A Randomized, Double-Blind, Placebo-Controlled, Trial of Lamotrigine Therapy in Bipolar Disorder, Depressed or Mixed Phase and Cocaine Dependence

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Bipolar disorder is associated with very high rates of substance dependence. Cocaine use is particularly common. However, limited data are available on the treatment of this population. A 10-week, randomized, double-blind, placebo-controlled trial of lamotrigine was conducted in 120 outpatients with bipolar disorder, depressed or mixed mood state, and cocaine dependence. Other substance use was not exclusionary. Cocaine use was quantified weekly by urine drug screens and participant report using the timeline follow-back method. Mood was assessed with the Hamilton rating scale for depression, quick inventory of depressive symptomatology self-report, and young mania rating scale. Cocaine craving was assessed with the cocaine-craving questionnaire. Data were analyzed using a random regression analysis that used all available data from participants with at least one postbaseline assessment ($n = 112$). Lamotrigine and placebo groups were similar demographically (age 45.1 ± 7.3 vs 43.5 ± 10.0 years, 41.8% vs 38.6% women). Urine drug screens (primary outcome measure) and mood symptoms were not significantly different between groups. However, dollars spent on cocaine showed a significant initial (baseline to week 1, $p = 0.01$) and by-week (weeks 1–10, $p = 0.05$) decrease in dollars spent on cocaine, favoring lamotrigine. Few positive trials of medications for cocaine use, other than stimulant replacement, have been reported, and none have been reported for bipolar disorder. Reduction in amount of cocaine use by self-report with lamotrigine suggests that a standard treatment for bipolar disorder may reduce cocaine use. A study limitation was weekly assessment of urine drug screens that decreased the ability to detect between-group differences.

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INTRODUCTION

Bipolar disorders are common, severe, and persistent illnesses affecting about 1.7–2.4% of the population (Kessler *et al*, 1994; Merikangas *et al*, 2011). Substance abuse is common in persons with bipolar disorder (Regier *et al*, 1990). Regier *et al* (1990) found a 61% lifetime prevalence of substance abuse in bipolar I disorder and 48% in bipolar II disorder. Abuse of and dependence on stimulants, such as cocaine, is especially common in people with bipolar disorder. Miller *et al* (1989) found 10% of hospitalized patients with bipolar disorder currently met criteria for a cocaine-use disorder. Mueser *et al* (1992) reported a lifetime prevalence of stimulant abuse of 34% among inpatients with bipolar disorder. Polysubstance abuse is also very common

in patients with bipolar disorder (Brown, 2005) with rates of 6–44% reported (Albanese and Pies, 2004; Estroff *et al*, 1985; Sonne *et al*, 1994). Another common comorbidity in patients with bipolar disorder is anxiety disorders. Anxiety disorders and substance use disorders occur together in about 15% of patients with bipolar disorder (Bauer *et al*, 2005). We previously reported high rates of anxiety disorders in patients enrolled in clinical trials for bipolar disorder and cocaine or alcohol use disorders (Mitchell *et al*, 2007). In this sample, PTSD was significantly more common in patients with bipolar disorder and cocaine use than patients with bipolar disorder and alcohol use, whereas the opposite was observed for generalized anxiety disorder.

Cocaine abuse or dependence in persons with bipolar disorder may be more severe and treatment refractory than in the general population. Using the general behavior inventory to screen for mood disorders among patients with psychoactive substance dependence, Saxon *et al* (1994) reported that bipolar disorder was associated with significantly more lifetime months of cocaine abuse and greater drug use during treatment when compared with patients without this illness. In addition, substance abuse

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may be associated with more hospitalizations and a poor response to lithium compared with patients with bipolar disorder not using these drugs (Aagaard and Vestergaard, 1990; Nunes *et al*, 1990; Sonne *et al*, 1994).

