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A Double-Blind, Placebo-Controlled Trial to Assess the Efficacy of Quetiapine Fumarate in Very Heavy Drinking Alcohol-Dependent Patients

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Abstract

Background—Despite advances in developing medications to treat alcohol dependence, few such medications have been approved by the Food and Drug Administration. Identified molecular targets are encouraging and can lead to the development and testing of new compounds. Atypical antipsychotic medications have been explored with varying results. Preliminary results suggest that the antipsychotic quetiapine may be beneficial in an alcohol-dependent population of very heavy drinkers.

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Methods—In this double-blind, placebo-controlled trial, 224 alcohol-dependent patients who reported very heavy drinking were recruited across 5 clinical sites. Patients received either quetiapine or placebo and Medical Management behavioral intervention. Patients were stratified on gender, clinical site, and reduction in drinking prior to randomization.

Results—No differences between the quetiapine and placebo groups were detected in the primary outcome, percent heavy drinking days, or other drinking outcomes. Quetiapine significantly reduced depressive symptoms and improved sleep but had no effect on other nondrinking outcomes. Results from a subgroup analysis suggest that patients who reduced their drinking prior to randomization had significantly better drinking outcomes during the maintenance phase ($p < 0.0001$). No significant interactions, however, were observed between reducer status and treatment group. Finally, quetiapine was generally well tolerated. Statistically significant adverse events that were more common with quetiapine versus placebo include dizziness (14% vs. 4%), dry mouth (32% vs. 9%), dyspepsia (13% vs. 2%), increased appetite (11% vs. 1%), sedation (15% vs. 3%), and somnolence (34% vs. 9%).

Conclusions—This multisite clinical trial showed no efficacy for quetiapine compared with placebo at reducing alcohol consumption in heavy drinking alcohol-dependent patients.

Keywords

Alcohol Dependence; Quetiapine; Seroquel®; Medications Development; Alcohol Use Disorder

Introduction

Alcohol Use Disorder (AUD) is a devastating complex disease that affects 18 million Americans (de Wit, 2010). Misuse of alcohol is responsible for a wide range of medical, psychological, social, personal, and economic problems. The cost to U.S. society is staggering at over \$235 billion annually (Rehm, 2009). Encouragingly, advances have been made in treatment approaches, especially with the use of medications specifically targeting alcohol drinking.

Currently there are four medications approved by the Food and Drug Administration (FDA) for the treatment of alcohol dependence: disulfiram (Antabuse® or Antabus®), oral naltrexone (Revia® or Depade®), acamprosate (Campral®), and injectable naltrexone (Vivitrol®) (Johnson, 2007; Litten et al., 2005). Moreover, topiramate (Topamax®) has recently been shown to be effective in treating alcohol dependence in a multisite clinical trial (Johnson, et al., 2007). Although these medications demonstrate efficacy in clinical trials, not all patients experience a benefit. Therefore, new molecular targets are being identified, new drug compounds are being tested, and new clinical trials are under way (see ClinicalTrials.gov).

Several atypical antipsychotic medications have been explored to treat alcohol dependence. The results, so far, have varied. Clozapine (Clozaril® or Fazaclo®) has been reported to reduce alcohol use in people with schizophrenia and co-occurring alcohol use disorder (Brunette et al., 2006; Drake et al., 2000). Additionally, olanzapine (Zyprexa®) appears to reduce urge to drink in heavy social drinkers after exposure to alcohol cues (Hutchinson et al., 2001). In a 12-week pilot study, olanzapine reduced alcohol craving and consumption in alcohol-dependent patients, particularly in those with the 7-repeat allele of the D4 receptor gene (Hutchinson, et al., 2006). In contrast, Guardia and colleagues (2004) found no differences in drinking outcomes between olanzapine and placebo groups in alcohol-dependent patients. Aripiprazole (Abilify® or Aripiprex®) appears to interact with alcohol, increasing the sedative effects and decreasing the euphoric effects associated with it (Kranzler, et al., 2008). In addition, in a clinical laboratory setting aripiprazole appeared to

decrease drinking in alcoholic patients who were not seeking treatment (Voronin et al., 2008). In a small clinical trial, aripiprazole seemed to be as effective as naltrexone in treating alcohol-dependent patients (Martinotti et al., 2009). However, in a multicenter trial, alcohol-dependent patients had similar drinking outcomes when treated with either aripiprazole or placebo (Anton et al., 2008).

Quetiapine (Seroquel®) is another atypical antipsychotic medication that has shown promise for the treatment of alcoholism. Croissant and colleagues (2006) noted 8 out of 9 alcoholic patients treated with quetiapine for 2 to 7 months reported having abstained from drinking during this period. In addition, two retrospective studies reported a beneficial effect from quetiapine. Sattar and colleagues (2004) followed 9 alcohol-dependent patients treated with quetiapine for 3 months and observed increased days when they were abstinent from drinking as well as decreases in depression, anxiety, and insomnia. Monnelly and colleagues (2004) observed that quetiapine-treated alcohol-dependent patients with disturbed sleep had more days abstinent, took longer to relapse to drinking, and were hospitalized less often during a 1-year period than those who were not treated with quetiapine. In a 4-month open-label trial, Martinotti and colleagues (2008) reported that quetiapine decreased alcohol intake, alcohol craving, and psychiatric symptoms in alcoholic patients with a concurrent axis I disorder. Finally, Kampman and colleagues (2007) conducted a pilot 12-week, double-blind, placebo-controlled trial of quetiapine for the treatment of Type A and Type B alcoholism. In this trial, Type B alcoholics were characterized by an earlier onset of problematic drinking, more severe alcohol dependence, and greater psychopathology and were more treatment resistant than the Type A alcoholics. The Type B alcoholics treated with quetiapine experienced more days abstinent, fewer heavy drinking days, and less alcohol craving than placebo-treated Type B alcoholics. By contrast, there were no differences in drinking outcomes between quetiapine and placebo among Type A alcoholics.

