Article

The Relationship between Alcohol Craving and Insomnia Symptoms in Alcohol-Dependent Individuals

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Abstract

Aim: This preliminary investigation evaluated the link between alcohol craving and insomnia in actively drinking patients with alcohol dependence (AD).

Methods: We conducted a secondary analysis of data from a clinical trial of treatment-seeking patients with AD who drank heavily ($N = 61$). The Penn Alcohol Craving Scale (PACS) evaluated alcohol craving, and the Short Sleep Index (SSI) assessed insomnia symptoms. We used linear regression models for baseline cross-sectional assessments. Linear mixed effects regression models evaluated craving scores longitudinally across insomnia groups (+/–), and insomnia scores longitudinally across craving groups (high/low). These longitudinal analyses were conducted separately in those treated with placebo ($N = 32$) and quetiapine ($N = 29$).

Results: The mean (standard deviation) for PACS total score was 15.9 (8.5) and for SSI was 2.1 (2.3). Alcohol craving was associated with the insomnia symptom of difficulty falling asleep ($P = 0.03$; effect size = -0.7) and with the SSI total score ($P = 0.04$, effect size = -0.7). In the longitudinal analysis, insomnia+ subjects had consistently higher PACS total scores, relative to the insomnia– group. The PACS score demonstrated significant group $\times$ time interactions in both treatment groups. Insomnia+ individuals demonstrated a relatively steeper rate of decline in the craving with quetiapine treatment ($P = 0.03$). Insomnia– individuals in the placebo group demonstrated a transient reduction in craving until week 8, followed by an increase in scores ($P = 0.004$). The SSI score did not demonstrate any interactive effect over time across the craving groups in either treatment arm.

Conclusion: Insomnia was associated with higher alcohol craving and quetiapine differentially reduced craving in those with insomnia.

INTRODUCTION

Insomnia is a disorder of sleep continuity characterized by difficulty falling asleep or staying asleep, with or without early morning

awakenings. Individuals with insomnia have a stronger preference for alcohol over non-alcoholic beverages (Roehrs *et al.*, 1999; Jefferson *et al.*, 2005) and hypnotic medications (Kaneita *et al.*,

2007) and they may rapidly develop tolerance to the hypnotic effects of alcohol, as shown in a recent study (Roehrs and Roth, 2018). This finding is understandable, as some prior studies in alcohol-dependent individuals have shown a link between insomnia and alcohol consumption. Some retrospective studies have demonstrated that many alcohol-dependent patients had insomnia in their pre-morbid state and used alcohol to self-medicate their insomnia symptoms (Brower *et al.*, 2001; Currie *et al.*, 2003). Moreover, some prospective studies have shown that alcohol-dependent individuals with disturbed sleep during treatment are at a higher risk of relapse when compared with those without impaired sleep (Skoloda *et al.*, 1979; Foster and Peters, 1999; Brower, 2003; Brooks *et al.*, 2018). Among sleep complaints, difficulty falling asleep is a specific insomnia symptom that has been linked to relapse (Foster and Peters, 1999; Conroy *et al.*, 2006). In summary, prior investigations have demonstrated that sleep continuity disturbance, and especially difficulty falling asleep, is related to an increased risk of alcohol consumption.

One aspect of alcohol use is the urge to use alcohol, an amorphous clinical construct that is referred to as alcohol craving (craving). Heavy drinkers and alcohol-dependent individuals report higher craving levels than social drinkers (Greeley *et al.*, 1993; Myrick *et al.*, 2003). Craving is an important clinical feature of pathological alcohol use and a diagnostic criterion for alcohol use disorder in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (American Psychiatric Association, 2013). It may be an important target for behavioral and pharmacologic treatment for alcohol dependence (AD; Flannery *et al.*, 2002; Browne *et al.*, 2016), as it is experienced by 54–72% of alcohol-dependent patients, and its presence is linked to alcohol consumption (Bottlender and Soyka, 2004; Chakravorty *et al.*, 2010).

