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8   **Cognitive Behavioral Therapy for Insomnia in Alcohol Dependent Veterans: A Randomized,**

9   **Controlled Pilot Study**

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41 **Abstract**

42 **Background:** Insomnia is highly prevalent in individuals recovering from Alcohol Dependence
43 (AD) and increases their risk of relapse. Two studies evaluating Cognitive Behavioral Therapy for

44 Insomnia (CBT-I) have demonstrated its efficacy in non-Veterans recovering from AD. The aim

45 of this study was to extend these findings in an 8-week trial of CBT-I in Veterans.

46 **Methods:** Veterans recovering from AD were randomly assigned to 8 weeks of treatment with

47 CBT-I (N=11) or a Monitor-Only (MO [n=11]) condition and were evaluated 3 (N=21/22) and 6

48 months post-treatment (N=18/22). The primary outcome measure was the Insomnia Severity

49 Index (ISI) score. Secondary outcome measures were sleep diary measures, percent days

50 abstinent (PDA), and scores on the Dysfunctional Beliefs and Attitudes About Sleep scale

51 (DBAS), Sleep Hygiene Index (SHI), Penn Alcohol Craving Scale (PACS), Quick Inventory of

52 Depressive Symptoms (QIDS), State-Trait Anxiety Inventory-Trait (STAI-T) scale and SF-12.

53 Mixed effects regression models, adjusted for race, evaluated differences in outcomes between

54 the groups over a 6-month period (clinicaltrials.gov identifier=NCT01603381).

55 **Results:** Subjects were male, aged 54.5 (SD=6.9) years, and had 26.4 (SD=26.3) days of

56 abstinence before their baseline evaluation. CBT-I produced a significantly greater

57 improvement in model-based estimates than MO (mean change at 6 months compared to their

58 baseline) for ISI, sleep latency from a daily sleep diary, DBAS mean score, and SHI total score.

59 PDA and QIDS improved over time, but there was no difference between the groups. PACS,

60 STAI-T or SF-12 scale did not show any improvement from their baseline scores.

61 **Conclusions:** CBT-I treatment demonstrated substantial efficacy in reducing insomnia,

62 associated negative cognitions and improving sleep hygiene in Veterans during early recovery,

63 though it did not reduce drinking behavior.

64 **Introduction**

65 Insomnia occurs in about two-thirds of recovering patients with alcohol dependence (AD), an

66 estimated prevalence that is up to 6.5 times that of the general population (Chakravorty et al.,

67 2016). Comorbid insomnia is linked with an increased risk of relapse during recovery from AD,

68 as well as suicidal behavior, daytime dysfunction, and decreased well-being (Chakravorty et al.,

69 2016).

70   Prior studies have investigated pharmacologic and behavioral treatments for insomnia in AD.
71   Treatment with medications such as gabapentin, trazodone, and quetiapine has not
72   consistently been shown to be beneficial in patients with these co-occurring disorders
73   (Chakravorty et al., 2016). In contrast, in this population, the efficacy of behavioral treatments
74   such as progressive muscle relaxation and cognitive behavior therapy for insomnia (CBT-I) is
75   well demonstrated. CBT-I, a multicomponent treatment, consists of both behavioral (e.g., sleep
76   restriction, stimulus control) and cognitive (e.g., cognitive restructuring) strategies, which target
77   factors that perpetuate insomnia over time. Two randomized trials evaluated the efficacy of
78   CBT-I in patients with AD. Currie and colleagues (2004) compared CBT-I to two other
79   conditions—a self-help condition (reading a manual along with telephone support sessions) and
80   a waitlist control (Currie et al., 2004)—in 60 community-dwelling individuals with AD. Subjects
81   treated with CBT-I and the self-help condition demonstrated significant improvements in sleep
82   continuity relative to pre-treatment and greater improvements than a waitlist control,
83   improvements that were maintained for 6 months after treatment. They found no effect of
84   CBT-I on alcohol use. Arnedt and colleagues (2011) conducted a randomized controlled trial
85   (RCT) of an 8-session version of CBT-I (N=9) or a behavioral placebo control (N=8) (Arnedt et al.,
86   2011). CBT-I-treated subjects showed significantly greater improvements in self-reported Sleep
87   Efficiency (SE) and Wake After Sleep Onset (WASO) than the control group, but no difference in
88   alcohol consumption. Thus, although both studies showed that CBT-I improved insomnia,
89   neither found that it reduced alcohol consumption.

90   While CBT-I may be efficacious for insomnia among community-dwelling patients with AD, it
91   has not been evaluated in Veterans with AD, a population with high prevalence rates of both
92   insomnia and AD (Tsai et al., 2014, Kelsall et al., 2015, Seal et al., 2011, Alexander et al., 2016,
93   Martin et al., 2017). Further, if CBT-I improves insomnia, does it also improve alcohol
94   abstinence, as insomnia is a risk factor for relapse (Chakravorty et al., 2016)? The primary aim
95   of this pilot study was to evaluate the efficacy of an 8-week CBT-I treatment for improving
96   insomnia and at 3- and 6-month post-treatment follow-up in Veterans with AD during early
97   recovery. Secondary aims of the study were to compare CBT-I to a Monitor-Only (MO) control
98   group on alcohol-related outcomes and to assess the effect of CBT-I treatment on daytime

99 functioning measures such as depressive symptoms, anxiety symptoms, and self-reported well-
100 being.

101

102 **Materials and Methods**

103 We conducted an 8-week, randomized, parallel-group trial of CBT-I in 22 individuals. The study
104 was conducted at the Cpl. Michael J Crescenz VA Medical Center (CMCVAMC) in Philadelphia,
105 PA. The CMCVAMC Institutional Review Board approved the study and all subjects gave
106 informed consent prior to participating in the study. Upon successful completion of screening,
107 prospective subjects were randomly assigned using the Research Randomizer software
108 (Urbaniak and Plous, 2013) to receive the active treatment or to a Monitor-Only arm (MO) and
109 followed up in-person for 8 consecutive weeks. They returned for follow-up visits 3 and 6
110 months later.

