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Protocol for the Project SAVE Randomized Controlled Trial Examining CBT for Insomnia among Veterans in Treatment for Alcohol Use Disorder

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Protocol for the Project SAVE Randomized Controlled Trial Examining CBT for Insomnia among Veterans in Treatment for Alcohol Use Disorder

Mary Beth Miller,[1,2] Jane Metrik,[2,3] John E. McGeary,[2,3] Brian Borsari,[2,4,5] Christina S. McCrae,[1] John Maddoux,[6] J. Todd Arnedt,[7] Jennifer E. Merrill,[2] and Kate B. Carey[2]

[1]Department of Psychiatry, University of Missouri, Columbia, MO

[2]Center for Alcohol and Addiction Studies, Brown University, Providence, RI

[3]Mental Health & Behavioral Sciences Service, Providence VA Medical Center, Providence, RI

[4]Mental Health Service, San Francisco VA Health Care System, San Francisco, CA

[5]Department of Psychiatry and Behavioral Sciences, University of California San Francisco, San Francisco, CA

[6]Addiction Treatment Program, Harry S. Truman Memorial Veterans Hospital, Columbia, MO

[7]Department of Psychiatry, University of Michigan, Ann Arbor, MI

Corresponding Author:
Mary Beth Miller, PhD
Department of Psychiatry
University of Missouri-Columbia
1 Hospital Drive, DC067.00
Columbia, MO 65212
Phone: 1-573-882-1813
Fax: 1-573-884-1070
millmary@health.missouri.edu

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ABSTRACT

Introduction: As many as 74% of Veterans with alcohol use disorders (AUD) report symptoms of insomnia. Insomnia represents a barrier to alcohol treatment because insomnia symptoms (a) may lead to relapse among those who use alcohol to help them sleep. Moreover, insomnia symptoms may negatively impact (b) executive functions and (c) emotion regulation skills that individuals need to avoid triggers for alcohol use. Cognitive Behavioral Therapy for Insomnia (CBT-I) is an efficacious first-line treatment for insomnia; however, no research has examined the impact of CBT-I on individuals' response to alcohol treatment. In the Sleep and Alcohol for VEterans (Project SAVE) randomized controlled trial, we hypothesize that CBT-I will enhance the efficacy of alcohol treatment among Veterans with insomnia by enhancing their abilities to attend to treatment, regulate emotions, and initiate sleep without alcohol.

Methods & Analysis: Eighty Veterans enrolled in alcohol treatment at the VA will be randomly assigned to receive either CBT-I or single-session sleep hygiene (SH) education. Individuals will be eligible to participate if they meet DSM-5 criteria for moderate to severe AUD and Insomnia Disorder of at least 1 month duration. Participants will complete assessments at baseline, post-treatment, and 6-week follow-up. Primary outcomes include recruitment, retention, treatment satisfaction, insomnia severity, sleep efficiency and quality, alcohol use and problems (measured using prospective daily diaries and retrospective self-report), and use of alcohol or marijuana to help with sleep. Secondary outcomes include treatment-related learning, attention, working memory, delay discounting, negative affect, emotion regulation, alcohol craving, satisfaction with life, and mental health symptoms (PTSD, depression, anxiety).

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Ethics & Dissemination: Ethics approval was obtained in October 2018. Data collection began in July 2019 and is expected to be complete by July 2021. Primary trial results are expected to be published by July 2023.

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ARTICLE SUMMARY

Strengths and Limitations of the Study

- Cognitive Behavioral Therapy for Insomnia (CBT-I) is an evidence-based treatment for insomnia that has not been tested among Veterans currently engaged in treatment for alcohol use disorder.
- This study utilizes a randomized controlled trial design to determine the extent to which CBT-I may impact potential cognitive and emotional mechanisms of treatment (e.g., treatment-related learning, working memory, emotion regulation).
- This research will advance previous studies by examining the impact of CBT-I on alcohol-related problems.
- Findings will be limited to short-term (6-week) outcomes.
- Although this study will document the short-term efficacy of CBT-I over "usual care" (a single session of sleep hygiene education), it will not control for non-specific therapy effects.

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INTRODUCTION

Up to 74% of Veterans seeking treatment for alcohol use disorder (AUD) report symptoms of insomnia.[1] These symptoms represent a barrier to AUD treatment for at least three reasons: (1) Approximately 50% of individuals with alcohol use disorders report using alcohol to help them sleep;[2-4] thus, those without alternative sleep aids may relapse to drinking if insomnia persists. Insomnia symptoms have also been associated with significant deficits in (2) attention/working memory[5 6] and (3) emotion regulation.[7-10] Because cognitive-behavioral therapy (CBT) for AUD capitalizes on individuals' executive cognitive functions to identify and respond to the stimuli that lead to alcohol use,[11] CBT-based treatment may have limited effectiveness for patients with insomnia. This combination of factors – insomnia and limited cognitive/emotional capacity to respond to treatment – may explain in part why insomnia symptoms precipitate relapse.[12] Indeed, 1 in 3 individuals relapse to problematic drinking within one year of alcohol treatment.[13 14]

Sleep disturbance has been established as a risk factor for poor alcohol treatment outcomes.[15 16] More than half of those in residential treatment programs report insomnia symptoms at admission, and the majority continue to report symptoms at discharge.[17 18] Yet prior research has not demonstrated how alcohol use may change as a result of insomnia treatment.[12] Research in animal models suggests that restoring normal sleep may reduce relapse to alcohol use.[19] Pharmacological treatment of sleep disturbance with gabapentin has also been found to reduce the risk of relapse in individuals with AUDs in the short term (at 6-12 weeks).[20 21] Because Cognitive Behavioral Therapy for Insomnia (CBT-I) has been associated with longer-term improvements in insomnia than pharmacological sleep treatment,[22] CBT-I may be a more effective adjunct to alcohol treatment than pharmacotherapy in the long term.

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CBT-I is a first-line treatment for chronic insomnia.[22 23] A number of randomized controlled trials have documented its efficacy in reducing symptoms of insomnia among military and Veteran populations.[24-28] CBT-I yields comparable effects for younger (18-64y) and older (65+y) Veterans[29] and has been effective in reducing insomnia severity in the presence of co-occurring medical,[30] psychiatric,[25 31] and alcohol use disorders.[32-34] Notably, CBT-I has also led to improvements in suicidal ideation,[35] symptoms of depression,[29] psychosocial functioning,[25] and quality of life.[29] While CBT-I has not reduced rates of relapse among alcohol dependent individuals with 25 or more days of abstinence,[33 34 36] these previous trials have been limited by small sample sizes (post-treatment *N*s ≤ 15/group), low rates of relapse, and use of non-treatment-seeking samples. These studies also did not evaluate changes in alcohol-related problems (beyond alcohol use itself) and did not examine the impact of CBT-I on engagement in alcohol treatment.[37]

Current Aims

The primary objective of the current study is to enhance alcohol treatment to account for the unique needs of Veterans with sleep complaints. The study involves three specific aims. First, we aim to test the feasibility and acceptability of CBT-I delivered concurrently with CBT for AUD via randomized controlled trial. Second, we aim to evaluate the initial efficacy of CBT-I in improving sleep and alcohol use outcomes. We hypothesize that Veterans receiving CBT-I will demonstrate greater improvements in primary sleep (insomnia severity, sleep efficiency, sleep quality) and alcohol use outcomes (percent days abstinent, percent heavy-drinking days, alcohol problems, use of alcohol or cannabis to help with sleep). Finally, we aim to examine CBT-I effects on proximal intervention outcomes (i.e., proposed mediators of the association between sleep and alcohol-related harm). These secondary outcomes include

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treatment-related learning, executive function (attention, working memory, delay discounting), negative affect, emotion regulation, and alcohol craving.

