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A Double-Blind, Placebo-Controlled Pilot Trial of Quetiapine for the Treatment of Type A and Type B Alcoholism

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Abstract

Background—Atypical antipsychotics may be useful in the treatment of alcohol dependence. Human trials suggest that atypical antipsychotics may reduce alcohol craving and consumption, especially among patients with comorbid psychopathology. Therefore, these medications may be more useful for treating more severely affected alcoholics, such as patients with Type B alcoholism. Type B alcoholics are characterized by an early age of onset of problem drinking, high severity of alcohol dependence, increased psychopathology, and treatment-resistance. Quetiapine is an atypical antipsychotic with a favorable side effect profile, and may be a promising medication for the treatment of alcohol dependence, particularly Type B alcoholism.

Methods—Male and female alcoholics (33 Type A and 28 Type B) were included in a 12-week, double-blind, placebo-controlled trial. After detoxification, patients were randomized to receive quetiapine (n = 29), 400 mg/d at bedtime, or placebo (n = 32). The primary outcome measure was the quantity and frequency of alcohol consumption, measured by the timeline follow back.

Results—Forty-seven patients (77%) completed the trial, with no significant between-group differences in treatment retention. Nine quetiapine-treated patients (31%) maintained complete abstinence compared with 2 placebo-treated patients (6%) ($\chi^2 = 6.3$, $P = 0.012$). There was a significant interaction between quetiapine and alcoholic subtype. As predicted, quetiapine- versus placebo-treated Type B alcoholics had significantly fewer days of drinking and fewer days of heavy drinking. Alcohol craving was also significantly reduced in quetiapine-treated compared with placebo-treated Type B alcoholics. Among Type A alcoholics, quetiapine provided no advantage over placebo in improving drinking outcomes.

Conclusions—Quetiapine may be effective for the treatment of alcohol dependence, particularly in the more complicated Type B, early-onset alcoholics.

There are now 4 medications approved for treating alcohol dependence in conjunction with psychosocial treatment. However, disulfiram is consistently efficacious only when compliance is regulated, and the effect sizes published for oral naltrexone and acamprosate are small to medium.^{1–3} Time will tell about the latest medication, a long-acting (30-day) injectable naltrexone that has recently been made commercially available to clinicians (June

2006). Therefore, researchers continue to look for more effective medications to treat this serious illness.

One novel approach to improving medication efficacy has been to identify alcoholic subtypes that may respond preferentially to a specific medication. One such subpopulation that we have been interested in are patients with Type B alcoholism, as described by Babor et al.⁴ Type B alcoholics are characterized by an early age of onset of alcohol problems, high severity of dependence, polydrug use, a high degree of concomitant psychopathology, and a poor prognosis after alcoholism treatment.⁴⁻⁶ In contrast, Type A alcoholics are characterized by a late onset of problem drinking, few childhood risk factors, low severity alcohol dependence, little drug use, few alcohol-related problems, little concomitant psychopathology, and a relatively promising prognosis with traditional alcoholism treatment.

Pettinati et al⁷ found that Type A alcoholics had an exceedingly high rate of total abstinence during a 14-week-trial of counseling plus 200 mg/d of sertraline (64% abstinent) compared with counseling plus placebo (<10% abstinent). In contrast, sertraline showed no benefit among the Type B alcoholics. In this trial, the Type B alcoholics had worse drinking outcomes with sertraline compared with placebo, although these differences were not statistically significant. Kranzler et al⁶ reported a similar lack of efficacy with counseling plus fluoxetine treatment among Type B alcoholics. These results suggest that patients with Type B alcoholism respond poorly when an SSRI is added to counseling, and may benefit from a pharmacotherapy that offers more than simply blocking serotonin reuptake.

