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## **Alcohol Dependence and its Relationship with Insomnia and Other Sleep Disorders**

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## Abstract

30

31

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

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

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

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

45

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

47

48

## Introduction

49

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

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

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

62  
63 This exponential growth in information has also started to change the way we conceptualize  
64 and treat insomnia and other sleep-related disturbances associated with AD. It is with these  
65 facts in mind that we decided to review this growing body of knowledge. The primary aim of  
66 this manuscript is to review the literature related to insomnia associated with AD with a focus  
67 on its clinical manifestations, etiology and pathogenesis, and associated treatment  
68 interventions. The secondary aim of this manuscript is to briefly review literature on other  
69 sleep-related disorders associated with AD that sometimes present as insomnia.

70

71

### **Methods**

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

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

89

90

### Results

91 In healthy subjects, the time lag after lying in bed with the intention to sleep and actual sleep is  
92 referred to as sleep onset latency (SOL). Once an individual falls asleep, s/he alternates  
93 between two states of sleep - Non-Rapid Eye Movement Sleep (NREM) and Rapid Eye  
94 Movement Sleep (REM). NREM is characterized by a succession of stages traditionally called 1 -  
95 4 (Rechtschaffen and Kales, 1968). Slow Wave Sleep (SWS) or deep sleep corresponds to stages  
96 3 and 4 combined. These stages correspond to a progressive increase in the depth of NREM  
97 sleep, with an associated decrease in frequency and an increase in amplitude of the brain  
98 waves, as measured by sleep electroencephalography (EEG). Nocturnal monitoring of sleep  
99 EEG, breathing, and movements in the sleep lab is known as polysomnography (PSG). About 90  
100 minutes after the onset of NREM sleep, a person enters into REM sleep characterized by a  
101 decrease in the EEG amplitude (height of the waves), mixed-frequency waves, rapid eye  
102 movements and loss of muscle tone (as reflected in a low chin electromyography tone (Iber et  
103 al., 2007, Siegel, 2017). Saw-tooth waves may also appear as a superimposed rhythm with a  
104 frequency of 2-3 Hz and triangular in shape with the appearance of teeth on a saw (Pearl et al.,  
105 2002, Berger et al., 1962). The timing and duration of each state and stage of sleep throughout  
106 the night is called sleep architecture. For further information on sleep-related variables see  
107 Table 1.

108

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

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

118

### 119 **Alcohol and its effect on sleep continuity in healthy subjects**

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

126

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

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

149  
150 In summary, moderate doses of alcohol may decrease the amount of REM sleep through the  
151 night. In doses mimicking heavy drinking, alcohol may initially improve sleep continuity during  
152 the first half of the night. But in the second half of the night, it may lead to fragmented sleep  
153 (more awakenings). Further, alcohol may continue to disturb sleep even after the breath  
154 alcohol concentration is undetectable.

155

## 156 **Insomnia**

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

167

## 168 **Alcohol Dependence (AD)**

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

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

175

### 176 During Active Alcohol Use

177 *A. Treatment Seeking AD subjects* – There is a limited body of literature on insomnia associated  
178 with active alcohol use in AD. These studies may be categorized based on their use of subjective  
179 or objective measures: a) Subjective measures. The prevalence rate of insomnia was 74% in a  
180 recent study that used the Insomnia Severity Index (Chaudhary et al., 2015). In one study, 30%  
181 of the subjects were actively drinking during treatment. They complained of increased sleep  
182 latency and fragmentation of their sleep (Skoloda et al., 1979). In another investigation, staff  
183 assessments in an inpatient rehabilitation unit demonstrated that those who continued to drink  
184 had sleep fragmentation and a reduction of their TST (Mello and Mendelson, 1970); b.  
185 Objective measures. PSG sleep studies in subjects with AD and alcohol consumption also found  
186 increased SOL and decreased TST, and sleep architectural changes including decreased REM  
187 sleep duration and increased REM sleep latency and SWS (Gross et al., 1973, Gross and Hasty,  
188 1975). These findings contrast with another study where increased TST with alcohol  
189 consumption was seen (Allen et al., 1980).