METHODS & ANALYSIS

Sample Size Calculation

Based on previous studies, we anticipate moderate to large effects on insomnia symptoms[26 27] and small effects on drinking quantity/frequency.[33 34] No previous studies have examined the impact of CBT-I on alcohol-related problems; therefore, the size of this potential treatment effect is unknown. Similarly, effect sizes of CBT-I on secondary outcomes (learning, executive function, negative affect, emotion regulation, craving) have not been well-established.[38 39] A priori power analyses (G*Power 3.1) indicated that a sample of 44 participants would provide sufficient power to detect a medium (f=.25) group by time interaction using repeated measures ANOVA (α=.05, groups=2, repetitions=3, correlation=.50). This study will be underpowered to detect small effects (N=260 participants for f=.10); however, we will utilize multilevel modeling to increase power to detect small effects. We propose recruitment of 80 participants to allow for high rates of attrition in this patient population.[33 34]

Participants

Individuals will be eligible to participate if they are Veterans (a) enrolled in the Addictions Treatment Program at the VA; (b) meet DSM-5 criteria for moderate or severe AUD; and (c) meet DSM-5 criteria for Insomnia Disorder, including acute and short-term insomnia (i.e., symptoms lasting less than 3 months but otherwise meeting all criteria). Participants will be excluded if they are (a) unable to provide informed consent, (b) demonstrate cognitive impairment (defined as a Mini Mental Status Exam score below 26), (c) report continuous sobriety for more than 2 months at baseline, (d) report contraindications for CBT-I (lifetime

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history of mania or current seizure disorder),[40] (e) have an untreated sleep disorder other than insomnia (e.g., obstructive sleep apnea), (f) have an inadequately controlled psychiatric disorder that requires immediate clinical attention (e.g., psychosis, suicidal ideation with intent and plan), or (g) began a new sleep medication in the past 6 weeks.

Procedures

Recruitment and screening. Eighty Veterans with AUD and insomnia will be recruited from the VA's Addiction Treatment Program to participate in an insomnia treatment study (see Figure 1). Individuals participating in the program's residential or outpatient groups will be informed of the research study at intake and reminded of the study periodically at the beginning of treatment groups. Both residential and outpatient treatment services utilize a variety of evidenced-based treatments for substance use disorders, including elements of Cognitive Behavioral Therapy, Mindfulness, and Motivational Interviewing. The residential treatment program has an average length of stay of 42 days (6 weeks), and outpatient treatment in the form of group therapy has no time duration. Interested participants will conduct a brief eligibility screen (~10 minutes) with the project coordinator, and those who remain interested after learning more about the study will be scheduled for the baseline assessment.

Baseline assessment. Research staff will review informed consent with each participant. Interested participants will provide written informed consent prior to completion of baseline (see Table 1 for list of measures and schedule of administration). The evaluation will involve assessment of eligibility criteria using the Mini International Neuropsychiatric Interview (MINI) 7.0.2 and a semi-structured clinical interview for sleep disorders. Those who endorse symptoms of sleep-related breathing disorders, restless legs syndrome, periodic limb movement disorder, or narcolepsy will be referred for polysomnography. Given the prevalence of sleep apnea in this

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population, individuals who meet all eligibility criteria but report symptoms of sleep apnea will complete one night of holter monitoring (using an Evo Holter Recorder, SpaceLabs Healthcare) at home in their own beds to establish severity of sleep apnea.[41] Those with apnea hypopnea index scores above 15 will be excluded from the study.

All eligible participants will complete one week of daily sleep diaries (between baseline and treatment session 1), which will be collected electronically and time-stamped each morning using the Qualtrics data management system. Participants who have not completed the diary each morning by noon will receive a reminder text or phone call from study staff. Participants will have the option of completing the daily sleep diaries using pen-and-paper surveys if unable to complete by computer or phone.

Randomization. Eligible participants will be randomly assigned in a 1:1 ratio to either the CBT-I or sleep hygiene condition using a random number generator. The project coordinator will assign participants to conditions and reveal their allocation to interventionists only after the principal investigator has confirmed eligibility.

Blinding. The principal investigator and study therapists will be blinded to assessment outcomes, and the research assistant conducting post- and follow-up assessments will be blinded to participant condition.

Follow-up assessments. The project coordinator will contact participants 5 weeks after baseline (post-treatment) and 6 weeks after the post-treatment assessment to complete follow-up assessments (see Figure 1).

Adaptations for remote treatment delivery. All assessments and interventions for this protocol were designed to be conducted in-person. However, because the catchment area for the proposed VA is largely rural, it quickly became clear that remote delivery of the intervention

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would be necessary to accommodate the needs of some participants. Therefore, treatment sessions will be completed remotely, either by phone or using the Department of Veterans Affairs' Video Connect service, when needed. VA Video Connect is a mobile application that allows Veterans and providers to hold secure virtual meetings from remote locations. For all remote appointments, research staff use their VA email and a VA-provided laptop. Participants may use a number of electronic devices (e.g., iPhone, iPad, Android, PC, laptop) to open the email invitation from the provider, which will include a link to the secure video session. VA Video Connect uses encryption to ensure that sessions are private and secure and is designed for Veterans in rural areas with limited access to healthcare facilities.

Retention strategies. To enhance follow-up rates, all appointments will be as brief as possible. Participants will receive $30, $40, and $50 dollars for completing the baseline (~2 hours), post-treatment (~1 hour), and 6-week follow-up assessments (~1 hour), respectively. At each assessment, they will receive an additional $10 for completing all seven daily diaries. Research assistants and the principal investigator will coordinate schedules so that lab phones and emails are monitored continuously during business hours. Interventionists will also provide after hours 'on-call' support for participants who are actively engaged in the intervention. We will implement a case management approach to participant retention, which aims to prevent foreseeable barriers to participation and address problems as they arise. This approach involves weekly contact with participants, monitoring of progress, regular appointment reminders, and thank you notes following assessment completion.

Interventions

Cognitive Behavioral Therapy for Insomnia (CBT-I). CBT-I will be delivered individually in five weekly one-hour sessions. Study therapists will follow the 2014 CBT-I in

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Veterans manual developed by leading researchers in the behavioral sleep medicine field and currently used throughout the VA.[40] Intervention components include (1) sleep hygiene: limiting naps; avoiding caffeine, tobacco, alcohol, and rich/heavy foods before bedtime; exercising; establishing a bedtime routine; and creating a comfortable sleep environment; (2) sleep restriction: limiting time in bed in order to improve sleep efficiency, or the percentage of time in bed that is actually spent sleeping; time in bed will be titrated each week based on sleep efficiency; (3) stimulus control: strengthening association between bedroom and sleep to decrease conditioned arousal; (4) relaxation: diaphragmatic breathing, progressive muscle relaxation, and visual imagery to reduce arousal; and (5) cognitive therapy: identifying and challenging thoughts that interfere with sleep using thought logs and behavioral experiments.

Sleep Hygiene (SH). Participants in both conditions will review a one-page handout on sleep hygiene with a trained study therapist. Interactions last 15-30 minutes (depending on the number of questions participants ask), and this is the only intervention that participants assigned to the sleep hygiene condition will receive. This feedback was designed to be consistent with what may be expected as "usual care" in a doctor's visit with a primary care physician. Upon completion of the study, sleep hygiene participants will be offered a referral for CBT-I, which is available with trained providers at the VA.

Study therapists. Study therapists will be graduate students in clinical or counseling psychology who receive training in use of the treatment manual via lecture, observation, and mock therapy sessions. The principal investigator, who is a licensed clinical psychologist, will evaluate audiotapes of mock sessions and provide corrective feedback. The principal investigator will also review session audiotapes for ongoing training and supervision. Each therapist will deliver both CBT-I and sleep hygiene treatment sessions.

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Treatment integrity. One member of the study team who is not involved in therapist training or supervision will evaluate 10 randomly selected CBT-I audiotapes for treatment integrity using a checklist of treatment elements.

Treatment credibility. At the end of session 3, participants will complete a 4-item treatment credibility questionnaire[42] assessing the extent to which (a) the technique appeared to be a reasonable, logical treatment for insomnia; (b) the participant liked and had confidence in his/her therapist; (c) the participant had confidence that the treatment would work; and (d) the participant would recommend this treatment to others with similar sleep disturbance.

Primary Outcomes

Recruitment and retention (Aim 1). The number of participants who complete baseline (relative to screening) will indicate participant recruitment. The number of participants who complete the single session of sleep hygiene and all five sessions of CBT-I will indicate retention in the sleep hygiene and CBT-I conditions, respectively.

Treatment satisfaction (Aim 1). The 8-item Client Satisfaction Questionnaire[43] will be used to assess participant satisfaction with insomnia and alcohol treatments (assessed separately) at the post-treatment assessment. It has been validated among individuals in treatment for substance use.[44] All items are scored 1 to 4, with higher scores indicating higher satisfaction with treatment. For example, in this study, participants will respond to the item, "How satisfied are you with the amount of help you received for your insomnia?" on a scale from 1 (*quite dissatisfied*) to 4 (*very satisfied*).

