202	13 (6.4)	188	5 (2.7)	100	1 (1.0)	202	38 (18.8)	188	16 (8.5)	.002
Fasting glucose											
Normal to high: < 100 to ≥ 126 mg/dL	127	5 (3.9)	118	1 (0.8)	58	1 (1.7)	127	7 (5.5)	119	1 (0.8)	.040
Impaired to high:											
≥ 100 and < 126 mg/dL to ≥ 126 mg/dL	57	9 (15.8)	58	5 (8.6)	32	4 (12.5)	57	12 (21.1)	59	6 (10.2)	.029
Normal/impaired to high:											
< 126 to ≥ 126 mg/dL	184	14 (7.6)	176	6 (3.4)	90	5 (5.6)	184	19 (10.3)	178	7 (3.9)	.022
Fasting total cholesterol											
Normal to borderline:											
< 200 to ≥ 200 mg/dL and < 240 mg/dL	92	17 (18.5)	97	11 (11.3)	49	7 (14.3)	92	23 (25.0)	98	21 (21.4)	.851
Normal to high: < 200 to ≥ 240 mg/dL	92	2 (2.2)	97	0 (0.0)	49	1 (2.0)	92	5 (5.4)	98	0 (0.0)	.011
Borderline to high:											
≥ 200 and < 240 mg/dL to ≥ 240 mg/dL	61	12 (19.7)	57	3 (5.3)	19	3 (15.8)	61	21 (34.4)	58	7 (12.1)	.022
Fasting triglycerides											
Normal to borderline:											
< 150 to ≥ 150 mg/dL and < 200 mg/dL	122	20 (16.4)	110	15 (13.6)	58	10 (17.2)	122	26 (21.3)	111	22 (19.8)	.849
Normal to high: < 150 to ≥ 200 mg/dL	122	14 (11.5)[e]	110	4 (3.6)	58	4 (6.9)	122	25 (20.5)	111	6 (5.4)	.001
Normal to extreme high:											
< 150 to ≥ 500 mg/dL	…	0 (0.0)	…	0 (0.0)	…	0 (0.0)	122	0 (0.0)	111	0 (0.0)	…
Borderline to high:											
≥ 150 and < 200 mg/dL to ≥ 200 mg/dL	37	15 (40.5)	29	8 (27.6)	17	5 (29.4)	37	25 (67.6)	30	12 (40.0)	.038
Borderline to extreme high:											
≥ 150 and < 200 mg/dL to ≥ 500 mg/dL	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	37	2 (5.4)	30	0 (0.0)	.286

[a]American Diabetes Association (ADA)[21] and National Cholesterol Education Program (NCEP)[20] criteria were used for analyses.
[b]Does not include patients randomly assigned to placebo during study period II.
[c]Patients with at least 1 baseline and corresponding treatment period value who met the given criteria at baseline.
[d]Cochran-Mantel-Haenszel test by investigator.
[e]p = .019 vs. divalproex (Cochran-Mantel-Haenszel test by investigator). No statistically significant differences for all other comparisons.
Symbol: … = not applicable.

Hematologic changes. Statistically significant differences in mean changes at endpoint of study period II and II/III were observed between treatment groups for several hematologic measures (Table 4). At endpoint of study period II, divalproex-treated patients had a significantly greater mean decrease in platelets than olanzapine- and placebo-treated patients ($p < .001$ for both). Olanzapine-treated patients had a significantly greater mean decrease in hemoglobin than divalproex- and placebo-treated patients ($p \leq .020$ for both). At endpoint of study period II/III, divalproex-treated patients had a significantly greater mean decrease in leukocytes and platelets than olanzapine-treated patients ($p = .044$ and $p < .001$, respectively; Table 4).

Vital signs, electrocardiograms, and extrapyramidal symptoms. In study period II, divalproex-treated patients had a significantly greater incidence of a change from normal to low supine systolic blood pressure compared with olanzapine-treated patients ($p = .048$, 1.6% [3/184] and 0% [0/201], respectively). In study period II/III, olanzapine-treated patients had a significantly greater incidence of patients who were normal at baseline and reported orthostatic hypotension at least once during study period II/III compared with divalproex-treated patients ($p = .029$, NNH [95% CI] = 26 [N/A], 6.1% [12/198] and 2.2% [4/184], respectively). No statistically significant differences were observed between treatment groups in the incidence of changes from normal to abnormal in any other vital sign for study period II or II/III.

The incidence of treatment-emergent potentially clinically significant changes from baseline in electrocardiogram interval or heart rate did not statistically differ between treatment groups for study period II or II/III.

