A Double-Blind, Randomized, Placebo-Controlled Trial of Divalproex Extended-Release in the Treatment of Bipolar Disorder in Children and Adolescents

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ABSTRACT

Objective: To compare the efficacy and safety of divalproex extended-release (ER) to placebo in a 28-day double-blind study of bipolar disorder in children and adolescents and evaluate the safety of divalproex ER in a 6-month open-label extension study. **Method:** In the double-blind study, 150 patients (manic or mixed episode, aged 10–17 years) with baseline Young Mania Rating Scale (YMRS) score of 20 or higher were randomized to once-daily placebo or divalproex ER, which was titrated to clinical response or serum valproate concentration of 80 to 125 μg/mL. Sixty-six patients enrolled in the extension study. **Results:** In the double-blind study, a treatment effect was not observed with divalproex ER based on change in mean YMRS score (divalproex ER −8.8 [$n = 74$]; placebo −7.9 [$n = 70$]) or secondary measures. Divalproex was similar to placebo based on incidence of adverse events. Four subjects treated with divalproex ER and three treated with placebo discontinued because of adverse events. Mean ammonia levels increased in the divalproex ER group, but only one patient was symptomatic. In the long-term study, YMRS scores decreased modestly (2.2 points from baseline). The most common adverse events were headache and vomiting. **Conclusions:** The results of the study do not provide support for the use of divalproex ER in the treatment of youths with bipolar I disorder, mixed or manic state. Further controlled trials are required to confirm or refute the findings from this study. *J. Am. Acad. Child Adolesc. Psychiatry*, 2009;48(5):519–532. **Key Words:** bipolar disorder, divalproex ER, treatment. Clinical trial registration information—An Outpatient Study of the Effectiveness and Safety of Depakote ER in the Treatment of Mania/Bipolar Disorder in Children and Adolescents. URL: *http://clinicaltrials.gov*. Unique identifier: NCT00067262. Evaluate the Safety of Depakote Extended Release Tablets in the Treatment of Mania Associate With Disorder in Children and Adolescents. URL: *http://clinicaltrials.gov*. Unique identifier: NCT00195767.

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Bipolar disorder in children and adolescents is a serious disorder that has a significant adverse impact on a child's overall functioning. Youths with bipolar disorder have episodes of long duration, high relapse rates, and a high risk for suicidality.[1–3] An early age of onset of this illness is associated with more severe mania and depression and less euthymic periods.[4] There is a compelling need to identify effective treatments for children and adolescents with bipolar disorder. To date, lithium, risperidone, and aripiprazole are the only agents that have Food and Drug Administration (FDA) approval for the treatment of bipolar disorder in adolescents.

In clinical practice, divalproex is commonly used for the treatment of bipolar disorder in children and adolescents, as supported by extensive data from open studies of divalproex in this age group. Kowatch et al.[5] reported a response rate of 53% and an effect size of 1.63 for divalproex in a 6-week open-label treatment study comparing lithium, divalproex, and carbamazepine for youths with bipolar disorder. In a 2- to 8-week open-label study of divalproex, 22 youths (61%) showed a 50% or greater improvement in the mania rating scale in this period.[6] A chart review of 15 children with bipolar disorder found that divalproex treatment improved long-term outcome.[7] A 73.5% response rate and a 52.9% remission rate were observed in a prospective 6-month open-label trial conducted in 36 child and adolescent patients with mixed mania.[8] Divalproex was compared with quetiapine in a double-blind randomized pilot study of adolescent inpatients with mania.[9] There was no statistically significant difference between divalproex and quetiapine in change in Young Mania Rating Scores (YMRS) across the 28 days of the study, although a quicker reduction of manic symptoms occurred with quetiapine as compared with divalproex. The Clinical Global Impressions-Bipolar Version-Improvement (CGI-BP-I) overall response rate (CGI-BP-I overall score >2 at endpoint) was significantly greater (p = .02) in the quetiapine group (18/25 [72%]) than in the divalproex group (10/25 [40%]).

Although chart reviews, open-label studies, and a small comparator study provide an evidence base for the use of divalproex in treating children and adolescents, it is important to examine the efficacy of divalproex in a large controlled trial.

In this article, we report the first multicenter double-blind, randomized, placebo-controlled trial of divalproex extended-release (ER) for the treatment of bipolar disorder in children and adolescents. The 4-week study design was consistent with the written request from the FDA, which recommended a randomized, double-blind, parallel group, placebo-controlled acute bipolar disorder trial, with a recommended duration of at least 3 weeks. We also include results from an optional 6-month open-label study of divalproex ER that followed the acute placebo-controlled trial.

METHOD

Study Population

The studies were conducted in accordance with ethical principles as described in the Declaration of Helsinki and all applicable local regulations. The protocols were approved by the institutional review board of each participating study site. Written informed assent was obtained from the patient, and written informed consent was obtained from the patient's legally authorized representative before enrollment into each study. During the course of the double-blind study, an independent Data Monitoring Committee reviewed and interpreted safety data on a regular basis.

Participants in the double-blind study were outpatients aged 10 to 17 years who weighed at least 27 kg (60 lb) and had a current *DSM-IV-TR* diagnosis of bipolar I disorder, manic or mixed episode.[10] All diagnostic and rating evaluations were based on information obtained from the subject and other pertinent sources (e.g., parent, caregiver). The Washington University at St. Louis Schedule for Affective Disorders and Schizophrenia interview[11,12] was administered by a qualified mental health professional, and the diagnosis was confirmed by a board eligible or board certified child and adolescent psychiatrist. Patients were required to have a Young Mania Rating Scale (YMRS)[13,14] total score of 20 or greater at the time of screening and at randomization. At an investigators meeting before the start of the study, training was conducted in administration of the Washington University at St. Louis Schedule for Affective Disorders and Schizophrenia by the author of the instrument (B.G.). Raters for the YMRS received training before the start of the study to establish uniformity across sites in the use and interpretation of the YMRS, and all raters were reassessed periodically throughout the study. Efforts were made to assure that the same rater performed ratings for each subject throughout the study. Clinical monitors examined source documents at the study sites to assess protocol adherence, and all data collected at the study sites were reviewed for protocol deviations.

