Lamotrigine in Patients With Bipolar Disorder and Cocaine Dependence

E. Sherwood Brown, Ph.D., M.D.; Vicki A. Nejtek, Ph.D.; Dana C. Perantie, B.S.; Paul J. Orsulak, Ph.D., M.B.A.; and Leonardo Bobadilla, B.A.

Background: Bipolar disorder is associated with the highest substance abuse rates of any psychiatric illness. Therefore, treatments that stabilize mood and decrease drug use or cravings are of great interest. Open-label lamotrigine was examined in 30 outpatients with DSM-IV bipolar disorder and cocaine dependence. Lamotrigine was either added to existing medication regimens or used as monotherapy.

Method: Lamotrigine was started at a dose of 25 mg/day (12.5 mg/day in those taking valproic acid) and titrated to a maximum dose of 300 mg/day. Subjects received a baseline evaluation including a structured clinical interview and weekly assessments for 12 weeks with the Hamilton Rating Scale for Depression (HAM-D), Young Mania Rating Scale (YMRS), Brief Psychiatric Rating Scale (BPRS), and Cocaine Craving Questionnaire (CCQ). At each appointment, a urine sample was obtained, and participants reported drug use during the previous week. The subjects consisted of 13 men and 17 women with cocaine dependence and bipolar I disorder (N = 22), bipolar II disorder (N = 7), or bipolar disorder not otherwise specified (N = 1), with a mean ± SD age of 35.4 ± 7.2 years. Data were analyzed using the last observation carried forward on all subjects who completed the baseline evaluation and at least 1 postbaseline assessment.

Results: Significant improvement was observed in HAM-D, YMRS, and BPRS scores ($p \leq .02$). Cravings also significantly decreased as measured by the CCQ ($p < .001$). Dollar amount spent on drugs decreased nonsignificantly. Lamotrigine was well tolerated, with no subjects discontinuing due to side effects.

Conclusion: Lamotrigine treatment was well tolerated in this sample and associated with statistically significant improvement in mood and drug cravings but not drug use. The findings suggest that larger controlled trials of lamotrigine are needed in this population.

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Corresponding author and reprints: E. Sherwood Brown, Ph.D., M.D., UT Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd., Dallas, TX 75390-8849 (e-mail:sherwood.brown@utsouthwestern.edu).

Bipolar disorder is a common and severe psychiatric illness with a 1.3% to 1.7% prevalence in the general population.[1,2] Substance abuse appears to be more common in people with bipolar disorder than with any other major mental illness.[3] Regier et al.[1] found a lifetime prevalence of substance abuse of 61% in people with bipolar I disorder and 48% in people with bipolar II disorder. Therefore, treatments that may be useful for both mood disorder and substance abuse in bipolar disordered patients are of great interest. However, minimal data are available on the treatment of substance abuse in these patients. Large clinical trials generally exclude patients with recent substance abuse. In addition, high rates of treatment noncompliance and attrition make research in this population challenging.[3]

Geller et al.[4] examined the use of lithium versus placebo for 6 weeks in 25 adolescents with bipolar disorders or recurrent depressive disorders and comorbid substance abuse and found that lithium treatment was associated with significant decreases in the number of positive urine drug screens ($p < .05$). Brady et al.[5] gave open-label valproic acid to a group of 9 bipolar patients with substance abuse and found a significant improvement in depressive and manic symptoms and a significant decrease in the number of days ($p < .0005$) and amount of illicit drugs used during a 16-week follow-up period. Brady et al.[6] compared carbamazepine with placebo and found a reduction in cocaine use in cocaine-dependent patients with a mood disorder (N = 57), but not in a group of cocaine-dependent patients without mood disorders (N = 82). Calabrese et al.[7] recently reported similar improvement in mood symptoms with a combination of lithium and divalproex in treatment-compliant patients with bipolar disorder and alcohol, cannabis, and/or cocaine abuse or dependence as in the group without substance-related disorders. However, in this sample, compliance with treatment was lower in the substance-abusing group.

Multicenter, randomized placebo-controlled trials suggest that a newer anticonvulsant, lamotrigine, is effective for rapid cycling and depression in patients with bipolar disorder.[8,9] Winther et al.[10] recently examined lamotrigine (125 mg or 250 mg) and placebo pretreatment 2 hours prior to cocaine exposure and found no between-group differences in the physiologic or subjective mood effects of the cocaine. However, a 12-week open-label study

found significant reductions in cocaine use and cravings in a group of human immunodeficiency virus–seropositive patients with cocaine dependence given lamotrigine slowly titrated to 300 mg/day.[11] Thus, the effects of chronic and acute treatment with lamotrigine may be different in people who use cocaine.

