A Comparison of the Efficacy, Safety, and Tolerability of Divalproex Sodium and Olanzapine in the Treatment of Bipolar Disorder

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Background: This study compared the efficacy, safety, and tolerability of divalproex and olanzapine in the treatment of acute mania associated with bipolar disorder.

Method: This randomized, 12-week, double-blind, parallel-group, multicenter study included DSM-IV–defined bipolar disorder type I patients hospitalized for acute mania and randomly assigned to treatment with divalproex or olanzapine. After an inpatient period of up to 21 days, subjects were followed as outpatients. Dose adjustment was permitted during the inpatient period. Efficacy was assessed using change from baseline in Mania Rating Scale (MRS) score to day 21; other efficacy measures included the Brief Psychiatric Rating Scale, the Hamilton Rating Scale for Depression, and the Clinical Global Impressions-Part I, Severity of Illness scale. The primary safety endpoint was change from baseline in weight. Other safety and tolerability endpoints included spontaneous adverse event reporting and changes from baseline in laboratory measures and vital signs.

Results: 120 subjects (N = 63 divalproex, N = 57 olanzapine) were randomly assigned to treatment. No significant differences between groups were found for any efficacy variable for change from baseline to day 21. Mean MRS score changes from baseline to day 21 were –14.8 for divalproex and –17.2 for olanzapine ($p = .210$). A significantly ($p < .05$) greater proportion of olanzapine-treated subjects experienced somnolence, weight gain, edema, rhinitis, and speech disorder (slurred speech); no adverse events were significantly greater in the divalproex group. A number of laboratory measures also demonstrated significant treatment differences, but the clinical significance of many of these is uncertain. Mean body weight changes were significantly greater in the olanzapine group (+ 8.8 lb [+ 4.0 kg]) than the divalproex group (+ 5.5 lb [+ 2.5 kg], $p < .050$). One death occurred during the study (olanzapine group, diabetic ketoacidosis).

Conclusion: No significant difference in efficacy was found between treatment groups. Divalproex was associated with a more favorable adverse event profile and significantly less weight gain than olanzapine.

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Bipolar disorder is a chronic, cyclic disorder affecting approximately 1% of the population.[1,2] Manic episodes can be particularly disruptive to the lives of bipolar patients; however, substantial strides have been made toward improvement of pharmacologic treatment of bipolar mania.

Divalproex is a mood stabilizer that was approved in 1995 for the treatment of acute mania associated with bipolar disorder. Although the exact mechanism of action is not known, divalproex appears to act by increasing activity of γ-aminobutyric acid in the brain and suppressing repetitive neuronal firing through inhibition of voltage-sensitive sodium channels. Clinical trials have demonstrated the safety and efficacy of divalproex for treating acute mania.[3–5]

Olanzapine is an atypical antipsychotic agent that may antagonize several receptor types, including dopamine D_1, D_2, and D_4; histamine H_1; muscarinic M_1; serotonin 5-HT_{2C}, 5-HT_6, and 5-HT_7; and α_1-noradrenergic.[6,7] The efficacy and safety of olanzapine in treating mania have recently been established[8–10]; olanzapine was approved in 2000 for treatment of acute manic episodes associated with bipolar disorder.

Data have been presented from a previous study by Tohen et al.[11] that compared the use of divalproex and olanzapine in acute mania. In that study, divalproex and olanzapine were provided to hospitalized patients under a flexible-dosing regimen; the results suggested that the

efficacy of olanzapine was superior to that of divalproex. However, the divalproex dosages used were lower than those used in other trials.[12]

The present study was designed to evaluate the acute efficacy and long-term safety and tolerability of divalproex in comparison with olanzapine in a controlled clinical trial, using divalproex and olanzapine doses that approximate clinical practice for inpatients with acute mania. The study involved an initial inpatient phase of up to 21 days, followed by outpatient treatment and evaluation, for a total treatment period of 12 weeks. Consistent with typical clinical practice to titrate dosage to stabilize symptoms and minimize side effects as rapidly as possible,[12–14] dosage adjustment was permitted as needed to stabilize clinical symptoms of mania.

