

A Randomized, Placebo-Controlled 12-Month Trial of Divalproex and Lithium in Treatment of Outpatients With Bipolar I Disorder

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Background: Long-term outcomes are often poor in patients with bipolar disorder despite treatment; more effective treatments are needed to reduce recurrences and morbidity. This study compared the efficacy of divalproex, lithium, and placebo as prophylactic therapy.

Methods: A randomized, double-blind, parallel-group multicenter study of treatment outcomes was conducted over a 52-week maintenance period. Patients who met the recovery criteria within 3 months of the onset of an index manic episode ($n = 372$) were randomized to maintenance treatment with divalproex, lithium, or placebo in a 2:1:1 ratio. Psychotropic medications were discontinued before randomization, except for open-label divalproex or lithium, which were gradually tapered over the first 2 weeks of maintenance treatment. The primary outcome measure was time to recurrence of any mood episode. Secondary measures were time to a manic episode, time to a depressive episode, average change from baseline in Schedule for Affective

Disorders and Schizophrenia–Change Version subscale scores for depression and mania, and Global Assessment of Function scores.

Results: The divalproex group did not differ significantly from the placebo group in time to any mood episode. Divalproex was superior to placebo in terms of lower rates of discontinuation for either a recurrent mood episode or depressive episode. Divalproex was superior to lithium in longer duration of successful prophylaxis in the study and less deterioration in depressive symptoms and Global Assessment Scale scores.

Conclusions: The treatments did not differ significantly on time to recurrence of any mood episode during maintenance therapy. Patients treated with divalproex had better outcomes than those treated with placebo or lithium on several secondary outcome measures.

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ALTHOUGH MOST treatment studies of bipolar disorder have focused on acute episodes, the maintenance phase of treatment dominates clinical treatment. Maintenance studies conducted a quarter of a century ago concluded that lithium was effective in preventing both manic and depressive episodes of bipolar disorder,¹⁻⁵ but more recent open-label studies of lithium have reported less favorable treatment outcomes.⁶⁻¹⁰

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No placebo-controlled studies of maintenance therapy for bipolar disorder have been conducted in more than 25 years. Even these early studies had limitations: most failed to employ established diagnostic criteria or outcome measures and included not only patients with bipolar disorder, but also those with recurrent unipolar depression.¹ Often, data were analyzed only for pa-

tients completing the trials, and the reasons for premature termination were inadequately described, preventing critical evaluation of possible sources of bias. In addition, artifactual differences between lithium and placebo treatment may have been created in some studies because of abrupt discontinuation of lithium at the point of randomization to placebo.^{1,3-5}

Double-blind, randomized controlled trials have demonstrated that divalproex is superior to placebo and comparable with lithium in reducing or eliminating manic symptoms.^{11,12} Although open-label studies¹³⁻¹⁵ also suggest that valproate reduces the frequency and intensity of recurrent manic and depressive episodes, to our knowledge, no double-blind, controlled maintenance studies of valproate in bipolar disorder have been reported until now. Our randomized double-blind, parallel-group trial compared the efficacy of divalproex with that of placebo and lithium in preventing new bipolar epi-

The affiliations of the authors appear in the acknowledgment section at the end of the article. A list of members of the Divalproex Maintenance Study Group appears on page 488.

PATIENTS AND METHODS

PATIENTS

To enter the initial open-label phase of the study, patients had to be between ages 18 and 75 years, meet the *DSM-III-R*^{16,17} criteria for bipolar disorder, have an index manic episode as diagnosed by the Structured Clinical Interview for *DSM-III-R*,¹⁶ and have had at least 1 other manic episode in the previous 3 years. Patients could be enrolled in the open-label phase while manic, partially recovered from the manic episode, or euthymic after the episode, but not while depressed. Patients had to be randomized to double-blind maintenance treatment within 3 months of the onset of the index episode. Randomization criteria included scores of 11 or less on the Mania Rating Scale (MRS), 13 or less on the Depressive Syndrome Scale (DSS), and more than 60 on the Global Assessment Scale (GAS) on 2 consecutive occasions at least 6 days apart; the second evaluation took place on the day of randomization.^{18,19}

Exclusion criteria included a history of intolerance of divalproex or lithium; alcohol abuse within the previous 6 months; current substance dependence or positive results on a urine toxicology test; concomitant drug treatment that could confound study results; the presence of any central nervous system, neuromuscular, or uncontrolled systemic disorders; serious suicidal risk; ongoing individual psychotherapy; or evidence of failure to adhere to the open-phase protocol. Female patients could not be pregnant.

After enrollment in the maintenance phase, patients were terminated from the study if they required hospitalization for depression or mania, had an MRS score of 16 or more, experienced intolerable side effects or other evidence of medical danger, became pregnant, or had a Schedule

for Affective Disorders and Schizophrenia suicide item score of 4 or more. If any of the above occurred, they were referred for treatment.

Patients signed informed consent forms approved by the centers' institutional review boards.