Persons with bipolar disorder and cocaine dependence represent a relatively unstudied but particularly challenging population for mental health professionals. Therefore, information about this population is of great importance. Minimal data are available on the pharmacotherapy of patients with bipolar disorder and cocaine dependence (Brown, 2005). Brady *et al* (2002) found significant reductions in cocaine use by cocaine-dependent individuals with affective disorders ($n=57$) but not in a group without affective illness ($n=82$). Brown *et al* randomized outpatients ($n=29$) with major mental illness (13 had bipolar I disorder), and cocaine or amphetamine use disorders, who were receiving traditional neuroleptics to either continue therapy the neuroleptic or switch to open-label quetiapine using an overlap and taper method (Brown *et al*, 2003b). The participants who switched to quetiapine had a significantly greater improvement in mood symptoms and cocaine craving than the treatment-as-usual group. In a more recent report, Brown *et al* (2002) randomized 12 outpatients with bipolar disorder and cocaine dependence to 12 weeks of quetiapine or placebo. No significant between-group differences were observed, although change in depressive symptoms favored quetiapine with a large effect size, and quetiapine was associated with a trend toward longer time in treatment. Brown *et al* (2007) reported that citicoline was associated with significantly greater likelihood of a cocaine-negative urine at study exit and improvement in aspects of declarative memory in outpatients ($n=44$) with bipolar disorder and cocaine dependence. Nejtek *et al* (2008) compared quetiapine and risperidone in outpatients ($n=124$) with bipolar disorder and cocaine or methamphetamine use and found that both treatments were associated with improvement in mood and reduced craving, but no significant between-group differences were observed.

Open-label trials in bipolar disorder and cocaine dependence have also been conducted with divalproex (Salloum *et al*, 2007), quetiapine (Brown *et al*, 2003b), and lamotrigine (Brown *et al*, 2003a). An open-label lamotrigine study observed improvement in both manic and depressive symptoms, as well as a decrease in dollars spent on cocaine but not in days of cocaine use (Brown *et al*, 2003a). In patients with cocaine dependence, but not bipolar disorder, an open-label study of lamotrigine reported an 85% reduction in cocaine use (Margolin *et al*, 1998). However, a small, controlled trial ($n=15$ /group) found no advantage with lamotrigine as compared with placebo on cocaine-positive urines (Berger *et al*, 2005).

Lamotrigine appears to be useful for depressive symptoms and relapse prevention in bipolar disorder (Calabrese *et al*, 1999, 2000, 2002). Lamotrigine inhibits the release of glutamate through modulation of high voltage-activated calcium currents (Pisani *et al*, 2004; Stefani *et al*, 1997; Wang *et al*, 2001) and sodium channels (Sitges *et al*, 2007; Stefani *et al*, 1997). Six recent reviews noted the potential of modulators of glutamate as targets for cocaine use (Gass and Olive, 2008; Javitt *et al*, 2011; Kalivas and Volkow, 2011; Schmidt and Pierce, 2010; Uys and LaLumiere, 2008; Uys

and Reissner, 2011). Medications that decrease glutamate release are potential neuroprotective agents that may decrease cerebral ischemia with cocaine dependence (Kosten, 1998). Interest has also focused on anticonvulsants for addiction owing to the possibility that kindling-like processes may contribute to drug use (Minozzi *et al*, 2008).

Given a strong mechanistic basis and open-label data suggesting a reduction in cocaine use in patients with bipolar disorder given lamotrigine, a placebo-controlled trial was conducted. The aims of the study were to determine the impact of lamotrigine therapy on cocaine use (primary aim) and cocaine craving, as well as manic and depressive symptoms (secondary aims). The primary outcome measure was urine drug screens with days and dollars spent on cocaine as secondary outcome measures of cocaine use.

