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Alcohol Dependence and its Relationship with Insomnia and Other Sleep Disorders

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Abstract

Sleep-related complaints are widely prevalent in those with Alcohol Dependence. Alcohol Dependence (AD) is not only associated with insomnia, but also with multiple sleep-related disorders as a growing body of literature has demonstrated.

This manuscript will review the various aspects of insomnia associated with AD. In addition, the association of AD with other sleep-related disorders will be briefly reviewed.

The association of AD with insomnia is bi-directional in nature. The etiopathogenesis of insomnia has demonstrated multiple associations and is an active focus of research. Treatment with cognitive behavioral therapy for insomnia is showing promise as an optimal intervention. In addition, AD may be associated with circadian abnormalities, short sleep duration, obstructive sleep apnea and sleep-related movement disorder.

The burgeoning knowledge on insomnia associated with moderate-to-severe alcohol use disorder has expanded our understanding of its underlying neurobiology, clinical features and treatment options.

Keywords: Alcohol, alcoholism, sleep, sleep initiation and maintenance disorders.

Introduction

Moderate-to-severe Alcohol Use Disorder (or Alcohol Dependence [AD]) has been associated with a range of sleep-related disturbances. These disturbances may have direct ramifications on the underlying AD and on the overall health and social well-being of the individual. The last comprehensive review on this topic was published in March 2005 (Stein and Friedmann, 2005).

Over this past decade, knowledge in the field of sleep-related disorders has grown considerably with the evolution of sleep medicine and behavioral sleep medicine as independent sub-specialties, and improved comprehension of sleep disorders and their treatments. Another ramification of this growing body of knowledge is the revision in the diagnostic criteria for sleep

disorders. These updated criteria are seen in the third edition of the International Classification of Sleep Disorders (ICSD-3) (AASM, 2014) and the fifth edition of the Diagnostic and Statistical Manual for Psychiatric disorders (DSM-5) (APA, 2013). In this manuscript we will adhere to the ICSD-3 classification for sleep disorders.

This exponential growth in information has also started to change the way we conceptualize and treat insomnia and other sleep-related disturbances associated with AD. It is with these facts in mind that we decided to review this growing body of knowledge. The primary aim of this manuscript is to review the literature related to insomnia associated with AD with a focus on its clinical manifestations, etiology and pathogenesis, and associated treatment interventions. The secondary aim of this manuscript is to briefly review literature on other sleep-related disorders associated with AD that sometimes present as insomnia.

Methods

The selection of manuscripts for this review was conducted in four steps. First, search terms were formulated to cover the effects of alcohol intoxication on sleep, the association of AD with various sleep-related disorders including insomnia, circadian rhythm sleep disorders, breathing-related sleep disorders, sleep-related movement disorders, and parasomnias. Second, appropriate search terms were applied to four different databases, namely Pubmed, Medline, Embase and Google Scholar in order to maximize retrieval of abstracts in the United States, European and other international databases. These searches were limited to human subjects, English language, and studies directly evaluating the relationships of alcohol use/disorder and sleep complaints/disorders. Wherever multiple studies were seen on the same topic, the largest studies and/or the most rigorous studies were evaluated. The dates of the literature were 1/1/1967 to 12/31/2015. Third, the references of the selected manuscripts were reviewed for additional manuscripts in our areas of interest. As a final step we also reviewed the last two literature reviews on this subject along with their references to extract additional manuscripts (Brower, 2001, Stein and Friedmann, 2005). A total of 135 manuscripts were reviewed for this manuscript. See Figure 1 for details. The primary author reviewed the articles and checked the

tables for accuracy and consistency. Alcohol's association with hypersomnia disorders was excluded from this review as it was considered beyond the scope of this current manuscript.

Results

In healthy subjects, the time lag after lying in bed with the intention to sleep and actual sleep is referred to as sleep onset latency (SOL). Once an individual falls asleep, s/he alternates between two states of sleep - Non-Rapid Eye Movement Sleep (NREM) and Rapid Eye Movement Sleep (REM). NREM is characterized by a succession of stages traditionally called 1 - 4 (Rechtschaffen and Kales, 1968). Slow Wave Sleep (SWS) or deep sleep corresponds to stages 3 and 4 combined. These stages correspond to a progressive increase in the depth of NREM sleep, with an associated decrease in frequency and an increase in amplitude of the brain waves, as measured by sleep electroencephalography (EEG). Nocturnal monitoring of sleep EEG, breathing, and movements in the sleep lab is known as polysomnography (PSG). About 90 minutes after the onset of NREM sleep, a person enters into REM sleep characterized by a decrease in the EEG amplitude (height of the waves), mixed-frequency waves, rapid eye movements and loss of muscle tone (as reflected in a low chin electromyography tone (Iber et al., 2007, Siegel, 2017). Saw-tooth waves may also appear as a superimposed rhythm with a frequency of 2-3 Hz and triangular in shape with the appearance of teeth on a saw (Pearl et al., 2002, Berger et al., 1962). The timing and duration of each state and stage of sleep throughout the night is called sleep architecture. For further information on sleep-related variables see Table 1.

In addition to the electrophysiologic mechanisms of sleep, Borbely and colleagues postulated a two-process model of sleep regulation (Borbely, 1982). In brief, this model posits that sleep is a function of two independent mechanisms, namely homeostatic sleep drive and circadian rhythmicity. The homeostatic mechanism is responsible for a build-up of the sleep drive with continued wakefulness through the day, whereas the circadian mechanism is responsible for maintenance of wakefulness and is influenced by zeitgebers such as ambient light and meal times. One or both mechanisms may be weakened or abnormal in insomnia. A mismatch

between the normally synergistic circadian and homeostatic mechanisms may also lead to circadian rhythm sleep disorders.