Pettinati et al⁷ also reported in their study that, through empirical analyses, there were 4 of 13 measures used to retrospectively classify patients as Type A or B that were strong, independent predictors of alcoholic subtype: (1) the average number of drinks per drinking day in the 3 months before entering treatment, (2) if the person reported an onset of problem drinking before age 25 years (as determined by the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [DSM-IV]* [SCID]), (3) a Hamilton Depression Rating Scale (HAM-D)⁸ score greater than 13 at the start of treatment, or (4) meeting 3 or more childhood criteria for Antisocial Personality Disorder. These 4 empirically derived predictors proved to be easily obtainable at pretreatment, which suggested that patients might be easily subtyped as A or B before randomization. In addition, because one of the 4 predictors is “early onset of alcohol problems,” there is a high correlation (overlapping but not identical) between the 2 most frequently cited alcoholic subtypes: early versus late onset, and Type A versus B.

The dopamine and serotonin neurotransmitter systems have been frequently implicated in the neurobiology of alcohol dependence.^{9,10} The dopaminergic system has been described as the principal neurotransmitter associated with reward from alcohol.¹¹⁻¹³ Medications that are able to block dopamine receptors may be able to reduce alcohol craving and assist patients in achieving abstinence from alcohol.¹⁴⁻¹⁶ The serotonergic system, which modulates dopamine release, has also been associated with drinking behaviors.^{9,17}

Atypical antipsychotics target both the dopamine and the serotonin systems. In naturalistic observational studies, atypical antipsychotics have shown benefit in reducing drinking among alcohol dependent patients. In the few randomized, controlled clinical trials conducted, results have been more mixed.^{16,18} Atypical antipsychotics also seem to be useful in alcohol-dependent patients with concomitant psychiatric illness.¹⁹ Clozapine, in particular, has been noted to be associated with reduced substance abuse among patients with drug dependence and schizophrenia.²⁰⁻²² The benefit of atypical antipsychotics in patients with alcohol dependence and concomitant psychiatric illness suggests that these

medications may be particularly useful in alcohol-dependent patients with more associated psychopathology, such as Type B alcoholics.

Quetiapine is licensed for the treatment of schizophrenia and for acute bipolar mania. It has both dopamine antagonist properties as well as affinity for 5-hydroxytryptamine type 2 (5HT₂) receptors and is similar to clozapine in its receptor activity profile.²³ In addition, like clozapine, it seems to be useful in reducing drug and alcohol use among alcoholics and drug-dependent patients with comorbid psychiatric illness.^{24,25} Quetiapine has a good safety profile compared with conventional antipsychotics, as well as other atypicals.^{26,27} Based on its activity at both dopaminergic and serotonergic receptors, and its excellent safety profile, quetiapine is a promising pharmacotherapy for treating alcoholics. It may be particularly well suited for treating the more severely addicted, comorbidly complicated, Type B alcoholics. This trial was intended to obtain data regarding the safety, tolerability, and potential efficacy of quetiapine in both Type A and Type B alcoholics before conducting a larger controlled clinical trial.

MATERIALS AND METHODS

Patients

Eighty-seven patients signed consent and entered screening. Eleven patients left treatment during screening, 5 withdrew consent, and 6 were lost to follow-up. Fifteen patients did not meet inclusion criteria and were excluded. Eight were excluded for medical reasons (7 had hepatitis C, and one had severe thyroid disease). The remaining 7 patients were excluded for various reasons, including 4 patients excluded because of other drug dependencies, one failed to meet minimum drinking criteria, one was mandated to treatment, and one had severe bipolar disorder.