Quetiapine is currently approved by the FDA for the treatment of schizophrenia, bipolar disorder, and depression. The preliminary results described above suggest that quetiapine may be beneficial as a treatment for alcohol dependency, particularly in a subpopulation of very heavy drinkers. This study was conducted to assess the efficacy and safety of quetiapine fumarate XR (extended-release) in very heavy drinking alcohol-dependent patients. A 3-month, multisite, placebo-controlled, double-blind trial was conducted assessing quetiapine's effects on drinking outcomes, alcohol-related consequences, quality of life, depression, anxiety, sleep, and safety.

Methods

Study Population

Randomized patients included 179 men and 45 women who were diagnosed with alcohol dependence (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [DSM-IV]; American Psychiatric Association 1994). Interested candidates responded by telephone to advertisements at 5 academic centers in the United States between December 2007 and May 2009. During the initial telephone call screen, a brief set of standardized questions about drinking were asked to preliminarily determine whether study drinking criteria could be met and to ascertain the caller's interest in study participation. Individuals who reported levels of drinking consistent with the study entry criteria were scheduled for an in-person screening visit, during which they received information on the study and signed an informed consent form (approved by each center's Institutional Review Board¹) before beginning any study assessments. Additionally, participants provided detailed baseline drinking histories,

¹Each center also obtained a certificate of confidentiality issued by NIAAA.

health screens, and psychosocial assessments. The screening visit required approximately 3.5 hours.

Key inclusion criteria included: 1) alcohol dependence, determined by DSM-IV criteria; 2) aged 18 to 64; 3) drank very heavily (10 or more drinks/drinking day for men; 8 or more drinks /drinking day for women) at least 40% of the days during the 60-day interval (days 31–90) before the in-clinic screening visit, with at least 1 day of very heavy drinking (10+/8+) occurring within the last 2 weeks before screening (a standard drink was 0.5 oz of absolute alcohol, equivalent to 10 oz of beer, 4 oz of wine, or 1 oz of 100-proof liquor) (Miller et al., 1991); 4) breath alcohol concentration (BAC) equal to 0.00 at informed consent signing; and 5) absolute neutrophil count (ANC) of $1.5 \times 10^9/L$ or greater.

Key exclusion criteria included: 1) past-year dependence on any psychoactive substances other than alcohol and nicotine, as defined by DSM-IV criteria; 2) positive urine screening test for benzodiazepines, cocaine, opioids, amphetamines, or methamphetamines; 3) participation in a behavioral and/or pharmacological intervention research study of alcoholism treatment within 3 months before signing the informed consent; 4) inability to be safely withdrawn from alcohol on an outpatient basis (e.g. CIWA-AR score ≥ 10); 5) lifetime diagnosis (using DSM-IV criteria) of panic disorder with or without agoraphobia, schizophrenia, bipolar disorder, or other psychosis, or a past-year diagnosis of major depression or eating disorder; 6) use of antidepressant medications within the last 30 days before randomization; and 7) use of anticonvulsants, hypnotics, antipsychotics, psychomotor stimulants, or antianxiety agents in the last 14 days before randomization. Additional exclusions addressed drug-specific safety precautions.

Assessments

Clinic assessments were carried out at screening, baseline, and at the beginning of weeks 2, 3, 4, 6, 8, 10, 12, and 13, while brief telephone assessments were conducted at the beginning of weeks 5, 7, 9, and 11 (Table 1). A follow-up telephone interview to assess safety and changes in drinking was done at week 17, approximately 4 weeks after the last in-clinic study visit. Patients were not allowed to complete in-clinic assessments unless they had a BAC of less than 0.02%.

Procedures

Patients who met eligibility criteria at the end of the screening visit were randomly assigned, within 28 days and in a 1:1 ratio, to receive either quetiapine or placebo. They were further stratified by clinical site and then by using an adaptive randomization procedure² based on two additional variables: reducer status (“reducers” vs. “nonreducers”) and gender. “Reducers” were defined as individuals who voluntarily reduced their average number of drinks per drinking day by at least 50% before randomization.³ Patients self-initiating withdrawal during the prerandomization period for which a medically managed withdrawal was indicated were still eligible to be placed in the “reducers” category for randomization purposes. The rationale for stratifying by reducer status lies with the observation that some of patients in alcohol clinical trials voluntarily reduce drinking around the time they make the decision to participate in a clinical trial, causing a rapid reduction in the average drinking level of the total sample before treatment is even initiated (Epstein et al., 2005). This prerandomization reduction in drinking has been linked to treatment outcome (Epstein et al.,

²The adaptive randomization procedure allocates treatment assignment based on the assignments and prognostic variable levels for all previously randomized patients (Efron, 1971; Pocock and Simon, 1975; Pocock, 1979; Stout et al., 1994)

³Percent reduction in drinks per drinking day = (average drinks/drinking day during the 31–90-day interval prior to the in-clinic screening – average drinks/drinking day during the 7-day period prior to randomization) / (average drinks/drinking day during the 31–90-day interval prior to the in-clinic screening visit) $\times 100$.

