Acute Efficacy of Divalproex Sodium Versus Placebo in Mood Stabilizer–Naive Bipolar I or II Depression: A Double-Blind, Randomized, Placebo-Controlled Trial

David J. Muzina, MD; Keming Gao, MD, PhD; David E. Kemp, MD; Sammy Khalife, MD; Stephen J. Ganocy, PhD; Philip K. Chan, MS; Mary Beth Serrano, MA; Carla M. Conroy, BA; and Joseph R. Calabrese, MD

Objective: To conduct an exploratory evaluation of the acute efficacy of extended-release divalproex sodium compared to placebo in patients with bipolar I or II depression.

Method: Outpatients aged 18–70 years with mood stabilizer–naive bipolar I or II disorder experiencing a major depressive episode (*DSM-IV*) were randomly assigned to 6 weeks of divalproex sodium monotherapy or placebo. The primary outcome measure was mean change from baseline to week 6 on the Montgomery-Åsberg Depression Rating Scale (MADRS) total score. Secondary outcomes included rates of response and remission, changes in the Clinical Global Impressions-Bipolar (CGI-BP) Severity of Illness scores, and changes in anxiety symptoms as measured by the Hamilton Anxiety Rating Scale. The study was conducted between 2003 and 2007.

Results: Fifty-four subjects with bipolar I (n = 20) or bipolar II (n = 34) disorder were randomly assigned to divalproex or placebo; 67% (36 of 54) met *DSM-IV* criteria for rapid cycling. Divalproex treatment produced statistically significant improvement in MADRS scores compared with placebo from week 3 onward. The proportions of patients meeting response criteria were 38.5% (10 of 26) in the divalproex group versus 10.7% (3 of 28) for the placebo group ($P = .017$). The proportions of patients meeting remission criteria were 23.1% (6 of 26) for divalproex versus 10.7% (3 of 28) for placebo ($P = .208$). Subgroup analysis revealed no separation between divalproex and placebo for those with bipolar II diagnoses. Nausea, increased appetite, diarrhea, dry mouth, and cramps were the most common side effects.

Conclusions: These data suggest that divalproex sodium is efficacious and reasonably well tolerated in the acute treatment of mood stabilizer–naive patients with bipolar depression, particularly for those with rapid-cycling type I presentations, and that confirmatory large-scale studies are indicated.

Trial Registration: clinicaltrials.gov Identifier: NCT00194116

J Clin Psychiatry 2011;72(6):813–819

Submitted: *July 30, 2009; accepted November 10, 2009.*
Online ahead of print: *August 24, 2010 (doi:10.4088/JCP.09m05570gre).*
Corresponding author: *Joseph R. Calabrese, MD, 10524 Euclid Ave, Cleveland, OH 44106 (Joseph.Calabrese@uhhospitals.org).*

The course of bipolar disorder is lifelong and chronic, and depressive symptoms dominate the lifetime course for most individuals.[1–4] Ongoing depressive symptoms are associated with functional and occupational deficits[1,5–7] and greater risk for recurrence.[8] Despite this, there are few US Food and Drug Administration (FDA)-approved treatments for acute depressive episodes in bipolar disorder.

The second-generation antipsychotic quetiapine is the only monotherapy approved for the acute treatment of bipolar depression.[9,10] The selective serotonin reuptake inhibitor fluoxetine, in combination with the second-generation antipsychotic olanzapine, is also FDA-approved for treatment of acute depression.[11] However, this treatment option involves 2 psychotropic medications, increasing the risk for adverse events and drug-drug interactions. In addition, the second-generation antipsychotic medications are associated with weight gain, dyslipidemia, hyperglycemia, altered electrocardiogram findings,[12,13] and increased risk for extrapyramidal symptoms,[14] generating concern about their safety in long-term use in vulnerable patients. The experience of adverse events may negatively impact patient adherence to treatment, already a challenge in the treatment of bipolar disorder.[15–17]

While antidepressant monotherapy is a mainstay of treatment for unipolar depression, published treatment guidelines in bipolar disorder caution against prescribing antidepressant monotherapy in patients with a history of mania.[18,19] This caution is due in part to the potential for inducing a switch into mania or hypomania[20–23] and to the lack of evidence for the effectiveness of antidepressants in treating bipolar depression.[24] Short-term studies of the acute efficacy of lamotrigine in bipolar I or II depression present a complicated picture, with only 2 of 6 large-scale studies showing evidence of efficacy.[25–27] Also, recently, the results of 2 controlled monotherapy trials for aripiprazole[28] and 2 for ziprasidone (clinicaltrials.gov: NCT00282464 and NCT00141271) failed to show evidence of efficacy for acute bipolar I depression.

There have been 3 randomized controlled trials assessing the benefit of divalproex for acute bipolar depression. In the first study,[29] divalproex did not separate from placebo. However, 2 recently published small studies (N = 25 and N = 18) support the effectiveness of divalproex in the acute treatment of bipolar depression.[30,31] Additional open data suggest that divalproex may be specifically helpful to those without previous exposure to traditional mood stabilizing

medication.[32] For these reasons, a 2-site, 6-week trial was designed and conducted to evaluate the efficacy and safety of extended-release divalproex sodium compared to placebo in mood stabilizer–naive patients with bipolar I or II depression.