Alcohol and its effect on sleep continuity in healthy subjects

The alcohol level in blood is determined by gender, weight, number of drinks consumed over a unit of time, and rate of metabolism. It is generally metabolized at a rate of 0.01 to 0.02 g% per hour (Arnedt et al., 2011b). When alcohol is consumed before bedtime, its effects on sleep architecture also differ based on the ascending or peak concentrations during the first 3-4 hours of the night (first half of the night) as compared to the descending phase of blood alcohol levels during the next 3-4 hours of sleep (second half of the night).

The effect of moderate and heavy alcohol on sleep in healthy adults has been investigated across multiple studies although most of these studies were limited with their small sample sizes. With moderate doses of alcohol (< 1 g/Kg), the only consistent PSG sleep finding has been decreased REM sleep duration (Williams et al., 1983, Miyata et al., 2004, Roehrs et al., 1991). Analysis of sleep across the first half of the night did not demonstrate any consistent changes in PSG sleep. In the second half of the night, the consistent finding was decreased REM sleep duration (Rundell et al., 1972, Miyata et al., 2004). Recently, Arnedt and colleagues conducted one of the largest studies of sleep in heavy drinking healthy adults. They demonstrated that alcohol at a dose of > 1 g/Kg, as compared with placebo, decreased SOL and sleep efficiency (SE; percentage of time in bed spent sleeping), and increased wake after sleep onset time (WASO). Alcohol's effect on sleep architecture was to increase the percentage of slow wave sleep (SWS%), stage 2 sleep, and REM latency, and to decrease REM%. During the 1st half of the night, alcohol as compared to placebo, increased Total Sleep Time (TST) and SE, and decreased the number and duration of awakenings. But, during the 2nd half of the night, TST and SE were decreased, with an increased number and duration of awakenings (Arnedt et al., 2011b). Similar findings of sleep disruption have been demonstrated in late adolescence (Chan et al., 2013), although their EEG power spectra analysis after alcohol consumption demonstrated

simultaneous increases in frontal delta and alpha powers during the earlier part of sleep, which may lead to sleep disturbance (Chan et al., 2015). Lastly, consumption of alcohol earlier in the evening and despite an undetectable breath alcohol level showed sleep to be superficial (subjectively) and with high frequency EEG activity (objectively), thus demonstrating an increased arousal within their sleep (Landolt et al., 1996).

In summary, moderate doses of alcohol may decrease the amount of REM sleep through the night. In doses mimicking heavy drinking, alcohol may initially improve sleep continuity during the first half of the night. But in the second half of the night, it may lead to fragmented sleep (more awakenings). Further, alcohol may continue to disturb sleep even after the breath alcohol concentration is undetectable.

Insomnia

Introduction. Insomnia is the most investigated sleep disorder, although some of these studies have evaluated insomnia symptoms in lieu of it as a disorder. Insomnia disorder as defined by the ICSD-3 requires the presence of ≥ 1 of the following complaints: difficulty initiating sleep, difficulty maintaining sleep, or waking up earlier than desired. These symptoms are associated with ≥ 1 of the following impairments: fatigue or malaise, attention or memory problems, impairment of psychosocial functioning, mood disturbance, daytime sleepiness, behavioral problems, reduced motivation or energy, proneness for errors, and concern or dissatisfaction with sleep. These complaints must occur despite adequate opportunity and circumstances for sleep and are present for most nights of the week for ≥ 3 months (AASM, 2014). The criteria for insomnia disorder in DSM-5 are nearly identical.

Alcohol Dependence (AD)

Insomnia or sleep disturbance is widely prevalent in alcohol dependence. The prevalence estimates range from 36-91% (Mello and Mendelson, 1970, Brower et al., 2001b, Chaudhary et al., 2015, Baekeland et al., 1974, Cohn et al., 2003). Alcohol dependence may be categorized into different stages based on the temporal relationship with exposure to alcohol. Insomnia has

been associated with all these stages and is briefly reviewed below, taking into account different populations, wherever applicable.

During Active Alcohol Use

A. Treatment Seeking AD subjects – There is a limited body of literature on insomnia associated with active alcohol use in AD. These studies may be categorized based on their use of subjective or objective measures: a) Subjective measures. The prevalence rate of insomnia was 74% in a recent study that used the Insomnia Severity Index (Chaudhary et al., 2015). In one study, 30% of the subjects were actively drinking during treatment. They complained of increased sleep latency and fragmentation of their sleep (Skoloda et al., 1979). In another investigation, staff assessments in an inpatient rehabilitation unit demonstrated that those who continued to drink had sleep fragmentation and a reduction of their TST (Mello and Mendelson, 1970); b. Objective measures. PSG sleep studies in subjects with AD and alcohol consumption also found increased SOL and decreased TST, and sleep architectural changes including decreased REM sleep duration and increased REM sleep latency and SWS (Gross et al., 1973, Gross and Hastey, 1975). These findings contrast with another study where increased TST with alcohol consumption was seen (Allen et al., 1980).

B. Non-treatment seeking problem drinkers - In a recent study of non-treatment seeking problem drinkers in the community (N = 295), Hartwell and colleagues used the Pittsburgh Sleep Quality Index (PSQI) (Hartwell et al., 2015) to demonstrate a 76% prevalence rate of sleep disturbance. They defined sleep disturbance using a PSQI total score > 5. In addition, they also used a 3-factor scoring model to evaluate insomnia; these factors consisted of sleep efficiency, perceived sleep quality and daily disturbances. This sleep disturbance was positively associated with alcohol problem severity.

C. Veterans - In a chart review of Veterans with AD (N = 84), insomnia symptoms included increased SOL (72±67 minutes), and WASO time (82±13 minutes), and poor sleep quality in 63% of patients. These insomnia symptoms were prevalent for 75±123 months (Chakravorty et al.,

2013). One of the strongest predictor of insomnia symptoms was the presence of psychiatric disorder (OR = 20.8).

In summary, the preponderance of studies report subjective and objective increase in sleep onset latency and sleep fragmentation with consequently decreased TST in actively drinking subjects with AD.