2005) and has been referred to as participation reactivity. The reasons for its occurrence are not understood but may include positive expectations on the part of the subject, or a response to the attention of the clinical staff and the initial assessments. This phenomenon introduces noise in the treatment outcome. Given the small effect sizes typical of many alcohol treatments, it can potentially make the detection of the “true” difference between the treatment and placebo groups more difficult. Consequently, reducer status was both included as a stratification variable to ensure equal proportions among the treatment groups and also as a covariate for primary and secondary drinking outcomes. Randomization was implemented via an interactive touch tone randomization system.

Study medication was dispensed to participants in a double-blind manner for three months. Quetiapine fumarate extended-release (Seroquel XR®, AstraZeneca, Wilmington, DE) was supplied in 50- and 200-mg tablets by AstraZeneca with identical matching placebos. During the first 2 weeks after randomization, the dose was titrated up to a target dose of 400 mg/day. This target dose was maintained during weeks 3 through 11, followed by a final week 12 during which the dose was tapered on a schedule as determined by the investigator. Patients assigned to the placebo group received matched placebo on the same schedule as the quetiapine group. Patients unable to tolerate the 400 mg/day target dose were allowed to continue in the study at a lower dose, with 50 mg/day as the lowest acceptable maintenance dose. Participants who discontinued medication during the study were allowed to remain in the study and participate in study assessments. The daily dose taken used to calculate drug compliance was derived by corroborating the patient's self-reported daily dose taken with the number of pills removed from the weekly blister pack returned by the patient at each clinic visit.

All participants received Medical Management (MM), a psychosocial, medically based, minimally intensive intervention developed and used in the COMBINE study (Pettinati et al., 2004). MM includes assessment of medication side effects, subject education about excessive drinking, abstinence advice, enhancement of adherence to the study medication regimen, support for recovery, and encouragement to attend mutual self-help groups such as Alcoholics Anonymous (AA). The first session was delivered at the randomization visit; with subsequent sessions occurring at each in-person clinic visit thereafter, for a total of 9 sessions. MM administrators were certified and monitored throughout the study.

Analytical Plan and Statistical Methods

The primary efficacy outcome measure was weekly percent heavy drinking days during study weeks 3 through 11. A grace period of the first 2 weeks was permitted for titration of quetiapine to the selected therapeutic target dose, while week 12 allowed for a dose tapering of quetiapine. Secondary outcome measures included other drinking measures (percent days abstinent, drinks per drinking day, drinks per day, percent very heavy drinking days, percent subjects abstinent, and percent subjects with no heavy drinking days) that were also assessed during weeks 3 through 11, as well as alcohol-related consequences, craving, depression, anxiety, poor sleep, and quality of life. Skewed variables were transformed as follows: log transformations (percent very heavy drinking days, HAM-A, MADRS, DSS score, weight, ALT, AST, GGT, triglycerides, and bilirubin), square root transformations (drinks per day, drinks per drinking day, DrInC, PSQI, and eosinophils), and inverse transformations (CIWA score).

The primary and secondary efficacy outcome measures were analyzed for a modified intention-to-treat (mITT) population that included only patients who took at least one dose of medication (n=218). Continuous outcomes were analyzed using a repeated-measures mixed model. A Toeplitz covariance matrix best fit the data and was used to model the correlations between repeated measures among participants. For descriptive purposes, least-

square means (LSMEANS), standard errors (SEs), and 95% confidence intervals (CIs) are presented for each treatment group and were derived from unadjusted models with untransformed outcome variables and two predictors: week and treatment group. Corresponding Cohen's d and p-values were derived from adjusted models with appropriately transformed outcome variables and included the covariates gender, clinical center, reducer status, and baseline value of the outcome. For continuous outcomes assessed at a single time (e.g., SF-12 outcomes), unadjusted means are presented on untransformed variables. Cohen's d and p-values were derived from general linear models (ANCOVAs) with appropriately transformed outcome variables and included the same covariate scheme as the repeated-measures models. Single dichotomous drinking outcomes (i.e., abstinence and no heavy drinking) were computed to reflect drinking across the entire maintenance period (weeks 3–11). Prevalence rates are presented on untransformed variables. Odds ratios (ORs) and p-values were derived from logistic regression models again with the same covariate scheme. However, since there was no variability in the baseline equivalents of these outcome variables, percent days abstinent was used as the covariate for the abstinence outcome, and percent heavy drinking days was used as the covariate for the no heavy drinking outcome. All baseline drinking measures were computed during a 60-day period (31–90-day interval before the first screening visit). Outcomes for laboratory tests, safety measures, and vital signs were analyzed using a similar approach as the primary and secondary outcomes, except that adjusted models did not include reducer status. To determine the effect of missing drinking data during treatment on the analyses involving drinking outcomes, all models were rerun where missing drinking data were imputed with the subject's average drinks per drinking day value during the prescreen period.