It is possible that a direct link exists between craving and insomnia in patients with AD. Evidence in favor of this association has been seen in animal studies, among individuals who use other drugs, and indirectly in patients with AD. In rats, sleep fragmentation has been linked to increased cocaine craving (Chen *et al.*, 2015). In humans, sleep disturbance has been linked to higher craving levels in nicotine dependence (Dugas *et al.*, 2017), opioid dependence (Barta *et al.*, 2009) and polysubstance use disorder (Serre *et al.*, 2015). Indirect evidence for this craving-insomnia relationship has emerged in a study of alcohol-dependent individuals during their transition from inpatient to outpatient treatment. Brooks and colleagues observed that those who relapsed to drinking following inpatient treatment had a significantly higher craving score. Moreover, individuals with ongoing sleep disturbance post-discharge had a non-significant yet higher craving score than those who did not (Brooks *et al.*, 2016). Thus, it is possible that a direct relationship between alcohol craving and sleep disturbance may exist.

This association between insomnia and craving has implications for clinical care. If such a relationship does exist, it is essential to identify whether a particular insomnia symptom places an individual at a higher risk for craving and which of these two variables may be improved with currently available medications. Quetiapine is one such medication that has been demonstrated to improve sleep continuity (Martinotti *et al.*, 2008; Chakravorty *et al.*, 2014), sleep quality (Litten *et al.*, 2012) and alcohol craving (Martinotti *et al.*, 2008; Ray *et al.*, 2011). In this preliminary investigation, we initially evaluated the relationship between insomnia and craving using baseline cross-sectional data from a sample of alcohol-dependent individuals who reported to the clinic for treatment. Next, we explored

the directionality of this association using longitudinal data from the placebo and quetiapine treatment arms.

METHODS

Design

We conducted a secondary analysis of cross-sectional baseline data and longitudinal treatment data from a randomized clinical trial of quetiapine in treatment-seeking alcohol-dependent patients (Kampman *et al.*, 2007). The staff at the Treatment Research Center of the University of Pennsylvania conducted the clinical trial (PI: Kyle Kampman, MD). The Institutional Review Board at the University of Pennsylvania's Perelman School of Medicine approved the conduct of this study, and all patients signed informed consent.

Participants

Treatment-seeking, alcohol-dependent individuals ($n = 61$) were solicited through advertisements and self-referrals from the Philadelphia metropolitan region, as reported earlier (Kampman *et al.*, 2007). Participants were recruited into the study if they were 18–65 years old, comprehended English, met past-year diagnostic criteria for AD on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (American Psychiatric Association, 1994), reported sustained drinking during the last 90 days, and were not in acute alcohol withdrawal at the time of assessment. Individuals were excluded from the study if they met criteria for other drug dependence (excluding nicotine or cannabis), had unstable or serious psychiatric or medical disorders, were using psychotropic medications, including hypnotic medications, and were pregnant or at risk of becoming pregnant (Kampman *et al.*, 2007).

Measures

1. Structured Clinical Interview for DSM-IV (SCID) (Spitzer *et al.*, 1992)—the SCID is a structured assessment instrument that was used to establish the diagnosis of current AD in potential participants; 2. Addiction Severity Index (ASI) (McLellan *et al.*, 1992)—this validated instrument comprehensively assesses the individuals' substance-related problems across several domains. We used the composite psychiatric scale and the Hollingshead index score for employment in the current analysis. The range of the psychiatric scale is 0–1, where '0' denotes lowest possible psychiatric score and '1' denotes the highest severity of psychiatric problems. The Hollingshead's index has a range of 1–7, with higher numbers representing a lower functioning level. A score of '1' represents 'higher execs, major professional, owners of large businesses,' and a score of '7' denotes 'unskilled and no occupation.' 3. Penn Alcohol Craving Scale (PACS)—the PACS is a validated scale that evaluates alcohol craving over the last 7 days. The PACS generates a global score ranging from 0–30, and a higher score indicates a greater urge to drink (Flannery *et al.*, 1999); 4. Timeline Follow-back interview (TLFB) (Sobell *et al.*, 1988): The TLFB interview assesses the number of standard alcoholic drinks consumed daily using a calendar format. We used this measure to evaluate drinking over the 28 days before entry into the study. Heavy drinking was determined as the consumption of ≥ 4 drinks per day in women and ≥ 5 drinks per day in men (NIAAA, 2012). We used the TLFB to compute the drinks per drinking day (DrPDD, a measure of the quantity of alcohol consumption) and proportion of days of heavy drinking (PDHD, a measure of the frequency of risky drinking days); 5. Short Sleep Index (SSI)—the SSI is a sensitive and validated scale of