Evaluating extrapyramidal symptoms with the Barnes Akathisia Scale revealed no statistical difference between treatment groups in the change of global score from baseline to endpoint of study period II or II/III. When extrapyramidal symptoms were evaluated with the Simpson-Angus Scale, there were no statistical differences between groups for study period II; however, there was a statistically significant difference in the mean change from baseline at endpoint of study period II/III. Olanzapine-treated patients had a mean ± SD change of 0.0 ± 1.34, and divalproex-treated patients had a mean ± SD change of -0.1 ± 0.73 ($p = .035$). For the Abnormal Involuntary Movement Scale, placebo-treated patients had a significantly greater mean ± SD change from baseline than olanzapine-treated patients ($p = .037$; 0.1 ± 0.75 and -0.1 ± 0.81, respectively). No other changes were statistically different between groups.

Hepatic enzymes. At endpoint of study period II, but not study period II/III, there was a significantly greater

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increase in fasting γ-glutamyltransferase, alanine transaminase/serum glutamic pyruvic transaminase, and aspartate transaminase/serum glutamic oxaloacetic transaminase in olanzapine-treated patients compared with divalproex- and placebo-treated patients (Table 4).

DISCUSSION

There was no significant difference in efficacy between olanzapine and divalproex at 3 weeks (the primary efficacy variable). Olanzapine was significantly more efficacious than placebo in patients with mild to moderate bipolar mania. There was, however, no significant difference in efficacy between divalproex and placebo at 3 weeks, although the direction and numerical size of the effect were comparable with those of olanzapine compared with placebo. After 12 weeks of double-blind treatment, olanzapine treatment was significantly more effective than divalproex, irrespective of whether this sample was grouped into manic or mixed episode (Table 2 and Figure 3). Statistically speaking, the study appeared to be of limited power to detect the apparent small difference in treatment effects between divalproex and olanzapine.

Mackin et al.[22] have suggested that the cultural background of the clinician may influence YMRS rating. In the present study, regional differences in YMRS scores were found at endpoint of study period II. However, the lack of treatment-by-region interaction suggests that the treatment effects were similar within each region.

To explain the apparent lack of efficacy of divalproex compared with placebo at the end of study period II (primary efficacy variable), post hoc analyses were conducted to evaluate the likelihood that diminished efficacy was associated with mean valproate plasma concentration below the recommended range (50–125 μg/mL).[14] At the end of study period II (observed cases), 35.4% (35/99) of the divalproex-treated patients had valproate plasma concentrations below this range, although significantly more patients had valproate plasma concentrations above/within range ($p = .009$, 64.6% [64/99]). At the end of study period II/III (observed cases), 57.1% (28/49) of the divalproex-treated patients had valproate plasma concentrations below the therapeutic range (Figure 4A). A limitation of the present study was the amount of missing data on divalproex dosing (Figure 4). In part, the missing data were a consequence of blood drawn outside the specified window (8–12 hours after the last dose of divalproex).

The daily dose of divalproex was adjusted upward or downward on the basis of the following protocol-defined criteria: (1) as clinically indicated, (2) to maintain valproate plasma concentrations within the recommended range of 50 to 125 μg/mL,[14] and (3) within approved labeling dosages.[14] It is possible that on the basis of these criteria, if patients were doing better, site investigators were not likely to increase the dose and therefore resulted in lower plasma concentrations of valproate.

Compared with patients with valproate plasma concentrations above/within the recommended range, patients with lower valproate plasma concentrations experienced greater reductions in YMRS total score from baseline to endpoint of both study periods (LS mean: study period II, –9.1 vs. –9.7, respectively; study period II/III, –10.4 vs. –13.8, respectively). These findings suggest that the numerically higher valproate plasma concentrations did not directly result in greater reductions in YMRS scores. In addition, these efficacy findings, along with the finding that the valproate plasma concentrations did not significantly differ between responders and nonresponders and remitters and nonremitters, suggest that site investigators predominantly dosed divalproex on the basis of the clinical presentation. It is also possible that tolerability influenced dosing. These findings suggest but do not prove that the lack of divalproex response was not necessarily caused by divalproex underdosing. It should be mentioned, however, that a study by Keck et al.[23] reported better outcomes in patients with medium therapeutic levels (75–99.9 μg/mL) of valproate compared with other therapeutic levels. The findings of Keck et al.,[23] however, may not be comparable with our findings because the populations were different. Keck et al.[23] evaluated patients with moderate to severe mania (Mania Rating Scale[24] ≤ 11) while the present study evaluated patients with mild to moderate mania.