MATERIALS AND METHODS

A total of 120 adult outpatients with bipolar I, II, NOS or cyclothymic disorders, and current cocaine dependence were recruited from local referral sources and newspaper advertisements for the 10-week randomized, double-blind (1:1 ratio of active medication to placebo) study. After complete description of the study to the subjects, IRB-approved, written informed consent was obtained. After obtaining consent, baseline assessment measures were administered including the structured clinical interview for DSM-IV clinician version (SCID-CV) (First *et al*, 1995). Consent was obtained and all study visits were conducted at our outpatient research clinic located in the UT Southwestern Medical Center.

Inclusion criteria were men or women aged 18–70 years, diagnosis of bipolar I, II, or NOS disorders currently depressed or mixed mood as determined by SCID-CV, current cocaine dependence with self-reported cocaine use within 14 days before randomization, English or Spanish speaking, and baseline Hamilton rating scale for depression 17-item version (HRSD₁₇) score ≥ 10 . Excluded were those currently taking an enzyme inducing or inhibiting anti-convulsant (eg, valproic acid, carbamazepine), currently experiencing severe psychotic features (eg, daily auditory hallucinations, fixed delusions, severely disorganized thought processes) that require antipsychotic therapy, and that do not appear to be secondary to cocaine use, active suicidal ideation (plan and intent) or ≥ 2 attempts in past 12 months or any attempt in the last month, highly unstable medical condition, change in concomitant psychiatric medications (eg, initiated antipsychotic) or in other substance abuse treatment (eg, began intensive outpatient treatment) within 7 days before study entry, and vulnerable populations (eg, pregnant or nursing women, incarcerated, or cognitively impaired individuals). Potential participants dependent on substances in addition to cocaine were not excluded.

Drug use was assessed at weekly visits using the timeline follow-back (TLFB) method to quantify days and amount of drug use (Fals-Stewart *et al*, 2000) and craving was assessed with the cocaine craving questionnaire (Tiffany *et al*, 1993). Urine drug screens were obtained each week. The total number of days of reported cocaine use, by TLFB, since the last visit was divided by the number of days since the last visit to determine the percent of days of cocaine use per

week since the last visit. The total amount spent on cocaine since the last visit was divided by the number of days since the last visit to determine the mean amount spent on cocaine per day since the last visit. Mood symptoms were quantified weekly with the HRSD₁₇ (Hamilton, 1960), quick inventory of depressive symptomatology-SR (QIDS-SR) (Rush *et al*, 2003), and young mania rating scale (YMRS) (Young *et al*, 1978). The psychobiology of recovery in depression III—somatic symptom scale (PRD-III) is a 24-item side effects rating scale developed for longitudinal depression studies (Thase *et al*, 1996). It covers a wide range of common medication side effects (eg, dizziness, diarrhea, somnolence) and can be quickly and easily administered by a clinician (Thase *et al*, 1996). It was administered every 2 weeks to track side effects. The items are scored on a three-point scale and reflect patient perception of the symptom severity. We have previously used this scale in clinical trials for bipolar disorder and substance dependence (Brown *et al*, 2007, 2009).

The study drug was added to existing psychiatric medications, when present, or given as monotherapy when participants were not taking other medications at baseline. Lamotrigine therapy was initiated at 25 mg/day and increased to 200 mg/day using a slow upward titration over 5 weeks, as outlined by Calabrese *et al* (2000), to minimize risk of rash. After that time additional increases in 100 mg/day increments to a maximum of 400 mg/day were made if the medication was well tolerated and the following signs of poor response were noted: HRSD₁₇ scores had decreased by $\leq 40\%$ from baseline, CCQ scores had decreased $\leq 25\%$ from baseline, and participants continued to use cocaine in the past week based on either TLFB or urine drug screens. Participants were paid for participation. Concomitant medications were managed with an algorithm, adapted from Bauer *et al* (2001) that, if necessary, allowed changes in other psychiatric medications. Study enrollment concluded, as planned, after enrollment of 120 participants. The study was registered at ClinicalTrials.gov (NCT00280293).