Efficacy was evaluated at the end of the initial 21-day inpatient period (or at discharge), using standardized assessments relevant to acute mania. Longer-term safety and tolerability were evaluated over the full 12-week treatment period. The primary safety measure was change in body weight; other safety measures included spontaneously reported adverse events and changes from baseline in laboratory measures and vital signs.

METHOD

This randomized, double-blind, parallel-group study was conducted at 21 centers. The study consisted of a screening period (1–3 days) and a double-blind period (12 weeks), including an initial inpatient period of up to 21 days. Prior to study participation and after complete description of the study, written informed consent was obtained from each subject. During the screening period, a physical examination was performed and medical and psychiatric histories were obtained for each subject; baseline assessments were made of vital signs, clinical laboratory parameters, and body weight; concomitant medications were recorded; and psychoactive medications were discontinued. The following assessments were also performed: Structured Clinical Interview for DSM-IV[15]; Schedule for Affective Disorders and Schizophrenia-Change Version (SADS-C), including the Mania Rating Scale (MRS)[16]; Brief Psychiatric Rating Scale (BPRS)[17]; Hamilton Rating Scale for Depression (HAM-D)[18]; and Clinical Global Impressions-Part I, Severity of Illness scale (CGI-S).[19] Additionally, movement rating scales, including the Simpson-Angus Scale[20] and the Barnes Akathisia Scale (BAS),[21] were administered.

Patients with the following conditions were excluded from the study: Axis I or II disorder that would interfere with compliance in the study, any unstable medical condition or required use of a medication that would interfere with the evaluation of the compounds being studied, drug or alcohol withdrawal symptoms, platelet count of $< 100{,}000$ mm^3, women who were pregnant or planning to become pregnant, or a mood disorder secondary to a medical condition. Subjects with previously failed trials of either divalproex sodium or olanzapine (in the opinion of the investigator) were also excluded.

To be randomly assigned to treatment, subjects also had to be between 18 and 65 years of age, have a DSM-IV primary diagnosis of bipolar disorder type I, and be hospitalized for an acute manic episode (defined as a score of ≥ 25 on the SADS-C MRS, with at least 4 scale items rated ≥ 3). Subjects were randomly assigned to receive either divalproex or olanzapine, in a 1:1 ratio, as part of a double-dummy design. Initial medication dosages were 20 mg/kg/day (divalproex delayed-release tablets) and 10 mg/day (olanzapine); both drugs were administered twice daily.

Typical clinical practice for patients hospitalized with acute mania is to rapidly titrate medication dosage to the level necessary to eliminate clinical symptoms of mania.[12–14] Therefore, dosage increases were permitted (by 500 mg/day for divalproex and 5 mg/day for olanzapine) on days 3 and 6 if clinical symptoms of mania persisted. The maximum allowed dosages were 20 mg/kg/day + 1000 mg (divalproex) and 20 mg/day (olanzapine). For the purposes of this study, divalproex sodium and olanzapine were expected to have equivalent efficacy at the protocol-specified doses.

Efficacy was measured by administering the MRS (on days 3, 5, 7, 10, 14, 21, 28, 42, 56, 70, and 84), BPRS (on days 3, 5, 7, 14, 21, 28, 42, 56, 70, and 84), HAM-D (on days 7, 14, 21, 28, 42, 56, 70, and 84), and CGI-S (on days 3, 7, 14, 21, 28, 42, 56, 70, and 84). Subjects meeting improvement criteria on or before day 21 (SADS-C MRS score reduced ≥ 30% from the last day of the screening period, with no SADS-C item score > 3, and discharge recommended by the investigator) were discharged from the hospital and were followed as outpatients for the remainder of the study. Subjects not qualifying for discharge by day 21 were discontinued from the study.

Per the protocol instructions, body weight measurements were obtained by the same technician, using the same scale, during the screening period and on days 3, 5, 7, 14, 21, 28, 42, 56, 70, and 84. Body weight was measured with the subject lightly dressed, without shoes; changes were assessed by comparing baseline measurements with body weight at the final evaluation.

Adverse events were monitored by spontaneous reporting of new-onset events throughout the study, and vital signs were obtained during the screening period and on days 7, 14, 21, 28, 42, 56, 70, and 84.

