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

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Objective: Divalproex sodium extended-release (ER) was examined for the treatment of acute mania in adults in 2 randomized, placebo-controlled clinical trials. One study demonstrated statistically significant improvements in mania symptoms compared to placebo, while an earlier study did not. Results of the earlier study are presented here.

Method: A total of 225 *DSM-IV*–diagnosed bipolar I disorder patients were randomly assigned in a 2:1 ratio to 21 days of double-blind treatment with divalproex ER (n = 147) or placebo (n = 78). The daily divalproex ER dosage was initiated at 20 mg/kg. The primary efficacy variable was the change from baseline to final evaluation in Mania Rating Scale (MRS) score. Subjects were discontinued from the study if they were discharged from the hospital or if they met prespecified improvement criteria. The study was conducted from May 1998 to July 1999 at centers in the United States.

Results: There was no statistically significant difference in MRS score change from baseline to final for patients treated with divalproex ER compared with those treated with placebo. With the exception of back pain and constipation, adverse event rates between placebo and divalproex ER were very similar. A large proportion of patients prematurely discontinued study treatment (divalproex ER: 83%, placebo: 82%). The mean daily dose of divalproex ER was 2,211 mg with a mean maximum serum valproic acid concentration of 77.9 μg/mL.

Conclusions: The results of the current study did not demonstrate statistically significant improvement in mania symptoms associated with divalproex ER treatment compared to placebo. A number of methodological considerations may have contributed to the negative findings, including allowance for early study discontinuation and lower than optimal dosing.

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Divalproex sodium and divalproex sodium extended-release (ER) are approved for the treatment of acute manic episodes associated with bipolar disorder. The extended-release formulation of divalproex sodium was developed in order to provide routine once-daily dosing and to reduce trough-to-peak serum concentration differences, prominent with divalproex. Elevated serum valproate concentrations have been associated with increased frequency of some side effects (eg, nausea, vomiting, tremor, decreased platelet count, and decreased white blood cell count).[1–3]

The efficacy and safety of divalproex ER for the treatment of acute mania was evaluated in 2 large, multicenter, placebo-controlled trials. Divalproex ER demonstrated statistically significant improvements in mania symptoms compared to placebo in 1 of the 2 studies,[4] while an earlier study did not demonstrate significant improvement associated with divalproex ER treatment. This article presents the efficacy and safety results from the earlier study and highlights key methodological considerations, which may have contributed to the disparate findings between the 2 studies.

METHOD

This study was conducted in accordance with ethical principles from the Declaration of Helsinki (as amended in October 1996) and with all applicable regulations. Each patient received an explanation of the study and signed an informed consent statement 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 May 1998 to July 1999 at centers in the United States.

Subjects

Eligible subjects were men and women aged 18 to 65 years meeting *Diagnostic and Statistical Manual of Mental*

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Disorders, Fourth Edition (*DSM-IV*) criteria for bipolar I disorder (manic or mixed type) confirmed by the Structured Clinical Interview for *DSM-IV* (SCID).[5] Participants had to have a Mania Rating Scale (MRS)[6] score ≥ 25 with at least any 4 items having a score ≥ 3 on the final day of the screening/washout period.

Patients were excluded if they had 1 of the 5 schizophrenia-like symptoms listed in the SCID as excluding a subject from the diagnosis of manic syndrome while not manic or if their first manic episode occurred when > 60 years of age. Patients with drug-induced mania, a history of AIDS-induced mania, a central nervous system disorder, a history of or active hepatitis or pancreatitis, current acute medical conditions, a history of valproate intolerance, or a history or current medical disorder that precluded study participation were also excluded. Patients with a history of a substance use disorder within 1 month prior to screening or those testing positive in a urine screen for phencyclidine, opiates, or amphetamines were not allowed to participate. A positive screen for cocaine was allowed provided the patient did not show signs of withdrawal at randomization. Additionally, the following patients were excluded: any patient needing medications that would have interfered with safety or efficacy outcomes, who had received a depot medication injection within the last 3 to 4 weeks, or who had a platelet count at screening < 100,000/mm^3. Women of childbearing potential were allowed to participate provided they were not pregnant and agreed to use an effective method of contraception.