No studies have examined the use of lamotrigine in patients with bipolar disorder and substance abuse. This is a particularly important population in which to examine the use of lamotrigine, given the frequent comorbidity of these disorders and the possible mood-stabilizing properties of lamotrigine. We report the results of a pilot study on the open-label use of lamotrigine in a group of outpatients with bipolar disorder and cocaine dependence. We hypothesized that lamotrigine add-on therapy would be associated with an improvement in mood symptoms and a reduction in drug use and cravings.

METHOD

Participants

Thirty-three outpatients with bipolar disorder and cocaine dependence volunteered to participate in a 12-week open-label study using lamotrigine with a weekly assessment schedule. The participants were recruited through flyers and staff referrals at local community mental health and substance abuse treatment programs. Prior to enrollment, all participants completed an informed consent process approved by the Institutional Review Board. Inclusion criteria included age of 18 to 65 years, DSM-IV diagnosis of bipolar I or II disorder or bipolar disorder not otherwise specified, and cocaine dependence within 3 months. Exclusion criteria included pregnancy or nursing, severe or life-threatening medical illness, and history of allergic reactions to lamotrigine. Participants were paid $50 at weeks 6 and 12 for time, transportation costs, and lost wages.

Psychiatric and Drug Assessments

At baseline, the Mini-International Neuropsychiatric Interview (MINI)[12] was conducted to confirm diagnoses. At baseline and every visit, psychiatric symptoms were assessed with the 17-item Hamilton Rating Scale for Depression (HAM-D),[13] the Young Mania Rating Scale (YMRS),[14] and the Brief Psychiatric Rating Scale (BPRS).[15] Cocaine cravings were evaluated at every visit with a 10-item version of the Cocaine Craving Questionnaire (CCQ).[16] Drug use was determined by patient self-report of the dollar amount spent on drugs and number of days of drug use in the past week. Urine samples for urine drug screens were collected at each visit with a cutoff of 300 ng/mL for positive benzoylecgonine levels.

Medication Dosing and Monitoring

Lamotrigine was either added to the participants' current medication regimen or given as monotherapy in participants not on treatment with psychotropic medications at baseline. No scheduled medications had been initiated within 4 weeks of initiating lamotrigine therapy. In 1 patient, an as-needed dose of trazodone for sleep had been initiated 1 week prior to study entry. A dosing schedule that used a slow upward titration of lamotrigine (25 mg/day for 2 weeks, 50 mg/day for 2 weeks, 75 mg for 1 week, 100 mg for 1 week, then weekly increases of 50 mg up to 300 mg) was employed, with an even slower titration in patients taking valproic acid (12.5 mg/day for 2 weeks, then 25 mg/day for 2 weeks) or when side effects were reported. Patients were asked about adverse events, side effects, and medication compliance at every visit.

Statistical Analyses

Changes from baseline to exit values for the BPRS, YMRS, HAM-D, CCQ, dollar amount spent on cocaine, days of cocaine use per week, and urine drug screens (positive versus negative) were analyzed using a last-observation-carried-forward (LOCF) analysis for all subjects who completed the baseline evaluation and at least 1 postbaseline assessment (intent-to-treat). In addition, subjects with current depressed phase or manic, hypomanic, or mixed phases were separately analyzed to examine antidepressant effects of lamotrigine in depressed patients and antimanic effects in those with manic/hypomanic/mixed episodes. Changes in scores for the BPRS, YMRS, HAM-D, CCQ, dollar amount spent on cocaine, and number of days per week of cocaine use were analyzed using paired Student t tests with the LOCF. Changes from baseline to exit in HAM-D, YMRS, BPRS, and CCQ scores of participants who continued to regularly use cocaine during the study as defined by > 50% positive urine drug screens were also analyzed separately using paired Student t tests. Urine drug screens at baseline and exit were analyzed using the McNemar test, which evaluates significance of changes in paired, dichotomous data with a binomial distribution. Correlations between changes in HAM-D, YMRS, BPRS, and CCQ scores, dollar amount spent on drugs, and number of days of drug use were also examined using the Pearson correlation coefficient.