During Acute Withdrawal

The withdrawal phase after acute cessation of sustained alcohol use lasts about 1-2 weeks with a prevalence rate of sleep complaints that is variable. Steinig and colleagues demonstrated that 92% of inpatients with AD acutely withdrawing from alcohol had sleep disturbance (Steinig et al., 2011). In a study of Brazilian subjects undergoing inpatient alcohol detoxification (N = 58), subjective sleep disturbance was prevalent in all women (100%, 13/13) and most men, 88.9% (40/45) (Escobar-Cordoba et al., 2009). In another investigation involving subjects in a residential treatment program, the symptom of "inability to sleep" differed in prevalence across race and ethnicity. In this treatment-seeking sample of male patients, the prevalence was the lowest in Blacks (54%), highest in Whites (82%), and with an intermediate prevalence of 65% in Mexican-Americans males (Caetano et al., 1998).

These insomnia symptoms may improve with time as the detoxification progresses. Bokstrom and colleagues demonstrated a decrease in the mean $\pm$ S.D. insomnia scores from 1.3 $\pm$ 1.1 (N = 48) to 0.8 $\pm$ 1.0 (N = 13), p = 0.01 for days 0 versus 7 after last alcohol use during inpatient detoxification (Bokstrom and Balldin, 1992). In the general population, the prevalence rate of insomnia as a withdrawal symptom was 32% among alcohol-dependent individuals (Brower and Perron, 2010).

In patients with delirium tremens (DTs), a higher percentage of Stage 1 sleep with REM (stage 1 period with low voltage EEG with REM) was demonstrated (Greenberg and Pearlman, 1967). In this study, one of the subjects had nightmares of hallucinatory intensity during alcohol

withdrawal and with 100% Stage 1-REM sleep. As DTs ended, recovery sleep set in as a response to sleep deprivation in most of these patients. However, a subset of patients may have fragmented sleep and disturbances of consciousness that predict a guarded prognosis for future episodes of DTs (Kotorii et al., 1982, Nakazawa et al., 1981).

During Recovery From Alcohol Use

Early Recovery (2-8 weeks after detoxification) - Some studies have reported a mild withdrawal syndrome persisting after the cessation of an acute withdrawal phase. This condition may be secondary to a hyperexcitable state of the central nervous system (Begleiter and Porjesz, 1979) and has been called protracted abstinence, protracted withdrawal phase, or late withdrawal symptoms (Heilig et al., 2010). Its main features include, mood disturbance, alcohol craving and sleep related disturbances, and they may persist for about 5 weeks (Alling et al., 1982).

Sleep problems are common during this phase and may be prevalent in about 65% of individuals during this phase (Brower et al., 2001a, Kolla et al., 2014). Subjective complaints in those with insomnia as compared to those without include longer SOL, increased WASO and lower sleep efficiency (Brower et al., 2001a, Conroy et al., 2006b). PSG sleep findings during the first 8 weeks of abstinence include increased SOL and stage 1 sleep and decreased TST and SWS % (Gillin et al., 1990b, Gillin et al., 1990a, Moeller et al., 1993, Le Bon et al., 1997, Brower et al., 2001a). REM sleep findings have been inconsistent during this phase with some studies reporting a decreased REM sleep latency and increased REM % (Gillin et al., 1990a, Williams and Rundell, 1981) whereas other studies did not (Gillin et al., 1990b, Le Bon et al., 1997). It is to be noted that individuals in early recovery may overestimate their subjective SOL but underestimate their WASO, as compared to their PSG estimated indices (Conroy et al., 2006b).

Those who relapse to alcohol use during treatment may have more disturbed sleep, as compared to abstainers (Brower, 2003, Currie et al., 2004, Conroy et al., 2006a, Smith et al., 2014). In contrast, two studies have failed to demonstrate such a relationship with subjective insomnia (Jakubczyk et al., 2013) (Feige et al., 2007) as measured by the Athens Insomnia Scale

and PSQI, respectively; although the latter study demonstrated an association of relapse with increased sleep EEG β2 spectral power. It is possible that use of alcohol as a sleep aid rather than sleep disturbance is associated with relapse, as demonstrated in a recent study (Kolla et al., 2015).

Sustained Recovery (≥ 3 months beyond detoxification phase) - Subjective and objective sleep related disturbances persist for up to 3 years into sobriety as demonstrated by cross-sectional and longitudinal studies. Subjective complaints of insomnia may persist up to 2 years into sobriety (Cohn et al., 2003, Wellman, 1954, Kissin, 1979). Longitudinal studies evaluating PSG sleep have demonstrated the presence of increased SOL and sleep fragmentation, a decreased TST, and, abnormalities in SWS and REM sleep stages. Although increased SOL reached normal levels by 5-9 months into recovery, sleep fragmentation persisted for 21 months and consequently TST was seen to normalize in ≤ 2 years (Adamson and Burdick, 1973, Williams and Rundell, 1981, Drummond et al., 1998). Slow wave sleep is decreased early in recovery and gradually normalizes over time and around 2 years of sobriety (Williams and Rundell, 1981, Imatoh et al., 1986, Drummond et al., 1998).

There is some inconsistency in the literature relating to REM sleep abnormalities during sustained recovery. In one study, REM sleep architecture demonstrated a reversal during early recovery, with the first REM sleep episode of the night being the longest, despite a lack of depressive disorder in these subjects. The REM sleep architecture normalized over time with continued recovery (Imatoh et al., 1986). This phenomenon may suggest a normalization of the acrophase of REM sleep with sobriety and may also account for increased REM % during early recovery. In a frequently cited study, decreased REM sleep latency and increased REM % was seen at 27 months into recovery (Drummond et al., 1998). These findings contrast with lack of REM sleep abnormalities reported in 2 other studies, as compared to healthy control subjects (Williams and Rundell, 1981, Schiavi et al., 1995). Discrepancies in REM sleep may reflect sample differences, duration of sobriety (where the REM sleep may have normalized over time)

(Williams and Rundell, 1981), or an interaction between REM sleep architecture and a circadian disruption (Imatoh et al., 1986).