METHOD

Study Design

This double-blind, randomized, placebo-controlled, parallel-group monotherapy study of the extended-release preparation of divalproex sodium versus placebo was conducted by the Bipolar Disorders Research Center at Case Western Reserve University, Cleveland, Ohio, between 2003 and 2007, and included 2 sites (Cleveland Clinic [D.J.M.] and University Hospitals Case Medical Center [J.R.C.], both in Cleveland, Ohio). After a washout period of at least 5 half-lives of any prior psychotropic medications other than lorazepam, subjects were treated for 6 weeks to evaluate the efficacy and safety of extended-release divalproex sodium in the treatment of depressive episodes in adult patients with bipolar I or II disorder.

The study was approved by the institutional review board for each site and was performed in accordance with the current amendment of the Declaration of Helsinki and the International Conference on Harmonization/Good Clinical Practice guidelines. Written informed consent was obtained from all subjects before participation.

Patient Population

Outpatients aged 18–70 years who met *DSM-IV* criteria for bipolar I or II disorder and were experiencing a major depressive episode were eligible for inclusion in the study. The diagnosis was confirmed with the Mini-International Neuropsychiatric Interview.[33] Patients who had both a Montgomery-Åsberg Depression Rating Scale (MADRS)[34] total score of ≥ 20 and a Young Mania Rating Scale (YMRS)[35] score of < 12 at baseline were eligible for randomization. Subjects were eligible if they had never been treated with a mood stabilizer (adequate dose and duration required); patients who previously were prescribed antipsychotics as hypnotics were allowed. Randomization took place in a ratio of 1:1 after stratification for type I versus type II. Subjects who were at significant risk for suicide were excluded from participation at the discretion of the investigator. Those with medically unstable conditions; alcohol, cocaine, or cannabis dependence within the past 3 months; or cocaine, hallucinogen, opiate, crystal methamphetamine, or 3,4-methylenedioxymethamphetamine (MMDA) abuse within 3 months of study entry were also excluded.

The vast majority of study participants (47 subjects) had been previously treated with an antidepressant: 9 had received benzodiazepines, 3 had received mood stabilizers of inadequate dose and duration (2 lamotrigine, 1 lithium), 5 had received antipsychotics of inadequate dose and duration (3 olanzapine, 2 quetiapine), and 2 had received other sedative hypnotics.

The mean ± SD age at onset of depressive symptoms was 16.9 ± 10.5 years. The mean ± SD number of depressive episodes in the 12 months prior to study entry was 6.6 ± 12.2 and, for hypomanic/manic episodes, was 3.8 ± 3.9. The mean ± SD duration of the index episode of depression at the time of study entry was 74.1 ± 78.2 days.

Study Medication

Participants were randomly assigned to receive either the extended-release preparation of divalproex sodium (hereafter referred to as "divalproex" throughout the article) or identically appearing placebo tablets. Tablets were available in 250-mg and 500-mg strengths to allow for gradual titration and flexible dosing. For patients whose weight was ≤ 90 kg, divalproex or placebo was dosed at bedtime—500 mg on day 1; 1,000 mg on day 2; and 1,500 mg on days 3 to 7. For patients whose weight was > 90 kg, they were also given 500 mg on day 1; 1,000 mg on day 2; and 1,500 mg on day 3, but they were then increased to 2,000 mg on days 4 to 7. After day 7, further adjustments were made for individual patients, targeting a blood level of ≥ 50 μg/mL. During the trial, routine laboratory monitoring was performed and trough levels of valproate were obtained on days 8 and 22, at the end-of-study visit, and as clinically necessary. The unblinded medical monitor was allowed to reduce or increase the dose of study medication to maintain blood levels of valproate at 50–100 μg/mL. The blinded treating psychiatrist was permitted to reduce the dose of study medication by 250 mg because of side effects without consulting the unblinded medical monitor.

No restriction was placed on the use of nonpsychiatric concurrent medications within the study (with the exception of over-the-counter diet pills or weight-loss medications). The concomitant use of lorazepam was allowed up to 2 mg/d for the first 5 days and up to 1 mg/d for the remainder of the study for treatment of anxiety, agitation, or insomnia. The concomitant use of zolpidem 5 mg for insomnia was permitted throughout the entire study.

Efficacy Assessments

Subjects were assessed weekly during this 6-week trial. Symptom severity was assessed at each visit using the MADRS,[34] the YMRS,[35] the Clinical Global Impressions-Bipolar (CGI-BP) Severity of Illness scores,[36] and the Hamilton Anxiety Rating Scale (HARS).[37]

Safety Assessments

A physical exam and laboratory monitoring (including a comprehensive metabolic profile, including liver function tests, and beta-human chorionic gonadotropin [β-hCG] test) were completed at baseline and end of study. Safety and tolerability were evaluated by assessing the incidence and severity of spontaneously reported adverse events at every visit. Clinical laboratory monitoring, vital sign monitoring (at 4 time points), and weight monitoring (at each visit) were also performed.

Subjects could be withdrawn from the study due to lack of efficacy for any of the following reasons: (1) nonresponse

Table 1. Baseline Demographic and Clinical Characteristics by Treatment Arm[a]