Exclusion criteria included a current manic episode that was drug induced or secondary to a medical disorder; a current diagnosis of a *DSM-IV-TR* Axis I disorder other than attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder, oppositional defiant disorder, conduct disorder, panic disorder, enuresis, encopresis, parasomnias, agoraphobia, specific phobia, social phobia or separation anxiety disorder; or a current Axis II disorder that would interfere with compliance or confound study results interpretation. Patients with a history of substance abuse within the month before screening, substance dependence within 3 months before screening, or evidence of drug or alcohol withdrawal/intoxication at the time of randomization were excluded. Mental retardation or cognitive deficits severe enough to confound study interpretation or interfere with compliance were exclusion criteria. Patients who had current

serious violent, homicidal, or suicidal ideation were excluded. Female patients who were pregnant or lactating were excluded. Other exclusion criteria included patients expected to require hospitalization for their manic or mixed episode and patients with clinically significant abnormal laboratory data, unstable medical conditions, or an underlying condition that would confound the interpretation of the study results.

The concurrent use of antipsychotic, antidepressant, and mood stabilizer/anticonvulsant medication other than the study drug was not allowed during the study participation. Patients who were taking a protocol-prohibited psychotropic medication within five elimination half-lives before randomization were excluded. The adjunctive use of zolpidem tartrate (up to 10 mg per day for insomnia) and lorazepam (up to 4 mg for severe agitation) was permitted, up to 3 times per week during the washout period and the first 14 days of double-blind period, except during the 8 hours before efficacy ratings. There were no restrictions on zolpidem tartrate or lorazepam during the long-term study. Treatment of ADHD with stimulant medications (with the exception of pemoline) was also allowed during both the double-blind and long-term studies for patients whose dosage had been stable for 3 months before day 1, and the investigator planned to maintain this stable dose throughout the study, and this medication was not exacerbating mood symptoms. Use of atomoxetine was not allowed.

Patients who either completed the double-blind study or prematurely discontinued because of ineffectiveness were eligible for the long-term study, unless they had experienced a serious adverse event, which was considered possibly or probably related to study drug.

Study Design

Double-Blind Study. This was a double-blind, randomized, placebo-controlled trial of divalproex ER as monotherapy in the outpatient treatment of children and adolescents with a diagnosis of bipolar I disorder, mixed or manic episode. The study consisted of a 3- to 14-day screening period, a 4-week double-blind treatment period, and an optional 1-week taper period during which the study blind was maintained. Once written informed assent/consent was obtained, each patient who met inclusion criteria entered the screening period of the double-blind study. During the screening period, any protocol-prohibited psychotropic medications were washed out. Patients were randomized in a 1:1 ratio to receive divalproex ER or matching placebo tablets. Study drug was initiated at 15 mg/kg per day (not to exceed 750 mg) and titrated in 250-mg increments every 1 to 3 days to clinical response and/or a serum valproate concentration within the target range of 80 to 125 μg/mL, as deemed appropriate by the investigator, to a maximum dosage of 35 mg/kg per day.

Blood samples for measurement of blinded serum valproate concentration were collected approximately 24 ± 3 hours after the previous dose of study drug on days 7, 14, and 28. Trough serum total valproate concentrations were reviewed by an unblinded qualified person at the central laboratory who was uninvolved with any study procedures other than blinded blood level reporting. In the event that a subject had a trough serum valproate concentration greater than 125 μg/mL on study day 7 or 14, the unblinded central laboratory person telephoned the appropriate investigator and reported that the level was high. In the event that a subject who had received active study medication had a trough serum valproate concentration less than 80 μg/mL on study day 7 or 14, the unblinded central laboratory person telephoned the investigator and reported that the level was low. In either event, to preserve the study blind, a corresponding sham call was also made. Each time that the central laboratory person reported a level as high or low for a subject who received active medication, he or she made a telephone call at an appropriate time during the study to a different investigator about a placebo subject at the same point (day 7 or 14) in the study and reported that the level was high or low. Every investigator that received a call from the central laboratory regarding valproate levels used clinical judgment to determine if an increase or decrease in dose was clinically warranted.

Long-Term Study. The long-term study was a 6-month extension of the double-blind study in which patients were treated with open-label divalproex ER. For patients who entered the long-term study directly from the double-blind study, with no interruption in study drug dosing, the dose of blinded study drug was reduced on the first day (by approximately 50%), again on day 3 or 4 of the long-term study, at the investigator's discretion, and discontinued altogether within 7 days. These patients, as well as those patients who had interrupted study drug and were not taking commercially available valproate at the time of enrollment in the long-term study, had open-label divalproex ER initiated at a target dosage of 15 mg/kg per day once daily, not to exceed 750 mg/day on day 1. For those patients who had interrupted study drug during the double-blind study and were taking commercially available valproate at enrollment in the long-term study, divalproex ER was continued at the same dose (as was taken just before enrollment) to maintain a satisfactory response.

The dosage of divalproex ER was adjusted, as needed, at the discretion of the investigator to achieve maximal clinical effect and/or a serum valproate concentration within the target range of 80 to 125 μg/mL to a maximum allowable dosage of 35 mg/kg per day. Blood samples for the measurement of trough valproate concentration were collected at months 1 and 6 as well as at premature discontinuation, if applicable.

Measures

Double-Blind Study. Participants were assessed with the YMRS and the CGI-Severity (CGI-S) and Improvement (CGI-I) scales[15] on day 1 (baseline) and at weekly visits during the 4-week double-blind treatment period. The Children's Depression Rating Scale-Revised (CDRS-R)[16,17] was used on days 1, 14, and 28. The Caregiver Strain Questionnaire (CGSQ),[18] the Children's Global Assessment Scale (CGAS),[19] and the ADHD Rating Scale-IV: Home Version[20] were administered on days 1 and 28.

Long-Term Study. The YMRS, CGI-S, CDRS-R, and C-GAS were administered at months 1, 2, 3, and 6. The CGSQ was assessed at month 6. These evaluations were also conducted on day 1 of the long-term study if they had not been performed in the previous 7 days in the double-blind study.

Safety Assessments

Study drug safety was assessed by monitoring of adverse events and changes in vital signs, body weight, height, body mass index (BMI), and laboratory tests. Adverse events were obtained by spontaneous report in response to open-ended questions.. Patients were monitored for adverse events from the time study drug was initiated until 30 days after its discontinuation in both the double-blind and long-term studies. Blood samples were collected for assessment of hematology and clinical chemistry indices at screening and on days 14 and 28 of the double-blind study (with the exception of ammonia, which was not measured on day 14) and at the months 1, 2, 3, and 6 visits during the long-term study. All laboratory tests were

performed using validated procedures by a central laboratory certified by the College of American Pathologists and Clinical Laboratory Improvement Amendments. Vital signs were measured at all study visits in the double-blind and long-term studies. Physical examination and electrocardiograms were performed at the screening and day 28 visits in the double-blind study and at the month 6 visit in the long-term study.

