A 6-Month, Double-Blind, Maintenance Trial of Lithium Monotherapy Versus the Combination of Lithium and Divalproex for Rapid-Cycling Bipolar Disorder and Co-Occurring Substance Abuse or Dependence

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Objective: To assess whether combination treatment with lithium and divalproex is more effective than lithium monotherapy in prolonging the time to mood episode recurrence in patients with rapid-cycling bipolar disorder and comorbid substance abuse and/or dependence.

Method: A 6-month, double-blind, parallel-group comparison was carried out in patients who met DSM-IV criteria for (1) bipolar I or II disorder; (2) alcohol, cannabis, or cocaine abuse within the last 3 months or dependence within the last 6 months; (3) rapid cycling during the 12 months preceding study entry; and (4) a history of at least 1 manic, hypomanic, or mixed episode within 3 months of study entry and who had demonstrated a persistent bimodal response to combined treatment with lithium and divalproex. Subjects were randomly assigned to remain on combination treatment or to discontinue divalproex and remain on lithium monotherapy. The study was conducted at an outpatient mood disorders program between October 1997 and October 2006.

Results: Of 149 patients enrolled into the open-label acute stabilization phase, 79% discontinued prematurely (poor adherence: 42%, nonresponse: 25%, intolerable side effects: 10%). Of 31 patients (21%) randomly assigned to double-blind maintenance treatment, 55% (N = 17) relapsed (24% [N = 4] into depression and 76% [N = 13] into a manic/hypomanic/mixed episode), 26% (N = 8) completed the study, and 19% (N = 6) were poorly adherent or exited prematurely. The median time to recurrence of a new mood episode was 15.9 weeks for patients receiving lithium monotherapy and 17.8 weeks for patients receiving the combination of lithium and divalproex (not significant). The rate of relapse into a mood episode for those receiving lithium monotherapy or the combination of lithium and divalproex was 56% (N = 9) and 53% (N = 8), respectively. The rate of depressive relapse in both arms was 13% (N = 2), while the rate of relapse into a manic, hypomanic, or mixed episode was 44% (N = 7) for lithium monotherapy and 40% (N = 6) for the combination of lithium and divalproex.

Conclusion: A small subgroup of patients in this study stabilized after 6 months of treatment with lithium plus divalproex. Of those who did, the addition of divalproex to lithium conferred no additional prophylactic benefit over lithium alone. Although depression is regarded as the hallmark of rapid-cycling bipolar disorder in general, these data suggest that recurrent episodes of mania tend to be more common in presentations accompanied by comorbid substance use.

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Rapid cycling is a variant of bipolar disorder characterized by 4 or more mood episodes during a 12-month period. A rapid-cycling course affects approximately 20% of patients with bipolar disorder[1,2] and occurs more commonly among females and the bipolar II subtype.[1] Rapid-cycling presentations are frequently accompanied by other Axis I comorbidities, including alcohol and drug use disorders.[3,4] In fact, more than 40% of rapid-cycling bipolar disorder patients enrolled in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) met criteria for comorbid substance abuse.[2]

The added morbidity associated with substance use disorders poses important public health implications. Substance abuse is widely known to negatively affect treatment outcomes in bipolar disorder, contributing to greater treatment nonadherence,[5] increased hospitalizations,[6] lower remission rates,[7] more lifetime mood episodes,[8] and decreased quality of life.[9]

Although recognized as a cornerstone in the maintenance treatment of bipolar disorder, lithium is ineffective for up to 40% of patients.[10] In addition, both rapid cycling[11] and co-occurring substance abuse[12] have been associated with lithium nonresponse. Open-label data suggest that patients with rapid-cycling bipolar disorder may respond better to divalproex than to lithium,[11,13] and divalproex has shown efficacy in the acute treatment of bipolar mood episodes complicated by substance abuse.[14,15] One small (N = 12) unblinded study found the combination of lithium and divalproex superior to lithium monotherapy during maintenance treatment of non–rapid-cycling bipolar disorder.[16]

The present study was conceptualized while undertaking the first double-blind maintenance trial in rapid-cycling bipolar disorder to evaluate outcomes with lithium and divalproex.[17] During the conduct of that trial, it became apparent that a critical mass of patients was being excluded from participation due to active substance use. This practice is common and serves to reduce potential sources of variance, yet substantially decreases clinical trial generalizability. The present study was intended to improve generalizability by focusing on a cohort with active substance use disorders. To our knowledge, it is 1 of only 3 placebo-controlled intervention trials to specifically evaluate mood outcomes in subjects with bipolar disorder and co-occurring substance use disorders[18–20]; it is the first study entirely composed of patients with rapid cycling.

