# Randomized, Double-Blind, Placebo-Controlled Study of Divalproex Extended Release Loading Monotherapy in Ambulatory Bipolar Spectrum Disorder Patients With Moderate-to-Severe Hypomania or Mild Mania

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***Objective:*** To determine whether divalproex extended release (ER) would be effective in outpatients with *DSM-IV-TR*–diagnosed ambulatory bipolar spectrum disorder (BSD) and moderate-to-severe hypomanic or mild manic symptoms (hypomania/mild mania).

***Method:*** An 8-week, randomized, double-blind, placebo-controlled trial of divalproex ER oral loading (begun at 15 mg/kg/d and titrated to a maximum of 30 mg/kg/d) in ambulatory BSD with hypomania/mild mania patients, operationally defined as a Young Mania Rating Scale (YMRS) score ≥ 10 but < 21 at baseline and at 1 other study visit at least 3 days apart over the 2 weeks before baseline, was conducted. Patients were enrolled from October 2003 through November 2007.

***Results:*** Sixty patients (n = 30 in the divalproex ER group) had at least 1 postbaseline assessment. The divalproex ER group showed a significantly greater rate of reduction in mean total YMRS score than the placebo group (longitudinal analysis, $P = .024$). The divalproex ER group also showed more improvement in depressive symptoms the greater the severity of baseline depression ($P = .11$ for analysis of covariance treatment-by-baseline interaction). Baseline-to-endpoint change scores using last-observation-carried-forward showed that divalproex ER was associated with a marginally significant change in mean total YMRS score ($P = .080$). Comparable numbers of patients discontinued divalproex ER (n = 17) and placebo (n = 15), including those that discontinued use because of adverse events (n = 4 and 3, respectively).

***Conclusions:*** Divalproex ER begun at 15 mg/kg/d was superior to placebo in reducing hypomanic/mild manic symptoms in ambulatory BSD. It was associated with fairly good tolerability but a high discontinuation rate. Controlled trials of divalproex ER and other mood stabilizers in larger groups of ambulatory BSD patients with hypomanic/mild manic symptoms appear warranted.

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Bipolar spectrum disorder (BSD) is more common than previously realized, due in part to increased recognition of cases with hypomanic and subthreshold hypomanic/manic symptoms.[1–7] For example, in the National Comorbidity Survey Replication (NCS-R), which found a total lifetime prevalence of BSD of 4.4%, the lifetime prevalences of bipolar I and II disorders were 1.0% and 1.1%, respectively, while the lifetime prevalence for subthreshold BSD was 2.4%.[7] The latter was defined as a recurrent hypomania without a major depressive episode or with fewer symptoms than required for threshold hypomania.

These findings suggest that some BSD patients who require mood stabilizers will have such agents begun when they have hypomanic or mild manic symptoms in outpatient settings. However, the majority of randomized, placebo-controlled pharmacotherapy studies in acutely symptomatic BSD patients with manic symptoms have been done, at least initially, in hospitalized patients with bipolar I manic or mixed episodes.[8–10] Very few randomized, placebo-controlled studies have been conducted exclusively in BSD outpatients with hypomania or mild mania.[11–14] The lack of such trials makes it less clear how to treat ambulatory BSD with hypomanic/ mild manic symptoms. Indeed, treatment guidelines for hypomania and mild mania in outpatients are largely generalized from the studies of moderate-to-severe mania conducted in inpatients,[8,15–17] sometimes modified with data from open-label reports in outpatients.[18]

Patients with ambulatory BSD may be more likely to present to general medical than to psychiatric practice settings, where they are more likely to receive antidepressants than mood stabilizers.[6,7,19] The NCS-R study found that although most people with BSD received lifetime professional treatment for emotional problems, use of antimanic medications was uncommon, especially in general medical settings.[6] The lack of empirically based treatment guidelines regarding

initiation of mood stabilizers in ambulatory BSD patients with hypomanic/mild manic symptoms, along with the likelihood that many ambulatory BSD patients are treated in general medical practice settings, suggests the need for controlled trials of mood stabilizers in this population.[20]

