The Effects of Quetiapine on Sleep in Recovering Alcohol-Dependent Subjects

A Pilot Study

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Objective: The aim of this hypothesis-generating pilot study was to assess prospectively the objective and subjective effects of treatment with quetiapine XR on sleep during early recovery from alcohol dependence (AD).

Methods: Recovering subjects with AD and sleep disturbance complaints were treated with quetiapine XR (n = 10) or matching placebo pills (n = 10) for 8 weeks. Polysomnography was used to assess sleep objectively, and the Insomnia Severity Index and Pittsburgh Sleep Quality Index were used to measure subjective insomnia. Other assessment measures included the 10-minute psychomotor vigilance task (for neurobehavioral functioning), the time-line follow-back measure (for alcohol consumption), the Penn Alcohol Craving Scale (for alcohol craving), the Patient Health Questionnaire-9 item scale (for depressive symptoms), and the Beck Anxiety Inventory (for anxiety symptoms).

Results: Although there was no effect of quetiapine XR on sleep efficiency (time spent asleep/total recording time), there was a pre-to-post reduction in wake after sleep onset time ($P = 0.03$) and nonsignificant trends for increases in sleep onset latency (SOL) and stage 2 sleep time. A time × drug interaction was seen for the subjective insomnia, such that quetiapine XR–treated subjects reported greater initial improvement in their subjective insomnia, but the difference was not sustained. There were no differences between treatment groups on other measures or medication compliance.

Conclusion: Quetiapine XR improves objective sleep continuity and transiently improves subjective insomnia early in recovery from AD.

Key Words: quetiapine, sleep, alcoholism, insomnia

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Insomnia is common in recovering alcohol-dependent (AD) patients and occurs at a rate that is 6 times higher than the 10% prevalence reported in the general population.[1–3] The consequences of insomnia include daytime sleepiness, fatigue, mood and anxiety symptoms,[4] and an increased risk of relapse in alcohol dependence.[1,2] Because of the risk for dependence of approved hypnotic medications, other medications are commonly used to treat insomnia "off-label."

Quetiapine is a novel antipsychotic medication that is approved by the US Food and Drug Administration to treat schizophrenia; bipolar I disorder, manic or mixed episodes; bipolar disorder, depressive episodes; and as an adjunct to antidepressants for major depressive disorder. It is commonly used off-label in addiction treatment centers as a hypnotic agent[5,6] and to manage dysphoric states during acute withdrawal from substances.[7] It is an antagonist at the dopamine (D_1 and D_2), serotonin ($5HT_{2A}$), histamine (H_1), adrenergic (α_1 and α_2), and orexin A[8] receptors. A long-acting formulation, quetiapine XR, reaches a peak plasma concentration at 6 hours after administration. The parent compound and its active metabolite norquetiapine have terminal half-lives of 7 and 12 hours, respectively.

In healthy control subjects, quetiapine treatment has been associated with an improvement in total sleep time, sleep efficiency, and percent time spent in stage 2 sleep.[9] In subjects with insomnia, treatment with open-label quetiapine was associated with improved sleep efficiency, total sleep time, and subjective sleep quality in 1 study,[10] although a small randomized, controlled trial failed to show any significant group differences.[11] In a case series of recovering patients, open-label quetiapine treatment was associated with decreased anxiety and drug craving, and improved sleep.[6] In a retrospective study of AD veterans with sleep-related disturbances, treatment with quetiapine during the first year was associated with more abstinent days and fewer hospitalizations.[5] However, a larger study by the same group showed that AD veterans had a higher rate of rehospitalization with quetiapine monotherapy.[7] A recent multicenter trial in AD subjects showed that quetiapine XR improved depressive symptoms and insomnia without affecting drinking outcomes.[12]

Some of the limitations of prior studies included the inclusion of subjects with polysubstance use,[6] failure to include a comparator arm,[6] absence of a standardized insomnia assessment,[6] retrospective data analysis and secondary analysis of insomnia symptoms,[5,7] lack of objective sleep measures, and the assessment of sleep continuity disturbances during alcohol withdrawal (when the severity of insomnia is the highest and likely to be transient). To address these limitations, we evaluated the effect of quetiapine XR on objective and subjective sleep in AD patients with a complaint of sleep-related disturbances during the first year of recovery. We hypothesized that treatment with quetiapine XR would be associated with a greater improvement in sleep efficiency, assessed polysomnographically,

and a reduction in insomnia severity as assessed by the Insomnia Severity Index (ISI).

MATERIALS AND METHODS

Overview

This 8-week randomized, double-blind, placebo-controlled trial of quetiapine XR evaluating objective and subjective sleep in recovering AD subjects was conducted within the Mental Illness Research, Education and Clinical Center of the Veterans Integrated Service Network 4 of the Philadelphia Veterans Affairs Medical Center (PVAMC). The PVAMC institutional review board approved the protocol, and written informed consent was obtained from all subjects (Clinicaltrials.gov identifier: NCT00434876).