Procedure

Upon entry into the study, subjects entered a screening/washout period lasting 3 to 21 days. Upon investigator approval, chloral hydrate (maximal daily dose: 4 g, washout through day 4, and 2 g, days 5 to 21) and/or lorazepam (maximal daily dose: 6 mg, during washout; 4 mg, days 1–4; and 2 mg, days 5–21) could be prescribed for the control of agitation, irritability, restlessness, insomnia, and hostility. Whenever possible, these medications were not to be administered within 8 hours prior to efficacy assessments. All other psychotropic medications were prohibited during the study. At the end of the screening/washout period, patients with an MRS score ≥ 25 with at least 4 items rated 3 or higher were allowed to continue in the study. Patients were randomly assigned in a 2:1 ratio to either divalproex sodium ER or placebo. Dosing was initiated at 20 mg/kg/d once daily with dose increases allowed on days 5, 10, and 15 at the investigator's discretion if significant mania symptoms persisted. Study medication was taken with the evening meal. Patients were discontinued from the study if they were discharged from the hospital or if both improvement criteria were met: (1) MRS score reduced by 50% or more from the last day of the washout period and (2) no MRS item was > 3 at the time of the last rating of the treatment period. Patients leaving the study entered a 7-day tapering period, during which time study medication was tapered at the investigator's discretion.

Efficacy

Efficacy was assessed using the MRS from the Schedule for Affective Disorders and Schizophrenia and its subscales, the Manic Syndrome Score and the Behavior and Ideation Score[6]; the Brief Agitation Rating Scale[7]; the Overt Aggression Scale[8]; and the Brief Psychiatric Rating Scale.[9] All ratings were to be performed by the same individual at approximately the same time of day for each subject within each site. The primary efficacy variable was the change from baseline to the final evaluation in MRS score.

Safety

Thyroid function tests, a urine drug screen, coagulation tests, and a urinalysis were performed on day 1 of the washout period. Hematology and blood chemistry tests, physical examinations (including vital signs), and pregnancy tests (for females of childbearing potential) were performed on day 1 of the washout period and day 21 (or the last day of the experimental period). Hematology, coagulation, and blood chemistry tests, and urine drug screen were to be repeated on the last day of the washout period, if the washout period lasted more than 7 days. Hematology and blood chemistry tests were also performed on day 10. Blinded serum valproate levels were obtained prior to dosing on days 5, 10, and 15 and on the last day of the treatment period. Adverse events and concomitant medications were assessed daily throughout the study.

Statistical Analyses

The planned sample size of 150 divalproex sodium ER and 75 placebo intent-to-treat (ITT) subjects should have detected a difference of 4.7 points in change from baseline between the 2 treatment groups at $P = .05$ level (2-tailed) with at least 80% power. This calculation was based on results from a previous study of divalproex sodium in acute mania and assumed a standard deviation of 11.7 for the MRS score mean change from baseline to final evaluation.

All efficacy analyses were performed in the ITT dataset. Subjects who had at least 1 dose of study drug and had both a baseline and at least 1 MRS rating postrandomization were included in the ITT dataset. All tests were 2-tailed, and type I error rate of .05 was used throughout the analyses. Baseline demographics and psychiatric variables were compared using a 1-way analysis of variance (ANOVA) with treatment group as the main effect for age, height, and weight; a Wilson rank sum test for age at first episode; a Cochran-Mantel-Haenszel test for the number of prior episodes; and Fisher exact test for gender and race. Baseline efficacy measurements were the rating scale scores obtained on the last day of the washout period. Change from baseline was calculated for each scheduled evaluation

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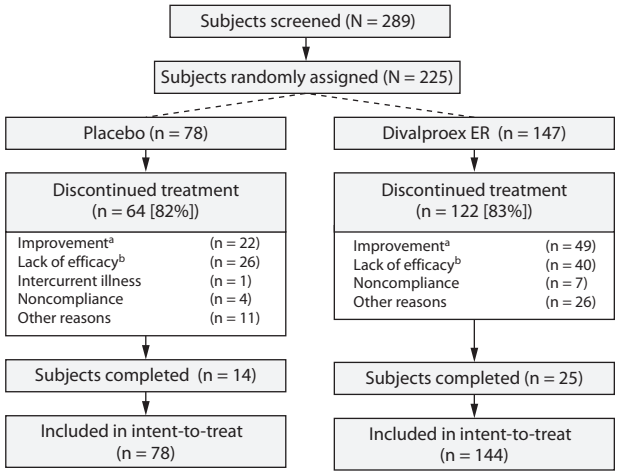
Figure 1. Subject Disposition