We hypothesized that lithium in combination with divalproex would be superior to lithium monotherapy in preventing maintenance phase relapse. The trial was designed to address the following questions:

1. Does the combination of lithium and divalproex compared with lithium monotherapy prolong the time to mood episode recurrence among patients with rapid-cycling bipolar disorder and co-occurring substance use disorders?
2. Do differences exist in the frequency and polarity of mood relapse among patients with rapid-cycling bipolar disorder and co-occurring substance use disorders?
3. How do stabilization and relapse rates during treatment with lithium and divalproex affect the design and feasibility of conducting future, large-scale maintenance trials in rapid-cycling bipolar disorder and co-occurring substance use disorders?

METHOD

The study was conducted at the outpatient Mood Disorders Program of Case Western Reserve University/University Hospitals Case Medical Center (Cleveland, Ohio) between October 1997 and October 2006. The University Hospitals Case Medical Center Institutional Review Board approved all study procedures. Written informed consent was obtained from each subject before any study-related procedures were performed. Patients could discontinue or be discontinued from any phase of the study for poor tolerance of study medications, lack of medication efficacy, investigator or patient unwillingness to continue the study for any reason, or nonadherence with study procedures. Participation could last up to 12.5 months, including a 2-week screening period, a 6-month open-label acute stabilization phase, and a 6-month double-blind, parallel-group maintenance phase.

Study Subjects

Patients eligible for participation were males and females, between 16 and 65 years of age, who met DSM-IV criteria for the following: (1) bipolar I or II disorder; (2) alcohol, cannabis, or cocaine abuse within the last 3 months or dependence within the last 6 months; (3) rapid cycling during the 12 months preceding study entry (confirmed by retrospective mood charting)[21]; and (4) a history of at least 1 manic, hypomanic, or mixed episode within 3 months of study entry. Patients were required to be in good physical health according to medical history, physical examination, and laboratory analyses conducted at the screening visit.

Patients were excluded from participation if they had previous intolerance to lithium or divalproex, were completely nonresponsive to past lithium treatment, had alcohol-related liver disease as reflected by diffuse elevations in liver function tests exceeding the upper limits of the normal range by 50%, were pregnant or planning to become pregnant, were taking exogenous steroids, required anticoagulant drug therapy, or were actively suicidal as evinced by a score ≥ 3 on item 3 of the 17-item Hamilton Rating Scale for Depression (HAM-D).[22]

Subjects met DSM-IV criteria for rapid-cycling bipolar disorder type I or II as ascertained by Extensive Clinical Interview and the Mini-International Neuropsychiatric Interview (MINI), performed by a research psychiatrist and research assistant.[23] For the diagnosis of substance use disorders, the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Version[24] (SCID-P) was used instead of the MINI. The Extensive Clinical Interview which is similar to the SCID-P, consists of questions and criteria for the diagnosis of DSM-IV Axis I disorders, but also contains items to assess mental status, severity of suicidality, demographics, and other variables of interest. To substantiate the clinical history, all subjects

were required to bring a significant other to the initial diagnostic assessment.

Pretreatment psychiatric assessments included the following measures: HAM-D, Young Mania Rating Scale[25] (YMRS), Global Assessment Scale[26] (GAS), and Addiction Severity Index.[27] Eligible patients were then enrolled in the open-label acute stabilization phase.

Open-Label Acute Stabilization Phase

During this phase, patients were seen by a research psychiatrist every 2 weeks and treated with the combination of lithium carbonate and divalproex sodium. Lithium monotherapy was initiated at 300 mg twice daily and titrated over 3 to 6 weeks to minimum blood levels of 0.8 mEq/L. Divalproex was then initiated at 250 mg twice daily and increased over 3 to 6 weeks to minimum blood levels of 50 μg/mL. If patients were already taking lithium, but not divalproex, divalproex was initiated as described. If patients were already taking divalproex, but not lithium, lithium was initiated and titrated as described. Any other psychotropic medications that patients were taking at study entry were gradually discontinued a minimum of 4 weeks before random assignment to double-blind treatment.