Statistical Analyses

Double-Blind Study. The primary efficacy endpoint was change from baseline to final evaluation on the YMRS total score. The definition of response was 50% or greater improvement on the YMRS total score from baseline. Remission was defined as a YMRS score of less than 12 at final evaluation. Secondary measures were the CGAS, CGI-I, CGI-S, CDRS-R, ADHD Rating Scale IV, and CGSQ.

A target sample size of 75 patients per treatment group was selected to provide 80% power for an effect size of 0.46, treatment difference of 5.3, pooled SD of 11.6, assuming a 2-tailed type I error rate of 0.05. All statistical tests were two tailed, and p values of .05 were considered statistically significant. All analyses were performed using the SAS system (Version 8.2; SAS Institute, Cary, NC).

Efficacy analyses were performed on the intent-to-treat data set, which included all patients who received at least one dose of randomized study medication and had a YMRS total score recorded at baseline and at least once during treatment. Baseline comparability between the placebo and divalproex ER groups for demographic and psychiatric history variables was assessed by a one-way analysis of variance (ANOVA) with treatment group as the main effect or a

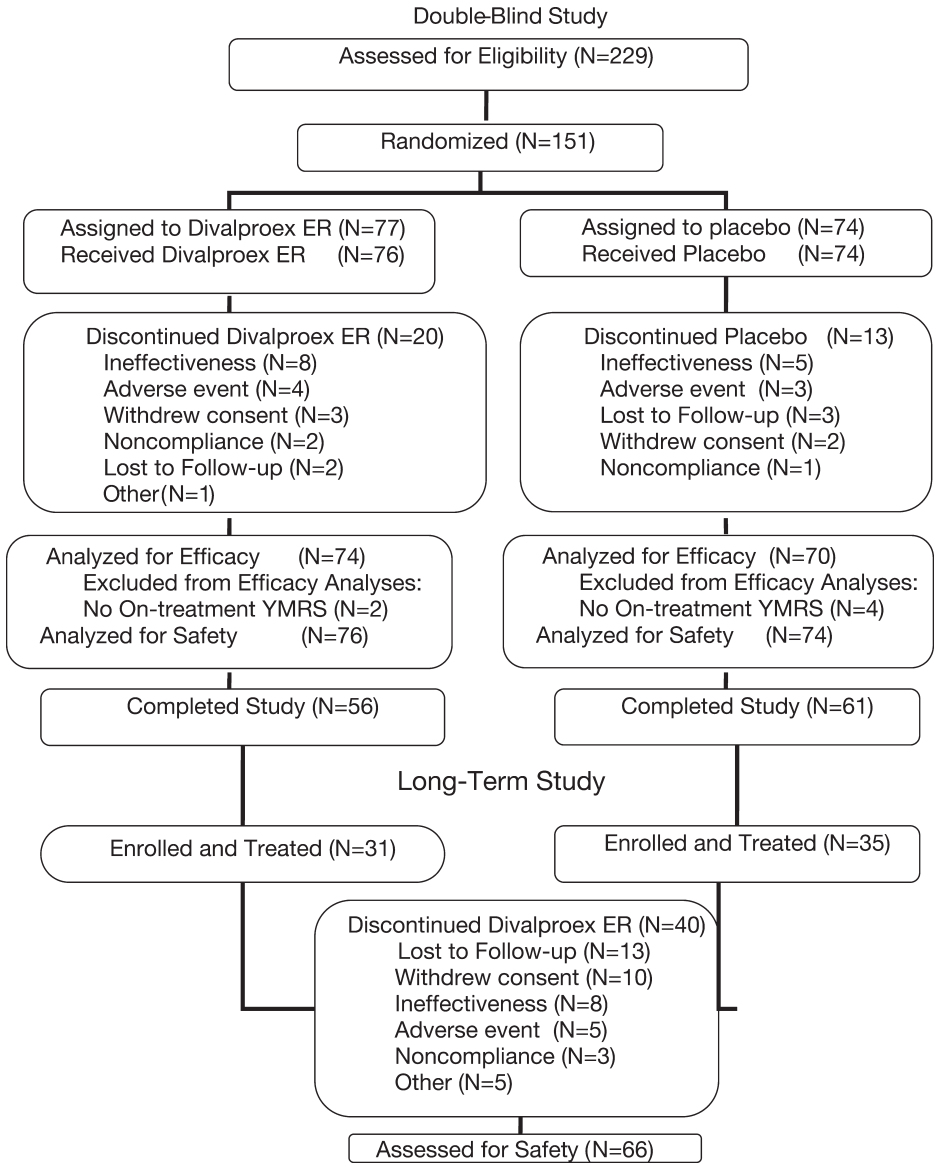

Fig. 1 Patient disposition. Patients may have reported more than one reason for premature discontinuation but are counted only once in the total.

Wilcoxon rank-sum test for quantitative variables, by the Cochran-Mantel-Haenszel test for ordered categorical variables, and by the Fisher exact test for qualitative variables.

The difference between treatment groups for change from baseline to each evaluation (with last observation carried forward) for all rating scale scores except the CGI-I was evaluated using a two-way ANOVA with factors for treatment and site. Treatment-group differences for the YMRS response rate, YMRS remission rate, and CGI-I score at each evaluation were evaluated using the Cochran-Mantel-Haenszel test with sites as strata.

Safety analyses were performed on the safety data set, which included all patients who received at least one dose of randomized study medication. Adverse events were coded with the Medical Dictionary for Regulatory Authorities.[21] Fisher exact test was used to assess treatment-group differences in treatment-emergent adverse event incidence rates. Treatment group differences in laboratory data and growth parameters (i.e., height, weight, BMI) for mean change from baseline to the final evaluation were assessed by one-way ANOVA.

Long-Term Study. The efficacy data set for the long-term study included all patients who received at least one dose of divalproex ER in the long-term study and for whom efficacy assessments were available at baseline and at least one on-treatment visit. Baseline was the last efficacy assessment before initiation of treatment in the long-term study. Efficacy data were summarized using descriptive statistics.