Statistical Methods

The number of subjects available for analysis was 112 (those with at least one postbaseline assessment). Of these, 55 received lamotrigine and 57 received placebo. The study was powered for cocaine use based on our pilot data from an open-label trial of lamotrigine and using the placebo group in a literature trial (Brown *et al*, 2003a). A sample size of 120 is sufficient to detect between-groups differences with a Cohen's *d* of approximately ≥ 0.5 (medium effect size). Randomization was conducted by the study statistician (TJC) through a computerized randomization process, which was downloaded to a spread-sheet used by unblinded clinic staff to allocate medication. All direct care staff (ie, study physicians and raters) were blinded.

Data were analyzed using a declining effects random-regression model (Kashner *et al*, 2003) where the treatment effect was divided into an initial period effect as measured by the change from the initiation of treatment at baseline to the first visit (week 1) and a subsequent time trend treatment effect as measured by the change from week 1 to week 12. The initial treatment effect was estimated separately from the subsequent time trend treatment effect

because the initial effect may relate primarily to the nonspecific effects of entering a cocaine treatment study and may be different with regard to size and direction from the time trend effect, which may more accurately reflect the effects of treatment. The division into two parts is done because treatment effect is frequently not constant over the course of the trial. If two distinct types of effects are present (initial effect and subsequent time trend effect), a model that allows for estimation of these effects will be more informative and better fitting than a model that does. Also, basing the initial effect on the change to the first measurement occasion means the maximum number of observations is available to estimate the subsequent time trend. Note that randomization does not have an effect on this nonconstant nature of treatment effect. All models included terms for time, treatment group, treatment group by time interaction, the baseline value of the outcome, and type of bipolar disorder (BP I vs other). Sample heterogeneity, potential baseline differences between-groups, and concomitant medication use were controlled by the use of covariates. A comprehensive list of additional baseline variables were considered as covariates to account for sample heterogeneity in demographic and clinical characteristics, substance use, concomitant medication use, anxiety disorder, and mood state as follows: age, gender, race, education level, income, family history of psychiatric illness, current psychiatric treatment, concomitant medication use (total number of concomitant meds, number of anticonvulsants, number of antipsychotics, number of antidepressants, lithium, number of sedatives/hypnotics), number of drinks, number of drinking days, number of heavy drinking days, current mood state, change in medication status during study (no change in meds, med increase during study, med decrease during study), percent days of cocaine use per week, amount spent on cocaine per week, HRSD, CCQ, YMRS, and scores from a baseline neuropsychological battery that included the Rey auditory verbal learning test and Stroop color word test. Each covariate was tested individually along with the covariate by time, covariate by treatment group, and covariate by time by treatment group interactions. A covariate (along with possible interaction terms) was selected if including the terms resulted in a significant maximum likelihood ratio test (ie, significantly improved the model's goodness of fit). All individually significant covariate terms were included together in a model and terms, which lost significance at this point were excluded from the final model. Thus, different outcome measures used different covariates. Covariates were selected without regard to whether they improved the significance of the treatment effect. No adjustment was made for multiple testing because it is preferable to err on the side of including unimportant covariates than to leave out important covariates. For continuous outcomes SAS Proc Mixed was used, and for binary outcomes (cocaine positive urine) SAS Proc GLIMMIX was used.

RESULTS

Table 1 shows the demographic and baseline characteristics of the two treatment groups. The lamotrigine and placebo

Table 1 Baseline Demographic and Clinical Characteristics of Lamotrigine and Placebo Groups (Intent-to-Treat Sample, $N = 112$)