A series of exploratory subgroup analyses were conducted to explore whether a differential treatment effect existed as a function of subgroup status for the primary outcome, percent heavy drinking days, and other measures of drinking. Subgroups included: reducer status, Type B alcoholism, sleep quality, side effects, and quantity of medication taken. Based on criteria approximating that used by Kampman and colleagues (2007), patients were characterized as Type B alcoholics if they averaged 12 or more drinks per drinking day in the 30–90 day period prior to screening, if male (female patients, 10 or more drinks per drinking day); and had either of the following 2 criteria: (1) onset of alcohol dependence prior to age 25 or (2) a MADRS score ≥ 7 before entering the trial (at least mild depressive symptoms). Sleep quality subgroups were created using a baseline PSQI cutoff of ≥ 6 as indicative of poor sleep. The “side effects” subgroup was determined by the presence of at least 1 of the following AEs occurring during treatment: dizziness, dry mouth, dyspepsia, increased appetite, sedation, and somnolence. Quantity of medication taken was computed as the total mg taken during the maintenance period (weeks 3–11) and was dichotomized using a 12,600 mg cutoff (i.e., 50% of 25,200mg, the total possible amount of medication that could be taken during this 63-day period). LSMEANS and 95% CIs were estimated from unadjusted mixed models on untransformed outcome variables (weeks 3–11). Treatment by subgroup interactions were tested for significance via mixed models on appropriately transformed outcome variables adjusted for gender, reducer status, center, and baseline value of the outcome. For bivariate comparisons, treatment group differences were tested for significance by t-tests for independent samples (for normally distributed variables) or Wilcoxon signed-rank tests (for skewed variables); prevalence rate differences were tested for significance via chi-square or Fisher's exact tests. For all statistical tests, $p < .05$ (two-tailed) is considered statistically significant. It was estimated that a sample size of 230 patients was required to obtain 190 evaluable patients (95 per treatment group), yielding 80% power to detect a treatment effect (Cohen's $d = .41$) using a two-tailed t-test at a .05 significance level. Data were analyzed with SAS version 9.2 (SAS Institute, Inc., Cary, NC).

Results

Baseline

A total of 416 patients were screened in the clinic. Of these, 192 were excluded for either not meeting eligibility criteria or choosing not to participate. A total of 224 patients were randomized, but only 218 patients actually took the first dose of medication and returned to the clinic. Of these 218 patients (the mITT population), 28% were “reducers”—persons who voluntarily reduced their average drinks per drinking day by 50% during the 7-day period before randomization, compared with the 31-90-day interval before the first screening visit. Patients in the quetiapine and placebo groups had similar proportions of reducers (34.1% quetiapine vs. 24.8%; $p=.275$) and all other values on baseline characteristics (Table 2). Randomized patients were mostly male, white, middle-aged, and employed. On average, they drank very heavily (approximately 76% of their days), and thus greatly exceeded the minimum threshold for study entry (40%). GGT was also elevated at levels consistent with heavy drinking (Litten et al., 2010). Despite high levels of heavy drinking, patients on average had low levels of depressive symptoms (MADRS score = 5.3) and anxiety (HAM-A score = 4.1), though their mental health functioning was below normal (SF-12 mental health aggregate score = 45.7) and sleep quality was somewhat compromised (PSQI score = 7.1).

Overall compliance with study medication, defined as the proportion of total prescribed medication taken during the maintenance phase of the study (weeks 3–11), was 95.5% and was similar between the treatment groups (96.1% for the quetiapine group vs. 95.1% for the placebo group; $p=.468$). The average dose of medication taken was 350.7 mg but was significantly lower in the quetiapine group compared with the placebo group (327.7 mg vs. 370.4 mg, respectively; $p<.001$).

Research participation rate, defined as percent of patients with complete drinking data, was 83.5% overall and did not differ significantly by treatment group (85.7% for the quetiapine group vs. 81.4% for the placebo group; $p=.39$).

Main Outcomes

Regarding the primary efficacy outcome, percent days heavy drinking, there were no statistically significant differences between the unadjusted treatment group means during any weeks of the study maintenance phase (weeks 3–11) for either the placebo or the quetiapine group (all $p>.41$) (Figure 1). Fully adjusted mixed models further failed to show significant differences between the groups on this outcome ($p=.68$) and all of the seven secondary drinking outcomes during weeks 3–11, including percent days abstinent ($p=.86$), drinks per day ($p=.97$), drinks per drinking day ($p=.92$), percent heavy drinking days ($p=.68$), percent very heavy drinking days ($p=.66$), percent patients with no heavy drinking days ($p=.14$), and percent patients abstinent ($p=.77$) (Table 3). Results were similar when models were repeated with missing data imputed using baseline data (data not shown).

Treatment groups did not differ on a number of nondrinking outcomes, including alcohol-related consequences (DrInC) ($p=.42$), alcohol craving (PAC) ($p=.36$), and anxiety (HAM-A) ($p=.37$). Although depression, as measured by the MADRS, improved in both groups overall, the quetiapine group showed greater improvement during the course of the study ($p=.01$). Sleep quality (PSQI) also improved in both groups overall and was greater in the quetiapine-treated group ($p=.009$). The quality of life mental subscale (SF-12) improved from baseline in both groups, but there was no difference between the two groups ($p=.45$). There was no change in the physical subscale of the SF-12 for either of the two groups during treatment ($p=.88$). As expected, analysis of the DSS revealed a significant effect between treatment groups, with the quetiapine group showing higher levels of daytime somnolence, especially early in treatment ($p<.0001$).

Subgroup Analyses

Patients who reduced their drinking before randomization had significantly better drinking outcomes during the treatment maintenance phase on drinks per day, drinks per drinking day, percent days abstinent, and percent heavy drinking days (all reducer main effects, $p < .0001$) (Figure 2). There were, however, no significant interactions between reducer status and treatment group. Four additional subgroup analyses were performed on the primary outcome measure percent heavy drinking days (Figure 3). The quetiapine and placebo groups did not significantly differ as a function of Type B status or sleep quality (PSQI score) at baseline, or the presence of side effects or quantity of medication taken during treatment⁴ (p -values for all treatment by group interactions $> .05$).

Safety and Adverse Events

Analyses of two safety measures, the Barnes Akathisia Rating Scale (BARS) and the Simpson Angus Scale (SAS), revealed no overall or treatment-related increases in motor movement impairment or neuroleptic-induced Parkinsonian symptoms over the course of the study (BARS, $p = .49$; SAS, $p = .97$).