Characteristic	Divalproex ER (n = 26), n (%)	Placebo (n = 28), n (%)	Overall (N = 54), n (%)
Sex			
Male	11 (42.3)	12 (42.9)	23 (42.6)
Female	15 (57.7)	16 (57.1)	31 (57.4)
Race			
White	20 (76.9)	22 (78.6)	42 (77.8)
African American	3 (11.5)	6 (21.4)	9 (16.7)
Asian/Pacific Islander	2 (7.7)	0 (0)	2 (3.7)
Hispanic/Latino	1 (3.8)	0 (0)	1 (1.9)
DSM-IV diagnosis			
Bipolar I disorder	10 (38.5)	10 (35.7)	20 (37.0)
Bipolar II disorder	16 (61.5)	18 (64.3)	34 (63.0)
DSM-IV rapid cycling	18 (69.2)	18 (64.3)	36 (66.7)
	Mean (SD)	Mean (SD)	Mean (SD)
Age, y	39.7 (10.3)	38.8 (14.4)	39.2 (12.5)
MADRS score	29.0 (5.1)	28.7 (4.8)	28.9 (4.9)
YMRS score	5.7 (4.1)	5.6 (3.5)	5.7 (3.8)
HARS score	14.1 (5.3)	15.4 (7.8)	14.8 (6.7)
CGI-BP score			
Mania	1.2 (0.4)	1.1 (0.4)	1.2 (0.4)
Depression	4.2 (0.6)	4.2 (0.7)	4.2 (0.6)
Overall	4.2 (0.6)	4.1 (0.7)	4.2 (0.6)

[a]No significant differences between treatment arms.
Abbreviations: CGI-BP = Clinical Global Impressions-Bipolar Severity of Illness scale, ER = extended release, HARS = Hamilton Anxiety Rating Scale, MADRS = Montgomery-Åsberg Depression Rating Scale, YMRS = Young Mania Rating Scale.

to study medication—at the discretion of the blinded investigator, (2) suicidal ideation—at the discretion of the blinded investigator—or a score of 4 on the suicide item of the MADRS, (3) worsening of symptoms as reflected by an increase of 1 point on the CGI-BP, or (4) a MADRS total score ≥ 35 for more than 2 weeks. Treatment-emergent hypomania or mania was defined by at least 1 YMRS total score of 12 or more at any time during the study.[35]

Statistical Analysis

Primary and secondary efficacy analyses were performed on the intent-to-treat population, which included all randomly assigned subjects who took at least 1 dose of study medication and had at least 1 postbaseline efficacy assessment. The primary efficacy analysis of change from baseline to endpoint in MADRS total score tested the superiority of divalproex in the intent-to-treat group (patients with bipolar I or II disorder) with a mixed-effects analysis of covariance. Analyses involving the comparison of treatment groups utilized the last-observation-carried-forward (LOCF) procedure to account for missing values. Site, study week, and bipolar subtype were treated as factors in the mixed-effects models. Covariates included the baseline value of the appropriate measure, gender, and subject's age at time of consent. Post hoc analyses included a Cohen *d* to estimate effect size.

Secondary efficacy analyses included a comparison of the proportion of patients achieving response (defined as a 50% decrease in baseline rating on the MADRS and/or a CGI-BP depression score of ≤ 2 (at least *much* or *very much* improved) and remission (defined as a MADRS score < 10). Time-to-response and time-to-remission analyses were also conducted using Kaplan-Meier survival analysis and Cox regression to examine other covariates of survival time. Other measures of secondary efficacy included change-from-baseline analyses on the CGI-BP (depression and overall) and the HARS. Post hoc analyses were also conducted to estimate effect size, which included the number needed to treat.[38]

RESULTS

Patients and Disposition

A total of 68 patients were screened, and 54 subjects with bipolar I (n = 20) or bipolar II (n = 34) disorder were randomly assigned to receive divalproex (n = 26) or placebo (n = 28). The mean dose of divalproex was 1,606 mg/d (SD = 44 mg/d; range = 1,000–2,000 mg/d). Valproate levels were obtained at day 8, day 22, and at the end-of-study visit. The mean of these 3 levels was 82 μg/mL (range = 29–143 μg/mL). A total of 3 patients had valproate blood levels of < 50 μg/mL, including 37 μg/mL at day 8; 46 μg/mL at day 22; and 29 μg/mL at study endpoint.

The divalproex and placebo groups did not differ on any demographic or baseline disease characteristics (Table 1). The subjects' mean age was 39 years (SD = 12.5 years), and 57% of subjects (31 of 54) were female. The mean MADRS total score at baseline was 28.9 (SD = 4.9), suggestive of high-moderate symptom severity at study entry.[39] About two-thirds of subjects in this study met *DSM-IV* criteria for a rapid-cycling presentation at study entry. Traditional antidepressants had been previously prescribed to 92% of subjects (24 of 26) randomly assigned to divalproex and 82% of those (23 of 28) assigned to placebo.

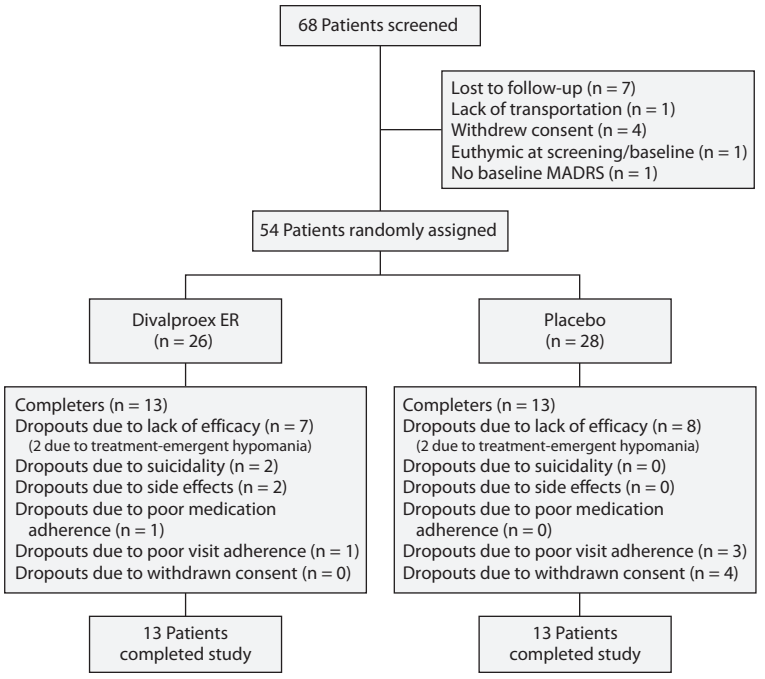
Thirteen patients completed each arm of the study. The most common reason for study withdrawal was some manifestation of lack of efficacy (divalproex, n = 9; placebo, n = 8). Two patients dropped out of the divalproex arm and none dropped out of the placebo arm due to side effects. One patient dropped out of the divalproex arm and 7 dropped out of the placebo arm due to poor visit adherence or withdrawn consent. See Figure 1 for additional detail.