Sleep (Aim 2). The 7-item Insomnia Severity Index[45] will be used to measure insomnia severity at baseline, post-treatment, and 6-week follow-up. Items assess difficulty falling or staying asleep, satisfaction with current sleep pattern, interference with daily functioning, the

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extent to which others notice their sleep problems, and worry/distress related to sleep problems. Response options range from 0 (*not at all worried*) to 4 (*very much worried*), with possible total scores ranging from 0 to 28. Notably, self-report is the recommended method of assessment for symptoms of insomnia in adults.[46]

Participants will also complete 7 consecutive days of diary assessments at baseline, post-treatment, and 6-week follow-up. Each day, participants will estimate what time they got into bed the previous night; what time they tried to go to sleep (bedtime); how long it took them to fall asleep (sleep onset latency); how many times they woke up, not counting their last awakening, and the total duration of these awakenings (wake after sleep onset); the time of their final awakening (waketime); and what time they got out of bed for the day. Time elapsed between getting into bed at night and out of bed the next day will represent time in bed. Sleep efficiency will be calculated by dividing the amount of time actually asleep at night by the total amount of time in bed. Participants will also be asked to rate the quality of their sleep each night on a scale from 0 (*very poor*) to 4 (*very good*).

Alcohol use and problems (Aim 2). The Timeline Followback (TLFB) will be used as a face-valid measure of change in drinking quantity and frequency from baseline to follow-up.[47] Using a calendar-based form, participants will indicate on which days in the past 6 weeks they consumed alcohol. Holidays and significant historical events will be labeled to enhance memory recall. A trained research assistant will then review days of alcohol use with the participant to determine the number of standard drinks consumed on each day. The TLFB will be used to estimate percentage of abstinent days and percentage of heavy-drinking days (4/5 or more drinks for women/men).

The Short Inventory of Problems is a 15-item measure of alcohol-related problems[48] that

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has demonstrated reliability and concurrent validity among individuals in treatment for substance use.[49] Sample items include, "My family has been hurt by my drinking," and, "I have failed to do what is expected of me because of my drinking." Response options range from 0 (*never*) to 3 (*daily or almost daily*). Responses will be summed to create a total problems score.

On daily diaries, participants will also be asked to report the number of standard drinks (e.g., 12oz beer) consumed the previous day and whether or not they used any form of cannabis. Individuals who indicate use of either substance will be asked (yes/no) if they used alcohol or cannabis specifically to help with sleep. Responses will be used to calculate the percentage of days participants used alcohol or cannabis to help with sleep at each assessment.

Secondary Outcomes (Aim 3)

Treatment-related learning. Baseline to post-treatment change in treatment-related learning will be assessed using a 10-item measure of AUD-specific CBT principles that was developed in collaboration with treatment providers at the Truman VA. Sample items include, "I can manage cravings and urges by changing my thoughts," and, "If I have a craving (or other emotion), I must act on it." Response options are true, false, and unsure. The instructions read, "Please indicate if the following statements are true or false. Please do not guess. If you are unsure, please respond 'unsure.'" Responses will be scored (with unsure responses coded as incorrect), and the percentage of correct responses will be used as the learning outcome.

Executive function. The Psychomotor Vigilance Task (PVT) is a behavioral test of sustained attention, during which the participant is asked to detect randomly occurring stimuli. It is free of learning effects and highly sensitive to sleep loss.[50] Multiple outcomes may be derived from the PVT including but not limited to: response speed (1/Reaction time), number of commission errors (responding when there is no stimulus), and number of omission errors

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(failing to respond to a stimulus within a critical timeframe). Standardized methods for scoring are established.[51]

The n-back task is a continuous performance measure of working memory.[52] Participants will be presented with a sequence of shapes and asked to indicate which shape was presented *n* letters back. Because individuals with AUD may have difficulty accurately identifying stimuli in the 2-back task,[53] an adaptive version of the task will be used.[54] Participants will complete 4 blocks of the task, beginning with the 1-back task and advancing to harder tasks (2-back and then 3-back) only if they respond correctly to 90% of the trials in each block. The proportion of correct responses (counting omissions as errors) will be used as the outcome variable.

The Monetary Choice Questionnaire will be used as a measure of delay discounting. It involves a series of 27 choice questions that present two monetary rewards that differ depending upon the timeframe for receipt (e.g., "*Would you prefer $49 today or $60 in 89 days?*"). There are two methods for scoring the MCQ. The rate of discounting will be estimated using *k* [V= A/(1+kD)], where V represents the present value of the reward (A) at delay (D)].[55] More recently, automated scoring has been made available.[56]

Negative affect. Negative affect will be measured with a 10-item Negative Affect subscale from the 20-item Positive and Negative Affect Schedule (PANAS), which is a measure of state affect (Watson, Clark, & Tellegen, 1988). Participants rated the degree to which they are currently experiencing a variety of feelings and emotions (e.g., irritable, afraid, distressed) on a 5-point Likert scale from 1 (*very slightly, or not at all*) to 5 (*extremely*) in the past week.

Emotion regulation. The 16-item Difficulties in Emotion Regulation Scale has demonstrated good convergent and discriminant validity in clinical and community samples.[57] On a scale from 1 (*almost never*) to 5 (*almost always*), participants will indicate how often in the

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past 6 weeks they would endorse items such as, "I have difficulty making sense out of my feelings," and, "When I am upset, I become out of control."

Alcohol Craving. The Penn Alcohol Craving Scale is a 5-item measure of alcohol craving in the past week. Participants rate the intensity, frequency, and duration of cravings, as well as their ability to resist acting on those cravings and their overall "average alcohol craving" for the past week. This measure has demonstrated good internal consistency and construct validity.[58]

Data Analysis Plan

Data management and confidentiality. Study data will be handled only by research staff and used strictly for research purposes. All research staff will be trained in responsible research conduct and the handling of private and confidential information. Identifying information will not be recorded in assessments; rather, study data will be identified and tracked using a unique study identification number for each participant. Missing outcome data will be handled using multiple imputation.

Aim 1: Feasibility and acceptability. Recruitment (goal ≥4pts/mo) and retention rates (≥70% complete 5/5 sessions) will indicate feasibility of the intervention. Treatment satisfaction (average score ≥3, indicating 'good' quality) will serve as an indicator of acceptability. Recruitment, retention, and satisfaction will be measured separately for insomnia and alcohol treatments. We do not expect group differences in recruitment. Descriptive statistics, chi-square, and t-tests will be used to determine between-group differences in retention and satisfaction.

Aims 2 and 3: Initial efficacy. Because the primary goal of this study is to test feasibility and acceptability, analyses will emphasize the direction and magnitude of between-group effects. Cohen's *d* (adjusted for baseline scores) and 95% CIs will be used to examine the

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magnitude of between-group differences at post-treatment and 6-week follow-up. We will use multilevel modeling to compare conditions at post-treatment and 6 weeks. We chose multilevel modeling over other statistical approaches (e.g., analysis of variance) because it requires fewer assumptions, has superior ability to handle missing data, and will yield greater statistical power. In each model, the Level 1 predictor will be time. Level 2 portions of the model will include the effect of condition and sex (the only a priori hypothesized covariate). Hypotheses will be tested by regressing condition on the Level 1 intercept and time effect. Analyses will be intent-to-treat. We will examine whether attrition is associated with any baseline variables and control for such variables when necessary.

Though underpowered for formal tests of mediation, we will also examine treatment effects on Aim 3 proximal outcomes (learning, executive function, negative affect, emotion regulation, craving). These outcomes may be tested as mediators of intervention effect in a subsequent, fully-powered trial.

Patient and Public Involvement

Clinical providers at the VA were included in the development of research questions and outcome measures, as well as plans for screening, recruitment, and retention. However, patients and other members of the public were not involved in study procedures.

ETHICS & DISSEMINATION

Ethics. All study procedures were approved by the Institutional Review Board at the university (IRB #2012262) and the Research and Development Committee at the VA. Given the pilot nature of the study and the minimal risks associated with participation, an independent data safety monitoring board was not assembled. Instead, the principal investigator will monitor adherence to the study protocol and adverse events on an ongoing basis and discuss these issues

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with the research team. All serious and unexpected adverse events will be reported to the IRB within 24 hours of receipt of information. Other adverse or potentially adverse events will be monitored and reported at annual continuing reviews. After discussion with the IRB, we will discontinue the trial if there is (a) compelling evidence from this or another study of a serious adverse effect of CBT-I that has potential to override potential benefit, (b) compelling evidence from this or another study of a significant beneficial effect of CBT-I, such that continued denial to other groups would be unethical, or (c) low probability of addressing study aims within a feasible time frame. Audits are conducted randomly.