Subjects

Alcohol-dependent subjects who complained of sleep-related disturbance were recruited via provider referrals from the addictive disorders clinic of the PVAMC, the Behavioral Health Laboratory of the PVAMC,[13] and through posted flyers. Subjects were included in the study if they were aged 18 to 65 years, had a past year diagnosis of alcohol dependence as determined by the Mini International Neuropsychiatric Interview,[14] had a Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised total score of less than 8,[15] were abstinent from alcohol for the month before study entry (to exclude transient insomnia during withdrawal), and comprehended instructions in English and able to provide informed consent. Subjects were excluded if they were currently dependent on drugs (excluding cannabis and nicotine) within the past year and had an unstable medical disorder, a significant psychiatric illness, or untreated severe obstructive sleep apnea. Subjects were compensated $100 for each polysomnography (PSG) assessment; $25 for each treatment session at 1, 4, and 9 weeks; and $15 for each of the other sessions.

Interventions

All subjects were block-randomized to either the quetiapine XR or placebo arm by the PVAMC investigational pharmacy. The medication was taken at bedtime, and the dose was flexibly titrated as follows over the first week: 50-mg dose for 2 nights, 200 mg/night for 2 nights, 300 mg/night for 2 nights, and then 400 mg/night, in a fashion similar to a prior study[16] and as recommended by AstraZeneca. Medication taper commenced at week 8 in the reverse stepwise fashion. Medication compliance was assessed by subjective report, and the number of tablets returned from the prior week. To support abstinence from alcohol and medication adherence, all subjects also received medical management, an individualized psychosocial intervention delivered by the study nurse or the principal investigator (S.C.) at baseline and at treatment weeks 2, 3, 5, 6, and 7.[17]

Outcomes

Objective Sleep Measures

Objective sleep measures include the following:

a. Polysomnography—overnight PSGs were conducted before the start of medication treatment and in week 8 of treatment, with the first PSG being the habituation night. The PSGs were conducted by a registered polysomnographic technologist using standard techniques.[18]
b. Portable sleep monitor—see Supplementary Section, Supplemental Digital Content 1 (http://links.lww.com/JCP/A238), for details on portable sleep monitor study and PSG, as well as for a figure on the study overview.

Subjective Sleep

Subjective sleep includes the following:

a. Insomnia Severity Index,[19] a 7-item self-rated instrument that yields a global insomnia score of 0 to 24 over the last 2 weeks, was completed at baseline and every 2 weeks during treatment.
b. The Pittsburgh Sleep Quality Index (PSQI),[20] a 19-item self-rated scale, evaluated the subjective quality of sleep over the previous 4 weeks at baseline and weeks 4 and 9.

Daytime Functioning

The Psychomotor Vigilance Task,[21] a 10-minute test of neurobehavioral functioning, provided a measure of lapses (response times ≥500 ms) and the number of 10% fast reaction times at baseline and at week 9 of the treatment.

Substance Use

Substance use includes the following:

a. The Time Line Follow Back measure[22] assessed drinking during the 90-day prestudy period and at visits 1 to 9.
b. The Penn Alcohol Craving Scale[23] evaluated alcohol craving over the prior 7 days at baseline and during weeks 1 to 9.
c. A urine drug screen was used to identify methadone, benzodiazepines, oxycodone, opiates, cocaine, and Δ^9 tetrahydrocannabinol at baseline and weeks 1, 4, and 9.

Psychiatric Symptoms

Psychiatric symptoms include the following:

a. The Mini International Neuropsychiatric Interview[14] was used at baseline to screen for current *Diagnostic and Statistic Manual of Mental Disorders, Fourth Edition* alcohol and drug use disorders, and lifetime mania or psychotic disorder.
b. The Patient Health Questionnaire 9-item scale (PHQ-9)[24] assessed the depressive symptoms at baseline and treatment weeks 4 and 9.
c. The Beck Anxiety Inventory (BAI)[25] measured anxiety symptoms over the last week at baseline and at weeks 4 and 9.

Adverse Events

Adverse events include the following:

a. The Systematic Assessment for Treatment Emergent Effects–General Inquiry[26] was administered at all study visits.
b. The Abnormal Involuntary Movement Scale[27] was used to assess dyskinesia at all treatment visits.
c. The Barnes Akathisia Rating Scale,[28] item 4 of this 4-item scale, was used to measure global akathisia at baseline and at each treatment visit.
d. Serum chemistry—serum glucose and lipid profile were measured at baseline and weeks 4 and 9 by the PVAMC laboratory services.