[a]Improvement was defined as a Mania Rating Scale score reduction ≥ 50% from the last day of washout period, with no Mania Rating Scale score > 3 at the time of the last rating during the experimental period.
[b]Lack of efficacy was defined as requiring additional psychotropic medication, depression requiring medication, and/or Mania Rating Scale score increase ≥ 30%.

for all efficacy variables using last observation carried forward. The primary efficacy variable (change from baseline to final in MRS score) was evaluated by a 2-way ANOVA with factors for treatment group, study site, and the treatment group by study site interaction. If the interaction term was not statistically significant at the .10 level, the analysis was a 2-way ANOVA with factors for treatment group and study center without the interaction. Sites that randomized < 3 subjects were combined together for statistical analysis. Individual MRS item scores were examined using the Cochran-Mantel-Haenszel technique using study centers as independent strata. In the event of missing data from individual rating scale items, an estimated score of the missing item was calculated by (1) calculating the ratio by dividing the total score by the maximum possible total score of nonmissing items and (2) multiplying the maximum possible score of the missing item by the ratio obtained in the first step.

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 dictionary. Treatment-emergent adverse events (events beginning or worsening on or after day 1) were summarized, and comparisons between treatment groups were made using Fisher exact test. Laboratory data were analyzed using a 1-way ANOVA with treatment as the main effect. Baseline comparability between groups was assessed by the overall *F*-test of the 1-way ANOVA. Laboratory values categorized as low or high and potential clinical significance, adjunctive medication use, and serum valproate levels were also summarized.

Table 1. Demographic and Clinical Characteristics of Bipolar I Disorder Patients Randomly Assigned to Divalproex ER or Placebo

Characteristic	Placebo (n = 78)	Divalproex ER (n = 144)	*P* Value[a]
Male, n (%)	34 (44)	80 (56)	.094
Caucasian, n (%)	62 (79)	117 (81)	.859
Age, mean (SD), y	40.4 (11.28)	38.5 (11.38)	.235
Height, mean (SD), in	66.6 (4.06)	67.9 (4.16)	.027*
Weight, mean (SD), lb	180.3 (47.25)	188.5 (56.40)	.273
Total no. of prior manic episodes, n (%)	n = 74	n = 143	.752
0	6 (8)	16 (11)	
1–5	27 (36)	45 (31)	
6–10	11 (15)	23 (16)	
11–15	6 (8)	6 (4)	
16–20	4 (5)	7 (5)	
> 20	20 (27)	46 (32)	
First manic episode	n = 69	n = 124	.017*
Age, mean (SD), y	27.2 (11.5)	23.5 (10.6)	
Total no. of prior mixed episodes, n (%)	n = 72	n = 129	.769
0	34 (47)	57 (44)	
1–5	18 (25)	26 (20)	
6–10	3 (4)	5 (4)	
11–15	2 (3)	2 (2)	
16–20	2 (3)	4 (3)	
> 20	13 (18)	35 (27)	
First mixed episode	n = 37	n = 69	.042*
Age, mean (SD), y	28.8 (11.7)	23.9 (9.8)	
Total no. of prior depressive episodes, n (%)	n = 73	n = 138	.301
0	22 (30)	28 (20)	
1–5	19 (26)	49 (36)	
6–10	6 (8)	16 (12)	
11–15	5 (7)	4 (3)	
16–20	3 (4)	9 (7)	
> 20	18 (25)	32 (23)	
First depressive episode	n = 53	n = 107	.271
Age, mean (SD), y	24.9 (11.5)	22.8 (11.1)	
Total no. of prior psychiatric hospitalizations, n (%)	n = 78	n = 143	.006*
0	10 (13)	25 (17)	
1–5	41 (53)	47 (33)	
6–10	11 (14)	34 (24)	
11–15	2 (3)	16 (11)	
16–20	2 (3)	9 (6)	
> 20	12 (15)	12 (8)	
First psychiatric hospitalization	n = 66	n = 114	.500
Age, mean (SD), y	26.6 (10.3)	25.5 (10.2)	