Thirty-eight percent of those in the divalproex arm (10 of 26) received at least 1 prescription for lorazepam during study participation compared to 21% for the placebo arm (6 of 28). Zolpidem use was 7.7% in the divalproex arm (2 of 26) and 3.6% in the placebo arm (1 of 28).

Primary Efficacy Measure

Montgomery-Åsberg Depression Rating Scale. Mean baseline MADRS scores were 29.0 (SD = 5.1) and 28.7 (SD = 4.8) in the divalproex and placebo groups, respectively. Those patients randomly assigned to divalproex exhibited significantly greater mean improvement in the MADRS total scores compared with the placebo group at weeks 3, 4, 5, and 6 in the intent-to-treat group of patients with bipolar I or II depression ($P = .03$) (Figure 2). The mean change in MADRS total score for divalproex over placebo from baseline to last assessment was 4.32, yielding a Cohen *d* effect size of 0.7. This effect was due primarily to the subgroup of patients

Figure 1. CONSORT Diagram



Abbreviations: CONSORT = Consolidated Standards of Reporting Trials, ER = extended release, MADRS = Montgomery-Åsberg Depression Rating Scale.

with bipolar I disorder (divalproex, n = 10; placebo, n = 10), with separation at weeks 1, 3, 5, and 6. Subgroup analysis of those with bipolar II disorder (divalproex, n = 16; placebo, n = 18) indicated that treatment groups did not separate at any time point (see Figure 2A, 2B, and 2C).

Secondary Outcome Measures

In the divalproex group, 10 of the 26 patients (38.5%) met responder criteria at the last observation compared to 3 of the 28 patients (10.7%) treated with placebo ($P = .017$). For remission, 6 of the 26 patients (23.1%) treated with divalproex met criteria at the last observation compared to 3 of the 28 patients (10.7%) treated with placebo ($P = .208$).

The mean number of days to response for divalproex patients (38.1 [SD = 2.6]) compared to placebo patients (20.4 [SD = 0.5]) was not different across treatment groups. The mean number of days to remission for divalproex patients was 38.3 (SD = 1.7) compared to 40.6 (SD = 1.4) for placebo patients (not significant).

Other measures of secondary efficacy included change-from-baseline analyses on the CGI-BP Severity of Illness scores and the HARS. The treatment groups did not differ on any of these secondary outcomes (Table 2).

The number needed to treat with divalproex to achieve a *response* in 6 weeks was 3.6 individuals, while the number needed to treat with divalproex to achieve a *remission* in 6 weeks was 8.1 individuals.

Safety

Subjects receiving divalproex, compared with those receiving placebo, reported, respectively, increased nausea (34.6% [9 of 26] vs 14.3% [4 of 28]), increased appetite (15.4% [4 of 26] vs 7.1% [2 of 28]), diarrhea (11.5% [3 of 26] vs 7.1% [2 of 28]), fatigue (11.5% [3 of 26] vs 10.7% [3 of 28]), dry mouth (11.5% [3 of 26] vs 3.6% [1 of 28]), and stomach cramps (11.5% [3 of 26] vs 0% [0 of 28]), but these findings were not statistically different based on a Fisher exact test. Two subjects in the divalproex group withdrew from the study due to side effects (1 each due to nausea and flatulence).

Mean baseline YMRS total scores were 5.7 (SD = 4.1) for the divalproex group versus 5.6 (SD = 3.5) for the placebo group. Six patients receiving placebo met criteria for treatment-emergent hypomania/mania, as defined by a YMRS total score of ≥ 12 (total YMRS scores: 12, 12, 13, 14, 15, 16), and 8 patients did so while being treated with divalproex (total YMRS scores: 12, 13, 14, 15, 15, 17, 17, 20). Of these, 4 patients withdrew from the study due to lack of efficacy associated with treatment-emergent hypomania/mania (2 from the placebo group with YMRS scores of 14 and 16—and 2 from the divalproex group with YMRS scores of 15 and 17).