Sixty-one outpatients (33 Type A and 28 Type B) were enrolled in a 12-week, double-blind, placebo-controlled, parallel group, randomized trial of quetiapine 400 mg/d for alcohol dependence. Study participants were recruited through community referrals and public announcements in the local media. Eligible patients had to be at least 18 years and meet *DSM-IV* criteria for alcohol dependence. In addition, in the 90 days before the trial, patients had to have a consecutive 30-day period in which they drank at least 48 standard drinks and must have had at least 2 days of heavy drinking (defined as 5 or more drinks for men and 4 or more drinks for women). Before receiving study medication, patients needed to be abstinent from alcohol and free from significant alcohol withdrawal symptoms, as defined by a minimum of 3 consecutive days of abstinence before the start of the study medication and a Clinical Institutes Withdrawal Assessment for Alcohol²⁸ score less than 8 on the day of randomization. Psychiatric diagnoses were obtained by master's level clinicians using the SCID.²⁹ Patients were not included if they had a current *DSM-IV* diagnosis of any psychoactive substance dependence other than alcohol or nicotine. Patients were excluded for evidence of current use of other psychoactive drugs as determined by a positive urine drug screen. Patients could not be taking psychotropic medications or have evidence of current severe psychiatric symptoms as determined by a review of the SCID and a clinical interview conducted by a board-certified psychiatrist (K.K.). Medical screening included a complete medical history and physical examination conducted by a certified nurse practitioner. Baseline laboratory testing included a chemistry screen, complete blood cell count, urinalysis, urine pregnancy testing (for women), and a 12-lead electrocardiogram. Patients could not have severe medical or physical illnesses. Patients could not have hepatitis C or active hepatitis A or B, and could not have significant hepatocellular injury as evidenced by elevated aspartate aminotransferase or alanine aminotransferase levels greater than 4.5 times the upper limit of normal. Patients were excluded for a history of seizures or severe head trauma. Female patients who were pregnant, nursing, or not using a reliable

method of contraception were also excluded. The study was reviewed and approved by the Institutional Review Board of the University of Pennsylvania, and all patients provided written informed consent before study participation.

Patients were characterized as Type A versus Type B based on an empirically derived analysis using cutoff scores on 4 criteria.⁷ To be characterized as Type B, patients had to average 12 or more drinks per drinking day in the 90 days before entering the trial, if they were male (female patients, 10 or more drinks per drinking day); and had to meet at least one of the following 3 criteria: (1) onset of alcohol dependence before age 25 years (as determined by the SCID), (2) a HAM-D score of 8 greater than or equal to 14 at the time of entry into the trial, or (3) 3 or more childhood criteria for Antisocial Personality Disorder. Patients were identified as Type A or Type B and then were separately randomized to quetiapine or placebo. All patients received weekly sessions of brief motivational and compliance enhancing therapy using the BRENDA technique.³⁰

Outcome Measures

The primary outcome was self-reported alcohol consumption as measured by the Time Line Follow-Back method.^{31,32} The Time Line Follow-Back method includes a semistructured interview that uses a calendar format to record the quantity and frequency of drinking per day during a stated period. In this instance, drinking reports were recorded at pretreatment of the 90 days before entering the trial, and then weekly during the treatment period after randomization. Quantity of alcohol was recorded in standard drinks (eg, a 12-oz beer, a 6-oz glass of wine, or a 1-oz shot of 100 proof hard liquor = 1 standard drink). The alcohol consumption outcomes of interest were (1) percent days of any drinking during the randomized medication phase of the trial, (2) percent days of heavy drinking (4 or more standard drinks per day for women, 5 or more standard drinks per day for men), (3) time in days to relapse to any drinking, (4) time in days to relapse to heavy drinking.

Other outcome measures included The Addiction Severity Index (ASI),³³ which was administered at baseline and at the end of the trial. The HAM-D⁸ and The Hamilton Anxiety Scale (HAM-A)³⁴ were also administered at baseline and on weeks 5, 9, and at the end of the study. Alcohol craving was measured weekly using the Penn Alcohol Craving Scale (PACS).³⁵ Medication adherence was measured using a method of blister cards and pill counts.³⁶ Treatment retention was measured by attendance at evaluation visits. Adverse events were monitored weekly by the nurse practitioner. Patients were asked at each evaluation visit if they had experienced any physical problems since the previous evaluation visit. Female patients received urinary pregnancy testing before starting medications and at monthly intervals throughout the study.