The safety data set for the long-term study consisted of all patients who received at least one dose of divalproex ER in the long-term study. For patients who received divalproex ER in the double-blind study and entered directly into the long-term study, the safety data set contained all safety data collected during divalproex ER treatment in both studies. Baseline was the last efficacy assessment before the first dose of divalproex ER in the double-blind study. For patients randomized to placebo in the double-blind study and for patients who were randomized to divalproex ER in the double-blind study but had a gap of at least 7 days before start of the long-term study, the safety data set contained safety data from only the long-term study. Baseline was the last assessment before the first dose of

TABLE 1
Demographic and Clinical Characteristics at Baseline

	Double-Blind, 28-Day Study		
Characteristic	Placebo (n = 70)	Divalproex ER (n = 74)	6-Month Long-Term Study Divalproex ER (n = 66)
Sex, n (%)			
Female	27 (39)	30 (41)	25 (38)
Male	43 (61)	44 (59)	41 (62)
Age, y, n (%)			
Mean (SD)	12.8 (2.20)	12.9 (2.28)	12.9 (2.25)
By age group			
10–13 y	47 (67)	47 (64)	43 (65)
14–17 y	23 (33)	27 (36)	23 (35)
Race, n (%)			
White	52 (74)	55 (74)	49 (74)
Black	14 (20)	15 (20)	13 (20)
Other	4 (6)	4 (5)	4 (6)
Weight, kg			
Mean (SD)	54.6 (19.36)	55.3 (19.52)	55.7 (20.36)
Range	27–99	30–105	29–106
Height, cm			
Mean (SD)	154.2 (12.9)	156.0 (13.23)	156.2 (13.00)
Range	130–188	127–188	135–188
BMI, kg/m^2			
Mean (SD)	22.4 (5.65)	22.2 (5.43)	22.3 (6.09)
Range	14.3–37.0	14.8–39.6	14.3–40.5
DSM-IV-TR bipolar I diagnosis, n (%)			
Manic episode	40 (57)	36 (49)	39 (59)
Mixed episode	30 (43)	38 (51)	27 (41)
Rapid cycling	27 (39)	25 (34)	16 (24)
Psychotic features	8 (11)	8 (11)	6 (9)
Mean (SD) YMRS total score	31.3 (5.44)	31.0 (0.5.42)	20.3[a] (10.15)

Note: $p > .05$ for all comparisons in the double-blind study. BMI = body mass index; ER = extended release; YMRS = Young Mania Rating Scale.

[a] n = 54.

divalproex ER in the long-term study. Safety data were summarized using descriptive statistics.

RESULTS

Double-Blind Study

Two hundred twenty-nine patients were screened, 151 were randomized, and 150 received study drug (76 divalproex ER and 74 placebo) at 24 U.S. investigative sites in the double-blind 28-day study (Fig. 1). Nine patients who were screened were not randomized because they did not meet all of the inclusion criteria (one subject) or they met at least one of the exclusion criteria (four of eight had a disallowed Axis I disorder). Of the 150 treated patients, 144 were included in the intent-to-treat analyses of efficacy, with 6 excluded because they did not have an on-treatment YMRS score. The double-blind randomized treatment groups were not significantly different at baseline based on demographics (Table 1), psychiatric history (Table 2), and mean YMRS score (Table 1).

A total of 33 patients (22%) prematurely discontinued their participation in the double-blind study; the most common reasons were ineffectiveness (8 [11%] divalproex ER patients and 5 [7%] placebo patients) and adverse events (4 [5%] divalproex ER patients and 3 [4%] placebo patients). No statistically significant between-group differences were noted for overall premature discontinuation rate or rate of premature discontinuation from the study for any specific reason.

Study Drug Dosing and Valproate Concentrations. The mean modal daily dose of divalproex ER was 24.3 mg/kg (1,286 mg) with mean doses of 11.4 mg/kg on day 1; 17.1 mg/kg on day 7; 23.4 mg/kg on day 14; 26.2 mg/kg

TABLE 2
Psychiatric History

Psychiatric History Variable	Double-Blind, 28-Day Study		6-Month Long-Term Study Divalproex ER
	Placebo	Divalproex ER	
Manic episodes, *n* (%)	*n* = 69	*n* = 73	*n* = 66
0	37 (54)	45 (62)	38 (58)
1–5	20 (29)	19 (26)	18 (27)
>5	12 (17)	9 (12)	10 (15)
Age (y) at first manic episode[a]	*n* = 32	*n* = 28	*n* = 28
Mean (SD)	10.3 (3.5)	10.4 (3.8)	10.0 (3.9)
Mixed episodes, *n* (%)	*n* = 67	*n* = 74	*n* = 65
0	44 (66)	44 (59)	43 (66)
1–5	10 (15)	13 (18)	11 (17)
>5	13 (19)	17 (23)	11 (17)
Age (y) at first mixed episode[a]	*n* = 23	*n* = 30	*n* = 22
Mean (SD)	9.0 (3.6)	9.6 (3.6)	9.7 (3.4)
Depressive episodes, *n* (%)	*n* = 69	*n* = 74	*n* = 65
0	51 (74)	60 (81)	60 (92)
1–5	12 (17)	13 (18)	3 (5)
>5	6 (9)	1 (1)	2 (3)
Age (y) at first depressive episode[a]	*n* = 17	*n* = 14	*n* = 5
Mean (SD)	9.9 (2.8)	9.5 (3.1)	9.6 (3.7)
≥1 bipolar hospitalizations	*n* = 69	*n* = 74	*n* = 65
n (%)	15 (22)	9 (12)	12 (18)
Age (y) at first bipolar hospitalization	*n* = 15	*n* = 9	*n* = 12
Mean (SD), y	12.8 (3.0)	12.0 (2.4)	11.5 (3.0)
≥1 suicide attempt,	*n* = 68	*n* = 74	*n* = 64
n (%)	9 (13)	6 (8)	6 (9)
Age (y) at first suicide attempt[a]	*n* = 9	*n* = 6	*n* = 6
Mean (SD)	12.7 (4.3)	10.6 (4.2)	11.8 (3.7)
Psychiatric history of ADHD,	*n* = 70	*n* = 74	*n* = 66
n (%)	49 (70)	48 (65)	41 (62)

Note: $p > .05$ for all comparisons, in the double-blind 28-day study. ADHD = attention-deficit/hyperactivity disorder; ER = extended release.
[a]Includes patients with one or more previous episodes.