Statistical Analyses

The longitudinal PSG and psychomotor vigilance task scores were analyzed using a linear mixed-effects modeling approach. Significance was set at $P < 0.05$ without adjustment for multiple comparisons because of the small sample size. Change scores from baseline were modeled to allow a clear interpretation of the direction of individual change. Body weight and baseline score were entered as fixed effects to adjust for baseline individual differences. Additional interaction terms were entered as fixed factors to test specific research hypotheses related to differences in response profile over time by intervention group.

TABLE 1. Polysomnographic Measures by Treatment Group

	Quetiapine XR (n = 10)		Placebo (n = 10)		Statistics	
Variable	**Pre Mean (SD)**	**Post Mean (SD)**	**Pre Mean (SD)**	**Post Mean (SD)**	**F (*df*)**	***P***
Polysomnographic measures						
SE, %	70.70 (17.49)	79.45 (16.52)	78.63 (12.89)	82.80 (11.57)	0.48 (1,18)	0.49
SOL, min	25.42 (14.12)	37.11 (40.06)	29.04 (29.51)	10.81 (9.64)	3.28 (1,18)	0.08
WASO, min	101.07 (81.80)	60.71 (71.41)	61.17 (37.77)	66.99 (60.62)	**5.05 (1,18)**	**0.03**
REM-L, min	108.10 (51.49)	115.00 (63.57)	92.60 (52.81)	88.75 (53.78)	0.13 (1,18)	0.74
Stage 1, %	24.20 (12.14)	20.70 (9.28)	23.35 (10.01)	26.00 (12.85)	1.87 (1,18)	0.18
Stage 2, %	189.95 (61.21)	251.20 (85.57)	207.30 (67.56)	207.50 (46.62)	3.15 (1,18)	0.09
SWS, %	26.25 (28.32)	29.60 (31.76)	26.70 (24.01)	32.25 (27.31)	0.02 (1,18)	0.88
REM, %	62.05 (29.15)	65.15 (24.54)	67.55 (21.62)	88.00 (36.18)	1.65 (1,18)	0.21
Arousals-NREM, events/h	85.50 (72.06)	76.30 (48.66)	63.40 (39.70)	47.40 (31.16)	0.16 (1,18)	0.69
Arousals-REM, events/h	13.30 (8.38)	13.70 (10.24)	16.10 (8.17)	15.50 (5.79)	0.06 (1,18)	0.80
AHI, events/h	12.74 (14.54)	7.37 (6.91)	9.59 (11.53)	4.01 (5.01)	0.002 (1,18)	0.96

Bold font denotes the only statistically significant difference in values with treatment across the 2 groups.

AHI indicates Apnea-Hypopnea Index; NREM, non-rapid eye movement; REM, percent of rapid eye movement sleep through the night; REM-L, rapid eye movement sleep latency; SE, sleep efficiency; SWS, percent of slow wave sleep through the night.

The effect of time was entered as a discrete fixed factor as follows: baseline, weeks 1, 3, 5, and 7 for ISI; baseline, weeks 4 and 9 for PSQI, PHQ-9, BAI, serum glucose, serum cholesterol, and serum triglyceride levels; and baseline, weeks 1 to 7 for Penn Alcohol Craving Scale. See Supplementary Methods, Supplemental Digital Content 1 (http://links.lww.com/JCP/A238), for more details.

RESULTS

Baseline Demographics

Eighty-two subjects were screened at baseline, with 35 subjects excluded because of comorbid drug dependence or significant psychiatric illness, 17 declined to participate, and 8 did not state a reason for refusal. Eleven subjects were randomized into each arm of the study with 1 subject in each arm lost to follow-up at the onset of treatment. Thus 20 subjects completed the study, with 10 subjects in each arm. The baseline demographics of the final sample were as follows: mean (SD) age, 52.45 (7.01) years; males (100%), an education level of a high school graduate or less, n (%), 11 (64.7%); African American race, n (%), 16 (95%); married or partnered, n (%), 5 (25%); unemployed, n (%), 19 (95%); and a body mass index, mean (SD), 26.72 (4.50) kg/m^2. Drinking during the 90 days before study entry was 7.68 (8.58) drinks per day, 34.64 (30.96) heavy drinking days, and 42.71 (30.14) abstinent days. There was no difference in characteristics between the treatment groups. The mean (SD) medication dose for quetiapine XR was 255 (142) mg and the equivalent of 370 (67) mg of placebo, $P < 0.05$.

Objective Sleep

There was no significant group difference in the sleep efficiency either before or during treatment. Quetiapine-treated subjects showed significantly greater improvement in the wake after sleep onset (WASO) during treatment ($P = 0.03$). There was a nonsignificant trend for quetiapine-treated subjects to have an increased sleep onset latency (SOL) ($P = 0.08$) and amount of stage 2 sleep ($P = 0.09$) with treatment. There were no differences in the other PSG measures across treatment groups (Table 1).