Procedures

Medications—At the start of the medication phase of the trial, patients were randomized to either quetiapine (n = 29, 16 Type A, and 13 Type B) or placebo (n = 32, 17 Type A, and 15 Type B). Patients received study medications for 12 weeks. The quetiapine dose was escalated during the first 2 weeks to 400 mg of quetiapine daily, given all at bedtime. On days 1 and 2, patients received 50 mg, this was increased on day 3 to 100 mg, and increased by 100 mg every 2 days up to 400 mg. Dose reductions were permitted if patients were not able to tolerate 400 mg. Patients on placebo received identical-appearing tablets according to the same regimen. AstraZeneca supplied study medication.

Psychosocial Treatment—In addition to study medications, patients received weekly psychosocial treatment consisting of a manualized advice and treatment adherence enhancement intervention called BRENDA.³⁰ BRENDA is an acronym for the following 6-

stage framework that comprises the treatment: Bio-psychosocial evaluation, Report to patient on assessment, Empathetic understanding of the patient's situation, Needs which must be addressed, Direct advice to patient on how to meet those needs, Assess reaction/ behaviors of patient to advice and adjust as necessary for best care. The BRENDA treatment was conducted by a nurse practitioner with sessions lasting 20 to 30 minutes. Each session focused on medication adherence, monitoring progress, and providing advice in reducing alcohol consumption. Although abstinence is the stated goal for each patient, reductions in drinking are encouraged while working toward this goal.

Statistical Analysis—Baseline measures between the medication groups within each alcoholism subtype were compared using t tests for continuous variables and χ^2 tests for dichotomous variables. Nonparametric tests were used when the data were skewed. Treatment retention was measured by comparing the number of visits attended. Drinking results were compared using Generalized Estimating Equations (GEE) models.³⁷ These primary measures were analyzed both as binary (absence/presence) and continuous (quantity/frequency) repeated measures. Time to first drinking day and time to first day of heavy drinking were compared using survival analysis. The GEE models were also used to compare the groups on various secondary outcome measures, including Hamilton Depression and Anxiety Scales, craving scales, and results from liver function tests. The models generally included the pretreatment version of the response as a covariate, together with treatment group, and time effects. To examine the influence of alcoholism type (A vs. B), the main effect of type, and its interactions with medication and time effects, were also included. The interactions among pretreatment response, medication group, and time were also considered for inclusion in these models by examining P values of regression coefficients. For responses with only a few time points, time was included as a categorical variable; for responses with a greater number of time points, linear and quadratic time trends were found to be sufficient. For the GEE models, the empirical SEs are known to be suspect for small sample sizes, so model-based SEs and P values were used. An exchangeable (compound symmetry) structure was used for the working correlation matrix.

In the descriptions later, we report only the medication effects and other significant effects from the final model. In those descriptions of the analyses on the drinking outcomes and secondary responses, note that all Z and χ^2 statistics quoted are obtained from the models.

RESULTS

Baseline Characteristics

For the overall sample, the mean age of the patients was 47 years (± 8.8 years). Most were men (77%), and roughly half were white (54%). The mean number of years of education was 13.8 (± 2.6 years) and 90.2% of patients were used at least part-time. Overall, patients drank a mean of 77% of days during the 90 days preceding detoxification, and drank heavily on an average of 72% of these days. Patients drank an average of 15.5 (± 10.3) drinks per drinking day during this period.

All the Type B patients averaged greater than 12 drinks per drinking day for men and 10 drinks per drinking day for women, whereas only 14 of 33 Type A patients met this criteria (8 quetiapine and 6 placebo). In addition, 18 Type B patients had their onset of alcohol dependence before age 25 years (8 quetiapine and 10 placebo); only 2 Type A patients had their onset of alcohol dependence before age 25 years (both placebo). Eight Type B patients had 3 or more childhood criteria for antisocial personality disorder (6 quetiapine and 2 placebo); 2 Type A patients met 3 or more childhood criteria for antisocial personality disorder (both placebo). Six Type B patients had scores greater than 14 on the HAM-D (4

quetiapine and 2 placebo); none of the Type A patients had scores greater than 14 on the HAM-D.

