Brief Report

NALTREXONE IN PATIENTS WITH BIPOLAR DISORDER AND ALCOHOL DEPENDENCE

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Bipolar disorder is associated with very high rates of substance abuse. However, few clinical trials are reported in this population. Naltrexone is effective for alcohol dependence, but its safety and efficacy are not established in patients with bipolar disorder and alcohol dependence. A 16-week, open-label, add-on pilot study of naltrexone was conducted in 34 outpatients with bipolar disorder and alcohol dependence. Assessments included the 17-item Hamilton Rating Scale for Depression (HRSD-17), Young Mania Rating Scale (YMRS), Brief Psychiatric Rating Scale (BPRS), and an alcohol craving scale. Alcohol use was quantified. Significant improvement was observed in the HRSD-17 and YMRS, and days of alcohol use and craving decreased significantly. Naltrexone was well tolerated. Controlled trials are warranted. Depression and Anxiety 23:492–495, 2006.

Key words: *mood disorders; substance dependence; depression; mania; opioid receptor*

INTRODUCTION

Substance abuse is more common in people with bipolar disorder than in those with any other major mental illness [Brown et al., 2001]. Alcohol is the most frequently abused substance in this population, with a 46% lifetime prevalence of alcohol-related disorders reported in a community-based study [Regier et al., 1990]. However, minimal data are available on the treatment of substance abuse in these patients

The limited data suggest that patients with bipolar disorder and alcohol use may respond favorably to pharmacotherapy. Salloum et al. [2005] randomized 59 lithium-treated patients with bipolar I disorder and alcohol dependence to receive treatment with valproate or placebo for 24 weeks. The group receiving valproate had significantly fewer heavy drinking days and a trend toward fewer drinks per heavy drinking day than the group receiving placebo. Longoria et al. [2004] reported decreased alcohol use and craving in 14 patients with bipolar disorder and alcohol and cocaine use given open-label quetiapine add-on therapy.

Naltrexone is approved by the U.S. Food and Drug Administration (FDA) for the treatment of alcohol dependence. Randomized, controlled trials have found that naltrexone is superior to placebo in preventing relapse in patients with alcohol dependence [Anton et al., 1999]. However, to our knowledge, no studies have examined the efficacy of naltrexone in patients with bipolar disorder and alcohol dependence.

Sonne and Brady [2000] reported two patients with bipolar disorder and alcohol dependence who discontinued naltrexone due to side effects, including feeling "jazzed up," nausea, tremor, diaphoresis, dysphoria, and muscle aches. The authors suggested that endogenous opiate release during manic states might increase sensitivity to opiate antagonists. Naltrexone might also induce depressive symptoms through antagonism of the effects of endorphins [Miotto et al., 2002]. Therefore, data are needed

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on naltrexone in patients with bipolar disorder and alcohol dependence.

This open-label, pilot study examined the tolerability, safety, and efficacy of naltrexone in outpatients with bipolar disorder and alcohol dependence. We hypothesized that naltrexone add-on therapy would be associated with a decrease in alcohol use and alcohol craving. We explored changes in psychiatric symptoms and the relationship between change in alcohol consumption and change in psychiatric symptom severity.

METHODS

Thirty-four outpatient adults with bipolar I, II, or not otherwise specified (NOS) disorders and current alcohol dependence confirmed by the Mini-International Neuropsychiatric Interview [MINI; Sheehan et al., 1998] were enrolled after signing a University of Texas Southwestern Institutional Review Board–approved informed consent form. Psychiatric symptoms were assessed with the 17-item Hamilton Rating Scale for Depression [HRSD-17; Hamilton, 1960], Young Mania Rating Scale [YMRS; Young et al., 1978], and the 18-item Brief Psychiatric Rating Scale [BPRS-18; Overall and Gorham, 1962]; alcohol use by self-reported number of drinks in the past 14 days; and alcohol craving using a version of the Cocaine Craving Questionnaire [a 10-item self-report measure that asks about current substance craving; Tiffany et al., 1993] modified to assess alcohol craving (cocaine changed to alcohol) as in Longoria et al. [2004]. Alcohol use was quantified by patient self-report and the amounts converted to standard drinks. Naltrexone at 50 mg/day was added to existing medication regimens. Psychiatric symptoms and alcohol use and craving were assessed every 2 weeks for 16 weeks

We compared means at baseline and exit for the HRSD-17, YMRS, BPRS-18, alcohol craving, and number of standard drinks in the past 14 days using paired *t*-tests. We assessed urine drug tests at baseline and exit using a χ^2 analysis. We explored relationships between baseline and baseline to exit changes in psychiatric symptoms and alcohol use and craving using Pearson's correlation coefficient. Significance was defined as $P \leq .05$ for all comparisons.