Like its parent compound divalproex delayed release (DR), divalproex extended release (ER) is approved for treatment of acute manic and mixed episodes associated with bipolar I disorder.[21,22] Because of its documented efficacy in bipolar I manic and mixed episodes, along with its favorable tolerability profile and convenient once-daily dosing, we hypothesized that divalproex ER would be effective for ambulatory BSD with moderate-to-severe hypomanic or mild manic symptoms, including when accompanied by mild-to-marked depressive symptoms (eg, mixed hypomania and mixed mild mania).[22–24] In light of reports of divalproex DR,[25–28] and more recently divalproex ER,[21,29] being successfully orally loaded in patients with acute bipolar mania (usually at doses of 20–30 mg/kg/d), we also hypothesized that divalproex ER could be initiated in ambulatory BSD patients with hypomanic/mild manic symptoms via a similar oral loading strategy, with subsequent dosing adjusted according to clinical response and tolerability. However, because we were concerned that such patients might not tolerate the same initial dosage regimens that hospitalized acutely manic patients have tolerated, we thought it prudent to choose a lower loading dose (15 mg/kg/d rather than 25–30 mg/kg/d) and to give the medication at bedtime (rather than in the morning).[21,29] Indeed, there are reports of patients with bipolar II and cyclothymic disorders responding to lower valproate doses (ie, 125–500 mg/d) and serum levels (ie, mean = 32.5 μg/mL) than are generally required for patients with bipolar I disorder.[30]

We, therefore, conducted a single-center, randomized, parallel-group, double-blind, placebo-controlled clinical trial to assess the efficacy and tolerability of divalproex ER loading monotherapy in BSD outpatients with moderate-to-severe hypomania or mild mania. Divalproex ER was begun at 15 mg/kg/d given at bedtime and adjusted according to response and side effects to a maximum dose of 30 mg/kg/d. Moderate-to-severe hypomania and mild mania were operationally defined as a Young Mania Rating Scale (YMRS)[31] score ≥ 10 and < 21 on 2 separate days, 3 or more days apart, and within the 2-week period prior to randomization.

## METHOD

### Patients

Study participants were outpatients at the University of Cincinnati Medical Center who were recruited by radio, newspaper, and television advertisements requesting volunteers for a study of a medication for persons with bipolar disorder who had manic symptoms. Patients were enrolled into the trial if they met the following inclusion criteria: (1) were male or female 18 years of age or older; (2) met *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision (*DSM-IV-TR*)[32] criteria for bipolar I or II disorder or bipolar disorder not otherwise specified and who were currently experiencing a hypomanic, manic, or mixed episode (as determined by the Structured Clinical Interview for *DSM-IV-TR*[33]); (3) had moderate-to-severe hypomania or mild mania within the past 2 weeks, operationally defined as having a YMRS score ≥ 10 and < 21 at the baseline assessment and at least 1 prior study screening visit at least 3 days, but no longer than 2 weeks, before baseline; (4) had an overall Clinical Global Impressions-Bipolar Version (CGI-BP) scale[34] score ≥ 2 and < 5; (5) were outpatients (ie, were ambulatory and did not require hospitalization for management of their bipolar symptoms); and (6) were receiving no psychotropics for the 1 week (4 weeks for fluoxetine or depot antipsychotics) before the baseline assessment, except as needed lorazepam (up to 2 mg/d) or zaleplon (up to 10 mg/d).

Patients were excluded from study participation if they met any of the following criteria: (1) were considered severely psychiatrically ill or in need of psychiatric hospitalization in the judgment of the clinical investigator; (2) had a baseline YMRS score ≥ 21, CGI-BP score ≥ 5, or Inventory of Depressive Symptoms (IDS)[35] score ≥ 39; (3) were experiencing clinically significant suicidal ideation, homicidal ideation, or psychotic features; (4) had a current *DSM-IV-TR* diagnosis of delirium, dementia, or other cognitive disorder or a lifetime *DSM-IV-TR* psychotic disorder; (5) had a *DSM-IV-TR* substance dependence disorder (except for nicotine dependence) within 3 months of study entry, a current *DSM-IV-TR* diagnosis of cocaine, stimulant, or hallucinogen abuse, or a urine drug screen positive for cocaine, stimulants, or hallucinogens; (6) had a clinically significant finding on medical history, physical examination, electrocardiogram, or laboratory testing; and (7) had a history of allergy or hypersensitivity to any valproate or divalproex preparation. Women were excluded if they were pregnant, lactating, or, if fertile, not practicing a form of medically accepted contraception.

The institutional review board at the University of Cincinnati Medical Center approved the study protocol, and the study was conducted in compliance with the Declaration of Helsinki. All patients signed approved written informed consent forms after the study procedures had been fully explained and before any study procedures were performed. Patients were enrolled from October 2003 through November 2007.