Other information on sleep in recovering alcoholics

Sleep Hygiene – Poor sleep hygiene may perpetuate insomnia. Napping was common during recovery in one study resulting in longer WASO times, decreased TST and lower SE (Currie et al., 2003a).

Dreams and Nightmares - Dreams and nightmares may lead to insomnia and sleep fragmentation. In a study of subjects with AD during acute alcohol detoxification, in addition to a poor sleep quality, only 21% had dreams about alcohol. Dream content was described as "strange, foreign" and as if "from another world". As abstinence progressed, dreams became less strange and aggressive (Steinig et al., 2011). An unreplicated finding is that drinking-related dreams were positively associated with length of abstinence (Choi, 1973).

Epidemiology of Insomnia in Alcohol Dependence

There is a growing body of literature demonstrating a bidirectional relationship of insomnia with alcohol consumption and alcohol misuse.

Sleep problems and future alcohol use. Retrospectively, subjects with AD reported the presence of insomnia prior to the onset of AD (Currie et al., 2003a). Sleep disturbance has been shown to predict subsequent alcohol consumption in adolescents and adults (Breslau et al., 1996, Wong et al., 2004, Wong et al., 2010, Wong et al., 2015, Ford and Kamerow, 1989, Weissman et al., 1997). This association may be secondary to subjects self-medicating their insomnia with alcohol (Kaneita et al., 2007, Ancoli-Israel and Roth, 1999, Johnson et al., 1998).

Does AD lead to Insomnia? In a longitudinal Swedish study (N = 2602), having alcohol dependence (CAGE questionnaire total score of ≥ 2) was associated with subsequent insomnia symptoms (OR = 1.75, 95% CI: 1.2-2.5) (Janson et al., 2001). Similarly, respondents with chronic

alcohol dependence (N = 248) during longitudinal follow-up, were more likely to report insomnia symptoms as compared to those who had remitted (N = 211) during the follow-up period (OR = 2.6, 95% CI: 1.1-6.0) (Crum et al., 2004).

What are the ramifications of insomnia in AD? Prior cross-sectional and longitudinal studies have demonstrated the following associations with AD: a) Relapse to drinking (Brower, 2003, Currie et al., 2003b, Conroy et al., 2006a); b) Higher psychosocial problems related to the drinking, including recent employment problems, conflicts with others in their environment and with impulse control (Zhabenko et al., 2012, Chaudhary et al., 2013, Chaudhary et al., 2015); c) Decreased self-reported quality of life (Zhabenko et al., 2012, Cohn et al., 2003); d) Recent and lifetime suicidal ideation (Klimkiewicz et al., 2012, Chaudhary et al., 2015); and, e) Insufficient sleep duration (John et al., 2005). The recommended range of sleep duration to support optimal health in adults is 7-9 hours (Consensus Conference et al., 2015). Sleep duration $\leq$ 6 hours a night has been linked with an increased risk for mortality, injuries, cardio-metabolic and psychiatric problems as well as suicide in adults (Consensus Conference et al., 2015).

What are the risk factors for insomnia/Sleep problems?

Demographic and other covariates – a) Age – Older age was associated with better subjective sleep quality in 2 studies (Chakravorty et al., 2013, Kolla et al., 2014), although it was inversely associated with objective PSG sleep continuity measures (Gillin et al., 1990b, Brower and Hall, 2001); b) relatively lower education (Zhabenko et al., 2012); c) marital/partner status – those who were single (Chakravorty et al., 2013, Perney et al., 2012); d) monetary problems (Zhabenko et al., 2012); e) severity of alcoholism (Brower et al., 2001a, Hartwell et al., 2015, Zhabenko et al., 2012); f) frequency of alcohol use (Zhabenko et al., 2012) although one study did not replicate this association (Currie et al., 2003a); and, g) a history of sexual or physical abuse (Zhabenko et al., 2012).

Family history of alcoholism – children and adolescents of parents with AD have demonstrated lower delta power in their NREM sleep, greater power in the alpha frequencies in NREM and

346 REM spectral PSG studies, and a shorter sleep duration (Tarokh and Carskadon, 2010, Dahl et
347 al., 2003, Conroy et al., 2015, Schuckit and Bernstein, 1981).
348
349 *Biomarkers of insomnia* – a few biomarkers that have been evaluated have included the
350 following: a) *Spectral PSG Studies.* High frequency EEG activity in the beta and gamma range is
351 increased in those with primary insomnia (Perlis et al., 2001a, Perlis et al., 2001b); b) *Studies*
352 *evaluating Autonomic Activity.* Increased sympathetic activity with simultaneously decreased
353 activity of the parasympathetic nervous system, especially during the first 4 hours of the night
354 was seen in those with AD and sleep disturbance (Irwin et al., 2006, de Zambotti et al., 2014). A
355 recent study has demonstrated that autonomic nervous system activity may improve with
356 sustained recovery (de Zambotti et al., 2015); c) *Cytokines.* Cytokines such as Interleukins (IL)
357 and Tumor Necrosis Factor (TNF) are humoral factors associated with sleep regulation (Krueger
358 and Toth, 1994, Krueger et al., 1998). Studies in subjects with AD, as compared to controls,
359 have demonstrated a decreased production of Interleukin (IL) - 6 in the early part of the night,
360 suppression of the Il-6/IL-10 through the night, increased nocturnal levels along with greater
361 increases in IL-6 and TNF-α levels with partial sleep deprivation (Redwine et al., 2003, Irwin and
362 Miller, 2000). Etanercept, a TNF-α antagonist medication, has been shown to decrease the
363 amount and % of REM sleep to a comparable level to age-comparable control subjects (Irwin et
364 al., 2009). Thus, studies involving spectral sleep studies and autonomic activity suggest an
365 increased arousal in sleep disturbance.
366
367 *Genetic Studies.* There is an emerging interest in the associations between AD and circadian
368 clock genes. In a Polish sample of individuals with AD (N = 285), PER3 $^{4/4}$ homozygotes reported
369 the highest insomnia scores, PER3 $^{5/5}$ genotype the lowest, and the heterozygotes PER$^{4/5}$ had an
370 intermediate score (Brower et al., 2012).
371
372 <u>*A Conceptual Model for Insomnia in AD*</u>
373 Sleep and wakefulness are two parallel and competing processes. Sleep onset occurs when
374 there are increased homeostatic (sleep-promoting) and decreased circadian (wake-promoting)