insomnia symptoms that we used to assess insomnia symptoms in this investigation (Perney *et al.*, 2015). The SSI is derived from the three insomnia items from the Hamilton Depression Rating Scale (HDRS) and one item related to sleep from the Hamilton Anxiety Rating Scale (HARS). The three sleep items in the HDRS include difficulty falling asleep, difficulty maintaining sleep, and early morning awakening. *Difficulty falling asleep* was evaluated using question 4 on the HDRS ('Insomnia: Early in the Night'). The options of responses to this question were 'no difficulty falling asleep' (coded as 0), 'complains of occasional difficulty falling asleep, i.e. more than ½ h' (coded as 1), and 'complains of nightly difficulty falling asleep' (coded as 2). *Difficulty staying asleep* was assessed using question 5 on the HDRS (Insomnia: Middle of the Night). The options of responses to this question were 'no difficulty' (coded as 0), 'patient complains of being restless and disturbed during the night' (coded as 1), and 'waking during the night—any getting out of bed rates 2 (except for the purposes of voiding)' (coded as 2). *Early morning awakening* was assessed using question 6 on the HDRS (Insomnia: Early Hours of the Morning). The available options of responses were as follows: 'no difficulty' (coded as 0), 'waking in early hours of the morning but goes back to sleep' (coded as 1), and 'unable to fall back asleep again if he/she gets out of bed' (coded as 2). The SSI also included the insomnia item (item # 4) from the HARS. This question asked about, 'difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors.' The response to this question was entered as one of the following options: 0 ('not present'), 1 ('mild'), 2 ('moderate'), 3 ('severe'), and 4 ('very severe'). The range of scores for the SSI was 0–10, with higher scores denoting more sleep-related problems. A cutoff score of 1.05 on the SSI was associated with a sensitivity of 89.9% (95% CI 83.7, 93.1) and a specificity of 69.1% (95% CI 56.7, 79.8) (Perney *et al.*, 2012).

Statistical analysis

Demographic and clinical differences between insomnia subgroups were assessed using independent samples *t*-test, Mann–Whitney *U*-test, or Chi-square test, as appropriate. The three individual insomnia items (difficulty falling asleep, staying asleep, and early morning awakening) were recoded into dichotomous variables (presence/absence of each symptom). Independent linear regression analyses were conducted to determine the associations between the PACS total score and dichotomous individual insomnia symptoms. The SSI total score demonstrated a bimodal distribution and was dichotomized using a cutoff score of ≥ 2 into a dichotomous variable, i.e. presence/absence of insomnia (Perney *et al.*, 2012). As a next step, we evaluated the link between PACS total score (outcome variable) and the dichotomized SSI score (predictor variable) using linear regression analysis to obtain unadjusted estimates of this relationship. Since we observed an association between the two variables, we built a multivariable model by inserting covariates into this model. These covariates included age, gender, occupation, PDHD, cannabis use at baseline and their psychiatric scale. The psychiatric scale was used (instead of the HDRS and HARS scores) in order to build a parsimonious model, minimize collinearity and capture the maximum variance of psychiatric symptoms using a single scale.

The longitudinal analysis of treatment data was conducted separately for the quetiapine-treated and placebo-treated individuals. In the first set of analyses, we compared the trajectories of the PACS total score across all 13 weeks of treatment in the groups with and without insomnia at baseline. In the next set of analyses, we

modeled the course of insomnia scores across all 4 time-points of assessment (weeks 1, 5, 9 and 13) between the groups with high craving (PACS total score range 16–30) and low craving (PACS total score range 0–15), as estimated at baseline. These treatment effects were evaluated using linear mixed effects regression models employing maximum likelihood estimation, adjusted for the same covariates used in the bivariate analysis (age, gender, occupation, baseline PDHD, cannabis use at baseline and the psychiatric scale). Each model considered categorical, continuous, and quadratic trends over time and treatment-by-time interactions. We evaluated each model for its appropriate variance-covariance matrix structure of random effects. The final models for each variable were selected for the most parsimonious Bayesian Information Criteria (BIC) score. An intent-to-treat effect was measured by the time-by-group interaction, where a statistically significant interaction indicated a difference in the specified outcome over time by group. All analyses were conducted using STATA 14 IC software (StataCorp, 2011).