STUDY DESIGN

This randomized, placebo-controlled, double-blind, parallel-group study was designed to compare the efficacy and safety of divalproex sodium therapy primarily with that of placebo and secondarily with that of lithium carbonate therapy. The initial open phase lasted 3 months or less, followed by a 52-week randomized maintenance phase. During the open phase, the index manic episode was treated at the discretion of the investigator, except that depot neuroleptics and electroconvulsive treatments were prohibited. The criteria for randomization could be met with or without drug treatment during the open phase. Any drugs other than divalproex or lithium given during the open phase were discontinued by the day before randomization.

Patients were randomized to divalproex, lithium, or placebo in a 2:1:1 ratio. Those taking divalproex or lithium on the day of randomization had the drug gradually reduced and withdrawn during the first 2 weeks of maintenance treatment. Patients who had received both drugs had to have one discontinued before randomization. The study drug was administered 3 times daily and the dose gradually increased based on body weight. Unless adverse events intervened, serum trough concentrations were maintained at 71 to 125 µg/mL for valproate and 0.8 to 1.2 mmol/L for lithium. Study visits were scheduled weekly or every other week for the first 12 weeks of the maintenance phase, then monthly.

Two courses of lorazepam were permitted: up to 6 mg/d for a 14-day maximum during the first month and no more than 7 days for the remainder of the study. Up to 10 mg of

sodes in patients whose disease was in remission. In addition, the relationship between acute treatment of a manic episode and subsequent maintenance therapy outcomes was studied, as this is the first prophylactic study with treatment of an acute bipolar episode.

RESULTS

COMPARABILITY OF TREATMENT GROUPS

Of 571 patients enrolled in the open phase, 372 were randomized to maintenance treatment. The reasons for exclusion of the other 199 patients from randomization are shown in **Table 1**. Because multiple reasons for failure could be reported, many patients were listed in the *other* category. Review of comments indicates that most patients in the other and noncompliant categories had uncontrolled manic symptoms as a major factor contributing to their discontinuation. During the open phase, 117 of the 372 subsequently randomized patients had been treated with divalproex only, 124 with lithium only, 50 with both drugs (usually sequentially), and 81 with neither drug; 187 of 372 were subsequently randomized to divalproex, 91 to lithium, and

94 to placebo. Two patients randomized to lithium never received the drug and one randomized to placebo was noncompliant, reducing the intent-to-treat sample to 369 patients. Twenty-five of the 37 participating centers randomized at least 1 patient to each of the 3 treatment groups; 80% of those in the intent-to-treat sample were treated at 16 centers. For purposes of comparisons across centers, the data from centers that enrolled fewer than 3 patients were pooled and treated as data from a single center. No significant treatment-investigator interactions were found in either baseline or mean change scores on the MRS or DSS.

Demographic characteristics were comparable among treatment groups in the intent-to-treat sample (**Table 2**), with 61% having at least one previous psychiatric hospitalization and 18% hospitalized for the index episode. Illness at the screening visit, conducted prior to open-phase treatment, was significantly less severe for randomized patients than for those not qualifying for randomization (MRS: 10.8 ± 9.5 vs 14.1 ± 10.5 ; $t_{559} = -3.69$; $P = .002$) (DSS: 12.1 ± 9.4 vs 14.5 ± 11.0 ; $t_{559} = -2.68$; $P = .008$). Baseline scores were also similar in the subsets of patients taking divalproex or lithium at the point of randomization.

haloperidol daily was permitted during the second consecutive week of lorazepam use in the first month only. These rescue medications were allowed to minimize the recurrence of manic symptoms caused by withdrawal of open-label medication. Neither lorazepam nor haloperidol was allowed within 8 hours before behavioral assessments.

OUTCOME MEASURES

The primary outcome measure was time to either a manic or depressive episode, subsequently referred to as *any mood episode*. The secondary measures were time to a manic episode, time to a depressive episode, and average change from baseline in scores on the MRS, DSS, and GAS during maintenance therapy. (Outcome measures were revised at the suggestion of reviewers.) A manic episode was defined as one accompanied by an MRS score of 16 or more or requiring hospitalization. A depressive episode was defined as one requiring antidepressant use or premature discontinuation from the study because of symptoms. Patients with DSS scores of 25 or higher were treated with sertraline or paroxetine, and their data were censored from the analyses of time to mania relapse on the day that antidepressant treatment began. Symptom severity was measured by the Schedule of Affective Disorders and Schizophrenia–Change Version, augmented to include all 11 items of the MRS.^{11,19} Subgroups of patients with elated and depressive manic symptoms were established using the depressive mania criteria of Swann et al²⁰ based on open-phase ratings at the point of the highest open-phase MRS score. Additional details of the study design and rationale appear elsewhere.^{21,22}

STATISTICAL ANALYSES

All tests were 2 tailed. Analyses were performed with the SAS system.²³ Values of $P \leq .05$ were considered

significant, with the following exception: a Bonferroni adjustment was made for the 3 pairwise efficacy and adverse effect comparisons, yielding an adjusted P value of .02 (equivalent to an unadjusted value of .05); this adjustment was also made for comparisons of adverse effects related to laboratory findings (adjusted $P = .03$).

