A Randomized, Placebo-Controlled, Multicenter Study of Divalproex Sodium Extended Release in the Treatment of Acute Mania

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Objective: The efficacy and safety of divalproex sodium extended release (divalproex ER) were evaluated in patients hospitalized for acute mania associated with bipolar I disorder, manic or mixed type (DSM-IV-TR criteria).

Method: Following screening and washout of psychotropic medications, 377 patients were randomly assigned in a 1:1 ratio to 21 days of double-blind treatment with divalproex ER (N = 192) or placebo (N = 185). Daily dosage was initiated at 25 mg/kg, increased 500 mg on day 3, and adjusted to serum valproate concentrations of 85 to 125 μg/mL. The Mania Rating Scale (MRS) was used to assess efficacy. Patients remained hospitalized at least 15 days during blinded treatment. The study was conducted from April 2003 to May 2004.

Results: Improvement from baseline on the MRS was significantly greater among patients who received divalproex ER compared with placebo at the first on-treatment rating assessment, day 5, and all subsequent ratings through day 21 ($p = .013$). Furthermore, the proportion of patients achieving at least 50% improvement from baseline in MRS was significantly higher in patients receiving divalproex ER (48%) than in patients receiving placebo (34%) ($p = .012$). Five of the 11 MRS items improved significantly more in patients receiving divalproex ER than placebo: less need for sleep ($p \leq .01$), more energetic ($p \leq .05$), increased activity ($p \leq .05$), generalized motor hyperactivity ($p \leq .05$), and racing thoughts ($p \leq .001$). Side effects associated with divalproex ER included somnolence, dizziness, and gastrointestinal complaints.

Conclusion: The results indicate that divalproex ER is effective and safe for the treatment of mania episodes in bipolar I patients.

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A list of participating study group members appears at the end of the article.

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Bipolar disorder is a chronic, severe disease experienced by approximately 3% of the population.[1–3] The acute manic phase of the disorder is characterized by symptoms and signs of elevated mood, irritability, reduced need for sleep, increased energy, hyperactivity, impulsivity, and impaired judgment.[4] In an acute mixed episode, symptoms of mania and depression occur together.[4]

Currently approved treatments of the acute manic phase of bipolar disorder can be categorized primarily as mood stabilizers (e.g., divalproex sodium, lithium, and carbamazepine) or as atypical antipsychotics (i.e., aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone).[5] Efficacy is generally similar among the treatments,[6] although safety and convenience profiles differ and limit the usefulness of all current treatments in some patients. The relatively narrow therapeutic index of lithium is well known.[7] Recent research indicates that some drugs cause clinically important metabolic disturbances to varying degrees, motivating efforts to characterize the metabolic consequences of commonly used psychotropics.[8–12]

Divalproex sodium delayed release (divalproex) was shown to be safe and effective for treatment of bipolar disorder when initiated at 750 mg/day in divided doses and rapidly escalated to clinical effect.[13,14] Subsequent studies have demonstrated that manic patients tolerate and respond to initial divalproex doses of 20 to 30 mg/kg body weight.[15–18] One analysis noted that serum valproate concentrations between 45 and 125 μg/mL were associated

with efficacy in acutely manic patients, while serum valproate concentrations ≥ 125 μg/mL were associated with an increased frequency of adverse effects.[19] A more recent analysis indicated improved acute antimanic efficacy with increasing serum valproate concentrations greater than 71 μg/mL.[20]

An extended-release formulation of divalproex sodium (divalproex ER) was developed in order to provide routine once-daily dosing and to reduce trough-peak serum concentration differences, prominent with divalproex. Elevated serum valproate concentrations have been associated with increased frequency of some side effects (e.g., nausea, vomiting, tremor, decreased platelet count, and decreased white blood cell count).[15,21,22] Once-daily dosing of medications enhances patient adherence, and extended-release formulations improve tolerability by achieving equivalent total drug exposure with lower peak concentrations.[23] Divalproex ER is approximately 11% less bioavailable than divalproex.[24] Proportional dosing with 8% to 20% higher daily doses of divalproex ER produces equivalent drug exposure (area under the concentration-time curve), as well as significantly lower peak serum levels, significantly reduced peak-to-trough fluctuations, and higher trough serum levels compared with divalproex.[24,25] Divalproex ER is approved for the treatment of absence and complex partial seizures in adults and children at least 10 years of age, for the prophylaxis of migraine headaches in adults, and most recently for the treatment of acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features.

We report a randomized, double-blind, placebo-controlled, parallel-group, multicenter study conducted to evaluate the efficacy and safety of divalproex ER for the treatment of acute mania, in support of the newest indication. Compared to the original studies with divalproex, this study incorporated larger initial doses of divalproex ER in order to achieve a more rapid onset of efficacy, while otherwise replicating fundamental design components from the earlier studies.[13,14]

METHOD

The study was conducted in accordance with ethical principles from the Declaration of Helsinki and with all applicable regulations. Each patient received an explanation of the study and signed an informed consent prior to the performance of any study-related procedures. A duly constituted Institutional Review Board reviewed and approved the protocol at each study site. The study was conducted from April 2003 to May 2004 at centers in the United States.