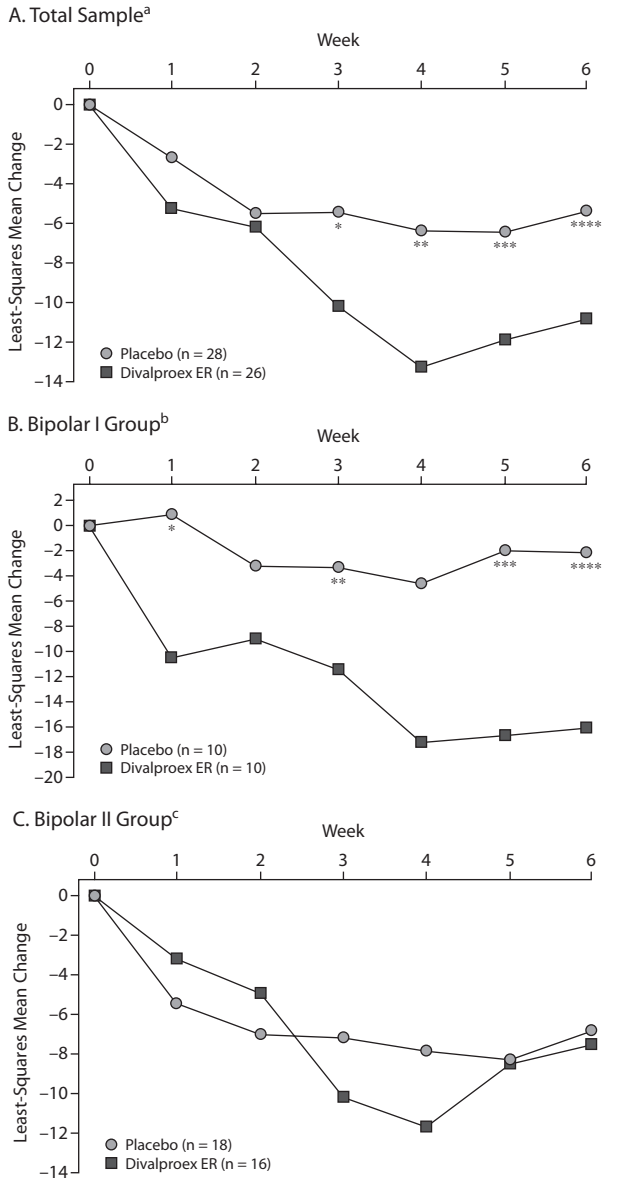
At baseline, body weight was obtained for 11 of 26 patients randomly assigned to divalproex (mean = 209.8 lb) and 15 of 28 patients randomly assigned to placebo (mean = 182.5 lb). Using end-of-study observations, patients assigned to divalproex gained 4.9 lb as compared to −0.5 lb for placebo, which was not statistically significant using a 2-sample *t* test. No patients in this study exhibited clinically significant weight gain (a 7% increase in body weight), and none dropped out of the study due to the adverse event of weight gain.

DISCUSSION

This is the first randomized, parallel-group, placebo-controlled trial to evaluate the short-term efficacy of the extended-release preparation of divalproex in mood stabilizer–naive patients with bipolar I or II depression. To our knowledge, this is also the largest controlled study to assess the efficacy and safety of divalproex in any group of patients with bipolar I or II depression—and one of few studies to examine the antidepressant effect of divalproex in a predominantly rapid-cycling patient population.

Patients in the divalproex group demonstrated significant improvement in MADRS total scores compared with patients in the placebo group from week 3 through the end of the study. The magnitude of the clinical effect was at the upper limits of moderate in size as reflected by a Cohen *d* effect size of 0.7. The proportion of patients meeting a priori response criteria in the group taking divalproex was 38.5% versus 10.7% for the placebo group, which led to a number needed to treat of 3.6 individuals. The proportions of patients meeting remission criteria were 23.1% for divalproex

Figure 2. Weekly Change in Montgomery-Åsberg Depression Rating Scale From Baseline Using Last Observation Carried Forward



[a]Total sample: *P = .05, **P = .01, ***P = .03, ****P = .04.
[b]Bipolar I group: *P = .003, **P = .05, ***P = .01, ****P = .02.
[c]Bipolar II group: no significance at any time point.
Abbreviation: ER = extended release.

versus 10.7% for placebo, which led to a number needed to treat of 8.1 individuals. The number needed to treat represents the number of patients who need to be treated with divalproex for 1 additional patient to achieve a response or remission. With the exception of response rates, all a priori–defined secondary outcome measures revealed no significant findings. Nausea, increased appetite, diarrhea, dry mouth, and cramps were the most common side effects.

These data suggest that divalproex is efficacious and reasonably well tolerated in the short-term management of mood stabilizer–naive patients with bipolar depression and that confirmatory studies are indicated. These data suggest that the acute efficacy of divalproex may have particular contribution to the short-term care of patients with mood stabilizer–naive bipolar I disorder and, possibly, for those with bipolar I disorder and a rapid-cycling specifier. These findings complement the existing pharmacotherapy available to this patient population, as lamotrigine monotherapy is effective for those with rapid-cycling bipolar II disorder, but not bipolar I disorder, over 6 months of monotherapy.[40] These findings are also consistent with our 1990 prospective, naturalistic study of the efficacy of divalproex in rapid-cycling bipolar disorder.[41]

Consistent with previously published reports, the majority of subjects in this trial had been either incorrectly diagnosed as having recurrent major depression and treated with an antidepressant or previously diagnosed as having bipolar disorder and treated only with a traditional antidepressant. Notable among these reports is the work by Baldessarini and colleagues,[42] who recently reported that antidepressant use was twice as common as the use of mood stabilizers for treatment of bipolar disorder after proper diagnosis, based on US national MarketScan research databases.[42] In addition to the prior history of unsuccessful treatment with antidepressants, the mean age at onset, the mean duration of depressive episodes, and other natural history data characterizing this patient population are also consistent with previously reported bipolar depression studies, suggesting these findings are generalizable.