190

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

198

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

202 2013). One of the strongest predictor of insomnia symptoms was the presence of psychiatric  
203 disorder (OR = 20.8).

204  
205 In summary, the preponderance of studies report subjective and objective increase in sleep  
206 onset latency and sleep fragmentation with consequently decreased TST in actively drinking  
207 subjects with AD.

208

209 *During Acute Withdrawal*

210 The withdrawal phase after acute cessation of sustained alcohol use lasts about 1-2 weeks with  
211 a prevalence rate of sleep complaints that is variable. Steinig and colleagues demonstrated that  
212 92% of inpatients with AD acutely withdrawing from alcohol had sleep disturbance (Steinig et  
213 al., 2011). In a study of Brazilian subjects undergoing inpatient alcohol detoxification (N = 58),  
214 subjective sleep disturbance was prevalent in all women (100%, 13/13) and most men, 88.9%  
215 (40/45) (Escobar-Cordoba et al., 2009). In another investigation involving subjects in a  
216 residential treatment program, the symptom of “inability to sleep” differed in prevalence  
217 across race and ethnicity. In this treatment-seeking sample of male patients, the prevalence  
218 was the lowest in Blacks (54%), highest in Whites (82%), and with an intermediate prevalence  
219 of 65% in Mexican-Americans males (Caetano et al., 1998).

220  
221 These insomnia symptoms may improve with time as the detoxification progresses. Bokstrom  
222 and colleagues demonstrated a decrease in the mean  $\pm$  S.D. insomnia scores from  $1.3 \pm 1.1$  (N =  
223 48) to  $0.8 \pm 1.0$  (N = 13),  $p = 0.01$  for days 0 versus 7 after last alcohol use during inpatient  
224 detoxification (Bokstrom and Balldin, 1992). In the general population, the prevalence rate of  
225 insomnia as a withdrawal symptom was 32% among alcohol-dependent individuals (Brower and  
226 Perron, 2010).

227  
228 In patients with delirium tremens (DTs), a higher percentage of Stage 1 sleep with REM (stage 1  
229 period with low voltage EEG with REM) was demonstrated (Greenberg and Pearlman, 1967). In  
230 this study, one of the subjects had nightmares of hallucinatory intensity during alcohol



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

#### 235 236 During Recovery From Alcohol Use

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

243  
244 Sleep problems are common during this phase and may be prevalent in about 65% of  
245 individuals during this phase (Brower et al., 2001a, Kolla et al., 2014). Subjective complaints in  
246 those with insomnia as compared to those without include longer SOL, increased WASO and  
247 lower sleep efficiency (Brower et al., 2001a, Conroy et al., 2006b). PSG sleep findings during the  
248 first 8 weeks of abstinence include increased SOL and stage 1 sleep and decreased TST and SWS  
249 % (Gillin et al., 1990b, Gillin et al., 1990a, Moeller et al., 1993, Le Bon et al., 1997, Brower et al.,  
250 2001a). REM sleep findings have been inconsistent during this phase with some studies  
251 reporting a decreased REM sleep latency and increased REM % (Gillin et al., 1990a, Williams  
252 and Rundell, 1981) whereas other studies did not (Gillin et al., 1990b, Le Bon et al., 1997). It is  
253 to be noted that individuals in early recovery may overestimate their subjective SOL but  
254 underestimate their WASO, as compared to their PSG estimated indices (Conroy et al., 2006b).

255  
256 Those who relapse to alcohol use during treatment may have more disturbed sleep, as  
257 compared to abstainers (Brower, 2003, Currie et al., 2004, Conroy et al., 2006a, Smith et al.,  
258 2014). In contrast, two studies have failed to demonstrate such a relationship with subjective  
259 insomnia (Jakubczyk et al., 2013) (Feige et al., 2007) as measured by the Athens Insomnia Scale

260 and PSQI, respectively; although the latter study demonstrated an association of relapse with  
261 increased sleep EEG  $\beta_2$  spectral power. It is possible that use of alcohol as a sleep aid rather  
262 than sleep disturbance is associated with relapse, as demonstrated in a recent study (Kolla et  
263 al., 2015).

