

REVIEW

Quetiapine for the treatment of alcoholism: Scientific rationale and review of the literature

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Abstract

Issues. The development of effective treatments for alcohol use disorders represents an important public health concern. Quetiapine, a multiple receptor antagonist at 5-HT_{1A} and 5-HT_{2A}, dopamine D₁ and D₂, histamine H₁, and adrenergic α_1 and α_2 receptors, is an atypical antipsychotic medication that has recently shown promise for the treatment of alcoholism. **Approach.** This manuscript reviews the rationale and empirical literature suggesting that quetiapine may be useful for the treatment of alcohol use disorders, including a discussion of its putative neurobiological and biobehavioural mechanisms of action. **Key Findings.** The effects of quetiapine on drinking outcomes may be due to its effects on mood, anxiety and sleep, which may help alleviate protracted withdrawal symptoms and address psychiatric comorbidities often associated with alcohol use disorders. **Implications.** These findings have implications to treatment development for alcoholism and suggest that the scientific study of quetiapine for alcoholism warrants further resources and attention. **Conclusion.** Quetiapine has advanced as a potentially promising pharmacotherapy for alcoholism. Additional research is needed to more clearly ascertain its clinical utility as a stand-alone treatment for this indication, as well as to identify patients who are more likely to respond favourably to this medication. [Ray LA, Heydari A, Zorick T. Quetiapine for the treatment of alcoholism: Scientific rationale and review of the literature. *Drug Alcohol Rev* 2010;29;568–575]

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Introduction

Alcohol abuse and dependence represent two frequently occurring psychiatric conditions. Findings from the National Epidemiological Survey on Alcohol and Related Conditions (NESARC; [1]) indicated that the 12 month prevalence of alcohol dependence in the USA was 3.8%, while the prevalence of alcohol abuse was 4.7% [2]. Alcoholism represents a significant public health concern associated with an estimated annual cost of \$185 billion [3]. Alcohol use disorders are major contributing factors to injuries, medical and psychiatric illnesses and alcoholism is estimated to cause more than 100 000 deaths annually [4,5]. Although treatments for alcoholism have improved in recent decades [6], there is still great need to develop more effective interventions.

Overview of pharmacotherapies for alcoholism

Pharmacotherapies for alcoholism are used less often than psychosocial interventions [7]. The limited use of pharmacotherapy for alcoholism is due, in part, to the relative lack of pharmacological options to treat alcohol use disorders. The only pharmacotherapies currently approved by the Food and Drug Administration (FDA) for the treatment of alcohol dependence are disulfiram (Antabuse®), naltrexone, acamprosate and Vivitrol, an injectable extended-release formulation of naltrexone.

Disulfiram has been used to treat alcoholism since the 1940s and works by inhibiting aldehyde dehydrogenase and in turn preventing the metabolism of acetaldehyde, alcohol's primary metabolite. The build up of acetaldehyde in the blood causes unpleasant effects, such as flushing and sympathetic overactivity, which in

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turn is thought to deter drinking. A large 52 week controlled trial of disulfiram revealed that it may help prevent relapse in compliant patients [8], yet it is not effective in promoting continuous abstinence. In short, major limitations of disulfiram for alcoholism treatment are compliance issues and the fact that this medication does not reduce alcohol craving. Acamprosate is an N-methyl-D-aspartate (NMDA) antagonist thought to address the dysregulation between excitatory and inhibitory neurotransmission thought to result from chronic alcohol use [9]. Several European studies supported the efficacy of acamprosate over placebo for the treatment of alcoholism (for a meta-analysis see [10]); however, results from the COMBINE Study did show a benefit for acamprosate [11]. The reason for the discrepancy between the European and US studies of acamprosate is unknown and future studies are needed to ascertain which patients are likely to benefit from this medication.