Patient Eligibility

Male and female patients, 18 to 65 years of age, hospitalized for an acute exacerbation of mania, were enrolled at sites in the United States. Patients had a current DSM-IV-TR[4] primary diagnosis of bipolar I disorder, manic or mixed type, as confirmed by the Structured Clinical Interview for DSM-IV-TR Axis I disorders (SCID).[26] The Mania Rating Scale (MRS; from the Schedule for Affective Disorders and Schizophrenia-Change Version [SADS-C])[27] score had to be at least 18, with at least 4 item scores > 1 at screening and on day 1 before randomization. Patients were hospitalized no more than 7 days immediately before screening/washout or were in the process of being hospitalized at the time of screening. At least 1 prior manic or mixed episode within the past 3 years was required.

Patients were excluded if they met any of the following criteria: history of schizophrenia or schizoaffective disorder; current Axis I or II disorder that could interfere with compliance or confound study interpretation; current manic or mixed episode that was drug-induced, antidepressant-associated, or secondary to a medical disorder; receipt of a protocol-prohibited psychotropic medication within the lesser of 5 half-lives or 10 days before randomization; receipt of a depot neuroleptic within 1 inter-injection period before randomization; history of clozapine use; history of active substance abuse within 3 months before screening; evidence of drug or alcohol withdrawal; positive urine screen for phencyclidine, opiates, cocaine, or amphetamines; history of intolerance or failure to respond to valproate therapy; or use of valproate regularly during the 30 days before screening.

Study Procedures

Following completion of a minimum 3-day screening/washout period, eligible patients were randomly assigned on day 1 in a 1:1 ratio to 21 days of treatment with divalproex ER or placebo (treatment period). Blinded medication was administered once daily in the morning. Daily dosage was initiated at 25 mg/kg body weight, rounded up to the nearest 500 mg. On day 3, all patients had the daily dose increased by an additional 500 mg. Additional dose adjustments could occur on days 7, 12, and 17 at the investigator's discretion based on clinical effect, adverse events, and serum valproate concentrations. Doses could be reduced below recommended levels for adverse events if clinically indicated. Blood samples for blinded serum valproate concentrations were obtained immediately prior to dosing (approximately 24 hours [± 3 hours] after the previous dose of study medication) on days 5, 10, 15, and 21. Target serum valproate trough concentrations were 85 to 125 μg/mL. Serum valproate concentrations were measured and monitored by a central laboratory; when concentrations were outside the target range, personnel at the central laboratory advised the investigator that the concentration was low or high. Similar instructions were given to the same site or another site for a placebo patient who was at the same point in the study in or-

der to maintain blinding. After the treatment period was completed, study drug could be tapered with blinded medications over 7 days in order to maintain the blind (taper period). Alternative medication regimens could be prescribed during this taper period, but no valproate assays were allowed during tapering.

No adjunctive psychotropic medications other than lorazepam were allowed during the washout and treatment periods. The maximum single dose of lorazepam allowed was 2 mg/dose; the maximum total daily dose allowed was 6 mg/day during screening, 4 mg/day during days 1 to 7 of the treatment period, and 2 mg/day during days 8 to 10 of the treatment period. Lorazepam was not permitted within 8 hours before efficacy evaluations or after day 10 of the treatment period.

Efficacy was evaluated during the treatment period with the SADS-C (including the MRS and Depressive Syndrome Scale [DSS])[27] and the Global Assessment Scale (GAS).[28] Ratings for the MRS and GAS were based on the 2 days preceding the evaluation and were assessed on days 1, 5, 10, 15, and 21 (or at discontinuation). The DSS was assessed on days 1 and 21 (or at discontinuation). Raters were trained and certified on the MRS, the primary efficacy scale, before they were allowed to rate patients. All raters were retrained approximately halfway through the enrollment period of the study. The same rater performed all evaluations for a patient when possible.

Patients were required to remain in the hospital at least 15 days during the treatment period. Hospital discharge with outpatient follow-up for remaining evaluations was permitted if all of the following criteria were met: MRS score was reduced by at least 50% from day 1 and was < 13; no MRS item score exceeded 2; GAS score exceeded 60; no lorazepam was required; adequate supervision was available; and, per the investigator, the patient had achieved adequate exposure to study drug sufficient to maintain stability.

Adverse events were monitored throughout the study. Hematology parameters were assessed during screening and on days 5, 10, and 21 (or at discontinuation). Fasting blood chemistry was assessed during screening and on days 5 and 21 (or at discontinuation). Vital signs were taken during screening and on days 1, 3, 5, 7, 10, 12, 15, 17, and 21 (or at discontinuation). A routine physical examination and urinalysis were performed during screening and on day 21 (or at discontinuation). Urine toxicology testing was performed during screening for all patients and on days 17 and 21 (or at discontinuation) for patients who had been discharged from the hospital.

Statistical Methods

All statistical tests were 2-tailed with a significance level of .05. Analyses were performed using the SAS System, Version 6.12 (SAS Institute Inc.; Cary, N.C.). Comparability of treatment groups at baseline was assessed with a 1-way analysis of variance (ANOVA) for age and weight and by a Wilcoxon rank sum test for age at first episode and age at first bipolar hospitalization. Treatment group differences for number of manic, mixed, and depressive episodes; number of hospitalizations for bipolar disorder; and number of suicide attempts (collected as 0, 1–5, 6–10, 11–15, 16–20, and > 20) were assessed with a Cochran-Mantel-Haenszel (CMH) test. Fisher exact test (FET) was used to assess treatment differences in qualitative baseline characteristics and in reason for discontinuation of study drug.