All randomized patients were evaluated for safety and reasons for premature discontinuation. Comparability of groups at baseline was assessed by one-way analysis of variance and Kruskal-Wallis tests. Differences between treatment groups in categorical measures were examined with Cochran-Mantel-Haenszel and Fisher exact tests. Survival analyses of time to occurrence of a manic or depressive episode were performed for the intent-to-treat sample (all patients receiving at least one dose of study drug). Life-table methods were employed to compare survival curves using the Wilcoxon test because of its sensitivity to early group differences.²⁴ Two-way analysis of variance models were used to evaluate differences in the change from baseline to the average of all scores on the Schedule for Affective Disorders–Change Version subscales and the GAS during the randomized phase. The first analysis of variance model included effects for treatment, center, and treatment-center interaction; the second included effects for treatment, mania type (depressive vs elated), and their interaction. The COSTART terms²⁵ were used to categorize treatment-emergent adverse events, defined as any event starting or worsening in severity after administration of the first dose of blinded study drug. Mean changes in laboratory values between treatment groups from baseline to final evaluation were compared using one-way analysis of variance. Sample-size estimation was based on a projected rate of manic relapse of 55% in the placebo group and 35% in the divalproex group, yielding an estimated power of 0.8 for a 2-tailed value of $\alpha = .05$ for an overall sample of 350 patients.

By day 30 of randomized treatment, the median and mean \pm SD serum concentrations were 83.9 and 84.8 \pm 29.9 $\mu\text{g/mL}$, respectively, for valproate and 0.9 and 1.0 \pm 0.48 mEq/L for lithium; concentrations remained stable in succeeding months. The minimum and maximum concentrations for the entire study were 0.6 to 156 $\mu\text{g/mL}$ for valproate and 0.1 to 2.7 mEq/L for lithium.

Premature termination rates for all reasons tended to be lower in the divalproex group than in the lithium and placebo groups ($P = .03$ and $P = .05$, respectively) (**Table 3**). The lithium group had significantly higher termination rates for study drug intolerance and non-compliance than the placebo group ($P = .001$), but more patients given placebo were prematurely dropped from the study for other reasons, including administrative reasons and loss to follow-up ($P = .01$). Patients in the divalproex group had a significantly lower termination rate for recurrent mania or depression than the placebo group ($P = .02$), and they were significantly less likely to be dropped from the study because of depressive episodes ($P = .02$).

Patients treated with divalproex continued treatment significantly longer than those treated with

lithium (mean \pm SD, 198 \pm 152 days vs 152 \pm 148 days) ($F_{1,366} = 5.96$; $P = .02$) and showed a trend toward longer treatment duration than the placebo group (mean \pm SD, 165 \pm 140 days) ($F_{1,366} = 3.11$; $P = .08$).

OUTCOME MEASURES

The time to development of any mood episode did not differ significantly among treatment groups, although a trend was observed favoring divalproex over lithium ($P = .06$; Wilcoxon $\chi^2_1 = 3.54$) (**Figure**). The median times to 50% survival without any mood episode, based on 4-week intervals, were 40 weeks for divalproex, 24 weeks for lithium, and 28 weeks for placebo.

The time in maintenance treatment before the occurrence of a protocol-defined manic episode did not differ significantly among groups. The time elapsed before development of depression tended to be longer in the divalproex group than in the lithium group ($P = .08$; Wilcoxon $\chi^2_1 = 3.11$).

The mean changes in the MRS during maintenance treatment were small and did not differ significantly for either the center effects or mania subtype model (**Table 4**). Treating the initial screening MRS score as a

Table 1. Reasons Open-Phase Patients Failed to Achieve Randomization Into the Maintenance Phase of the Study

Reason	No. (%)
Continuing or recurrent manic symptoms	28 (14.1)
Depressive symptoms	11 (5.5)
Noncompliant in open phase	31 (15.6)
Withdrew consent	15 (7.5)
Intolerant of divalproex or lithium	10 (5.0)
Other illness	8 (4.0)
Drug abuse	6 (3.0)
Other*	90 (45.2)
Total	199 (100)

*Most patients listed in the other category had uncontrolled manic symptoms as a factor in their termination.

covariate resulted in no significant differences between treatment groups for mean change in scores.

The mean change from baseline in DSS scores using the center effects model indicated a trend for less deterioration in depressive symptoms in the divalproex group than in the placebo group ($F_{1,289} = 2.86; P = .09$). With the mania subtype model, DSS scores worsened less for the divalproex group than for the lithium group ($F_{1,358} = 11.58; P < .001$) and less for the placebo group than for the lithium group ($F_{1,358} = 5.20; P = .02$). The interaction effect between treatment and mania subtype ($F_{1,358} = 11.38; P < .001$) indicated that the treatment difference was a function of a poorer response to lithium prophylaxis among patients without depression in the index manic episode. Results were similar when either screening or baseline DSS was treated as a covariate.