111 *Subjects.* Subjects were recruited using flyers posted within the medical center or as direct
112 referrals from their care providers in addiction psychiatry, general psychiatry, and primary care
113 clinics. Subjects were included if they were: Veterans aged 18-65 years; reported insomnia
114 symptoms, as assessed by a score of ≥ 8 on the Insomnia Severity Index; had < 1 year of
115 abstinence from risky drinking, a past-year diagnosis of alcohol dependence as determined by
116 the MINI (Sheehan et al., 1998), no significant evidence of alcohol withdrawal [Clinical Institute
117 Withdrawal Assessment (CIWA) scale score ≤ 8 (Sullivan et al., 1989)], ≥ 3 consecutive days of
118 abstinence from alcohol prior to a portable home sleep apnea test (HST); and were capable of
119 communicating in English and giving written informed consent.

120 Subjects were excluded if they had a past-year diagnosis of a drug use disorder other than
121 nicotine or cannabis, current unstable or serious psychiatric conditions (e.g., schizophrenia,
122 bipolar disorder), unstable or serious medical illness, chronic pain leading to insomnia, evidence
123 of severe cognitive impairment on the Blessed Orientation-Memory-Concentration test
124 (Blessed et al., 1968), or untreated, moderate-to-severe obstructive sleep apnea (OSA)
125 diagnosed by HST or non-adherence with positive airway pressure (PAP) treatment, defined as

126 PAP use <60% of the days with use ≤ 4 hours per night on the nights they used the device,

127 based on their objective PAP compliance data.

128 *Procedures.* Prospective subjects underwent screening over a 2-4 week period, during which

129 time staff comprehensively assessed their sleep, medical, and psychiatric disorders, which

130 included an HST and clinical evaluation for sleep-related disorders. Subjects were required to

131 be totally abstinent from alcohol for ≥ 3 consecutive days prior to the HST. Following screening,

132 subjects entered an 8-week treatment phase with weekly visits to the research clinic. They

133 were followed up at 3 and 6 months post-treatment to evaluate changes in sleep, drinking, and

134 daytime outcomes. All questionnaires were completed during the clinic visit, except sleep

135 diaries, which were filled out at home.

136 *Treatments*. Cognitive Behavioral Therapy for Insomnia (CBT-I): The CBT-I treatment was based

137 on the published treatment manual CBT-I (Perlis et al., 2005) and established procedures at the

138 Penn Behavioral Sleep Medicine clinic. Eleven subjects met individually with the study clinician

139 (JF), a certified behavioral sleep medicine provider, for CBT-I. Session 1 served as an orientation

140 session and the initiation of Sleep Restriction Therapy (SRT) (Spielman et al., 1987a, Spielman et

141 al., 1987b) and Stimulus Control therapy (Bootzin and Perlis, 2011, Bootzin, 1972, Bootzin,

142 1984). *Sleep restriction therapy* required that subjects limit their time in bed to an amount

143 similar to their average total sleep time. Subsequently, the provider gradually increased time in

144 bed in 15-30 minute increments to the targeted sleep duration while ensuring that 85-90% of

145 the time in bed was spent sleeping. The sleep opportunity was decreased by 15-30 minutes if

146 the time spent sleeping did not reach 85% or decreased below 85%. *Stimulus control*

147 instructions limit the amount of time one may spend in the bedroom while awake and the kind

148 of behaviors one may engage in while in the bed or the bedroom, in order to strengthen the

149 relationship between the bed or bedroom and consolidated sleep, i.e., with the subject lying

150 down to sleep only when sleepy and avoiding the bed for anything other than sleep or sexual

151 activity. Sessions 2 covered Sleep Hygiene (Stepanski and Wyatt, 2003, Zarcone, 1989, Posner

152 and Gehrman, 2011), which addresses behaviors that influence sleep quality and quantity, such

153 as arising at the same time every day; avoiding alcohol, especially in the evenings; and avoiding

154   daytime naps. Sessions 4-7 were dedicated to a titration of time in bed and ensuring patient

155   adherence. Session 4 also delivered a specific form of *cognitive therapy*, which was introduced

156   initially in Session 3 (as a request to the patient to monitor his maladaptive cognitions for that

157   week). The Cognitive Therapy was modeled on Barlow's approach to the cognitive restructuring

158   of catastrophic thinking as it occurs with panic disorder (Barlow, 1992). This approach was

159   adapted to address catastrophic thinking in relation to insomnia, such as "I will never be able to

160   sleep on my own, ever again." The final session (session 8) focused on insomnia relapse

161   prevention strategies. Adherence with CBT-I was assessed by calculating the difference

162   between the prescribed Time-in-Bed and the reported Time-in-Bed on the sleep diaries.

163   Deviations ≥ 105 min each week were recoded into a dichotomous measure with subjects being

164   considered compliant or noncompliant for that specified week (Perlis et al., 2004). <u>Standard

165   Care Monitor-Only Condition (M.O.):</u> The eleven subjects in this condition were seen weekly by

166   the study coordinator to complete and review assessments of their sleep, alcohol use, and

167   daytime functioning. The review was interrogative in nature and no directed form of therapy

168   was provided to help with sleep or reduce alcohol use, similar to other CBT-I studies that have

169   used this control condition (Jungquist et al., 2010). As with the CBT-I sessions, the duration of

170   the initial MO session was 45 minutes and each of the follow-up sessions was 30 minutes. MO

171   subjects continued to receive ongoing medical and or mental health care. This condition

172   controlled for the effects of observation and self-monitoring (Frank and Kaul, 1978, McCarney

173   et al., 2007). <u>Group therapy provided to Veterans at CMCVAMC for substance use disorders:</u>

174   The primary psychosocial treatment for addictive disorders at CMCVAMC is group therapy. It is

175   grounded in the principles of 12-step meetings and Motivational Enhancement Therapy and

176   modified by individual clinicians using either relapse prevention techniques or behavioral

177   therapies (by employing techniques from Rational Emotive Behavioral Therapy and Cognitive

178   Behavioral Therapy). No sleep-related intervention is employed in these groups but the

179   importance of having a good sleep pattern is encouraged in one of the sessions to help prevent

180   relapse.