264  
265 *Sustained Recovery* ( $\geq 3$  months beyond detoxification phase) - Subjective and objective sleep  
266 related disturbances persist for up to 3 years into sobriety as demonstrated by cross-sectional  
267 and longitudinal studies. Subjective complaints of insomnia may persist up to 2 years into  
268 sobriety (Cohn et al., 2003, Wellman, 1954, Kissin, 1979). Longitudinal studies evaluating PSG  
269 sleep have demonstrated the presence of increased SOL and sleep fragmentation, a decreased  
270 TST, and, abnormalities in SWS and REM sleep stages. Although increased SOL reached normal  
271 levels by 5-9 months into recovery, sleep fragmentation persisted for 21 months and  
272 consequently TST was seen to normalize in  $\leq 2$  years (Adamson and Burdick, 1973, Williams and  
273 Rundell, 1981, Drummond et al., 1998). Slow wave sleep is decreased early in recovery and  
274 gradually normalizes over time and around 2 years of sobriety (Williams and Rundell, 1981,  
275 Imatoh et al., 1986, Drummond et al., 1998).

276  
277 There is some inconsistency in the literature relating to REM sleep abnormalities during  
278 sustained recovery. In one study, REM sleep architecture demonstrated a reversal during early  
279 recovery, with the first REM sleep episode of the night being the longest, despite a lack of  
280 depressive disorder in these subjects. The REM sleep architecture normalized over time with  
281 continued recovery (Imatoh et al., 1986). This phenomenon may suggest a normalization of the  
282 acrophase of REM sleep with sobriety and may also account for increased REM % during early  
283 recovery. In a frequently cited study, decreased REM sleep latency and increased REM % was  
284 seen at 27 months into recovery (Drummond et al., 1998). These findings contrast with lack of  
285 REM sleep abnormalities reported in 2 other studies, as compared to healthy control subjects  
286 (Williams and Rundell, 1981, Schiavi et al., 1995). Discrepancies in REM sleep may reflect  
287 sample differences, duration of sobriety (where the REM sleep may have normalized over time)

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

290

291 *Other information on sleep in recovering alcoholics*

292 *Sleep Hygiene* – Poor sleep hygiene may perpetuate insomnia. Napping was common during  
293 recovery in one study resulting in longer WASO times, decreased TST and lower SE (Currie et al.,  
294 2003a).

295

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

302

303 *Epidemiology of Insomnia in Alcohol Dependence*

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

306

307 *Sleep problems and future alcohol use.* Retrospectively, subjects with AD reported the presence  
308 of insomnia prior to the onset of AD (Currie et al., 2003a). Sleep disturbance has been shown to  
309 predict subsequent alcohol consumption in adolescents and adults (Breslau et al., 1996, Wong  
310 et al., 2004, Wong et al., 2010, Wong et al., 2015, Ford and Kamerow, 1989, Weissman et al.,  
311 1997). This association may be secondary to subjects self-medicating their insomnia with  
312 alcohol (Kaneita et al., 2007, Ancoli-Israel and Roth, 1999, Johnson et al., 1998).

313

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

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

320  
321 *What are the ramifications of insomnia in AD?* Prior cross-sectional and longitudinal studies  
322 have demonstrated the following associations with AD: a) Relapse to drinking (Brower, 2003,  
323 Currie et al., 2003b, Conroy et al., 2006a); b) Higher psychosocial problems related to the  
324 drinking, including recent employment problems, conflicts with others in their environment and  
325 with impulse control (Zhabenko et al., 2012, Chaudhary et al., 2013, Chaudhary et al., 2015); c)  
326 Decreased self-reported quality of life (Zhabenko et al., 2012, Cohn et al., 2003); d) Recent and  
327 lifetime suicidal ideation (Klimkiewicz et al., 2012, Chaudhary et al., 2015); and, e) Insufficient  
328 sleep duration (John et al., 2005). The recommended range of sleep duration to support  
329 optimal health in adults is 7-9 hours (Consensus Conference et al., 2015). Sleep duration  $\leq$  6  
330 hours a night has been linked with an increased risk for mortality, injuries, cardio-metabolic and  
331 psychiatric problems as well as suicide in adults (Consensus Conference et al., 2015).