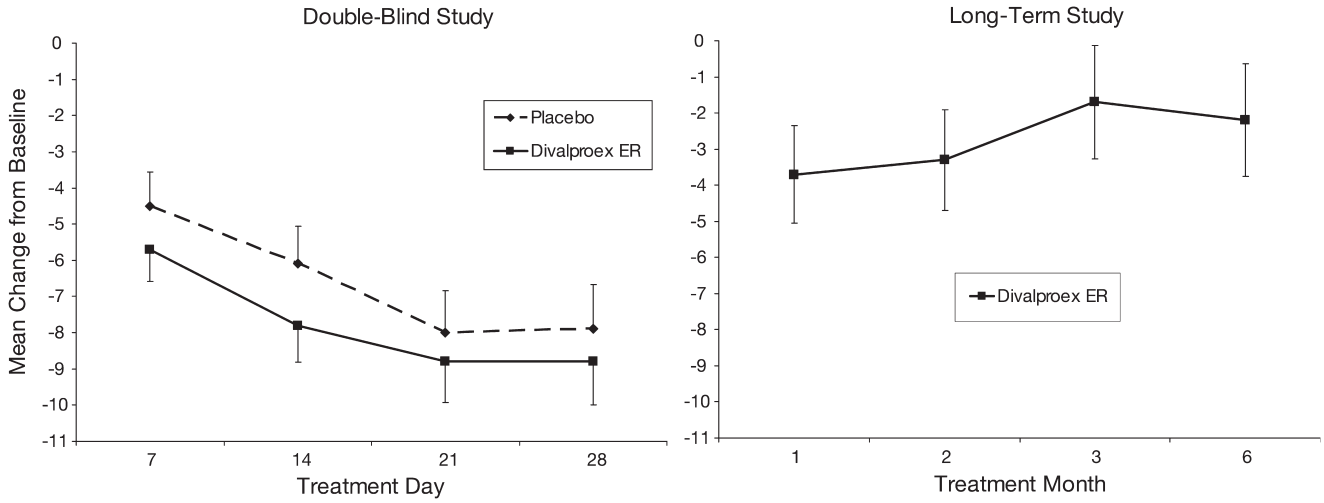

Fig. 2 Mean change in Young Mania Rating Scale total scores during double-blind (LOCF: $n = 70$, placebo; $n = 74$, divalproex ER) and long-term studies (LOCF: $n = 54$, divalproex ER). LOCF = last observation carried forward.

on day 21; and 27.1 mg/kg on day 28 of the study. Mean (SD) serum valproate concentrations (micrograms per milliliter) were 77.3 (33.6) on day 7; 90.6 (40.8) on day 14; 82.2 (44.0) on day 28; and 79.9 (43.7) at final evaluation (endpoint).

Efficacy Results. There was no statistically significant difference between divalproex ER and placebo in the YMRS total score mean change from baseline to final evaluation (−8.8 versus −7.9, respectively, $p = .604$; Fig. 2 and Table 3). Likewise, a treatment-group difference was not observed with respect to the proportion of responders (24% of divalproex ER patients and 23% of placebo patients) or proportion of patients who achieved remission (16% and 19% of patients in the divalproex ER and placebo groups, respectively). Treatment effect was not a function of age group (10–13 years versus 14–17 years) or use of stimulant medication during the study. When divalproex-treated patients were grouped according to valproate concentrations at endpoint based on quartiles, neither response rate nor mean change from baseline in YMRS scores increased systematically as a function of valproate concentration. Furthermore, a treatment effect was not observed for any of the other secondary efficacy measures, including C-GAS, CGI-S, CGI-I, CDRS-R, CGSQ, and ADHD Rating Scale-IV (Table 3).

Safety Results. The overall incidence of treatment-emergent adverse events was 67% with divalproex ER and 59% with placebo. There were no statistically significant differences in the overall incidence of adverse events or in the incidence of any individual adverse events (Table 4).

Four patients treated with divalproex ER and three patients treated with placebo prematurely discontinued due to adverse events. These adverse events in the divalproex ER group included one case of migraine; one case of depression; one case of increased ammonia level resulting in disorientation and hospitalization; and one case of intentional overdose of a combination of prescription and over the counter analgesics, which resulted in hospitalization. These adverse events in the placebo group included one case of pharyngolaryngeal pain, one case of swollen face and maculopapular rash, and one case of generalized rash. In addition, one patient on placebo had suicidal ideation that required hospitalization. The three adverse events that resulted in hospitalization met the regulatory definition of a serious adverse event. There were no suicides in the divalproex ER or placebo group.

Weight gain was significantly greater in the divalproex ER group (1.0 kg) than in the placebo group (0.3 kg; $p < .01$), as was the BMI (0.5 kg/m^2 for divalproex ER and 0.1 kg/m^2 for placebo). There was no significant difference in change in height between treatment groups. There were no significant treatment differences for vital signs (blood pressure, heart rate, temperature). Results for changes in laboratory parameters with statistically significant treatment differences are shown in Table 5. In general, the mean changes from baseline to endpoint for

TABLE 3
Primary Efficacy and Secondary Measures of Response (Change From Baseline to Final Evaluation With LOCF) in the Double-Blind and Long-Term Studies

	Double-Blind Study			Long-Term Study
	Mean[a] (± SE)			Mean (±SD)
Response Measure	Placebo	Divalproex ER	p^b	Divalproex ER
YMRS				
n	70	74		54
Baseline	31.3 (0.65)	31.0 (0.63)	.716	20.3 (10.15)
Change from baseline at endpoint	−7.9 (1.23)	−8.8 (1.19)	.604	−2.2 (11.48)
CGAS				
n	65	61		53
Baseline	49.9 (0.95)	49.7 (0.99)	.891	61.8 (11.39)
Change from baseline at endpoint	6.6 (1.42)	7.3 (1.49)	.679	0.2 (11.49)
CGI-S				
n	70	74		53
Baseline	4.6 (0.08)	4.7 (0.07)	.529	3.5 (1.28)
Change from baseline at endpoint	−0.7 (0.14)	−0.8 (0.13)	.756	−0.1 (1.44)
CGI-I[c]				
n	70	74		
Score at endpoint	3.3 (0.17)	3.1 (0.13)	.385	
Responders[d], *n* (%)	25 (36)	23 (31)	.782	
CDRS-R				
n	69	68		52
Baseline	37.6 (1.34)	38.5 (1.34)	.598	28.4 (10.04)
Change from baseline at endpoint	−2.8 (1.43)	−4.9 (1.43)	.269	−0.6 (10.00)
CGSQ				
n	61	61		34
Baseline	67.3 (2.38)	68.5 (2.39)	.678	56.4 (16.47)
Change from baseline at endpoint	−3.4 (1.69)	−5.4 (1.70)	.351	−1.4 (16.04)
ADHD Rating Scale-IV				
n	65	60		
Baseline	37.8 (1.76)	34.6 (1.87)	.157	
Change from baseline at endpoint	−3.7 (1.49)	−5.1 (1.59)	.478	