Baseline characteristic	Lamotrigine (N = 55)	Placebo (N = 57)
Age in years, mean (SD)	45.1 (7.3)	43.5 (10.0)
Gender, N (%)		
Female	23 (41.8)	22 (38.6)
Male	32 (58.2)	35 (61.4)
Ethnicity, N (%)		
Caucasian	17 (30.9)	17 (29.8)
African-American	34 (61.8)	36 (63.2)
Hispanic	3 (5.5)	3 (5.3)
Asian-Pacific islander/other	1 (1.8)	1 (1.8)
Income, N (%)		
< \$15 000	33 (60.0)	33 (57.9)
≥ \$15 000	22 (40.0)	24 (42.1)
Education in years, mean (SD)	13.5 (2.2)	13.5 (2.4)
Mood diagnosis, N (%)		
Bipolar I	30 (54.5)	29 (50.9)
Bipolar II	21 (38.2)	21 (36.8)
Bipolar NOS	4 (7.3)	7 (12.3)
Mood state, N (%)		
Depressed	49 (89.1)	52 (91.2)
Mixed	6 (10.9)	5 (8.8)
Primary form of cocaine used, N (%)		
Crack	38 (69.1)	40 (70.2)
Intranasal	14 (25.5)	15 (26.3)
Intravenous	3 (5.5)	2 (3.5)
Other substance use disorders, N (%)		
Alcohol dependence		
Current	28 (50.9)	33 (57.9)
Past	0 (0.0)	2 (3.5)
Alcohol abuse		
Current	4 (7.3)	3 (5.3)
Past	1 (1.8)	0 (0.0)
Cannabis dependence		
Current	9 (16.4)	10 (17.5)
Past	0 (0.0)	4 (7.0)
Cannabis abuse		
Current	7 (12.7)	9 (15.8)
Past	0 (0.0)	0 (0.0)

Table 1 Continued

Baseline characteristic	Lamotrigine (N = 55)	Placebo (N = 57)
Amphetamine dependence		
Current	3 (5.5)	4 (7.0)
Past	5 (9.1)	6 (10.5)
Amphetamine abuse		
Current	0 (0.0)	0 (0.0)
Past	0 (0.0)	1 (1.8)
Opioid dependence		
Current	3 (5.5)	6 (10.5)
Past	1 (1.8)	0 (0.0)
Opioid abuse		
Current	0 (0.0)	2 (3.5)
Past	0 (0.0)	0 (0.0)
Hallucinogen dependence		
Current	1 (1.8)	2 (3.5)
Past	1 (1.8)	2 (3.5)
Hallucinogen abuse		
Current	0 (0.0)	0 (0.0)
Past	0 (0.0)	0 (0.0)
Sedative/hypnotic/anxiolytic		
Current	0 (0.0)	2 (3.5)
Past	1 (1.8)	0 (0.0)
Sedative/hypnotic/anxiolytic abuse		
Current	0 (0.0)	1 (1.8)
Past	1 (1.8)	0 (0.0)
Other substance dependence		
Current	0 (0.0)	0 (0.0)
Past	1 (1.8)	0 (0.0)
Other substance abuse		
Current	0 (0.0)	0 (0.0)
Past	1 (1.8)	0 (0.0)
Anxiety disorders, N (%)		
Post-traumatic stress disorder		
Current	6 (10.9)	5 (8.8)
Past	5 (9.1)	4 (7.0)
Panic disorder with agoraphobia		
Current	1 (1.8)	1 (1.8)
Past	1 (1.8)	1 (1.8)

Table 1 Continued

Baseline characteristic	Lamotrigine (N = 55)	Placebo (N = 57)
<i>Panic disorder without agoraphobia</i>		
Current	2 (3.6)	0 (0.0)
Past	7 (12.7)	2 (3.5)
<i>Agoraphobia without panic disorder</i>		
Current	2 (3.6)	1 (1.8)
Past	1 (1.8)	0 (0.0)
<i>Generalized anxiety disorder</i>		
Current	6 (10.9)	0 (0.0)
Past	1 (1.8)	0 (0.0)
<i>Specific phobia</i>		
Current	3 (5.5)	2 (3.5)
Past	0 (0.0)	1 (1.8)
<i>Obsessive compulsive disorder</i>		
Current	1 (1.8)	0 (0.0)
Past	2 (3.6)	0 (0.0)
<i>Social phobia</i>		
Current	2 (3.6)	0 (0.0)
Past	0 (0.0)	1 (1.8)
<i>Anxiety disorder NOS</i>		
Current	1 (1.8)	0 (0.0)
Past	0 (0.0)	0 (0.0)