Laboratory values were measured prerandomization and throughout the trial. Over the course of the trial patients taking quetiapine gained more weight than those on placebo (3 lbs. vs. 0.7 lbs; $p = .006$) and had larger increases in triglycerides (26.4 mg/dl vs. 6.5 mg/dl, $p = .02$). Placebo patients had greater reductions in cholesterol compared with quetiapine patients (-9.8 mmol/L vs. 0.1 mmol/L, $p = .001$). Consistent with observed decreases drinking during the trial, GGT decreased in both groups, however the decrease was greater in placebo patients (-21 U/L vs. -14 U/L; $p < .04$). Glucose levels did not significantly differ between the two groups ($p = .65$), nor did any of the other laboratory measures assessed.

Treatment-emergent AEs that were reported to occur in at least 10% of study participants were dizziness, dry mouth, dyspepsia, increased appetite, sedation, and somnolence; all were significantly more frequent in the quetiapine group than the placebo group (Table 4). Twelve unique serious AEs occurred during the maintenance phase of the trial; 7 were for alcohol detoxification (quetiapine group=3 vs. placebo group=4). The remainder included suicidal ideation (quetiapine group), automobile accident (quetiapine group), falling accident (quetiapine group), pre-ventricular contractions (placebo group), and behavioral disturbance while intoxicated (placebo group).

Discussion

Compelling reasons exist to study the efficacy and safety of quetiapine as a treatment for alcohol-dependent patients. Quetiapine binds to multiple targets, including serotonin 5-HT_{1A}, 5-HT_{2A}, dopamine D₁ and D₂, histamine H₁, and adrenergic α_1 and α_2 receptors (AstraZeneca, 2010), which have been shown to alter alcohol-seeking and drinking behavior, primarily in animal models (Litten et al., 2005; Johnson, 2007). Moreover, recent preliminary clinical results have suggested that quetiapine reduces heavy drinking in alcohol-dependent patients (Ray et al., 2010). Nonetheless, in this multisite study, there was no effect on the primary outcome measure percent days heavy drinking. Similarly, there was no difference between quetiapine and placebo groups in other drinking outcome measures, including percent days abstinent, drinks per drinking day, and drinks per day, as well as the dichotomous measures—percent of subjects with no heavy drinking days and percent of subjects who are abstinent. Moreover, the negative result with the primary outcome measure

⁴A follow-up analytic approach using Loess curves indicated no difference between quetiapine and placebo groups on the primary outcome across the entire continuous range of quantity of medication taken (data not shown).

was not moderated by quantity of medication taken, the presence of side effects, nor the presence of sleep disturbances. The negative findings in this study, in contrast with promising earlier studies, demonstrate the complexity of biological mechanisms associated with alcohol addiction in humans, as well as the need for adequately powered studies.

Quetiapine has been approved to treat depression in bipolar patients and also has been shown to improve sleep disturbances (Endicott et al., 2008; Robert et al., 2005). In the current study, quetiapine also significantly reduced depressive symptoms and improved sleep compared to placebo, although both depression and sleep scores were near normal in patients at baseline (Tables 2 and 3). This was similar to the results reported by Kampman et al. (2007) in a study of quetiapine for alcohol dependent patients. In their study, depression and anxiety scores were also in the normal range at baseline and during treatment, yet a significant decrease in depression and anxiety was observed during treatment. In other nondrinking outcomes, quetiapine failed to improve anxiety, alcohol craving, quality of life, and alcohol-related consequences (Table 3).

So far, the alcohol medications that have shown effectiveness do not work in all individuals, only in subgroups. A previous study by Kampman and colleagues (2007) suggested that the immediate-release formulation of quetiapine may be beneficial for Type B alcoholics. In that study, Type B participants exhibited very heavy drinking at baseline (average 20 drinks/drinking day), and at least one of the following: early onset of alcohol dependence, depression, or antisocial personality disorder. Approximating this definition of Type B alcoholism, we conducted a subgroup analysis, but found no significant differential treatment effect for quetiapine above placebo as a function of Type B status on the primary outcome drinking measure. One reason for this lack of concordance between the Kampman et al. study and our study may be that our Type B definition did not include antisocial personality disorder since these data were available in our study. Another more likely reason may have to do with study population differences between the two studies. For example, in the Kampman et al. study, 49 percent of study participants had a comorbid psychiatric illness, including major depression, posttraumatic stress disorder (PTSD), or other anxiety disorders. While quetiapine has been shown to improve many symptoms of these disorders (Endicott et al., 2008; Martinotti et al., 2008; Croissant et al., 2006; Robert et al., 2005), our study recruited very heavy drinking alcohol-dependent patients without serious psychiatric comorbidity, a design factor that may account for the treatment effect differences between our study and that of Kampman and colleagues (2007). Even though we excluded people with major psychiatric disorders in our study, we expected patients with chronic very heavy levels of drinking at baseline would also concurrently report elevated levels of anxiety, depressive symptoms, and poor sleep. This hypothesis is supported by recent theories of allostasis and addiction—that long-term drinking results in a homeostatic dysregulation, resulting in negative emotion (e.g., dysphoria, depression, irritability, and anxiety) and an elevation of the reward set point (Koob, 2008; Koob and Le Moal, 2006). However, counter to our assumptions, despite consuming very large amounts of alcohol for an extended period of time, these study participants on average reported normal levels of levels of anxiety and depression, and only modest sleep disturbances at baseline. It is likely that quetiapine's efficacy in reducing drinking observed in previous studies was due to the amelioration of psychiatric symptoms experienced by those patients. Our failure to find an effect for quetiapine in this study may be in part due to the high functionality and lack of psychiatric symptoms of the study population. An argument can be made that if depression, anxiety, and sleep disturbance mediate or moderate the effects of quetiapine on drinking outcome, larger treatment effects might potentially be found in a population with higher pathology of these factors. We cannot discount this possibility and recommend that future studies of quetiapine test its efficacy in comorbid alcohol dependent populations.