The mean change in GAS scores showed somewhat less worsening in the divalproex group than in the lithium group with the center effects model ($F_{1,262} = 2.60; P = .12$). With the mania subtype model, GAS scores worsened less for the divalproex group than for the lithium group ($F_{1,325} = 11.22; P = .001$) and less for the placebo group than for the lithium group ($F_{1,325} = 4.92; P = .03$), with the interaction between treatment and mania subtype ($F_{1,325} = 4.71; P = .03$) indicating worse prophylactic response to lithium among patients without depression during the index manic episode.

RELATIONSHIP OF TREATMENT OUTCOME TO OPEN-PHASE TREATMENT

Among patients taking divalproex at the end of the open phase, those randomized to divalproex had a 46% longer duration of prophylaxis in the maintenance phase ($P = .03$) than those randomized to placebo; they were also 42% less likely to be prematurely dropped from the study for any major affective episode ($P = .04$) and 32% less likely to be prematurely terminated for any reason ($P = .002$) (**Table 5**). The divalproex group showed a trend for longer time to recurrence of any major affective episode than the lithium group. Among patients taking lithium as their last open-phase drug, no significant differences were observed in the 3 randomized treatment groups in premature discontinuation rates or time to recurrence of any affective episode (Figure). There was a trend ($P = .07$)

Table 2. Characteristics of Patients in the Intent-to-Treat Sample Before Treatment*

Characteristic	Treatment Group†		
	Divalproex (n = 187)	Lithium (n = 90)	Placebo (n = 92)
Age, y‡	38.9 ± 12.7	40.3 ± 9.8	38.7 ± 11.9
Sex, No. (%)			
Male	93 (50)	43 (48)	44 (48)
Female	94 (50)	47 (52)	48 (52)
Race, No. (%)			
White	168 (90)	82 (91)	87 (95)
Black	10 (5)	4 (4)	1 (1)
Other	9 (5)	4 (4)	4 (4)
Prior manic episodes, No. (%)§			
1-10	96 (51)	44 (51)	40 (44)
11-20	29 (16)	9 (10)	11 (12)
>20	62 (33)	34 (39)	39 (43)
Prior depressive episodes, No. (%)			
0	7 (4)	5 (6)	6 (7)
1-10	81 (44)	45 (51)	39 (43)
>10	96 (52)	38 (43)	46 (50)
Age at first manic episode, y‡¶	24.1 ± 10.4	25.4 ± 11.0	24.4 ± 10.9
Age at first depressive episode, y‡#	21.0 ± 9.9	23.1 ± 10.3	21.1 ± 9.8
Time since first manic episode, y‡**	14.9 ± 11.4	15.0 ± 10.1	14.7 ± 10.9
Use of divalproex in open phase, No. (%)††	70 (37)	41 (46)	38 (41)
Use of lithium in open phase, No. (%)††	79 (42)	31 (34)	32 (35)
Time of open phase, d§§	35.7 (24.6)	38.3 (24.7)	35.8 (23.6)
Time from start of index episode to randomization, d§§	74.2 (22.9)	75.1 (21.5)	72.8 (24.0)
MRS at baseline‡	3.4 ± 3.7	3.2 ± 3.7	3.4 ± 3.4
DSS at baseline‡	4.6 ± 4.6	4.5 ± 4.6	5.3 ± 4.2
GAS at baseline‡	69.8 ± 8.2	70.4 ± 7.7	70.5 ± 7.4

*MRS indicates Mania Rating Scale; DSS, Depressive Syndrome Scale; and GAS, Global Assessment Scale.

†Percentages may not add to 100% due to rounding.

‡Values are mean ± SD.

§One hundred eighty-seven patients were randomized to divalproex; 87 to lithium; and 90 to placebo.

¶One hundred eighty-four patients were randomized to divalproex; 88 to lithium; and 91 to placebo.

‡One hundred eighty-seven patients were randomized to divalproex; 86 to lithium; and 90 to placebo.

#One hundred seventy-seven patients were randomized to divalproex; 83 to lithium; and 85 to placebo.

**One hundred eighty-seven were randomized to divalproex; 89 to lithium; and 92 to placebo.

††Based on use closest to randomization.

§§Values are mean (SD).

for longer mean duration of prophylaxis with divalproex than with lithium (Table 5).

ADVERSE EFFECTS

The divalproex group had a significantly higher incidence of tremor and weight gain than the placebo group (**Table 6**). Tremor was significantly more common in the lithium group than in the placebo group. The divalproex group also had a significantly higher incidence of sedation, infection, and tinnitus than the lithium group.