Patients meeting stabilization criteria for a minimum of 4 consecutive weeks were eligible for random assignment to double-blind maintenance treatment. Entry criteria included a 17-item HAM-D score ≤ 20, YMRS score ≤ 12.5, GAS score ≥ 51, lithium levels ≥ 0.8 mEq/L, and valproate levels ≥ 50 μg/mL. Patients not meeting these criteria by 24 weeks were discontinued from the study.

Double-Blind Maintenance Phase

Patients were assigned in a 1:1 ratio to treatment with lithium monotherapy or the combination of lithium and divalproex after stratification for illness type (bipolar I vs. bipolar II). At random assignment, patients were continued on the same lithium dose as during the acute stabilization phase and on equal capsules of double-blind divalproex or matching placebo. Patients assigned to lithium monotherapy underwent divalproex-placebo substitution at a rate of 250-mg decrements every week until discontinued. Patients assigned to the combination group were continued on lithium and blinded divalproex. The maintenance phase and survival analysis began at the point of randomization, coinciding with the beginning of the medication taper.

After the taper was completed, the number of capsules of lithium and blinded divalproex or placebo remained unchanged for the remainder of the maintenance phase, except for adjustments made by the unblinded medical monitor when blood levels decreased to less than 0.8 mEq/L for lithium and 50 μg/mL for valproate. Trough divalproex and lithium levels were performed twice monthly during the first 3 months of the maintenance phase and monthly thereafter. Dose adjustments were made according to blood levels.

To maintain the blind design and the exact number of capsules being administered during the maintenance phase, each change in the dose of active divalproex was accompanied by a matching change in the placebo dose. The number of placebo capsules was decreased commensurately if the number of capsules of the active compound was increased, and vice versa for decreases. Dosing of lithium or divalproex could be decreased if patients were believed to be experiencing dose-related side effects (such as tremors) as long as minimum blood levels were maintained. If this was not possible, patients reached study endpoint due to intolerable side effects. Patients were seen by the research psychiatrist every 2 weeks during the first 3 months of the maintenance phase and monthly thereafter for up to 6 months.

Concomitant Medications

Patients could receive lorazepam in doses up to 2 mg/day for anxiety, agitation, and insomnia. For severe insomnia, zolpidem up to 10 mg/day could be prescribed. Initiation of psychotherapy was not permitted during the study.

Safety Monitoring

For each study phase, the safety population comprised all patients who received at least 1 dose of study drug. Safety was assessed by summarizing treatment-emergent adverse events and evaluating clinical laboratory test results, including white blood cell count, platelet count, free thyroxine index, thyroid-stimulating hormone level, and liver function tests (alanine aminotransferase and aspartate aminotransferase).

Data Analysis

Time to treatment for a mood episode (i.e., time to treatment for emerging symptoms of a mood relapse) was the primary outcome measure. This outcome measure was evaluated by statistical methods designed for the time-to-event data. Weibull distribution curves were generated to plot the survival function, and differences between treatment groups were compared using log rank tests at an $\alpha = .05$ level of significance. Patients who did not relapse, including those who discontinued early for other reasons, were censored on the date of their last efficacy evaluation or the last dose of study medication.

Secondary efficacy outcome measures were evaluated using log rank tests and included time to study discontinuation for any reason, time to depressive relapse, and time to manic/hypomanic/mixed relapse. A Cox proportional hazards model was used to evaluate differences for the following predictors of outcome: treatment arm assignment, bipolar subtype, index episode at study entry, and substance use disorder diagnosis. A repeated-measures mixed-effects model was used to analyze mean changes in symptom severity scores.

