Divalproex in the Treatment of Acute Bipolar Depression: A Preliminary Double-Blind, Randomized, Placebo-Controlled Pilot Study

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Objective: To determine the efficacy of divalproex (extended release) in the treatment of acute nonrefractory bipolar depression.

Method: In a stratified, double-blind, randomized, placebo-controlled trial, 18 acutely depressed bipolar outpatients (DSM-IV criteria) received either divalproex monotherapy (target dose level, 70–90 ng/dL) (N = 9) or placebo (N = 9) for 6 weeks. Patients were recruited between January 2004 and May 2005. Clinical assessment on the Montgomery-Asberg Depression Rating Scale (MADRS) determined primary efficacy.

Results: The divalproex treatment group showed significantly greater reduction in MADRS scores compared to placebo (group × time interaction, p = .0078). Absolute effect size of estimated MADRS total score reduction over time was 13.6 points with divalproex versus 1.4 points with placebo (p = .003, linear growth curve model). Standardized effect size was large (Cohen d = 0.81). MADRS item analyses demonstrated improvement in core mood symptoms more than in anxiety or insomnia symptoms. There was also a modest but significant association between MADRS and Mania Rating Scale scores in the divalproex group (r = 0.29, df = 51, p = .03), but not in the placebo group (r = –0.15, df = 35, p = .36).

Conclusions: Divalproex appeared to be an effective treatment for acute nonrefractory bipolar depression, which is consistent with previous small randomized studies. Some evidence of benefit in the depressive mixed state was observed. Confirmation or refutation with larger randomized clinical trials is warranted.

Clinical trial registration: ClinicalTrials.gov identifier NCT00226343.

(J Clin Psychiatry 2007;68:1840–1844)

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Supported by a grant from Abbott Laboratories, Chicago, Ill. All data collection, analysis, and writing were conducted solely by the authors.

Financial disclosure appears at the end of this article.

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Depressive symptoms are the major morbidity of bipolar disorder.[1] Treatment of bipolar depression remains a major clinical need,[2] with limited evidence of benefit[3] and some evidence of risk[4] with standard antidepressants. Limited data also exist on mood stabilizer or antipsychotic efficacy for acute bipolar depression.[5,6] Previous open data and limited randomized data suggest that divalproex may be effective in nonrefractory bipolar depression (type I or type II).[7–12]

The objective of this study was to corroborate or refute the previous limited randomized controlled trial (RCT) literature of antidepressant efficacy of divalproex versus placebo for acute bipolar depression, as well as to assess secondary benefit for comorbid anxiety symptoms.

METHOD

In a 6-week, stratified, double-blind, randomized design, divalproex was compared to placebo in 19 outpatients meeting DSM-IV criteria for bipolar disorder type I, type II, or not otherwise specified (NOS), current major depressive episode (along with Montgomery-Asberg Depression Rating Scale [MADRS][13] score > 17 and Mania Rating Scale [MRS][14] score < 12). Patients were recruited between January 2004 and May 2005 at the Bipolar

Table 1. Clinical and Demographic Characteristics of Sample

Measure	Total Group	Divalproex	Placebo
Age, mean ± SD (range), y	37.4 ± 10.6 (22–57)	32.7 ± 2.3 (22–44)	43.3 ± 4.1 (22–57)
Gender, N			
Female	9	7	2
Male	9	3	6
Race, N			
White	10	4	6
Nonwhite	8	6	2
Bipolar subtype, N			
I	9	3	6
II/not otherwise specified	9	5	4
Rapid cycling, N			
Yes	5	3	2
No	13	7	6
Number of concomitant medications, mean ± SD (range)	0.94 ± 1.35 (0–4)	0.33 ± 0.71 (0–2)	1.63 ± 1.59 (0–4)
Early termination, N			
Yes	6	3	3
No	12	7	5
Valproic acid level, ng/dL		70.3 ± 27.5[a]	

[a]Data based on 7 of 9 valproate-treated patients; serum levels missing in 2 patients.

Disorder Research Program at the Cambridge Health Alliance, Cambridge, Mass.; the Bipolar Research Clinic at the Zucker Hillside Hospital, Glen Oaks, N.Y.; and the Asher Depression Center at Northwestern University, Chicago, Ill. Exclusion criteria included use of any other psychotropic medications; past nonresponse or intolerance of monotherapy with divalproex, lithium, or carbamazepine; past nonresponse to a full antidepressant trial along with a mood stabilizer for the current major depressive episode; current psychosis; severe suicidality; current substance abuse; or any unstable medical condition (including hepatitis B or C or past pancreatitis). After complete description of the study to subjects, written informed consent was obtained. The protocol was reviewed and approved at institutional review boards at participating study sites.