groups were similar demographically (age 45.1 ± 7.3 vs 43.5 ± 10.0 years, 41.8% vs 38.6% women, 54.5% vs 50.9% bipolar I, 89.1% vs 91.2% depressed). Many of the participants used substances in addition to cocaine. Anxiety disorders were also common. The mean exit dose of lamotrigine was 221.8 ± 148.0 mg in the active medication group and pills dispensed equivalent to 192.1 ± 146.8 mg in the placebo group. Adherence, based on pills dispensed and returned, was 92% with lamotrigine and 93% with placebo. However, at 8% of appointments with lamotrigine and 7% with placebo, participants did not return the unused pills. In addition, participants were no shows for 9% of appointments with lamotrigine and 12% for placebo. These missing data were not included in the pill count adherence estimate. Because failure to return unused pills and missing appointments could be signs of medication nonadherence, actual medication adherence may have been lower than the above estimate. No participants were receiving intensive outpatient therapy for substance use. Some participants were taking concomitant psychiatric medications at baseline. These medications were lithium ($n = 1$), antidepressants ($n = 10$), antipsychotics ($n = 2$), and sedative/hypnotic/anxiolytics ($n = 5$) in the lamotrigine group and lithium ($n = 6$), antidepressants ($n = 10$), antipsychotics ($n = 2$), and sedative/hypnotic/anxiolytics ($n = 4$) in the placebo group.

Table 2 Results of Between-Groups Analysis ($N = 112$)

Outcome measures	F-value	Significance (p-value)
<i>Cocaine use (probability of +UDS)</i>		
Initial effect: weeks 0–1	$F(1,113) = 1.1$	0.30
By week effect: weeks 1–10	$F(1,80) = 0.0$	0.99
<i>Percent days used cocaine</i>		
Initial effect: weeks 0–1	$F(1,147) = 2.5$	0.12
By week effect: weeks 1–10	$F(1,96) = 1.1$	0.31
<i>Dollar amount spent on cocaine</i>		
Initial effect: weeks 0–1	$F(1,93) = 11.2$	0.01
By week effect: weeks 1–10	$F(1,62) = 3.9$	0.05
<i>Cocaine craving questionnaire</i>		
Initial effect: weeks 0–1	$F(1,100) = 1.3$	0.26
By week effect: weeks 1–10	$F(1,83) = 0.4$	0.53
<i>HRSD (depression scale rating)</i>		
Initial effect: weeks 0–1	$F(1,104) = 0.6$	0.44
By week effect: weeks 1–10	$F(1,79) = 0.3$	0.57
<i>QIDS-SR (self-rated depression)</i>		
Initial effect: weeks 0–1	$t(106) = 0.0$	0.97
By week effect: weeks 1–10	$t(77) = 0.1$	0.89
<i>YMRS (mania)</i>		
Initial effect: weeks 0–1	$F(1,174) = 0.3$	0.56
By week effect: weeks 1–10	$F(1,190) = 0.5$	0.47
<i>PRD-III score (repeated measures)</i>		
Initial effect: weeks 0–1	$F(1,93) = 0.5$	0.49
By week effect: weeks 1–10	$F(1,71) = 1.3$	0.26

Results of the random regression analyses are given in Table 2. Percentage of cocaine-positive urine drug screens (baseline covariates: bipolar type, sedative/hypnotic use, days of alcohol use) and CCQ scores, (baseline covariates: bipolar type, HRSD scores, income) did not differ between groups. The relative risk was 1.67 at week 1 and 1.72 at week 10 with those taking lamotrigine nonsignificantly more likely to be cocaine-negative than those taking placebo. However, dollars spent on cocaine (baseline covariates: bipolar type, sedative/hypnotic use, cocaine use, Stroop color word scores, CCQ score) showed a significant between-group difference on both initial ($p = 0.01$) and by-week effect ($p = 0.05$).

