ORIGINAL ARTICLE

Efficacy of Valproate Maintenance in Patients With Bipolar Disorder and Alcoholism

A Double-blind Placebo-Controlled Study

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Background: More than half of all individuals with bipolar disorder have a substance abuse problem at some point in their lifetime. Patients with comorbid substance abuse disorders often are excluded from clinical trials. Thus, treatments targeting this high-risk clinical population are lacking.

Objective: To evaluate the efficacy of divalproex sodium (hereafter referred to as valproate) in decreasing alcohol use and stabilizing mood symptoms in acutely ill patients with bipolar disorder and alcoholism.

Design: A 24-week, double-blind, placebo-controlled, randomized parallel-group trial.

Setting: A university hospital serving as a primary catchment-area hospital and tertiary-care facility.

Participants: Fifty-nine subjects with diagnoses of bipolar I disorder and alcohol dependence.

Intervention: All study subjects received treatment as usual, including lithium carbonate and psychosocial interventions, and were randomized to receive valproate or placebo.

Main Outcome Measures: Primary alcohol use outcomes included changes in alcohol use as indicated by changes in proportion of heavy drinking days and number of drinks per heavy drinking day. Other alcohol use outcomes included proportion of any drinking days, number of drinks per drinking day, and relapse to sustained heavy drinking. Mood outcomes included changes in depressive and manic symptoms. We used the mixed model to analyze longitudinal data. The first model used time of assessment, bipolar subtype (mixed, manic, or depressed), and treatment group (placebo or valproate) as covariates. The second nested model included the additional covariate of medication adherence.

Results: The valproate group had a significantly lower proportion of heavy drinking days ($P=.02$) and a trend toward fewer drinks per heavy drinking day ($P=.055$) than the placebo group. When medication adherence was added as covariate, the valproate group had significantly fewer drinks per heavy drinking day ($P=.02$) and fewer drinks per drinking day ($P=.02$). Higher valproate serum concentration significantly correlated with improved alcohol use outcomes. Manic and depressive symptoms improved equally in both groups. Level of γ-glutamyl transpeptidase was significantly higher in the placebo group compared with the valproate group.

Conclusions: Valproate therapy decreases heavy drinking in patients with comorbid bipolar disorder and alcohol dependence. The results of this study indicate the potential clinical utility of the anticonvulsant mood stabilizer, valproate, in bipolar disorder with co-occurring alcohol dependence.

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Co-occurring alcoholism and bipolar disorder are associated with severe disability, morbidity, and heightened suicide risk.[1] Bipolar disorder has a higher association with alcohol or other substance use disorders (SUD) than any major psychiatric disorder such as schizophrenia, major depression, or anxiety disorder.[2,3] More than 61% of all patients with bipolar disorder (hereafter referred to as bipolar patients) had any substance use disorder according to the Epidemiologic Catchment Area Study.[2] The National Comorbidity Survey[3] reported that bipolar patients were almost 10-fold more likely to have alcohol dependence and 8-fold more likely to have other SUDs than the general population. The scope of this problem is more serious when considering the broader concept of bipolar spectrum disorder,[4] and the high incidence of alcohol and other SUDs among adolescent-onset bipolar disorders.[5]

Alcoholism complicates the treatment of bipolar disorder and worsens treatment adherence.[6,7] It hinders treatment interventions[8] and increases use of costly psychiatric services.[9] Alcoholism increases medical morbidity, worsens cognitive functioning,[10-12] and increases suicide risk.[8,13,14] Bipolar patients who drink excessive amounts of alcohol have higher burdens of manic and depressive symptoms, marked impulsivity, and violence.[15] Depression is particularly pronounced among bipolar female patients with alcoholism.[16] Conversely, bipolar disorder may also increase the vulnerability to alcoholism and other SUDs.[1]

Despite the public health significance of this comorbid condition, effective interventions are lacking. Clinical trials for bipolar disorder and those for alcoholism systematically excluded serious co-occurring conditions to reduce sources of variance. Thus, a gap exists in our knowledge regarding effective treatment for bipolar patients with alcoholism (hereafter referred to as bipolar alcoholic patients).[17]

Lithium carbonate was ineffective in decreasing alcohol consumption in a large multicenter Veterans Affairs trial.[18] Lithium may not be effective in bipolar variants such as dysphoric, mixed, or rapid cycling, which are overrepresented among bipolar alcoholic patients.[19,20] Recent studies suggest usefulness of certain anticonvulsants such as carbamazepine, topiramate, and divalproex sodium in the treatment of noncomorbid alcoholism.[21-23] Johnson and colleagues[21] reported an advantage of topiramate compared with placebo on multiple measures of alcohol use. Brady and colleagues[23] reported an advantage of valproate compared with placebo on relapse to heavy drinking. Valproate has also been found useful in alleviating alcohol withdrawal.[24-27] Furthermore, valproate has established antimanic efficacy, including in lithium-resistant bipolar subtypes.[28-32] Thus, valproate, with potential dual therapeutic actions, may provide a targeted pharmacotherapy for comorbid bipolar disorder and alcoholism.