Routine clinical laboratory evaluations, including hematology (white blood cell count/differential, red blood cell count, hemoglobin, hematocrit, platelet count) and detailed blood chemistry (complete lipid profile, glucose, serum glutamic-oxaloacetic transaminase [SGOT], serum glutamate pyruvate transaminase [SGPT], lactate dehydrogenase [LDH], alkaline phosphatase, bilirubin, blood

urea nitrogen, creatinine, uric acid, albumin, total protein, phosphorus, calcium, electrolytes) were performed during the screening period and on the final day of evaluation. The Simpson-Angus Scale and BAS were administered on days 3, 5, 7, 14, 21, 28, 42, 56, 70, and 84.

To assess total valproate levels, serum samples were obtained on the mornings of days 3, 6, and 10, prior to eating and within an hour prior to the morning administration of medication. Results were reported to a qualified unblinded associate, who then advised an investigator to reduce the number of divalproex tablets taken by any subject with a serum valproate level ≥ 125 μg/mL. To preserve the study blind, the unblinded associate concurrently advised that the number of placebo tablets taken by a subject randomly assigned to receive olanzapine also be reduced.

Investigators could prescribe rescue medications, including lorazepam, benztropine mesylate, chloral hydrate, and zolpidem, as adjunctive therapy. Lorazepam was allowed in single doses up to 3 mg/dose, but not exceeding 4 mg/day from days 1 through 7, 3 mg/day from days 8 through 14, and 2 mg/day from day 15 through the end of the study. Benztropine mesylate was permitted in single doses up to 2 mg/dose, but not exceeding 4 mg/day. Chloral hydrate use was allowed in single doses up to 1 g/dose, but not exceeding 3 g/day. Zolpidem was permitted in dosages up to 10 mg/day. Chloral hydrate and zolpidem were not to be administered concurrently. Adjunctive therapy was not to be administered within 8 hours prior to efficacy ratings.

The primary efficacy timepoint was 21 days of treatment (the traditional length for trials of psychotropic medications); change in MRS score from baseline to the day-21 evaluation (or final evaluation if prior to day 21) was measured. Raters were trained in the use of the MRS prior to the start of the study, and each subject was evaluated by the same rater throughout the study. The sample size used for this study (described below) provided for an 80% power to detect a 5-point difference (effect size = 0.51) in change in MRS score (which can range from 0–52) between groups. Other efficacy variables included changes from baseline to day 21 (or final evaluation if prior to day 21) for the BPRS, HAM-D, and CGI-S and change from baseline at each visit up to day 84 for the MRS, with the last observation carried forward. Treatment differences were evaluated by 2-way analysis of variance (ANOVA), with factors for treatment and investigator. Analyses were also performed with baseline as a covariate. To control for effects of somnolence, treatment differences for change in MRS were assessed in a post hoc analysis by 2-way ANOVA, with factors for treatment and presence or absence of somnolence as an adverse event. All tests were 2-tailed at the p = .050 level of significance. Efficacy analyses were performed on the intent-to-treat dataset, which included all subjects receiving at least 1 dose of randomized study medication with both a baseline and an on-treatment MRS score.

Table 1. Summary of Demographic Characteristics

Characteristic	Divalproex (N = 63)	Olanzapine (N = 57)	Total (N = 120)	p Value
Gender, N (%)				
Female	28 (44)	27 (47)	55 (46)	.855
Male	35 (56)	30 (53)	65 (54)	
Race, N (%)				
Asian/Pacific Islander	2 (3)	1 (2)	3 (3)	.294
White	50 (79)	40 (70)	90 (75)	
Black	8 (13)	14 (25)	22 (18)	
Other	3 (5)	2 (4)	5 (4)	
Age, mean ± SD, y	38.9 ± 12.1	38.1 ± 12.2	38.5 ± 12.1	.709[a]
Height, mean ± SD, in	67.4 ± 4.3	67.3 ± 4.1	67.3 ± 4.2	.864[b]
Weight, mean ± SD, lb	181.2 ± 42.3	183.3 ± 45.2	182.2 ± 43.5	.786[c]

[a]F = 0.14, df = 1,118.
[b]F = 0.03, df = 1,115.
[c]F = 0.07, df = 1,118.