181   *Assessments.*

182   Sleep.

      183   a) Insomnia Severity Index (ISI) (Bastien et al., 2001) is a 7-item, self-report questionnaire that yields a global score from 0-28, with higher scores representing greater insomnia severity. The ISI was the primary outcome measure in this study and was recorded every 2 weeks during treatment and at the post-treatment assessment visits;

      187   b) Subjects completed the Perelman School of Medicine version of the daily sleep diary to assess subjective sleep variables at every treatment visit and at the 3- and 6-month post-treatment visits. The sleep diary variables used in this study included *Sleep Latency* (SL, time in minutes required to fall asleep initially); *Wake After Sleep Onset* time (WASO, duration of wakefulness during the night in minutes), *Number of Awakenings* (NAW, frequency of awakenings each night); and *Total Sleep Time* (TST, total time of sleep each night, in minutes).

      194   c) Dysfunctional Beliefs and Attitudes About Sleep Scale (DBAS) (Morin et al., 2007). This 16-item questionnaire was completed at all assessment visits to evaluate unhelpful sleep-related cognitions.

      197   d) Sleep Hygiene Index (SHI) (Mastin et al., 2006). This 13-item, patient-reported questionnaire assessed sleep hygiene behaviors at all assessment visits.

      199   e) Epworth Sleepiness Scale scores (ESS) (Johns, 1991). This 8-item self-report measure evaluated daytime sleepiness at all assessment visits.

201   Alcohol Consumption.

      202   a) Time Line Follow-back interview (Sobel and Sobell, 1992) was used to assess the percent days abstinent (PDA) for the 90 days during the baseline screening phase, during the 8-week treatment phase, and at the 3- and 6-month follow-up visits. Heavy drinking was defined as the consumption of $\geq$ 5 alcoholic drinks in a day.

      206   b) Penn Alcohol Craving Scale (Flannery et al., 1999), a 5-item, self-report measure, was used to evaluate alcohol craving over the preceding 7 days at all assessment visits.

208   Daytime functioning.

209   a) <u>Quick Inventory of Depressive Symptoms (QIDS)</u> (Rush et al., 2003). This 16-item self-
210   report instrument assessed depressive symptoms at all assessment visits.

211   b) <u>Trait sub-scale from the State-Trait Anxiety Inventory (STAI)</u> (Spielberger et al., 1970).
212   This 40-item subject-rated scale was used to evaluate anxiety symptoms at all
213   assessment visits.

214   c) <u>Short Form 12-item (SF-12)</u> (Ware et al., 1996) inquired about physical and mental
215   wellbeing with the Physical and Mental Composite Scores (PCS and MCS), at baseline,
216   weeks 4 and 8 of the treatment phase, and at 3- and 6-month post-treatment follow-up
217   visits.

218 *Statistical Analysis.* We assessed baseline demographics and other characteristics across the
219 treatment groups using a Wilcoxon Sign-rank test, t-test, chi-square or Fisher's test, as
220 appropriate. Because the treatment groups were not balanced on self-reported race it was
221 treated as a confounding variable in the analysis of longitudinal data. We used the intent-to-
222 treat principle to analyze the data. Linear mixed effects regression models employing maximum
223 likelihood estimation were used to compare the outcome trajectory by treatment conditions
224 across 10 time points (8 weekly treatment visits and 2 post-treatment follow-up visits).
225 Exceptions to this rule were made with the ISI score, which was evaluated during 7 visits
226 (baseline, treatment visits 2, 4, 6 and 8 and the two follow-up visits), and the PCS and MCS
227 scores of the SF-12 scale, which was completed during 5 visits (treatment weeks 1, 4, and 8 and
228 the two follow-up visits). Each model considered categorical, continuous, and quadratic trends
229 over time and treatment by time interactions. We evaluated each of the models for the
230 appropriate variance-covariance matrix structure of random effects. The final models for each
231 variable were selected for the most parsimonious Bayesian Information Criterion score. The
232 treatment effect was measured by the time-by-group interaction, where a statistically
233 significant interaction indicated a difference in the outcome over time by group. Results are
234 presented as scores of the model-estimated change from baseline along with their 95%
235 confidence intervals. Remission from insomnia was defined by a subject-specific, model-
236 estimated ISI total score <8. Treatment response was defined as a decrease of >8 points in the
237 ISI total score (Morin et al., 2011).

238   A Generalized Estimating Equation was used to model the days abstinent from alcohol over

239   time across treatment groups using a natural log link function and an independent within-group

240   correlation structure, considering the Poisson distribution of PDA. The four time-segments used

241   in this analysis were pretreatment (90 days), treatment (56 days), and 3- and 6-month post-

242   treatment periods (each 90 days). We used the predicted value for each outcome generated

243   from the longitudinal analysis to compute the difference scores and generate graphs, except in

244   the evaluation of effect sizes (for ISI). The within-group effect sizes from baseline were assessed

245   using the mean and standard deviation of the change score from baseline. Here, values of 0.20,

246   0.50, and 0.80 represent small, moderate, and large effect sizes, respectively (Friedmann et al.,

247   2008). We used Stata 13.0 IC (StataCorp, 2011) to conduct statistical analysis and Stata 15.0 to

248   create the graphs as Stata 13.0 was no longer available.

249

250   **Results**

251   ***Subjects.*** Twenty-four of 109 prospective subjects were eligible for the study, of whom two

252   opted not to participate before randomization; see Figure 1 for a CONSORT flow chart. We

253   randomly assigned 22 subjects to the CBT-I (N=11) or Monitor-Only (MO [n=11]) condition.

254   Sixteen of the 22 subjects were receiving psychosocial treatment for their AD, including 7 of 11

255   subjects in the CBT-I arm and 9 of 11 subjects in the MO arm, (p=NS, not statistically

256   significant). All 22 subjects completed the 8-week treatment period and 21 subjects completed

257   the 3-month and 18 completed the 6-month post-treatment follow-up visits. During their study

258   participation, 13 subjects relapsed to alcohol use (7 in the CBT-I arm and 6 in the MO arm,

259   p=NS). Four subjects dropped out during the post-treatment follow-up period (2 in the CBT-I

260   arm and 2 in the MO arm, NS). A comparison of subjects who dropped out of the study with

261   those who completed it showed no difference on treatment allocation, pretreatment PDA, age,

262   race, marital status, education or baseline ISI scores (p's all NS).