drives (Borbely, 1982). From a general neurophysiological perspective, the onset and maintenance of sleep involves depolarizations of the thalamocortical neural circuits (Saper et al., 2010). The 'sleep-wake switching system' resides within the lateral hypothalamus, the ventrolateral preoptic area, and the median preoptic area. In contrast to generalized sleep activity across the brain, "local" sleep involves activities in certain neurons or neuronal assemblies leading to regional sleep-like neuronal activity patterns. These activities are then propagated to other brain regions via signaling systems. Insomnia results from a mismatch involving persistent activity in wake-promoting structures during NREM sleep, leading to simultaneous sleep and wake activity along with psychophysiological arousal (Buysse et al., 2011). From a clinical perspective, insomnia occurs in vulnerable patients with predisposing factors, such as having a family history of AD or certain genetic traits. Acute insomnia is triggered in them by stress promoting events (precipitating factors). This acute insomnia becomes persistent because of perpetuating factors such as reading in bed (Spielman et al., 1987) or drinking alcohol. Figure 2 presents a conceptual model for insomnia in AD during recovery.

Treatments for Insomnia in AD

Despite the prevalence of insomnia in those with AD, it is not aggressively treated (Friedmann et al., 2003). We have summarized the pharmacologic and behavioral treatments for insomnia in AD in Table 2. These studies have been reviewed in more detail elsewhere (Brooks and Wallen, 2014, Brower, 2016, Kolla et al., 2011a). Medication treatments have demonstrated mixed efficacy. Trazodone was demonstrated to increase alcohol use in one randomized, placebo-controlled trial (Friedmann et al., 2008), although this finding was not replicated in an observational study (Kolla et al., 2011b). Similarly, Brower and colleagues did not demonstrate any superiority of gabapentin over placebo, although Mason and colleagues did report an improvement. In their study of non-treatment seeking patients with AD, Mason and colleagues demonstrated an improvement in sleep quality for those treated with gabapentin (1200 mg a day), as compared to placebo, and after 1 week of treatment, with a mean difference of – 2.38, $p < 0.05$ favoring gabapentin (Mason et al., 2009). In a follow up larger study, the authors

replicated the finding of an improvement in sleep quality with gabapentin. It is to be noted that in this latter study, some of the subjects in the treatment arms did not meet criterion for sleep disturbance at baseline (Mason et al., 2014). In a randomized, placebo-controlled trial of heavy drinking subjects with AD (N = 224), quetiapine XR at a dose of 400 mg a day improved sleep quality, as compared to placebo (Litten et al., 2012). Behavioral treatments for insomnia have demonstrated consistent efficacy with moderate to large effect sizes, although these studies have small sample sizes and employed modified versions of CBT-I, such as CBTI-AD (Brooks and Wallen, 2014).

In summary, insomnia is prevalent across all stages of AD and may have psychosocial, addiction and psychiatric ramifications. "Although some encouraging results have been seen with gabapentin, quetiapine and CBT-I, these findings need to be replicated using adequately powered studies in individuals with insomnia comorbid with alcohol dependence".

Alcohol Dependence and Insomnia Associated with Other Sleep Disorders

Other primary sleep disorders may occur more commonly with AD and present as insomnia in the clinical setting. These include obstructive sleep apnea (OSA), periodic limb movement disorder (PLMD), and delayed phase sleep disorder (DSPD). AD has also been linked with periodic limb movement disorder, circadian rhythm abnormalities, and obstructive sleep apnea, which are discussed below. There is a lack of evidence that alcohol consumption is a trigger for sleepwalking (Pressman et al., 2007), although it has been linked epidemiologically to night terrors, which is another parasomnia (Ohayon et al., 1999).

Alcohol Dependence and Period Limb Movement Disorder (PLMD).

The patient with PLMD may present with disturbed sleep and resultant impairment of functioning, which are not explained by another sleep/medical/neurologic/psychiatric disorder (AASM, 2014). It is diagnosed with polysomnography using a criterion of > 15 repetitive limb movements per hour of sleep in adults, mostly in the lower extremities. PLMD is associated with restless legs syndrome (Fulda, 2015) and may masquerade as insomnia.

Among those with AD, treatment-seeking subjects have been demonstrated to have a higher Periodic Limb Movement Index (PLMI) as compared to controls (Brower and Hall, 2001). A longitudinal study involving patients sober for 2-3 weeks after withdrawal, demonstrated higher baseline PLMI and PLMI with arousals versus healthy controls (Gann et al., 2002). At the 6-month follow-up, subjects with AD who relapsed had significantly higher PLMI and PLMI with arousals, than those who did not. Conversely, another study failed to find a difference in PLMI between those with AD in early recovery and controls (Le Bon et al., 1997). Magnesium supplementation had a mixed result on PLMs in an open-label trial of AD patients (Hornyak et al., 2004).

Alcohol and Circadian Rhythm Sleep-Wake Disorders.

Circadian rhythms are a manifestation of the activity of the primary endogenous pacemaker, the suprachiasmatic nucleus in the hypothalamus, upon which melatonin acts. Dim Light Melatonin Onset (DLMO) is a commonly used marker for evaluating the activity of the circadian pacemaker and for assessing the changes in circadian phase, i.e. delayed or advanced (Pandi-Perumal et al., 2007). The peak of the salivary melatonin curve occurs around 2AM in middle-aged males (Zhou et al., 2003). This peak may be blunted or delayed in those with AD (Kuhlwein et al., 2003). Consequently, AD subjects may be more likely to manifest a delayed phase type disorder, which may present as difficulty falling asleep.