Table 3. Reasons for Premature Termination for Randomized Patients*

Reason	Treatment Group†			Significant Differences (P)‡
	Divalproex (n = 187)	Lithium (n = 91)	Placebo (n = 94)	
Any mood episode	45 (24)	28 (31)	36 (38)	Divalproex < placebo (.02)
Mania	33 (18)	19 (21)	21 (22)	
Depression	12 (6)	9 (10)	15 (16)	Divalproex < placebo (.02)
Intolerance or noncompliance	41 (22)	32 (35)	11 (12)	Divalproex > placebo (.05) Lithium > placebo (<.001) Divalproex < lithium (.02)
Other§	30 (16)	9 (10)	24 (25)	Lithium < placebo (.01)
Total terminations	116 (62)	69 (76)	71 (75)	Divalproex < placebo (.05) Divalproex < lithium (.03)
Relapse time				
Time to 50% relapse with any mood episode, d (95% CL)	275 (167, NC)	189 (88, NC)	173 (101, NC)	
Time to 25% relapse with mania, d (95% CL)	>365 (NC)	293 (71, NC)	189 (84, NC)	
Time to 25% relapse with depression, d (95% CL)	126 (100, 204)	81 (33, 234)	101 (55, 190)	

*CL indicates confidence limits; NC, not calculable.

†Values are presented as No. (%) unless otherwise indicated.

‡By Fisher exact test.

§Lost to follow-up, intercurrent illness, administrative reasons, or other reasons.

Patients treated with lithium had a significantly higher incidence of polyuria and thirst than those treated with divalproex. When compared with patients in the placebo group, patients in the divalproex group had significant reductions in platelet count ($-53 \pm 52.1 \times 10^9/L$ vs $3.4 \pm 44.5 \times 10^9/L$) and white blood cell count ($-1.1 \pm 2.0 \times 10^9/L$ vs $-0.3 \pm 2.2 \times 10^9/L$) ($F_{1,233} = 69.7$, $P < .001$, and $F_{1,234} = 6.91$, $P = .009$, respectively). Reductions below normal values were observed in 6.5% of patients for platelet count and 9.1% for white blood cell count. When compared with the placebo group, the lithium group had significant increases in white blood cell count ($1.2 \pm 1.7 \times 10^9/L$ vs $-0.3 \pm 2.2 \times 10^9/L$) ($F_{1,145} = 20.82$; $P < .001$); uric acid level (0.03 ± 0.08 vs -0.001 ± 0.07 mmol/L [0.49 ± 1.3 vs -0.16 ± 1.1 mg/dL]) ($F_{1,145} = 10.85$; $P = .001$); creatinine level (3.5 ± 11.5 vs -1.8 ± 12.4 $\mu\text{mol/L}$ [0.04 ± 0.13 vs -0.02 ± 0.14 mg/dL]) ($F_{1,145} = 8.99$; $P = .003$); and calcium level (0.04 ± 0.10 vs -0.12 ± 0.11 mmol/L [0.16 ± 0.40 vs -0.05 ± 0.43 mg/dL]) ($F_{1,145} = 9.14$; $P = .003$). Increases to above-normal values were observed in 10.8% of patients for white blood cell count, 11.9% for uric acid level, and 3.1% for calcium level; no above-normal increases were observed in creatinine level. No significant differences in hepatic enzyme changes were observed among groups.

RELATIONSHIP OF OUTCOME MEASURES TO SERUM VALPROATE AND LITHIUM LEVELS

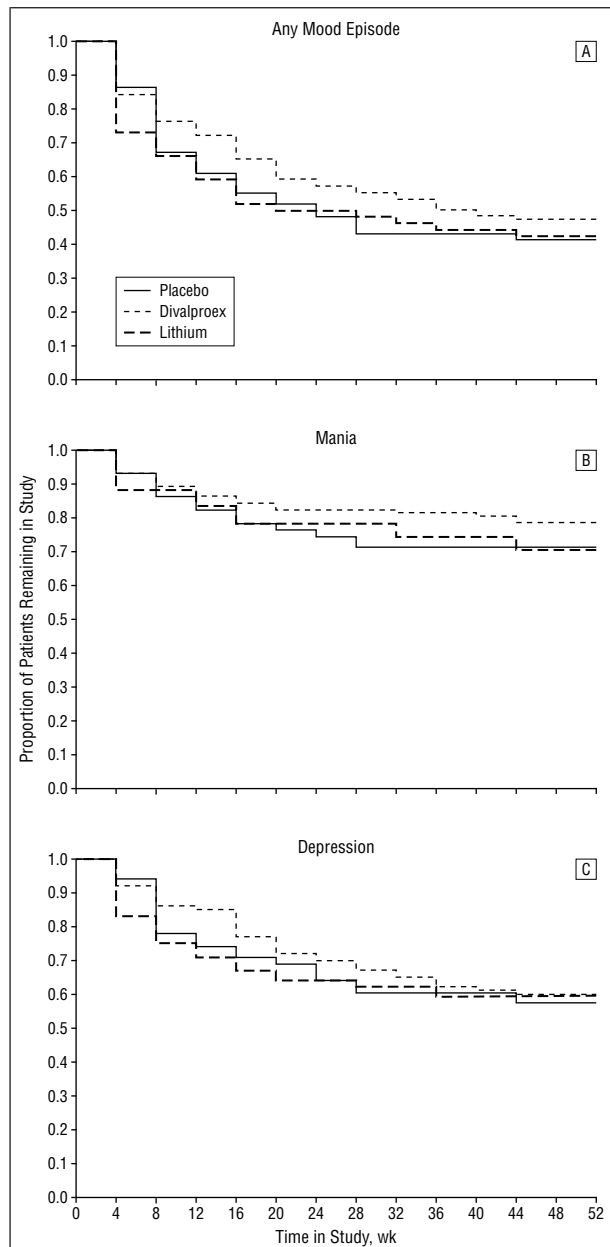
Serum lithium levels were unrelated to average change in MRS ($n = 74$) ($r = 0.08$) or DSS ($r = 0.01$) scores; valproate serum levels correlated with average change in MRS score ($n = 169$; $r = 0.17$; $P = .03$). Serum lithium levels above 1.5 mEq/L correlated with the incidence of diarrhea and tremor. Weight gain was associated with serum valproate levels above 125 $\mu\text{g/mL}$; serum valproate levels correlated with reductions in white blood cell count