The apparently low placebo response rate in this study is entirely consistent with most,[30,31,43,44] but not all,[29] published placebo response rates in small investigator-initiated bipolar depression studies. Differences in improvement on the MADRS for both divalproex and placebo in patients with bipolar I compared to bipolar II disorder were quite noteworthy. Not only was improvement on placebo treatment in subjects with bipolar I versus bipolar II disorder much smaller (least-squares [LS] mean = −2.47 [SE = 2.38] vs LS mean = −7.70 [SE = 1.64], respectively), but also improvement on divalproex treatment was remarkably greater for bipolar I compared to bipolar II disorder. In fact, those with bipolar II disorder actually worsened slightly (bipolar I: LS mean = −11.02 [SE = 3.47], P = .007 versus bipolar II: LS mean = 0.58 [SE = 2.23], P = .80), which is unusual in bipolar depression treatment trials. The primary efficacy outcome in this study was almost entirely driven by separation from placebo in those subjects with bipolar I disorder. The interpretation of the mean number of days to response in the intent-to-treat cohort was also complicated by low placebo response rates in subjects with bipolar I disorder and high placebo response rates in patients with bipolar II disorder.

The current study adds to a growing body of literature regarding the acute efficacy of divalproex in bipolar depression. It was the early pilot data published by Winsberg and colleagues[32] that prompted the most unique design feature of our randomized controlled trial, limiting enrollment to mood stabilizer–naive patients. However, that study[32] included only 19 subjects in the depressed phase of bipolar II disorder and utilized an open design. We improved the methodology by

Table 2. Least-Squares Mean Change From Baseline in Primary and Secondary Outcome Measures in the Intent-to-Treat Population Utilizing Last Observation Carried Forward (N = 54)

Measure and Treatment Arm	n	Baseline Score, Mean (SE)	Change in Score at End of Treatment Phase, LS Mean (SE)	Comparison With Placebo	
				LS Mean (SE)	*P* Value
MADRS, bipolar I and II					
Divalproex	26	29.04 (1.01)	−9.64 (1.49)	−4.32 (1.92)	.03
Placebo	28	28.68 (0.92)	−5.32 (1.40)		
MADRS, bipolar I					
Divalproex	10	28.70 (1.34)	−13.49 (2.92)	−11.02 (3.47)	.007
Placebo	10	28.20 (1.29)	−2.47 (2.38)		
MADRS, bipolar II					
Divalproex	16	29.25 (1.44)	−7.12 (1.54)	0.58 (2.23)	.80
Placebo	18	28.94 (1.25)	−7.70 (1.64)		
HARS					
Divalproex	26	14.12 (1.04)	−3.71 (0.87)	−1.54 (1.07)	.16
Placebo	28	15.36 (1.48)	−2.17 (0.79)		
CGI-BP, depression					
Divalproex	26	4.24 (0.12)	−0.42 (0.24)	−0.07 (0.23)	.77
Placebo	28	4.19 (0.13)	−0.35 (0.20)		
CGI-BP, overall					
Divalproex	26	4.20 (0.13)	−0.48 (0.21)	−0.14 (0.22)	.53
Placebo	28	4.15 (0.13)	−0.34 (0.18)		

Abbreviations: CGI-BP = Clinical Global Impressions-Bipolar Severity of Illness scale, HARS = Hamilton Anxiety Rating Scale, LS = least squares, MADRS = Montgomery-Åsberg Depression Rating Scale.

utilizing randomized controlled design, and we enrolled almost twice the number of patients diagnosed with bipolar II disorder. We demonstrated that the effectiveness of divalproex in acute treatment of bipolar depression was limited to those with bipolar I disorder, with no separation between divalproex and placebo in those with bipolar II disorder. Further work is needed to reconcile these disparate findings.

In the earliest of double-blind placebo-controlled studies of divalproex in acute bipolar I or II depression, Sachs and colleagues[29] randomly assigned 43 outpatients with bipolar I or II depression to divalproex or placebo over 8 weeks in a 4-site study. Although the divalproex group revealed no significant differences in the primary efficacy analysis, change from baseline on the Hamilton Depression Rating Scale, patients assigned to divalproex did demonstrate significant improvement at weeks 2, 4, and 5 of the 8 weeks. In addition, the responder analysis showed a numerical superiority for divalproex over placebo (43% vs 27%) but did not achieve statistical significance.[29] In contrast to this earlier study, our dosing schedule resulted in a mean divalproex dose of 1,606 mg/d, 215 mg/d higher than that attained in the Sachs study.

In a small trial[30] of 25 outpatients with bipolar I depression, divalproex was superior to placebo in reducing symptoms of both anxiety and depression. The dosing employed in this study[30] resulted in similar mean blood levels to those achieved in the current trial. In our study, as in that of Ghaemi and colleagues,[31] we did not observe a comparable decrease in anxiety symptom scores. Subjects in our study presented with clinically significant levels of anxiety (mean HARS score ≥ 14), and anxiety was reduced to levels below that threshold during the 6-week treatment period. Further work to understand the anxiolytic benefits of divalproex in this patient population would be helpful.

Although the findings of our study make a unique contribution to the literature, there are methodological considerations that limit the generalizability of these findings. First, the exclusion of patients meeting criteria for substance abuse or dependence limits the relevance of these data substantially. Second, 67% of subjects in our study presented with a recent history of rapid cycling, which further limits generalizability. Third, and most important, studies that limit enrollment to a small number of clinical sites have a substantial likelihood of generating biased results and require large-scale replication.

Given the severity and persistence of depressive symptoms experienced by patients with bipolar I or II depression, there continues to be an urgent, unmet need for more effective treatments that successfully target the depressed phase of the disorder. The current study adds to a small body of randomized controlled trials that suggest the benefit of divalproex for this population, in particular those with bipolar I rapid-cycling presentations.