Dissemination. Results of this trial will be disseminated widely to enhance the impact of preliminary findings, and de-identified data will be made available to other qualified investigators upon request. Planned manuscripts include a primary outcomes paper describing feasibility and acceptability as well as treatment effects on sleep and alcohol use outcomes and a secondary outcomes paper describing treatment effects on proximal intervention outcomes. We also plan to examine daily associations between sleep, substance use, and mood using the daily diary data collected for all participants at baseline. Any other analyses will be exploratory in nature. Results of these analyses will be presented at national conferences, including the Research Society on Alcoholism and the annual SLEEP conference of the American Academy of Sleep Medicine and the Sleep Research Society. Results will also be shared with national VA networks of providers, as multiple members of the research team are consultants for the VA's CBT for insomnia and CBT for substance use disorder training and implementation programs.

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Author Contributions

All authors contributed to the conceptualization and design of the study. Miller drafted the initial proposal, with input from all authors. Miller, Carey, Metrik, and McGeary drafted screening and assessment procedures, which were reviewed and finalized in collaboration with Maddoux. Carey, Borsari, McCrae, and Arnedt refined procedures for treatment delivery and integrity. Merrill drafted the statistical analysis plan. Miller drafted the manuscript, which all authors reviewed and revised.

Funding Statement

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Disclaimer

NIH is not actively responsible or involved in the study design and will have no involvement in data collection, management, analysis or interpretation. NIH will have no involvement in future manuscript preparation or decision to submit for publication. This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy. The contents do not represent the views of the U.S. Department of Veterans Affairs or the United States Government.

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Competing Interests

None declared

Ethics Approval

The study and methods were evaluated and approved by the Institutional Review Board at the University of Missouri (IRB #2012262) and the Research and Development Committee at the Harry S. Truman Memorial Veterans' Hospital.

Provenance and Peer Review

This proposal was externally peer reviewed at the National Institute of Alcohol Abuse and Alcoholism at the National Institute of Health.

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Table 1

Survey instruments and schedule of administration.

Use	Construct	Measure(s)	BL	Post	FU
Descr	Demographics	Age, sex, gender, race/ethnicity, education, military history, marital status, employment, housing	X		
	Other drug use	From the National Survey of Drug Use and Health	X	X	X
	Use of sleep medication	Daily Sleep Diary	X	X	X
Aim 1	Recruitment	Completion of ≥ 1 session of CBT-I		X	
	Retention	Completion of 5/5 sessions of CBT-I		X	
	Treatment satisfaction	Client Satisfaction Questionnaire		X	
Aim 2	Insomnia severity	Insomnia Severity Index	X	X	X
	Sleep efficiency	Daily Sleep Diary	X	X	X
	Sleep quality	Daily Sleep Diary	X	X	X
	% days abstinent % days heavy drinking	Timeline Follow-back (TLFB) for alcohol	X	X	X
	Alcohol problems	Short Inventory of Problems	X	X	X
	Use of alcohol or other drugs to help with sleep	Daily Sleep Diary	X	X	X
Aim 3	Treatment-related learning	Project SAVE Alcohol Quiz Project SAVE Alcohol Vignette	X	X	X
	Executive function	Psychomotor Vigilance Task (attention) *N*-back Task (working memory) Monetary Choice Questionnaire (delay discounting)	X	X	X
	Negative affect	Positive and Negative Affect Schedule	X	X	X
	Emotion regulation	Brief Difficulties in Emotion Regulation Scale	X	X	X
	Alcohol craving	Penn Alcohol Craving Scale	X	X	X

Note. BL=baseline. Descr=descriptives. Post=post-treatment. FU=follow-up.

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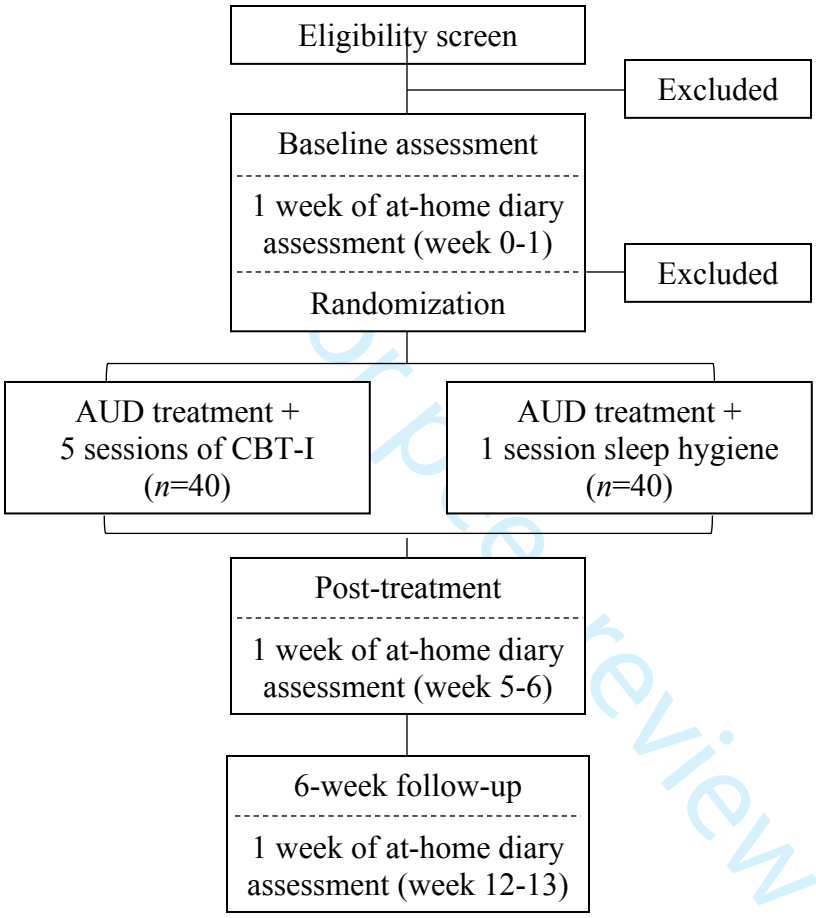
Figure 1

Participant flow diagram (N=80).



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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

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Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	#3	Date and version identifier	3
Funding	#4	Sources and types of financial, material, and other support	19
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	19
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	19
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	19
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	19

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		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	11
Objectives	#7	Specific objectives or hypotheses	6-7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8

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Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-11
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	17-18
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-16

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Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	9

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		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8-9

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Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16-17
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further	17-18

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		details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17-18
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17-18
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17-18
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	17-18
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	17-18

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Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	11
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18

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Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	19
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A

Appendices

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

None The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-BY-ND 3.0. This checklist can be completed online using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

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BMJ Open

Protocol for the Project SAVE Randomized Controlled Trial Examining CBT for Insomnia among Veterans in Treatment for Alcohol Use Disorder

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Protocol for the Project SAVE Randomized Controlled Trial Examining CBT for Insomnia among Veterans in Treatment for Alcohol Use Disorder

Mary Beth Miller,[1,2] Jane Metrik,[2,3] John E. McGeary,[2,3] Brian Borsari,[2,4,5] Christina S. McCrae,[1] John Maddoux,[6] J. Todd Arnedt,[7] Jennifer E. Merrill,[2] and Kate B. Carey[2]

[1]Department of Psychiatry, University of Missouri, Columbia, MO

[2]Center for Alcohol and Addiction Studies, Brown University, Providence, RI

[3]Mental Health & Behavioral Sciences Service, Providence VA Medical Center, Providence, RI

[4]Mental Health Service, San Francisco VA Health Care System, San Francisco, CA

[5]Department of Psychiatry and Behavioral Sciences, University of California San Francisco, San Francisco, CA

[6]Addiction Treatment Program, Harry S. Truman Memorial Veterans Hospital, Columbia, MO

[7]Department of Psychiatry, University of Michigan, Ann Arbor, MI

Corresponding Author:
Mary Beth Miller, PhD
Department of Psychiatry
University of Missouri-Columbia
1 Hospital Drive, DC067.00
Columbia, MO 65212
Phone: 1-573-882-1813
Fax: 1-573-884-1070
millmary@health.missouri.edu

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ABSTRACT

Introduction: As many as 74% of Veterans with alcohol use disorders (AUD) report symptoms of insomnia. Insomnia represents a barrier to alcohol treatment because insomnia symptoms (a) may lead to relapse among those who use alcohol to help them sleep and may negatively impact (b) executive functions and (c) emotion regulation skills. Cognitive Behavioral Therapy for Insomnia (CBT-I) is an efficacious first-line treatment for insomnia; however, no research has examined the impact of CBT-I on individuals' response to alcohol treatment. In the Sleep and Alcohol for VEterans (Project SAVE) randomized controlled trial, we hypothesize that CBT-I will enhance the efficacy of alcohol treatment among Veterans with insomnia by enhancing their abilities to attend to treatment, regulate emotions, and initiate sleep without alcohol.