The protocol-specified primary efficacy endpoint was change from baseline to final evaluation in the MRS score (i.e., last observation carried forward [LOCF] at day 21). Supportive secondary endpoints included change from baseline to each scheduled visit for the MRS and its subscales, the Manic Syndrome Scale (MSS) and the Behavior and Ideation Scale (BIS),[27] and for the DSS and GAS. MRS response rate (defined as ≥ 50% decrease in MRS score from baseline) and MRS remission rate (defined as MRS score ≤ 12) were also evaluated. In addition, an effectiveness analysis was conducted that required that the patient achieve an MRS score ≤ 12 and a DSS score ≤ 13 at the final evaluation and not have been discontinued for an adverse event.

All efficacy analyses are reported for the intent-to-treat data set (ITT), defined as all patients who received study drug and who had a baseline and at least 1 follow-up evaluation with the MRS. Baseline was defined as the last evaluation before randomization, usually the day 1 evaluation. Data from small centers, defined as centers that did not have patients in both treatment groups, were combined for all efficacy analyses. Based on previous studies of divalproex in the treatment of acute mania, power for testing treatment differences on MRS score was estimated in the protocol as approximately 90% for a 2-sided test at .05 alpha level with the planned 185 patients per group (effect size = 0.34).

The treatment group difference in the mean change from baseline to final evaluation for MRS was evaluated with a 2-way ANOVA with factors for treatment and site. The treatment-by-site interaction was evaluated to examine if treatment effects were homogeneous across sites.

A mixed-model repeated-measures ANOVA was performed as a post hoc analysis on the MRS observed-cases data with treatment and time (days 5, 10, 15, 21) as fixed factors, patient as a random factor, and a first-order autoregressive [AR(1)] covariance structure. Treatment group differences in mean change from baseline to final evaluation for MRS item scores and responder rates were assessed by a CMH with sites as strata. Treatment group differences for remission and effectiveness rates were assessed in post hoc analyses with the CMH analysis with sites as strata.

Table 1. Demographic Characteristics

Characteristic	Placebo (N = 177)	Divalproex ER (N = 187)	p Value[b]
Male, N (%)	96 (54)	113 (60)	.245
White, N (%)	135 (76)	135 (72)	.403
Age, mean (SD), y	38.1 (10.28)	37.0 (10.71)	.322
Weight, mean (SD), kg	87.1 (21.39)	87.4 (22.23)	.888
Mixed episode,[a] N (%)	79 (45)	80 (43)	.752
Psychotic features,[a] N (%)	39 (22)	36 (19)	.520

[a]Based on DSM-IV-TR criteria; patients displaying these characteristics at study entry.
[b]p Values from Fisher exact test (sex, race, mixed episodes, psychotic features) and 1-way analysis of variance (age, weight).
Abbreviation: ER = extended release.

Table 2. Psychiatric History

Characteristic	Placebo[a]	Divalproex ER[b]	p Value[c]
< 6 Manic episodes, N (%)	79 (45)	68 (37)	.032
< 6 Mixed episodes, N (%)	105 (60)	112 (61)	.593
< 6 Depressive episodes, N (%)	104 (60)	114 (62)	.820
Rapid cycling,[d] N (%)	13 (7)	9 (5)	.381
Age at first manic episode, mean (SD), y	23.8 (10.8)	22.6 (9.8)	.564
Age at first mixed episode, mean (SD), y	25.7 (10.8)	25.4 (9.7)	.912
Age at first depressive episode, mean (SD), y	22.2 (9.7)	20.9 (9.1)	.381
< 6 Bipolar hospitalizations,[e] N (%)	117 (66)	109 (58)	.553
Age at first bipolar hospitalization, mean (SD), y	28.3 (11.7)	26.6 (10.2)	.284
Suicide attempt, N (%)	95 (54)	105 (56)	.603

[a]N varies from 122 to 177, depending on availability of data.
[b]N varies from 134 to 187, depending on availability of data.
[c]p Value for reported number of events is from Cochran-Mantel-Haenszel test, but results are dichotomized (< 6, ≥ 6) for ease of presentation. p Value is from Fisher exact test for rapid cycling and suicide attempt; p value is from Wilcoxon rank sum test for age at first episode.
[d]Based on DSM-IV-TR criteria.
[e]Includes hospitalization at time of study enrollment.
Abbreviation: ER = extended release.

Exploratory analyses evaluated whether the treatment difference was a function of gender, race, age, manic versus mixed episode, presence of psychotic features, presence of rapid cycling, prior number of manic episodes, age at first mixed or manic episode, history of drug abuse, baseline MRS, baseline MSS, or baseline DSS. Analyses of variance included factors for treatment group, baseline characteristics, and the treatment group–by–baseline characteristic interaction.