[a]*P* Values from Fisher exact test comparing treatment groups (sex, race) or a 1-way analysis of variance model comparing treatment groups (age, height, and weight). Values for number of episodes from Cochran-Mantel-Haenszel test, otherwise from Kruskal-Wallis test.
*$P < .05$, 2-tailed.
Abbreviation: ER = extended-release.

RESULTS

Of the 289 patients screened, 225 were randomized (78 to placebo and 147 to divalproex ER), and 222 were in the ITT population (78 to placebo and 144 to divalproex ER) (Figure 1). The demographic and baseline characteristics of the 2 treatment groups were similar (Table 1). Approximately half of the sample was male and predominantly Caucasian with a mean age of approximately 40 and a mean weight of

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Figure 2. Divalproex ER (All Treated Subjects) for the Current Study and a Recent Comparator Study (Bowden et al,[4] 2006)

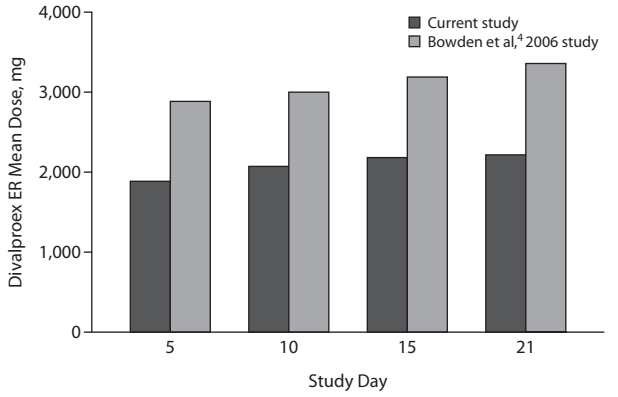
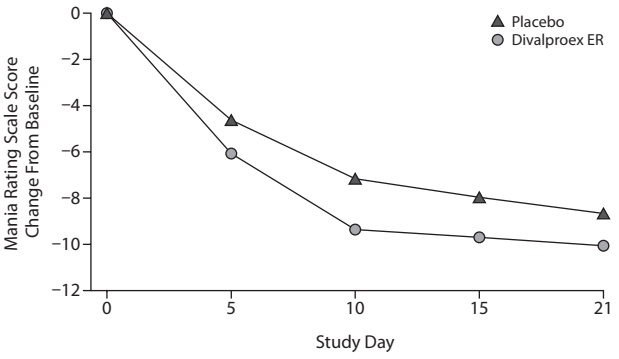


Figure 3. Change in Mania Rating Scale Scores Over Time



approximately 180 lb. Mean baseline MRS score was 32.3 for the divalproex ER and 32.7 for placebo.

A total of 25 patients completed the study in the divalproex ER group, and 14 completed the study in the placebo group. One hundred twenty-two of the patients (83%) in the divalproex ER group and 64 (82%) in the placebo group discontinued prematurely, with the most common reasons being improvement and lack of efficacy (Figure 1). Approximately 40% of patients in both treatment groups took study drug for less than 7 days. Mean daily doses of divalproex ER over time are presented in Figure 2 (for the purpose of comparison, dosing results from the second study are also presented).[4] Blinded serum valproate levels were collected approximately 12 hours post dose in the current study, which would approximate near maximum (peak) serum levels. In the current study, the mean (SD) daily dose on study day 21 was 2,210.5 mg (769.48), with a mean maximum valproic acid concentration of 77.9 μg/mL on day 21 in the remaining 22 patients. The mean maximum valproate concentration on day 5 was 78.4 μg/mL (n = 112), on day 10 was 84.64 μg/mL (n = 63), and on day 15 was 83.24 μg/mL (n = 42).

