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, but more recent open-label studies of lithium have reported less favorable treatment outcomes.

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No placebo-controlled studies of 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. Often, data were analyzed only for patients 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.

Double-blind, randomized controlled trials have demonstrated that divalproex is superior to placebo and comparable with lithium in reducing or eliminating manic symptoms. Although open-label studies 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-
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.

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; 599 = −3.69; P = .002) (DSS: 12.1 ± 9.4 vs 14.9 ± 11.0; 599 = −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. Subgroups of patients with elated and depressive manic symptoms were established using the depressive mania criteria of Swann et al 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.

STATISTICAL ANALYSES

All tests were 2 tailed. Analyses were performed with the SAS system. Values of P=.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. 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 terms 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 53% in the placebo group and 33% in the divalproex group, yielding an estimated power of 0.8 for a 2-tailed value of α = .05 for an overall sample of 350 patients.

By day 30 of randomized treatment, the median and mean ± SD serum concentrations were 83.9 and 84.8 ± 29.9 µg/mL, respectively, for valproate and 0.9 and 1.0 ± 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 µg/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 ± SD, 198 ± 152 days vs 152 ± 148 days) (F1,366 = 5.96; P = .02) and showed a trend toward longer treatment duration than the placebo group (mean ± SD, 165 ± 140 days) (F1,366 = 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 χ2 = 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 χ2 = 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
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 \( (F_{1,262} = 2.60; P = .09) \). 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 \( (F_{1,358} = 11.22; P = .001) \) and less for the placebo group than for the lithium group \( (F_{1,358} = 4.92; P = .03) \), with the interaction between treatment and mania subtype \( (F_{1,358} = 4.71; P = .03) \) 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 \( (P = .07) \) 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.
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 ± 52.1 × 10^9/L vs 3.4 ± 44.5 × 10^9/L) and white blood cell count (−1.1 ± 2.0 × 10^9/L vs −0.3 ± 2.2 × 10^9/L) (F_1,233 = 69.7, P < .001; and F_1,235 = 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 ± 1.7 × 10^9/L vs −0.3 ± 2.2 × 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 µmol/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 µg/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 ≤ .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.5-10,26,27 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

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**Table 3. Reasons for Premature Termination for Randomized Patients**

<table>
<thead>
<tr>
<th>Treatment Group†</th>
<th>Divalproex (n = 187)</th>
<th>Lithium (n = 91)</th>
<th>Placebo (n = 94)</th>
<th>Significant Differences (P)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reason</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any mood episode</td>
<td>45 (24)</td>
<td>28 (31)</td>
<td>36 (38)</td>
<td>Divalproex &lt; placebo (.02)</td>
</tr>
<tr>
<td>Mania</td>
<td>33 (18)</td>
<td>19 (21)</td>
<td>21 (22)</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>12 (6)</td>
<td>9 (10)</td>
<td>15 (16)</td>
<td>Divalproex &lt; placebo (.02)</td>
</tr>
<tr>
<td>Intolerance or noncompliance</td>
<td>41 (22)</td>
<td>32 (35)</td>
<td>11 (12)</td>
<td>Divalproex &lt; placebo (.05)</td>
</tr>
<tr>
<td>Other§</td>
<td>30 (16)</td>
<td>9 (10)</td>
<td>24 (25)</td>
<td>Lithium &lt; placebo (.01)</td>
</tr>
<tr>
<td>Total terminations</td>
<td>116 (62)</td>
<td>69 (76)</td>
<td>71 (73)</td>
<td>Divalproex &lt; placebo (.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lithium &lt; lithium (.03)</td>
</tr>
</tbody>
</table>

Differences (P)‡: By Fisher exact test.

§Lost to follow-up, intercurrent illness, administrative reasons, or other reasons.
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 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. 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. 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. Another factor influencing the favorable outcomes in the placebo group may have been the standard prophylactic treatment for bipolar disorder.
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).

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

<table>
<thead>
<tr>
<th>Treatment Group*</th>
<th>Divalproex</th>
<th>Lithium</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in maintenance phase of study, d, mean ± SD</td>
<td>209 ± 155</td>
<td>162 ± 146</td>
<td>143 ± 123</td>
</tr>
<tr>
<td>Early termination for mania or depression</td>
<td>20 (29)</td>
<td>15 (37)</td>
<td>19 (50)</td>
</tr>
<tr>
<td>Early termination for intolerance to study drug or noncompliance</td>
<td>12 (17)</td>
<td>14 (34)</td>
<td>7 (19)</td>
</tr>
<tr>
<td>Early termination for any reason</td>
<td>41 (59)</td>
<td></td>
<td>31 (76)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Treatment Group, No. (%)</th>
<th>Divalproex (n = 187)</th>
<th>Lithium (n = 94)</th>
<th>Placebo (n = 94)</th>
<th>Significant Differences (P)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>79 (42)</td>
<td>41 (45)</td>
<td>29 (31)</td>
<td>Lithium &gt; placebo (0.05)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>65 (35)</td>
<td>42 (46)</td>
<td>28 (30)</td>
<td>Lithium &gt; placebo (0.02)</td>
</tr>
<tr>
<td>Tremor</td>
<td>77 (41)</td>
<td>38 (42)</td>
<td>12 (13)</td>
<td>Lithium &gt; placebo (&lt;0.001)</td>
</tr>
<tr>
<td>Sedation</td>
<td>78 (42)</td>
<td>24 (26)</td>
<td>33 (35)</td>
<td>Divalproex &gt; placebo (&lt;0.001)</td>
</tr>
<tr>
<td>Weight gain</td>
<td>39 (21)</td>
<td>12 (13)</td>
<td>7 (7)</td>
<td>Divalproex &gt; placebo (0.004)</td>
</tr>
<tr>
<td>Polyuria</td>
<td>15 (8)</td>
<td>17 (19)</td>
<td>9 (10)</td>
<td>Lithium &gt; divalproex (0.01)</td>
</tr>
<tr>
<td>Thirst</td>
<td>11 (6)</td>
<td>14 (15)</td>
<td>7 (7)</td>
<td>Lithium &gt; divalproex (0.01)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>30 (16)</td>
<td>7 (8)</td>
<td>6 (6)</td>
<td>Divalproex &gt; placebo (0.03)</td>
</tr>
<tr>
<td>Infection</td>
<td>51 (27)</td>
<td>12 (13)</td>
<td>18 (19)</td>
<td>Divalproex &gt; lithium (0.009)</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>11 (6)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>Divalproex &gt; lithium (0.01)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1 (&lt;1)</td>
<td>4 (4)</td>
<td>1 (1)</td>
<td>Lithium &gt; divalproex (0.34)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (&lt;1)</td>
<td>4 (4)</td>
<td>1 (1)</td>
<td>Lithium &gt; divalproex (0.34)</td>
</tr>
<tr>
<td>Dry eyes</td>
<td>0 (0)</td>
<td>3 (3)</td>
<td>0 (0)</td>
<td>Lithium &gt; divalproex (0.33)</td>
</tr>
</tbody>
</table>

*By Fisher exact test.

17-year maintenance study reported by Harrow et al, 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). 

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 following members of the study group took part in this study:

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The Divalproex Maintenance Study Group

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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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