All patients who received study drug were included in safety analyses. Adverse events were coded with the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART V).[29] Treatment-emergent adverse events (events beginning or worsening on or after day 1) were compared between treatments with FET. Valproate concentrations of patients who prematurely discontinued for adverse events and patients who prematurely discontinued for gastrointestinal adverse events were compared by a t test to valproate concentrations of patients who did not prematurely discontinue for adverse events. Changes from baseline to final evaluation in clinical laboratory findings and vital signs were analyzed by the 1-way ANOVA. Treatment differences in the percentage of patients with a weight gain of ≥ 7% at the final visit were assessed by FET. Dose of divalproex ER, concentration of valproate, lorazepam use, and hospital discharge data were summarized descriptively.

RESULTS

Thirty-three sites treated 192 patients with divalproex ER and 185 patients with placebo between April 2003 and May 2004. Completion rates were comparable between the divalproex ER (58%) and placebo (52%) treatment groups. A higher percentage of placebo patients (26%) than divalproex ER patients (13%) discontinued for ineffectiveness (p = .001, FET), while a lower percentage of placebo patients (3%) than divalproex ER patients (10%) discontinued for adverse events (p = .003, FET). Thirteen patients (8 placebo, 5 divalproex ER) were excluded from the ITT data set for 1 or more reasons: 11 had no on-treatment MRS evaluation (7 placebo, 4 divalproex ER), and 3 (1 placebo, 2 divalproex ER) had enrollment violations.

Patients had a mean age of 37.6 years, 74% were white, and 57% were male. Demographic and baseline characteristics of the treatment groups were generally similar (Table 1). Upon study entry, 55% of placebo patients and 57% of divalproex ER patients were in a manic episode, while 45% of placebo patients and 43% of divalproex ER patients were in a mixed episode. Psychotic features were present for 22% of placebo patients and 19% of divalproex ER patients. Psychiatric history was generally similar for the treatment groups (Table 2). A statistically significant difference was observed between the treatment groups for the total number of manic episodes, with a tendency toward more manic episodes for divalproex ER patients than for placebo. Few patients in either treatment group met DSM-IV-TR criteria for rapid cycling (placebo 7%, divalproex ER 5%).

The mean dose of divalproex ER on day 5 was 2874 mg (33.2 mg/kg). The mean final dose (on day 21 or at discontinuation) was 3057 mg (35.4 mg/kg), and the mean modal dose was 2961 mg (34.5 mg/kg). The mean serum valproate concentration on day 5 was 96.5 μg/mL, and the mean final serum valproate concentration was 95.9 μg/mL. Only 15 patients in either treatment group tapered study drug at the end of the study.

Efficacy

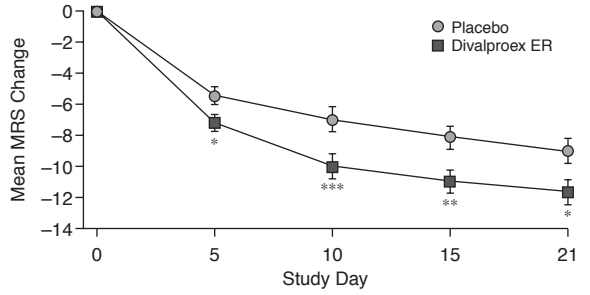
Improvement from baseline on the MRS was significantly greater among patients who received divalproex ER

Table 3. Baseline and Mean Change From Baseline to Final Mania Rating Scale (MRS), Manic Syndrome Scale (MSS), and Behavior and Ideation Scale (BIS) Scores Using Last Observation Carried Forward[a]

	Baseline, Mean (SD)		Change to Final Evaluation, Mean (SD)		ANOVA Results[b]	
Scale	Placebo	Divalproex ER	Placebo	Divalproex ER	F (df = 1,331)[c]	p Value
MRS	26.6 (5.6)	26.6 (5.6)	–9.0 (10.9)	–11.5 (10.9)	6.23	.013
MSS	13.7 (3.7)	13.7 (3.8)	–5.3 (6.0)	–6.7 (6.0)	6.95	.009
BIS	11.4 (2.7)	11.5 (2.7)	–3.4 (5.1)	–4.5 (5.1)	5.57	.019

[a]N = 177 for placebo, and N = 187 for divalproex ER.
[b]p Value and SD from ANOVA with factors for site and treatment; p value is for treatment.
[c]Degrees of freedom for F statistic from ANOVA.
Abbreviations: ANOVA = analysis of variance, ER = extended release.

Figure 1. Mean Change From Baseline to Days 5, 10, 15, and 21 for Mania Rating Scale (MRS), Using Last Observation Carried Forward



*p ≤ .05 vs. placebo.
**p ≤ .01 vs. placebo.
***p ≤ .001 vs. placebo.
Abbreviation: ER = extended release.

than patients who received placebo (–11.5 vs. –9.0, respectively; p = .013; Table 3). A significantly greater improvement on the MRS was observed with divalproex ER as early as day 5 (first on-treatment assessment) compared to placebo and was maintained through day 21 (Figure 1). A mixed-model repeated-measures ANOVA of MRS mean change from baseline scores yielded results (p = .007 for treatment difference) similar to that of the primary analysis.