### Study Design

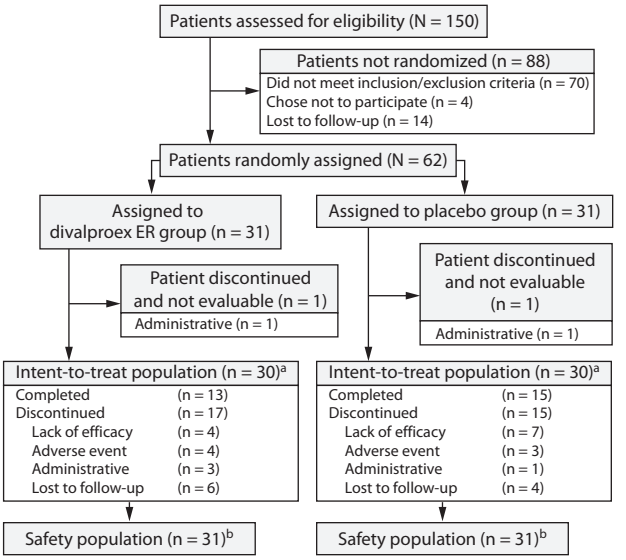
This was an 8-week, outpatient, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose study conducted at the University of Cincinnati Medical

Center. The trial consisted of 2 phases: a 1- to 2-week screening period and an 8-week double-blind treatment period. Patients were evaluated at least twice during the screening period and after 1, 2, 3, 4, 6, and 8 weeks during the treatment period. They were also evaluated on at least one occasion 1 week after study medication discontinuation.

All study medication was in identical 500-mg tablets supplied in numbered containers and dispensed to patients according to a predetermined randomization schedule. Divalproex ER was administered at an initial dose of 15 mg/kg/d, rounded up or down to the nearest 500 mg, and subsequently adjusted to a dose considered optimal based on the patient's clinical response and side effects, but not to exceed 30 mg/kg/d. As needed (prn) use of lorazepam 0.5–2.0 mg/d was allowed for the management of affective symptoms for the first 2 weeks of the study; prn lorazepam 0.5–1.0 mg/d was allowed for the next 2 weeks. No lorazepam was permitted for the final 4 weeks. As needed zaleplon (10–20 mg/d at bedtime) was allowed for management of insomnia throughout the study.

Patients were randomly assigned to receive divalproex ER or placebo in a 1:1 ratio according to computer-generated coding. Randomization was balanced by use of permuted blocks. Allocation concealment was achieved by having the research pharmacy perform the randomization, package the study medication, and maintain the integrity of the blinded information throughout the trial.

**Figure 1. Population Flow Outline**




[a]All randomly assigned patients who received study medication and had at least 1 valid post-baseline efficacy evaluation.
[b]All randomly assigned patients for whom at least 1 post-baseline safety measure was available.
Abbreviation: ER = extended release.

## Outcome Measures

The primary outcome measure was change in hypomanic/mild manic symptoms as assessed by the YMRS.[31] The YMRS is an extensively validated 11-item health care professional–administered test that has been in use since 1978. Secondary measures were the IDS,[35] the CGI-BP scale,[34] the Hamilton Anxiety Rating Scale (HARS),[36] and the Global Assessment of Functioning (GAF) scale.[32] Response was defined as a 50% or greater decrease in baseline YMRS score at treatment endpoint.

The following safety measures were assessed: adverse events, clinical laboratory data, physical examination findings, and vital signs. Hematology parameters, liver function tests, and blood chemistries were collected at screening and weeks 1, 2, 4, and 8 (or at discontinuation). A physical examination and urinalysis were performed at screening and week 8 (or at discontinuation). Serum valproate levels, generally drawn 12–18 hours after study drug was taken, were obtained after 1, 2, 4, and 8 weeks of treatment (or at discontinuation) and monitored by blinded investigators (A.I.G., P.E.K.). Unblinded investigators were to be notified only of concentrations ≥ 150 µg/mL. To maintain the blind, similar notifications were to be given for a placebo patient who was at the same point in the study. No serum valproate levels, however, exceeded 150 µg/mL.

Adherence with study medication was evaluated with returned capsule count. Patients who missed ≥ 5 consecutive days of study medication were considered nonadherent and discontinued from the trial.

## Statistical Methods

The baseline characteristics of each treatment group were compared using the Fisher exact test for categorical variables and independent samples *t* tests for continuous variables.

Two efficacy analyses were used to compare change between the groups over the treatment period. These were applied to scores on the YMRS total score (the primary efficacy measure) as well as the IDS, CGI-BP (severity of mania, depression, and overall bipolar disorder), HARS, and GAF scales (secondary efficacy measures). The difference in rate of change was estimated by random regression methods for longitudinal data, as described in Fitzmaurice et al[37] and Gibbons et al,[38] and by a comparison of baseline-to-endpoint change scores (with the last available observation substituted for the week-8 observation for patients who discontinued the trial early). These analyses differ in the assumptions they make about the data that would have been observed following dropout for patients who failed to complete the trial. The regression analysis carries the assumption that the linear trend observed for each patient up to the point of dropout would have continued until the end of the trial. The analysis of change scores, by substituting the last available observation, assumes that scores would remain constant following dropout (ie, the last observation is implicitly carried forward and used as