Methods & Analysis: Eighty Veterans enrolled in alcohol treatment at the VA will be randomly assigned to receive either CBT-I or single-session sleep hygiene (SH) education. Individuals will be eligible to participate if they meet DSM-5 criteria for moderate to severe AUD and Insomnia Disorder of at least 1 month duration. Participants will complete assessments at baseline, post-treatment, and 6-week follow-up. Preliminary process outcomes include retention/recruitments rates and treatment satisfaction (feasibility and acceptability, respectively). Primary outcomes are insomnia severity, percentage of heavy-drinking days, and alcohol-related problems. We will assess a variety of secondary clinical and mechanistic outcomes (e.g., PTSD symptoms, attention, working memory).

Ethics & Dissemination: Ethics approval was obtained in October 2018. Data collection began in July 2019 and is planned for completion by July 2021. Trial results will be disseminated at local and national conferences, in peer-reviewed publications, and through media outlets, as

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available. Results will also be shared with interested participants and clinical collaborators at the end of the trial.

Registration Details: clinicaltrials.gov identifier NCT03806491

Keywords: alcohol, insomnia, treatment, Veterans, protocol

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ARTICLE SUMMARY

Strengths and Limitations of the Study

- Cognitive Behavioral Therapy for Insomnia (CBT-I) is an evidence-based treatment for insomnia that has not been tested among Veterans currently engaged in treatment for alcohol use disorder.
- This study utilizes a randomized controlled trial design to determine the extent to which CBT-I may impact potential cognitive and emotional mechanisms of treatment (e.g., treatment-related learning, working memory, emotion regulation).
- This research will advance previous studies by examining the impact of CBT-I on alcohol-related problems.
- Findings will be limited to short-term (6-week) outcomes.
- Although this study will document the short-term efficacy of CBT-I over "usual care" (a single session of sleep hygiene education), it will not control for non-specific therapy effects.

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INTRODUCTION

Up to 74% of Veterans seeking treatment for alcohol use disorder (AUD) report symptoms of insomnia.[1] These symptoms represent a barrier to AUD treatment for at least three reasons: (1) Approximately 50% of individuals with alcohol use disorders report using alcohol to help them sleep;[2-4] thus, those without alternative sleep aids may relapse to drinking if insomnia persists. Insomnia symptoms have also been associated with significant deficits in (2) attention/working memory[5 6] and (3) emotion regulation.[7-10] Because cognitive-behavioral therapy (CBT) for AUD capitalizes on individuals' executive cognitive functions to identify and respond to the stimuli that lead to alcohol use,[11] CBT-based treatment may have limited effectiveness for patients with insomnia. This combination of factors – insomnia and limited cognitive/emotional capacity to respond to treatment – may explain in part why insomnia symptoms precipitate relapse.[12] Indeed, 1 in 3 individuals relapse to problematic drinking within one year of alcohol treatment.[13 14]

Sleep disturbance has been established as a risk factor for poor alcohol treatment outcomes.[15 16] More than half of those in residential treatment programs report insomnia symptoms at admission, and the majority continue to report symptoms at discharge.[17 18] Yet prior research has not demonstrated how alcohol use may change as a result of insomnia treatment.[12] Research in animal models suggests that restoring normal sleep may reduce relapse to alcohol use.[19] Pharmacological treatment of sleep disturbance with gabapentin has also been found to reduce the risk of relapse in individuals with AUDs in the short term (at 6-12 weeks).[20 21] Because Cognitive Behavioral Therapy for Insomnia (CBT-I) has been associated with longer-term improvements in insomnia than pharmacological sleep treatment,[22] CBT-I may be a more effective adjunct to alcohol treatment than pharmacotherapy in the long term.

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CBT-I is a first-line treatment for chronic insomnia.[22 23] A number of randomized controlled trials have documented its efficacy in reducing symptoms of insomnia among military and Veteran populations.[24-28] CBT-I yields comparable effects for younger (18-64y) and older (65+y) Veterans[29] and has been effective in reducing insomnia severity in the presence of co-occurring medical,[30] psychiatric,[25 31] and alcohol use disorders.[32-34] Notably, CBT-I has also led to improvements in suicidal ideation,[35] symptoms of depression,[29] psychosocial functioning,[25] and quality of life.[29] While CBT-I has not reduced rates of relapse among individuals with AUD reporting 25 or more days of abstinence,[33 34 36] these previous trials have been limited by small sample sizes (post-treatment *N*s ≤ 16/group), low rates of relapse, and use of non-treatment-seeking samples. These studies also did not evaluate changes in alcohol-related problems (beyond alcohol use itself) and did not examine the impact of CBT-I on engagement in alcohol treatment.[37]

Current Aims

The primary objective of the current study is to enhance alcohol treatment to account for the unique needs of Veterans with sleep complaints. The study involves three specific aims. First, we aim to test the feasibility and acceptability of CBT-I delivered concurrently with CBT for AUD via randomized controlled trial. Second, we aim to evaluate the initial efficacy of CBT-I in improving sleep and alcohol use outcomes. We hypothesize that Veterans receiving CBT-I will demonstrate greater reductions in insomnia severity, percent heavy-drinking days, and alcohol-related problems than those receiving sleep hygiene only. Finally, we aim to examine CBT-I effects on secondary clinical and mechanistic outcomes (see conceptual framework in Figure 1). Secondary clinical outcomes include sleep efficiency (percentage of time spent in bed that is actually spent sleeping – a core treatment target in CBT-I) as well as

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symptoms of PTSD, depression, and anxiety. Proposed mechanistic outcomes include treatment-related learning, use of alcohol as a sleep aid, incentive salience (specifically alcohol craving), negative emotionality, and executive function. Incentive salience, negative emotionality, and executive function were included because these are the neuroscience domains considered especially salient within the binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation phases of addiction, respectively[38]; and sleep has also been posited as a neurobiological contributor to each of these stages of addiction.[39]

METHODS & ANALYSIS

Sample Size Calculation

Based on previous studies, we anticipate moderate to large effects on insomnia severity[26] [27] and small effects on drinking quantity/frequency.[33] [34] No previous studies have examined the impact of CBT-I on alcohol-related problems; therefore, the size of this potential treatment effect is unknown. Similarly, effect sizes of CBT-I on secondary outcomes (learning, executive function, negative affect, emotion regulation, craving) have not been well-established.[40] [41] A priori power analyses (G*Power 3.1) indicated that a sample of 44 participants would provide sufficient power to detect a medium (f=.25) group by time interaction using repeated measures ANOVA (α=.05, groups=2, repetitions=3, correlation=.50). This study will be underpowered to detect small effects (N=260 participants for f=.10); however, we will utilize multilevel modeling to increase power to detect small effects. Multiple imputation will be used to handle missing data, given historically high rates of attrition in this patient population.[33] [34]

Participants

Individuals will be eligible to participate if they are Veterans (a) enrolled in the Addictions Treatment Program at the Harry S. Truman Memorial Veterans' Hospital (Truman

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VA) in Columbia, MO; (b) meet DSM-5 criteria for moderate or severe AUD; (c) report substance use in the past 2 months; and (d) meet DSM-5 and research diagnostic criteria for acute or chronic Insomnia Disorder. Criteria for insomnia include difficulty falling asleep or staying asleep (defined as >30 minutes) at least 3 nights per week for at least 1 month, accompanied by daytime impairment.[42] Participants will be excluded if they are (a) unable to provide informed consent, (b) demonstrate cognitive impairment (defined as a Mini Mental Status Exam score below 26), (c) report continuous sobriety for more than 2 months at baseline, (d) report a manic episode or seizure in the past year (contraindications for CBT-I[43]), (e) have a severe psychiatric disorder that requires immediate clinical attention (e.g., psychosis, suicidal ideation with intent and plan), or (f) report a new sleep medication in the past 6 weeks at baseline.

Procedures

Recruitment and screening. Eighty Veterans with AUD and insomnia will be recruited from the VA's Addiction Treatment Program between July 2019 and July 2021 to participate in an insomnia treatment study (see Figure 2). Individuals participating in the program's residential or outpatient groups will be informed of the research study at intake and reminded of the study periodically at the beginning of treatment groups. Both residential and outpatient treatment services utilize a variety of evidenced-based treatments for substance use disorders, including elements of Cognitive Behavioral Therapy, Mindfulness, and Motivational Interviewing. The residential treatment program has an average length of stay of 42 days (6 weeks), and outpatient treatment in the form of group therapy has no time duration. Interested participants will conduct a brief eligibility screen (~10 minutes) with the project coordinator, and those who remain interested after learning more about the study will be scheduled for the baseline assessment.