Safety and tolerability were assessed over the entire 12 weeks (84 days) of the study. Safety was evaluated using incidence rates for adverse events, as well as change from baseline to the final evaluation in laboratory values, vital signs, movement rating scale scores, and body weight. The sample size for the study was chosen so that a 2-sided test with a significance level of .05 would have 80% power to detect a 5-lb (2.3-kg) difference (effect size = 0.71) in body weight between treatment groups for a sample size of 30 completers per group. For all laboratory measurements (vital signs, safety endpoints), 1-way ANOVAs were performed at the p = .050 level of significance. The Fisher exact test was used to compare incidence of treatment-emergent adverse events between groups. Safety analyses included subjects receiving at least 1 dose of randomized study medication.

RESULTS

One hundred twenty subjects were randomly assigned to receive study drug (N = 63 divalproex, N = 57 olanzapine). No significant differences existed between treatment groups at baseline for age, weight, height, race, or gender (Table 1). No significant differences between groups were noted for the proportion of subjects meeting DSM-IV criteria for mixed mania (divalproex, N = 31 [49%]; olanzapine, N = 26 [46%]) or rapid cycling (divalproex, N = 19 [30%]; olanzapine, N = 16 [28%]).

Mean duration of study drug exposure was 39.9 days for divalproex and 45.1 days for olanzapine. Mean maximum daily drug dosages were 2115 mg (range, 750–3250 mg) for divalproex and 14.7 mg (range, 5–25 mg) for olanzapine. No significant difference between treatment groups existed with regard to the use of rescue medications.

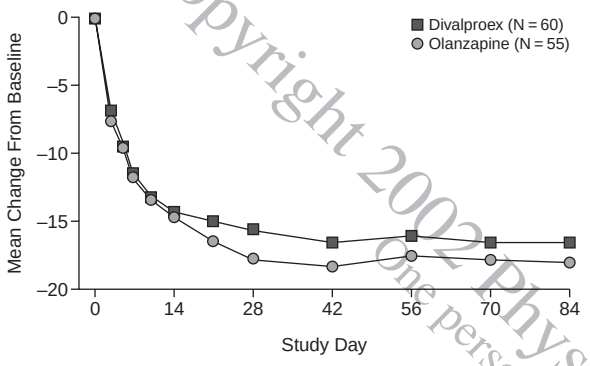
A mean total valproate concentration of 84.6 ± 36.8 μg/mL (N = 61) was observed at the final visit (up to 84 days). For day 3, the mean total valproate concentration was 77.9 ± 25.4 μg/mL (N = 57), rising to 97.1 ± 23.3

Table 2. Reasons for Premature Discontinuation, N (%)[a]

Reason	Divalproex (N = 63)	Olanzapine (N = 57)	p Value
Adverse events	7 (11)	5 (9)	.766
Lack of efficacy	14 (22)	11 (19)	.823
Lost to follow-up	7 (11)	9 (16)	.592
Noncompliance	4 (6)	2 (4)	.682
Other	13 (21)	11 (19)	> .999
Total	45 (71)	38 (67)	.693

[a]Prior to study day 84.

Figure 1. Mean Change in MRS Score From Baseline to Each Evaluation With Baseline as a Covariate (LOCF)[a]



[a]The difference between groups in change in MRS score was not statistically significant. Abbreviations: LOCF = last observation carried forward, MRS = Mania Rating Scale.