Table 1. Demographic and Clinical Characteristics of Rapid-Cycling Bipolar Disorder Patients Treated With a Combination of Lithium and Divalproex Followed by Double-Blind Maintenance With Lithium Monotherapy or a Combination of Lithium and Divalproex Upon Stabilization

Characteristic	Open-Label Acute Stabilization (N = 149)	Double-Blind Maintenance Therapy (N = 31)	
		Lithium (N = 16)	Lithium and Divalproex (N = 15)
Female, N (%)	54 (36)	4 (25)	6 (40)
Male, N (%)	95 (64)	12 (75)	9 (60)
Illness type, N (%)			
Bipolar I disorder	112 (75)	13 (81)	13 (87)
Bipolar II disorder	37 (25)	3 (19)	2 (13)
Age, mean (SD), y	36.2 (10.1)	40 (10.6)	37.1 (10.9)
Age at first diagnosis, mean (SD), y	33.4 (10.3)	34.8 (10.6)	36.5 (11.2)
Age at first manic/hypomanic/mixed episode, mean (SD), y	15.5 (7.2)	15.7 (9.2)	14.4 (6.5)
Age at first depression, mean (SD), y	13.6 (6.9)	11.5 (7.7)	12.1 (5.7)
No. of mood episodes in past year, mean (SD)	12.2 (7.7)	11.5 (7.4)	7.9 (3.1)
Depression	6 (3.9)	5.8 (4.0)	4 (1.6)
Hypomania/mania/mixed	6.1 (3.9)	5.8 (3.7)	4 (1.6)
No. of psychiatric admissions (lifetime), mean (SD)	2.1 (3.7)	2.1 (3.1)	1.2 (1.4)
No. of alcohol or drug rehabilitation admissions (lifetime), mean (SD)	1.4 (2.2)	1.0 (2.2)	1.7 (2.6)
Mood state at screening, N (%)			
Depressed	70 (47)	5 (31)	6 (40)
Hypomanic	28 (19)	3 (19)	3 (20)
Manic	25 (17)	5 (31)	2 (13)
Mixed	21 (14)	2 (13)	4 (27)
Euthymic	5 (3)	1 (6)	0 (0)
Clinical history (lifetime), N (%)			
Anxiety disorder comorbidity	67 (45)	5 (31)	10 (67)
Psychotic episode	79 (53)	10 (63)	10 (67)
Suicide attempt	69 (46)	8 (50)	8 (53)
Sexual abuse	33 (22)	5 (31)	3 (20)
Physical abuse	50 (34)	5 (31)	4 (27)
Previous treatment with bipolar medications, N (%)	99 (66)	10 (63)	8 (53)
Medications received (lifetime), N (%)			
Lithium	72 (48)	6 (38)	6 (40)
Divalproex	78 (52)	7 (44)	8 (53)
Antidepressants	104 (70)	12 (75)	8 (53)
Antipsychotics	37 (25)	7 (44)	1 (7)

Baseline clinical characteristics were compared using a Fisher exact test or χ^2 for nominal or ordinal data, and Student t test or Wilcoxon rank sum test for continuous data.

RESULTS

Demographics and Baseline Clinical Characteristics

Patients enrolled in this study were more likely to be male and to have a diagnosis of bipolar I disorder (Table 1). Study patients exhibited severe illness as reflected by the number of mood episodes in the last 12 months, lifetime history of physical and/or sexual abuse, and number of patients with a comorbid anxiety disorder (Table 1). Fifty-eight percent of the sample (N = 86) had a prior psychiatric hospitalization, 46% (N = 69) had attempted suicide, and 53% (N = 79) had experienced past psychotic episodes.