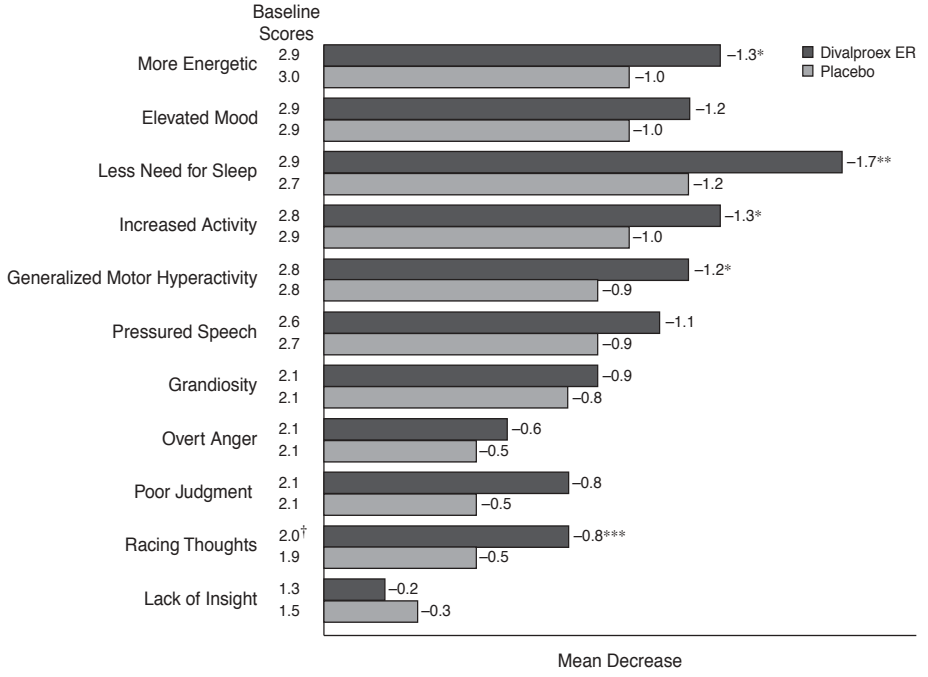
Divalproex ER was superior to placebo on change from baseline to final evaluation on the BIS and MSS. Analyses of the 11 items comprising the MRS indicated significant improvement in items for more energetic, less need for sleep, increased activity, generalized motor hyperactivity, and racing thoughts (Figure 2). There was a tendency for divalproex ER to show statistically significantly greater improvement from baseline than placebo for items with more elevated baseline scores (Figure 2).

At the final evaluation, 48% of divalproex ER–treated patients and 34% of placebo-treated patients were classified as responders, having had experienced at least 50% improvement from baseline in MRS score (p = .012, CMH). The treatment difference in responder rate was statistically significant at all evaluations beginning with day 10 (Figure 3). Remission was observed at endpoint in 48% of patients treated with divalproex ER and 35% of patients treated with placebo (p = .015, CMH). Effectiveness was achieved in 38% of patients treated with divalproex ER and 26% of patients treated with placebo (p = .032, CMH).

For the mean change from baseline for the MRS, the treatment-by-site interaction was statistically significant (p = .006). To help understand this interaction, a series of analyses was performed to evaluate the effects of baseline characteristics on treatment differences for the MRS. Stratification by MSS scores at baseline indicated that higher baseline MSS predicted a greater difference from placebo. Mean change in MRS from baseline to final evaluation was –15.0 for divalproex ER and –9.6 for placebo when baseline MSS was greater than the median (13). When baseline MSS was at or below the median, mean change was –7.5 for divalproex ER and –7.7 for placebo. Additional exploratory analyses demonstrated that the treatment difference was not a function of gender, race, age, manic versus mixed episode, presence of psychotic features, presence of rapid cycling, prior number of manic episodes, age at first mixed or manic episode, history of drug abuse, or baseline DSS. We plan to report in a separate article a detailed exploration of the site-related differences and the implications for study design and execution.

No significant treatment difference in change from baseline to final evaluation was observed for the GAS or DSS. The majority of patients in both treatment groups used lorazepam at least once during the study (79%, placebo; 74%, divalproex ER). No consistent differences were observed across time in the proportions of patients using lorazepam or the dose of lorazepam administered. The mean dose of lorazepam prescribed on day 1 was statistically significantly higher in the placebo group (2.4 mg) compared to the divalproex ER group (2.1 mg; p < .05). On days 2 through 10, the mean daily dose of lorazepam prescribed was similar between the treatment groups, and did not exceed 2.4 mg. Few patients were discharged from the hospital (20% placebo, 17% divalproex ER) during the study.

Figure 2. Mean Decrease From Baseline to Final Evaluation for Items of the Mania Rating Scale, Using Last Observation Carried Forward



†p ≤ .01 vs. placebo at baseline.
*p ≤ .05 vs. placebo; from ANOVA.
**p ≤ .01 vs. placebo; from ANOVA.
***p ≤ .001 vs. placebo; from ANOVA.
Abbreviations: ANOVA = analysis of variance, ER = extended release.