The aim of this study was to test the efficacy of divalproex sodium (hereafter referred to as valproate) in reducing alcohol use and stabilizing the acute bipolar I episode in patients with comorbid *DSM-IV* alcohol dependence. We hypothesized that the valproate-treated group would consume less alcohol, have a longer time to relapse to sustained alcohol use, and achieve earlier remission from an acute bipolar episode than the placebo-treated group.

METHODS

STUDY DESIGN

We tested the study hypotheses in a sample of treatment-seeking subjects meeting *DSM-IV* criteria for current alcohol dependence with a co-occurring acute episode of bipolar I disorder in a randomized, double-blind, placebo-controlled, parallel-group design of 24 weeks' duration. The study was conducted at the Addiction Medicine Services of the Western Psychiatric Institute and Clinic of the University of Pittsburgh Medical Center, Pittsburgh, Pa.

After the initial screening, a 1-week period for alcohol and other-drug detoxification was undertaken when clinically indicated, as assessed by means of the Revised Clinical Institute Withdrawal Assessment for Alcohol Scale.[33] Patients next underwent a pretreatment assessment and, after confirmation of eligibility, were randomly allocated (1:1) to receive valproate or an identical-appearing, inert placebo. We used the balanced-coin randomization method[34] to stratify groups on number of past bipolar episodes (1 vs ≥2 episodes), duration of alcohol use (<5 vs ≥5 years), and past response to lithium therapy (response, nonresponse, and unknown).

Patients received standardized treatment as usual, consisting of lithium and weekly individual counseling. The decision to construct the study on a treatment-as-usual condition, guaranteeing that all patients received at least 1 active medication (lithium), was based on ethical concerns about withholding active treatment from patients with serious psychiatric comorbidity. Moreover, inpatient studies of mania have been compromised by attrition rates of up to 80% in placebo-treated arms by the end of 3 weeks.[35] Lithium, a first-line medication for bipolar disorders, is the most acceptable choice. Postrandomization assessments were undertaken every 2 weeks through a 24-week period.

STUDY PARTICIPANTS

Men and nonpregnant, nonnursing women aged 18 to 65 years were recruited and underwent assessment using the Structured Clinical Interview for *DSM-IV*[36] after acute withdrawal symptoms cleared (ascertained by means of the Revised Clinical Institute Withdrawal Assessment for Alcohol Scale[33]). Patients were eligible if they met 4 of the 7 *DSM-IV* alcohol dependence criteria (only 3 are required to meet diagnostic threshold), were actively drinking alcohol in the past month, and had a concurrent acute episode of bipolar I disorder (manic, mixed, or depressed).

Exclusion criteria included the following: (1) schizophrenia, schizoaffective disorder, any nonbipolar psychotic disorder, mental retardation, or signs of impaired cognitive functioning; (2) current *DSM-IV* diagnoses of opioid or cocaine dependence, or current use of intravenous drugs; (3) epilepsy, history of brain injury, or any organic brain syndrome; (4) severe cardiac, liver, kidney, endocrine, hematologic, or any other unstable medical condition; (5) persistent elevation of liver function enzyme levels greater than 3-fold above the reference range of γ-glutamyl transpeptidase (γ-GTP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP)[37]; (6) inability or unwillingness to use contraception; and (7) inability to read or understand study forms and agree to informed consent. Patients were not excluded for other *DSM-IV* substance use disorders such as cannabis abuse or dependence, nicotine dependence, or other substance abuse disorders.

STUDY PROCEDURES

Participants met with a study physician to review the protocol and signed an informed consent approved by the University of Pittsburgh Institutional Review Board. A pretreatment medical evaluation included a physical examination; complete blood cell count with differential; measurement of electrolyte, serum urea nitrogen, creatinine, and thyrotropin levels; liver function tests (measurement of total bilirubin, ALP, γ-GTP, ALT, and AST levels); serum pregnancy test (where appropriate); urinalysis; urine drug screen; breath alcohol concentration; and electrocardiography.

Pretreatment psychiatric assessment included the following measures: Structured Clinical Interview for *DSM-IV*,[36] Addiction Severity Index,[38] Alcohol Use Inventory,[39] Life-Time

Charting of Bipolar Episodes,[40] Bech-Rafaelsen Mania Scale (BRMS),[41] Hamilton Rating Scale for Depression (HRSD-25),[42] Global Assessment Scale,[43] Timeline Follow-Back for Recent Drinking,[44] Modified Quantitative Alcohol Inventory/Craving Scales,[45] Weekly Self-Help Activity Questionnaire, and Somatic Symptoms Checklist and Medication Adherence Form to assess medication adverse effects and self-report of medication adherence.