Note: Baseline was the last observation on or before the first dose of divalproex ER treatment in the long-term study; if no baseline was recorded, the last value in the double-blind study was used as the baseline if it was collected within 7 days before the first dose of study drug in the long-term study. Final evaluation was day 28 in the double-blind study and month 6 in the long-term study. CGAS = Children's Global Assessment Scale; CGI-I = Clinical Global Impression-Improvement; CDRS-R = Children's Depression Rating Scale-Revised; CGI-S = Clinical Global Impression-Severity; CGSQ = Caregiver Strain Questionnaire; ER = extended release; LOCF = last observation carried forward; YMRS = Young Mania Rating Scale.

[a]Mean = least squares mean from analysis of variance.

[b]Based on two-way analysis of variance that included factors for treatment and investigator for all measures except CGI-I for which the Cochran-Mantel-Haenszel test was used.

[c]Improvement Scale: 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; 7 = very much worse.

[d]Subjects who were much or very much improved on CGI scale (CGI-I ≤2).

each laboratory parameter were small, with the exception of the larger decrease in mean platelet count and larger increase in mean serum ammonia level for the divalproex ER group compared with the placebo group. Two subjects had final platelet counts below the lower limit of normal, defined as below 130,000/μL (one was 118,000/μL, and one was 125,000/μL).

The normal range for ammonia provided by the analytical laboratory was less than 48 μmol/L; the

TABLE 4
Most Frequently Reported[a] Treatment-Emergent Adverse Events

Event	Double-Blind, 28-Day Study, *n* (%)		6-Month Long-Term Study, *n* (%) Divalproex ER (*n* = 66)
	Placebo (*n* = 74)	Divalproex ER (*n* = 76)	
Any adverse event	44 (59)	51 (67)	44 (67)
Headache	11 (15)	12 (16)	11 (17)
Vomiting	6 (8)	10 (13)	6 (9)
Nausea	1 (1)	7 (9)	4 (6)
Upper abdominal pain	1 (1)	6 (8)	4 (6)
Somnolence	1 (1)	5 (7)	1 (2)
Rash	1 (1)	4 (5)	1 (2)
Sedation	9 (12)	4 (5)	1 (2)
Ammonia increased	0 (0)	4 (5)	2 (3)
Gastritis	0 (0)	4 (5)	1 (2)
Nasal congestion	4 (5)	1 (1)	1 (2)
Dyspepsia	0 (0)	2 (3)	4 (6)
Pharyngolaryngeal pain	2 (3)	1 (1)	4 (6)
Pharyngitis streptococcal	0 (0)	3 (4)	3 (5)
Upper respiratory tract infection	1 (1)	1 (1)	3 (5)
Weight increased	1 (1)	2 (3)	3 (5)

Note: $p > .05$ for all adverse event comparisons in the double-blind study.
[a]5% or greater of patients.

mean ammonia level at baseline was 37.71 μmol/L. A mean increase from baseline in serum ammonia level was observed in the divalproex ER group (18.63 ± 25.72 μmol/L) compared with the placebo group (2.12 ± 22.21 μmol/L). An empirically predefined ammonia level of 90 μmol/L was used to monitor potential clinically significant changes in ammonia levels. Ammonia levels equal to or higher than 90 μmol/L were observed in four divalproex ER patients and two placebo patients. One patient on divalproex ER was hospitalized for adverse events of increased ammonia and disorientation. This patient's screening ammonia level was 31 μmol/L; in the emergency department (study day 8), the level was 47 μmol/L. The next day, the level was 199 μmol/L; after lactulose treatment on the same evening, the level was 80 μmol/L and 19 μmol/L on the following morning. No other patients with elevated ammonia levels were symptomatic.

Long-Term Study

Sixty-six patients (from 17 sites) treated in the double-blind study were subsequently enrolled in the long-term study, 31 and 35 patients from the randomized divalproex ER and placebo groups, respectively. Because of the interval of time that elapsed between the completion of the double-blind portion and the initiation (approval and activation of sites) of the open-label extension study, a large number of the subjects were lost to follow-up and could not be recruited into the open-label extension. Of the patients enrolled in the open study, 61% (40/66) prematurely discontinued study drug, with 75% (30/40) of those patients discontinuing in the first 3 months of the study. The most common reasons were "lost to follow-up" (13 [20%]) and "withdrew consent" (10 [15%]).

Mean retention time in the study was 117 days. For the double-blind and long-term studies combined, 20 patients were continuously treated with divalproex ER for 6 months or more. The mean modal daily dose of divalproex ER during the study was 25.7 mg/kg

TABLE 5
Mean Change From Baseline in Laboratory Parameters With a Statistically Significant Treatment Difference in the Double-Blind Study

	Baseline		Endpoint		
	Placebo	Divalproex ER	Placebo	Divalproex ER	*p*
Platelet count	281.9	277.2	−4.4	−50.4	<.001
White blood cells ($\times 10^9$/L)	6.24	6.12	0.6	−0.11	.024
Monocytes, %	6.00	5.39	−0.17	2.12	<.001
BUN, mmol/L	3.88	4.23	0.14	0.79	.003
Total protein, g/L	73.57	73.12	−1.59	−3.96	.003
Albumin, g/L	45.40	45.72	−0.6	−3.09	<.001
Total bilirubin, μmol/L	7.59	9.19	−0.05	−2.88	<.001
SGOT/AST, U/L	22.07	22.81	−0.76	−2.27	.035
SGPT/ALT, U/L	15.57	16.27	0.06	−4.24	<.001
Potassium, mmol/L	4.39	4.36	−0.12	0.05	.028
Calcium, mmol/L	2.43	2.44	−0.01	−0.08	.001
Cholesterol, mmol/L	4.34	4.47	−0.12	−0.35	.013
Ammonia, μmol/L[a]	39.05	34.37	2.12	18.63	<.001

Note: Sample sizes range from 67 to 68 for placebo and from 66 to 68 for divalproex ER. BUN = blood urea nitrogen; SGOT/AST = serum glutamic-oxaloacetic transaminase/aspartate aminotransferase; SGPT/ALT = serum glutamic pyruvic transaminase/alanine aminotransferase.
[a]*n* = 57 for placebo, *n* = 54 for divalproex.