An important finding of potential value for future clinical trial design is that the response to active treatment and to placebo in patients with mild to moderate mania may not be as robust as in patients with severe mania. Thus, approximately 40% of the patients treated with either olanzapine or divalproex responded to treatment, compared with an approximately 50% response rate reported for both compounds in patients with severe mania.[1,2,4] The response rate in placebo-treated patients was 31%, which was higher than the 24% to 25% placebo response for both compounds reported by Tohen et al.[4] and Bowden et al.,[1] but lower than the 43% placebo response reported in a second olanzapine placebo-controlled trial.[3]

In fact, a previous study reported that a low baseline on the Manic Syndrome Scale (a subscale of the Schedule for Affective Disorders and Schizophrenia-change version Mania Rating Scale) predicted a smaller difference from placebo after treatment.[24] This was, however, a post hoc analysis from a randomized, double-blind study of patients with bipolar mania (N = 377) who were treated with divalproex extended release or placebo. The authors concluded that enrolling patients with mild to moderate manic symptoms was likely to yield equivocal improvement and make it difficult to identify divalproex-placebo differences (placebo response was within range for acute mania).[24] The small effect sizes and large NNTs for both

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olanzapine and divalproex in the present study suggest only modest efficacy but may also be explained by a larger placebo response in less severely ill patients.

The findings from the present study confirm the suggestion that inclusion of milder manic states will reduce assay sensitivity and should be considered in designing future trials in patients with mild bipolar mania. Investigators should not assume that differences with placebo or between active treatments are similar in severe mania and in mild or moderate mania.

The safety of olanzapine and divalproex was consistent with the known safety profiles of the drugs (Tables 3–5).[1,3–6,14,15,24] Compared with olanzapine-treated patients, significantly more divalproex-treated patients reported nausea and insomnia in study period II and nausea and vomiting in study period II/III. Significantly more olanzapine-treated patients than divalproex-treated reported weight increase and somnolence in study period II or study period II/III (Table 4). During study period II, there was a significantly greater increase in fasting uric acid, fasting glucose, fasting triglycerides, fasting cholesterol, and prolactin in olanzapine-treated patients compared with divalproex-treated patients or placebo-treated patients. During study period II/III, olanzapine-treated patients compared with divalproex-treated patients experienced significantly greater increases in fasting uric acid, fasting glucose, fasting triglycerides, fasting cholesterol, and prolactin. The incidence of potentially clinically significant weight gain (≥ 7%) from baseline to the end of 12 weeks was significantly greater in olanzapine-treated patients than divalproex-treated patients. After 3 weeks of treatment, olanzapine-treated patients had a significantly greater incidence of potentially clinically significant changes in fasting triglycerides from normal to high compared with divalproex-treated patients. Also after 3 weeks of treatment, divalproex-treated patients had a significantly greater mean decrease in platelets than olanzapine-treated patients. After 12 weeks of treatment, compared with divalproex-treated patients, olanzapine-treated patients had a significantly greater incidence of potentially clinically significant abnormal changes in fasting glucose, cholesterol, and triglycerides (Table 5). Another finding after 12 weeks of treatment was that divalproex-treated patients had a significantly greater mean decrease in leukocytes and platelets than olanzapine-treated patients (Table 4).

CONCLUSIONS

There was no statistical difference on the primary efficacy measure between olanzapine and divalproex or divalproex and placebo at 3 weeks. Olanzapine was significantly more efficacious than placebo at 3 weeks and significantly more efficacious than divalproex at 12 weeks. It is possible, however, that the lack of separation between divalproex and placebo (and superiority of olanzapine over divalproex at 12 weeks) may be explained by the low valproate plasma concentrations.

The safety profiles were similar to what had been previously reported. Olanzapine-treated patients experienced a significantly greater incidence of treatment-emergent weight gain and significantly greater increases in weight, glucose, cholesterol, triglycerides, uric acid, and prolactin at the end of 12 weeks compared with patients treated with divalproex. In patients treated with divalproex, there was a significantly greater incidence of treatment-emergent nausea and vomiting, and significantly greater abnormal changes in some hematologic measures after 12 weeks compared with patients treated with olanzapine.

Clinicians and investigators should not assume that response to treatment or to placebo will be the same in mild to moderate mania as in severe mania. Our findings indicate that the response is smaller in magnitude for both active drug and placebo. These findings have important implications both in clinical practice and in clinical trial design.

Drug names: benztropine (Cogentin and others), biperiden (Akineton), divalproex (Depakote), lorazepam (Ativan and others), olanzapine (Zyprexa).

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