Each postrandomization assessment visit included the BRMS, HRSD-25, Global Assessment Scale, Timeline Follow-Back for Recent Drinking, Modified Quantitative Alcohol Inventory/Craving Scales, Weekly Self-Help Activity Questionnaire, Somatic Symptoms Checklist and Medication Adherence Form, breath alcohol concentration, and urine drug screen (qualitative method screening for opioids, cocaine and other stimulants, marijuana, benzodiazepines, and barbiturates). Liver function tests and trough valproate and lithium serum concentration measurements were performed at weeks 2, 4, 8, 12, 16, 20, and 24. At week 24, a thyrotropin test was repeated. Serum pregnancy tests were performed and the Revised Clinical Institute Withdrawal Assessment for Alcohol Scale was administered when clinically indicated. The Reasons for Early Termination Form[46] was completed whenever possible for those who terminated the protocol early.

STUDY THERAPIES

Treatment as Usual

Subjects started to receive lithium as soon as it was safe to do so during the stabilization phase, which was within the first few days for most subjects. Dosage was adjusted using the level-dose ratio strategy[47,48] to reach a target trough serum concentration (0.7-1.2 mEq/L). Compliance was monitored by measuring lithium concentration in red blood cells. Lithium concentration in red blood cells takes longer to reach equilibrium with the plasma compartment and to achieve a steady state; therefore it is not subject to wide dosing-interval variations.[49] Increased variability of lithium concentration in red blood cells is an indication of poor compliance.

Adjunctive and rescue medications were allowed temporarily, and, when possible, these therapies were discontinued. Perphenazine was permitted for treatment of psychotic symptoms. Benztropine mesylate was used to treat extrapyramidal adverse effects. Sertraline hydrochloride was permitted for treatment of unremitting depressive symptoms, as defined by a score on the HRSD-25 of at least 15 that had persisted longer than 2 weeks with therapeutic lithium levels. Trazodone hydrochloride (25-150 mg) was permitted for persistent insomnia. Medications not allowed included other mood stabilizers such as carbamazepine and medications for alcoholism such as disulfiram or naltrexone.

The psychosocial intervention, dual diagnosis recovery counseling, consisted of weekly individual sessions that integrated psychoeducation and cognitive-behavioral principles.[50] Counseling focused on helping patients to manage cravings to use alcohol or other substances, cope with negative thoughts about illness or treatment, develop structure and routine in daily living, identify warning signs of relapse/recurrence of bipolar illness, manage relapse warning signs, identify high-risk situations, and manage painful affects. Counseling emphasized use of social support systems and participation in self-help groups such as Alcoholics Anonymous, Dual Recovery Anonymous, and/or manic-depressive support groups. Adjunctive group therapy through the regular clinical program was allowed if requested by subjects, and sessions attended were recorded.

Valproate vs Placebo

These treatments were administered in a double-blind fashion via an equal number of identical-looking capsules on a twice-daily schedule. Valproate (divalproex sodium) therapy was initiated at a dosage of 750 mg/d, usually within a week of starting lithium therapy. Patients were instructed to take medication 30 minutes after meals. Dosages increased as tolerated to reach a target trough serum concentration of 50 to 100 µg/mL. Dosage adjustment was conducted by one of us (J.R.C.) who did not participate in the clinical evaluations and was not blinded to treatment randomization. This coinvestigator monitored tolerability and clinical response and made appropriate dosage adjustments. Compliance included monitoring serum valproate concentrations and assessing the frequency and pattern of medication intake using the unit-dosage method. Unit-dosage packets consisted of pillboxes labeled with specific day and time of dose intake. These were collected at each visit. There was no difference between the 2 groups on time from study entry to randomization to study medication (placebo group mean, 7.9 days [SD, 6.2 days]; valproate group mean, 9.2 days [SD, 8.6 days]; $t_{55} = -0.65$; $P = .52$).

OUTCOME MEASURES

We used the timeline follow-back method to measure alcohol consumption during the study period. At each assessment visit, the number of standard drinks consumed was recorded. Primary alcohol use outcome included proportion of heavy drinking days (defined as ≥4 drinks per day for women and ≥5 drinks per day for men) and number of drinks per heavy drinking day. Additional alcohol use outcomes included proportion of any drinking days, number of drinks per any drinking day, and time to relapse to sustained heavy drinking (defined as 3 consecutive heavy drinking days). Outcome measures for bipolar disorder included the HRSD-25 and the BRMS for mania. Mood outcomes included remission of mania (defined as a score of ≤7 on the BRMS) and remission of depression (defined as a score of ≤7 on the HRSD-25).