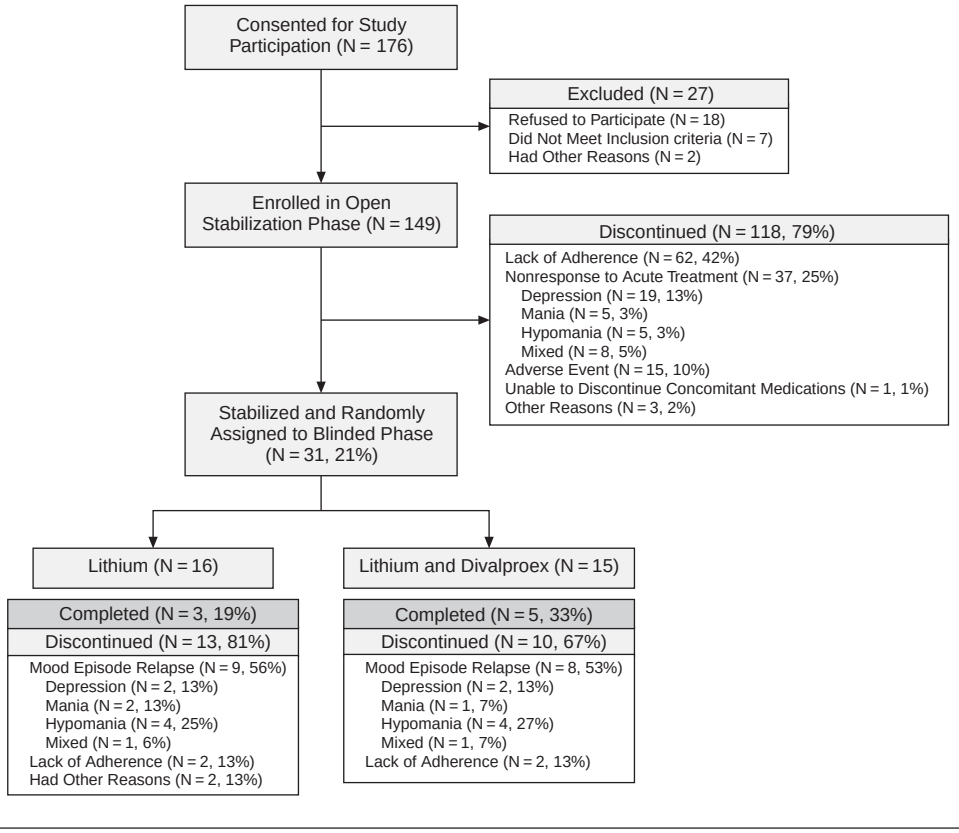
Disposition

Of 149 patients enrolled in the open-label acute stabilization phase of the study, 42% (N = 62) exited because of poor adherence, 25% (N = 37) exhibited nonresponse to the combination of lithium plus divalproex and exited because of the need for additional treatment, and 10% (N = 15) exited because of adverse events. Only 21% (N = 31) completed the stabilization phase and were randomly assigned to double-blind maintenance treatment for up to 6 months (lithium: N = 16, lithium plus divalproex: N = 15). Of the 37 subjects not responding to the combination of lithium plus divalproex, 51% (N = 19) exhibited refractory depression, 14% (N = 5) refractory hypomania, 14% (N = 5) refractory mania, and 22% (N = 8) a refractory mixed state (Figure 1). Of 31 patients entering the 6-month, double-blind maintenance phase, 26% (N = 8) completed the phase, 55% (N = 17) required treatment for a mood episode, and 19% (N = 6) discontinued prematurely for reasons other than a mood relapse (Figure 1). Among the patients requiring treatment for a mood episode (N = 17), relapse into a manic/hypomanic/mixed state (N = 13) was more common than relapse into depression (N = 4, p = .029).

Intervention

The mean dose of lithium during the double-blind maintenance phase was 1440 mg/day (range, 900–2400 mg) for the lithium monotherapy group, and the mean

Figure 1. Enrollment and Outcome: Disposition of Patients With Rapid-Cycling Bipolar Disorder and Co-Occurring Substance Use Disorders Treated With the Combination of Lithium and Divalproex Followed by Double-Blind Maintenance With Lithium Monotherapy or the Combination of Lithium and Divalproex After Stabilization



lithium level was 0.88 mEq/L. For the combination group, the mean dose of lithium was 1400 mg/day (range, 600–2100 mg), and the mean dose of divalproex was 1583 mg/day (range, 1000–3250 mg). The mean lithium level was 0.89 mEq/L, and the mean valproate level was 67 μg/mL.

During the double-blind maintenance phase, lorazepam use occurred in 2 of 16 patients assigned to lithium monotherapy and 1 of 15 patients assigned to the combination of lithium and divalproex. Zolpidem use occurred in 1 subject in each of the treatment arms.

Efficacy Data

There were no significant differences in time to treatment for a mood episode (Figure 2), time to premature discontinuation for any reason, time to treatment for depression, and time to treatment for a manic/hypomanic/mixed episode. The median time to a mood episode recurrence was 15.9 weeks for lithium and 17.8 weeks for the combination of lithium and divalproex (hazard ratio = 0.72 [p = .44, 95% CI = 0.32 to 1.65]). The median time to discontinuation for any reason was 12.3 weeks for lithium and 16.1 weeks for the combination of lithium and divalproex. The Cox regression predictors of outcome analysis yielded no effect for treatment arm assignment, bipolar subtype, substance use disorder diagnosis, or index episode.