Table 2. Treatment-Emergent Adverse Events Reported by ≥ 10% of Subjects in Either Treatment Group or With Statistically Significant Treatment Differences (All Treated Subjects)[a]

COSTART Term	Placebo (n = 78), n (%)	Divalproex ER (n = 147), n (%)
Any event	54 (69)	109 (74)
Back pain	4 (5)	1 (1)*
Dyspepsia	9 (12)	21 (14)
Somnolence	5 (6)	21 (14)
Headache	9 (12)	19 (13)
Diarrhea	2 (3)	14 (10)
Constipation	9 (12)	6 (4)*

[a]Data presented as n (%).
*Statistically significant versus placebo at .05 level, 2-tailed.
Abbreviation: COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms.

Eighty-six percent of patients in both treatment groups used either chloral hydrate or lorazepam at least once during the study. There were no significant differences between the treatment groups in the use of adjunctive medication.

Efficacy

There were no statistically significant differences in MRS change from baseline to any timepoint for patients treated with divalproex ER compared with those treated with placebo (Figure 3). The mean change from baseline to final evaluation was −10.1 for divalproex ER and −8.7 for placebo. There were no differences between treatment groups on the Manic Syndrome Scale or the Behavior and Ideation Scale.

There were no statistically significant differences in any secondary efficacy measure, including change from baseline to final evaluation for Manic Syndrome Score, Behavior and Ideation Score, Brief Agitation Rating Scale, Overt Aggression Scale, and the Brief Psychiatric Rating Scale total scores and subscale scores.

Safety and Tolerability

Adverse events. Of the 225 patients who were randomized and took study drug, 62 of the placebo patients (79%) and 120 of the divalproex ER patients (82%) experienced an adverse event during the study. Most adverse events were mild to moderate in severity and were considered either not related or probably not related to study drugs. Treatment-emergent adverse events occurring in more than 10% of patients in either treatment group or those with statistically significant treatment differences are presented in Table 2. The rates between placebo and divalproex ER were generally similar. One patient in the placebo group discontinued due to adverse events of pruritus and rash.

Serious adverse events. Three patients experienced serious adverse events requiring hospitalization: 1 case of edema 4 days after the taper period ended (placebo), 1 case of depression 2 days after the taper period ended (divalproex ER), and 1 overdose 7 days after the taper period ended (divalproex ER).

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Table 3. Key Design Differences Between the Current Study and the Bowden et al,[4] 2006 Study

Characteristic	Current Study	Bowden et al,[4] 2006 Study
Inclusion criteria	MRS score ≥ 25 with at least 4 items having a score ≥ 3 on final day of washout Hospitalized during participation Prior episode not required	MRS score ≥ 18 with at least 4 items having a score > 2 at screening and on day prior to randomization Hospitalized for at least 15 d; could not be hospitalized for more than 7 d prior to screening/washout At least 1 prior manic or mixed episode within the last 3 yr
Randomization	2:1 divalproex ER to placebo	1:1 divalproex ER to placebo
Number of randomized subjects	225	377
Number of subjects/center, mean	7.8	11.4
Frequency of MRS assessments	Days 1–7, 10, 15, 21	Days 1, 5, 10, 15, 21
Dosing	Initiated at 20 mg/kg/d, rounded to nearest 500 mg, QD Dose adjusted at the discretion of the investigator on days 5, 10, and 15 if symptoms persisted	Initiated at 25 mg/kg/d, rounded to nearest 500 mg, QD On day 3, dose was increased by 500 mg for all subjects Additional dose adjustments on days 7, 12, and 17 (if thought necessary by investigator) based on tolerability, symptoms, and valproate levels A central laboratory notified investigators in a blinded fashion if trough serum valproate levels were not within a range of 85 to 125 μg/mL Doses could be reduced for safety reasons
Serum valproate level collection time	Approximately 12 h postdose (near peak)	Approximately 24 h ± 3 h postdose (trough)
Hospitalization criteria	Subjects remained hospitalized for the duration of the study Subjects were discontinued if they were discharged from the hospital or if they met improvement criteria (MRS score reduced by 50% and no MRS item score > 3)	Subjects remained hospitalized for at least 15 d during treatment Subjects could be discharged from hospital and return for outpatient visits for remaining assessments provided all following criteria were met: MRS score was reduced by 50% from day 1 and was < 13 No MRS item was > 2 GAS score was > 60 No lorazepam was needed Subject would be adequately supervised Investigator believed the subject had received enough study drug to remain stable
Adjunctive medication use	Chloral hydrate Maximal daily dose: Washout period through day 4: 4 g/d Study days 5 to 21: 2 g/d Lorazepam Maximal daily dose: Washout period: 6 mg Day 1 through day 4: 4 mg Day 5 through day 21: 2 mg If at all possible, adjunctive medications were not to be administered within 8 hours of efficacy ratings	Lorazepam was permitted if: It was not administered within 8 h of efficacy ratings Total daily dose did not exceed 6 mg during screening, 4 mg on days 1 through 7, and 2 mg on days 8 through 10 No lorazepam was allowed past day 10