**Table 1. Demographic and Baseline Illness Characteristics of 60 Patients With Ambulatory Bipolar Spectrum Disorder Treated With Divalproex ER or Placebo for Hypomania or Mild Mania**

| Characteristic | Divalproex ER (n = 30) | Placebo (n = 30) | Odds Ratio | Test Statistic | *P* Value |
|---|---|---|---|---|---|
| Diagnosis by subtype, n (%) | | | | | |
| BP I | 19 (63) | 19 (63) | 1.0 | FET | > .99 |
| BP II | 9 (30) | 7 (23) | 1.41 | FET | .77 |
| BP NOS | 2 (7) | 4 (13) | 0.46 | FET | .67 |
| Mood episode at entry, n (%) | | | | | |
| Mania | 4 (13) | 3 (10) | 1.38 | FET | > .99 |
| Mixed mania | 3 (10) | 6 (20) | 0.44 | FET | .47 |
| Hypomania | 7 (23) | 13 (43) | 0.40 | FET | .17 |
| Mixed hypomania | 16 (53) | 8 (27) | 3.14 | FET | .06 |
| Female, n (%) | 20 (67) | 16 (53) | 0.57 | FET | .43 |
| White, n (%) | 23 (38) | 25 (42) | 1.52 | FET | .75 |
| Age, mean (SD), y | 35.7 (11.3) | 37.1 (14.6) | NA | $t_{58} = 0.43$ | .67 |
| Age at onset, mean (SD), y | 16.7 (8.0) | 18.2 (8.3) | NA | $t_{49} = 0.66$ | .51 |
| Young Mania Rating Scale score, mean (SD) | 15.9 (3.2) | 15.0 (3.4) | NA | $t_{58} = 0.99$ | .33 |
| Inventory for Depressive Symptoms score, mean (SD) | 26.1 (10.7) | 23.3 (8.5) | NA | $t_{58} = 1.12$ | .27 |
| CGI-BP mania score, mean (SD) | 3.6 (0.5) | 3.6 (0.5) | NA | $t_{58} = 0.00$ | > .99 |
| CGI-BP depression score, mean (SD) | 3.4 (0.9) | 3.1 (1.0) | NA | $t_{58} = 1.11$ | .27 |
| CGI-BP overall score, mean (SD) | 3.9 (0.4) | 3.7 (0.4) | NA | $t_{58} = 1.17$ | .25 |
| HARS score, mean (SD) | 13.9 (5.9) | 12.9 (5.7) | NA | $t_{58} = 0.69$ | .49 |
| GAF score, mean (SD) | 56.2 (5.7) | 57.6 (5.3) | NA | $t_{58} = 0.96$ | .34 |

Abbreviations: BP I = bipolar I disorder, BP II = bipolar II disorder, BP NOS = bipolar disorder not otherwise specified, CGI-BP = Clinical Global Impressions-Bipolar Version, ER = extended release, FET = Fisher exact test for 2 × 2 tables, GAF = Global Assessment of Functioning scale, HARS = Hamilton Anxiety Rating Scale, NA = not available.

**Table 2. Reasons for Medication Discontinuation in Patients With Ambulatory Bipolar Spectrum Disorder Receiving Divalproex ER or Placebo for Hypomania or Mild Mania**

| Reason for Discontinuation | Active (n = 30), n (%) | Placebo (n = 30), n (%) | Odds Ratio | *P* Value |
|---|---|---|---|---|
| Total | 17 (57) | 15 (50) | 1.31 | .80 |
| Lack of efficacy | 4 (24) | 7 (47) | 0.51 | .51 |
| Side effect | 4 (24) | 3 (20) | 1.38 | > .99 |
| Administrative | 3 (18) | 1 (7) | 3.22 | .61 |
| Lost to follow-up | 6 (35) | 4 (27) | 1.63 | .73 |

Abbreviation: ER = extended release.

an estimate for the week-8 observation). Since both scenarios are plausible and neither can be empirically verified, we did not designate 1 model as the preferred analysis. Rather, we considered similar results as evidence of robustness against the influence of sample attrition.

For the longitudinal regression models, a model for the mean of the outcome variable that included terms for treatment, time, and treatment-by-time interaction was used. Time was modeled as a continuous variable, expressed as the square root of days since randomization (baseline). To simultaneously account for individual differences in initial level of the outcome, rate of change over time, and serial autocorrelation, we used the SAS version 9.1 procedure MIXED (SAS Institute, Inc, Cary, North Carolina) with random intercept and slope terms and a first-order antedependence structure for the residual correlation matrix. The longitudinal analyses were intent-to-treat, using all available observations from all time-points from all patients who completed a baseline evaluation.

The Fisher exact test was used to analyze categorical response to treatment and rates of adverse events. All statistical tests and confidence intervals were 2-sided, $\alpha = .05$.