RESULTS

A total of 33 patients were enrolled in the study. Three patients did not return after the baseline evaluation; thus, 30 patients were included in the data analysis. Demographic information about these subjects is provided in Table 1. Since lamotrigine was an add-on treatment, participants continued to take the psychotropic medications they were using when enrolled, including valproic acid (N = 6), venlafaxine (N = 2), bupropion (N = 2), gabapentin (N = 2), zolpidem (N = 2), olanzapine (N = 3), paroxetine (N = 3), buspirone (N = 1), imipramine (N = 2), doxepin (N = 2), risperidone (N = 1),

Table 1. Demographic Characteristics of Subjects (N = 30)

Characteristic	Value
Age, mean (SD), y	35.4 (7.2)
Gender, N (%)	
Male	13 (43)
Female	17 (57)
Race, N (%)	
White	17 (57)
African American	11 (37)
Hispanic	1 (3)
Native American	1 (3)
Other substance abuse treatment, N (%)	
In treatment at baseline	24 (80)
Not in treatment at baseline	6 (20)
Primary diagnosis, N (%)	
Bipolar I	22 (73)
Bipolar II	7 (23)
Bipolar NOS	1 (3)
Baseline mood state, N (%)	
Manic	9 (30)
Mixed	7 (23)
Hypomanic	1 (3)
Depressed	10 (33)
Did not meet criteria for a current mood state	3 (10)
Alcohol-related disorders, N (%)	
Alcohol dependence	14 (47)
Alcohol abuse	1 (3)
Classes of drugs used > 2 times in the 12 months prior to baseline, N (%)	
Marijuana	22 (73)
Stimulants	14 (47)
Narcotics	9 (30)
Tranquilizers	8 (27)
Hallucinogens	7 (23)
Other (nonprescription sleep or diet pills)	2 (7)
Lamotrigine dosage, mg	
Daily dose at exit, mean (SD)	196.3 (109.3)
Daily dose at exit, median	250
Duration of participation, mean (SD), wk	8.2 (4.2)
Duration of participation, N (%)	
1–4 wk	24 (80)
5–8 wk	17 (57)
9–12 wk	15 (50)

Abbreviation: NOS = not otherwise specified.

Table 2. Outcome Measures, Baseline to Exit, Mean (± SD) (N = 30)

Measure	Baseline	Exit	p
HAM-D	16.9 (6.6)	12.9 (8.0)	.02
YMRS	14.4 (5.3)	10.5 (4.2)	.001
BPRS	38.7 (6.6)	34.4 (7.7)	.01
CCQ	30.6 (16.5)	17.5 (11.0)	< .001
No. of days per week cocaine used	0.5 (1.2)	0.2 (0.5)	.2
$/Week spent on cocaine	88.3 (259.2)	7.3 (20.8)	.1

Abbreviations: BPRS = Brief Psychiatric Rating Scale, CCQ = Cocaine Craving Questionnaire, HAM-D = Hamilton Rating Scale for Depression, YMRS = Young Mania Rating Scale.

quetiapine (N = 3), topiramate (N = 1), mirtazapine (N = 1), hydroxyzine (N = 2), citalopram (N = 8), clonazepam (N = 2), trazodone (N = 7), and lithium (N = 3). Nine subjects were taking no other medications. Although we attempted to keep all other medications stable during the study, a total of 12 changes were made by physicians outside the study. These medication changes included increases in zolpidem from 10 mg/day to 35 mg/day (week 5), valproic acid from 1000 mg/day to 1500 mg/day (week 4), valproic acid from 250 mg/day to 500 mg/day (week 1, 2 participants), olanzapine from 5 mg/day to 20 mg/day (week 4), and doxepin from 50 mg/day to 150 mg/day (weeks 7–9). Changes also included the addition of bupropion, 150 mg/day (week 7); mirtazapine, 15 mg/day (week 4); citalopram, 20 mg/day (week 2); and gabapentin, 800 mg/day (week 4), and the discontinuation of clonazepam (week 2) and citalopram (weeks 7–8).