During the past 20 years, the majority of patients recruited for alcohol clinical trials have been required to be abstinent for at least 3 to 4 days before randomization. However, in several recent alcohol trials, patients were allowed or even required to drink right up to randomization (Garbutt et al., 2005; Johnson et al., 2007). Considerable discussion has ensued among alcohol researchers as to whether a relapse prevention study model, where pre-randomization abstinence is required, versus a more naturalistic cessation-initiation model is more appropriate and optimally sensitive for proof of concept testing of new medications. Each of these models has different practical and theoretical merits. Abstinence or significant reduction in drinking before randomization appears to influence treatment outcome. For example, Epstein and colleagues (2005) showed that patients who cut back on drinking before treatment had better drinking outcomes. However, as treatment outcome improves in the placebo group, it may become more difficult to demonstrate a significant medication treatment effect, as observed in depression and schizophrenia studies (Kemp et al., 2010; Kirsch et al., 2008; Mallinckrodt et al., 2010; Walsh et al., 2002). Epstein et al (2005) provided several explanations for this self initiated reduction in drinking prior to treatment. The reduction in drinking may be prompted by merely (1) viewing an advertisement, (2) discussing the decision to seek help with individuals within in the same social network, or (3) the realization of the extent and severity of the drinking problem by acknowledging and discussing one's drinking with another individual (Epstein et al., 2005; Sobell et al., 2003). In this study, we elected to allow patients to regulate their own drinking before randomization. We then evaluated analytically whether those patients who reduced their drinking before randomization had better treatment outcomes, and whether prerandomization “reducer status” would increase the sensitivity to detect a treatment effect. Approximately 30% of the patients reduced their drinks per drinking day by at least 50% before starting study medication. These “reducers,” of whom 44% were abstinent one week before randomization, had better treatment outcomes on all drinking measures, including drinks per drinking day, percent days abstinence, drinks per day, and percent heavy drinking days than the “nonreducers” (Figure 2). Similar results were also obtained when drinks per day and number of heavy drinking days were the endpoints used to define reducers and nonreducers (data not shown). Interestingly, however, there was no reducer by treatment interaction, suggesting that neither of the prerandomization drinking models had a clear advantage in detecting a treatment effect.

At present, there is no single medication that decreases alcohol use in all alcohol-dependent individuals. Although disulfiram—a medication that causes aversive symptoms when taken with alcohol—should have high efficacy among patients who take the therapeutic dosage, disulfiram has had limited success in treatment due to poor compliance (Allen & Litten, 1992; Jorgensen et al., 2011). Development of more effective medications may, in part, require a better understanding of brain circuits and mechanisms underpinning alcohol addiction, as well as a more accurate delineation of its subtypes. In essence, a more targeted approach may be required to foster the creation of medications that will be truly efficacious. For now, alcohol pharmacotherapy trials need to focus on subpopulations that appear most likely to respond to medication. In this study, we hypothesized and recruited an alcohol-dependent population of very heavy drinkers as the cohort who would most likely respond to quetiapine. Even though the primary analyses were negative, further secondary analyses will be continued, exploring various subgroups that might benefit from quetiapine. For the present, however, we cannot recommend the use of quetiapine as a medication to treat alcohol-dependent individuals.

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Figure 1.
 Percent Heavy Drinking Days during Treatment
 Means are LSMEANS obtained from a mixed model that includes only study week and treatment group. Error bars are 95% confidence intervals.
 All $p > .41$, except Week 1 ($p = .05$).
 Note: treatment*week interaction ($p = .323$).

Figure 2.

Drinking Outcomes during Treatment (Weeks 3–11) by Prandomization Reducer Status Means are LSMEANS from unadjusted mixed models on nontransformed outcome variables (Weeks 3–11). Error bars are 95% confidence intervals.

P-values for main effects and interactions are from mixed models on appropriately transformed outcome variables adjusted for gender, reducer status, center, and baseline value of the outcome. All main effects for Reducer Status are significant ($p < .0001$).

Figure 3.**Additional Subgroup Analyses**

Means are LSMEANS from unadjusted mixed models on nontransformed outcome variables (Weeks 3–11). Error bars are 95% confidence intervals.

P-values for interactions are from mixed models on appropriately transformed outcome variables adjusted for gender, reducer status, center, and baseline value of the outcome.

^aThe variable “side effects” was determined by the presence of at least 1 of the following adverse events: dizziness, dry mouth, dyspepsia, increased appetite, sedation, and somnolence.

^bThe cut-off, 12,600mg, is 50% of 25,200mg, the total possible amount of medication that could be taken during the maintenance period (weeks 3–11).

^cA score of >5 is indicative of poor sleep quality.