## RESULTS

Of 150 individuals assessed for eligibility, 88 were not enrolled because they chose not to participate (n = 19) or did not meet entry criteria (n = 69) (Figure 1). Sixty-two patients who met entry criteria were randomly assigned to divalproex ER (n = 31) or placebo (n = 31). Sixty patients (n = 30 receiving divalproex ER and n = 30 receiving placebo) had at least 1 postrandomization efficacy measure. Thirty-six patients (60%) were women, 48 (80%) were white, and 10 (17%) were African American. Forty-four patients (73%) were hypomanic and 16 (27%) were mildly manic; 33 (55%) were mixed, which was defined as meeting *DSM-IV-TR* criteria for a major depressive episode and hypomania (n = 24) or mania (n = 9) within the month prior to baseline. There were no significant differences between the treatment groups in demographic or clinical variables at baseline, though there was a trend for the divalproex ER group to have more patients with mixed hypomania (Table 1).

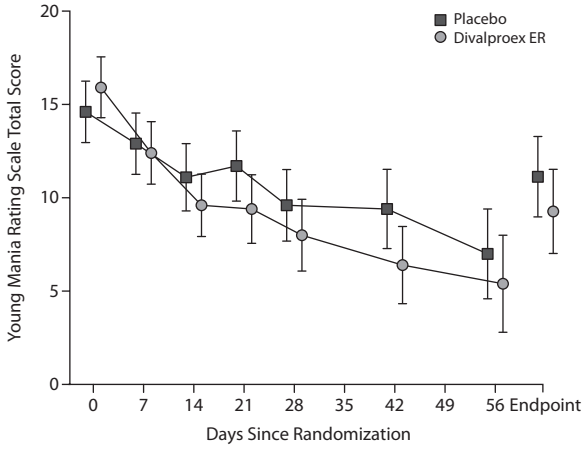
Seventeen patients (57%) in the divalproex ER group and 15 patients (50%) in the placebo group did not complete all 8 weeks of treatment (Fisher exact test, $P = .796$). Seven patients withdrew from the study because of adverse events, 11 withdrew because of lack of efficacy, 4 withdrew for administrative reasons, and 10 were lost to follow-up (Table 2). The remaining 28 patients (47%) completed the

**Table 3. Mean Model-Based Differences Between Divalproex ER and Placebo Groups From Baseline to Week 8 for Patients With Bipolar Spectrum Disorder Randomly Assigned to 8 Weeks of Double-Blind Treatment With Divalproex ER or Placebo**

| | Longitudinal Analysis | | | | | Endpoint Analysis | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Outcome Measure | Estimate[a] | 95% CI | $\chi^2_1$ | $P$[b] | Effect size ($d$) | Estimate | 95% CI | $t_{58}$ | $P$ | Effect size ($d$) |
| YMRS total | 3.6 | 0.4 to 6.7 | 5.08 | **.024** | 0.59 | 2.7 | −0.3 to 5.7 | 1.78 | .080 | 0.47 |
| IDS total | 3.0 | −1.8 to 8.7 | 1.21 | .271 | 0.29 | 2.4 | −3.4 to 8.2 | 0.83 | .408 | 0.22 |
| CGI-BP mania | 0.6 | 0.0 to 1.1 | 4.09 | **.044** | 0.53 | 0.3 | −0.2 to 0.9 | 1.23 | .224 | 0.32 |
| CGI-BP depression | 0.5 | −0.2 to 1.2 | 1.74 | .187 | 0.35 | 0.3 | −0.4 to 0.9 | 0.80 | .425 | 0.21 |
| CGI-BP overall | 0.5 | 0.0 to 1.1 | 4.00 | **.047** | 0.53 | 0.4 | −0.1 to 0.9 | 1.50 | .141 | 0.39 |
| HARS | 1.2 | −2.2 to 4.6 | 0.47 | .494 | 0.18 | −0.1 | −3.2 to 3.1 | 0.04 | .966 | 0.01 |
| GAF total | −3.4 | −8.3 to 2.4 | 1.64 | .200 | 0.34 | −2.6 | −8.1 to 2.9 | −0.96 | .344 | 0.25 |

[a]Estimate is the difference between the model-predicted mean change from baseline to week 8 for divalproex ER and the model-predicted mean change from baseline to week 8 for placebo. Test statistic is for the treatment-to-time interaction term, which represents the difference in rate of change between the divalproex ER and placebo groups, with time modeled as square root of days since randomization.
[b]Bolded $P$ values denote significance.
Abbreviations: CGI-BP = Clinical Global Impressions-Bipolar Version, ER = extended release, GAF = Global Assessment of Functioning scale, HARS = Hamilton Anxiety Rating Scale, IDS = Inventory for Depressive Symptoms, YMRS = Young Mania Rating Scale.