RESULTS

The sample was mostly male (77.05%), white (51.6%), and single (68.8%). Study participants consumed a mean of 13.5 drinks each drinking day, as reported previously (Kampman *et al.*, 2007). There was no difference in baseline demographics between individuals with (+) and without (–) insomnia, other than on the psychiatric score ($P = 0.001$), Table 1. About half of study participants (49.2%) complained of insomnia. Difficulty falling asleep was reported by 32.7% of participants, difficulty staying asleep by 42.6%, and early morning awakening by 24.5%. Nearly, all the insomnia+ subgroup of AD participants reported DFA ($P < 0.001$), with 85% also reporting DSA ($P < 0.001$) and 87% reporting EMA ($P = 0.001$). Bivariate correlations among the variables ranged from 0.29 to 0.79 (Table 2), with moderate correlation among SSI and the other variables, and the highest correlations between the HDRS and HARS total scores (without their sleep items).

An analysis of the association between PACS total score and insomnia symptoms demonstrated that those who reported DFA had a 5.89-point higher model-estimated mean PACS score than those without DFA ($P = 0.01$), Figure 1, Table 3. We observed a non-significant trend between the PACS total score and DSA ($P = 0.07$), such that those with DSA had a 4.04-point higher model-estimated mean PACS score compared with those without DSA. We did not observe any association between craving and EMA ($P = 0.16$).

Next, we evaluated the relationship between PACS total score and the insomnia global score. In the unadjusted model, individuals who self-reported insomnia demonstrated a six-point higher mean PACS score than those without insomnia ($P = 0.006$), Table 3. When the model was adjusted for socio-demographic covariates and PDHD, the insomnia+ subgroup continued to report a six-point higher model-adjusted PACS mean score ($P = 0.007$). In the final model, also adjusted for the psychiatric covariate (derived from the ASI), the insomnia group had a 4.5-point higher model-adjusted mean score ($P = 0.04$). The Cohen's *d* estimates of the association with alcohol craving demonstrated large effect sizes for the SSI total score (-0.7 [95% CI -1.2 , -0.2]) and for DFA (-0.7 [95% CI -1.2 , -0.1]), whereas medium effect sizes were seen for DSA (-0.4 [95% CI -1.0 , 0.04]) and EMA (-0.4 [95% CI -1.0 , 0.1]) (Fig. 1).

The trajectory of the PACS score in the insomnia groups demonstrated the following findings: (1) the PACS score was consistently higher in the insomnia+ group over time, as compared with those in

Table 1. Demographic and clinical variables.

Variable	Total sample (N = 61) Mean (SD)	Sample stratified by insomnia status		P
		Insomnia + (N = 30) Mean (SD)	Insomnia- (N = 31) Mean (SD)	
Age	46.3 (10.6)	47.3(8.9)	45.4 (12.2)	0.49
Race (white)	31 (31/60)	19	11	0.07
Gender (male) N (%)	47 (77%)	22/30	25/31	0.49
Employment (unemployed)	4.5 (1.6)	4.5 (1.6)	4.5 (1.7)	0.85
Marital Status (single) N (%)	42 (69%)	22	20	0.45
Education (years)	13.8 (2.6)	14.1(2.8)	13.5 (2.3)	0.44
Drinks per drinking day	13.5 (13.7)	12.4 (12.5)	14.7 (15.3)	0.60
PDHD	0.5 (0.4)	0.5(0.4)	0.4 (0.4)	0.49
Psychiatric score	0.1 (0.1)	0.2 (0.2)	0.04 (0.1)	0.001
Alcohol craving (PACS total)	15.9 (8.5)	19.0 (7.2)	13.0 (8.8)	0.006
Cannabis use—past 30 days N (%)	5 (8.2%)	1 (1.6%)	4 (6.6%)	0.35
SSI total score	2.1 (2.2)	4.2 (1.4)	0.1 (0.4)	-

Legend: SD = standard deviation; PDHD = proportion of days of heavy drinking; PACS = Penn Alcohol Craving Scale; SSI = Short Sleep Index.