Table 3. Mean Change From Baseline to Day 21 (LOCF) for Psychiatric Rating Scales[a]

Scale	Divalproex	Olanzapine	Statistic F	df	p
MRS[b]					
N	60	55			
Baseline	30.8	32.3	4.09	1,95	.046[c]
Change from baseline	–14.8	–17.2	1.60	1,95	.210
MRS[d]					
N	60	55			
Baseline	30.8	32.3	4.09	1,95	.046[c]
Change from baseline	–14.9	–16.6	0.82	1,94	.368
BPRS[d,e]					
N	59	54			
Baseline	24.8	25.8	0.36	1,94	.553
Change from baseline	–8.1	–10.2	1.08	1,93	.302
HAM-D[d,f]					
N	56	53			
Baseline	14.9	15.1	0.02	1,89	.878
Change from baseline	–6.7	–8.1	1.51	1,88	.222
CGI-S[d]					
N	59	54			
Baseline	4.5	4.6	0.13	1,93	.562
Change from baseline	–0.8	–1.0	0.60	1,92	.439

[a]Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Part I, Severity of Illness scale, HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward, MRS = Mania Rating Scale.
[b]Analysis of variance.
[c]Statistically significant difference.
[d]Analysis of covariance.
[e]Includes items 1 through 18.
[f]Includes items 1 through 21.

μg/mL (N = 55) and 101.2 ± 27.1 μg/mL (N = 43) on days 6 and 10, respectively.

Prior to day 21, 24 divalproex-treated subjects (38%) and 18 olanzapine-treated subjects (32%) prematurely discontinued. Forty-five divalproex-treated subjects (71%) and 38 olanzapine-treated subjects (67%) prematurely discontinued prior to day 84. No significant differences between groups were noted for the overall percentage of premature discontinuations (p = .693) or the percentage of premature discontinuations for any particular reason (p > .5 for each reason) (Table 2).

Efficacy Results

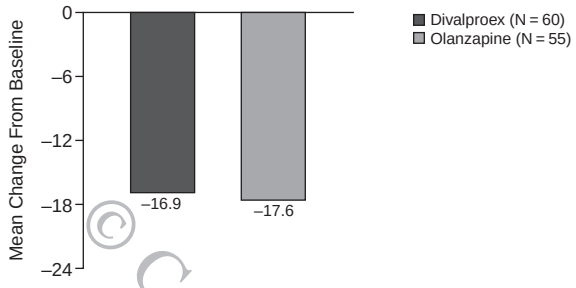
No significant treatment differences existed for mean change from baseline to day 21 in MRS score (divalproex, –14.8, N = 60; olanzapine, –17.2, N = 55; F = 1.60, df = 1,95; p = .210). Mean baseline MRS scores were significantly different between groups (divalproex, 30.8, N = 60; olanzapine, 32.3, N = 55; F = 4.09, df = 1,95; p = .046). When baseline was included as a covariate, the difference in mean MRS change from baseline (divalproex, –14.9, N = 60; olanzapine, –16.6, N = 55; F = 0.82, df = 1,94; p = .368) decreased slightly and remained nonsignificant (Figure 1, Table 3).

To determine the possible role of somnolence in the apparent antimanic effects, secondary to direct medication effects, an analysis adjusting for somnolence as an adverse event was performed. In this analysis, the mean changes in MRS score were –16.9 for divalproex (N = 60) and –17.6 for olanzapine (N = 55); F = 0.16, df = 1,111; p = .694 (Figure 2).

Mean change from baseline to day 21 for BPRS, HAM-D, and CGI-S scores were similar between groups (Table 3). No significant treatment differences were noted for change from baseline to day 84 for any efficacy variable, and the improvements in efficacy observed at day 21 persisted throughout the study.

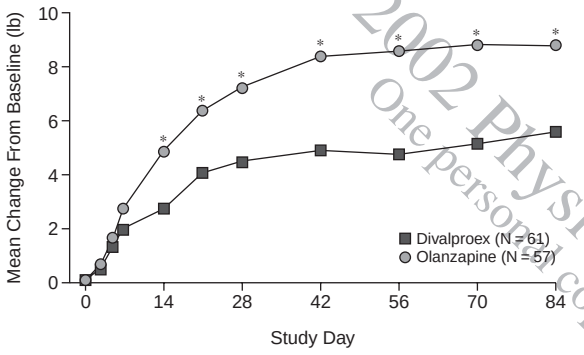
There were no significant treatment differences in mean change from baseline to day 21 for BPRS total scores (F = 0.91, df = 1,24; p = .350) or BPRS positive symptom scores (F = 0.19, df = 1,24; p = .669) in subjects with psychotic symptoms. Presence of psychotic symptoms was defined as a baseline sum of scores ≥ 6 on any 2 of the 4 positive BPRS symptoms (hallucinatory behavior, unusual thought content, conceptual disorganization, and suspiciousness). This study demonstrated no difference between treatments with regard to antipsychotic effect, although the number of subjects displaying psychotic symptoms was small (divalproex, N = 20 [33%]; olanzapine, N = 20 [36%]), and variability of change in BPRS scores was high.