Alcohol and Obstructive Sleep Apnea (OSA).

Alcohol use and AD have been associated with OSA in prior studies. Alcohol can impair normal breathing by impairing the normal arousal response to airway obstruction and by relaxing the upper airway musculature, leading to initiation or worsening of existing snoring, sleep-disordered breathing (SDB) and sleep fragmentation (Peppard et al., 2007, Vitiello, 1997, Sakurai et al., 2007).

In one study, subjects with AD in acute withdrawal demonstrated a higher intensity of respiratory events in their sleep (12.6 ± 12.3 events/hour), as compared to healthy controls (3.6 ± 3.4 events/hour) (Le Bon et al., 1997). In another study, a higher prevalence rate of SDB was seen in treatment-seeking patients with AD (41%), as compared to control subjects (23%). In this study, SDB was a significant contributor to sleep disturbance in a substantial proportion of male AD subjects above the age of 40 years (Aldrich et al., 1993). To the best of our knowledge, there is no data on the association of AD with central sleep apnea in the absence of other risk factors, such as comorbid congestive heart failure and opioid use.

Discussion

A growing body of literature has demonstrated an association between AD and sleep-related disorders. The preponderance of this literature is on insomnia. Insomnia is being increasingly evaluated as a disorder of inappropriate arousal during sleep associated with involvement of multiple underlying mechanisms, and downstream cognitive and behavioral manifestations. In addition, the role of circadian factors and sleep drive mechanisms in mediating and moderating insomnia are being recognized. The implications of this understanding have been the use of behavioral interventions for its treatment and the role of newer medications such as ramelteon, which may also have the ability to advance circadian phase (Richardson et al., 2008). In addition, AD is being increasingly implicated with insufficient sleep duration, obstructive sleep apnea, and periodic limb movement disorder.

One of the limitations associated with prior literature is assessment of insomnia symptoms rather than insomnia as a disorder in people with AD. This may stem from the difficulty in distinguishing alcohol-induced insomnia from other causes of insomnia. Other limitations include small sample sizes, use of different assessment instruments across studies, lack of PSG to rule out other alcohol-associated sleep disorders, and heterogeneous samples with and without insomnia in PSG or treatment studies of recovering AD patients. Future studies should investigate the underlying mechanisms of insomnia in AD, the role of pharmacologic and

behavioral treatments of insomnia using PSG, and the relationships of AD with other sleep disorders such as parasomnias.

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Table 1. Terminologies used in sleep related assessments

Term	Description
Time in Bed (TIB)	The total time spent in bed
Total Sleep Time (TST, min)	The total duration of sleep through the night
Sleep Efficiency (SE, %)	The percentage of time spent sleeping through the night, i.e. TST/TIB
NREM sleep	The initial part of sleep; consists of stages 1, 2 and slow wave sleep (SWS); quiet sleep; about 80% of sleep
Stage 1 (N1) sleep	Consists of slow eye movements, and waves with low amplitude and predominantly 4-7 Hz activity
Stage 2 (N2) sleep	The sleep stage characterized by the onset of sleep spindles and K complexes
Slow Wave (N3) Sleep (stages 3 & 4)	The presence of low frequency and high amplitude delta waves (0.5-2Hz) for ≥ 20% of the epoch
REM sleep	Sleep with low amplitude and mixed frequency waveforms, rapid eye movements and low muscle tone
Sleep Onset Latency (min)	Time from "lights out" until the onset of sleep
REM Onset Latency (min)	Interval of time from sleep onset to the appearance of the first epoch of REM sleep
Stage 1 %	The percentage of time in sleep that is spent in Stage 1 sleep, i.e. 100 X total Stage 1 sleep/TST; usually about 4-5%
Stage 2%	The percentage of time in sleep that is spent in Stage 2 sleep, i.e. 100 X total Stage 2 sleep/TST; usually about 45-55%
Slow Wave Sleep (SWS) %	The percentage of time in sleep that is spent in SWS sleep, i.e. 100 X total SWS sleep/TST; usually about 16-21%
REM %	The percentage of time in sleep that is spent in REM sleep, i.e. 100 X total REM sleep/TST; usually about 20-25%
Apnea Hypopnea Index (AHI, #/Hour)	The number of apneas and hypopneas through the night, i.e. total number of apneas and hypopneas/TST (in hours)
Periodic Limb Movement	Limb movements with an amplitude of ≥ 8 μV, lasting 0.5-10 seconds, 5-90 sec apart, and ≥ 4 in a row
Periodic Limb Movement Index (number/hour)	The number of periodic limb movements during sleep/TST.
Phase Advance	Shift of the sleep cycle to an earlier time during the 24-hour period
Phase Delay	Shift of the sleep cycle to a later time during the 24-hour period

Information gathered from the following sources: 1) The AASM Manual for the scoring of Sleep and Associated Events, AASM, 2007; 2) http://www.sleepnet.com/definition.html
(Updated for the scoring criteria replacing Stages 1-4 with N1-N3, from the American Academy of Sleep Medicine, 2012.)