Baseline demographics and drug use data are recorded in Table 1. By definition, Type B patients had a higher number of drinks per drinking day than the Type A patients. In addition, the Type B patients tended to be younger than the Type A patients. Finally, Hamilton Anxiety scores were higher in the Type B patients compared with Type A patients. However, there were no significant differences between quetiapine- and placebo-treated patients on socio-demographics or pretreatment drinking data within alcoholic subtype.

Comorbid psychiatric diagnoses were relatively rare and did not occur at statistically significantly higher rates in any of the 4 groups. Comorbid psychiatric illnesses noted among randomized patients included: major depression (9 patients), antisocial personality disorder (7 patients), posttraumatic stress disorder (5 patients), panic disorder (3 patients), social phobia (3 patients), generalized anxiety disorder (2 patients), and obsessive compulsive disorder (1 patient).

Treatment Retention

Forty-seven patients (77%) completed the entire trial. Overall, there were no significant differences between medication and placebo groups in treatment completion (23/29, 77% for the quetiapine group; and 24/32, 75% for the placebo group). Type B patients were less likely to complete treatment (Type A 90%, Type B 64%, $\chi^2 = 4.8$, $df = 1$, $P = 0.03$). There was no significant difference in treatment completion rates between medication and placebo treated groups within alcohol subtype (quetiapine A 88%, placebo A 88%, quetiapine B 69%, placebo B 60%). Treatment attendance also did not differ significantly between medication groups. There were 13 scheduled evaluation visits. On average, quetiapine-treated patients attended 9.3 (2.8) visits and placebo-treated patients attended 8.2 (4.3) visits ($t = 1.2$, $df = 59$, non-significant [NS]). There was a significant difference in number of visits attended between Type A and B alcoholics: 9.8 (3.0) for Type A and 7.5 (4.0) for Type B ($t = 2.5$, $df = 59$, $P = 0.02$). There was no significant medication group-by-alcohol type interaction for treatment attendance.

Drinking Outcomes During Treatment

Overall Abstinence Models—Eleven of the 61 patients (18%) achieved total abstinence from alcohol during the 12-week treatment period. Significantly more quetiapine-treated patients achieved complete abstinence (9/29 [31%]) compared with placebo-treated patients (2/32 [6%]; $\chi^2 = 6.3$, $df = 1$, $P = 0.012$). Among the quetiapine-treated abstinent patients, 5 were Type A, and 4 were Type B. Among the placebo-treated abstinent patients, one was Type A, and one was Type B. Other drinking outcomes are summarized in Table 2.

GEE Models—There were no significant medication by time or alcohol by time interactions for (log-transformed) percent days of any drinking during the 12-week of the trial and no significant time main effects. There was a significant quetiapine main effect ($\chi^2 = 13.99$, $df = 1$, $P = 0.0002$), and a significant quetiapine-by-alcohol type interaction ($\chi^2 = 5.66$, $df = 1$, $P = 0.017$). Examination of least-squares means showed that the percentage of days of any drinking among Type B patients was significantly lower in quetiapine-treated compared with placebo-treated patients ($\chi^2 = 8.32$, $df = 1$, $P = 0.004$), although there was no difference in the Type A patients ($\chi^2 = 0.59$, $df = 1$, $P = 0.44$). In addition, placebo-treated Type B patients had greater percent days of drinking compared with quetiapine-treated Type A patients ($\chi^2 = 7.39$, $df = 1$, $P = 0.007$). The second outcome of interest was percent days of heavy drinking. Again, there were no significant main or interaction effects of time, and there was a significant quetiapine main effect ($\chi^2 = 15.29$, $df = 1$, $P < 0.0001$), and a

significant quetiapine-by-alcohol type interaction ($\chi^2 = 9.61$, $df = 1$, $P = 0.002$). Placebo-treated Type B patients had a significantly higher percent days of heavy drinking compared with quetiapine-treated Type B patients ($\chi^2 = 7.85$, $df = 1$, $P = 0.005$), with no significant difference among Type A patients ($\chi^2 = 0.37$, $df = 1$, $P = 0.55$). Placebo-treated Type B patients had a significantly higher percent days of heavy drinking compared with placebo-treated Type A patients ($\chi^2 = 6.76$, $df = 1$, $P = 0.009$), whereas placebo-treated Type B patients had a significantly higher percent days of heavy drinking compared with quetiapine-treated Type A patients ($\chi^2 = 6.17$, $df = 1$, $P = 0.013$). The percent days of heavy drinking for quetiapine- and placebo-treated Type A and Type B patients are shown in Figure 1.

