# A Randomized, Double-Blind, Placebo-Controlled Add-On Trial of Quetiapine in Outpatients With Bipolar Disorder and Alcohol Use Disorders

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***Objective:*** Alcohol dependence is extremely common in patients with bipolar disorder, and it is associated with unfavorable outcomes, including treatment nonadherence, violence, and cognitive impairment. However, few treatment trials have been conducted in this population. Quetiapine is an atypical antipsychotic medication that is used to treat the mood symptoms of bipolar disorder. In this study, the efficacy of quetiapine in reducing alcohol use and improving mood symptoms was assessed in patients with bipolar disorder and alcohol abuse or dependence.

***Method:*** One hundred fifteen outpatients with bipolar disorder and alcohol abuse or dependence were randomly assigned to 12 weeks of quetiapine (titrated to 600 mg/day) add-on therapy or placebo. Alcohol use and mood were assessed. The study was conducted from November 2002 to September 2005.

***Results:*** One hundred two participants (49% with bipolar I disorder, 82% depressed, and 97% with alcohol dependence) returned for at least 1 postbaseline assessment and were used in the random regression analysis. No statistically significant between-group differences were found on alcohol use measures or the Young Mania Rating Scale. However, based on a random regression analysis, scores on the Hamilton Rating Scale for Depression (HAM-D) decreased statistically significantly more in the quetiapine than in the placebo group during the trial ($p < .05$). The between-group difference was largely due to differences in HAM-D scores during the first 6 weeks of the trial, with the placebo group showing greater improvement during the second half of the trial.

***Conclusions:*** Quetiapine therapy was associated with a statistically significant decrease in depressive symptoms, but not alcohol use, in patients with bipolar disorder and alcohol dependence ($p < .05$).

***Trial Registration:*** clinicaltrials.gov Identifier: NCT00223249

*(J Clin Psychiatry 2008;69:701–705)*

*Received May 17, 2007; accepted Aug. 6, 2007. From the Department of Psychiatry (Dr. Brown and Ms. Garza) and the Division of Biostatistics of the Department of Clinical Sciences (Dr. Carmody), University of Texas Southwestern Medical Center, Dallas.*

*This study was funded by an investigator-initiated grant from AstraZeneca.*

*Dr. Brown has served as a consultant to Forest and Pfizer; has received grant/research support from AstraZeneca, Forest, and Bristol-Myers Squibb; and has served on the speakers/advisory board for Bristol-Myers Squibb. Ms. Garza and Dr. Carmody report no additional financial affiliations or other relationships relevant to the subject of this article.*

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Lifetime rates of substance use disorders of approximately 60% are reported in bipolar disorder patients.[1,2] When present in persons with bipolar disorder, substance use disorders are associated with decreased quality of life,[3] increased hospitalization,[4,5] increased violence,[6,7] and treatment nonadherence.[8] Thus, the treatment of patients with bipolar disorder and substance use disorders is a major public health concern. However, to our knowledge, only 1 randomized, controlled trial has studied patients with bipolar disorder and alcohol dependence.[9] In this report, valproate therapy was associated with a significant reduction in heavy drinking days.

Quetiapine is an atypical antipsychotic medication that is used to treat the mood symptoms of bipolar disorder. Our group has published 3 pilot studies using quetiapine in dual-diagnosis patients[10–12] that suggest reductions in alcohol and cocaine use. We now report findings from a randomized, double-blind, placebo-controlled trial of quetiapine in 115 outpatients with bipolar disorder and alcohol use disorders. The primary aim was to assess alcohol use between groups, with changes in mood and tolerability as secondary aims.

## METHOD

After giving institutional review board–approved written, informed consent, 115 patients were enrolled from the community. The study was conducted from November 2002 to September 2005. Inclusion criteria were bipolar I or II disorders confirmed by the Mini-International

Neuropsychiatric Interview (MINI), current alcohol abuse or dependence with use within 14 days of random assignment, age 18 to 55 years, and no changes in concomitant psychiatric medications within 7 days of random assignment. Exclusion criteria included history of cataracts or likely cataracts on ocular examination, history of hepatic cirrhosis or aspartate aminotransferase or alanine aminotransferase levels greater than 3 times normal, current active suicidal or homicidal ideation, current antipsychotic treatment, pregnancy or nursing, or contraindications to quetiapine therapy.