263   ***Baseline Demographics and Clinical Measures (Table 1).*** On average, subjects were middle-

264   aged, male, and African American (AA). The groups differed only on race, as the MO group was

265   comprised entirely of AAs, while only 45% of the CBT-I arm was (p = 0.01). On average, subjects

266 initially reported insomnia of moderate severity at baseline, with a mean sleep latency of 51
267 minutes. They were abstinent on about 26% of days during the 90-day pretreatment period
268 and reported heavy drinking on 80% of drinking days. There was no baseline treatment-group
269 difference on the use of alcohol as a sleep aid.

270 ***Sleep Outcomes.*** 1) <u>Insomnia Severity Index.</u> Both groups showed a decrease in insomnia
271 scores. However, at the end of treatment, there was a greater reduction in the ISI total score in
272 the CBT-I group than the MO group, a difference that persisted at the 3- and 6-month follow-up
273 visits (see Table 2 and Figure 2). When compared to their baseline values, the within-group
274 magnitude of improvement at the end of treatment, and at the 3-month and 6-month follow-
275 up visits, were 1.9, 2.2 and 1.9 for the CBT-I group, compared to 0.4, 0.5 and 0.4 for the MO
276 group. All CBT-I treated subjects were remitted from their insomnia at week 8, an effect that
277 was maintained until the 6-month post-treatment follow-up visit. In contrast, none of the
278 subjects in the MO arm were in remission from insomnia at the end of treatment or at the post-
279 treatment follow-up visits; 2) <u>Sleep diary variables.</u> i) In a quadratic model, there was a
280 treatment effect on SL, such that it initially decreased in the CBT-I group, but then increased in
281 the post-treatment phase while remaining lower than in the MO at the 6-month follow-up visit
282 (Figure 3). Exclusion of an outlier in the CBT-I group did not change the results; ii) WASO, TST
283 and NAW – there was no treatment effect (Supplementary Figure 2); 3) <u>Dysfunctional Beliefs</u>
284 <u>and Attitudes About Sleep scale.</u> There was a significant treatment effect, such that CBT-I
285 subjects reported a lower DBAS mean score than the MO subjects (Figure 4). 4) <u>Sleep Hygiene</u>
286 <u>Index.</u> There was a significant treatment effect, such that the CBT-I group reported a greater
287 decrease in SHS total score over time, (Supplementary Figure 1). 5) <u>Epworth Sleepiness Scale.</u>
288 Although there was not a significant effect of the intervention or time, there was a non-
289 significant Treatment x Time interaction effect (p=0.05). 6) <u>*Treatment adherence with CBT-I.*</u>
290 Only one subject met criteria for non-adherence, which occurred at visits 3, 4, 6, and 7 and at
291 the post-treatment follow-up visits.

292 ***Alcohol Consumption.*** 1) <u>Percent Days Abstinent (PDA).</u> At the beginning of treatment, 21
293 subjects were abstinent for all days in the preceding week; 1 subject in the MO arm had one

294   drink on a single day. Our longitudinal assessment of PDA indicated that both groups improved

295   over time, with no between-group difference (Supplemental Figure 3). During the 8 weeks of

296   treatment, 18 subjects reported remaining abstinent from alcohol (10 in the CBT-I arm and 8 in

297   the MO arm). At the 3-month follow-up visit, 14 of these 18 subjects reported remaining

298   abstinent from alcohol (8 in the CBT-I arm and 6 in the MO arm, χ^2 = 0.38, p = 0.50). Of these 14

299   subjects, 8 subjects remained abstinent at the 6-month follow-up visit (4 subjects in each

300   treatment group). The subjects who relapsed during the study frequently drank heavily at those

301   times and all received concomitant psychosocial treatment to reduce their drinking. Subjects

302   who relapsed to drinking were not differentiated from the other participants on age, years of

303   education, marital status, race, baseline PDA or ISI score, or treatment arm, or whether they

304   received psychosocial treatment for AD. 2) Alcohol craving (PACS). There was no evidence of

305   any change in the PACS score with time.

306   ***Daytime Functioning.*** We found that depressive symptoms, as measured by the QIDS,

307   improved over time equally in both groups. There was no significant change in either State-

308   Trait Anxiety Inventory (STAI)-trait scale, PCS, or MCS (SF-12) scores.

309

310   **Discussion**

311   The primary goal of this pilot study was to evaluate the potential efficacy of CBT-I in Veterans

312   complaining of insomnia during early recovery from AD. We found that CBT-I improved

313   insomnia more than a control treatment, effects that persisted after treatment ended.

314   Treatment with CBT-I also improved the self-reported SL, decreased dysfunctional sleep-related

315   cognitions, and improved sleep hygiene behaviors more than control. However, CBT-I was not

316   superior to MO in improving PDA or daytime outcomes.

317   CBT-I exerted a large effect size on insomnia scores, consistent with those reported in prior

318   studies (Currie et al., 2004, Arnedt et al., 2011). Thus, CBT-I may be beneficial in treating

319   insomnia in alcohol dependent Veterans. The durability of improvement in insomnia after the

320 end of CBT-I treatment has also been demonstrated in subjects with AD as well as in primary
321 insomnia (Sivertsen et al., 2006, Currie et al., 2004).

322 Insomnia in AD has been linked with cognitive distortions and dysfunctional beliefs about sleep
323 (Brooks et al., 2016, Brower et al., 2001). Arnedt and colleagues reported an improvement in
324 sleep-related cognitive distortions in a series of subjects treated with CBT-I (Arnedt et al.,
325 2007). Our study extends this finding in the context of an RCT of CBT-I. Inadequate sleep
326 hygiene-related behaviors such as daytime naps, which are commonly seen in this population,
327 can perpetuate insomnia (Currie et al., 2003). We also extend the literature by demonstrating
328 that CBT-I treatment differentially improved subjects' sleep hygiene scores.