Table 1**Assessment Schedule**

Assessment & Source	Schedule (weeks)^a
Adverse events	1 & 2 (daily telephone), weekly after
Barnes Akathisia Rating Scale (BARS) (Barnes, 1989)	SCR, 2, 3, 6,13
Breath alcohol concentration (BAC)	SCR, BL, 2, 3,4, 6, 8,10,12,13
Blood chemistries ^b	SCR, 4, 8,12
Clinical Institute Withdrawal Assessment for Alcohol - Revised (CIWR-AR) (Sullivan et al., 1989)	SCR, BL, 1 & 2 (daily telephone), weekly after
Concomitant medications	BL, 1 & 2 (daily telephone), weekly after
Daytime Somnolence Scale ^c (DSS)	BL, 1 & 2 (daily telephone), weekly after
Drinker Inventory of Consequences (DrInC) (Miller, 1995)	BL, 6,12
Electrocardiogram (ECG)	SCR, 13
Fagerström Test for Nicotine Dependence (Heatherton et al., 1991)	BL, 6,12
Family Tree Questionnaire ^d (Mann et al., 1985)	BL
Hamilton Anxiety Scale (HAM-A) (Guy, 1976)	BL, 4, 6, 8,10,12
Height	SCR
Hematology	SCR, 4, 8,12
Locator form	SCR
Medical history	SCR
Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979)	SCR, BL, 4, 6, 8,10,12
Penn Alcohol Craving Scale (PACS) (Flannery et al., 1999)	BL, 4, 6, 8,10,12
Physical exam	SCR, 13
Pittsburgh Sleep Quality Index (PSQI) (Buysee et al., 1989)	BL, 4, 8,12
Prior medications (past 30 days)	SCR
Quality of Life Short Form 12 (SF-12) (Szabo, 1996)	BL, 12
Simpson-Angus Scale ^e (SAS) (Simpson and Angus, 1970)	SCR, 10,13
Services utilization	BL, 1, 2, 3,4, 6, 8,10,12,13
Structured Clinical Interview for the DSM-IV (SCID) Module E ^f (First et al., 1996)	SCR
Suicidality monitoring	1 & 2 (daily telephone), 5, 7, 9,11
Thoughts About Abstinence Scale (Marlatt et al., 1988; Hall et al., 1990)	BL, 6,12
Time-Line Follow-Back (Sobell and Sobell, 1992) ^a	SCR, BL, 2, 3,4, 6, 8,10,12,13
Treatment compliance	2, 3,4, 6, 8,10,12,13
Urine drug screen	SCR, BL, 4, 8,12,13
Urine pregnancy test	SCR, BL, 4, 8,12
Vital signs (blood pressure, heart rate, and respiration rate) and weight	SCR, BL, 2, 3,4, 6, 8,10,12,13

SCR=screening; BL=baseline

^a All assessments were conducted in the clinic, except for weeks 5, 7,9,11 which were conducted via telephone. Where noted, daily telephone calls were also use for some safety assessments during the first 2 weeks of titration.

^b Blood chemistries were assessed after ≥ 2 hours of fasting; repeated after ≥ 8 hours if blood glucose or triglycerides were elevated.

^c DSS was adapted from the Stanford Sleepiness Scale (Hoddes et al, 1973).

^d Family Tree Questionnaire assesses family history of alcohol problems.

^e SAS assesses neuroleptic-induced parkinsonism.

^f SCID Module E assesses alcohol dependence. gTLFB assesses daily drinking for the past 90 days at baseline and since the last assessment during treatment.

Table 2

Baseline Characteristics of Participants (Modified Intention-to-Treat [mITT] Population)

	Placebo (n=113)			Quetiapine (n=105)			p-value ^a
	n	Mean or %	SD	n	Mean or %	SD	
Demographics							
Age	113	45.5	9.8	105	45.4	9.3	0.885
Male	87	77.0		88	83.8		0.206
Employed	84	74.3		73	69.5		0.429
Married	53	46.9		38	36.2		0.109
Education (> high school)	67	59.3		58	55.2		0.545
Race/Ethnicity							0.200
White	88	77.9		91	86.7		0.091
Black	18	15.9		12	11.4		0.335
Hispanic	4	3.5		2	1.9		0.684
Other	3	2.7		0	0.0		0.248
Self-Reported Alcohol Consumption^b							
Drinks per day	113	12.9	4.5	105	14.4	6.3	0.105
Drinks per drinking day	113	14.4	5.0	105	16.1	7.0	0.111
Percent days abstinent	113	9.3	14.4	105	9.6	15.6	0.889
Percent heavy drinking days	113	86.9	16.1	105	89.1	16.5	0.325
Percent very heavy drinking days (8+/10+)	113	75.1	23.2	105	76.5	23.8	0.584
Other Substance-Related Indicators							
GGT (U/L)	113	82.0	127.7	104	90.1	123.7	0.185
Drinker Inventory of Consequences (DInC) score (45-item)	113	39.7	19.1	105	41.5	21.4	0.758
Penn Alcohol Craving Scale (PACS) score	113	17.7	6.3	105	18.0	6.6	0.684
Age onset alcohol dependence	111	30.4	11.9	104	27.8	10.5	0.087
Age onset regular drinking	113	21.2	8.2	105	20.5	7.3	0.853
Type B alcoholism	42	37.2		34	32.4		0.459
Parental problematic drinking	68	60.2		57	54.3		0.380
Drinking goal: permanent abstinence ^c	42	38.2		51	50.5		0.072

	Placebo (n=113)			Quetiapine (n=105)			p-value ^a
	n	Mean or %	SD	n	Mean or %	SD	
Current smoker ^d	58	51.3		61	58.7		0.279
Marijuana use ^e	15	13.3		19	18.1		0.327
Psychiatric Characteristics^f							
Montgomery-Asberg Depression Rating Scale (MADRS) score	113	5.8	5.7	105	4.8	6.5	0.093
Pittsburgh Sleep Quality Index (PSQI) score	108	7.1	3.6	101	7.0	4.0	0.575
Daytime Somnolence Scale (DSS) score	112	1.2	1.1	104	1.1	1.0	0.832
Hamilton Anxiety (HAM-A) score	113	4.0	3.3	105	4.1	4.3	0.686
SF-12 Mental Aggregate score	113	45.9	10.9	105	45.4	11.7	0.803
SF-12 Physical Aggregate score	113	50.6	9.3	105	51.1	8.7	0.536
Clinical Institute Withdrawal Assessment of Alcohol (CIWA) score	111	1.7	1.9	102	2.2	2.5	0.285

^a Group mean differences are tested for significance by t-tests for independent samples or Wilcoxon signed-rank tests. Group prevalence rate differences are tested for significance via chi-square or Fisher's exact tests.