Abbreviations: GAS = Global Assessment Scale, MRS = Mania Rating Scale.

There was 1 death in the study, which occurred during the screening period. The patient was admitted for extreme manic behavior, signed a consent form, and had some screening procedures performed. However, the patient was too agitated to be adequately evaluated, was not enrolled in the study, and was not randomized. He did not receive any study medication. Two days later, the patient died of a cardiac arrest.

Laboratory evaluation. Statistically significant differences between treatment groups were noted for mean changes from baseline to final for the following hematology tests: platelet count (divalproex ER: -26.8×10^9/L, placebo: 2.6×10^9/L; $P = .001$), white blood cells (divalproex ER: -0.94×10^9/L, placebo: 0.09×10^9/L; $P = .005$), and monocytes (divalproex ER: 1.26%, placebo: −0.10%; $P = .001$). There were statistically different mean changes from baseline in the following chemistry tests: glucose, total protein, albumin, total bilirubin, alkaline phosphatase, and calcium. Although several subjects had hematology or clinical chemistry values that met criteria for possibly clinically significant values, none of these subjects prematurely discontinued study drug because of the abnormality. Results of other safety analyses, including vital signs and physical examinations, were unremarkable for the treatment groups.

DISCUSSION

In this study, divalproex ER did not demonstrate a statistically significant improvement compared to placebo in the primary and secondary efficacy variables. There were relatively few differences in tolerability and safety measures

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between the divalproex ER– and placebo-treated patients. The results of this study were unusual because previous studies of divalproex sodium monotherapy in the acute treatment of mania had been positive.[10,11] A subsequent study did, in fact, demonstrate statistically significant improvements in mania symptoms associated with divalproex ER treatment compared to placebo.[4] There were several differences in methodology, which likely contributed to the different results of the 2 studies (Table 3).

Dosing and titration. Dosing and titration differed substantially between the 2 divalproex ER studies. In the current study, the initial dose of divalproex ER was 20 mg/kg/d, with titrations allowed at the investigator's discretion on study days 5, 10, and 15. The final mean daily dose of divalproex ER was only 2,211 mg/d (see Figure 2). Experience with divalproex ER was modest at the time of the study design, and therefore dosing and titration was based on knowledge of divalproex sodium. Subsequent experience led to higher initial dosing and a higher target dose. In the second study,[4] the initial dosing for divalproex ER was 25 mg/kg/d with a mandatory dose increase of 500 mg at day 3. The final mean daily dose of divalproex ER was 3,353 mg/d (see Figure 2).

The lower drug exposure in the current study also likely contributed to the numerically lower rates of adverse effects, as approximately half the rate of adverse effects such as somnolence, nausea, dyspepsia, dizziness, and vomiting were observed in this study compared with the second study.[4] The knowledge gained from the experience with the current study resulted in different dosing and titration schedules in the later study. Current practice is consistent with that employed in the later study.