STATISTICAL ANALYSIS

The clinical and demographic characteristics of the 2 groups were compared with independent, 2-tailed *t* tests for continuous variables and Fisher exact test or χ^2 test as appropriate for categorical variables. Statistical analyses were completed on a modified intent-to-treat study group, as defined by completion of at least 1 assessment while the subject was receiving double-blind therapy. We used the mixed model with restricted maximum likelihood estimation method and unrestricted covariance matrix as the primary analytic strategy to analyze longitudinal data. Basic advantages of using the mixed model in longitudinal analysis are (1) variance terms can be allowed to increase over time; (2) this technique is capable of handling missing data, therefore, each individual contributes to data analysis regardless of number of data points; (3) uneven time spacing between measurements is permitted; and (4) interaction terms between the grouping variable and assessment time can be tested, along with the group and assessment time effects.[51]

First, we used the mixed model with the following covariates: time of assessment, bipolar subtype (mixed, manic, or depressed), and treatment group (placebo or valproate). The second nested model included medication adherence as an additional covariate. We used survival analysis to test time to remission and relapse/recurrences (failure time) by means of the Kaplan-Meier procedure.

Table 1. Comparison of Randomized Subjects on Demographic and Baseline Clinical Characteristics*

Variable	Treatment Group: Placebo (n = 30)	Treatment Group: Valproate (n = 29)	*P* Value
Age, y	38 (9)	37 (9)	.58†
Male, No. (%)	23 (77)	21 (72)	.70‡
African American, No. (%)	7 (23)	8 (28)	.70‡
Married, No. (%)	3 (10)	5 (17)	.42‡
Employed, No. (%)	19 (63)	17 (59)	.71‡
With >12 y of education, No. (%)	16 (53)	15 (52)	.92‡
Social class V, No. (%)§	11 (37)	13 (45)	.96‡
Recruited from inpatient treatment, No. (%)	18 (60)	18 (62)	.87‡
Drinking to intoxication, y	17.2 (8.6)	15.7 (10.3)	.58†
Drinking to intoxication, d (past 30 d)	16.3 (10.7)	12.3 (11.5)	.19†
No. of drinks per week	104 (89)	88 (99)	.53†
HRSD-25 score (depression measure)	21.2 (13.3)	20.3 (13.4)	.80†
BRMS score (mania measure)	15.3 (10.7)	15.2 (13.0)	.99†
Global Assessment of Functioning score	38.4 (11.0)	38.1 (14.9)	.93†
Duration of bipolar disorder, y	15.6 (10.3)	13.0 (10.8)	.40†
No. of medical conditions	1.39 (1.29)	1.49 (1.25)	.85†
Other substance use disorders, No. (%)	15 (50)	15 (52)	>.99‡

Abbreviations: BRMS, Bech-Rafaelsen Mania Scale; HRSD-25, Hamilton Rating Scale for Depression.
*Unless otherwise indicated, data are expressed as mean (SD). Valproate refers to divalproex sodium.
†By *t* test.
‡By χ^2 test.
§Based on Hollingshead.[52]

RESULTS

Among 72 subjects who provided informed consent, 13 were disqualified before randomization (8 were lost to follow-up, 4 withdrew consent, and 1 was excluded for medical condition). These 13 subjects were similar to the randomized subjects on age, sex, ethnicity, and years of education, but differed on higher likelihood of employment (100% [n = 13] vs 61% [n = 36]; $P<.01$), higher socioeconomic status (92% [n = 12] vs 19% [n = 11] of social class III or higher[52]; $P<.001$), and lower likelihood of being married (0% [n = 0] vs 14% [n = 8]; $P = .05$). Of 59 randomized subjects (valproate group, n = 29; placebo group, n = 30), 7 dropped out before completing the first assessment while receiving therapy. Modified intent-to-treat efficacy analyses were performed on 59 (82%) consenting subjects and 52 (88%) of those beginning double-blind therapy (valproate group, n = 27; placebo group, n = 25).

There were no significant differences between treatment groups on pretreatment demographic and clinical variables (**Table 1**). Fifteen (29%) participants who began double-blind therapy were women and 13 (25%) were African American. Mean age was 38 years (SD, 9.3 years). Eight (15%) were married. Although 30 (58%) were employed, 39 (75%) earned less than $20 000 annually. At study entry, 30 (58%) met criteria for mixed bipolar subtype, 11 (21%) were manic, and 11 (21%) were depressed. Six patients (17%) of those recruited from the inpatient unit had attempted suicide during the index episode. Half of the subjects (n = 26) had other substance use disorders. Cannabis abuse or dependence (15 subjects [29%]) and cocaine abuse (15 [29%]) were the most frequent diagnoses. Other substances abused included opioids, other sedative hypnotics, and other stimulants. Thirty-five subjects (71%) smoked cigarettes, with an average of 136 cigarettes per week (SD, 127 cigarettes per week) (ie, 0.9 packs per day).