332  
333 *What are the risk factors for insomnia/Sleep problems?*

334 *Demographic and other covariates* – a) Age – Older age was associated with better subjective  
335 sleep quality in 2 studies (Chakravorty et al., 2013, Kolla et al., 2014), although it was inversely  
336 associated with objective PSG sleep continuity measures (Gillin et al., 1990b, Brower and Hall,  
337 2001); b) relatively lower education (Zhabenko et al., 2012); c) marital/partner status – those  
338 who were single (Chakravorty et al., 2013, Perney et al., 2012); d) monetary problems  
339 (Zhabenko et al., 2012); e) severity of alcoholism (Brower et al., 2001a, Hartwell et al., 2015,  
340 Zhabenko et al., 2012); f) frequency of alcohol use (Zhabenko et al., 2012) although one study  
341 did not replicate this association (Currie et al., 2003a); and, g) a history of sexual or physical  
342 abuse (Zhabenko et al., 2012).

343  
344 *Family history of alcoholism* – children and adolescents of parents with AD have demonstrated  
345 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- $\alpha$  levels with partial sleep deprivation (Redwine et al., 2003, Irwin and  
362 Miller, 2000). Etanercept, a TNF- $\alpha$  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<sup>4/4</sup> homozygotes reported  
369 the highest insomnia scores, PER3<sup>5/5</sup> genotype the lowest, and the heterozygotes PER<sup>4/5</sup> had an  
370 intermediate score (Brower et al., 2012).

371  
372 *A Conceptual Model for Insomnia in AD*

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)

375 drives (Borbely, 1982). From a general neurophysiological perspective, the onset and  
376 maintenance of sleep involves depolarizations of the thalamocortical neural circuits (Saper et  
377 al., 2010). The ‘sleep-wake switching system’ resides within the lateral hypothalamus, the  
378 ventrolateral preoptic area, and the median preoptic area. In contrast to generalized sleep  
379 activity across the brain, “local” sleep involves activities in certain neurons or neuronal  
380 assemblies leading to regional sleep-like neuronal activity patterns. These activities are then  
381 propagated to other brain regions via signaling systems. Insomnia results from a mismatch  
382 involving persistent activity in wake-promoting structures during NREM sleep, leading to  
383 simultaneous sleep and wake activity along with psychophysiological arousal (Buysse et al.,  
384 2011). From a clinical perspective, insomnia occurs in vulnerable patients with predisposing  
385 factors, such as having a family history of AD or certain genetic traits. Acute insomnia is  
386 triggered in them by stress promoting events (precipitating factors). This acute insomnia  
387 becomes persistent because of perpetuating factors such as reading in bed (Spielman et al.,  
388 1987) or drinking alcohol. Figure 2 presents a conceptual model for insomnia in AD during  
389 recovery.

390

### 391 Treatments for Insomnia in AD

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

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

412  
413 In summary, insomnia is prevalent across all stages of AD and may have psychosocial, addiction  
414 and psychiatric ramifications. “Although some encouraging results have been seen with  
415 gabapentin, quetiapine and CBT-I, these findings need to be replicated using adequately  
416 powered studies in individuals with insomnia comorbid with alcohol dependence”.