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Baseline assessment. Research staff will review informed consent with each participant. Interested participants will provide written informed consent prior to completion of baseline (see Table 1 for list of measures and schedule of administration). Participants will complete a Timeline Followback interview[44] to confirm alcohol use in the past 2 months and the Mini Mental Status Exam to confirm cognitive capacity. The Mini International Neuropsychiatric Interview (MINI) 7.0.2 and a semi-structured clinical interview for sleep disorders will be used to assess diagnostic criteria for AUD and Insomnia Disorder, as well as co-occurring physical and mental health conditions (e.g., mania, seizures, psychiatric disorders) and use of sleep medications. Those who endorse symptoms of sleep-related breathing disorders, restless legs syndrome, periodic limb movement disorder, or narcolepsy will be referred for polysomnography. Given the prevalence of sleep apnea in this population, individuals who meet all eligibility criteria but report symptoms of sleep apnea will complete one night of holter monitoring (using an Evo Holter Recorder, SpaceLabs Healthcare) at home in their own beds to establish severity of sleep apnea.[45]

The baseline period will include one week of daily sleep diaries, which will be collected electronically and time-stamped each morning using the Qualtrics data management system. Baseline diaries will be used in part to confirm diagnosis of insomnia; specifically, that participants report at least 3 nights of sleep onset latency or wake after sleep onset >30 minutes. Participants who have not completed the diary each morning by noon will receive a reminder text or phone call from study staff. Participants will have the option of completing the daily sleep diaries using pen-and-paper surveys if unable to complete by computer or phone.

Randomization. Following the 7-day baseline period, eligible participants will be randomly assigned in a 1:1 ratio to either the CBT-I or sleep hygiene condition using a random

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number generator. The project coordinator will assign participants to conditions and reveal their allocation to interventionists only after the principal investigator has confirmed eligibility. Randomization will be stratified by sex, PTSD diagnosis, and residential versus outpatient AUD treatment.

Blinding. The principal investigator and study therapists will be blinded to assessment outcomes, and the research assistant conducting post- and follow-up assessments will be blinded to participant condition.

Follow-up assessments. The project coordinator will contact participants 5 weeks after baseline (post-treatment) and 6 weeks after the post-treatment assessment to complete follow-up assessments (see Figure 2).

Adaptations for remote treatment delivery. All assessments and interventions for this protocol were designed to be conducted in-person. However, because the catchment area for the proposed VA is largely rural, it quickly became clear that remote delivery of the intervention would be necessary to accommodate the needs of some participants. Therefore, treatment sessions will be completed remotely, either by phone or using the Department of Veterans Affairs' Video Connect service, when needed. VA Video Connect is a mobile application that allows Veterans and providers to hold secure virtual meetings from remote locations. For all remote appointments, research staff use their VA email and a VA-provided laptop. Participants may use a number of electronic devices (e.g., iPhone, iPad, Android, PC, laptop) to open the email invitation from the provider, which will include a link to the secure video session. VA Video Connect uses encryption to ensure that sessions are private and secure and is designed for Veterans in rural areas with limited access to healthcare facilities.

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Retention strategies. To enhance follow-up rates, all appointments will be as brief as possible. Participants will receive $30, $40, and $50 dollars for completing the baseline (~2 hours), post-treatment (~1 hour), and 6-week follow-up assessments (~1 hour), respectively. At each assessment, they will receive an additional $10 for completing all seven daily diaries. Research assistants and the principal investigator will coordinate schedules so that lab phones and emails are monitored continuously during business hours. Interventionists will also provide after hours 'on-call' support for participants who are actively engaged in the intervention. We will implement a case management approach to participant retention, which aims to prevent foreseeable barriers to participation and address problems as they arise. This approach involves weekly contact with participants, monitoring of progress, regular appointment reminders, and thank you notes following assessment completion.

Interventions

Cognitive Behavioral Therapy for Insomnia (CBT-I). CBT-I will be delivered individually in five weekly one-hour sessions. Study therapists will follow the 2014 CBT-I in Veterans manual developed by leading researchers in the behavioral sleep medicine field and currently used throughout the VA.[43] Intervention components include (1) sleep hygiene: limiting naps; avoiding caffeine, tobacco, alcohol, and rich/heavy foods before bedtime; exercising; establishing a bedtime routine; and creating a comfortable sleep environment; (2) sleep restriction: limiting time in bed in order to improve sleep efficiency, or the percentage of time in bed that is actually spent sleeping; time in bed will be titrated each week based on sleep efficiency; (3) stimulus control: strengthening association between bedroom and sleep to decrease conditioned arousal; (4) relaxation: diaphragmatic breathing, progressive muscle

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relaxation, and visual imagery to reduce arousal; and (5) cognitive therapy: identifying and challenging thoughts that interfere with sleep using thought logs and behavioral experiments.

Sleep Hygiene (SH). Participants in both conditions will review a one-page handout on sleep hygiene with a trained study therapist. Interactions last 15-30 minutes (depending on the number of questions participants ask), and this is the only intervention that participants assigned to the sleep hygiene condition will receive. This feedback was designed to be consistent with what may be expected as "usual care" in a doctor's visit with a primary care physician. Upon completion of the study, sleep hygiene participants will be offered a referral for CBT-I, which is available with trained providers at the VA.

Treatment integrity. Study therapists will be graduate students in clinical or counseling psychology. Consistent with recommendations for clinical trials,[46] treatment integrity will be assessed at the point of (a) delivery, (b) receipt, and (c) enactment. In terms of treatment delivery, study therapists will receive training in use of the treatment manual via lecture, observation, and mock therapy sessions. Prior to seeing participants, each therapist will audiotape mock therapy sessions, which the principal investigator (a licensed clinical psychologist supervised by a psychologist board certified in behavioral sleep medicine) will evaluate in order to provide corrective feedback. The principal investigator will also review session audiotapes for ongoing training and supervision. A member of the study team who is not involved in therapist training or supervision will then evaluate the integrity of 10 randomly selected CBT-I audiotapes using a checklist of treatment elements.

To facilitate participant receipt and comprehension of the treatment, participants will receive a workbook of treatment materials. They will also be asked to summarize and ask questions about the rationale for various recommendations throughout treatment, and they will

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be asked to review and record the most helpful things they learned at the end of treatment. Participants will also complete a "sleep quiz" testing their knowledge of treatment recommendations at baseline and post-treatment so comprehension can be assessed.

Finally, in regards to participant enactment, participants will maintain logs of home assignment completion. Therapists will ask participants about their adherence to treatment recommendations at the beginning of each session and discuss and problem-solve barriers to treatment compliance as necessary. Following session 3 and session 5, study therapists also rate their agreement with the statement, "*This participant adheres to treatment recommendations*" on a scale from 1 (*strongly disagree*) to 7 (*strongly agree*).

Treatment credibility. At the end of the treatment phase (the post-treatment assessment), participants will complete a 5-item treatment credibility questionnaire[47] assessing the extent to which (a) treatment techniques appeared to be a logical treatment for insomnia; (b) the participant liked and (c) had confidence in his/her therapist; (d) the participant had confidence that the treatment would work; and (e) the participant would recommend this treatment to others with insomnia.

Preliminary Process Outcomes (Aim 1)

Recruitment and retention. The number of participants who complete baseline (relative to screening) will indicate participant recruitment. The number of participants who complete the single session of sleep hygiene and all five sessions of CBT-I will indicate retention in the sleep hygiene and CBT-I conditions, respectively.

Treatment satisfaction. The 8-item Client Satisfaction Questionnaire[48] will be used to assess participant satisfaction with insomnia and alcohol treatments (assessed separately) at the post-treatment assessment. It has been validated among individuals in treatment for substance

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use.[49] All items are scored 1 to 4, with higher scores indicating higher satisfaction with treatment. For example, in this study, participants will respond to the item, "How satisfied are you with the amount of help you received for your insomnia?" on a scale from 1 (*quite dissatisfied*) to 4 (*very satisfied*).

Primary Outcomes (Aim 2)

Insomnia severity. The 7-item Insomnia Severity Index[50] will be used to measure insomnia severity at baseline, post-treatment, and 6-week follow-up. Items assess difficulty falling or staying asleep, satisfaction with current sleep pattern, interference with daily functioning, the extent to which others notice their sleep problems, and worry/distress related to sleep problems. Response options range from 0 (*not at all worried*) to 4 (*very much worried*), with possible total scores ranging from 0 to 28. Notably, self-report is the recommended method of assessment for symptoms of insomnia in adults.[51]

Percentage of heavy-drinking days. The Timeline Followback (TLFB) will be used as a face-valid measure of change in drinking from baseline to follow-up.[44] Using a calendar-based form, participants will indicate on which days in the past 6 weeks they consumed alcohol. Holidays and significant historical events will be labeled to enhance memory recall. A trained research assistant will then review days of alcohol use with the participant to determine the number of standard drinks consumed on each day. The TLFB will be used to estimate percentage of heavy-drinking days (4+ drinks per day for women; 5+ drinks per day for men).