ATTRITION AND STUDY COMPLETION RATES

Twenty subjects (38%) completed the 24-week study, 12 (44%) from the valproate group and 8 (32%) from the placebo group. Of the 15 valproate group dropouts, 1 subject withdrew consent, 3 were unavailable for follow-up, 4 were noncompliant with study protocols, 1 was incarcerated, 2 discontinued owing to unrelated medical conditions, 3 required psychiatric hospitalization, and 1 discontinued owing to adverse effects of the medication. Of the 17 placebo group dropouts, 2 withdrew consent, 3 were unavailable for follow-up, 3 were noncompliant with study protocols, 2 moved away, 2 discontinued for medical conditions, and 5 required psychiatric hospitalization. Most of the dropouts (21 [65%]) occurred within the first 8 weeks of the study. The 2 groups were not significantly different on average duration in the study (112 days [SD, 69 days] for the valproate group vs 102 days [SD, 67 days] for the placebo group) (log-rank test, $\chi^2_1=0.98$; $P=.32$). On average, 86% of available subjects underwent assessment at each assessment point. Percentages undergoing assessment at key evaluation points were as follows: 84% at week 2; 77% at week 4; 88% at week 8; 82% at week 12; 87% at week 16; 81% at week 20, and 100% at week 24.

MEDICATION ADHERENCE AND ADJUNCTIVE TREATMENT

Medication adherence was assessed by means of self-report and lithium and valproate serum concentration levels. Self-reported medication adherence was assessed at each visit and included days of missed medication since the previous assessment visit. Both groups reported similar rates of medication adherence (placebo group, 86% [SD, 23%]; valproate group, 87% [SD, 22%]; $t_{258}=-0.58$; $P=.55$). They were also similar on average lithium serum concentration (placebo group, 0.66 mEq/L [SD, 0.30 mEq/L]; valproate group, 0.68 mEq/L [SD, 0.33 mEq/L]; $t_{155}=-0.52$; $P=.60$) and average red blood cell lithium concentration (placebo group, 0.32 mEq/L [SD, 0.21 mEq/L]; valproate group, 0.27 mEq/L [SD, 0.17 mEq/L]; $t_{94}=1.12$; $P=.26$). The average valproate serum concentration was 51.5 µg/mL (median, 52.5 µg/mL; SD, 29 µg/mL). Self-reported medication adherence significantly correlated with serum lithium concentrations in mixed-model analysis (estimate, 0.12; $t_{114}=2.36$; $P=.02$). A similar trend was evident for serum valproate concentrations (estimate, 0.001; $t_{93}=1.96$; $P=.053$).

Table 2. Alcohol Use and Mood Symptoms Outcome Measures by Treatment Groups and Results of the Mixed-Model Analyses

Variable	Treatment Group, Overall Mean (SD)*		Mixed Model			
	Placebo (n = 25)	Valproate (n = 27)†	Estimation	*t* Test	*df*	*P* Value
Proportion of heavy drinking days	0.19 (0.31)	0.09 (0.22)	0.08	2.45	25.1	.02
No. of drinks per heavy drinking day‡	10.2 (10.8)	5.59 (8.89)	2.88	2.49	31.1	.02
Proportion of drinks per drinking days‡	0.24 (0.32)	0.17 (0.27)	0.08	1.77	33.2	.08
No. of drinks per drinking day‡	8.9 (10.1)	5.14 (8.52)	2.40	2.41	29.0	.02
Mania	6.10 (7.80)	5.56 (7.73)	–0.03	–0.16	44.2	.87
Depression	14.4 (9.72)	16.3 (10.2)	0.12	0.91	44.7	.36

*Overall means of assessments were entered in the mixed-model analysis.
†Valproate refers to divalproex sodium.
‡Medication adherence was added to the mixed-model analysis.

Both groups were similar on nonpharmacological treatment received; 21 (78%) of the valproate group and 19 (76%) of the placebo group participated in any psychosocial treatment. Attendance at individual and group therapy sessions, however, was limited (placebo group mean, 3.6 sessions [SD, 4.8 sessions]; valproate group mean, 5.7 sessions [SD, 9.0 sessions]; $t_{50}=-1.04$; $P=.30$).

The 2 groups had similar adjunctive use of antidepressants and antipsychotics. Eleven patients (48%) in the valproate group (n = 23) and 10 (48%) in the placebo group (n = 21) received antidepressants, whereas 8 (35%) in the valproate group and 6 (29%) in the placebo group received antipsychotics. However, a greater proportion of the placebo group was prescribed trazodone as a hypnotic (9 [43%] vs 2 [9%]; Fisher exact test, $P=.03$).