Naltrexone is the most studied of the medications for alcoholism. Shortly after two initial trials suggested that naltrexone resulted in significantly fewer drinking days and lower rates of relapse after 3 months of treatment [12,13], naltrexone was advanced as a promising pharmacotherapy for alcoholism [14]. These initial results have been supported by more recent trials of naltrexone that demonstrate significant reductions in heavy drinking [15–19]. A few trials, however, have reported no significant differences between naltrexone and placebo [20,21]. Recent studies have found that a subset of patients with at least one copy of the Asp40 allele of the OPRM1 gene may respond better to naltrexone [22,23] and that this differential response may be due to greater naltrexone-induced blunting of alcohol ‘highs’ among Asp40 carriers [24]. In sum, studies of naltrexone suggest only a modest effect on drinking outcomes and highlight the need to develop more effective pharmacological interventions for alcoholism.

Ondansetron and topiramate are two pharmacotherapies that have recently shown promise for the treatment of alcohol dependence. Ondansetron is a 5-HT₃ antagonist of demonstrated effectiveness, relative to placebo, in the reduction of drinking among patients with early onset alcoholism [25]. It has been speculated that ondansetron may address the serotonergic dysfunction thought to characterise early onset alcoholism [25,26] and that it reduces craving for alcohol through the influence of a 5-HT projection to mesolimbic dopaminergic connections in the midbrain [25,26].

Topiramate is an anti-epileptic medication that was only recently tested for alcoholism. Results indicated that topiramate reduced drinking and alcohol craving over the 12 week trial [27]. The mechanisms of action of topiramate remain unclear. In general, topiramate reduces neuronal excitability through inhibition at

glutamate AMPA/kainate receptors and L-type calcium channels. Topiramate also facilitates γ -aminobutyric (GABA) function and may even increase GABA levels. Both of these effects (i.e. glutamate blockade, GABA facilitation) can reduce or inhibit mesolimbic dopamine activity. Topiramate may also indirectly influence mid-brain dopaminergic activity, thereby reducing alcohol craving [27]; although these findings have not been supported in a laboratory study of cue-induced craving [28].

Effects of quetiapine on drinking outcomes

Initial support for quetiapine as a pharmacotherapy for alcoholism came from a retrospective chart review [29] demonstrating that this medication, used to treat disturbed sleep, resulted in a significantly higher number of days abstinent and fewer hospitalisations, as compared to non-quetiapine treated patients. An additional retrospective chart review of nine patients admitted to a 28 day residential rehabilitation program suggested that quetiapine was well-tolerated and associated with significant decreases in anxiety, improved sleep and decreased craving for alcohol [30]. Published single case [31] and observational studies [32] have also suggested that quetiapine is well-tolerated and may be beneficial in treating alcohol dependence. A recent open-label trial of quetiapine in patients with comorbid schizophrenia-spectrum and substance use disorders suggested that the severity of substance abuse decreased over the course of a 12 week trial of quetiapine, as indicated by reduced number of substance use days and money spent on alcohol/drugs [33]. The aforementioned studies lack random assignment, which precludes causal inferences regarding the effects of quetiapine for alcoholism.

The first placebo-controlled trial of quetiapine for alcoholism was recently published [34] and included 87 participants, 61 of whom completed the 12 week trial. Participants were randomised to quetiapine (400 mg day⁻¹) or placebo and quetiapine produced significantly higher abstinence rates. Medication effects were found by stratifying the sample into type A and type B alcohol-dependent patients. Quetiapine was superior to placebo and was associated with fewer drinking days, fewer days of heavy drinking and blunted alcohol craving among patients classified as type B alcoholics [34], but not among type A patients.

As noted by Kampman and colleagues [34], this initial study, although promising, is limited by the small sample size, the lack of verification of quetiapine compliance through blood levels, and the concurrent administration of a psychosocial treatment (BRENDA), which may obscure the true pharmacological effects of quetiapine. Importantly, the mecha-

Table 1. Review of studies investigating quetiapine for the treatment of alcoholism