329 Commonly reported insomnia symptoms include SL (difficulty falling asleep), NAW (multiple
330 awakenings after falling asleep) and WASO (time spent awake after initially falling asleep). We
331 showed a significant decrease in SL with CBT-I treatment, a finding that is consistent with two
332 prior studies (Currie et al., 2004, Arnedt et al., 2011). However, in our study, CBT-I treatment
333 was associated with a non-significant improvement in WASO, while in prior studies CBT-I
334 resulted in significantly greater improvements in WASO. Prior studies have demonstrated that
335 sustained abstinence from alcohol over time leads to improvements in objective sleep
336 measures of sleep onset latency, slow wave sleep stages, and REM-sleep-related variables.
337 However, fragmentation of sleep through the night may persist for up to two years into
338 sobriety and may increase the risk of relapse (Drummond et al., 1998, Adamson and Burdick,
339 1973, Williams and Rundell, 1981). In our study, subjects were abstinent on only 27% of the
340 days during the pretreatment period, whereas in the previous studies they were sober for an
341 average of 2-4 months (Currie et al., 2004, Arnedt et al., 2011). Thus, it is possible that the
342 persistent effects of alcohol on sleep maintenance were more evident in our subjects because
343 they were still drinking at study entry. The small sample in our study may also have contributed
344 to the non-significant effect on WASO.

345 The two prior RCTs reported no effect of CBT-I treatment on the number of subjects who
346 relapsed to alcohol use or the number of days abstinent. Currie and colleagues found that
347 during the 7-week treatment phase of their study, subjects in individual therapy consumed an

348   average of 31.8 drinks on 10.3 drinking days, compared to 60 drinks on 9.7 drinking days in the
349   wait-list control group. These numbers suggest that either more subjects in the control
350   condition drank heavily or those who consumed alcohol drank heavily. This contrasts with the
351   findings of Arnedt et al., where four subjects relapsed to heavy drinking in the CBT-I (N=9) and
352   behavioral placebo (N=8) groups. However, Arnedt and colleagues used a very stringent
353   criterion for relapse by considering all dropouts as having relapsed to drinking (Arnedt et al.,
354   2011). In our study, 1 subject in the CBT-I and 2 in the MO groups relapsed to heavy drinking
355   during the treatment phase. By the end of the post-treatment follow-up phase, three subjects
356   in each arm had relapsed to heavy drinking. These preliminary data suggest that CBT-I
357   treatment may not protect against relapse to drinking in recovering subjects. Lastly, the lack of
358   differential improvement in the daytime functioning measures with CBT-I is similar to that
359   reported in the prior two clinical trials.

360   A majority of Veterans who receive care at the Philadelphia CMCVAMC primary site identify
361   themselves as African American. In addition to being located in Philadelphia, where the
362   population is evenly divided between European Americans and African Americans, some prior
363   studies have shown that African-American Veterans are more likely to be treated for substance
364   use disorders than European-American Veterans (Glass et al., 2010, Williams et al., 2012).
365   Therefore, it is not surprising that 73% of Veterans in this study identified themselves as African
366   American. Because of the racial imbalance between the treatment arms, we treated race as a
367   covariate in our statistical models. Race was an independent predictor of the change in percent
368   days abstinent over time (β = -9.0, 95% C.I.: -9.7, -8.2), with African-American subjects reporting
369   a decrease of 9% in the model-estimated mean PDA over time. It is possible that participation in
370   the study bolstered the social support for these middle-aged, African-American subjects with
371   co-occurring insomnia, leading to improved self-efficacy and consequently a relatively greater
372   proportion of abstinent days, as shown previously (Warren et al., 2007, Walton et al., 2001).
373   However, race was not a significant predictor of improvement in the sleep-related measures (ISI
374   total score, sleep diary variables, DBAS or SHI), which could have been secondary to the small
375   sample size that provided inadequate statistical power to detect a difference based on race or
376   to evaluate psychosocial factors as mediators of racial differences.

377 Although we replicated some findings from prior trials and report some novel findings, the
378 selection of treatment-seeking, alcohol-dependent subjects introduced a selection bias so that
379 these results may not generalize to all Veterans with AD. The effect sizes could have been
380 skewed because of the decrease in sample size during the follow-up visits because of the
381 dropouts. Furthermore, the sample size did not yield sufficient power to detect a difference in
382 drinking outcomes between the treatment groups over time. Future studies should attempt to
383 replicate these findings with a larger sample over a longer duration to provide adequate power
384 to detect differences in drinking outcomes. Future studies should also use polysomnography to
385 quantify objective sleep and spectral polysomnographic changes with treatment and evaluate
386 the role of alcohol as a hypnotic agent.

387

388 **Conclusions.**

389 CBT-I was efficacious for treating insomnia in alcohol-dependent Veterans during early
390 recovery. However, in this small RCT, it was not superior to the control group in improving
391 abstinence from alcohol. Adequately-powered studies are required to evaluate the effect of
392 CBT-I on drinking outcomes and to identify potential moderators of treatment response.

393

398

399 **Contributors.** SC, MLP and JTA conceptualized the study; SC and JF evaluated subjects; SC,
400 KHM, JTA and MLP analyzed data; SC, KHM, JTA, MLP, HRK, DWO and JF collaborated in the
401 generation of the final manuscript.