Safety and Tolerability

A significantly greater percentage of patients in the divalproex ER group (10%) than in the placebo group (3%) discontinued the study because of adverse events. Of the 19 divalproex ER patients who discontinued for treatment-emergent adverse events, 14 discontinued for adverse events related to the digestive system. Treatment-emergent adverse events reported by a greater percentage of patients in the divalproex ER group than in the placebo group were somnolence, nausea, dyspepsia, dizziness, vomiting, abdominal pain, and pharyngitis (Table 4). The majority of adverse events reported in both treatment groups were mild or moderate in severity.

Exploratory analyses indicated that patients taking divalproex ER who discontinued the study for adverse events had statistically significantly higher mean serum valproate concentrations at final evaluation than patients who did not (114.1 μg/mL vs. 94.0 μg/mL, p = .012, t test). This relationship was also present for the divalproex ER patients who discontinued for gastrointestinal adverse events versus patients who did not discontinue for adverse events (123.2 μg/mL vs. 94.0 μg/mL, p = .002, t test). A similar pattern was observed for the individual treatment-emergent adverse events of nausea, vomiting, and dyspepsia. In general, mean serum valproate concentrations above 105 μg/mL were associated with increased incidence of gastrointestinal adverse events.

Two cases of pancreatitis requiring hospitalization occurred during the study. One case occurred during the double-blind phase in a divalproex ER patient with a current diagnosis of gallstones. The second case occurred after completion of the study. The treating physician prescribed divalproex ER to a patient previously randomly assigned to the placebo arm, and 11 days later the patient was hospitalized. The final diagnosis was chronic pancreatitis with an alternative etiology of previous alcohol abuse. Both patients recovered fully after discontinuation of divalproex ER. One death occurred in a divalproex ER patient 4 days after study completion due to acute intoxication by the combined effects of opiates and cocaine. The investigator considered the death to be "not related" to study drug.

Statistically significant differences were observed between the treatment groups for the mean change from baseline to final value for red blood cells, platelet count, monocytes, basophils, total protein, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, sodium, and calcium (Table 5).

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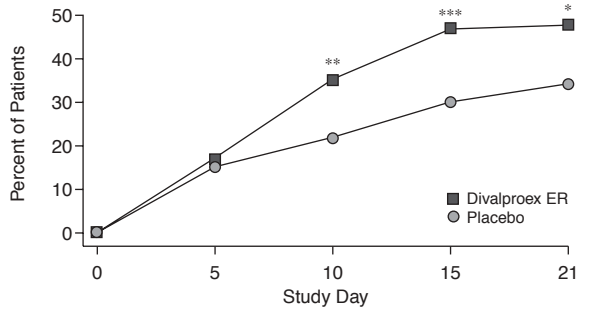
Figure 3. Percent of Patients Experiencing at Least 50% Improvement From Baseline Mania Rating Scale Score by Study Day



*p ≤ .05 vs. placebo.
**p ≤ .01 vs. placebo.
***p ≤ .001 vs. placebo.
Abbreviation: ER = extended release.

Table 4. Adverse Events With a Statistically Significantly Greater Incidence in Divalproex ER Patients (N = 192) Than Placebo Patients (N = 185) or With ≥ 10% Incidence in Either Treatment Group

Adverse Event	Placebo, N (%)	Divalproex ER, N (%)	p Value[a]
Any event	134 (72)	162 (84)	.006
Somnolence	26 (14)	64 (33)	< .001
Nausea	28 (15)	53 (28)	.004
Dyspepsia	18 (10)	49 (26)	< .001
Headache	40 (22)	40 (21)	.900
Dizziness	15 (8)	36 (19)	.003
Vomiting	12 (6)	35 (18)	.001
Diarrhea	18 (10)	28 (15)	.160
Pain	16 (9)	23 (12)	.314
Abdominal pain	8 (4)	19 (10)	.045
Pharyngitis	8 (4)	19 (10)	.045

[a]p Value from Fisher exact test.
Abbreviation: ER = extended release.

Table 5. Nonmetabolic Clinical Laboratory Results With Statistically Significant Differences Between Divalproex ER and Placebo Patients in Mean Change From Baseline to Final Evaluation[a]

	Baseline, Mean (SD)		Change to Final Evaluation, Mean (SD)	
Clinical Laboratory Parameter	Placebo	Divalproex ER	Placebo	Divalproex ER[b]
Red blood cells, × 10^{12}/L	4.64 (0.41)	4.72 (0.41)	0.05 (0.28)	–0.01 (0.28)*
Platelets, × 10^{9}/L	270.9 (77.4)	268.6 (79.7)	–1.2 (49.6)	–58.8 (59.9)***
Monocytes, %	5.58 (2.05)	5.63 (1.98)	0.29 (2.37)	1.88 (3.03)***
Basophils, %	0.33 (0.19)	0.34 (0.18)	0.02 (0.25)	–0.05 (0.23)**
Total protein, g/dL	7.18 (0.44)	7.27 (0.49)	0.03 (0.52)	–0.27 (0.51)***
Albumin, g/dL	4.32 (0.29)	4.35 (0.29)	0.02 (0.28)	–0.19 (0.31)***
Total bilirubin, mg/dL	0.53 (0.26)	0.51 (0.22)	0.01 (0.26)	–0.09 (0.21)***
Alkaline phosphatase, IU/L	79.23 (24.02)	76.57 (22.12)	–1.58 (14.91)	–12.15 (13.07)***
Aspartate aminotransferase, IU/L	21.76 (9.66)	22.41 (11.18)	–0.19 (10.32)	–3.93 (11.42)***
Alanine aminotransferase, IU/L	23.80 (17.44)	23.28 (15.66)	1.92 (17.76)	–6.41 (18.13)***
Sodium, mEq/L	140.78 (2.32)	140.66 (2.32)	0.03 (2.85)	0.64 (2.63)*
Calcium, mg/dL	9.52 (0.40)	9.53 (0.41)	0.07 (0.43)	–0.20 (0.43)***