Survival Analyses—Time to relapse to any drinking and time to relapse to heavy drinking were generally longer in quetiapine-treated patients. However, in this small sample, survival analysis did not show any significant medication group-by-alcohol type interactions (Table 2).

Alcohol Craving

The PACS is a 5-item, single-factor, self-report questionnaire that measures intensity, duration, and frequency of craving for alcohol during the previous week. Each response on the PACS is made on a 0 to 6 Likert scale, and the sum of all responses (maximum, 30) serves as the overall craving summary score. Although this measure is not completely continuous, its distribution was reasonably symmetric, and it was appropriate for the mixed-effects models. There was a significant quetiapine-by-alcohol type interaction ($z = -1.99$, $P = 0.05$). Craving among Type B alcoholics declined significantly more in quetiapine-treated compared with placebo-treated patients ($\chi^2 = 3.74$, $P = 0.04$). There were no significant differences in craving between quetiapine-treated and the placebo-treated Type A patients, or between either quetiapine or placebo-treated Type A patients and quetiapine-treated Type B patients.

Depression, Anxiety, and ASI Measures

The HAM-D scores in-trial showed a significant quetiapine-by-alcohol type interaction ($z = -2.09$, $P = 0.04$). Similar to other outcomes noted in this trial, the highest HAM-D scores (more depressed symptoms) were seen among placebo-treated patients with lower scores associated with quetiapine treatment in Type B patients. However, none of the pairwise comparisons were significant ($P > 0.05$ for all). The HAM-A scores also showed a significant quetiapine-by-alcohol type interaction ($z = 2.48$, $P = 0.01$). Again, the highest anxiety symptom counts were seen among the placebo-treated Type B patients, and none of the pairwise comparisons were significant ($P > 0.05$ for all). None of the 7 ASI composite scores changed significantly in any of the 4 treatment groups from pretreatment to end of study.

Medication Adherence

Medication adherence was measured by pill count. The percentage of pills taken was calculated by subtracting the number of pills returned each week from the number of pills dispensed. Both medication groups showed good adherence. Medication adherence was not significantly different in the quetiapine-treated compared with the placebo-treated patients (77% vs. 70%, $t = 0.77$, $df = 59$, NS). There was no significant difference in medication adherence between medication groups sorted by alcohol type: quetiapine Type A 80%, quetiapine Type B 72%, placebo Type A 76%, placebo Type B 63% ($f = 0.74$, $df = 3$, NS). The average dose of quetiapine was 303 mg (± 142 mg), with a range between 25 mg and 400 mg.

Safety Analyses—Adverse events were assessed at each visit. Patients were asked if there were any changes in their health since the last visit. Quetiapine was generally well tolerated. There were no medication-associated serious adverse events. One placebo-treated patient discontinued the trial early because of adverse events. Adverse events were mainly mild and evenly distributed between the quetiapine and placebo groups (Table 3). The most commonly reported adverse events included aches and pains ($n = 31$), upper respiratory tract infection ($n = 21$), sedation ($n = 21$), headache ($n = 17$), and dysphoria ($n = 16$). Quetiapine-treated patients were significantly more likely than placebo-treated patients to report sedation (52% vs. 19% $\chi^2 = 7.3$, $df = 1$, $P = 0.007$), and dry mouth (31% vs. 0%, Fisher exact test, $P = 0.001$). The sedation was rated as mild to moderate in almost all cases and responded well to dose reductions. Among the 15 quetiapine-treated patients reporting sedation, dose reduction was required in 9 patients, which resulted in complete resolution of the sedation in 6 of 9 patients or 67% of cases. Sedation was not associated with treatment dropout or worse drinking outcomes. Liver function tests (aspartate aminotransferase, alanine aminotransferase, and γ -glutamyltransferase) declined over time in all groups, but there were no significant differences between groups.