Exploratory mixed-model analyses showed that the use of hypnotics (trazodone) was associated with a significant decrease in the number of drinks per drinking day (estimate, 2.66; $t_{65.4}=2.00$; $P=.04$). Additional antidepressants, antipsychotics, and attendance at psychosocial treatment were not associated with significant change in alcohol, mood, or functioning outcomes.

EFFICACY

Alcohol Use Outcome

Twelve (44%) of 27 subjects in the valproate group reported heavy drinking days compared with 17 (68%) of 25 in the placebo group. Mixed-effect analysis showed a significant advantage for valproate therapy on proportion of heavy drinking days (placebo group mean, 0.19 [SD, 0.31]; valproate group mean, 0.09 [SD, 0.22]; estimate, 0.08; $t_{25.1}=2.45$; $P=.02$). There was also a trend favoring valproate therapy on drinks per heavy drinking day (mean, 5.6 [SD, 8.9]) compared with the placebo group (mean, 10.2 [SD, 10.8]; estimate, 2.21; $t_{35}=1.98$; $P=.055$). This was significant when medication adherence was added to the model (estimate, 2.88; $t_{31.1}=2.49$; $P=.02$) (**Table 2**). Furthermore, the valproate group had significantly fewer cumulative heavy drinking days compared with the placebo group (11.3 days [SD, 9.2 days] vs 18.4 days [SD, 14.5 days]; $t_{47}=2.05$; $P=.046$). Valproate therapy also prolonged the time to relapse to sustained heavy drinking to 93 days (SD, 74 days; median, 75 days) compared with 62 days in the placebo group (SD, 61 days; median, 44 days; log-rank test, 3.90; $df=1$; $P=.048$) (**Figure**).

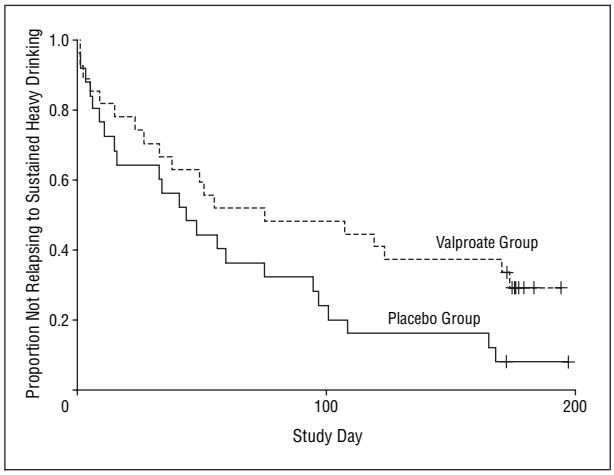

Figure. Kaplan-Meier survival curve for time to relapse to sustained heavy drinking (3 consecutive heavy drinking days [≥5 drinks per day for men and ≥4 drinks per day for women]), by treatment group (log-rank test, $P=.048$).

Mixed-model analysis showed an advantage for valproate therapy on the number of drinks per drinking day when medication adherence was included in the model (mean, 5.1 [SD, 8.5]), compared with placebo treatment (mean, 8.9 [SD, 10.1]; estimate, 2.4; $t_{29}=2.41$; $P=.02$). There was also a trend for valproate therapy on having a lower proportion of any drinking days (estimate, 0.08; $t_{32.2}=1.77$; $P=.08$) (Table 2).

Mixed-model exploratory analyses of the effects of valproate and lithium serum concentration on alcohol use outcome showed a consistent association between increase in valproate serum concentration and decrease in drinking behavior. Significant correlations existed between higher valproate serum concentration and lower proportions of any drinking days (estimate, –0.006; $t_{134}=-3.11$; $P=.002$) and heavy drinking days (estimate, –0.004; $t_{130}=-2.18$; $P=.03$). There were also trends toward predicting a lower number of drinks per drinking day (estimate, –0.07; $t_{108}=-1.92$; $P=.06$) and a lower number of drinks per heavy drinking day (estimate, –0.07; $t_{116}=-1.85$; $P=.06$). Conversely, the analyses showed only a trend for lithium serum concentration toward predicting a lower proportion of any drinking days (estimate, –0.19; $t_{127}=-1.89$; $P=.06$).