(1,383 mg). Mean (SD) serum valproate concentrations were 77.7 μg/mL (40.9 μg/mL) at 1 month; 83.0 μg/mL (50.4 μg/mL) at month 6; and 80.1 μg/mL (44.6 μg/mL) at endpoint. Mean YMRS score decreased by 2.2 points from a baseline of 20.3 (Fig. 2; Table 3).

The two most commonly reported adverse events were headache (17% [11/66]) and vomiting (9% [6/66]) (Table 4). One patient reported hallucinations 9 days after the last dose of study drug that resulted in hospitalization. There was no information available as to whether divalproex was abruptly discontinued in this patient. As per hospital discharge summary, this patient was receiving risperidone, aripiprazole, and oxcarbazepine. Five patients discontinued prematurely because of an adverse event: two for alopecia, one for obesity, one for decreased platelet count, and one for increased ammonia.

From baseline to the end of the study, patients had a mean weight gain of 3.1 kg, mean increase in height of 2.4 cm, and mean increase in BMI of 0.6 kg/m^2. The mean ammonia level at baseline was 43.05 μmol/L. Ammonia levels equal to or higher than 90 μmol/L (empirically predefine potential clinically significant value) were observed in 11 divalproex ER patients; two of these elevations were reported by the investigator as adverse events. In general, the mean changes from baseline to final value for each laboratory parameter were small, with the exceptions of decreased platelet count and increased ammonia (Table 6). Seven subjects had platelet counts below the lower limit of normal defined as below 130,000/μL; two of these were below 100,000/μL (one was 81,000/μL, and one was 92,000/μL).

TABLE 6
Mean Change From Baseline in Laboratory Parameters in the Long-Term Study

	Baseline	Change to Final Evaluation
Platelet count	286.0	−44.9
White blood cells (×10^9/L)	6.80	−1.16
Monocytes, %	5.29	1.91
BUN, mmol/L	4.00	0.77
Total protein, g/L	72.50	−2.13
Albumin, g/L	45.00	−1.05
Total bilirubin, μmol/L	8.35	−0.29
SGOT/AST, U/L	21.22	1.7
SGPT/ALT, U/L	14.80	0.63
Potassium, mmol/L	4.34	0.09
Calcium, mmol/L	2.44	−0.07
Cholesterol, mmol/L	4.16	−0.1
Ammonia, μmol/L	43.05	18.63

Note: Sample sizes range from 57 to 60. BUN = blood urea nitrogen; SGOT/AST = serum glutamic-oxaloacetic transaminase/aspartate aminotransferase; SGPT/ALT = serum glutamic pyruvic transaminase/alanine aminotransferase.

DISCUSSION

Divalproex ER was not significantly superior to placebo on the primary efficacy measure, which was change in the mean YMRS total score from baseline to endpoint. The YMRS scores decreased for both the divalproex ER and placebo groups but not of a magnitude that would be considered clinically significant. There were no significant differences between the treatment groups on any of the secondary efficacy measures of change from baseline to final evaluation in the CDRS-R, CGI-I, CGI-S, CSQ, CGAS, and ADHD Rating Scale–IV.

The response rate (defined as a reduction of ≥50% in YMRS scores from baseline to final evaluation) in the double-blind trial of 24% in the divalproex ER patients was lower than the response rates found in previous divalproex open-label trials that ranged in duration from 2 to 8 weeks.[5,6] The design of this double-blind trial was 4 weeks in duration, the same duration as the comparator study of divalproex and quetiapine, which showed a divalproex overall response rate of 40%.[9] However, the comparator study did not include a placebo arm and was inpatient based, which may have accounted for the higher divalproex response rate compared with the current double-blind study.

In the double-blind study, there was no statistically significant difference between the divalproex ER and placebo groups in the overall incidence of adverse events or in the incidence of any individual adverse event. The rate of discontinuation because of adverse events was similar for the divalproex ER–treated patients and the placebo-treated patients (5% versus 4%, respectively). In the long-term study, the most commonly reported adverse events were headache (17%) and vomiting (9%). Adverse events reported in these studies are consistent with those reported in short-term divalproex ER studies in adults.[22]

Two subjects in the double-blind study and five subjects in the open-label extension phase had platelet counts below normal. Valproate has been associated with decreased platelet count and thrombocytopenia in

children.[23–26] Thrombocytopenia is described under the warnings and precautions in the Depakote ER label.[27]

Mean weight gain during the course of the 4-week trial was 1.0 kg in the divalproex ER group compared with 0.3 kg for the placebo group. Mean weight gain during the course of the long-term open-label trial was 3.1 kg. Weight gain has been associated with the use of mood stabilizers and antipsychotics in children and adolescents,[28] thus making it important to monitor weight during the course of treatment with these agents.

Hyperammonemia has been reported in association with valproate therapy and is described under warnings and precautions in the Depakote ER label.[27] However, asymptomatic elevations of ammonia are more common than hyperammonemia.[27] The clinical significance of asymptomatic elevations in ammonia concentrations is unclear. Ammonia levels are not routinely measured during valproate therapy, and up to 48% of elevated ammonia false positives have been reported in pediatric patients.[29] Reasons for false positives include time elapsed after collection, venipuncture technique and temperature of the sample. To minimize the likelihood of false positives, blood should be collected in an ammonia-free prechilled tube and transported on ice quickly to the laboratory for analysis.[30] Venous ammonia levels have greater variability than arterial samples.[29] In a group of 56 children treated with valproate for epilepsy, 73% of the patients had elevated venous ammonia levels and were asymptomatic.[31] In the current studies, an increase in mean serum venous ammonia levels was observed in divalproex ER–treated patients. Only one patient was symptomatic for hyperammonemia (i.e., disoriented and required hospitalization). Based on these results, systematic ammonia level monitoring does not seem warranted in all pediatric patients treated with divalproex ER. However, in patients who develop unexplained lethargy and vomiting or changes in mental status, hyperammonemic encephalopathy should be considered, and an ammonia level should be measured. If ammonia is increased, divalproex ER should be discontinued.