RESULTS

We enrolled 34 patients in the study. Eight patients did not return after the baseline evaluation; thus, data on 26 patients were analyzed. The mean age was 37.1 ± 8.3 years, 19 participants (73%) were male, 22 (84%) were white, 12 (46%) had bipolar I disorder, 13 (50%) had bipolar II disorder and 1 (4%) had bipolar disorder NOS, 8 (29%) were manic/hypomanic or mixed at baseline, whereas 17 participants (65%) were depressed and 1 (4%) was euthymic. Among the eight participants who withdrew after the baseline assessment, 63% were male, 50% had bipolar II disorder, 50% had a current mixed state, 25% had hypomania and depression, and 25% had depression only. Three of these eight individuals reported side effects, whereas five were lost to follow-up. Among all participants, mean participation was 9.5 ± 5.6 weeks. Eight (31%) participants completed all 16 weeks of the study.

Naltrexone treatment was added to existing medications that included selective serotonin reuptake inhibitors ($n = 14$), trazodone ($n = 11$), benzodiazepines ($n = 10$), valproic acid ($n = 8$), antipsychotics ($n = 8$), carbamazepine ($n = 4$), venlafaxine ($n = 4$), lithium ($n = 3$), buspirone ($n = 2$), gabapentin ($n = 2$), zolpidem ($n = 2$), mirtazapine ($n = 1$), and tricyclic antidepressants ($n = 1$). Changes in concomitant medications during the study included initiation of an antidepressant ($n = 3$), change in antidepressant dosage ($n = 2$), change in antidepressant ($n = 3$), discontinuation of antidepressant ($n = 1$), change in antipsychotic ($n = 1$), discontinuation of zolpidem ($n = 1$), discontinuation of gabapentin ($n = 1$), and discontinuation of valproic acid ($n = 1$). Substance abuse disorders, in addition to alcohol dependence, included cannabis abuse/dependence ($n = 4$); cocaine dependence ($n = 6$); and amphetamine, cocaine, and cannabis abuse ($n = 2$).

Values for psychiatric symptoms and alcohol-related measures are shown in Table 1. HRSD-17 and YMRS, but not BPRS, scores decreased significantly during naltrexone therapy. Alcohol craving and total drinks significantly decreased during the study.

Reduction in alcohol craving (baseline to exit) positively correlated with reduction in YMRS scores ($r = .43$, $P = .03$) and tended toward an association with reduction in BPRS scores ($r = .39$, $P = .06$). Reduction in drinks positively correlated with reduction in YMRS scores ($r = .45$, $P = .03$), and tended to be associated with reduction in HRSD-17 scores ($r = .38$, $P = .07$). Reduction in alcohol craving did not correlate significantly with reduction in alcohol use.

We assessed changes in cannabis and stimulant (cocaine or amphetamine) use in those ($n = 6$ for cannabis and $n = 8$ for stimulants) with abuse or dependence on these substances. Other drugs were too infrequently used for meaningful analysis. Change in days of cannabis use (3.50 ± 5.24 to 6.67 ± 6.28, $P =$ not significant), days of stimulant use (1.17 ± 0.98 to 3.17 ± 5.42, $P =$ not significant), and frequency

TABLE 1. Baseline to exit values for ITT sample ($n = 26$) with LOCF

Assessment	Baseline	Exit	*P*
$HRSD_{17}$	17.2 (6.8)	12.4 (9.7)	.028
YMRS	11.4 (7.7)	7.5 (5.9)	.049
BPRS	32.2 (10.1)	29.2 (13.1)	.375
Alcohol craving	39.2 (17.5)	19.9 (12.7)	.000
Number of drinks in past 2 weeks	57.3 (49.0)	28.4 (0.5)	.039

of positive urines for either cannabis (5/6 to 5/6, P = not significant) or stimulants (4/8 to 4/8, P = not significant) did not change significantly.