Table 3. Treatment-Emergent Adverse Events

Event	Treatment Group, No. (%)		*P* Value, Fisher Exact Test
	Placebo (n = 25)	Valproate (n = 27)*	
Tremor	14 (66.7)	11 (47.8)	.50
Dry mouth	9 (42.9)	15 (65.2)	.22
Fatigue	10 (47.6)	7 (30.4)	.47
Increased thirst	10 (47.6)	9 (39.1)	.90
Nausea or vomiting	2 (9.5)	9 (39.1)	.07
Headaches	7 (33.3)	9 (39.1)	.91
Blurred vision	7 (33.3)	7 (30.4)	.71
Stomach difficulties	4 (19.0)	7 (30.4)	.62
Diarrhea	4 (19.0)	7 (30.4)	.56
Decreased appetite	6 (28.6)	4 (19.0)	.31
Increased appetite	5 (23.8)	6 (28.6)	>.99
Increased urination	5 (23.8)	6 (28.6)	.90
Nervousness	4 (19.0)	6 (28.6)	.92
Feeling of clumsiness	5 (23.8)	5 (21.7)	>.99
Weight gain	5 (23.8)	3 (14.3)	.25
Constipation	6 (28.6)	4 (19.0)	.37
Excessive perspiration	5 (23.8)	2 (9.5)	.40

*Valproate refers to divalproex sodium.

Mood Outcome

There was no difference between treatment groups on manic (estimate, –0.03; $t_{44.2}$=–0.16; *P*=.87) or depressive (estimate, 0.12; $t_{44.7}$=0.91; *P*=.36) symptoms. Levels of manic symptoms decreased substantially in both treatment groups. Overall, average BRMS scores decreased by approximately 60% during double-blind therapy, with final scores of 5.6 (SD, 7.7) and 6.1 (SD, 7.8) for the valproate and placebo groups, respectively. Depressive symptom levels, however, remained at relatively high levels for both groups, and the final mean HRSD-25 scores were 16.3 (SD, 10.2) and 14.4 (SD, 9.7) for the valproate and placebo groups, respectively (Table 2). Likewise, remission from mania (BRMS score, ≤7) occurred within 2 to 3 weeks from treatment onset. By contrast, remission from depression (HRSD-25 score, ≤7) occurred within 8 to 9 weeks of treatment onset. Remission of mania tended to occur more rapidly for the valproate group (log-rank test, 3.21; *df*=1; *P*=.07). Ultimately, both groups had high rates of remission from mania, with 21 (78%) in the valproate group and 20 (80%) in the placebo group. Only 17 subjects (63%) in the valproate group and 12 (48%) in the placebo group achieved remission from depression.

There was a trend for valproate serum concentration in predicting improvements in HRSD-25 scores (estimate, –0.11; t_{154}=–1.83; *P*=.06) and functioning (estimate, 0.15; t_{135}=1.89; *P*=.06).

RELATIONSHIP BETWEEN MOOD SYMPTOMS, FUNCTIONING, AND ALCOHOL USE

Mean functioning scores also equally improved for both groups (valproate group, 57 [SD, 14]; placebo group, 57 [SD, 13]). Manic and depressive symptoms were highly associated with alcohol use outcomes and functioning (*P*=.006 to *P*<.001 in mixed-model analyses) during the study period. Functioning also was highly associated with alcohol use outcomes (*P*<.001 in mixed-model analyses).

TOLERABILITY

There were no serious drug-related adverse events. One subject (randomized to valproate therapy) discontinued owing to adverse effects, and another (randomized to placebo) discontinued owing to increased liver function test values. **Table 3** displays the most common adverse effects reported. Only nausea and vomiting were more common in the valproate group.

Furthermore, we examined whether treatment groups were associated with significant changes in liver functions test results (γ-GTP, ALT, and AST levels) or with reporting of adverse effects. The following covariates were included in the mixed-model analysis, as they might influence liver function test results or reporting of adverse effects: assessment time, age, sex, race, bipolar subtype, weekly alcohol use, additional medications, and medical problems. Reporting of adverse effects of medication did not differentiate between the treatments. Also, ALT and AST levels did not differentiate between the groups. Conversely, γ-GTP levels were significantly higher in the placebo group (overall postrandomization mean level, 81 IU/L [SD, 146.6 IU/L] vs 66 IU/L [SD, 91.7 IU/L] for the valproate therapy) (estimate, –62.08; $t_{23.5}$=–2.12; *P*=.045). The γ-GTP level was the only liver function test result to correlate positively with weekly alcohol use (estimate=0.49; $t_{11.1}$=2.87; *P*=.02).

COMMENT

To our knowledge, this is the first double-blind placebo-controlled study of valproate completed in alcoholic patients with bipolar I disorder. Results of this study indicate that valproate is useful, specifically for decreasing heavy alcohol use among bipolar alcoholic patients.

A differential change in γ-GTP level, an objective consequence of alcohol use, also appears to corroborate the difference in self-reported decrease in heavy drinking between the 2 groups. Moreover, although we did not confirm the hypothesis that the combination of valproate and lithium would significantly reduce depressive or manic symptoms more than lithium alone, there were modest differences between groups in rapidity of remission of mania and probability of remission of depression that warrant further study in a larger sample.