[a]N for placebo varies from 175 to 178, and N for divalproex ER varies from 180 to 184.
[b]p Value for treatment difference from 1-way analysis of variance, denoted by: *p ≤ .05, **p ≤ .01, ***p ≤ .001.
Abbreviation: ER = extended release.

In general, the mean changes from baseline to final value for each of the laboratory variables were small, with the exception of the larger decrease in platelet count for the divalproex ER group (–58.8 × 10^{9}/L) compared to the placebo group (–1.2 × 10^{9}/L). There were no serious adverse events due to abnormal laboratory values.

Metabolic Changes

Weight gain was greater in the divalproex ER group (1.8 kg) than in the placebo group (0.5 kg). Weight gain of 7% or greater from baseline occurred in 9% of patients taking divalproex ER and 3% of patients taking placebo (p = .036). Mean changes in fasting serum glucose were small in both groups (divalproex ER, –1.2 mg/dL; placebo, 1.7 mg/dL) and did not differ significantly (Table 6).

Total cholesterol decreased significantly more in the divalproex ER group than in the placebo group (–13.47 mg/dL vs. –2.46 mg/dL, p = .001). Mean decreases in high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol were also significantly greater in the divalproex ER group than in the placebo group; HDL/LDL ratio did not change from baseline in either treatment group. Stratification by baseline total cholesterol (≥ 200 mg/dL vs. < 200 mg/dL) indicated that the differences between divalproex ER and placebo in mean change for total cholesterol were greater in the stratum with higher mean baseline values (–18.6 mg/dL vs. –6.5 mg/dL, respectively). Since this was a post hoc analysis, these results should be considered hypothesis generating rather than confirmatory.

DISCUSSION

This multicenter randomized study demonstrated that divalproex ER, the extended-release formulation of divalproex, is efficacious and safe for the treatment of acute mania associated with bipolar disorder. Divalproex ER produced significantly greater improvement in manic

Table 6. Mean Baseline and Mean Change From Baseline for Metabolic Measures[a]

	Baseline, Mean (SD)		Change to Final Evaluation, Mean (SD)		
Clinical Laboratory Parameter	Placebo	Divalproex ER	Placebo	Divalproex ER	p Value[b]
Body weight, kg	87.0 (21.24)	87.3 (22.17)	0.5 (2.89)	1.8 (3.43)	< .001
Body mass index, kg/m^2	30.34 (15.20)	29.06 (7.24)	0.14 (1.06)	0.61 (1.14)	< .001
Glucose, mg/dL	99.68 (22.50)	100.72 (26.34)	1.71 (26.10)	–1.24 (35.49)	.371
Total cholesterol, mg/dL	198.78 (41.91)	197.71 (44.86)	–2.46 (32.76)	–13.47 (30.93)	.001
HDL cholesterol, mg/dL	50.01 (14.94)	49.28 (13.36)	–2.79 (10.56)	–6.00 (9.84)	.003
LDL cholesterol, mg/dL	113.60 (35.21)	113.30 (36.13)	–0.07 (29.90)	–7.89 (28.92)	.015
HDL/LDL ratio	0.49 (0.22)	0.48 (0.19)	–0.02 (0.17)	0.00 (0.22)	.453
Triglycerides, mg/dL	182.18 (111.61)	177.85 (106.45)	–4.34 (98.66)	1.53 (90.73)	.556

[a]N for placebo varies from 161 to 177, and N for divalproex ER varies from 165 to 184.
[b]p Value for treatment difference from 1-way analysis of variance.
Abbreviations: ER = extended release, HDL = high-density lipoprotein, LDL = low-density lipoprotein.

symptoms than placebo on the primary efficacy measure by day 5 that was maintained throughout the 21 days of treatment, and was not associated with any worsening of depressive symptoms. Improvements on the MSS and BIS, but not the GAS, also were significantly superior in the divalproex ER group. A mixed-model repeated-measures ANOVA demonstrated greater improvement on the MRS for divalproex ER than for placebo over the 21 days of the study, which was consistent with the primary outcome analysis. The mixed-model repeated-measures ANOVA uses observed-cases data and so avoids reliance on LOCF for the handling of missing data. Additionally, responder, remission, and effectiveness rates were significantly higher for divalproex ER than for placebo.

Improvement for divalproex ER compared to placebo was predominantly seen in 5 core manic symptoms (less need for sleep, more energetic, increased activity, generalized motor hyperactivity, and racing thoughts). There was a tendency for divalproex ER to show statistically significantly greater improvement from baseline than placebo for those items with higher mean baseline scores. In order to incorporate both symptomatic remission and good tolerability, we defined effectiveness as an MRS score ≤ 12 and a DSS score ≤ 13 at the final evaluation and not having discontinued for an adverse event. The proportion of divalproex ER–treated patients to achieve this criterion was significantly greater than the proportion of placebo-treated patients (38% vs. 26%). This is the first reported definition of effectiveness that has successfully identified an active drug in the acute treatment of mania, and helps to confirm the clinical relevance of the other observed improvements.