Alcohol-related problems. The Short Inventory of Problems is a 15-item measure of alcohol-related problems[52] that has demonstrated reliability and concurrent validity among individuals in treatment for substance use.[53] Sample items include, "*My family has been hurt by my drinking*," and, "*I have failed to do what is expected of me because of my drinking*."

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Response options range from 0 (*never*) to 3 (*daily or almost daily*). Responses will be summed to create a total problems score.

Secondary Outcomes (Aim 3)

Secondary outcome measures, time frames, and scoring are depicted in Table 1. We plan to examine four clinical and four mechanistic secondary outcomes. Secondary clinical outcomes include sleep efficiency (percentage of time spent in bed that is actually spent sleeping) and symptoms of PTSD, depression, and anxiety. Mechanistic secondary outcomes include treatment-related learning, use of alcohol as a sleep aid, incentive salience, negative emotionality, and executive function. Treatment-related learning will be assessed using a 10-item measure of AUD-specific CBT principles that was developed in collaboration with treatment providers at the VA where alcohol treatment takes place. Sample items include, "*I can manage cravings and urges by changing my thoughts*," and, "*If I have a craving (or other emotion), I must act on it*" (see Table 1 for response options and scoring). Because research regarding optimal measures for the incentive salience, negative emotionality, and executive function domains of the Addictions Neuroclinical Assessment[54] is ongoing, we included a variety of measures for each of these domains, where possible (see Table 1).

Data Analysis Plan

Data management and confidentiality. Study data will be handled only by research staff and used strictly for research purposes. All research staff will be trained in responsible research conduct and the handling of private and confidential information. Identifying information will not be recorded in assessments; rather, study data will be identified and tracked using a unique study identification number for each participant.

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Missing data. Missing outcome data will be handled using linear multiple regression with 20 imputations.[55 56] Predictors for imputation models will include treatment group, baseline levels of outcome variables, any baseline variables correlated with missingness, and baseline variables that have been associated with alcohol use or insomnia in other studies (e.g., sex, education, age, drinking quantity, comorbid substance use and mental health symptoms).

Aim 1: Feasibility and acceptability. Recruitment (goal ≥4pts/mo) and retention rates (≥70% complete 5/5 sessions) will indicate feasibility of the intervention. Treatment satisfaction (average score ≥3, indicating 'good' quality) will serve as an indicator of acceptability. Recruitment, retention, and satisfaction will be measured separately for insomnia and alcohol treatments. We do not expect group differences in recruitment. Descriptive statistics, chi-square, and t-tests will be used to determine between-group differences in retention and satisfaction.

Aim 2: Initial efficacy. Analyses will be intent-to-treat. Cohen's *d* (adjusted for baseline scores) and 95% CIs will be used to examine the magnitude of between-group differences at post-treatment and 6-week follow-up. We will use multilevel modeling to compare conditions at post-treatment and 6 weeks. We chose multilevel modeling over other statistical approaches (e.g., analysis of variance) because it requires fewer assumptions, has superior ability to handle missing data, and will yield greater statistical power. In each model, the Level 1 predictor will be time. Level 2 portions of the model will include the effect of condition and sex (the only a priori hypothesized covariate). Hypotheses will be tested by regressing condition on the Level 1 intercept and time effect.

We do not anticipate including covariates beyond sex in models because participants will be randomized to groups, in which case any between-group differences in confounding variables should be random. However, we will examine between-group differences in several potential

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confounding variables at baseline and control for these when necessary. These include alcohol use severity, insomnia severity and course (e.g., persistent versus episodic), hours of addiction treatment engagement, treatment history, other substance use, use of sleep aids (e.g., sleep medications), and physical and mental health comorbidities. We will also examine whether attrition is associated with any baseline variables and control for such variables when necessary.

We will also examine post-treatment change in insomnia severity as a mediator of treatment effects on alcohol use outcomes. Mediation will be tested using asymmetric 95% bootstrapped confidence intervals for indirect effects, with 5,000 sampling estimates.[57-59] Covariates in these models will include sex, baseline levels of the outcome, and between-person differences in drinking quantity.

Aim 3: Impact on secondary outcomes. Multilevel modeling will also be used to examine treatment effects on secondary clinical and mechanistic outcomes (see Table 1), again using an intent-to-treat approach.

Patient and Public Involvement

Clinical providers at the VA were included in the development of research questions and outcome measures, as well as plans for screening, recruitment, and retention. However, patients and other members of the public were not involved in study procedures.

ETHICS & DISSEMINATION

Ethics. All study procedures were approved by the Institutional Review Board (IRB) at the University of Missouri (IRB#2012262) and the Research and Development Committee at the Truman VA. Given the pilot nature of the study and the minimal risks associated with participation, an independent data safety monitoring board was not assembled. Instead, the principal investigator will monitor adherence to the study protocol and adverse events on an

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ongoing basis and discuss these issues with the research team. All serious and unexpected adverse events will be reported to the IRB within 24 hours of receipt of information. Other adverse or potentially adverse events will be monitored and reported at annual continuing reviews. After discussion with the IRB, we will discontinue the trial if there is (a) compelling evidence from this or another study of a serious adverse effect of CBT-I that has potential to override potential benefit, (b) compelling evidence from this or another study of a significant beneficial effect of CBT-I, such that continued denial to other groups would be unethical, or (c) low probability of addressing study aims within a feasible time frame. Audits are conducted randomly.

Dissemination. Results of this trial will be disseminated widely to enhance the impact of preliminary findings, and de-identified data will be made available to other qualified investigators upon request. Planned manuscripts include a primary outcomes paper describing feasibility and acceptability as well as treatment effects on sleep and alcohol use outcomes and a secondary outcomes paper describing treatment effects on proximal intervention outcomes. We also plan to examine daily associations between sleep, substance use, and mood using the daily diary data collected for all participants at baseline. Any other analyses will be exploratory in nature. Results of these analyses will be presented at national conferences, including the Research Society on Alcoholism and the annual SLEEP conference of the American Academy of Sleep Medicine and the Sleep Research Society. Results will also be shared with national VA networks of providers, as multiple members of the research team are consultants for the VA's CBT for insomnia and CBT for substance use disorder training and implementation programs.[60]

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Acknowledgements

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Author Contributions

All authors contributed to the conceptualization and design of the study. Miller drafted the initial proposal, with input from all authors. Miller, Carey, Metrik, and McGeary drafted screening and assessment procedures, which were reviewed and finalized in collaboration with Maddoux. Carey, Borsari, McCrae, and Arnedt refined procedures for treatment delivery and integrity. Merrill and Miller drafted the statistical analysis plan. Miller drafted the manuscript, which all authors reviewed and revised.

Funding Statement

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Disclaimer

NIH is not actively responsible or involved in the study design and will have no involvement in data collection, management, analysis or interpretation. NIH will have no involvement in future manuscript preparation or decision to submit for publication. This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy. The contents do not represent the views of the U.S. Department of Veterans Affairs or the United States Government.

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Competing Interests

None declared

Ethics Approval

The study and methods were evaluated and approved by the Institutional Review Board at the University of Missouri (IRB #2012262) and the Research and Development Committee at the Harry S. Truman Memorial Veterans' Hospital.

Provenance and Peer Review

This proposal was externally peer reviewed at the National Institute of Alcohol Abuse and Alcoholism at the National Institute of Health.

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Table 1

Secondary clinical and mechanistic outcomes.