Table 2. Bivariate correlations between sleep and psychiatric symptoms (N = 61).

	PACS	SSI	HDRS	HARS	Psychiatric
PACS					
SSI	0.35, $P = 0.006$				
HDRS	0.41, $P = 0.001$	0.40, $P = 0.001$			
HARS	0.45, $P = 0.003$	0.39, $P = 0.001$	0.79, $P < 0.001$		
Psychiatric	0.29, $P = 0.025$	0.41, $P < 0.001$	0.68, $P < 0.001$	0.50, $P < 0.001$	

Legend: values stated here are Pearson's correlation index along with the P values; PACS = Penn Alcohol Craving Scale total score; SSI = Short Sleep Index; HDRS = Hamilton Depression Rating Scale without the sleep items; HARS = Hamilton Anxiety Rating Scale without the sleep item; Psychiatric = interviewer-rated psychiatric scale from the Addiction Severity Index.

the insomnia- group, in both quetiapine and placebo treatment groups; (2) although all quetiapine-treated subjects demonstrated a decrease in PACS total scores over time, an insomnia group $\times$ time interaction was seen, Fig. 2. The insomnia+ group had a relatively steeper slope of decline in the PACS score until about week 10. Beyond this time point, the PACS total scores plateaued for both groups; 3) in those treated with placebo, an insomnia group $\times$ time interaction was also seen, Fig. 3. Although the PACS total scores declined in both insomnia groups over time, the insomnia- group demonstrated a relatively steeper decline in their PACS total score until week 8. Beyond week 8, their craving scores started to increase. In contrast, the insomnia+ group demonstrated a slower rate of decline in their craving scores over time.

In the second set of longitudinal analysis, the trajectories of the SSI total score were evaluated over time across the high and low craving groups. In the quetiapine-treated group, only an effect of craving groups ($\beta = 1.2$, $P = 0.04$) was seen without any effect of either Time or Craving Group $\times$ Time interaction, when categorical time trends and an unstructured covariance matrix were used (BIC = 457.51). In the placebo-treated group, there was neither a main effect (for craving groups or time) nor an interaction effect of craving groups $\times$ time.

DISCUSSION

The goal of this study was to probe for an association between alcohol craving and insomnia in a sample of heavy drinking alcohol-dependent patients. Our results demonstrated that higher craving

was associated with the insomnia symptom of difficulty falling asleep as well as the global insomnia score. In the longitudinal analysis, the insomnia+ group had consistently higher craving relative to the insomnia- group in both intervention arms. The insomnia+ group demonstrated a relatively greater reduction in alcohol craving with quetiapine treatment. In the placebo arm, the insomnia- group demonstrated a steeper rate of reduction in craving until week 8, followed by an increase in craving scores beyond this time. There was no interactive effect between craving group $\times$ time for their insomnia scores in either treatment groups.

The relationship between craving and insomnia may be comprehended using either the operant conditioning theory (a learning process that modifies behavior by reinforcement), aversive conditioning theory (Staddon and Cerutti, 2003), or the social learning theory (Rohsenow and Monti, 1999). Insomnia is prevalent in actively drinking, alcohol-dependent individuals (Mello and Mendelson, 1970; Brower *et al.*, 2001; Chaudhary *et al.*, 2015), many of whom use alcohol to self-medicate their insomnia (Brower *et al.*, 2001), a learned behavior. The drinking initially helped them fall or stay asleep, but with time this continued alcohol use leads to the development of tolerance to the hypnotic effect of alcohol (Roehrs and Roth, 2018) and/or a propagation of their insomnia symptoms (Brower *et al.*, 2001; Haario *et al.*, 2013). The growing sleeplessness may foster a negative mood state and/or tiredness (Seo and Sinha, 2014; Chakravorty *et al.*, 2016). These symptoms, coupled with an ineffective coping response to insomnia or positive expectancies about the effect of alcohol may in turn increase their urge to drink. Alcohol consumption may occur when this increased urge to drink

Table 3. Alcohol craving's association with insomnia symptoms and the insomnia global score.