The response to divalproex ER was robust in that 48% of patients achieved at least 50% improvement from baseline. The observed response rate is consistent with that reported for prior divalproex multicenter (48% using MSS score) and single-center (53% using Young Mania Rating Scale score in an evaluable data set) studies, and with that recently reported for monotherapy with atypical antipsychotics.[13,14,30] The impact of prior valproate use on results was minimized in this study by excluding patients who had previously failed adequate valproate therapy or had taken valproate regularly during the 30 days before screening. The placebo response in this study was within the range reported for acute mania, but greater than that observed in the early divalproex studies.[13,14,30]

In this study, severity of baseline manic symptoms predicted response to divalproex ER. Stratification by MSS at baseline indicated that low baseline MSS predicted a smaller difference from placebo. Exploratory analyses demonstrated that the treatment difference was not a function of gender, race, age, manic versus mixed episode, presence of psychotic features, presence of rapid cycling, prior number of manic episodes, age at first mixed or manic episode, history of drug abuse, or baseline DSS. Therefore, we infer that enrollment of patients without moderate or greater core manic symptoms is likely to yield equivocal improvement and make it difficult to identify a drug-placebo difference when studying bona fide efficacious antimanic regimens. This observation may be useful in planning other studies of treatments for mania.

The initial dose of divalproex ER (25 mg/kg/day) and the dose escalation regimen were higher in the current study than in prior divalproex trials, which initiated divalproex dosing with 750 mg/day in divided doses.[13,14] The rapid dose titration in the current study was designed to achieve therapeutic serum concentrations early in treatment, and indeed yielded a mean serum valproate level of 96.5 μg/mL on day 5 with a mean divalproex ER dose of 2874 mg (33.2 mg/kg). Initial dosing with 20 to 30 mg/kg/day has appeared well-tolerated in published studies of divalproex and has been associated with early treatment response.[16–19]

In the current study, the mean final dose (day 21 or at discontinuation) was 3057 mg (35.4 mg/kg), and the mean final serum valproate concentration was 95.9 μg/mL. This final dose and final serum valproate level are generally higher than what has been reported in other divalproex trials,[13,14] and are likely not reflective of the general patient population due to sample bias. For example, those subjects with the higher doses and higher se-

rum valproate concentrations at the final visit are a combination of people who tolerated the rapid dose titration well and those who required higher doses to control their symptoms.

The profile and rates of adverse effects with divalproex ER in this study are generally similar to other studies of divalproex in mania.[13,14] However, some adverse effects were more frequent with divalproex ER as dosed in this study than in the earlier multicenter divalproex study.[14] Patients receiving divalproex ER who discontinued the study for any adverse event or for gastrointestinal-related adverse events had significantly higher mean serum valproate concentrations at final evaluation than patients who did not discontinue due to an adverse event; a pattern was also observed for the individual adverse events of nausea, vomiting, and dyspepsia. Mean serum valproate concentrations above 105 μg/mL were associated with increased incidence of gastrointestinal adverse events. On the basis of these results and previous acute and maintenance studies, serum valproate concentrations should generally not exceed approximately 100 μg/mL for manic patients whose clinical improvement is adequate with such regimens.[13,14,19,31,32]

Divalproex ER administration was associated with a statistically significant mean decrease in platelet count, while indices of hepatic function tended to improve with divalproex ER treatment, both consistent with previous trials of divalproex.[11,14] Despite the mean decrease in aspartate aminotransferase and alanine aminotransferase in the current and previous trials, idiosyncratic hepatotoxicity has been associated with valproic acid use, and liver function tests should be performed as described in the product label.[33] A mean weight gain of 1.8 kg was associated with divalproex ER administration compared to a 0.5-kg weight gain with placebo. Serum glucose was not altered by either treatment, and cholesterol decreased significantly with divalproex ER treatment compared to placebo, generally consistent with other studies of divalproex.[34–38]

Because of the protocol-driven plan to increase the divalproex ER dose to achieve serum levels of at least 85 μg/mL in individual subjects, intended to assure that the somewhat lower bioavailability associated with the ER formulation did not result in subtherapeutic serum levels, the serum levels achieved were somewhat higher than anticipated. The results suggest that most patients tolerate adequately and improve symptomatically with serum levels in the 85 to 100 μg/mL range, but that higher levels are associated with reduced tolerability, particularly for gastrointestinal adverse events.

The principal finding of this study is that the extended-release formulation of divalproex is effective and safe for the treatment of acute mania associated with bipolar disorder. Results of this study add to the expanding array of evidence-based information for divalproex ER and other treatments for bipolar disorder and warrant further testing of divalproex ER in the extended treatment of bipolar disorder.

Drug names: aripiprazole (Abilify), carbamazepine (Equetro, Carbatrol, and others), clozapine (FazaClo, Clozaril, and others), divalproex sodium extended release (Depakote ER), lithium (Eskolith, Lithobid, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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