Setting	Design	Dosage	Results	Reference
Clinical research setting	Double-blind, placebo-controlled, randomised. Subjects received medication and weekly psychosocial treatment for 12 weeks.	Target dose was 400 mg daily ⁻¹	Among type B alcohol-dependent patients, quetiapine reduced drinking days, days of heavy drinking and blunted alcohol craving. Nine quetiapine-treated patients maintained abstinence compared with two placebo-treated patients.	[34]
Day-hospital for substance use disorders	Open-label study. Patients dually diagnosed with alcohol dependence and other axis I disorders.	Orally treated with flexible doses of 300–800 mg day ⁻¹ for 16 weeks.	Quetiapine decreased alcohol consumption, craving for alcohol and psychiatric symptoms severity	[36]
Rehabilitation centre	Retrospective study: patients were alcohol dependent and/or, cocaine, methamphetamine dependent with substance-induced anxiety disorder.	Dose ranged from 50 to 300 mg day ⁻¹ , average dose was 153 mg day ⁻¹ .	All eight completers showed a decrease on Ham-D subscales of insomnia, agitation, somatic anxiety, hypochondriasis and obsessional symptoms.	[30]
VA hospital	Non-randomised/blind Quetiapine given to alcohol-dependents for disturbed sleep, 1 year study, retrospective. Participants dually diagnosed	Initially: 25 or 50 mg at bedtime Dose raised up to 200 mg day ⁻¹	Quetiapine group had a higher mean number of days abstinent, longer time to relapse, and lower number of hospitalisations during study.	[29]
Cases observed in naturalistic clinical setting	Nine outpatients diagnosed with alcohol dependence and treated with quetiapine	Initially: 100 mg day ⁻¹ Increased up to 200 mg day ⁻¹ in increments of 25 mg day ⁻¹ if daytime sleepiness reported	Eight/nine patients remained abstinent during 2–7 months of quetiapine treatment	[32]

nisms of action of quetiapine have yet to be elucidated. The alcohol typology used to identify individuals who are most likely to respond to quetiapine may be limited as well. A recent review of the literature on clinical subtyping of alcohol dependence found mixed results in terms of construct, concurrent and predictive validity and concluded that further research is needed before these typologies could be reliably used in clinical practice [35]. Therefore, it is important to consider alternative moderators of treatment response. Table 1 describes studies of quetiapine for alcoholism.

Neurobiological mechanisms of quetiapine

Quetiapine is a multiple receptor antagonist at 5-HT_{1A} and 5-HT_{2A}, dopamine D₁ and D₂, histamine H₁, and adrenergic α_1 and α_2 receptors. Quetiapine is thought to act as an antagonist to 5-HT_{2A}, which are also localised on the dopaminergic neurons in the substantia nigra and ventral tegmental area. Importantly, 5-HT_{2A}

receptor antagonism may modulate the activity of dopamine neurons in the nigrostriatal, mesolimbic and mesocortical projections [37,38]. Based on the neurobiological effects and targets of quetiapine, understanding its effects on serotonergic and dopaminergic activity may be especially relevant to elucidating its clinical effects for alcoholism.

Quetiapine-induced blockade of the 5-HT_{2A} receptors may interact with antagonism of D₂ receptors, which in fact is an important pharmacological mechanism differentiating conventional from atypical antipsychotics. Medications that potently block dopamine in the reward pathway could lower the effects of alcohol, but may actually be counter-effective by leading to increased alcohol consumption in an attempt to feel the previously experienced rewarding effects [30]. Quetiapine has significantly lower dopamine antagonism properties compared to other antipsychotic medications [30,39]. Due to this decrease in dopamine blockade potency, quetiapine might not lead to the increase in

substance abuse associated with other dopamine antagonists [39].

Indeed, higher affinity for 5-HT_{2A} receptors than for D₂ receptors is one of the hallmarks of atypical antipsychotic medications [40], also thought to underlie the better tolerability profile observed in atypical antipsychotics. In particular, 5-HT_{2A} and D₂ antagonism on the mesolimbic dopaminergic pathway into the nucleus accumbens causes decreased dopaminergic output in those areas, as 5-HT_{2A} antagonism modulates the activity of dopaminergic neurons differentially in the mesocortical areas [37]. It remains unclear which neurobiological mechanism, beyond the D₂ receptor antagonism, is the therapeutic target responsible for the beneficial effects of atypical antipsychotics on psychotic disorders. Nevertheless, quetiapine's 5-HT_{2A} and D₂ antagonism leading to decreased dopaminergic activity in the mesolimbic pathway may be especially important to understanding its clinical effects in the treatment of alcoholism as dopaminergic activity in the nucleus accumbens and ventral tegmental area have long been associated with addictive processes, such as craving, loss of control over alcohol/drug use and relapse for various drugs of abuse, such as cocaine, heroin, alcohol and tobacco (for a review see [39,41,42]).