Table 2. Pharmacologic and behavioral treatments for insomnia in alcohol dependence

Authors	Selected for insomnia	N	RCT	Daily Dose, Treatment Duration	Primary Outcome Measure	Time Since Last Drink	Effect on Insomnia	Effect on Drinking
PHARMACOLOGIC								
Acamprosate								
(Staner et al., 2006)	No	24	Yes	1998 mg/day; 23 days	PSG	0	↓	↓
(Perney et al., 2012)	Yes[1]	239	Yes	2-3 gm/day; 6 months	Short Sleep Index	≤ 10 days	↓	? ↓
Agomelatine								
(Grosshans et al., 2014)	Yes	9	No	25-50 mg/day; 6 wks	Sleep Quality	NA	↓	NA
Chlormethiazole								
(Gann et al., 2004)	No	20	Yes	Taper protocol; 5 days	PSG	0	↑	NA
Gabapentin								
(Karam-Hage and Brower, 2000)	Yes	15	No	Gabapentin 200 – 1500 mg; 4-6 wks	SPQ	4 wks	↓	↓
(Karam-Hage and Brower, 2003)	Yes	50	No	Gabapentin (888±418 mg) or Trazodone (105±57 mg); 4-6 wks	SPQ	≥ 4 wks	↓ G > T	↓ (Two subjects in each group)
(Malcolm et al., 2007)	No	68	Yes	Gabapentin/lorazepam taper	Insomnia questions[2]	0	↓ (G > L)	∅
(Brower et al., 2008)	Yes	21	Yes	1500 mg; 6 wks	PSG	≥ 1 week	∅	↓

Quetiapine XR								
(Chakravorty et al., 2014)	Yes	20	Yes	400 mg; 8 wks	PSG	≥ 1 month	↓	NA
Ramelteon								
(Brower et al., 2011)	Yes	5	No	8 mg; 4 wks	ISI	2-13 wks	↓	Lapse to HD (N=1)
Trazodone								
(Le Bon et al., 2003)	Yes	18	Yes	150-200 mg; 4 wks	PSG	≥ 2 wks	↓	NA
(Friedmann et al., 2008)	Yes	173	Yes	50-150 mg; 12 wks	Sleep Quality	Day 3-5 post-detox	↓	↑
Triazolam								
(Fabre et al., 1977)	Yes	12	No	0.5 – 1.0 mg; 28 days	Sleep diary & Q	5-15 days	↓	? ↓
BEHAVIORAL								
Authors	**Selected for insomnia**	**N**	**RCT**	**Treatment Duration**	**Primary Outcome Measure**	**Time Since Last Drink**	**Effect on Insomnia**	**Effect on Drinking**
PR								
(Greeff and Conradie, 1998)	Yes	22	Yes	2 wks	Quality of Sleep	≥ 1 month in RTP	↓	NA
CBT-I								
(Currie et al., 2004)	Yes	60	Yes	7 wks	Sleep diary	≥ 1 month	↓	∅
(Arnedt et al., 2007)	Yes	7	No	8 wks	Sleep diary	27-433 days	↓	↓
(Arnedt et al., 2011a)	Yes	17	Yes	8 wks	Sleep diary	8-433 days	↓	∅

Legend: Selection criteria = studies with sleep as the primary outcome; [1] = this was the secondary aim of this manuscript, which is in itself a secondary analysis of data from a clinical trial; [2] = insomnia questions from the CIWA (Clinical Institute Withdrawal Assessment Scale for Alcohol – Revised) and BDI (Beck Depression Inventory) questionnaires; N = number of subjects in the study; RCT = Randomized-controlled trial; SPQ = Sleep Problems Questionnaire; PSG = Polysomnography; G = Gabapentin; T = Trazodone; L = Lorazepam; wks = weeks; ISI = Insomnia Severity Index; RTP = Residential Treatment Program; Q = Questionnaire; HD = Heavy Drinking; ↑ = increased; ↓ = decreased; ? = unknown effect; NA = not applicable as not investigated; ∅ = no difference; day 3-5 post-detox = evaluated after 3-5 day detoxification protocol; PR = Progressive Relaxation (including muscle relaxation); CBT-I = Cognitive Behavioral Therapy for Insomnia.