Menstrual irregularities and polycystic ovaries are important issues with divalproex. Because the double-blind portion of this study was only 4 weeks, these events could not be adequately addressed in the time frame of this study. These events were not assessed in the open-label extension study. Menstrual irregularities and issues related to polycystic ovaries were examined in a longer-duration (12 week) study of divalproex ER in adolescents with migraines that was designed around the same period as the present study and was recently reported.[32] Elevated testosterone and decreased levels of testosterone-binding protein (sex hormone–binding globulin) is associated with polycystic ovary syndrome.[33] In the migraine study, it was found that for postmenarchal female subjects, who were not taking hormonal contraceptives or other steroids, there was not a statistically significant change in testosterone levels. There was a divalproex ER dose-dependent increase in levels of sex hormone–binding globulin, which is in the opposite direction of what would be found for polycystic ovary syndrome.

One patient in the double-blind portion of the study was hospitalized for suicidal ideation. A potential relation between the use of antiepileptic drugs and suicidality has engendered concern regarding the use of these medications.[34] In a recent meta-analysis conducted by the FDA on 11 different antiepileptic drugs used in children and adults for a variety of indications (epilepsy, bipolar disorder, migraine, etc.), the estimated overall odds ratio for suicidal behavior or ideation among drug-treated versus placebo-treated patients was 1.80 (95% confidence interval 1.24–2.66). However, compared with placebo-treated patients, the odds ratio for divalproex-treated patients was 0.72 (95% confidence interval 0.29–1.84).[35] Although the divalproex data analyzed by the FDA included primarily studies in adults, no pattern in drug effect with respect to age subgroups was observed in the overall analysis for all antiepileptics.

In addition to the current study, recent double-blind placebo-controlled trials of anticonvulsants for pediatric bipolar disorder have failed to show statistically significant superiority to placebo.[36,37] A number of methodological issues may have contributed, in part, to these outcomes, including a large number of study sites, small number of patients per site, trial length, and use of the YMRS as an outcome measure, which is an adult-derived instrument. However, recent multicenter double-blind placebo-controlled 3-week trials of atypical antipsychotics in children and adolescents with bipolar disorder using similar methodology have demonstrated superiority of medication to placebo.[38–41]

The characteristics of this study sample were similar to other studies of youths with bipolar disorder. Mixed

episodes were common, and comorbidity with ADHD was high.

It is interesting to speculate whether the dose of divalproex affected the outcome of the double-blind study. The mean serum valproate concentration at endpoint was 80 μg/mL. However, this level was comparable to other open-label studies [5,6] with response rates of 53% and 61% (mean divalproex serum levels of 83 and 83 μg/mL, respectively). Importantly, the design of double-blind study allowed for the investigator to increase medications on days 7 and 14 (if the trough serum valproate level was less than 80 μg/mL) based on the investigator's clinical judgment. Neither response rate nor mean change from baseline in YMRS scores increased systematically as a function of valproate concentration.

Previous studies conducted in children and adolescents used the delayed-release form of divalproex. Although no head-to-head comparisons of the ER and delayed-release forms of divalproex have been conducted, efficacy of both forms for bipolar disorder in adults was established by randomized, double-blind, placebo-controlled trials.[42–44] Also, the pharmacokinetic profile of divalproex ER was shown to be similar among children and adolescents and did not differ significantly from the profile observed in an adult historical control group.[45] Therefore, it is unlikely that a formulation difference accounts for the results seen in this trial.

Although the course of bipolar disorder in youths tends to be chronic,[1] treatment adherence tends to be low. In the current long-term study in which patients received open-label treatment with divalproex ER, 61% of the patients prematurely discontinued study medication, with the majority discontinuing in the first 3 months. DelBello et al.[46] found that only 35% of adolescents who had been hospitalized for mania fully adhered to medication during the 12 months after hospitalization. Similarly, only 34% of the adolescents with bipolar disorder interviewed in an outpatient clinic reported full adherence to a medication regimen.[47] Thus, our discontinuation rates were typical for the population studied.

Another consideration is whether treatment response may be optimized by the use of two pharmacological agents in youths with bipolar disorder. Response rates to divalproex plus quetiapine were reported to be 87% compared with divalproex plus placebo (53%) in a 6-week double-blind placebo-controlled trial for adolescents with mania.[48] A remission rate of 47% was found with the combination of divalproex and lithium for youths with bipolar disorder treated for up to 20 weeks in an open-label trial.[49] In a 6-month open-label trial, response rates for divalproex plus risperidone were 80% for youths with bipolar disorder.[8] In a 6-month extension of an acute 6- to 8-week study of monotherapy treatment with mood stabilizers, it was found that 20 (58%) of 35 subjects required combination medication treatment.[50] However, large controlled trials of combination medication compared with monotherapy are necessary before any definitive conclusions can be drawn about recommending initial treatment with two agents for pediatric bipolar disorder. In adults, combined pharmacotherapy is often needed to stabilize bipolar disorder.[51–53]

Limitations of the current study include limited ethnic diversity, exclusion of concomitant psychotropic medication with the exception of stimulants, restriction on comorbid diagnoses, and exclusion of inpatients and patients at high risk for suicidality.

Conclusions

This is the first report of a multicenter double-blind, randomized, placebo-controlled trial of divalproex ER in the treatment of bipolar I disorder, mixed or manic, in children and adolescents (aged 10–17 years). There was no statistically significant difference between the divalproex ER–treated patients and the placebo-treated patients on the primary efficacy measure or secondary measures. At the present time, based on the results of this study, there is not evidence to support the use of divalproex ER in the treatment of youths with bipolar I disorder, manic or mixed state. Because this is the only reported double-blind placebo-controlled trial of divalproex ER in youths with bipolar disorder, it would be reasonable to conduct another controlled trial to confirm or refute the findings from this study. The incidence of adverse events was similar between the divalproex ER– and placebo-treated patients. Decreased platelet count was more frequent in the divalproex ER group than in the placebo group. An increase in mean ammonia level occurred more frequently in the divalproex ER group, although only one patient was symptomatic. Clinicians should be alert to the possibility of hyperammonemia, which may manifest as disorientation and lethargy in a child.

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