Using a repeated-measures mixed-effects model, the mean ± SE change in HAM-D total score from baseline to endpoint of the double-blind phase did not differ between lithium monotherapy and the combination of lithium and divalproex (0.4 ± 1.1 vs. -0.2 ± 1.3, $p = .3$). Likewise, the mean ± SE change from baseline to endpoint in the YMRS total score did not differ between lithium monotherapy and the combination of lithium and divalproex (1.4 ± 1.1 vs. 1.5 ± 1.3, $p = .7$).

Effects on Alcohol and Substance Use

A completer analysis of subjects assigned to a double-blind treatment arm found the rate of active substance use disorders to diminish from study entry to completion of the acute stabilization phase. Of 19 subjects abusing or dependent on alcohol, 58% (N = 11) no longer met criteria for active abuse or had entered into early full remission after receiving up to 6 months of open-label treatment with lithium and divalproex. Similarly, among 15 subjects

Figure 2. Time-to-Treatment Intervention for Any Mood Episode Among Stabilized Rapid-Cycling Bipolar Disorder Patients Randomly Assigned to Double-Blind Lithium Monotherapy or the Combination of Lithium and Divalproex

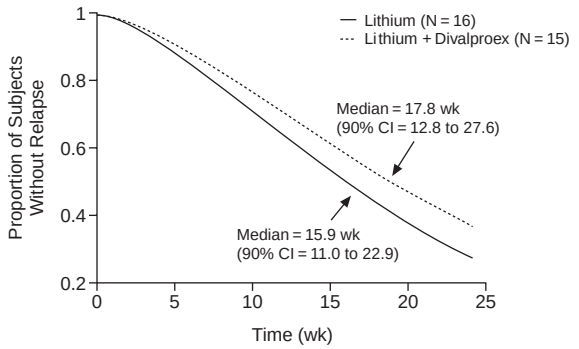


Table 2. Common Adverse Events Experienced by ≥ 10% of Rapid-Cycling Bipolar Disorder Patients During the Double-Blind Maintenance Phase

Adverse Event, N (%)	Lithium (N = 16)	Lithium and Divalproex (N = 15)
Tremors	10 (63)	10 (67)
Polyuria/polydipsia	5 (31)	6 (40)
Diarrhea	6 (38)	4 (27)
Weight gain	5 (31)	2 (13)
Fatigue	1 (6)	5 (33)
Nausea	3 (19)	2 (13)
Alopecia	1 (6)	3 (20)
Dry mouth	0 (0)	3 (20)
Sexual dysfunction	2 (13)	2 (13)
Cognitive dysfunction	2 (13)	2 (13)
Blurred vision	1 (6)	2 (13)
Increased appetite	2 (13)	0 (0)
Acne	2 (13)	0 (0)

with cannabis use disorders, 53% (N = 8) no longer met criteria for active cannabis abuse or had entered into early full remission. Among 9 subjects with cocaine use disorders, 78% (N = 7) no longer met criteria for active cocaine abuse or had entered into early full remission.

Results from the Addiction Severity Index confirmed that bimodal responders to the combination of lithium and divalproex were less likely to be troubled by alcohol problems (0.3 vs. 1.2, p = .005) and to experience fewer days of alcohol use in the month prior to random assignment (0.9 vs. 5.8, p = .001) as compared with treatment nonresponders. However, given the limited sample size, no statistical difference was found when comparing bimodal responders and nonresponders in the number of days of cannabis (3.2 vs. 4.3, p = .6) or cocaine (0 vs. 1, p = .06) use in the month prior to randomization, nor were treatment responders less likely to report being troubled by drug problems (0.3 vs. 0.5, p = .5).

Changes in Symptom Severity and Overall Function

For those subjects entering the study in a depressive episode and eventually assigned to a double-blind maintenance group, HAM-D–based symptom severity at baseline (mean ± SD) diminished substantially by the time of random assignment from 19.6 ± 6.0 to 8.2 ± 4.5 (p = .001). For those patients entering the study in a manic/hypomanic/mixed state, YMRS-based symptom severity at baseline diminished by the time of random assignment from 16.6 ± 5.44 to 4.53 ± 2.48 (p = .001). Among all subjects randomly assigned to the double-blind maintenance phase, GAS-based functional impairment improved from 52.4 ± 5.13 to 74.9 ± 10.78 (p < .001).