402

417

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551 **Figure Legends**

552 **Figure 2. Legend:** ISI = Insomnia Severity Index; wk = week number of visit in the treatment

553 phase; 6 mo. = 6-month post-treatment follow-up visit; model statistics of mixed effects

554 maximum likelihood regression using unstructured covariance matrix and adjusted for Race;

555 time: β = -1.05, p=0.01; treatment: β = 1.5, p = 0.5; treatment x time: β = -1.3, p = 0.03;

556

557 **Figure 3. Legend:** SL = Sleep Latency (from their sleep diaries); wk = week number of visit in the

558 treatment phase; 6 mo. = 6-month post-intervention follow-up visit; model statistics of mixed

559 effects maximum likelihood regression using unstructured covariance matrix and adjusted for

560 Race; time: β = 2.5, p=0.29; treatment: β = 47.7, p = 0.002; treatment x time: β = 1.5, p <0.0001.

561

562 **Figure 4. Legend:** DBAS = Dysfunctional Attitudes and Beliefs about Sleep scale; wk = week

563 number of visit in the treatment phase; 6 mo. = 6-month post-intervention follow-up visit;

564 model statistics of mixed effects maximum likelihood regression using independent covariance

565 matrix and adjusted for Race; time: β = 0.03, p=0.49; treatment: β = 0.1, p = 0.84; treatment x

566 time: β = -0.2, p <0.0001

Table 1. Baseline demographic and clinical variables for the total sample and by treatment groups

Variable	Total Sample mean (SD) (N = 22)	Treatment groups mean (SD)	
		MO (N = 11)	CBT-I (N = 11)
Demographic			
Age (yr)	54.5 (6.9)	56 (6)	52 (7)
Gender (male), N (%)	22 (100%)	11 (100%)	11 (100%)
Race (African American), N (%)	16 (73%)	11 (100%)	5 (45%)*
Education (yr)	12 (0.8)	12 (0.9)	12 (0.8)
Unemployed (past month), N (%)	14 (64%)	6 (55%)	8 (73%)
Marital Status (single), N (%)	18 (82%)	9 (82%)	9 (82%)
Sleep			
Insomnia Severity Index total score	18.9 (5.4)	19.8 (5.6)	18.0 (5.3)
Sleep Latency (sleep diary, min)	51.4 (50.6)	33.9 (20.3)	69.0 (65.5)
Wake time after sleep onset (sleep diary, min)	38.6 (27.2)	33.7 (26.4)	43.6 (28.4)
Total Sleep Time (sleep diary, min)	286.4 (98.8)	283.1 (115.3)	289.6 (84.7)
Number of Awakenings (sleep diary, min)	1.8 (1.1)	1.6 (1.0)	1.9 (1.2)
Dysfunctional Beliefs & Attitudes mean score	5.4 (1.6)	5.6 (1.7)	5.1 (1.6)
Sleep Hygiene Scale total score	34.7 (5.2)	36.6 (4.0)	32.9 (5.8)
Epworth Sleepiness Scale total score	11.1 (5.2)	13.1 (5.6)	9.1 (4.1)
Alcohol Consumption (TLFB)			
Percent Days Abstinent	26.4 (26.3)	25.4 (30.9)	27.4 (22.3)
Proportion of Heavy Drinking Days	0.8 (0.1)	0.8 (0.1)	0.9 (0.2)
Penn Alcohol Craving Scale total score	7.6 (6.8)	9.0 (6.3)	6.1 (7.2)
Daytime Dysfunction			
Quick Inventory of Depressive Symptoms[1]	22.1 (8.3)	22.0 (8.6)	22.3 (8.5)
Trait Subscale (State Trait Anxiety Inventory)	47.3 (7.6)	48.0 (8.7)	46.7 (6.6)
Physical Composite Score (SF-12 scale)	39.6 (4.6)	39.3 (4.0)	40.0 (5.3)
Mental Composite Score (SF-12 scale)	40.1 (5.6)	40.6 (5.0)	39.5 (6.2)

Hypnotic Medication Prescriptions (N=20)			
Any medication for insomnia	8 (40%)	3 (30%)	5 (50%)
Trazodone	4 (20%)	3 (30%)	1 (10%)
Mirtazapine	2 (10%)	0 (0%)	2 (20%)
Gabapentin	1 (5%)	0 (0%)	1 (10%)

yr = years; *p = 0.01; [1]without the three sleep items

Table 2. Model-estimated mean change in clinical outcomes over time across treatment groups (change from baseline values)

Variable	Change at end of treatment[1]				Change at 3-month post-treatment follow-up[1]				Change at 6-month post-treatment follow-up [1]			
	MO	95% C.I.	CBT-I	95% C.I.	MO	95% C.I.	CBT-I	95% C.I.	MO	95% C.I.	CBT-I	95% C.I.
Sleep												
ISI total score	**-8.4**	-16.3, -0.5	**-12.7**	-15.5, -10.0	**-9.4**	-18.3, -0.5	**-13.4**	-16.0, -10.9	**-10.5**	-20.4, -0.6	**-13.9**	-16.3, -11.6
SL (min)	**20.6**	-18.2, 59.5	**-45.1**	-78.0, -12.2	**23.2**	-20.5, 67.0	**-36.8**	-75.9, 2.3	**25.8**	-22.7, 74.4	**-25.4**	-71.9, 20.9
WASO (min)	-1.7	-17.8, 14.3	-24.5	-40.8, -8.3	-1.9	-20.1, 16.1	-27.6	-45.9, -9.3	-2.1	-22.3, 17.9	-30.7	-51.0, -10.4
TST (min)	45.2	0.8, 89.6	102.4	57.5, 147.3	50.9	0.9, 100.8	115.2	64.7, 165.7	56.5	1.0, 112.0	128.0	71.9, 184.1
NAW	-0.06	-1.0, 0.8	-0.27	-1.2, 0.6	-0.07	-1.1, 0.9	-0.30	-1.3, 0.7	-0.08	-1.2, 1.0	-0.3	-1.5, 0.8
DBAS	**0.2**	-0.5, 1.1	**-1.8**	-2.6, -0.9	**0.3**	-0.6, 1.2	**-2.0**	-2.9, -1.1	**0.3**	-0.6, 1.3	**-2.2**	-3.2. -1.2
SHI	**-0.8**	-3.4, 1.7	**-4.6**	-7.1, -2.0	**-0.9**	-3.8, 1.9	**-5.1**	-8.0, -2.3	**-1.0**	-4.2, 2.2	**-5.7**	-8.9, -2.5
ESS	-0.6	-2.4, 1.0	-3.1	-4.9, -1.4	-0.7	-2.7, 1.1	-3.5	-5.5, -1.5	-0.8	-3.0, 1.3	-3.9	-6.1, -1.7
Alcohol												
PDA	0.7	0.6, 0.8	0.7	0.6, 0.8	0.7	0.6, 0.8	0.7	0.6, 0.8	0.7	0.6, 0.8	0.7	0.6, 0.8