Drug names: aripiprazole (Abilify), divalproex (Depakote and others), fluoxetine (Prozac and others), lamotrigine (Lamictal and others), lithium (Lithobid and others), lorazepam (Ativan and others), olanzapine (Zyprexa), quetiapine (Seroquel), ziprasidone (Geodon), zolpidem (Ambien, Zolpimist, and others).

Author affiliations: Department of Psychiatry and Psychology, Neurological Institute, Cleveland Clinic Foundation (Drs Muzina and Khalife); and Department of Psychiatry, University Hospitals Case Medical Center (Drs Gao, Kemp, Ganocy, and Calabrese; Mr Chan; and Mss Serrano and Conroy), Cleveland, Ohio.

Potential conflicts of interest: **Dr Muzina** has received grant/research support from Abbott and Repligen; is a member of the scientific advisory board for AstraZeneca; and is a member of the speakers boards for AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Pfizer, Sepracor, and Wyeth. **Dr Gao** has received grant support from AstraZeneca and NARSAD and has been a consultant to, has received honoraria from, and has served as an advisory board member for Schering-Plough. **Dr Kemp** has been a consultant for Bristol-Myers Squibb; has received research support from the International Society for Bipolar Disorders (Research Fellowship Award), the National Institutes of Health (grant 1KL2RR024990), NARSAD, and Takeda; has completed continuing medical education (CME) activities with Schering-Plough; has received honoraria from Servier; and has been a member of the speakers or advisory board of Pfizer. **Dr Calabrese** has received federal funding from the Department of Defense, the Health Resources Services Administration, and the National Institute of Mental Health; has received grant/research support from Abbott, AstraZeneca, Bristol-Myers Squibb, Cephalon, Cleveland Foundation, Eli Lilly, GlaxoSmithKline, Janssen, NARSAD, Repligen, The Stanley Medical Research Institute, Takeda, and Wyeth; has been an advisory board member for Abbott, AstraZeneca, Bristol-Myers Squibb, Dainippon Sumitomo, EPI-Q, Forest, France Foundation, GlaxoSmithKline, Janssen, Johnson & Johnson, Lundbeck, NeuroSearch, Ortho-McNeil, Otsuka, Pfizer, Repligen, Schering-Plough, Servier, Solvay, Supernus, Synosia, and Wyeth; and has been involved in CME activities supported by AstraZeneca, Bristol-Myers Squibb, France Foundation, GlaxoSmithKline, Janssen, Johnson & Johnson, Sanofi-Aventis, Schering-Plough, Pfizer, Solvay, and Wyeth. **Drs Khalife** and **Ganocy**, **Mr Chan**, and **Mss Serrano** and **Conroy** report no potential conflicts of interest.

Funding/support: Funding and study medications were provided by Abbott Laboratories, Abbott Park, Illinois. Additional infrastructure

support was provided by the National Institute of Mental Health (grant P20 MH-66054 to Dr Calabrese), Bethesda, Maryland.
Previous presentation: Presented at the 161st Annual Meeting of the American Psychiatric Association; May 3–8, 2008; Washington, DC; and at the 48th Annual Meeting of the National Institute of Mental Health New Clinical Drug Evaluation Unit (NCDEU); May 27–30, 2008; Phoenix, Arizona.
Acknowledgment: We thank Ellen B. Dennehy, PhD, of the Department of Psychological Sciences, Purdue University, West Lafayette, Indiana, for assistance with manuscript preparation. Dr Dennehy has no financial or other relationships relevant to the subject of this article.