Clinical Outcomes	**Measure**	**Outcome**
Sleep efficiency (past week)	Daily sleep diaries[61]	Sleep efficiency will be calculated by dividing amount of time actually spent asleep at night by amount of time spent in bed (range 0-100%).
PTSD symptoms (past month)	PTSD Checklist for DSM-5 (PCL-5)[62]	Total scores range from 0-80, with higher scores indicating more severe PTSD symptoms.
Depression symptoms (past 2 weeks)	Patient Health Questionnaire (PHQ-9)[63]	Total scores range from 0-27, with higher scores indicating more severe symptoms of depression.
Anxiety symptoms (past 2 weeks)	Generalized Anxiety Disorder (GAD-7)[64]	Total scores range from 0-21, with higher scores indicating more severe symptoms of anxiety.
Mechanistic Outcomes	**Measure**	**Outcome**
Treatment-related learning	10-item measure of AUD-specific CBT principles	Response options are true, false, and unsure. Percentage of correct responses is the outcome (unsure coded as incorrect; range 0-100%).
Use of alcohol as a sleep aid	Daily sleep diaries[61]	Each day, participants indicate (yes/no) if they used alcohol "*specifically to help with sleep*."
Incentive Salience		
Alcohol craving (past week)	Penn Alcohol Craving Scale[65]	Total scores range from 0-30, with higher scores indicating stronger past-week alcohol craving.
Negative Emotionality		
Negative affect (current)	Positive and Negative Affect Schedule (PANAS)[66]	Negative affect subscale scores range from 10-50, with higher scores indicating more extreme negative affect (measured "right now").
Emotion regulation (past month)	Difficulties in Emotion Regulation Scale (DERS)[67]	Total scores range from 36-180, with higher scores indicating more frequent difficulty regulating emotions.
Clinical symptoms	---	PTSD, depression, and anxiety symptoms will be explored as indicators of negative emotionality and included as such if relevant.
Executive Function		
Attention (current)	Psychomotor Vigilance Task (PVT)[68 69]	Participant are asked to respond to randomly occurring stimuli. Reaction time is the outcome.
Working memory (current)	Adaptive *n*-back task[70]	Participants are presented with a sequence of shapes and asked to indicate which shape was presented *n* letters back. Proportion of correct responses will be used as the outcome variable.
Delay discounting (current)	Monetary Choice Questionnaire[71]	Rate of discounting (*k*) will be calculated using Gray and colleagues' (2016) syntax.[72]
Impulsivity (current)	UPPS-P Impulsive Behavior Scale (20 item)[73]	Total scores on the negative urgency, lack of perseverance, lack of premeditation, sensation seeking, and positive urgency subscales.

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Figure Captions

Figure 1. *Conceptual framework.*

Figure 2. *Participant flow diagram (N=80).*

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Figure 1

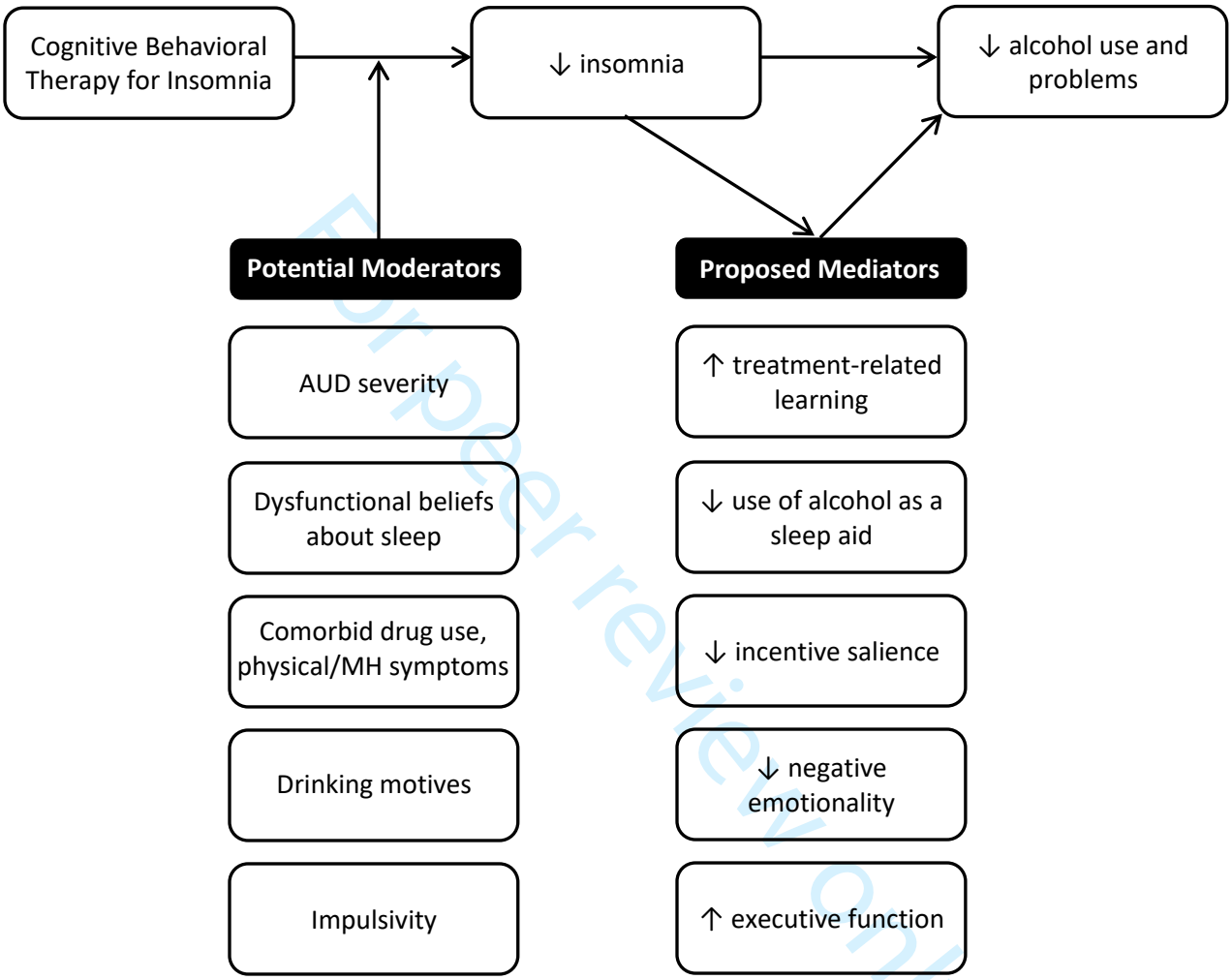

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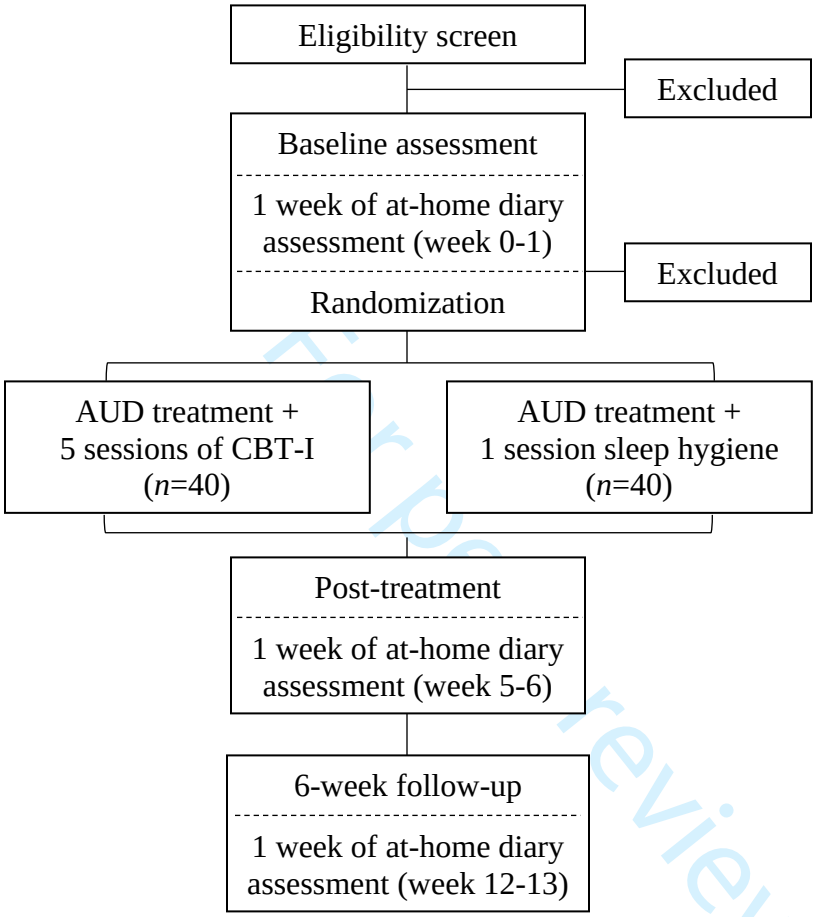
Figure 2



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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

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Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	#3	Date and version identifier	3
Funding	#4	Sources and types of financial, material, and other support	19
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	19
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	19
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	19
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	19

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		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	12
Objectives	#7	Specific objectives or hypotheses	6-7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7-8

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Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-12
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	18
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	12-13
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	14-15 and Table 1

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Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9-10
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	9-10

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		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9-10
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9-10
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-10

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Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16-17
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-17
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16-17
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and	17-18

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		competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17-18
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17-18
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17-18
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	17-18
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	17-18

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Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	17-18
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	11
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18

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Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	19
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	3
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Supp. 1
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

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