Scores on the QIDS-SR (baseline covariates: bipolar type, anxiety disorder diagnosis), HRSD (baseline covariates: bipolar type), YMRS (baseline covariates: bipolar type, age, gender, income, previous psychological treatment), and PRD-III (baseline covariates: bipolar type, RAVLT total score) were not significantly different between groups in the sample as a whole.

Although between-group differences in mood were not observed, improvement in cocaine use observed in both treatment groups could be due, at least in part, to improvement in mood symptoms. Therefore, we conducted a *post hoc* analysis of cocaine use including mood as a time-varying covariate. Adding this covariate allowed us to estimate the treatment effect as if mood were held constant during the study. Thus, we could estimate change over time in cocaine use that was independent of mood. When the HRSD was included as a time-varying covariate in the analysis of amount spent on cocaine per week we found that HRSD was a significant covariate ($p < 0.0001$). The initial treatment effect remained significant ($p = 0.03$ rather than $p = 0.01$ without the time-varying covariate) but the time effect lost its significance ($p = 0.01$ in the original analysis but $p = 0.08$ with the HRSD added), as did the time by treatment group interaction ($p = 0.05$ in the original analysis but $p = 0.08$ with HRSD added). YMRS was also a significant covariate ($p = 0.002$) for amount spent on cocaine per week. The initial treatment effect remained significant ($p = 0.02$ rather than $p = 0.01$ without the time-varying covariate). The time effect was still significant ($p = 0.01$ in the original analysis, $p = 0.004$ with the YMRS added). The time by treatment group interaction lost its significance ($p = 0.05$ in the original analysis but $p = 0.07$ with YMRS added). Baseline to exit change in HRSD scores correlated significantly with change in days of cocaine use in the combined treatment groups ($r = 0.29$, $p = 0.002$), as well as those in the lamotrigine ($r = 0.30$, $p = 0.03$) and placebo groups ($r = 0.28$, $p = 0.04$), and change in CCQ scores in the combined ($r = 0.45$, $p < 0.0001$), lamotrigine ($r = 0.50$, $p = 0.0002$) and placebo groups ($r = 0.42$, $p = 0.001$). Change in amount spent on cocaine did not correlate significantly with changes in HRSD scores. Changes in YMRS scores correlated significantly with changes in days of cocaine use in the combined group ($r = 0.19$, $p = 0.05$) and with change in the CCQ in the combined ($r = 0.23$, $p = 0.02$) and placebo groups ($r = 0.30$, $p = 0.02$).

The literature suggested that lamotrigine has efficacy for the treatment of bipolar depression only in patients with baseline HRSD scores > 24 (Geddes *et al*, 2009). Therefore, we conducted a *post-hoc* analysis of this subgroup and found a trend favoring lamotrigine for the YMRS ($n = 36$, initial effect: $F(1, 42) = 2.7$, $p = 0.11$, by week effect: $F(1, 50) = 3.2$, $p = 0.08$) but no difference was observed for the HRSD ($n = 40$, initial effect: $F(1, 33) = 0.08$, $p = 0.78$, by week effect: $F(1, 20) = 0.02$, $p = 0.88$) or QIDS-SR ($n = 40$, initial effect: $F(1, 35) = 0.82$, $p = 0.37$, by week effect: $F(1, 24) = 0.22$, $p = 0.64$).

Survival in the study was similar in the two groups. See a Kaplan–Meier Survival Curve in Figure 1. Of the 120 participants enrolled, 63 completed the study. Reasons for discontinuation included: 26 lost to follow-up, 5 moved, 3 withdrew consent, 3 unrelated medical reasons, 1 severe treatment nonadherence, 2 suicidal ideation and 2 suicide attempt, 2 inpatient admissions for unrelated medical conditions, 1 rash that was determined to not be related to lamotrigine, 1 related to a probation violation, 1 due to incarceration, and 2 for other reasons.