**Figure 2. Observed Mean ± 95% CI for Young Mania Rating Scale Total Score in 60 Bipolar Spectrum Disorder Patients With Hypomania/Mild Mania[a]**




[a]The mean rate of change for the divalproex ER group, estimated by random-effects regression, was significantly greater than for the placebo group ($P$ = .024).

8 weeks of treatment (n = 13 receiving divalproex ER and n = 15 receiving placebo).

The efficacy analysis using random regression showed that patients receiving divalproex ER had a significantly greater rate of reduction in mean total YMRS score than patients receiving placebo (Table 3; Figure 2). They also had significantly greater rates of reduction in CGI-BP mania and CGI-BP overall scores. The associated standardized effect sizes were moderate (Cohen $d$ = 0.59, 0.53, and 0.52, respectively). There were no differences in the rates of change in the IDS, CGI-BP depression, HARS, or GAF scores. However, change in IDS score as a function of baseline IDS score showed a trend wherein, compared with the placebo group, the divalproex ER group showed more improvement in depression the greater the severity of baseline depression ($P$ = .11 for analysis of covariance treatment-by-baseline interaction) (Figure 3).

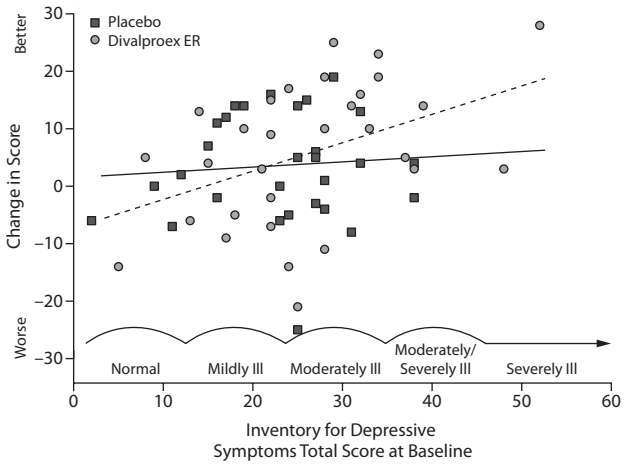
In the efficacy analysis of baseline-to-endpoint change scores using last-observation-carried-forward, divalproex ER was associated with a marginally significant change for the mean total YMRS score but not with any of the secondary outcome variables (Table 3). There were no significant differences between treatment groups for any global or categorical response analyses (all intent-to-treat), though response rates in the divalproex ER groups were numerically greater than response rates in the placebo groups in each category (Table 4).

The mean (SD) daily dose of divalproex ER at endpoint evaluation for the 27 patients with available data was 2,204 (524) mg (range, 1,500–3,000). The mean (SD) serum valproate concentration for this group was 68.1 (45.7) μg/mL. The mean (SD) number of hours at which these levels were drawn after the last divalproex ER dose was 14.9 (7.8) hours (range, 2–35). The mean (SD) daily dose for the 12 patients who completed the 8-week trial was 2,091 (437) mg. The mean (SD) serum valproate concentration for this group was 55.4 (45.5) μg/mL. The mean (SD) number of hours at which the levels were drawn after the last divalproex ER dose was 11.2 (6.2) hours (range, 2-19).

The groups were comparable with respect to percentages of patients administered lorazepam (n = 1 [3.3%] for divalproex ER versus n = 1 [3.3%] for placebo) or zaleplon (n = 3 [10%] for divalproex ER versus n = 3 [10%] for placebo; $P$ > .99 for comparison of usage rates for both concomitant medications).

Adverse events occurring in at least 2 patients receiving divalproex ER are listed in Table 5. There were no statistically significant differences between treatment groups in the incidence of individual events, although the sample size was too small to detect moderate differences in event rates. A comparable number of patients discontinued divalproex

**Figure 3. Change in Inventory for Depressive Symptoms Total Score in 60 Bipolar Spectrum Disorder Patients With Hypomania/Mild Mania[a]**




[a]A trend was observed for the treatment groups to have different slopes ($P = .11$ for analysis of covariance treatment-by-baseline interaction), suggesting that the effect of divalproex ER treatment on depressive symptoms might be greater in patients with higher levels of baseline depression.

ER (n = 4) and placebo (n = 3) for adverse events. Adverse events causing discontinuation among divalproex ER–treated patients were thrombocytopenia, severe nausea, menstrual irregularity, and rash (1 per patient). Adverse events causing discontinuation in placebo-treated patients were spontaneous pneumothorax, "ocular migraine versus transient ischemic attack," and blurry vision (1 per patient). Of note, 2 of these latter events (spontaneous pneumothorax and "ocular migraine versus transient ischemic attack") were considered serious adverse events. No patient receiving divalproex ER experienced a serious adverse event.