REFERENCES

1. Judd LL, Akiskal HS, Schettler PJ, et al. Psychosocial disability in the course of bipolar I and II disorders: a prospective, comparative, longitudinal study. *Arch Gen Psychiatry*. 2005;62(12):1322–1330.
2. Judd LL, Akiskal HS, Schettler PJ, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. *Arch Gen Psychiatry*. 2003;60(3):261–269.
3. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry*. 2002;59(6):530–537.
4. Kupka RW, Altshuler LL, Nolen WA, et al. Three times more days depressed than manic or hypomanic in both bipolar I and bipolar II disorder. *Bipolar Disord*. 2007;9(5):531–535.
5. Bauer MS, Kirk GF, Gavin C, et al. Determinants of functional outcome and healthcare costs in bipolar disorder: a high-intensity follow-up study. *J Affect Disord*. 2001;65(3):231–241.
6. Calabrese JR, Hirschfeld RM, Frye MA, et al. Impact of depressive symptoms compared with manic symptoms in bipolar disorder: results of a US community-based sample. *J Clin Psychiatry*. 2004;65(11):1499–1504.
7. Kessler RC, Akiskal HS, Ames M, et al. Prevalence and effects of mood disorders on work performance in a nationally representative sample of US workers. *Am J Psychiatry*. 2006;163(9):1561–1568.
8. Perlis RH, Ostacher MJ, Patel JK, et al. Predictors of recurrence in bipolar disorder: primary outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Am J Psychiatry*. 2006;163(2): 217–224.
9. Calabrese JR, Keck PE Jr, Macfadden W, et al. The BOLDER Study Group. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. *Am J Psychiatry*. 2005;162(7): 1351–1360.
10. Thase ME, Macfadden W, Weisler RH, et al. BOLDER II Study Group. Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). *J Clin Psychopharmacol*. 2006;26(6):600–609.
11. Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry*. 2003;60(11):1079–1088.
12. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS Drugs*. 2005;19(suppl 1):1–93.
13. Marder SR, Essock SM, Miller AL, et al. Physical health monitoring of patients with schizophrenia. *Am J Psychiatry*. 2004;161(8):1334–1349.
14. Gao K, Kemp DE, Ganocy SJ, et al. Antipsychotic-induced extrapyramidal side effects in bipolar disorder and schizophrenia: a systematic review. *J Clin Psychopharmacol*. 2008;28(2):203–209.
15. Baldessarini RJ, Perry R, Pike J. Factors associated with treatment nonadherence among US bipolar disorder patients. *Hum Psychopharmacol*. 2008;23(2):95–105.
16. Gaudiano BA, Weinstock LM, Miller IW. Improving treatment adherence in bipolar disorder: a review of current psychosocial treatment efficacy and recommendations for future treatment development. *Behav Modif*. 2008;32(3):267–301.
17. Sajatovic M, Davies M, Hrouda DR. Enhancement of treatment adherence among patients with bipolar disorder. *Psychiatr Serv*. 2004;55(3):264–269.
18. American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder (revision). *Am J Psychiatry*. 2002; 159(4 suppl):1–50.
19. Suppes T, Dennehy EB, Hirschfeld RMA, et al; Texas Consensus Conference Panel on Medication Treatment of Bipolar Disorder. The Texas implementation of medication algorithms: update to the algorithms for treatment of bipolar I disorder. *J Clin Psychiatry*. 2005;66(7):870–886.
20. Altshuler LL, Post RM, Leverich GS, et al. Antidepressant-induced mania and cycle acceleration: a controversy revisited. *Am J Psychiatry*. 1995;152(8):1130–1138.
21. Gao K, Kemp DE, Ganocy SJ, et al. Treatment-emergent mania/hypomania during antidepressant monotherapy in patients with rapid cycling bipolar disorder. *Bipolar Disord*. 2008;10(8):907–915.
22. Joffe RT, MacQueen GM, Marriott M, et al. Induction of mania and cycle acceleration in bipolar disorder: effect of different classes of antidepressant. *Acta Psychiatr Scand*. 2002;105(6):427–430.
23. Leverich GS, Altshuler LL, Frye MA, et al. Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers. *Am J Psychiatry*. 2006;163(2):232–239.
24. Sachs GS, Nierenberg AA, Calabrese JR, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. *N Engl J Med*. 2007; 356(17):1711–1722.
25. Calabrese JR, Huffman RF, White RL, et al. Lamotrigine in the acute treatment of bipolar depression: results of five double-blind, placebo-controlled clinical trials. *Bipolar Disord*. 2008;10(2):323–333.
26. Geddes JR, Calabrese JR, Goodwin GM. Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomized trials. *Br J Psychiatry*. 2009;194(1):4–9.
27. van der Loos ML, Mulder PG, Hartong EG, et al. Efficacy and safety of lamotrigine as add-on treatment to lithium in bipolar depression: a multicenter, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2009; 70(2):223–231.
28. Thase ME, Jonas A, Khan A, et al. Aripiprazole monotherapy in nonpsychotic bipolar I depression: results of 2 randomized, placebo-controlled studies. *J Clin Psychopharmacol*. 2008;28(1):13–20.
29. Sachs G, Altshuler L, Ketter T, et al. Divalproex versus placebo for the treatment of bipolar depression. Presented at the 154th Annual Meeting of the American Psychiatric Association; May 5–10, 2001; New Orleans, LA.
30. Davis LL, Bartolucci A, Petty F. Divalproex in the treatment of bipolar depression: a placebo-controlled study. *J Affect Disord*. 2005;85(3):259–266.
31. Ghaemi SN, Gilmer WS, Goldberg JF, et al. Divalproex in the treatment of acute bipolar depression: a preliminary double-blind, randomized, placebo-controlled pilot study. *J Clin Psychiatry*. 2007;68(12):1840–1844.
32. Winsberg ME, DeGolia SG, Strong CM, et al. Divalproex therapy in medication-naive and mood-stabilizer-naive bipolar II depression. *J Affect Disord*. 2001;67(1-3):207–212.
33. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. 1998;59(suppl 20):22–33, quiz 34–57.
34. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.
35. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. 1978;133(5):429–435.
36. Spearing MK, Post RM, Leverich GS, et al. Modification of the Clinical Global Impressions (CGI) scale for use in bipolar illness (BP): the CGI-BP. *Psychiatry Res*. 1997;73(3):159–171.
37. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol*. 1959;32(1):50–55.
38. Altman DG. Confidence intervals for the number needed to treat. *BMJ*. 1998;317(7168):1309–1312.
39. Müller MJ, Himmerich H, Kienzle B, et al. Differentiating moderate and severe depression using the Montgomery-Åsberg Depression Rating Scale (MADRS). *J Affect Disord*. 2003;77(3):255–260.
40. Calabrese JR, Suppes T, Bowden CL, et al. Lamictal 614 Study Group. A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder. *J Clin Psychiatry*. 2000;61(11):841–850.
41. Calabrese JR, Delucchi GA. Spectrum of efficacy of valproate in 55 patients with rapid-cycling bipolar disorder. *Am J Psychiatry*. 1990;147(4): 431–434.
42. Baldessarini RJ, Leahy L, Arcona S, et al. Patterns of psychotropic drug prescription for US patients with diagnoses of bipolar disorders. *Psychiatr Serv*. 2007;58(1):85–91.
43. Zarate CA Jr, Payne JL, Singh J, et al. Pramipexole for bipolar II depression: a placebo-controlled proof of concept study. *Biol Psychiatry*. 2004; 56(1):54–60.
44. Goldberg JF, Burdick KE, Endick CJ. Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression. *Am J Psychiatry*. 2004;161(3): 564–566.