DISCUSSION

Quetiapine treatment (400 mg/d) added to weekly medical management–based counseling for 12 weeks was associated with reduced drinking and promoted abstinence. Quetiapine versus placebo-treated alcoholics were more likely to remain completely abstinent during the trial (31% vs. 6%, respectively). The benefit of quetiapine was primarily observed in the more difficult-to-treat subgroup of Type B alcoholics, who were younger, heavy drinkers, and more psychiatrically impaired. Among these difficult-to-treat patients, quetiapine treatment was associated with significantly more days of abstinence and significantly fewer days of heavy drinking. Time to relapse to any drinking and time to relapse to heavy drinking were longer for quetiapine compared with placebo-treated patients, although survival analyses did not reach statistical significance in this small pilot trial.

The efficacy of quetiapine in Type B alcoholics may be important because Type B alcoholics make up a relatively high percentage of alcoholics who present for treatment, and Type B alcoholics are resistant to conventional treatment methods. In his original study of alcohol typology, Babor et al⁴ found that in a sample of 313 alcoholics, 153 (49%) met criteria for Type B alcoholism. In another trial, using methods comparable to those used in the current trial to define Type B alcoholics, Pettinati et al⁷ found that Type B patients made up 45% of a sample of treatment-seeking alcoholics without a diagnosis of major depression. Other studies have shown that Type B alcoholics make up 30% to 50% of alcoholics entering treatment.^{6,38} Thus, Type B alcoholics are relatively common in treatment-seeking populations. They are also difficult to treat. Babor et al⁴ found that Type B alcoholics were significantly more likely to relapse after inpatient treatment compared with Type A alcoholics. Poor outcomes among Type B alcoholics have been documented by other researchers as well.^{39,40} The ability of quetiapine to assist in the effective management of these patients would be a great advance for the field of alcoholism treatment.

The precise mechanism of action of quetiapine for alcohol dependence is not clear. As a dopamine type 2 antagonist, quetiapine may reduce the rewarding properties of alcohol and reduce alcohol craving.^{14,15} In this trial, there was a significant quetiapine by Type B interaction, showing a significant reduction in alcohol craving in quetiapine-treated Type B patients compared with placebo-treated Type B patients. Quetiapine may also have reduced drinking based on its blockade of serotonin 5HT_{2a} receptors. Preclinical studies have shown that 5HT_{2a} receptor antagonists reduced alcohol self-administrations in rats bred to be heavy drinkers.^{41,42} It is interesting that these high alcohol–preferring rats were also shown

to be deficient in cerebral serotonin.⁴³ These data suggest that Type B patients, who are more heavy drinkers and who likely have deficiencies in serotonergic neurotransmission, may respond preferentially to the 5HT_{2a} blockade afforded by quetiapine. However, in a large-scale clinical trial, the nonspecific 5HT₂ receptor antagonist ritanerlin was not superior to placebo in promoting abstinence among recently detoxified alcoholics.⁴⁴ Other medications, such as ondansetron, that affect serotonergic neurotransmission have shown efficacy for the treatment of alcohol-dependent patients, particularly alcohol-dependent patients with early-onset alcoholism.⁴⁵ Early-onset alcoholics share many characteristics in common with Type B alcoholics.^{38,45}

This trial has several weaknesses. First, this was a pilot study, and so the number of patients was small, thus making detection of small to moderate effect sizes difficult. Based on a trial of this size, it is impossible to definitively state that quetiapine is only effective in Type B patients. This finding will need to be replicated in a larger trial. Quetiapine was sedating, and this may have affected the blinding of the study. There were no blood levels of quetiapine obtained, and adherence with medication was only evaluated by pill counts. The psychosocial treatment chosen for this trial, BRENDA therapy, mainly emphasized medication and treatment adherence, and therefore it is impossible to say if quetiapine might have a stronger effect if accompanied by a more robust treatment approach, such as cognitive behavioral relapse prevention psychotherapy or a 12-step facilitation therapy. Clinicians should be reminded that despite the positive results of this small pilot trial, quetiapine is not approved for the treatment of alcoholism. Therefore, caution should be used if quetiapine is considered for the treatment of alcohol dependence and appropriate monitoring for adverse events should be conducted.