Figure 1. Manuscript selection process for the current review

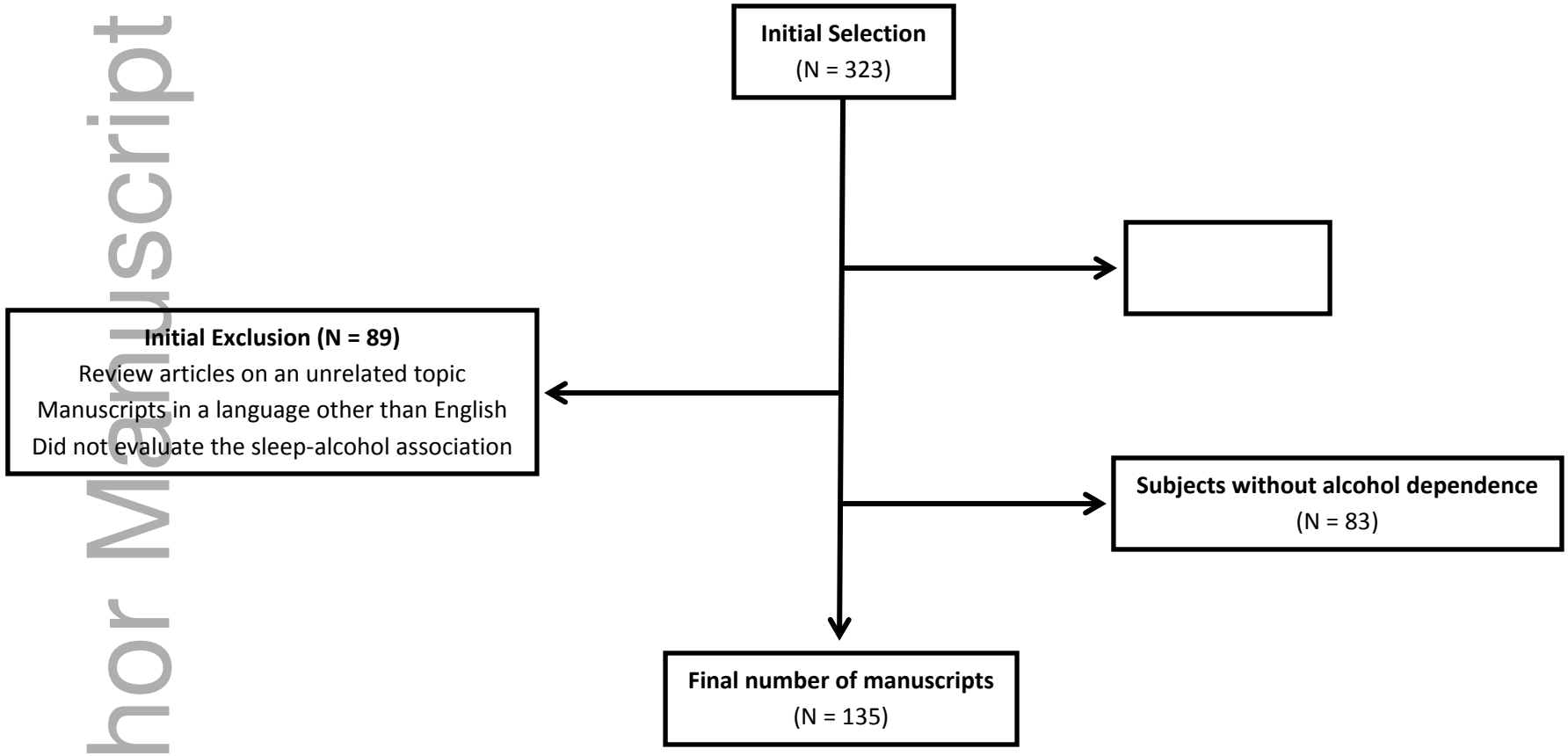
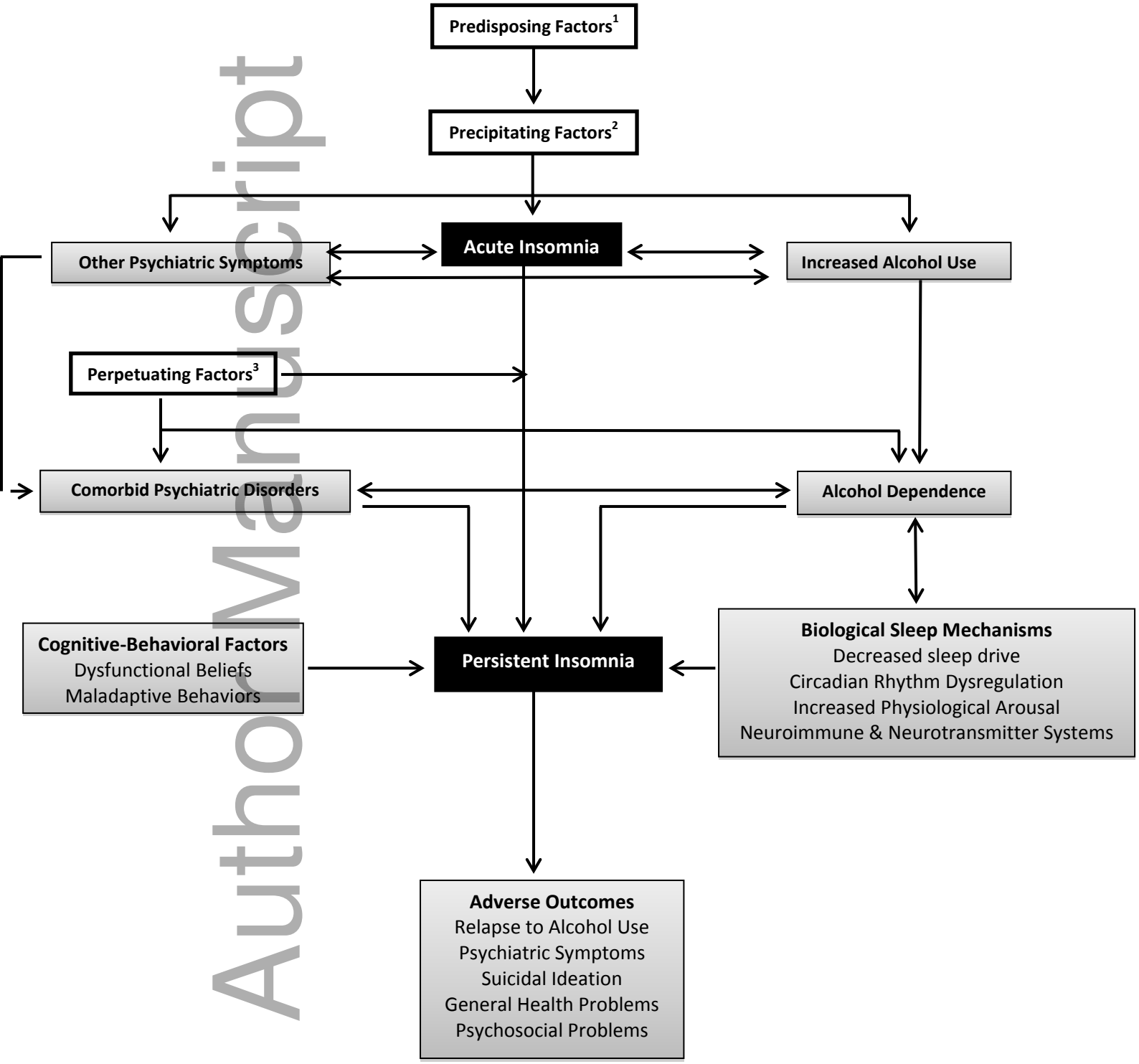


Figure 2. A conceptual model of insomnia in alcohol dependence



Legend: [1] Predisposing Factors: Familial AD, genetic (clock gene polymorphism), chronotype (evening type), childhood trauma, childhood sleep problems; [2] Precipitating Factors: Acute life events or psychosocial stressors; [3] Perpetuating Factors: Compensatory behaviors that are adopted by the individual in order to cope with the insomnia, but that actually reinforce the sleep problem. These factors can include the practice of non-sleep behaviors in the bedroom, staying in bed while awake, watching television or reading while in bed, and spending excessive amounts of time in bed (Spielman et al., 1987).