Mood was assessed with the 17-item Hamilton Rating Scale for Depression (HAM-D)[13] and Young Mania Rating Scale (YMRS),[14] alcohol craving with the Penn Alcohol Craving Scale (PACS),[15] alcohol use with the time-line follow-back method, and antipsychotic side effects with the Abnormal Involuntary Movement Scale (AIMS),[16] Simpson-Angus Scale (SAS),[17] and Barnes Akathisia Scale (BAS).[18] Participants returned at weeks 1 and 2 and then every 2 weeks thereafter, for mood, alcohol, and side-effects assessments.

Participants were randomly assigned to quetiapine or identical-appearing placebo add-on therapy in a double-blind fashion for 12 weeks. Quetiapine was titrated using the following schedule: baseline to week 1: 25 mg b.i.d., week 1 to 2: 50 mg b.i.d., week 2 to 4: 100 mg b.i.d., week 4 to 6: 200 mg b.i.d., week 6 to exit: 300 mg b.i.d. This slow titration was used because (1) we wanted to minimize side effects in a study with an add-on design in patients who did not necessarily have mood symptoms, (2) this titration was similar to that used in our open-label pilot study,[12] and (3) the study was initiated prior to the widespread use of rapid quetiapine titration.

### Statistical Analysis

Of the 115 patients enrolled, 102 returned for at least 1 postbaseline assessment and were used in the analysis. Demographic characteristics were compared between groups using 2-sided, independent sample t tests for continuous measures and $\chi^2$ tests for discrete measures.

A random regression analysis was performed on HAM-D and YMRS scores, PACS scores, days per week of alcohol use, drinks per week, and heavy drinking days per week. A declining-effects approach was used in which initial effect (baseline to week 1) and effect for the period from week 1 to week 12 were estimated (using measurements at weeks 1, 2, 4, 6, 8, 10, and 12).[19] The model contained terms for week, treatment group, treatment group-by-week interaction, and baseline level of the outcome measure as a covariate. Some models required a week-squared term to best fit the data. Drinking measures were transformed using the square root to create a more normally distributed measure. For each model, we examined the need for covariates such as age, gender, and marital status.

**Table 1. Demographic Information for the Intent-to-Treat Sample (N = 102) at Baseline**

| Characteristic | Quetiapine (N = 52) | Placebo (N = 50) | p Value |
|---|---|---|---|
| Age, mean (SD), y | 39.2 (10.4) | 37.5 (9.1) | .38 |
| Sex, N (%) | | | |
| Male | 35 (67.3) | 29 (58.0) | .33 |
| Ethnicity, N (%) | | | .61 |
| White | 34 (65.4) | 28 (56.0) | |
| African American | 13 (25.0) | 15 (30.0) | .03 |
| Hispanic | 3 (5.8) | 6 (12.0) | |
| Other | 2 (3.8) | 1 (2.0) | |
| Bipolar diagnosis, N (%) | | | .55 |
| Bipolar I disorder | 27 (51.9) | 23 (46.0) | |
| Bipolar II disorder | 25 (48.1) | 27 (54.0) | |
| Mood state, N (%) | | | .42 |
| Euthymic | 7 (13.5) | 3 (6.0) | |
| Depressed | 43 (82.7) | 41 (82.0) | |
| Manic | 1 (1.9) | 2 (4.0) | |
| Mixed | 1 (1.9) | 4 (8.0) | |
| Alcohol use diagnosis, N (%) | | | .58 |
| Dependence | 50 (96.2) | 49 (98.0) | |
| Abuse | 2 (3.8) | 1 (2.0) | |

Baseline-to-exit changes in PACS scores, number of drinks per week, number of drinking days per week, number of heavy drinking days per week, and number of drinks per drinking day were correlated with baseline-to-exit change in HAM-D and YMRS scores. For the AIMS, BAS, and SAS changes from baseline to exit, scores were compared for participants with baseline and at least 1 postbaseline observation (evaluable sample) between quetiapine and placebo groups using 2-sided, independent sample t tests. The last available observation was used in cases of early withdrawal.