The divalproex ER group gained a mean (SD) of 4.2 (5.3) pounds over the course of the trial, versus 1.0 (3.6) pounds for the placebo group ($P = .010$). There were no other significant changes in physical examination findings or vital signs. The divalproex ER group had a significant mean decrease in platelet count (from 279.62 to 235.59 thousand/μL, versus 259.27 to 256.57 thousand/μL in the placebo group, $P < .001$) and a significant mean increase in blood urea nitrogen (from 11.37 to 12.81 mg/dL, versus 14.47 to 12.67 mg/dL in the placebo group, $P = .005$) and red cell distribution width (from 13.43% to 14.09%, versus 13.97% to 13.71% in the placebo group, $P = .008$). In addition, in the divalproex ER group, alanine transaminase decreased by a significant amount (from 25.64 to 20.46 U/L, versus 19.53 to 20.70 U/L in the placebo group, $P = .011$), and aspartate transaminase also decreased by a marginally significant amount (from 21.93 to 19.07 U/L, respectively, versus 18.27 to 18.43 U/L, respectively, in the placebo group, $P = .052$).

**Table 4. Categorical and Global Response**

| Response | Divalproex ER (n = 30), n (%) | Placebo (n = 30), n (%) | $P$[a] |
|---|---|---|---|
| YMRS, decreased by ≥ 50% | 14 (47) | 11 (37) | .60 |
| CGI-BP mania, "much or very much improved" | 15 (50) | 13 (43) | .80 |
| CGI-BP depression, "much or very much improved" | 14 (47) | 10 (33) | .43 |
| CGI-BP overall, "much or very much improved" | 16 (53) | 10 (33) | .19 |

[a]Fisher exact test.
Abbreviations: CGI-BP = Clinical Global Impressions-Bipolar Version, ER = extended release, YMRS = Young Mania Rating Scale.

**Table 5. Adverse Events Reported by ≥2 Patients With Ambulatory Bipolar Spectrum Disorder and Hypomania/Mild Mania Receiving Treatment With Divalproex ER**

| | Treatment Groups | | | | |
|---|---|---|---|---|---|
| | Divalproex ER (n = 31) | | Placebo (n = 31) | | |
| Adverse Event | n | % | n | % | $P$ |
| Nausea | 12 | 38.7 | 7 | 22.6 | .270 |
| Sedation | 10 | 32.3 | 8 | 25.8 | .780 |
| Headache | 8 | 25.8 | 7 | 22.6 | > .99 |
| Increased appetite | 7 | 22.6 | 7 | 22.6 | > .99 |
| Upper respiratory infection | 7 | 22.6 | 1 | 3.2 | .053 |
| Diarrhea | 6 | 19.4 | 9 | 29.0 | .554 |
| Weight gain | 6 | 19.4 | 1 | 3.2 | .104 |
| Abdominal pain | 4 | 12.9 | 1 | 3.2 | .354 |
| Abnormal dreams | 4 | 12.9 | 0 | 0.0 | .113 |
| Cystitis | 4 | 12.9 | 1 | 3.2 | .354 |
| Vomiting | 4 | 12.9 | 0 | 0.0 | .113 |
| Back pain | 3 | 9.7 | 1 | 3.2 | > .99 |
| Dry mouth | 3 | 9.7 | 2 | 6.5 | > .99 |
| Hot flashes | 3 | 9.7 | 0 | 0.0 | .238 |
| Rash | 3 | 9.7 | 1 | 3.2 | .238 |
| Sinusitis | 3 | 9.7 | 1 | 3.2 | .612 |
| Tremor | 3 | 9.7 | 0 | 0.0 | .238 |
| Anorexia | 2 | 6.5 | 0 | 0.0 | .492 |
| Arthralgia | 2 | 6.5 | 0 | 0.0 | .492 |
| Constipation | 2 | 6.5 | 3 | 9.7 | > .99 |
| Dyspepsia | 2 | 6.5 | 1 | 3.2 | > .99 |
| Edema | 2 | 6.5 | 0 | 0.0 | .492 |
| Fatigue | 2 | 6.5 | 1 | 3.2 | > .99 |
| Hypertension | 2 | 6.5 | 0 | 0.0 | .492 |
| Insomnia | 2 | 6.5 | 1 | 3.2 | > .99 |
| Photophobia | 2 | 6.5 | 0 | 0.0 | .492 |

Abbreviation: ER = extended release.