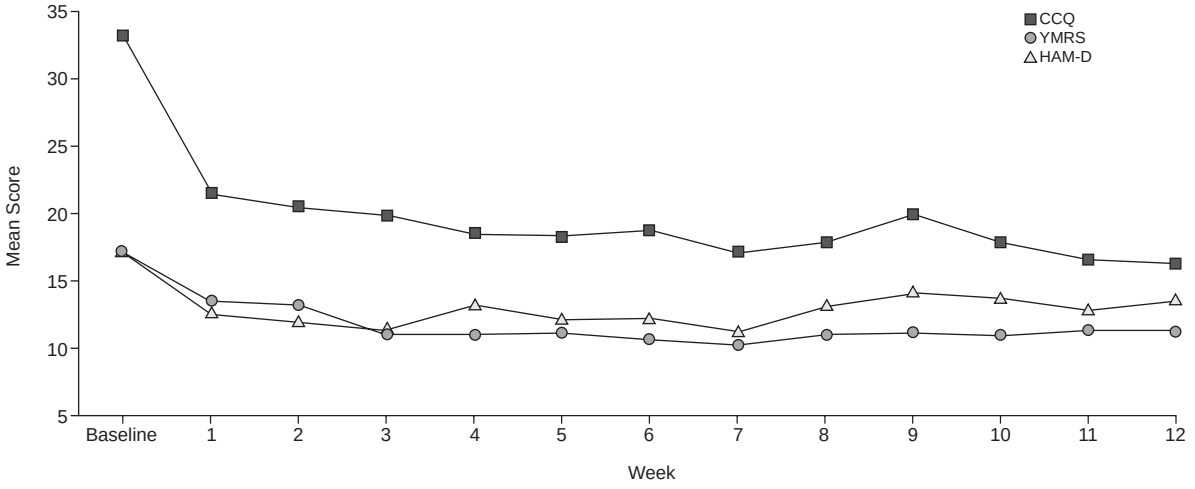
HAM-D, YMRS, and BPRS scores significantly decreased during lamotrigine therapy (Table 2). Cocaine cravings significantly decreased, as indicated by the CCQ. Dollar amount spent on cocaine each week showed a modest trend toward a decrease from baseline to exit ($p = .1$). Number of days of cocaine use per week ($p = .2$) and positive urine cocaine screens ($p = .25$) did not show a significant decrease during the study.

Changes in HAM-D score showed a modest correlation with changes in CCQ score ($r = 0.45$, $p = .01$). No other significant correlations between changes in psychiatric symptoms and drug cravings or use were found. Participants who continued to regularly use cocaine during the study, as defined by > 50% positive urine drug screens (N = 5), did not have significant mean reductions in baseline to exit HAM-D score (0.0 points), YMRS score (+ 0.2 points), BPRS score (–1.4 points), or CCQ score (–4.0 points) (all p values NS).

The patient sample was divided according to mood state for further analysis of mood changes in patients with bipolar disorder who were given lamotrigine (Figures 1 and 2). Subjects with current manic, hypomanic, or mixed mood states at baseline showed a highly significant reduction in YMRS scores ($p < .001$) from baseline to exit. Similarly, subjects meeting criteria for bipolar depression at baseline demonstrated a significant reduction in baseline to exit HAM-D scores ($p = .03$).

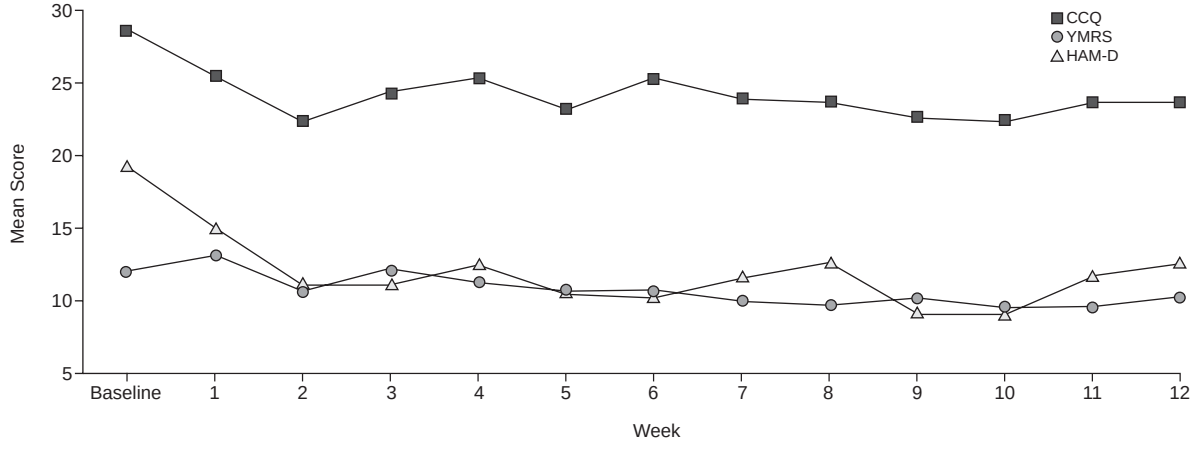
Lamotrigine was well tolerated; to our knowledge, no subjects dropped out of the study secondary to medication side effects. Side effects reported during the study included headache (N = 8), nausea (N = 3), dizziness (N = 2), tremor (N = 2), decreased libido (N = 2), fatigue (N = 1), and diarrhea (N = 1). Four subjects developed rashes during the study. One rash resolved prior to the next visit with the investigator. Two rashes were evaluated by an allergist, and 1, by a dermatologist. None of the 4 rashes were severe in nature, and none were felt to be related to lamotrigine use. Increases in manic symptoms in the depressed patients ("switches") did not appear severe in nature. Figure 2 shows week-by-week scores on the YMRS in participants who were depressed at baseline. Of the 10 participants in a depressed phase at baseline, 4 had an increase in YMRS score of ≥ 5 at some point in the study. However, only 1 of these patients had a YMRS score

Figure 1. YMRS, HAM-D, and CCQ Scores (LOCF) in Subjects With Manic, Mixed, or Hypomanic Baseline Mood State (N = 17)



Abbreviations: CCQ = Cocaine Craving Questionnaire, HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward, YMRS = Young Mania Rating Scale.