Adverse Events

Of 149 subjects enrolled in the study, 15 (10%) discontinued during the open-label phase because of adverse events. Weight gain (33% [N = 5]), gastrointestinal discomfort (27% [N = 4]), tremors (20% [N = 3]), dizziness (7% [N = 1]), cognitive difficulties (7% [N = 1]), and polyuria/polydipsia (7% [N = 1]) were the most common adverse events leading to premature discontinuation. Table 2 summarizes the adverse events observed in at least 10% of patients during the double-blind maintenance phase; none of the subjects discontinued because of adverse events. Tremors and polyuria/polydipsia were the most common adverse events in the total sample. A significant increase in alanine transaminase levels occurred in the lithium and divalproex combination group (+19.60 U/L) compared with the lithium monotherapy group (–30.83 U/L, p = .029). There were no differences in white blood cell count, platelet count, free thyroxine index, thyroid-stimulating hormone levels, or aspartate transaminase levels between treatment groups during the randomized phase.

DISCUSSION

This 6-month, randomized, double-blind, placebo-controlled trial is the first maintenance study in rapid-cycling bipolar disorder to compare combination mood stabilizer treatment (lithium and divalproex) with lithium monotherapy. To our knowledge, it is also the first double-blind maintenance trial of rapid-cycling bipolar disorder to be conducted in subjects with a co-occurring alcohol and/or drug use disorder. This study complements a 20-month maintenance trial previously conducted by our group comparing double-blind treatment with lithium or divalproex monotherapy in rapid-cycling bipolar disorder uncomplicated by substance use disorders.[17]

After random assignment, no significant difference was observed on the primary outcome measure of time to relapse into a new mood episode or on the secondary outcome measure of time to discontinuation for any reason. Although a numeric benefit was observed in the estimated hazard ratio (0.72), this value was nonsignificant and

suggests the difference in prophylactic efficacy between lithium monotherapy and the combination of lithium and divalproex is small when used in the maintenance treatment of rapid-cycling bipolar disorder comorbid with substance use disorders.

Similar to other controlled maintenance studies of subjects with bipolar disorder, this trial employed an enriched design requiring subjects to respond to lithium and divalproex prior to entering the double-blind, placebo-controlled phase.[17,28,29] This design served to enrich the randomized population with compliant subjects tolerant of the medications under investigation, effectively reducing bias due to differences in tolerability. Consistent with this expectation, no dropouts due to adverse events were observed during the double-blind maintenance phase.

In maintenance studies conducted over 6 to 18 months, rates of discontinuation due to lack of efficacy are higher among trials that employ more rigorous stabilization criteria.[28–29] In the present trial, 25% of subjects discontinued due to lack of efficacy, reflective of the requirement for stabilization to be sustained over 4 consecutive weeks (HAM-D score ≤ 20, YMRS score ≤ 12.5, and GAS score ≥ 51), as well as the difficulty encountered when treating subjects with co-occurring substance use disorders. Of 149 patients who received open lithium and divalproex, 118 (79%) exited the study prior to random assignment to the blinded maintenance phase. The attrition rate in previously conducted maintenance trials of non–substance abusing bipolar patients has ranged from 50% to 72%.[28–30]

During open stabilization, 37 patients demonstrated mood symptoms nonresponsive to combination treatment with lithium and divalproex. Approximately equal numbers experienced refractory depression or refractory manic/hypomanic/mixed states. This finding is novel and stands in contrast to rapid-cycling bipolar disorder populations without co-occurring substance use disorders, for which the predominant mood presentation is depression.[17] Furthermore, the majority of subjects relapsed into manic/hypomanic/mixed states as opposed to depression during maintenance phase treatment. This finding also distinguishes rapid-cycling bipolar disorder populations with co-occurring substance use disorders, as relapse into depression is more prevalent in populations without substance use comorbidity.[17]

Although depression is regarded as the hallmark of rapid-cycling bipolar disorder, manic, hypomanic, or mixed states appear to be the major mood morbidity in the setting of alcohol and/or other substance use disorders. This observation is supported by other authors who identified a higher rate of mixed states and dysphoric mania among bipolar patients who abuse substances.[7,31] Mania was identified as the most common index episode in a post hoc analysis of patients with bipolar disorder and comorbid cannabis abuse,[32] and manic or mixed states were the most common presentations among patients with comorbid alcoholism.[20]