Allowance for early termination. The current study had an unusual combination of criteria that resulted in very early protocol-authorized discharge from the hospital and study discontinuation. The earlier study was designed to minimize time in the hospital. A 50% reduction in baseline MRS score from day 1 on study drug could result in discharge from the hospital and termination from the study. To our knowledge, no other study of an intervention for mania in hospitalized patients has allowed such actions. Additionally, no core items on the MRS were required to be improved to levels consistent with recovery. This, therefore, allowed early nonspecific improvement, which is a major contributor to loss of power in acute illness trials in psychiatric disorders. This study also had scheduled symptom ratings on days 1 through 7, allowing for discharge and study discontinuation at each of these 7 time periods. In contrast, the second study had 3 scheduled symptom ratings on days 1, 5, and 7 during the first week of randomized treatment.[4]

That study also required a minimum period of hospitalization of 15 days, therefore ensuring this period of assessments in the structured setting of the hospital and providing sufficient time to observe a true drug effect on manic symptoms.[4] The consequence of these methodological differences was that in the current study, 82% and 83% of divalproex ER– and placebo-treated patients had early discontinuation, compared with 48% and 42% in the other study, respectively.

Adjunctive medication for agitation, anxiety, and insomnia. The current study had relatively liberal allowance for use of lorazepam and/or chloral hydrate, with no time limit on usage. In contrast, the second study allowed for lorazepam for a limited period of time only (10 days) and allowed no other adjunctive psychotropic medications.[4] Although the proportions of patients who used adjunctive medications do not appear to differ between the 2 studies, the cumulative amount and use close to periods of scheduled ratings may have vitiated drug-placebo differences.

Randomization scheme. The current study had a 2:1 ratio for active drug versus placebo, whereas the second study had a 1:1 ratio.[4] Higher proportions of subjects receiving active treatment impacts both recruitment and rater behavior. Patients and raters are likely to have greater anticipation of improvement if they know that the proportion of subjects receiving active drug is higher than that receiving placebo, resulting in increased response rates among placebo subjects. Subjects are also more likely to consent to studies in which the likelihood of receiving an "active" treatment is increased.

In conclusion, analysis of these 2 acute mania trials of divalproex ER versus placebo provided an unusual opportunity to address a secondary, important aim: to determine which design features serve to support drug-placebo differences when established, effective agents are employed in treatment of mania. Equally important, the contrasts on several points in design of the 2 studies indicate design features to avoid in planning of future studies in mania.

Drug names: divalproex (Depakote and others), lorazepam (Ativan and others), valproate (Depacon and others).

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REFERENCES

1. Keck PE Jr, McElroy SL, Tugrul KC, et al. Valproate oral loading in the treatment of acute mania. *J Clin Psychiatry*. 1993;54(8):305–308.
2. Zarate CA Jr, Tohen M, Narendran R, et al. The adverse effect profile and efficacy of divalproex sodium compared with valproic acid: a pharmacoepidemiology study. *J Clin Psychiatry*. 1999;60(4):232–236.
3. Wilder BJ, Karas BJ, Penry JK, et al. Gastrointestinal tolerance of divalproex sodium. *Neurology*. 1983;33(6):808–811.
4. Bowden CL, Swann AC, Calabrese JR, et al. Depakote ER Mania Study Group. A randomized, placebo-controlled, multicenter study of divalproex sodium extended release in the treatment of acute mania. *J Clin Psychiatry*. 2006;67(10):1501–1510.
5. First MB, Spitzer RL, Gibbon M, et al. *Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV)*. Washington, DC: American Psychiatric Press, Inc.; 1996.
6. Endicott J, Spitzer RL. A diagnostic interview: the schedule for affective disorders and schizophrenia. *Arch Gen Psychiatry*. 1978;35(7):837–844.
7. Finkel SI, Lyons JS, Anderson RL. A Brief Agitation Rating Scale (BARS) for nursing home elderly. *J Am Geriatr Soc*. 1993;41(1):50–52.
8. Yudofsky SC, Silver JM, Jackson W, et al. The Overt Aggression Scale for the objective rating of verbal and physical aggression. *Am J Psychiatry*. 1986;143(1):35–39.
9. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychol Rep*. 1962;10:799–812.
10. Pope HG Jr, McElroy SL, Keck PE Jr, et al. Valproate in the treatment of acute mania: a placebo-controlled study. *Arch Gen Psychiatry*. 1991;48(1):62–68.
11. Bowden CL, Brugger AM, Swann AC, et al. The Depakote Mania Study Group. Efficacy of divalproex vs lithium and placebo in the treatment of mania. *JAMA*. 1994;271(12):918–924.

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