A stratified randomization design was utilized, with 3 relevant items: the presence or absence of rapid cycling, the bipolar subtype (I vs. II/NOS), and the length of the current major depressive episode as defined by the DSM-IV (more or less than 3 months).

Data from 1 patient were excluded due to withdrawal of consent, resulting in an analysis sample size of 18. Subjects began divalproex (extended-release formulation) at 250 mg/day with a dosing escalation of 250 mg/day every 1 to 2 days with a weekly minimum increase of 500 mg as tolerated to the target level range of 70 to 90 ng/dL. Computer-generated sham levels were obtained for subjects receiving placebo. Study visits occurred weekly. The primary outcome measure was diminishment of the patient's depressive symptoms as measured by the MADRS, based on continuous scores. A secondary outcome was a categorical assessment of treatment response, as defined by a 50% reduction in MADRS ratings. The 31-item Hamilton Rating Scale for Depression (HAM-D)[15] and the Hamilton Rating Scale for Anxiety (HAM-A)[16] scores were secondary outcome measures, along with the Clinical Global Impressions (CGI) scale for bipolar disorder.[17] An intent-to-treat (ITT) analysis was performed using a linear growth curve model[18] for the weekly MADRS scores as well as the HAM-A total score. A random intercept was included to control for individual level sources of variance.[19] For the item-level data, which is ordinal and thus not truly continuous, we performed a similar growth curve analysis by using repeated proportional odds regression fit using generalized estimating equations. Ordinal regression models the probabilities associated with each anchor of the scale; thus, to demonstrate the longitudinal effects, we used the estimated prevalence of a moderate to severe response (anchors 4 through 6) at each time point and calculated the change in that prevalence from pretreatment to posttreatment for each group.

RESULTS

Clinical and demographic characteristics of the sample are provided in Table 1.

In the primary outcome, patients in the divalproex treatment group showed a significantly greater reduction in MADRS scores from baseline to week 6 when compared to patients that took placebo (group × time interaction, $p = .0078$). Analysis of the slope of change in MADRS scores over time revealed a significant group-by-time interaction, indicating that there was a significant difference in MADRS score change over time in the placebo and divalproex groups (group × time interaction: 2.04, SE = 0.67, $t = -3.05$, $p = .003$). Further examination of the estimates revealed that this was due to a significant decrease in MADRS scores in the divalproex group while

Table 2. Treatment Characteristics of Sample (available cases means) and Tests of Group Differences in Change Over Time (N = 18)[a]

Measure	Divalproex	Placebo	Interaction Effect p Value (group difference in time effect)
MADRS score			.003
Baseline	29.5 (7.6)	25.1 (8.5)	
Week 6	15.3 (13.9)	22.5 (6.1)	
p Value	< .0001	.66	
HAM-A score			.13
Baseline	22.4 (11.4)	17.8 (7.8)	
Week 6	10.9 (13.5)	14.5 (5.1)	
p Value	< .0001	.10	
HAM-D score			.09
Baseline	29.4 (6.2)	32.5 (9.7)	
Week 6	16.8 (11.6)	23.7 (8.3)	
p Value	< .0001	.11	
MRS score			.01
Baseline	5.9 (2.4)	6.3 (3.8)	
Week 6	5.3 (4.2)	11.5 (8.7)	
p Value	.19	.03	
CGI-mania score			.84
Baseline	1.8 (0.79)	2.4 (1.1)	
Week 6	1.4 (0.53)	1.8 (0.96)	
p Value	.002	.007	
CGI-depression score			< .0001
Baseline	4.6 (0.97)	4.5 (0.76)	
Week 6	2.7 (1.8)	4.3 (0.96)	
p Value	< .0001	.63	
CGI-overall score			< .0001
Baseline	4.5 (0.97)	4.4 (0.74)	
Week 6	2.9 (1.7)	4.3 (0.96)	
p Value	< .0001	.88	

[a]Values are expressed as mean (SD).
Abbreviations: CGI = Clinical Global Impressions, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, MRS = Mania Rating Scale.

there was no significant change in the placebo group (MADRS total score estimated change over time in symptoms, –13.6 for divalproex vs. –1.4 for placebo, p = .003; based on linear growth curve model). Standardized effect size calculations demonstrated a large effect (Cohen d = 0.81). Table 2 demonstrates absolute rating scale scores at baseline and over time.