($n = 154$; $r = -0.27$; $P < .001$) and platelet count ($n = 153$; $r = -0.32$; $P \leq .001$).

COMMENT

Our study is the first randomized, blinded clinical trial to compare divalproex with placebo and lithium in the maintenance treatment of patients with bipolar disorder. Our data indicated no greater efficacy for divalproex than for placebo or lithium in preventing the recurrence of mania sufficiently severe to require hospitalization and/or associated with an MRS score of 16 or more, the development of a depressive episode, or the development of the first mood episode of either type. However, divalproex was significantly more effective than either placebo or lithium on several other outcome measures, including the rates of recurrence of affective episodes severe enough to warrant patients' discontinuation from the study. Divalproex was somewhat more effective than lithium in controlling subsyndromal depressive symptoms. Among patients treated with divalproex during the open phase of the study, continued administration of divalproex as the randomized treatment was more effective than placebo treatment in terms of patients' ability to continue in the maintenance phase.

The effectiveness of lithium was less than that reported in other placebo-controlled studies, but consistent with the outcomes of naturalistic studies of lithium as maintenance therapy in bipolar disorder over the past decade.^{8-10,26,27} Several factors may have contributed to the unexpectedly poor response to lithium. First, the lithium group had a larger proportion of patients dropped from the study for intolerance to treatment or noncompliance than the divalproex or placebo group. In addition, fewer patients were randomized to the lithium group than to the divalproex group, reducing the power for lithium-placebo comparisons; lithium was included in



A, Time to any affective episode: Kaplan-Meier survival curves (placebo, $n = 92$; divalproex, $n = 187$; lithium, $n = 90$). Wilcoxon $\chi^2_1 = 0.95$, $P = .33$ for divalproex vs placebo; Wilcoxon $\chi^2_1 = 1.03$, $P = .31$ for lithium vs placebo; and Wilcoxon $\chi^2_1 = 3.54$, $P = .06$ for divalproex vs lithium. B, Time to mania, censoring for antidepressant use: Wilcoxon $\chi^2_1 = 0.69$, $P = .41$ for divalproex vs placebo; Wilcoxon $\chi^2_1 = 0.26$, $P = .61$ for lithium vs placebo; and Wilcoxon $\chi^2_1 = 1.74$, $P = .19$ for divalproex vs lithium. C, Time to depression: Wilcoxon $\chi^2_1 = 0.47$, $P = .49$ for divalproex vs placebo; Wilcoxon $\chi^2_1 = 1.30$, $P = .25$ for lithium vs placebo; and Wilcoxon $\chi^2_1 = 3.11$, $P = .08$ for divalproex vs lithium.

the study primarily for comparison purposes, as it is considered the standard prophylactic treatment for bipolar disorder.

Mean serum levels of lithium were relatively high in patients treated with lithium but were unrelated to changes in depressive or manic symptoms. Possibly the high serum levels of lithium had an adverse effect on efficacy measures in a manner not revealed by statistical analyses. Among patients treated with divalproex, serum valproate levels correlated positively with manic

Table 4. Mean Changes From Baseline in Mania Rating Scale (MRS), Depressive Syndrome Scale (DSS), and Global Assessment Scale (GAS) Scores for Randomized Patients

Measure	Model	Treatment Group, Mean \pm SD		
		Divalproex	Lithium	Placebo
MRS	Center effects	3.1 \pm 10.6	3.0 \pm 10.5	3.4 \pm 9.5
	Mania subtype	1.7 \pm 6.3	2.6 \pm 7.1	2.7 \pm 6.5
DSS	Center effects	3.9 \pm 10.7	5.7 \pm 10.7	6.1 \pm 9.7
	Mania subtype	3.6 \pm 6.9	7.0 \pm 8.0	4.4 \pm 7.2
GAS	Center effects	-4.7 \pm 14.7	-7.8 \pm 13.8	-5.7 \pm 13.2
	Mania subtype	-4.7 \pm 12.1	-10.8 \pm 13.7	-6.2 \pm 12.5

symptoms. While this relationship may be causal, it probably also reflects increases in divalproex dosage prescribed by investigators to deal with continuing manic symptoms in some patients.