Side effects were similar in the two groups. The two treatment conditions were associated with nonsignificantly different levels of somatic complaints as assessed by the

PRD-III somatic symptom scale. Of a total of 17 adverse events reported (10 lamotrigine, 7 placebo), 2 adverse events were considered study-related and included drying and peeling of the skin, and increased sweating (both reported by the same patient on two different visits (lamotrigine group)). A total of 15 additional adverse events were classified as unexpected and unrelated to the study.

DISCUSSION

To our knowledge, this is the largest clinical trial reported, to date, in patients with bipolar disorder and cocaine dependence and the second largest in patients with bipolar disorder and any substance use disorder. A significantly greater decrease in the amount spent on cocaine by participant report was observed with lamotrigine. Although the percentage of cocaine-positive urines during treatment were smaller with lamotrigine, the findings were not statistically significant. The discrepancy between the reported amount of cocaine use (dollars spent) and the urine drug screens could be due to several factors. The participants may not have given entirely accurate assessments of their use. Although underreporting of substance use is common, two treatment groups that were otherwise similar might be expected to have similar rates of misreporting. Owing to a concern that it would not be feasible to get patients with both bipolar disorder and cocaine dependence to return for thrice weekly urines drug screens, as is customary in cocaine trials, we only obtained weekly urine samples. This design feature decreased our number of observations, and hence statistical power, and did not provide us with a complete picture of cocaine use between weekly visits. Alternatively, lamotrigine could decrease the amount of cocaine use more than the frequency of cocaine use. Consistent with this possibility is observation that dollars spent on cocaine (a measure of amount and frequency) decreased with lamotrigine, whereas days of cocaine use (a measure of frequency of use) did not significantly decrease. Similar findings were reported in an open-label trial of lamotrigine in bipolar disorder and cocaine dependence (Brown *et al*, 2003a).

The treatment groups did not differ significantly on changes in depressive or manic symptoms. As almost all of the participants were depressed at baseline, the negative results for manic symptoms could be due to the low baseline scores on the YMRS. Prior research suggested that lamotrigine only showed a separation from placebo for the acute treatment of bipolar depression when baseline HRSD scores are > 24 (Geddes *et al*, 2009). Therefore, we conducted a *post-hoc* analysis of this more severely depressed subgroup. This exploratory analysis revealed a significant effect of lamotrigine on manic but not depressive symptoms. The inability to see a difference in depressive symptoms in this subgroup may have been due to the small number of participants with HRSD scores ≥ 24 at baseline. The trend toward a reduction in YMRS scores in this subgroup with greater depressive symptom severity is also interesting. To our knowledge, changes in manic symptoms with lamotrigine in patients with greater depressive symptom severity have not been previously examined. Perhaps the reduction in manic symptoms was, at least in part, related to

Figure 1 Kaplan-Meier survival curve for the lamotrigine and placebo groups.

a reduction in the amount of cocaine used. Consistent with this idea was the observation that changes in the YMRS correlated with some cocaine use outcomes. However, the correlations were generally stronger between changes in the HRSD and changes in cocaine use and craving.

Lamotrigine was well tolerated. Side effects were non-significantly different in the treatment groups. The two groups had similar retention (Figure 1). Thus, lamotrigine appears to be relatively safe to use in this population.

In summary, lamotrigine appeared to be safe and well tolerated by bipolar disorder patients with active cocaine use. Cocaine use, as measured by amount spent per week, decreased per patient report but not as assessed by urine drug screen. Additional research with lamotrigine using more frequent urine drug screens and a larger patient sample is needed. In addition, because lamotrigine appears to work better in preventing mood symptoms with bipolar disorder than as an acute treatment, trials of lamotrigine for relapse prevention in those with recent cocaine abstinence may be warranted.

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