Figure 2. Mean Change From Baseline to Day 21 for MRS Score With Adjustment for Presence or Absence of Somnolence as an Adverse Event[a]



[a]Baseline MRS scores were 30.4 for the divalproex group and 31.7 for the olanzapine group. Abbreviation: MRS = Mania Rating Scale.

Figure 3. Body Weight Change Over Time (LOCF)[a]



[a]Abbreviation: LOCF = last observation carried forward.
*Statistically significant difference from divalproex ($p \leq .05$).

Figure 4. Distribution of Weight Change

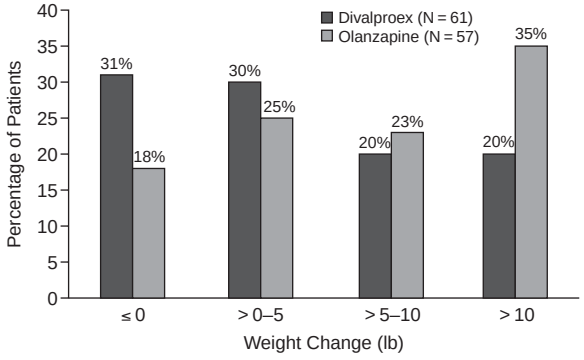
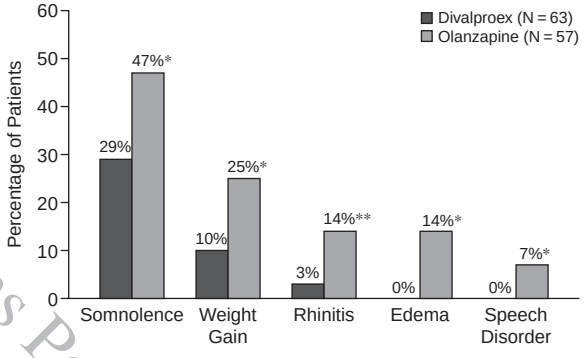


Figure 5. Adverse Events With Statistically Significant Differences in Incidence Between Groups



*$p \leq .05$.
**$p \leq .01$.

Safety/Tolerability Results

One hundred eighteen subjects (divalproex, N = 61; olanzapine, N = 57) had baseline and postbaseline body weight measurements available for analysis. Mean baseline weights were 181.8 lb (81.8 kg) for patients taking divalproex and 183.3 lb (82.5 kg) for patients taking olanzapine. Mean increase from baseline body weight at the final evaluation was significantly greater in the olanzapine group (8.8 lb [4.0 kg]) than in the divalproex group (5.5 lb [2.5 kg], $F = 3.97$, $df = 1,116$; $p = .049$). There was no evidence of a correlation between baseline weight and weight change at the final evaluation ($r = –0.08$, $N = 118$, $p = .389$). A significant difference in weight gain between groups was first seen at day 14 and persisted through day 84 (Figure 3). Distribution of weight change is presented in Figure 4.

One hundred twenty subjects (N = 63 divalproex, N = 57 olanzapine) were included in the analysis of adverse events. Somnolence, weight gain, rhinitis, edema, and speech disorder (i.e., slurred speech) were each reported as an adverse event in a significantly greater proportion of olanzapine-treated subjects than divalproex-treated subjects (Figure 5). No adverse events were reported in a significantly greater proportion of divalproex-treated subjects than olanzapine-treated subjects. Eleven percent (7/63) of divalproex-treated subjects and 9% (5/57) of olanzapine-treated subjects prematurely discontinued due to adverse events ($p = .766$). All reports of somnolence as an adverse event in the divalproex group began on or before day 21. However, in the olanzapine group, 26% of subjects remaining in the study after day 21 reported onset of somnolence after day 21.