Biobehavioural mechanisms of pharmacotherapies for alcoholism

Although reports from clinical observation, case studies and retrospective chart reviews have suggested that quetiapine may reach its clinical effects for alcoholism by reducing craving [32], improving sleep [29,31] and increasing sedation/decreasing anxiety [30], no experimental studies to date have examined the mechanisms of action of this pharmacotherapy. Knowledge of the mechanisms of action of quetiapine has the potential to improve the available treatments for alcoholism by: [1] informing more targeted interventions that are guided by the pharmacotherapy's mechanisms in combination with an assessment of the patient's needs [2]; elucidating the underlying pathophysiology of alcohol dependence itself; and [3] informing efforts at combining pharmacotherapies on the basis of their neurobiological and biobehavioural effects. Pharmacotherapies for alcoholism could have beneficial clinical effects through a variety of biobehavioural mechanisms [43]. Putative biobehavioural mechanisms of action of quetiapine include the following:

Reduction of alcohol cravings/urge to drink

Medications may reduce drinking by dampening urges to drink. Alcohol craving has been examined in many contemporary models of alcoholism (e.g. [44,45]). As

demonstrated by Monti and colleagues [46,47], when exposed to their usual alcoholic beverage, most alcohol-dependent individuals respond with increased urge to drink. Medications that dampen urge to drink hold promise for promoting abstinence and reducing alcohol consumption. A number of recent pharmacotherapy trials for alcoholism have examined medication effects on urge to drink under laboratory conditions, such as naltrexone [18,48], olanzapine [49] and topiramate [28]. Quetiapine, however, has not yet been subjected to such investigations. Nevertheless, the study by Kampman *et al.* [34] collected self-report data on urge to drink using the Penn Alcohol Craving Scale [50] and found that quetiapine significantly reduced alcohol craving (effect size, $d = 0.56$).

Blunting of the stimulant effects of alcohol

A medication may reduce alcohol intake by blunting the rewarding and stimulant effects of alcohol. This mechanism may be particularly salient in the effects of naltrexone on drinking outcomes (e.g. [24,51,52]). Although alcohol is typically classified as a central nervous system depressant, studies have shown that the pharmacological effects of alcohol are biphasic in nature, such that during the ascending limb of the Blood Alcohol Concentration (BAC), in other words, when blood alcohol levels are rising, the effects of alcohol are primarily stimulant. Conversely, during the descending limb of BAC (i.e. when blood alcohol levels are declining), the effects of alcohol are primarily sedative [53,54]. Pharmacotherapies that blunt the rewarding and stimulatory effects of alcohol upon consumption may be useful in decreasing relapse and frequency of heavy and harmful drinking. Given that Kampman and colleagues [34] found that quetiapine was superior to placebo in reducing percentage heavy drinking days among type B alcoholics, it is possible that quetiapine may alter the subjective effects of alcohol upon consumption, which in turn reduces the likelihood of heavy drinking during a drinking episode. This hypothesis would be optimally tested using an alcohol administration paradigm.

Potentiation of the sedative and unpleasant effects of alcohol

A medication may reduce drinking by increasing the likelihood that drinking will lead to alcohol-induced sedation, which is marked by unpleasant and dysphoric feelings, such as down, heavy-headed, sluggish, inactive and sedated (items from the Biphasic Alcohol Effects Scale; BAES) [53,55]. Given the sedative properties of quetiapine, potentiation of the sedative and unpleasant effects of alcohol is one of the hypothesised mechanisms by which quetiapine may exert its beneficial

effects on drinking outcomes. Two studies have examined the safety of co-administering quetiapine and alcohol and found no significant evidence of counter indications yet the potentiation of alcohol's sedative effect has not been examined.