Despite its weaknesses, the results of this trial suggest that quetiapine may be useful for the treatment of alcohol dependence, specifically in Type B alcoholics. Quetiapine may be efficacious at both promoting complete abstinence from alcohol as well as reducing relapse to heavy drinking. Larger trials would be useful to further delineate the efficacy of quetiapine in both Type A and B alcoholics.

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FIGURE 1.
Percent days of heavy drinking for each medication group by alcohol type.

TABLE 1

Baseline Demographics and Drinking Data

	Quetiapine Type A (n = 16)	Placebo Type A (n = 17)	Quetiapine Type B (n = 13)	Placebo Type B (n = 15)
Age (yrs)	47.0 (8.0)	52.0 (7.4)	45.8 (9.8)	43.3 (8.6)
% Male	62.5	76.5	84.6	86.6
% White	37.5	58.8	46.2	73.3
% Married	37.5	41.2	15.4	26.7
Education	13.9 (2.8)	14.6 (3.3)	12.8 (1.3)	13.7 (2.3)
% Employed	81.2	88.2	100.0	93.3
% Days drinking	75.9 (22.2)	84.1 (24.2)	77.1 (25.5)	70.1 (26.8)
% Days of heavy drinking	69.4 (26.3)	76.1 (30.0)	75.4 (24.7)	70.2 (26.5)
Drinks/drinking day	13.1 (8.5)	10.0 (5.6)	21.7 (9.4)	18.9 (13.1)
ASI Alcohol Composite Score	0.611 (0.180)	0.588 (0.195)	0.673 (0.164)	0.670 (0.216)
HAM-D	4.4 (4.0)	6.7 (6.6)	7.0 (7.6)	10.2 (6.5)
HAM-A	3.2 (4.0)	4.4 (3.6)	4.6 (6.1)	8.0 (5.3)

Values are expressed as mean (SD) or %.

TABLE 2

During Treatment Drinking Characteristics of the Sample

	Quetiapine Type A (n = 16)	Placebo Type A (n = 17)	Quetiapine Type B (n = 13)	Placebo Type B (n=15)	Medication by Alcohol Type Interaction	
					Test Stat	P
% Days drinking	4.1 (6.7)	7.9 (8.3)	3.3 (3.8)	21.7 (29.1)*	5.66 [†]	0.017
% Days heavy drinking	2.8 (6.0)	2.3 (3.1)	1.2 (2.0)	20.3 (30.0)*	9.61 [†]	0.002
Time to relapse to any drinking, days	43.5 (37.4)	30.6 (30.0)	47.4 (33.8)	25.7 (29.6)	3.46 [‡]	NS
Time to relapse to heavy drinking, days	58.7 (33.6)	45.9 (32.8)	58.4 (35.3)	33.8 (37.5)	2.36 [‡]	NS

Values are reported as mean (SD).

* Significantly higher than quetiapine Type B.

[†] χ^2 .[‡] Log rank.

TABLE 3

Adverse Events

Adverse Event	Quetiapine (n = 29)	Placebo (n = 32)
Aches and pains	45%	56%
Sedation [*]	52%	19%
Gastrointestinal complaints	41%	37%
Upper respiratory tract infection	38%	31%
Headache	28%	28%
Dysphoria	31%	22%
Dry mouth [†]	31%	0
Lightheaded	17%	12.5%
Insomnia	3.4%	19%
Skin rash	10.3%	3.1%

^{*} $\chi^2 = 7.3$, $P = 0.007$.

[†] Fisher exact test, $P = 0.001$.