The prevalence of rapid cycling is believed to be highest among women[1,33] and those with bipolar II disorder.[1] The positive association between women and rapid cycling may partly be attributed to the greater depressive morbidity experienced by women over their lifetime.[34] Contrarily, in this trial, the patient composition was weighted toward males and subjects with bipolar I disorder, consistent with previous research identifying these variables to be associated with higher rates of alcohol and drug abuse.[2] This finding suggests the tendency for relapse into manic/hypomanic/mixed states may be more heavily influenced by comorbid substance use than rapid-cycling status per se.

The present study has several strengths, perhaps foremost its attempt to assess mood outcomes in a population with bipolar disorder and co-occurring substance use disorders. This area has recently been articulated as a priority for clinical investigation by a "call to action" report, given the scarcity of clinical trials addressing substance use comorbidity.[35] In fact, bipolar patients with substance use disorders have been identified as a population exhibiting the greatest level of unmet need, followed closely by those with rapid cycling.[36] The present trial addresses both understudied areas and is highly generalizable to clinical practices, providing the first estimate of the difference in median survival for 2 commonly used drug regimens.

There is evidence that clinicians undertreat bipolar disorder when a comorbid substance use disorder is present, as STEP-BD data show nearly half of patients do not receive adequate mood stabilizer treatment.[37] Our findings suggest that combination mood stabilizer therapy can be efficacious and safe when prescribed to substance-abusing individuals with bipolar disorder. Relatedly, Salloum and colleagues[20] found the addition of valproate to lithium among individuals with alcohol dependence reduced the number of heavy drinking days and prolonged the time to relapse to sustained heavy drinking. However, divalproex did not reduce depressive or manic symptoms more effectively than lithium alone.[20] Collectively, these results emphasize that clinicians should not abandon or delay mood stabilizer treatment as a result of substance use.

The intent of this single-site pilot trial was to generate an estimate of the difference in overall survival between treatment arms for designing a future, large-scale maintenance study. Consequently, the lack of power to detect a small difference in overall survival between treatments is a valid but expected methodological limitation. The estimated hazard ratio of 0.72 indicates that patients randomly assigned to combination treatment had a tendency toward lower risk of discontinuation for any reason. Thus,

a future study would need to enroll 193 to 225 subjects per treatment arm in order to achieve statistical power of 0.80 with an α set at .05, 2-tailed. Given the large sample size requirement and relatively small effect size demonstrated by this pilot study, it is unlikely that a future, large-scale trial involving these 2 first-line mood stabilizers will ever be conducted. Furthermore, the high dropout rate during the open stabilization phase highlights the complexity of treating patients with comorbid rapid-cycling bipolar disorder.

A further limitation concerns the nominal data on substance use outcomes. We were not able to quantify the change in frequency of alcohol or drug use. In addition, toxicology screens were not collected to verify the presence of a substance use disorder or relapse into substance use. Future maintenance trials of rapid-cycling bipolar disorder with co-occurring substance use disorders should specifically evaluate the quantity and frequency of substance use as a primary outcome measure, in addition to measuring relapse rates and time to relapse.

There is a need for future maintenance studies that combine conventional mood stabilizers with agents able to reduce depression symptoms and also protect against mood elevation. Members of the atypical antipsychotic drug class offer promise of satisfying this unmet need and may also reduce drug and alcohol consumption.[38–40]

In conclusion, this is the first controlled investigation to compare lithium monotherapy with combination mood stabilizer therapy (lithium plus divalproex) in rapid-cycling presentations of bipolar I or II disorder and co-occurring substance use disorders. The similar time to relapse between treatment arms suggests a small effect size when combining divalproex with lithium. The high rate of dropout observed during the open-label stabilization phase suggests that combination therapy with lithium and divalproex will be inadequate for the majority of patients with rapid-cycling bipolar disorder and comorbid substance abuse or dependence. Greater efforts are needed to identify adjunctive pharmacotherapy or psychosocial interventions that are effective in such highly comorbid populations.

Drug names: divalproex (Depakote), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), valproate (Depacon and others), zolpidem (Ambien and others).

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