## DISCUSSION

In the longitudinal analysis of this randomized, double-blind trial in 60 ambulatory patients with BSD and moderate-to-severe hypomania or mild mania, over one-half (55%) with mixed features, divalproex ER was significantly superior to placebo in reducing hypomanic/mild manic symptoms and overall severity of illness. These findings had moderate effect sizes. In the change from baseline to endpoint analysis using last-observation-carried-forward, divalproex ER was marginally significant in reducing manic symptoms. Taken together, these

findings provide preliminary evidence for the efficacy of divalproex ER, initiated via the oral loading dose of 15 mg/kg, in ambulatory BSD with hypomanic/mild manic symptoms, including when associated with mixed features. This finding is consistent with previous studies showing that divalproex is effective in mania and mixed mania when begun in inpatients with bipolar I disorder and suggests it is also efficacious for hypomania and mixed hypomania when started in outpatients with BSD.

In contrast to manic symptoms, neither depressive nor anxious symptoms were significantly improved, inconsistent with recent findings that divalproex may have acute antidepressant and anxiolytic effects in bipolar I depression, bipolar II depression, and mixed bipolar depression.[39–41] Although over one-half of the sample (55%) had mixed features, these negative findings may have been due to lack of adequate power to detect an effect. This possibility was supported by the divalproex ER group showing more improvement in depressive symptoms the greater the severity of baseline depression.

Several other limitations of this study should be considered. One is that the attrition rate was high, with 32 patients (53%) withdrawing before study completion. Indeed, this attrition rate is somewhat higher than that seen in acute inpatient mania trials[9,21] and renders the results heavily dependent on assumptions regarding missing data. While the longitudinal analysis, unlike the endpoint analysis, allows that the reasons for missing data can depend on observations obtained before withdrawal (eg, a patient who is failing to improve may be more likely to withdraw), it is, nevertheless, vulnerable to factors that are not measured prior to withdrawal. Moreover, the high attrition rate among patients receiving divalproex ER (43%) suggests a high treatment unacceptability rate and is consistent with high rates of mood stabilizer nonadherence in patients with BSD.[42,43] This, in turn, underscores the need for novel treatments for bipolar disorder and for further research into treatment acceptability in this patient population.[43]

Another limitation is that optimal divalproex ER doses and/or serum valproate concentrations may not have been obtained for some patients.[21,44] In the pivotal trial of divalproex ER in hospitalized patients with bipolar mania, in which medication was administered once daily in the morning and blood samples for valproate concentrations were obtained approximately 24 hours later prior to the next divalproex ER dose, the mean final dose (on day 21 or at discontinuation) was 3,057 mg/d and the mean serum valproate concentration was 95.9 μg/mL.[21] By contrast, in the present study, the mean final dose was 2,204 mg/d and the mean final serum valproate concentration was 68 μg/mL. Moreover, because patients generally took the study drug at night and had blood samples collected 11–16 hours later, the mean level may have been higher (possibly up to 25%) than the trough value.[45–47] It is, therefore, possible that higher divalproex ER doses or higher serum valproate levels would have led to a greater degree of response. However, it is also possible that higher doses and/or levels would have led to a greater attrition rate. Additionally, as noted earlier, there are reports of patients with bipolar II and cyclothymic disorders responding to doses and serum levels of valproate lower than those generally required for patients with bipolar I disorder.[30] Unfortunately, this study does not resolve the issue of what the optimal initial dosing strategy of divalproex ER specifically, or of mood stabilizers in general, is for ambulatory BSD with hypomanic/mild manic symptoms.

As this is one of the first randomized, placebo-controlled studies of a mood stabilizer given as monotherapy in ambulatory BSD patients with hypomanic/mild manic symptoms, there might have been important ways to improve the design. Inclusion criteria might have been narrowed to generate a more homogenous study population, for example, by excluding patients with bipolar disorder not otherwise specified or using an alternative operational definition of hypomania/mild mania, such as a YMRS score ≥ 12 or 14 but < 22 or 25 (rather than ≥ 10 but < 21). In addition, divalproex ER could have been administered via a different dosing strategy—either beginning with a higher initial loading dose (eg, 20 or 25 mg/kg/d) or given once daily in the morning.[21]

Conversely, another limitation is that because persons with substance use disorders, severe personality disorders, and unstable medical disorders were excluded, the results may not generalize to ambulatory BSD when it co-occurs with these conditions. Similarly, because this study was not conducted in a primary care population, it is unknown if its results could be generalized to BSD patients treated in such settings.

In summary, in an 8-week trial in ambulatory BSD, divalproex ER initiated via an oral loading strategy of 15 mg/kg/d was found to be superior to placebo in reducing hypomanic/mild manic symptoms. It was also associated with fairly good tolerability but a high treatment discontinuation rate. Controlled trials of divalproex ER and other mood stabilizers in larger groups of ambulatory BSD patients with hypomanic/mild manic symptoms appear warranted.

***Drug names:*** divalproex (Depakote and others), fluoxetine (Prozac and others), lorazepam (Ativan and others), valproate (Depacon and others), zaleplon (Sonata and others).

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