Reduction of anxiety symptoms

A medication may decrease drinking by reducing symptoms of anxiety, an important source of vulnerability to relapse. Laboratory studies have demonstrated that stress and exposure to alcohol cues may produce anxiety and alcohol craving, which in turn increase one's susceptibility to relapse [56]. Quetiapine's sedative and anxiolytic effects may ameliorate symptoms of anxiety, thereby reducing the risk of relapse to heavy drinking.

Improvements in sleep efficiency and quantity

Chronic alcohol use affects sleep topography and insomnia represents a frequent symptom among alcohol-dependent individuals [57,58]. The association between sleep difficulties and relapse is well-documented [59]. Alcohol use decreases the time it takes to fall asleep and increases slow-wave sleep in the first half of the night and decreases sleep quality in the second half of the night [60]. During chronic alcohol use, individuals become tolerant to the sedative affects of alcohol and sleep is severely disturbed [60]. A medication, such as quetiapine, may promote recovery by improving symptoms of insomnia, a condition estimated to occur in 36–72% of alcohol-dependent patients and likely to persist after alcohol abstinence is initiated [57].

Pharmacokinetics & adverse events

Quetiapine fumarate is a dibenzothiazepine derivative that is eliminated primarily by hepatic metabolism. The pharmacokinetics of the immediate release formulation of quetiapine fumarate in humans has been extensively studied [61,62]. Quetiapine is rapidly absorbed after oral administration, with the median time to reach maximum observed plasma concentration ranging from 1 to 1.5 h and the mean apparent terminal elimination half-life ranging from 3.1 to 3.5 h. A sustained release formulation of quetiapine is also commercially available. Pharmacokinetics studies of the sustained release formulation of quetiapine demonstrated a linear pattern of absorption over time and the single dose of 300 mg using the sustained release formulation was bioequivalent to the same dose delivered twice per day using the immediate release formulation.

Quetiapine is FDA approved for treatment of bipolar depression, acute mania in bipolar I and maintenance treatment for bipolar I [63]. Additionally, many clinical studies have shown efficacy of quetiapine for adjunctive treatment of anxiety, personality, psychotic and mood disorders, and it is frequently implemented by clinicians for such 'off label' indications [64]. In large clinical trials, quetiapine had rates of discontinuation higher than placebo for somnolence (0.8% vs. 0%) and hypotension (0.4% vs. 0%), but the overall rate of discontinuation did not differ from placebo groups (Physicians Desk Reference (PDR)). Other side effects reported more frequently than in placebo groups include (in order of descending frequency): headache, somnolence, dizziness, tachycardia, dry mouth, constipation and weight gain (PDR). Based upon post-marketing surveillance, quetiapine has 'black box warnings', which are included in the package insert for prescribers and patients for suicidality (applied based upon its indication for treatment of bipolar depression) and increased mortality for dementia-associated psychosis (applied to all second-generation antipsychotics; PDR). Quetiapine, by virtue of its relatively low affinity for the D₂ dopamine receptor, has a low likelihood of inducing extrapyramidal side effects, parkinsonism and tardive dyskinesia compared to other antipsychotics, except clozapine [65]. Quetiapine has been found by extensive post-marketing surveillance to be generally safe and well-tolerated in clinical practice [66].

Given the extensive utility of quetiapine, it has been widely prescribed along with other second generation antipsychotics in psychiatric practice, particularly for schizophrenia and bipolar disorder [67]. This has led to the recognition that treatment with second generation antipsychotics is generally associated with weight gain, an increase in insulin resistance and diabetes mellitus type II, hyperlipidemia and metabolic syndrome [68]. In a recent comparative study, quetiapine was found to produce overall less severe effects on weight gain, hyperlipidemia and insulin resistance as compared to the second-generation antipsychotics olanzapine and risperidone [68]. Taken together, the side effect profile of quetiapine is favourable and suggests that it may be safely used as a pharmacotherapy for alcoholism.