A placebo group was included in our study in part because no placebo-controlled maintenance study of pharmacotherapy for bipolar disorder had been conducted in more than 25 years, and the outcomes in these early studies may have been biased against placebo because of risk of early relapse associated with the abrupt withdrawal of lithium at the point of randomization to placebo.²⁸⁻³⁰ In our study, the risk of relapse associated with the withdrawal of active drug in the placebo group was reduced by tapering the dose of open-phase lithium or divalproex over the first 2 weeks of randomized treatment. In addition, adjunctive medications were permitted in the first month of maintenance to minimize symptoms related to withdrawal of any open-phase drug. We found no evidence of rebound symptoms in patients withdrawn from one drug and randomized to another, as judged by lack of significant differences in treatment-emergent manic or depressive episodes between patients taking the same drugs during the open and maintenance phases and those switched to another drug or placebo.

Several factors may have contributed to the surprisingly good outcomes in the placebo group.²² Patients with mild forms of bipolar disorder may have been selected for the study because of the enrollment requirement that 2 consecutive GAS scores had to be above 60. Bias may also have been introduced by the requirement that remission of mania had to be achieved within 3 months of the manic episode, as failure to meet this criterion was a major reason for exclusion from randomization. Also, some patients were randomized whose manic episodes resolved without specific treatment. In addition, a number of study candidates with histories of severe illness were reluctant to enroll in the study because of the chance of receiving placebo for up to 1 year, with minimal use of rescue medications. Moreover, the index episodes of mania seemed to be more severe in patients who failed to qualify for randomization than in those randomized. Drug-placebo differences are known to be greater when patients with more severe forms of illness are studied.³¹⁻³³ Another factor influencing the favorable outcomes in the pla-

Table 5. Outcome Measures Among Patients Receiving Divalproex or Lithium in the Open Phase

	Treatment Group*		
	Divalproex	Lithium	Placebo
Divalproex in open phase (n = 149)†			
Time in maintenance phase of study, d, mean ± SD	209 ± 155‡	162 ± 146	143 ± 123
Early termination for mania or depression	20 (29)§	15 (37)	19 (50)
Early termination for intolerance to study drug or noncompliance	12 (17)	14 (34)	7 (19)
Early termination for any reason	41 (59)	31 (76)	33 (87)
Lithium in open phase (n = 142)¶			
Time in maintenance phase of study, d, mean ± SD	188 ± 150	130 ± 146	183 ± 151
Early termination for mania or depression	12 (15)	10 (32)	12 (38)
Early termination for intolerance to study drug or noncompliance	16 (20)#	10 (32)**	1 (3)
Early termination for any reason	51 (65)	25 (81)	21 (66)

*Values are No. (%) unless otherwise indicated.

†Seventy patients were randomized to divalproex; 41 to lithium; and 38 to placebo.

‡ $F_{1,145} = 5.01$; $P = .03$ for divalproex vs placebo.

§ $P = .07$ by Fisher exact test for divalproex vs placebo.

|| $P = .002$ by Fisher exact test for divalproex vs placebo.

¶Seventy-nine patients were randomized to divalproex; 31 to lithium; and 32 to placebo.

$P = .02$ by Fisher exact test for divalproex vs placebo.

** $P = .003$ by Fisher exact test for lithium vs placebo.

cebo group may have been the structured therapeutic environment in which patients received treatment, the high level of support and encouragement given by study personnel, the ready access of patients and their families to educational information about bipolar disorder, and staff attention to patient compliance. In addition, bias favoring the placebo group may have been introduced by the relatively high rate of premature terminations associated with protocol violations and loss to follow-up; this may have resulted in lowering the proportion of those remaining at risk for developing mania or depression. Survival analysis of an intent-to-treat sample may inflate placebo response rates, since premature study terminations for withdrawn consent and protocol violations tend to occur disproportionately in patients receiving placebo. The aggregate result of these factors was a lower proportion of manic relapses in the placebo group than projected, yielding inadequate power to test the primary outcome variable (ie, 0.3 rather than the planned power of greater than 0.8).