	Variable	Coefficient	SE	<i>t</i>	<i>P</i>	95% CI
Individual insomnia symptoms	DFA	5.8	2.2	2.5	0.01	1.3, 10.4
	DSA	4.0	2.2	1.8	0.07	−0.3, 8.4
	EMA	3.5	2.5	1.4	0.16	−1.5, 8.6
Insomnia global score	<i>Model 1: Crude model ($R^2 = 0.12$, $P = 0.006$)</i>					
	SSI	6	2.1	2.8	0.006	1.7, 10.2
	<i>Model 2: With demographic covariates (adj. $R^2 = 0.14$, $P = 0.03$)</i>					
	SSI	5.9	2.0	2.8	0.007	1.7, 10.1
	Age	−0.1	0.09	−1.4	0.14	−0.3, 0.05
	Gender	1.8	2.4	−0.7	0.45	−3.0, 6.7
	Occupation	−0.8	0.6	−1.3	0.19	−2.0, 0.4
	PDHD	2.0	2.2	0.8	0.37	−2.5, 6.6
	Cannabis	0.06	0.2	0.2	0.78	−0.3, 0.5
	<i>Model 3: Final model (adj. $R^2 = 0.17$, $P = 0.02$)</i>					
	SSI	4.5	2.2	2.0	0.04	0.04, 8.9
	Age	−0.1	0.09	−1.5	0.14	−0.3, 0.04
	Gender	1.6	2.4	0.6	0.49	−3.1, 6.5
	Occupation	−0.8	0.6	−1.3	0.19	−2.0, 0.4
	PDHD	2.0	2.2	0.9	0.36	−2.4, 6.5
	Cannabis	0.08	0.2	0.3	0.71	−0.3, 0.5
	Psychiatric	9.3	5.6	1.6	0.10	−2.0, 20.7

Legend: DFA = Difficulty Falling Asleep; DSA, Difficulty Staying Asleep; EMA = Early Morning Awakening; SSI = Short Sleep Index; PDHD = Proportion of Days of Heavy Drinking; Occupation = Hollingshead scale from the Addiction Severity Index; Psychiatric = Interviewer-rated psychiatric scale from the Addiction Severity Index; all three insomnia symptoms (DFA, DSA and EMA) were arrayed on a scale from 0 (absent) to 2 (most severe) and were dichotomized into 0 (absence) or 1 (presence) of specific symptoms based on the distribution of subject responses; Insomnia global score, SSI total score dichotomized using a cutoff score of ≥ 2 for the presence of insomnia symptoms.

Fig. 1. The association between alcohol craving and insomnia symptoms.
Legend: DFA = Difficulty Falling Asleep; DSA = Difficulty Staying Asleep; EMA = Early Morning Awakening; β = Coefficient.

is coupled with impaired impulse control or autonomic arousal (Irwin *et al.*, 2006; Chaudhary *et al.*, 2013; de Zambotti *et al.*, 2015).

The ventral tegmental area (VTA) in the midbrain has numerous reciprocal inputs and projections to and from other areas of the brain. Recent studies demonstrate that neurons of the VTA may promote wakefulness, especially under conditions of high motivation (Eban-Rothschild *et al.*, 2016; Sun *et al.*, 2017) through their projection to the orexinergic neuron in the lateral hypothalamus. Orexins are neuropeptides that help maintain arousal, especially when animals are stressed or are seeking reward (Boutrel *et al.*, 2010; Mahler *et al.*, 2014). The VTA also has interconnectivity with the nucleus accumbens (abnormalities in which have been linked to reward anticipation, craving and pathological alcohol consumption (Seo and

Sinha, 2014)). Thus, the VTA is involved in pathological alcohol consumption, craving, and arousal, with motivated behavior. Furthermore, these functions may be augmented by inputs from the orexinergic neurons, a system that also contributes to arousal and motivated behavior (Hrabovszky *et al.*, 2013).