## RESULTS

Participant characteristics are given in Tables 1 and 2. The 2 groups were similar in all characteristics examined, except baseline YMRS scores, which were statistically significantly higher in the placebo group ($t = 2.2$, $df = 100$, $p = .03$). (See Table 2.) Concomitant medications at baseline and changes in concomitant medication in the quetiapine and placebo groups are presented in Table 3. Baseline concomitant medications and changes in concomitant medications did not differ significantly between groups (Table 3).

Number of drinking days per week and number of heavy drinking days per week showed no significant differences between groups either initially (baseline to week 1: $F = 1.3$, $df = 1,165$; $p = .26$, $F = 0.18$, $df = 1,168$; $p = .68$, respectively) or subsequently (week 1 to week 12: $F = 0.03$, $df = 1,110$; $p = .86$, $F = 0.02$, $df = 1,129$; $p = .88$, respectively). Number of drinks per week also showed no significant differences between groups either initially ($F = 0.67$, $df = 1,168$; $p = .41$) or subsequently ($F = 0.01$, $df = 1,118$; $p = .92$). The random regression

**Table 2. Baseline and Exit Data for Quetiapine and Placebo Groups (N = 102)**

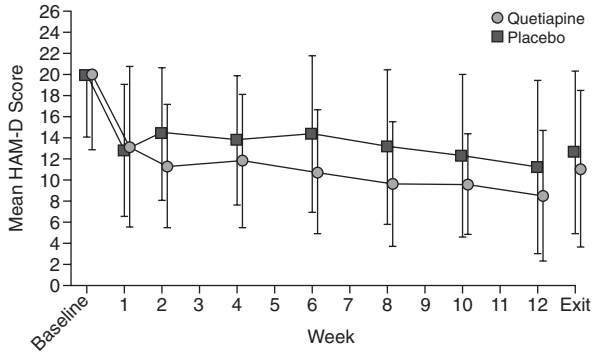
| | Quetiapine | | Placebo | |
|---|---|---|---|---|
| Outcome Measure | Baseline | Exit | Baseline | Exit |
| HAM-D score, mean ± SD | 19.8 ± 6.9 | 11.1 ± 7.4 | 20.0 ± 5.9 | 12.6 ± 7.7 |
| YMRS score,* mean ± SD | 9.5 ± 7.0 | 5.0 ± 3.8 | 12.3 ± 5.8 | 6.9 ± 5.8 |
| PACS score, mean ± SD | 19.6 ± 7.1 | 12.6 ± 7.8 | 18.3 ± 6.6 | 11.4 ± 9.1 |
| Drinking d/wk, mean ± SD | 3.3 ± 2.2 | 2.1 ± 2.1 | 3.0 ± 1.6 | 1.7 ± 2.1 |
| Drinks/wk, median | 15 | 6 | 17 | 3 |
| Heavy drinking d/wk, mean ± SD | 2.4 ± 2.3 | 1.2 ± 1.7 | 2.1 ± 1.6 | 1.0 ± 1.6 |

*p = .03 for between-group difference in baseline scores.
Abbreviations: HAM-D = 17-item Hamilton Rating Scale for Depression, PACS = Penn Alcohol Craving Scale, YMRS = Young Mania Rating Scale.

**Table 3. Percentage of Patients Receiving Concomitant Medications and Changes in Concomitant Medication During the Pilot Study (N = 102, intent-to-treat sample)**