Perhaps outcome measures resembling those used in previous bipolar maintenance studies would have provided greater sensitivity to group treatment differences than our primary outcome measure, time to any mood episode. In placebo-controlled studies of lithium published in the 1970s, the duration of symptom-free maintenance therapy was used as the strongest evidence of lithium efficacy.^{1,2,4,5,34,35} For example, Fieve et al³⁵ reported that patients treated with lithium remained in treatment for 40.1 months compared with 18.2 months for those treated with placebo ($P < .01$). Greil et al³⁶ found no significant difference between lithium and carbamazepine in survival time to an affective episode, but when the outcome criteria were broadened to include the time to use of concomitant medication, lithium was superior to carbamazepine. Variations in severity of illness in different patient populations contribute to difficulties in interpreting outcome measures. For example, in the open

Table 6. Incidence of Adverse Effects With Significantly Greater Frequency by Treatment Group

Adverse Effect	Treatment Group, No. (%)			Significant Differences (P)*
	Divalproex (n = 187)	Lithium (n = 94)	Placebo (n = 94)	
Nausea	79 (42)	41 (45)	29 (31)	Lithium > placebo (.05)
Diarrhea	65 (35)	42 (46)	28 (30)	Lithium > placebo (.02)
Tremor	77 (41)	38 (42)	12 (13)	Lithium > placebo (<.001) Divalproex > placebo (<.001)
Sedation	78 (42)	24 (26)	33 (35)	Divalproex > lithium (.02)
Weight gain	39 (21)	12 (13)	7 (7)	Divalproex > placebo (.004)
Polyuria	15 (8)	17 (19)	9 (10)	Lithium > divalproex (.01)
Thirst	11 (6)	14 (15)	7 (7)	Lithium > divalproex (.01)
Alopecia	30 (16)	7 (8)	6 (6)	Divalproex > placebo (.03)
Infection	51 (27)	12 (13)	18 (19)	Divalproex > lithium (.009)
Tinnitus	11 (6)	0 (0)	1 (1)	Divalproex > lithium (.01)
Tachycardia	1 (<1)	4 (4)	1 (1)	Lithium > divalproex (.04)
Akathisia	1 (<1)	4 (4)	1 (1)	Lithium > divalproex (.04)
Dry eyes	0 (0)	3 (3)	0 (0)	Lithium > divalproex (.03)

*By Fisher exact test.

17-year maintenance study reported by Harrow et al,⁶ all patients were initially hospitalized for mania, indicating severe disease; indeed, 78% were considered psychotic. Although placebo controls would not have been possible among such severely ill patients, the authors reported an outcome similar to that found in our study (ie, the occurrence of new affective episodes in more than half of patients, with recurrence rates unrelated to lithium treatment).²²

In the aggregate, the time patients were able to continue receiving maintenance therapy was longer in the divalproex group than in either the placebo or lithium group. Although only some comparisons were significant, our findings were consistent with those of open-label studies in which valproate was found to be

The Divalproex Maintenance Study Group

The following members of the study group took part in this study: Paul E. Alexander, MD, Psychiatric Foundation for Research and Education, Warwick, RI; Jeffrey Clothier, MD, University of Arkansas Medical School, Little Rock; Robert Cooke, MD, Clarke Institute of Psychiatry, Toronto, Ontario; William Coryell, MD, University of Iowa Hospitals and Clinics, Iowa City; Scott Crow, MD, University of Minnesota Hospital, Minneapolis; Pedro Delgado, MD, University of Arizona College of Medicine, Tucson; Dwight Evans, MD, University of Florida College of Medicine, Gainesville; Arlene F. Frank, MD, Brookside Hospital, Nashua, NH; Robert Gerner, MD, University of California Center for Mood Disorders, Los Angeles; William J. Giakas, MD, Rockford Psychiatric Medical Services, Rockford, Ill; Ira David Glick, MD, Stanford University School of Medicine, Stanford, Calif; Steven Parker James, MD, Yorba Hills Medical Plaza, Yorba Linda, Calif; Philip G. Janicak, MD, Illinois State Psychiatric Institute, Chicago; James W. Jefferson, MD, Dean Foundation for Health, Research, and Education, Madison, Wis; Barbara L. Kennedy, MD, PhD, University of Louisville, Louisville, Ky; K. Ranga Rama Krishnan, MD, Duke University Medical Center, Durham, NC; B. Raj Nakra, MD, Washington University School of Medicine, St Louis, Mo; Henry A. Nasrallah, MD, Ohio State University College of Medicine, Columbus; Charles B. Nemeroff, MD, Emory University School of Medicine, Atlanta, Ga; William M. Patterson, MD, Birmingham Research Group Inc, Birmingham, Ala; Samuel Craig Risch, MD, Medical University of South Carolina, Charleston; Alan H. Rosenbaum, MD, Comprehensive Psychiatric Services, Farmington Hills, Mich; David Vincent Sheehan, MD, University of South Florida Psychiatry Center, Tampa; Richard L. Wang, MD, Milwaukee County Medical Complex, Milwaukee, Wis; Richard H. Weisler, MD, Raleigh, NC; Phillip Wilner, MD, Payne Whitney Psychiatric Clinic, New York, NY; John Downs, MD, University of Tennessee, Memphis.

effective in preventing new episodes of both mania and depression.¹³⁻¹⁵ Our results also indicated complex relationships between illness characteristics and treatments during the index manic episode and subsequent maintenance treatments (to be addressed in forthcoming articles). We recommend that future studies of prophylactic therapy for bipolar disorder focus on more sensitive indicators of drug efficacy than time to relapse with a full bipolar episode. Such measures should include subsyndromal symptoms, time spent in remission, and time to premature discontinuation for any reason.

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