^b Reflects mean values during the 60-day period (days 31–90) before screening.

^c Denominator sample size is 110 for the placebo and 101 for the quetiapine group.

^d Denominator sample size for the quetiapine group is 104.

^e Marijuana use based on positive urine drug screen.

^f Scale range and interpretive values are as follows:
MADRS: (0–60) 0–6 normal/recovered; 7–19 mild depression; 20–34 moderate; 35–60 severe
PSQI: (0–21) ≥6 poor sleep quality
DSS: (0–4) 0 alert/well-rested; 1 high-level functioning/not peak, 2 awake/not fully responsive, 3 somewhat foggy, 4 very tired, fighting sleep
HAM-A: (0–56) <17 mild anxiety; 18–24 mild-moderate; 35–30 moderate-severe
SF-12: (T-score 0–100) 50 normal functioning
CIWA: (0–70) ≥10 indicative of alcohol withdrawal

Table 3

Treatment Outcomes: Differences Between Placebo and Quetiapine

	Placebo			Quetiapine			p-value
	LSMEAN ^a	SE	95% CI	LSMEAN	SE	95% CI	
Drinking Outcomes							
Drinks per day	4.4	0.41	3.6–5.2	4.3	0.43	3.5–5.2	0.972
Drinks per drinking day	6.3	0.45	5.4–7.1	6.2	0.47	5.3–7.1	0.924
Percent heavy drinking days	37.9	3.34	31.3–44.5	37.1	3.50	30.2–44.0	0.681
Percent very heavy drinking days (8+/10+)	18.8	2.44	14.0–23.6	16.5	2.56	11.5–21.6	0.657
Percent days abstinent	47.1	3.54	40.1–54.0	49.5	3.71	42.2–56.8	0.858
	%	n	denom	%	n	denom	OR(95%CI) ^b
Percent subjects abstinent	10.6	12	113	11.8	12	102	1.2 (0.5–3.0)
Percent subjects with no heavy drinking days	21.2	24	113	16.7	17	102	1.8 (0.8–3.9)
Non- Drinking Outcomes							
Montgomery-Asberg Depression Rating Scale (MADRS) score	4.1	0.37	3.4–4.9	2.8	0.39	2.0–3.5	0.011
Pittsburgh Sleep Quality Index (PSQI) score	5.1	0.26	4.6–5.6	4.1	0.27	3.6–4.6	0.009
Daytime Somnolence Scale (DSS) score	0.6	0.06	0.5–0.7	0.9	0.06	0.8–1.0	0.000
Penn Alcohol Craving Scale (PACS) score	12.8	0.60	11.6–14.0	12.1	0.63	10.8–13.3	0.363
Drinker Inventory of Consequences (DInC) score	22.5	1.78	19.0–26.0	18.5	1.87	14.9–22.2	0.417
Hamilton Anxiety (HAM-A) score	3.0	0.24	2.5–3.4	2.4	0.26	1.9–2.9	0.371
SF-12 Physical Aggregate score ^c	50.6	0.93	48.8–52.4	51.0	0.82	49.3–52.6	0.877
SF-12 Mental Aggregate score ^c	50.7	1.08	48.6–52.8	51.5	1.12	49.3–53.8	0.450

Abbreviations: LSMEAN = least square means; SE = standard error; 95% CI = 95% confidence interval; |d| = absolute value of Cohen's d; OR = odds ratio; n = numerator sample size; denom = denominator sample size.

^aUnless otherwise noted, LSMEAN are based on the outcome variable (untransformed) and were obtained from a mixed model that includes only study week and treatment group. Corresponding Cohen's d and p-values are based on the outcome variable (appropriately transformed) and were obtained from a mixed model that also includes the covariates gender, clinical center, reducer status, and the baseline value of the outcome.

^bOdds ratios and corresponding p-values are derived from a logistic regression model that includes the covariates gender, clinical center, reducer status, and baseline drinking. For the outcome percent subjects abstinent, percent days abstinent was used as the baselinedrinkingcovariate. For the outcome percent heavy drinking days, percent heavy drinking days was used as the baseline drinking covariate.

^c For the SF-12 outcomes, unadjusted means are presented on the untransformed variables. Correlates of Cohen's d and p -values are based on the outcome variables (appropriately transformed) and were obtained from a general linear model that includes the covariates gender, clinical center, reducer status, and the baseline value of the outcome.

Table 4Statistically Significant Adverse Events Occurring in $\geq 10\%$ of the Participants

	Number (%) of Participants with Adverse Events		
Adverse Event	Quetiapine	Placebo	p-value ^a
Dizziness	15 (14)	5 (4)	0.017
Dry Mouth	34 (32)	10 (9)	<.0001
Dyspepsia	14 (13)	2 (2)	0.001
Increased Appetite	12 (11)	1 (1)	0.001
Sedation	16 (15)	3 (3)	0.001
Somnolence	36 (34)	10 (9)	<.0001

^a Group prevalence rate differences are tested for significance via chi-square or Fisher's exact tests.