[1]As compared to the baseline phase; MO = Standard Care Monitor-Only condition; CBT-I = Cognitive Behavioral Therapy for Insomnia; ISI = Insomnia Severity Index total score; SL = Sleep Latency; min = minutes; WASO = Wake After Sleep Onset time; TST = Total Sleep Time; NAW = Number of Awakenings; DBAS = Dysfunctional Beliefs and Attitudes about Sleep Scale mean score; SHI = Sleep Hygiene Index total score; ESS = Epworth Sleepiness Scale total score; PDA = Percent Days Abstinent; PACS = Penn Alcohol Craving Scale total score; QIDS = 16-item Quick Inventory of Depressive Symptomatology; STAI-Trait = State Trait Anxiety Inventory – Trait subscale; PCS = Physical Composite Summary Score (from the Short Form 12-item measure); MCS = Mental Composite Summary Score (from the Short Form 12-item measure). The significant between-group differences over time are shown in bold.

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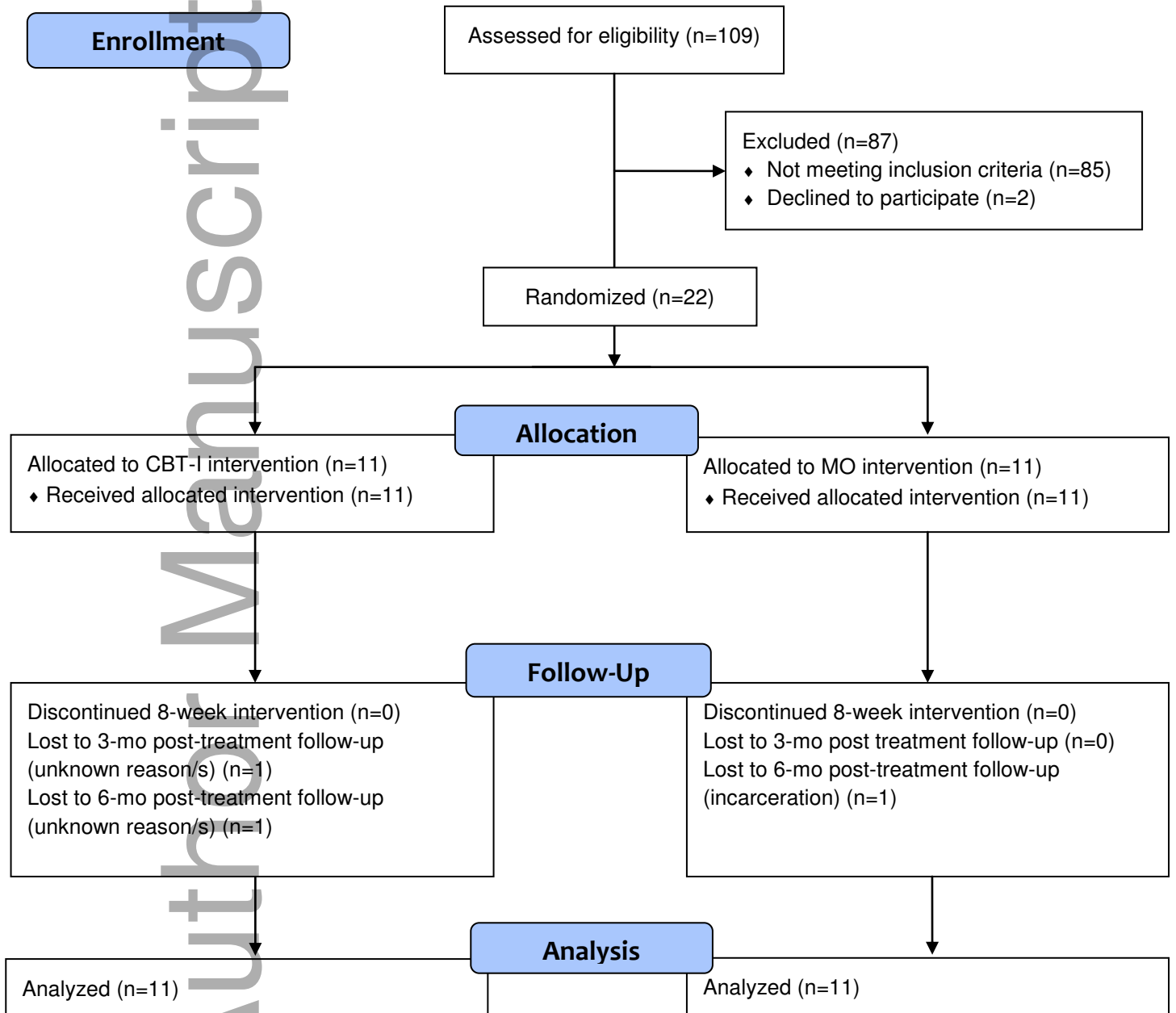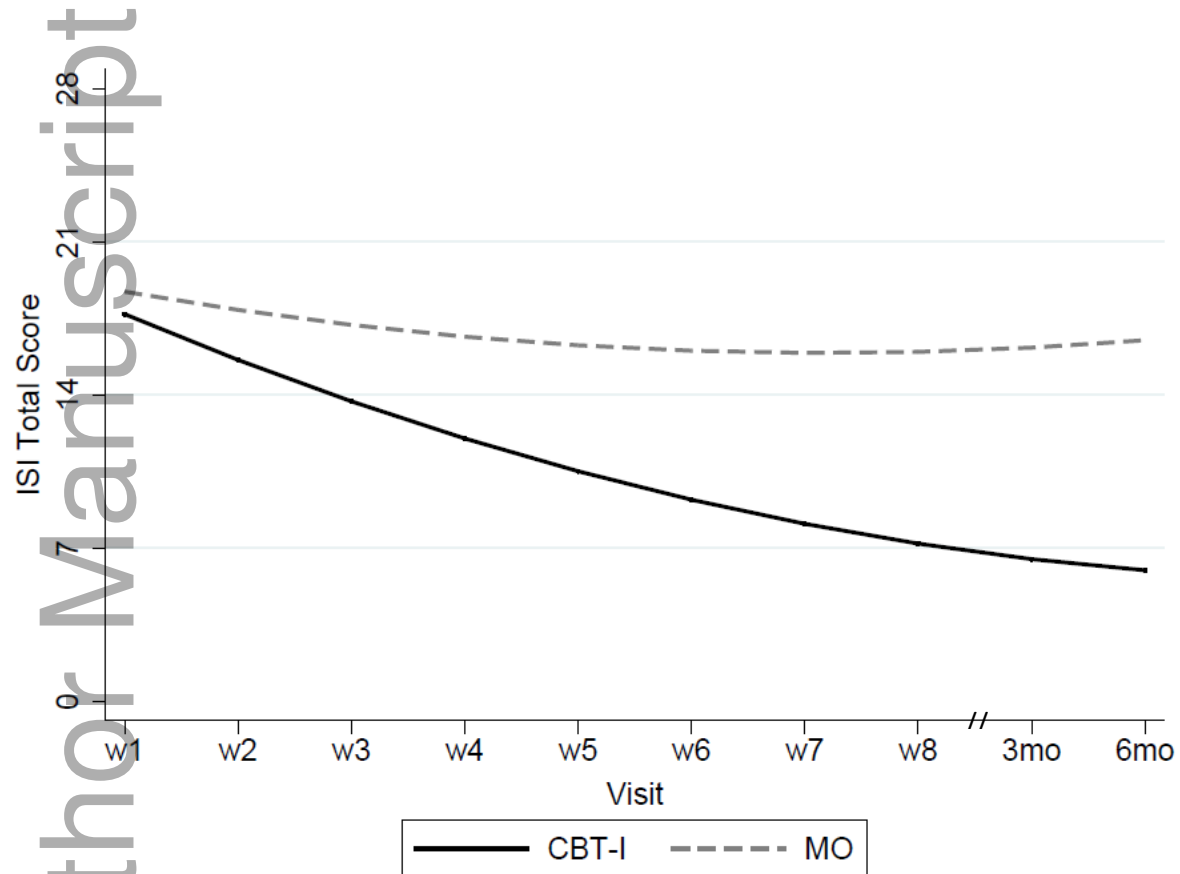**Figure 1. CONSORT Flow Diagram of Subjects in the Study**