Figure 2. HAM-D, YMRS, and CCQ Scores (LOCF) in Subjects With Depressed Baseline Mood State (N = 10)



Abbreviations: CCQ = Cocaine Craving Questionnaire, HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward, YMRS = Young Mania Rating Scale.

elevation of ≥ 5 above baseline at the time of exit. In 1 patient, the YMRS score increased from 5 to 17 (baseline to week 3), but the score had decreased to 8 at the time of exit (week 12).

DISCUSSION

The results from this pilot study support our hypothesis that lamotrigine improves mood symptoms in subjects with bipolar disorder. Both depressive and manic symptoms significantly improved during lamotrigine therapy. This is the first clinical investigation that has examined the efficacy of lamotrigine in bipolar patients with cocaine abuse or dependence. Thus, the results suggest that lamotrigine may be useful in treating psychiatric symptoms in a dual-diagnosis population.

Lamotrigine was also associated with a reduction in cravings for cocaine in the patients studied. In addition, dollar amount spent on cocaine and number of days of cocaine use showed trends toward reduction that did not reach statistical significance, perhaps due to the large standard deviations of these values. Positive urine drug screens did not change significantly during the study. This negative finding may be due to the infrequency of positive urine drug screens at baseline and the fact that the drug screens were administered weekly—cocaine

metabolites are generally detectable in the urine for only 2 to 3 days after use.

The mechanism by which lamotrigine might reduce drug cravings or use is not known. Given the weak correlations between changes in psychiatric symptoms and cocaine cravings, the reductions in cocaine use and cravings do not appear to be mostly or entirely accounted for by improvement in mood. However, participants who continued to regularly use cocaine throughout the study did not show the improvement in mood observed in the other participants, suggesting that decreased drug use may, in part, account for the improvement in mood. In terms of pharmacologic mechanisms, lamotrigine appears to modulate sodium and calcium channels[17] and inhibit glutamate release.[18] Inhibition of glutamate release has been suggested as a possible strategy to decrease cocaine use in humans.[10,11]

Limitations of this pilot study include its open design and lack of a control group. Given the lack of a control group and the early mood symptom response, nonspecific effects (e.g., weekly visits) or regression to the mean cannot be ruled out as an explanation for some of the symptomatic improvement (Figures 1 and 2). The use of concomitant medications (i.e., mood stabilizers) with lamotrigine is a limitation, although this add-on design closely parallels actual clinical practice. In addition, the changes in other medications during the study included increases, decreases, additions, and discontinuations in medications of several different classes. Thus, the only consistent change in the patient sample as a whole was the addition of lamotrigine. Another limitation is that we were not able to assess the patients for weeks or months prior to initiating lamotrigine therapy to quantify typical cocaine use patterns. However, we had ethical concerns with this approach, given the fact that these were often symptomatic patients with bipolar disorder.

The strength of this study is that it is the first to examine the use of a newer anticonvulsant in patients with bipolar disorder and substance abuse, an important and challenging clinical population. The study examined patients from community mental health settings, many of whom had severe symptoms, including psychotic features. Thus, the findings should be useful to clinicians in the community. The results also suggest that lamotrigine was well tolerated in this population. No serious, medication-related adverse events or rashes were reported. The medication appeared to reduce cravings and improve mood in the subjects studied. The findings from this pilot study are promising and suggest that larger controlled studies of lamotrigine in this population are needed.

Drug names: bupropion (Wellbutrin and others), buspirone (BuSpar and others), carbamazepine (Tegretol and others), citalopram (Celexa), clonazepam (Klonopin and others), divalproex (Depakote), doxepin (Sinequan and others), gabapentin (Neurontin), hydroxyzine (Hydra-Zide), imipramine (Tofranil and others), lamotrigine (Lamictal), mirtazapine (Remeron), olanzapine (Zyprexa), paroxetine (Paxil), quetiapine (Seroquel), risperidone (Risperdal), topiramate (Topamax), trazodone (Desyrel and others), valproic acid (Depakene and others), venlafaxine (Effexor), zolpidem (Ambien).

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