417

#### 418 **Alcohol Dependence and Insomnia Associated with Other Sleep Disorders**

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

426

#### 427 **Alcohol Dependence and Period Limb Movement Disorder (PLMD).**

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

433

434 Among those with AD, treatment-seeking subjects have been demonstrated to have a higher  
435 Periodic Limb Movement Index (PLMI) as compared to controls (Brower and Hall, 2001). A  
436 longitudinal study involving patients sober for 2-3 weeks after withdrawal, demonstrated  
437 higher baseline PLMI and PLMI with arousals versus healthy controls (Gann et al., 2002). At the  
438 6-month follow-up, subjects with AD who relapsed had significantly higher PLMI and PLMI with  
439 arousals, than those who did not. Conversely, another study failed to find a difference in PLMI  
440 between those with AD in early recovery and controls (Le Bon et al., 1997). Magnesium  
441 supplementation had a mixed result on PLMs in an open-label trial of AD patients (Hornyak et  
442 al., 2004).

443

#### 444 **Alcohol and Circadian Rhythm Sleep-Wake Disorders.**

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

453

#### 454 **Alcohol and Obstructive Sleep Apnea (OSA).**

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

460



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

469

470

### Discussion

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

481

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

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

491

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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 $\geq 20\%$ 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. $100 \times \text{total Stage 1 sleep}/\text{TST}$ ; usually about 4-5%
Stage 2%	The percentage of time in sleep that is spent in Stage 2 sleep, i.e. $100 \times \text{total Stage 2 sleep}/\text{TST}$ ; usually about 45-55%
Slow Wave Sleep (SWS) %	The percentage of time in sleep that is spent in SWS sleep, i.e. $100 \times \text{total SWS sleep}/\text{TST}$ ; usually about 16-21%
REM %	The percentage of time in sleep that is spent in REM sleep, i.e. $100 \times \text{total REM sleep}/\text{TST}$ ; 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 $\geq 8 \mu\text{V}$ , lasting 0.5-10 seconds, 5-90 sec apart, and $\geq 4$ 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

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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
<b>PHARMACOLOGIC</b>								
<b>Acamprosate</b>								
(Staner et al., 2006)	No	24	Yes	1998 mg/day; 23 days	PSG	0	↓	↓
(Perney et al., 2012)	Yes <sup>1</sup>	239	Yes	2-3 gm/day; 6 months	Short Sleep Index	≤ 10 days	↓	? ↓
<b>Agomelatine</b>								
(Grosshans et al., 2014)	Yes	9	No	25-50 mg/day; 6 wks	Sleep Quality	NA	↓	NA
<b>Chlormethiazole</b>								
(Gann et al., 2004)	No	20	Yes	Taper protocol; 5 days	PSG	0	↑	NA
<b>Gabapentin</b>								
(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 <sup>2</sup>	0	↓ (G > L)	∅
(Brower et al., 2008)	Yes	21	Yes	1500 mg; 6 wks	PSG	≥ 1 week	∅	↓



<b>Quetiapine XR</b>								
(Chakravorty et al., 2014)	Yes	20	Yes	400 mg; 8 wks	PSG	≥ 1 month	↓	NA
<b>Ramelteon</b>								
(Brower et al., 2011)	Yes	5	No	8 mg; 4 wks	ISI	2-13 wks	↓	Lapse to HD (N=1)
<b>Trazodone</b>								
(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	↓	↑
<b>Triazolam</b>								
(Fabre et al., 1977)	Yes	12	No	0.5 – 1.0 mg; 28 days	Sleep diary & Q	5-15 days	↓	? ↓
<b>BEHAVIORAL</b>								
<b>Authors</b>	<b>Selected for insomnia</b>	<b>N</b>	<b>RCT</b>	<b>Treatment Duration</b>	<b>Primary Outcome Measure</b>	<b>Time Since Last Drink</b>	<b>Effect on Insomnia</b>	<b>Effect on Drinking</b>
<b>PR</b>								
(Greeff and Conradie, 1998)	Yes	22	Yes	2 wks	Quality of Sleep	≥ 1 month in RTP	↓	NA
<b>CBT-I</b>								
(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; <sup>1</sup> = this was the secondary aim of this manuscript, which is in itself a secondary analysis of data from a clinical trial; <sup>2</sup> = 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