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Figure 2. Model-estimated changes in Insomnia Severity Index (ISI) total score over time by treatment arm
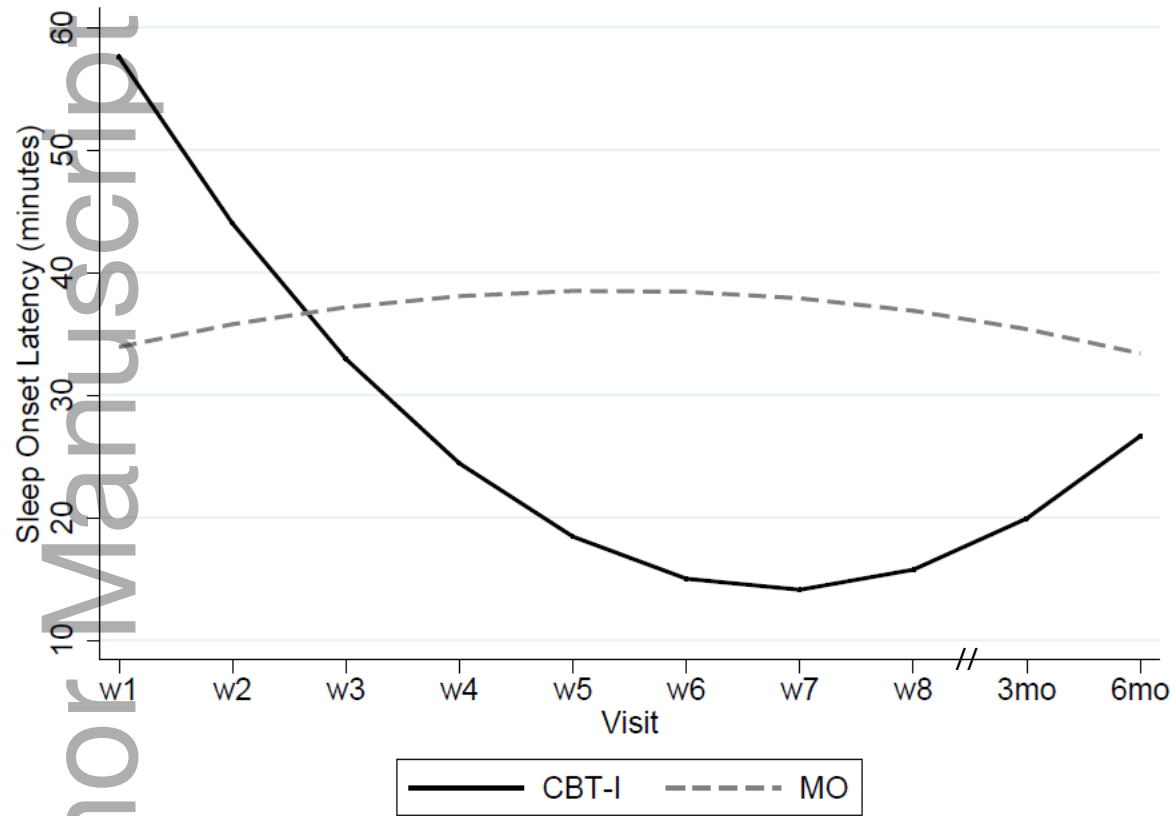
Figure 3. Model-estimated changes in subjective Sleep Latency (SL) over time by treatment arm

Figure 4. Model-estimated changes in Dysfunctional Beliefs and Attitudes About Sleep (DBAS) mean score over time by treatment arm