There were significant differences between treatment groups for several laboratory variables in the change from baseline to final evaluation (Table 4). These included total cholesterol, low-density lipoprotein (LDL) cholesterol, alkaline phosphatase, albumin, and platelet count.

No significant treatment differences were noted in change from baseline to the final visit for blood pressure or pulse rate. There were no significant treatment differences for mean change from baseline to day 21 or day 84 for the Simpson-Angus Scale or BAS.

Table 4. Mean Change From Baseline to Final Values for Laboratory Variables With Statistically Significant Differences Between Groups[a]

	Divalproex			Olanzapine			Statistic		
Laboratory Variable	Mean	SD	N	Mean	SD	N	F	df	p
Total cholesterol, mg/dL	–1.69	29.12	45	13.29	29.46	42	5.68	1,85	.019
LDL cholesterol, mg/dL	–4.43	22.87	42	8.78	28.45	41	5.45	1,81	.022
Albumin, g/dL	–0.22	0.29	46	0.02	0.38	42	11.21	1,86	.001
Alkaline phosphatase, IU/L	–11.30	12.75	46	3.72	13.15	40	28.88	1,84	< .001
Total protein, g/dL	–0.23	0.56	46	0.09	0.57	42	7.16	1,86	.009
Platelet count ($\times 10^9$/L)	–52.19	55.67	43	0.78	40.88	41	24.51	1,82	< .001
Eosinophils, %	0.36	1.79	45	–0.48	1.47	41	5.61	1,84	.020
Monocytes, %	1.11	2.06	45	0.21	1.77	41	4.68	1,84	.033
Neutrophils, %	–4.43	9.44	45	0.03	8.46	41	5.29	1,84	.024

[a]Abbreviation: LDL = low-density lipoprotein.

Serious adverse events were reported in 5 divalproex-treated subjects (abnormal electrocardiogram results, anticholinergic syndrome, catatonic reaction, psychotic depression, and somnolence) and 2 olanzapine-treated subjects (depression and diabetic ketoacidosis). Serious adverse events considered to be possibly or probably related to the study drug included somnolence (divalproex-treated subject) and diabetic ketoacidosis (olanzapine-treated subject).

The olanzapine-treated subject with diabetic ketoacidosis, a man aged 53 years, died during the study; the death was attributed to diabetic ketoacidosis. The subject's baseline glucose level was 86 mg/dL, and he had no past history and no family history of diabetes mellitus. His glucose level at autopsy was 843 mg/dL.

DISCUSSION

This study showed no significant differences in the efficacy of divalproex and olanzapine for the treatment of bipolar mania. Efficacy results from this study for both treatments were comparable to those of previous reports.[3–5,8–10] Mean improvement in MRS score was 14.8 for divalproex and 17.2 for olanzapine, which represents a difference of 2.4 (effect size = 0.22) for the primary analysis, which did not correct for baseline MRS score or presence of somnolence as an adverse event. The clinical relevance of this difference is unknown.

There were no significant differences in efficacy between treatment groups for the subset of subjects displaying psychotic symptoms. However, the number of subjects displaying such symptoms was relatively small (N = 20 for both groups), and the variability of the change in BPRS scores was relatively high.

While both treatments were associated with weight gain, divalproex was associated with significantly less weight gain than olanzapine. Furthermore, significantly fewer divalproex- than olanzapine-treated subjects reported weight gain as an adverse event.

Subjects in the olanzapine group reported several types of adverse events significantly more often than those in the divalproex group. These included somnolence, weight gain, rhinitis, edema, and slurred speech (coded as speech disorder). No adverse events occurred significantly more frequently in the divalproex group than in the olanzapine group, even though an initial divalproex dosage of 20 mg/kg/day was used. Such loading doses have been previously successfully used and reported in clinical practice.[12–14]

The most commonly reported adverse event for both treatment groups was somnolence. Somnolence was reported in significantly more subjects in the olanzapine group (47%) than in the divalproex group (29%). Additionally, there were new reports of somnolence subsequent to day 21 in the olanzapine group but not in the divalproex group.