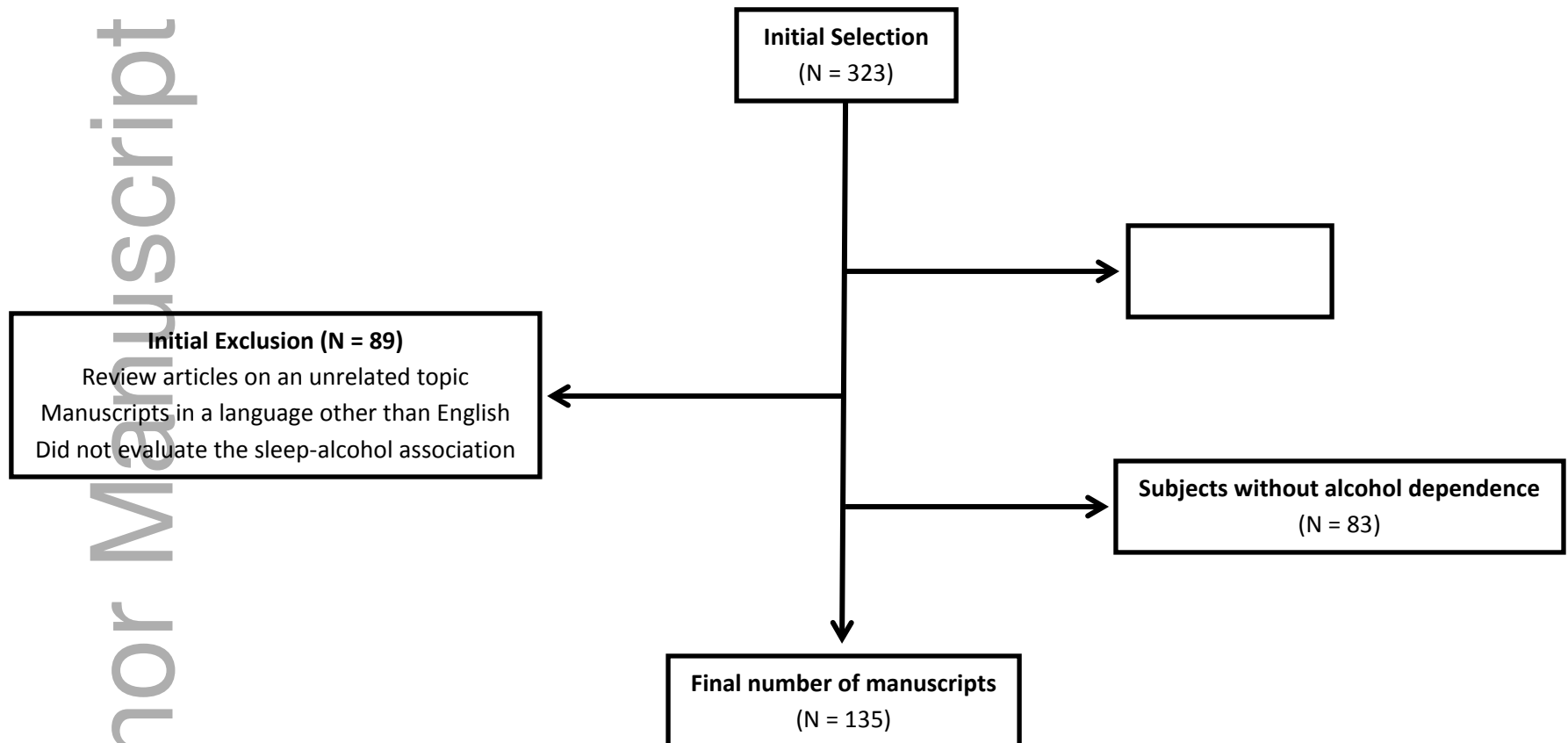
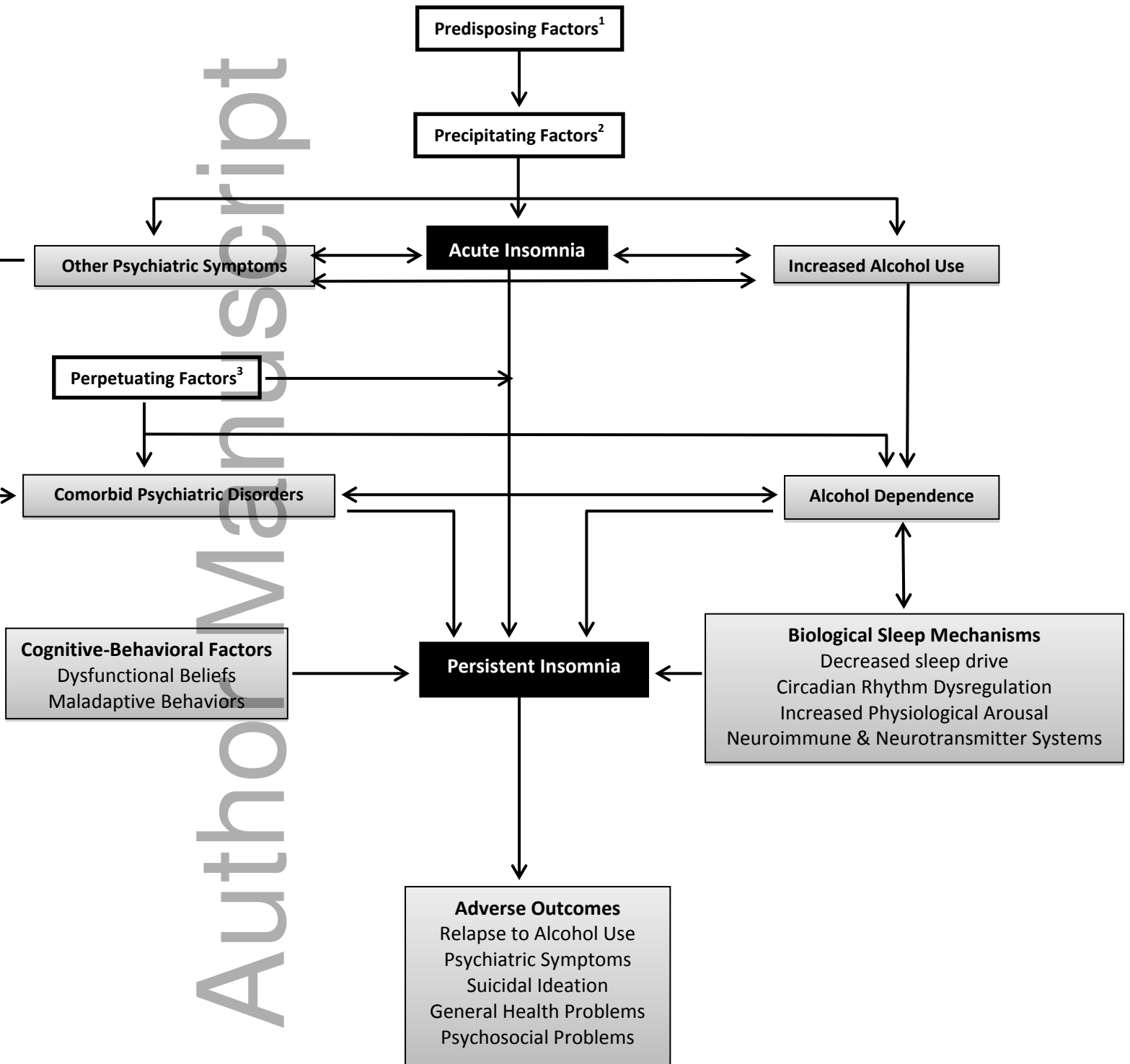


Figure 2. A conceptual model of insomnia in alcohol dependence



Legend: <sup>1</sup>Predisposing Factors: Familial AD, genetic (clock gene polymorphism), chronotype (evening type), childhood trauma, childhood sleep problems; <sup>2</sup>Precipitating Factors: Acute life events, acute psychiatric symptoms; <sup>3</sup>Perpetuating factors: maladaptive 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).