Subjective Sleep

a. Insomnia Severity Index—there was a significant greater improvement in insomnia symptoms in the quetiapine group over time ($F_{4,57} = 2.57$, $P = 0.04$; Fig. 1). No significant time × group differences were seen when the ISI was dichotomized for sleep symptoms and impairment ratings (first and second 4 questions on the ISI) or if the ISI was assessed on a weekly basis.
b. Pittsburgh Sleep Quality Index remained persistently increased through the study; no significant effect of drug, time, or time × drug was seen ($P = 0.57$).

Neurobehavioral Test

There were no significant group differences for the number of lapses ($P = 0.33$) or the 10% fast reaction times ($P = 0.38$).

Alcohol Consumption

a. During treatment, 4 subjects reported drinking. In the quetiapine arm, 1 subject had 4 episodes of nonheavy drinking, and a second subject had 11 heavy drinking episodes. In the placebo arm, 1 subject had 1 episode of heavy drinking, and 1 subject had 4 drinking days, of which 2 were heavy.

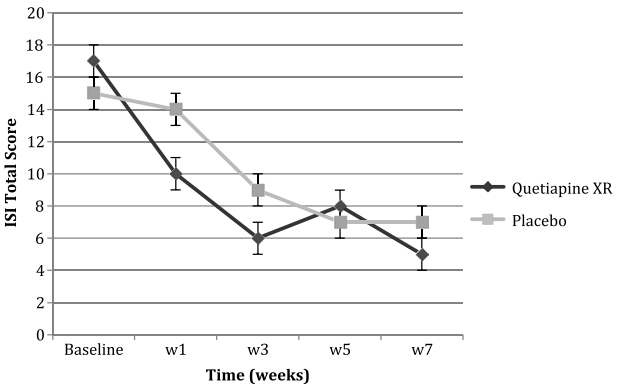

FIGURE 1. Insomnia scores over time by treatment groups, quetiapine XR (n = 10), and placebo (n = 10).

b. Penn Alcohol Craving Scale—there was a nonsignificant trend for decreased craving over time ($P = 0.09$) but no drug or time × drug effects.

Psychiatric Symptoms

a. The PHQ-9 score decreased over time ($P = 0.03$), but there was no drug ($P = 0.46$) or time × drug effects ($P = 0.65$);
b. The BAI decreased nonsignificantly over time ($P = 0.07$), but there was no drug effect ($P = 0.11$) or time × drug interaction ($P = 0.44$).

Adverse Events

The most common adverse events in both treatment arms were somnolence and dry mouth, which were more common in the quetiapine XR arm (see the Supplementary Section, Supplemental Digital Content 1 [http://links.lww.com/JCP/A238].

DISCUSSION

Despite the widespread off-label use of quetiapine as a hypnotic medication in patients with substance use disorders,[5,6] its efficacy has not been demonstrated. We found that quetiapine XR improved the objective sleep continuity (WASO) without improving sleep efficiency and improved subjective insomnia scores (ISI) without improving sleep quality (PSQI) or other relevant measures despite abstinence from heavy drinking in most subjects.

The orexinergic system, which is located in the lateral and posterior hypothalamus, secretes orexin A and B neuropeptides, promotes wakefulness, and drives feeding and the use of psychoactive substances.[29] Recent studies of almorexant, a hypnotic medication with orexin receptor antagonistic properties, have shown its efficacy in improving sleep continuity without having significant effects on SOL.[30,31] It is possible that the improved sleep continuity effects seen here were related to quetiapine's antagonist effects at the orexinergic receptors.[8] The hypnotic effect of the long-acting quetiapine XR may have persisted the next day, leading to the adverse event of daytime somnolence in some subjects. In our study, there was a nonsignificant trend for an increase in SOL with quetiapine XR that was similar to a prior study.[10] The lack of a hypothesized improvement in sleep efficiency may reflect improvement in WASO being offset by greater SOL in the quetiapine XR–treated subjects.

The lack of efficacy for anxiety and depressive symptoms may have been due to biased measurement at week 9, that is, after the medication taper. The implication of these findings is that the therapeutic effects of quetiapine XR seem to be short-lived in this population. Other limitations include a small sample size, lack of a positive control group, the use of quetiapine XR, and a 1-month waiting period before the intervention. The strict exclusionary criteria may have improved the internal validity of the findings but at the cost of the external validity. Subsequent studies should use an adequately powered sample (≥100 subjects) and evaluate the effects of the quetiapine IR formulation, which may be more efficacious for insomnia.[32]

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AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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