The percentage of treatment responders was also higher with divalproex (33.3%) versus placebo (14.3%) (relative risk = 3.0; 95% CI = 0.34 to 20.8; Fisher exact test, p = .585) but not statistically significant. The mean ± SD divalproex dose used was 1027.8 ± 404.0 mg/day, with a mean blood level of 70.3 ± 27.5 ng/dL.

Improvement, though not statistically significant, was also seen on the HAM-D and HAM-A total scores (HAM-A total score estimated change over time, –10.2 for divalproex vs. –4.7 for placebo, p = .13; HAM-D total score estimated change over time, –13.4 for divalproex vs. –5.6 for placebo, p = .09; based on linear growth curve model).

As seen in Table 3, MADRS item analyses demonstrated statistically significant improvement with divalproex ($p \leq .05$) in core mood symptoms of apparent sadness, concentration difficulties, and pessimistic thoughts, more so than in anxiety symptoms like inner tension and with no difference in insomnia symptoms.

To analyze the impact of potential subthreshold mixed states, we found a modest but significant correlation between MADRS and MRS scores in the divalproex group (r = 0.29, df = 51, p = .03) but not in the placebo group (r = –0.15, df = 35, p = .36). One or more mania criteria (excluding psychomotor agitation) were present in 13 (72.2%) of 18 subjects. Distribution of baseline MRS scores divided equally around a median of 7.0.

Side effects observed with divalproex included sedation (N = 6), myalgias/weakness and headache (N = 4 each), dizziness or nausea (N = 3 each), decreased appetite or dry mouth (N = 2 each), and insomnia or easy bruising (N = 1 each). Side effects observed with placebo were sedation (N = 3); dry mouth, weakness, or dizziness (N = 2 each); and confusion, jitteriness, flatulence, headache, nausea, or diarrhea (N = 1 each). Mean ± SD weight was unchanged with divalproex (159.8 ± 37.4 lb at baseline vs. 158.1 ± 23.6 lb at termination) and decreased somewhat with placebo (184.1 ± 51.7 lb at baseline vs. 172.0 ± 19.7 lb at termination).

Completion rates were not significantly higher in the divalproex group (78% [7/9]: N = 1, lost to follow up;

Table 3. Comparison of Progression of Individual MADRS Symptoms in Divalproex and Placebo: Results of Repeated Proportional Odds Models (N = 18)

Symptom	Estimated Change in Prevalence of Moderate to Severe Symptoms Over Time (wk 6 vs. wk 0)		Significance of Interaction Effect (drug × time), p[a]
	Placebo	Divalproex	
Apparent sadness	–0.02	–0.40	.02
Reported sadness	–0.05	–0.43	.07
Inner tension	–0.04	–0.23	.08
Reduced sleep	–0.11	–0.18	.65
Reduced appetite	–0.02	–0.02	.63
Concentration difficulties	–0.02	–0.53	.05
Lassitude	–0.17	–0.41	.43
Inability to feel	–0.10	–0.41	.11
Pessimistic thoughts	0.06	–0.31	.008
Suicidal thoughts	–0.13	–0.18	.64

[a]p Values ≤ .05 indicate a significant group difference in change over time.
Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

N = 1, discontinuation for inefficacy) than they were in the placebo group (57% [4/9]: N = 2, lost to follow up; N = 1, discontinuation for inefficacy/hospitalization; N = 2, patient decision).

DISCUSSION

Depressive symptoms were significantly improved within the treatment group over the course of this 6-week study of the efficacy of divalproex in bipolar depression. This result adds further support to the current evidence for the efficacy of divalproex in treating bipolar depression, and it is consistent with previous observations of reduction in depressive morbidity and reduced probability of depressive relapse during maintenance treatment with divalproex for bipolar disorder.[11] However, the relatively modest overall rate of response seen with divalproex in the present study points to a need for continued efforts to identify more robust treatments for bipolar depression.