Medication compliance

Compliance with quetiapine and overall study retention rates have been notably high in the studies reviewed herein. The study by Kampman *et al.* [34] found no significant differences between the quetiapine-treated group and the placebo-treated group in medication adherence; 77% and 70%, respectively. Participants in this study received either quetiapine or placebo for a total of 12 weeks, with escalating dosage during the first

2 weeks. Medication compliance was measured by pill count on a weekly basis. There was also a favourable retention rate in the study done by Martinotti *et al.* [36].

In the studies reviewed herein quetiapine dosage was continuously monitored based on self-reported subjective feelings and adverse events throughout the study duration, and the dosage was modified appropriately [29,30,32,34,36]. The individual attention could have contributed to the favourable medication compliance and retention rates in the studies. Nevertheless, the level of medical oversight in these trials effectively replicates those expected in clinical practice. Hence these compliance results can be seen as largely favourable.

Abuse potential

As a relatively low-affinity D₂ receptor antagonist with mood stabilising and antipsychotic efficacy, there is no *a priori* reason to suspect an abuse potential for quetiapine in human populations [69]. To date, no pattern of abuse of quetiapine has been documented in a clinical trial [69]. However, since 2004, several case reports of quetiapine abuse have emerged, primarily among incarcerated populations, where reports of oral [70], intranasal [71] and intravenous [72,73] illicit abuse of quetiapine have surfaced. These reports generally describe patients who will abuse quetiapine for its sedative and anxiolytic properties. Some of the street names used for quetiapine include 'quell', Baby heroin, 'Q-ball' and 'Susie-Q'. All case reports to date involved individuals with a significant history of substance use disorder, many of whom had secondary gains associated with remaining sedated in an incarcerated setting, and all of whom had very little access to drugs of abuse [69]. These individual case reports are of unclear clinical significance, given both the large number of quetiapine prescriptions worldwide, the small number of reported cases of abuse and the absence of any evidence for quetiapine abuse in clinical trials. Nevertheless, quetiapine abuse represents the majority of reports of antipsychotic abuse in the literature, suggesting that perhaps the sedative effects of this medication enhance its abuse liability.

Interestingly, all reports of quetiapine abuse to date involved immediate release quetiapine. Of note, immediate release quetiapine has been shown to produce a significantly increased subjective effect of 'sedation' compared to the same dosage of extended release quetiapine 1 h after dosing, which may contribute to the case reports of abuse in some individuals [74]. Taken together, there is no evidence from controlled studies of systematic potential for abuse of quetiapine in any clinical population, including substance abusing patient populations. However, the case report literature sug-

gests that clinicians must consider the abuse potential of quetiapine, particularly among patients with substance use disorders. Controlled studies are necessary to fully ascertain the abuse potential of quetiapine in the context of alcoholism treatment. It is particularly important to discern whether patients will abuse quetiapine while actively engaged in treatment, as compared to patients who may mangle in order to obtain the substance with the clear intention to abuse it.

Conclusions

This manuscript reviewed the rationale for quetiapine as a treatment for alcoholism, including neurobiological and biobehavioural mechanisms of action. In addition, a variety of clinical issues, such as adverse events, medication compliance and abuse potential, were discussed. The extant literature on quetiapine for alcoholism consists mostly of single blind studies, trials in dually diagnosed samples and case reports, with the notable exception of a placebo-controlled randomised trial [34]. The results of the studies reviewed herein have generally supported the utility of quetiapine as an adjunctive pharmacotherapy for alcoholism and have suggested that this medication may reach its clinical effects by reducing alcohol craving, dampening anxiety symptoms and improving sleep. Quetiapine may be especially useful in treating dually diagnosed patients or type B alcohol-dependent individuals. Considerable work remains to be done before these findings can be translated into clinical practice, including larger randomised-controlled trials and additional studies of moderators of treatment response. It is particularly important to discern the extent to which quetiapine is effective as a stand-alone pharmacotherapy for alcoholism or whether the effects observed on alcohol use are secondary to overall improvement in other axis I conditions, such as mood and psychotic disorders. In conclusion, quetiapine has emerged as a potentially promising pharmacotherapy for alcoholism yet additional research is needed to more clearly ascertain its clinical utility for this indication, as well as to identify patients who are more likely to benefit from this medication.

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