Significant treatment differences were seen for a number of laboratory variables. Changes in serum total cholesterol and LDL levels were significantly different with olanzapine treatment compared with divalproex treatment; a slight decrease in both values was reported for the divalproex group, whereas both values increased in the olanzapine group. Previous studies have observed that olanzapine is associated with increases in serum lipid levels, including cholesterol and triglycerides,[22–24] and further study is warranted to evaluate the possible role of dibenzodiazepine atypical antipsychotic drugs in the modulation of serum lipid parameters.

A significant treatment difference was seen for platelet count, with divalproex-treated subjects having a decreased platelet count from baseline levels. Decreased platelet counts associated with divalproex have been previously reported.[25] Notably, no subjects in the present study reported adverse events related to decreased platelet count, and no subjects prematurely discontinued due to decreased platelet count.

Change in other laboratory variables, including albumin, alkaline phosphatase, total protein, eosinophils, monocytes, and neutrophils, displayed significant differences between divalproex and olanzapine; however, the clinical significance of these differences is uncertain. No adverse events were reported that were related to these laboratory changes. However, in the absence of established guidelines, the extent of these changes suggests that

clinicians need to remain vigilant for potential changes in laboratory values and tailor both the choice of mood stabilizer and subsequent monitoring of laboratory values according to the needs of the individual patient.

The only serious adverse events that were considered possibly or probably related to the study drug were somnolence in a divalproex-treated subject, which resolved within 24 hours of the discontinuation of study medication, and diabetic ketoacidosis in an olanzapine-treated subject, which resulted in death. Glucose intolerance and diabetic ketoacidosis associated with olanzapine have been previously reported in subjects without a history of diabetes.[26–32] No significant treatment differences in change from baseline for blood glucose levels were observed in this study.[22,28,32,33] Further studies are needed to clarify any possible association between the use of mood stabilizers and the risk of glucose intolerance and diabetic ketoacidosis, to provide clinicians with guidance regarding the evaluation of glucose metabolism parameters.

One other study has been presented that directly compared the safety and efficacy of divalproex and olanzapine for the treatment of bipolar mania.[11] A detailed comparison of our study and the previous study is limited by the differences in study design and the fact that the previous study has not been formally published. However, some similarities between the studies are noteworthy. In both studies, divalproex and olanzapine demonstrated efficacy for the treatment of acute mania. In both studies, weight gain with olanzapine treatment was significantly greater than that observed with divalproex treatment; in addition, the adverse event profile of divalproex was generally more favorable than that of olanzapine. In the previous study, somnolence, dry mouth, headache, increased appetite, nausea, neck rigidity, speech disorder, and sleep disorder were reported significantly more often as adverse events in olanzapine-treated subjects, while only nausea and diarrhea were reported significantly more often in divalproex-treated subjects.[11]

In contrast to the present study, the previous study by Tohen et al.[11] showed that the efficacy of olanzapine (based on change from baseline in Young Mania Rating Scale scores) was significantly greater than that of divalproex. However, the dosing strategy for the current study was selected to reflect typical clinical practice; in the earlier study, both the mean modal dose of divalproex (1401 mg/day vs. 2115 mg/day) and the mean value of all serum valproate levels obtained (79.4 μg/mL vs. 77.9, 97.1, and 101.2 μg/mL on days 3, 6, and 10, respectively) were lower than in this study.[11] The difference in efficacy results between the 2 studies may reflect these differences in dosing strategy.

This study suggests that divalproex and olanzapine, when administered in dosages that reflect current clinical practice, demonstrate equivalent efficacy in the treatment of acute mania in bipolar disorder. Divalproex exhibited a more favorable long-term safety and tolerability profile than olanzapine, specifically with respect to weight gain, reported adverse events, and lipid profile.

The results of this study reinforce the need for clinicians involved in the treatment of acute mania to carefully tailor that treatment according to the needs of the individual patient. Clinicians should consider dosing strategy to achieve maximal efficacy and minimal side effects as well as longer-term safety and tolerability issues.

Drug names: benztropine (Cogentin and others), divalproex sodium (Depakote), lorazepam (Ativan and others), olanzapine (Zyprexa), zolpidem (Ambien).

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