Only 2 double-blind, RCTs of divalproex for acute bipolar depression have previously been conducted: 1 unpublished[10] and 1 published.[12] The present findings agree with the only published data,[12] in which divalproex was superior to placebo in reducing depressive and anxiety symptoms, using the HAM-D and HAM-A (N = 25). In the unpublished RCT[10] (N = 45), 43% of subjects responded to valproate versus 27% with placebo, which was not statistically significant. A reanalysis of those data using effect estimates indicates some benefit with divalproex (relative risk = 1.50, 95% CI = 0.64 to 3.50), but wide confidence intervals raise the possibility of false-negative (type II) error. Indeed, improvement in depressive symptom scores with divalproex was noted (a decrease of about 10 points on the HAM-D), but, unlike the present study, placebo response was elevated. Predictors of placebo response in such short-term studies will include rapid cycling, brief major depressive episodes, and bipolar subtype. A priori stratification on those factors, as in the present study, should reduce potential confounding bias, especially with small sample sizes, which is indeed suggested by the low placebo response in the present study. This low placebo response in turn allowed the effect size (drug vs. placebo difference) to be much larger, as shown in the calculations of a large standardized effect size (as would be expected with statistically significant results in a study with a small sample). Another relevant factor may be that any potential advantage for divalproex in the previous study may have been attenuated by suboptimal serum valproate levels, again in contrast to the present study.

Observed improvement in core (e.g., psychic) depressive symptoms indicates benefit in domains beyond anxiolytic or anti-insomnia effects, which may be differentiable from frank antidepressant effects. Also, the HAM-D scale captured depressive symptom benefits in this study less robustly than did the MADRS scale, which is consistent with prior suggestions[20] that the MADRS may best measure longitudinal change in bipolar depression.

The modest but significant correlation between depression and mania rating scales in the divalproex group suggests that some, though not all, of the observed benefit for depressive symptoms may have reflected subclinical mixed states. Indeed, it has been reported that up to one half of major depressive episodes in bipolar disorder involves the presence of up to 3 manic symptoms.[21] In our study, 72% of patients had at least 1 concomitant manic symptom (excluding psychomotor agitation). This syndrome, which has been called the *depressive mixed state*, is subthreshold for DSM-IV–defined mixed episodes but may nonetheless be a predictor of benefit with anticonvulsants or antipsychotics, as suggested by evidence of benefit with those agents in full mixed episodes.[22,23] Future clinical trials of acute bipolar depression would benefit from careful assessment of depressive mixed states, which currently are included in such studies using DSM-IV criteria. Some of the evidence of benefit with anticonvulsants, or even perhaps some antipsychotics

like quetiapine,[6] may reflect benefit for such depressive mixed state presentations. Indeed, emerging data from the National Institute of Mental Health Systematic Treatment Enhancement Program for Bipolar Disorder study suggest that antidepressants may not be effective in this subgroup of DSM-IV major depressive disorder.[24]

The relatively small sample sizes in both the present study and in prior open[7–9] or randomized[10–12] trials of divalproex for bipolar depression pose the main limitation for discerning validity of divalproex efficacy. Thus, while the collective existing database appears to support a role for divalproex in bipolar depression, large-scale multisite trials are needed to affirm or refute these observations.

Drug names: carbamazepine (Equetro, Tegretol, and others), divalproex (Depakote), lithium (Eskalith, Lithobid, and others).

Financial disclosure: **Dr. Ghaemi** currently receives research grants from GlaxoSmithKline and Pfizer; serves on the speakers bureaus of GlaxoSmithKline, AstraZeneca, Pfizer, Janssen, and Abbott; and has served on the advisory boards of GlaxoSmithKline, Janssen, Pfizer, Shire, and Abbott. Neither he nor his family holds equity positions in pharmaceutical corporations. **Dr. Gilmer** has received grant/research support from Abbott. **Dr. Goldberg** has been a consultant to Cephalon, AstraZeneca, GlaxoSmithKline, and Eli Lilly and has served on speakers or advisory boards for Abbott, AstraZeneca, Eli Lilly, GlaxoSmithKline, and Pfizer. **Dr. Kemp** has received grant/research support from GlaxoSmithKline and has received educational grants from Abbott and Bristol-Myers Squibb. **Dr. Dunn** has received grant/research support from Pfizer, GlaxoSmithKline, National Alliance for Research on Schizophrenia and Depression, Janssen, Abbott, and Bristol-Myers Squibb and has served on speakers or advisory boards for Janssen. **Dr. Kelley**, **Mr. Zablotsky**, and **Mss. Bauer**, **Fleck**, **Filkowski**, and **Stan** report no additional financial or other relationship related to the subject of this article.

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