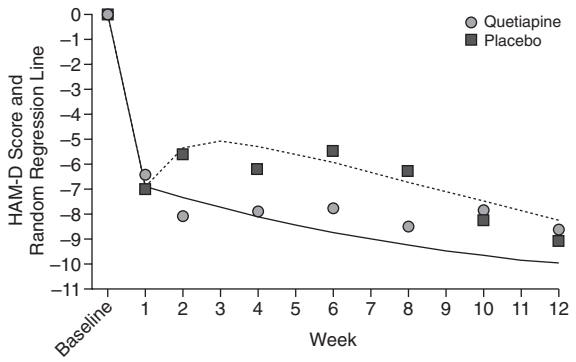
| Concomitant Medications | Quetiapine, % | Placebo, % |
|---|---|---|
| Lithium | 13.5 | 4.0 |
| Anticonvulsants | 25.0 | 18.0 |
| Antidepressants | 38.5 | 28.0 |
| Sedative/hypnotic/anxiolytics | 3.8 | 2.0 |
| No concomitant medications | 50.0 | 68.0 |
| 1 concomitant medication | 17.3 | 12.0 |
| 2 or more concomitant medications | 32.7 | 20.0 |
| Changes in Concomitant Medication During the Study | | |
| Increase in dose | 11.5 | 8.0 |
| Decrease in dose | 9.6 | 2.0 |
| Addition | 15.4 | 10.0 |
| Discontinuation | 17.3 | 14.0 |

**Figure 1. Mean (± SD) Total HAM-D Scores for Quetiapine and Placebo Groups**




Abbreviation: HAM-D = 17-item Hamilton Rating Scale for Depression.

**Figure 2. HAM-D Scores Showing Mean Change From Baseline for Quetiapine and Placebo Groups and Curve for Random Regression Model**




Abbreviation: HAM-D = 17-item Hamilton Rating Scale for Depression.

model for the PACS showed no significant treatment effect either initially (F = 0.12, df = 1,163; p = .73) or subsequently (F = 0.05, df = 1,104; p = .82). For both groups combined, there was a statistically significant initial improvement of 2.6 points by week 1 (F = 7.8, df = 1,135; p < .01) and an improvement of 9.6 points by the end of the study (week 12: F = 49.6, df = 1,106; p < .0001).

Figure 1 shows mean HAM-D scores, while Figure 2 shows mean change-from-baseline scores and the curve for the random regression model. A declining-effects random regression analysis of HAM-D showed an initial decline of 6.8 points in the quetiapine group and 6.6 points in the placebo group. Initial decline was statistically significant in both groups (p < .0001); however, the difference between groups was not significant (F = 0.02, df = 1,190; p = .88). For the period from week 1 to week 12, there was a statistically significant treatment group-by-week interaction (F = 4.2, df = 1,234; p = .04) favoring quetiapine. The random regression model showed that the quetiapine group improved more during the first half of the study, while the placebo group slightly worsened. During the second half of the study, the quetiapine group continued to improve; however, the placebo group improved at a faster rate, so that by week 12 the between-group difference in improvement was not statistically significant (F = 1.2, df = 1,43; p = .28). Specifically, in the quetiapine group, HAM-D scores improved from baseline levels by 8.7 points at week 6 and by 10.1 points at week 12. In the placebo group, improvement from baseline was only 5.9 points at week 6 (placebo patients actually worsened slightly from week 1 to week 6) and 9.0 points at week 12.

The declining-effects random regression model for YMRS showed a statistically significant initial improvement of 3.9 points in the quetiapine group and 2.6 points in the placebo group ($p < .0001$), with no significant difference between groups ($F = 2.6$, $df = 1,140$; $p = .11$). A statistically significant improvement over time was observed overall ($F = 18.1$, $df = 1,126$; $p < .0001$), but the change over time after week 1 did not differ between groups (group-by-week interaction, $F = 0.02$, $df = 1,126$; $p = .88$). Quetiapine patients improved by an estimated 6.0 points from baseline to week 12, while placebo patients improved by a numerically lesser amount of 4.9 points.

In the quetiapine group, change in PACS score ($r = 0.30$, $p = .03$), number of drinking days ($r = 0.30$, $p = .04$), and number of drinks ($r = 0.28$, $p = .04$) correlated statistically significantly with change in HAM-D scores, but no measures correlated significantly with change in YMRS scores. In the placebo group, only change in PACS scores and change in HAM-D scores were statistically significantly correlated ($r = 0.34$, $p = .02$).