Despite the overall reduction in craving scores across the insomnia groups, those with insomnia showed a relatively higher craving level and a steeper slope of reduction in alcohol craving over time with quetiapine treatment. Although quetiapine reduced alcohol craving in some prior studies (Martinotti *et al.*, 2008; Ray *et al.*, 2011), this finding was not replicated in a multi-center randomized, placebo-controlled trial (Litten *et al.*, 2012). The differential reduction in alcohol craving in our study is a unique finding and may partially explain the heterogeneity of quetiapine's effect on alcohol craving. It may be possible that quetiapine's effect on reducing craving especially in those with insomnia may involve its antagonistic effect on the orexinergic system (Monda *et al.*, 2006), a set of neurons linked to arousal and craving for drugs (Hrabovszky *et al.*, 2013; James *et al.*, 2018). The lack of an interactive effect on longitudinal insomnia scores in either craving group with treatment may be due to the small sample size of the study that was unable to detect a true difference between the groups.

We did not demonstrate a relationship between alcohol craving and alcohol consumption measures such as the proportion of heavy drinking days, DrPDD or drinking days (results not shown). Although alcohol craving is an important aspect of AD, the relationship between them is unclear. Some prior studies have shown that increased craving may lead to increased drinking (Flannery *et al.*, 2003; Kavanagh *et al.*, 2009; Browne *et al.*, 2016), decreased drinking (Monti *et al.*, 1993) or have no association with drinking (Rohsenow *et al.*, 1994; Cooney *et al.*, 1997; Kolla *et al.*, 2015). It is possible that increased craving interacts with other characteristics

Fig. 2. Alcohol craving scores over time with quetiapine treatment in subjects with and without insomnia. **Legend:** PACS = Penn Alcohol Craving Scale; Insomnia+ = subjects complaining of insomnia ($N = 12$); Insomnia- = subjects without insomnia complaint ($N = 17$); Visit = week; model statistics of mixed effects maximum likelihood regression using independent covariance matrix and adjusted for age, gender, occupation, proportion of days of heavy drinking at baseline, cannabis use at baseline and psychiatric scale score from the addiction severity index scale. Model statistics included, Insomnia status: $\beta = 4.7$, $P = 0.07$; time: $\beta = -0.8$, $P = 0.002$; insomnia status $\times$ time interaction: $\beta = 0.03$, $P = 0.03$; Bayesian Information Criteria score = 1951.09.

Fig. 3. Alcohol craving scores over time in placebo-treated subjects with and without insomnia. **Legend:** PACS = Penn Alcohol Craving Scale; Insomnia+ = subjects complaining of insomnia ($N = 14$); Insomnia- = subjects without insomnia complaint ($N = 18$); Visit = week; model statistics of mixed effects maximum likelihood regression using independent covariance matrix and adjusted for age, gender, occupation, proportion of days of heavy drinking at baseline, cannabis use at baseline and psychiatric scale score from the addiction severity index scale. Model statistics included, Insomnia status: $\beta = 0.8$, $P = 0.68$; time: $\beta = -1.9$, $P < 0.0001$; insomnia status $\times$ time interaction: $\beta = -0.08$, $P = 0.004$; Bayesian Information Criteria score = 1854.25.

(such as decreased motivation, a negative mood state, positive expectations from drinking or autonomic arousal) to promote drinking (Rohsenow and Monti, 1999). The lack of an association between craving and drinking in our treatment-seeking subjects may have been due to their negative expectations from drinking or their motivation to achieve abstinence.

Despite the novelty of these findings, limitations are inherent in this investigation. The current study may have oversampled for insomnia, as the SSI only considered the insomnia symptoms without their associated burden of daytime dysfunction. However, the oversampling may have been minimal, as our prevalence estimate of insomnia was within the 30–74% range reported in prior studies (Skoloda *et al.*, 1979; Chaudhary *et al.*, 2015). Although some readers may consider the evaluation of a biased sample of treatment-seeking individuals as a limitation of this study, this association also provides the first step in devising treatment interventions in them. Future longitudinal studies should evaluate this insomnia-craving relationship using an adequately-powered sample size, employing detailed insomnia assessments, and characterizing their chronotypes (i.e. their preferred sleep-wake times), since an evening chronotype has been linked to increased alcohol consumption (Wittmann *et al.*, 2010; Watson *et al.*, 2013).

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CONFLICTS OF INTERESTS

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