We examined subsamples to determine possible predictors of response. Participants with only an alcohol-related diagnosis showed statistically significant reductions in the HRSD-17 (18.6±4.5 to 12.6±9.4, P=.048), alcohol use (39.5±29.6 to 18.0±25.4 drinks, P=.021) and alcohol craving (38.1±16.7 to 19.4±14.5, P=.005), whereas those with concomitant substance-related disorders showed a significant reduction in alcohol craving (39.7±19.2 to 19.8±12.3, P=.023) but not on the HRSD-17 (15.3±8.8 to 12.8±10.9, P=.581) or alcohol use (46.1±37.4 to 33.4±41.4 drinks, P=.376). Participants meeting criteria for mania or hypomania at baseline showed significant reductions in the HRSD-17 (17.9±6.4 to 12.1±8.2, P=.025), and alcohol craving (42.6±19.7 to 19.8±15.0, P=.006), whereas participants with baseline depression only showed a significant reduction in alcohol craving (34.5±14.2 to 19.9±10.5, P=.022). Participants with bipolar I disorder had a significant reduction in alcohol craving (38.9±17.5 to 18.3±11.9, P=.006), whereas participants with bipolar II disorder had significant reductions in alcohol craving (39.1±17.6 to 22.5±13.5, P=.013) and the HRSD-17 (17.0±7.0 to 12.2±7.7, P=.031). Participants without a family history of alcohol-related disorder showed significant reductions in the YMRS (11.7±7.7 to 5.9±4.8, P=.004), HRSD-17 (17.3±6.5 to 9.9±7.2, P=.001), BPRS-18 (34.0±11.1 to 25.4±5.4, P=.002), alcohol use (49.6±36.3 to 26.2±35.1 drinks, P=.047), and alcohol craving (42.4±17.0 to 19.2±12.1, P<.001), whereas participants with a positive family history did not show significant changes in the YMRS (10.6±8.0 to 11.0±7.1, P=.918), HRSD-17 (17.0±7.8 to 17.8±12.9, P=.906), BPRS-18 (28.1±6.1 to 37.6±20.5, P=.283), alcohol use (35.9±40.1 to 34.9±56.1 drinks, P=.969) or alcohol craving (31.3±15.8 to 23.1±14.4, P=.145).

We also examined changes in alcohol craving and use in those with reductions in HRSD-17, YMRS, and BPRS-18 above and below the mean. Greater than average reduction in HRSD-17 and YMRS scores was associated with statistically significant reductions in both alcohol use and craving while less than average reduction in these scales was associated with non-significant changes in alcohol use and craving. On the BPRS-18, either greater or less than mean change was associated with statistically significant reduction in alcohol craving, but neither was associated with significant reduction in alcohol use.

Side effects reported during the study included nausea or emesis (n = 7), sweating (n = 2), dizziness (n = 2), abdominal pain (n = 2), tremor or muscle spasms (n = 2), headaches (n = 1), fatigue (n = 1), somnolence (n = 1), dry mouth (n = 1), decreased appetite (n = 1), blurred vision (n = 1), shortness of breath (n = 1), constipation (n = 1), insomnia (n = 1), diarrhea (n = 1), and sexual dysfunction (n = 1). Twelve men and three women reported at least one side effect during the study.

DISCUSSION

Naltrexone add-on therapy was well tolerated and associated with a statistically significant improvement in manic and depressive symptom severity, as well as alcohol use and craving. These findings suggest that naltrexone may be associated with a reduction in alcohol use and alcohol craving, and a modest improvement in psychiatric symptoms, in persons with bipolar disorder. Reduction in alcohol use was not necessarily associated with a reduction in the use of other substances by the participants.

Given the open-label design, lack of a control group, and occasional changes in concomitant psychotropic medications, the findings must be interpreted with caution. Because the sample consisted of mostly symptomatic patients with bipolar disorder, the number of medication changes was modest, and included both additions and discontinuations of medications from several classes. Thus, the only consistent medication change was the addition of naltrexone. We found that naltrexone was generally well tolerated. We did not find that naltrexone was associated with induction of depressive symptoms. However, attrition was high in the study. Eight participants withdrew after the baseline visit. This early attrition may have been due to medication side effects. Six of the eight early dropouts met current criteria for either mania or hypomania, consistent with the suggestion by Sonne and Brady [2000] that these mood states might be particularly sensitive to the effects of naltrexone.

The relationship between change in alcohol use or craving and mood may be quite complicated. Both depressive and manic symptoms showed a modest but statistically significant reduction during naltrexone therapy. Changes in YMRS scores were associated with changes in alcohol use and craving. We also found greater reduction in alcohol use in participants with greater than average reduction in mood symptom scales. Several explanations for these findings are possible. Naltrexone might be useful for manic or depressive symptoms. Improvement in mood may be mediated through a number of mechanisms, including reduction in alcohol use through amelioration of the either direct effects of alcohol on mood or alcohol withdrawal symptoms, greater adherence in medication for mood symptoms, or improved well-being or self-esteem from achieving the goal of a reduction in alcohol use.

Given the small sample size, it is difficult to interpret data from subgroups, because changes in only a few participants could alter the findings. However, poor response in participants with a family history of an alcohol-related disorder is noteworthy. Some

other studies of naltrexone have suggested that a positive family history is associated with a favorable response [King et al., 1997; Monterosso et al., 2001; Rubio et al., 2005].

The study has a number of limitations. First, given the open-label, uncontrolled design, we cannot rule out the possibility that some of the observed changes are due to nonspecific effects of treatment or other factors unrelated to naltrexone. Second, the sample size is small. Third, we are not able to determine the etiology of the observed improvement in psychiatric symptoms. A larger trial of naltrexone in patients with both bipolar disorder and alcohol dependence is needed to confirm these preliminary observations.

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