Mean ± SD change from baseline to exit was not significantly different between groups for the AIMS scores ($1.2 \pm 14.0$ vs. $-2.9 \pm 24.6$, $p = .30$), BAS scores ($-1.3 \pm 2.2$ vs. $-1.7 \pm 2.0$, $p = .38$), or the SAS scores ($3.9 \pm 19.2$ vs. $1.7 \pm 31.5$, $p = .67$). Side effects in 5% or more of quetiapine or placebo groups, respectively, included sedation (24% vs. 16%), dizziness (22% vs. 0%), dry mouth (18% vs. 6%), fatigue (8% vs. 4%), and indigestion (6% vs. 0%).

## DISCUSSION

No significant between-group differences were found in alcohol use or craving. The negative finding on the primary aim of the study may be due to inclusion of participants with relatively low levels of baseline alcohol use. A recent study demonstrated that quetiapine was more effective in reducing alcohol use than placebo in patients with type B alcoholism—characterized by an early onset of alcohol use, depressive symptoms, the presence of other substance use, concomitant psychopathology, heavy drinking, and poor response to treatment—but not in patients with type A alcoholism—characterized by the later onset of alcohol use, few depressive symptoms, little use of other substances or concomitant psychopathology, more modest levels of alcohol use, and a better response to treatment.[20] Our study did not classify participants based on type A and B definitions, and we did not have the available data to identify patients with type B alcoholism in our sample based on a post hoc data analysis. Thus, we do not know how many, if any, of our participants had type B alcoholism. However, a post hoc analysis on number of drinks per week showed that a greater number of drinks per week at baseline, one feature of type B alcoholism, was associated with a larger treatment effect (results not shown). Given this relationship and the findings of the study by Kampman et al.,[20] future quetiapine research should focus on bipolar disorder patients with heavy baseline alcohol consumption.

A statistically significant reduction in HAM-D scores favoring quetiapine over placebo was found. The overall HAM-D decline during the study, using all data from weeks 1 to 12, was greater with quetiapine than placebo. The greater overall decline in HAM-D scores with quetiapine was largely due to decline in HAM-D scores with quetiapine during the first half of the study. During the second half of the study, the placebo group showed greater decline than the quetiapine group (Figure 2). Thus, the antidepressant effect of quetiapine appeared to occur early in treatment. It is not clear why the placebo group showed a greater decline in HAM-D scores than the quetiapine group during the second half of the study. The effect does not appear to be due to a worsening in depressive symptoms in the quetiapine group but may be due to attrition in the placebo group. Two prior studies have reported that quetiapine is more effective than placebo for bipolar depression.[21,22] The prior studies were of 8 weeks' duration, while the current study was of 12 weeks' duration. In the prior studies, depressive symptom improvement occurred early in treatment, with significant differences in remission detected by week 2 and some decrease in effect size, apparently due to placebo response in bipolar II patients, at week 8.[23] Our report suggests that quetiapine is effective for depressive symptoms of bipolar disorder even in patients with alcohol-related disorders and current alcohol use. This finding is clinically significant because of the high rates of alcohol-related disorders in patients with bipolar disorder.[1,2]

No significant differences were found on the YMRS, perhaps due to the low levels of baseline manic symptoms in this sample. Antipsychotic side effects were similar in the 2 groups.

The study has several strengths and limitations. The sample size was, to our knowledge, the largest of any clinical trial in patients with bipolar disorder and a substance use disorder. The randomized, placebo-controlled design is also a strength of the study. This is only the second placebo-controlled trial in patients with bipolar disorder and alcohol dependence. Limitations of the study include the relatively low mean level of alcohol use at baseline and the sample heterogeneity.

In summary, we found a statistically significantly greater reduction in HAM-D scores in patients with bipolar disorder and alcohol abuse or dependence given quetiapine than in those given placebo. The between-group difference was largely due to differences in HAM-D scores during the first 6 weeks of the trial, with the placebo group showing greater improvement during the second

half of the trial. By study end, the between-group difference in HAM-D score was not statistically significant. These findings support prior research suggesting that quetiapine is effective for bipolar depression and extend these findings to bipolar patients with active alcohol use. Perhaps due to inclusion of patients with modest levels of alcohol consumption at baseline, a significant effect of quetiapine was not found on alcohol use measures.

***Drug names:*** lithium (Eskalith, Lithobid, and others), quetiapine (Seroquel).

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