We are aware of several published treatment trials on comorbid substance abuse and bipolar disorder that are pertinent to the present findings. Geller and colleagues[53] reported an advantage of lithium compared with placebo in improving mood symptoms and substance use in a small, 6-week, double-blind placebo-controlled study of adolescents with bipolar disorder and secondary substance use. In that study, however, the placebo group did not receive pharmacotherapy to stabilize their mood state. The lithium-placebo group in our study showed a significant decrease in their alcohol use compared with baseline. However, they still drank significantly more

than the valproate group, especially on measures of heavy drinking, and relapsed 1 month earlier to sustained heavy drinking. Studies have reported equivocal usefulness of lithium in mood disorder with alcoholism and other substance use.[54] Lithium was not found to be superior to placebo in reducing alcohol consumption in large controlled trials of alcoholism without comorbid psychopathology.[18,55] Several studies indicate that mood disorders not treated with medication, such as major depression, may increase alcohol relapse[56-58] and that treatment of mood symptoms leads to significant decrease in use of alcohol or other substances. This is corroborated by our own study and those of others.[53,59,60]

In this study, valproate appears to decrease heavy drinking independent of any measurable effect on mood state, as both treatment groups were similar in terms of manic and depressive symptoms. This finding agrees with emerging evidence of the usefulness of some anticonvulsants in the treatment of withdrawal syndromes of alcohol and other drugs[24,27,61] and in decreasing alcohol use.[23] The γ-aminobutyric acid–mimetic (GABA-ergic) properties of valproate and its effects on central dopaminergic activities, along with its inhibition of neuronal excitation and antikindling properties, are hypothesized mechanisms involved in reducing alcohol use and alleviating withdrawal symptoms.

The addition of valproate to lithium was well tolerated in our study. Nausea and vomiting were the only adverse effects higher in the valproate group. Notably, no deleterious effects of valproate on liver function enzymes occurred in this alcohol-dependent sample. These results concur with available evidence suggesting that the combination of valproate and lithium is generally safe and well tolerated.[62] However, additive adverse effects are a potential risk. These may include tremors, gastrointestinal tract effects, and weight gain.[62]

Thus, our results suggest that valproate, perhaps through its antikindling-sensitization and GABA–mimetic properties, may have a dual role in effectively stabilizing mood symptoms and reducing heavy alcohol use in bipolar alcoholic patients. These findings are noteworthy given the number of factors mitigating positive findings on drinking behavior in this sample. First, this was an enriched treatment trial. Additional medications and psychotherapy were allowed whenever necessary. Both groups, however, required a similar number of interventions, with the only exception being that the placebo group required more trazodone for sleep disturbance. Despite the finding of decreased drinking in those who received trazodone, the valproate therapy still had an advantage on alcohol use outcomes. However, additional treatments may have obscured differences on mood symptoms and precluded significant differential dropout rates between the groups.

Studies of comorbid populations where a single medication was compared with placebo are more difficult to interpret in terms of efficacy on drinking behavior as an independent property from their effects on mood state. For example, fluoxetine hydrochloride decreased alcohol use when compared with placebo in depressed alcoholic patients[58]; however, fluoxetine was not better than placebo in a nondepressed alcohol-dependent sample.[60] Our findings of a strong association between mood symptoms and alcohol use also suggest that maximizing treatment of mood symptoms may improve alcohol use outcome. Valproate therapy may help decrease alcohol use by its effects on mood states and, presumably, by an independent effect on drinking behavior. Higher serum concentrations of valproate were consistently associated with decreased alcohol use outcomes. Our findings of slow improvement of depressive symptoms suggest that bipolar alcoholic patients may be similar to nonalcoholic bipolar patients in terms of time spent in a depressive state.[63]

Limitations of our study include the high attrition rate, leading to relatively few patients completing the full 24-week trial. Nevertheless, the average participant received the study medication for 65% of the study duration. Attrition rates were comparable to those reported in maintenance studies of bipolar disorder without comorbid alcoholism.[64,65] One advantage of our statistical method was its ability to handle missing observations.

A second limitation is that our study group may not be representative of patients with bipolar I disorder and other comorbid substance use disorders, especially opioid or cocaine dependence, as they were excluded from the study. However, our study group was socioeconomically and ethnically diverse and, as our treatment facility serves the primary catchment areas and tertiary care populations, patients are likely representative of real-world populations seeking treatment for bipolar disorder and alcoholism.

A final limitation is that our sample size was relatively small and lacked statistical power to detect smaller differences between treatments. Because patients could enter in manic, depressed, or mixed states, the ability to detect change in mood symptoms was further reduced.

Despite these limitations, the study results suggest the clinical utility of an adjunctive role for valproate in decreasing heavy alcohol use among this prevalent and clinically challenging population. Studies are warranted to replicate our current findings, determine whether those effects persist in long-term treatment, and clarify valproate mechanism of action in reducing heavy drinking.

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