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Protocol for the Project SAVE randomised controlled trial examining CBT for insomnia among veterans in treatment for alcohol use disorder

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ABSTRACT

Introduction As many as 74% of veterans with alcohol use disorders (AUDS) report symptoms of insomnia. Insomnia represents a barrier to alcohol treatment because insomnia symptoms (1) may lead to relapse among those who use alcohol to help them sleep and may negatively impact (2) executive functions and (3) emotion regulation skills. Cognitive–behavioural 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) randomised controlled trial, we hypothesise 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 and analysis Eighty Veterans enrolled in alcohol treatment at the Veterans Administration (VA) hospital 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 *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (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/recruitment 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 (eg, post-traumatic stress disorder (PTSD) symptoms, attention and working memory).

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

Trial registration number clinicaltrials.gov identifier NCT03806491 (pre-results).

Strengths and limitations of this study

- Cognitive–behavioural 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 uses a randomised controlled trial design to determine the extent to which CBT-I may impact potential cognitive and emotional mechanisms of treatment (eg, treatment-related learning, working memory and 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.

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 AUD 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–behavioural therapy (CBT) for AUD capitalises 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, one in three individuals relapse to problematic drinking within 1 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 programmes 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 Behavioural 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.

CBT-I is a first-line treatment for chronic insomnia.[22 23] A number of randomised 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 (18–64 years) and older (65+ years) veterans[29] and has been effective in reducing insomnia severity in the presence of co-occurring medical,[30] psychiatric[25 31] and AUDs.[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≤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 aimed to test the feasibility and acceptability of CBT-I delivered concurrently with CBT for AUD via randomised controlled trial. Second, we aimed to evaluate the initial efficacy of CBT-I in improving sleep and alcohol use outcomes. We hypothesise that veterans undergoing CBT-I will demonstrate greater reductions in insomnia severity, per cent heavy-drinking days and alcohol-related problems than those receiving sleep hygiene (SH) only. Finally, we aimed 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 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/

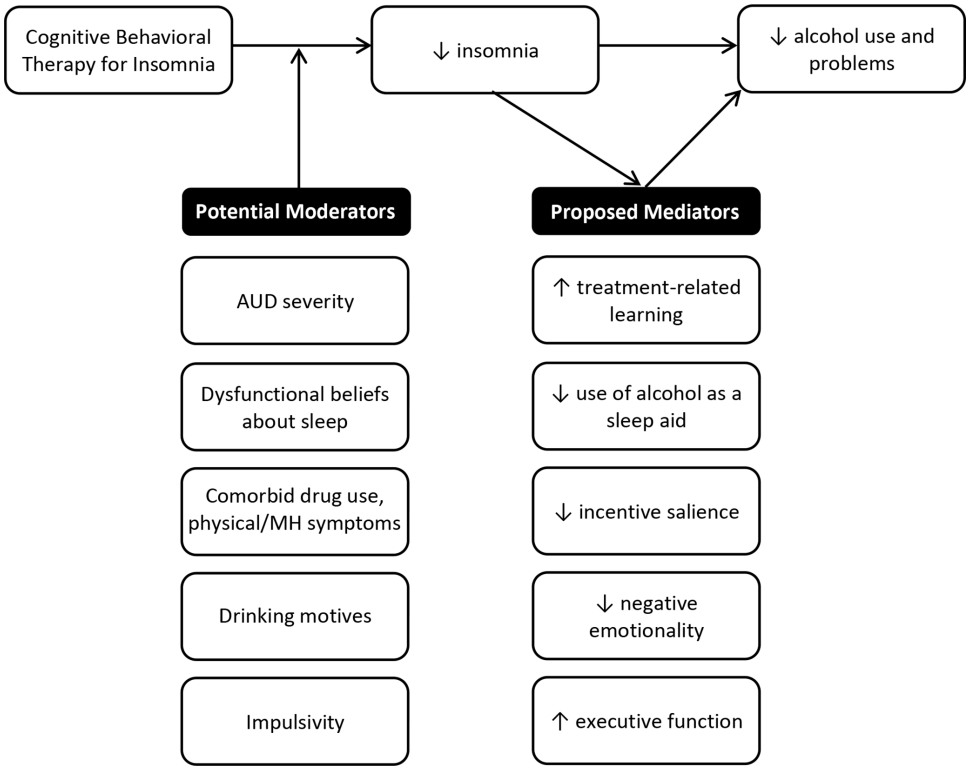

Figure 1 Conceptual framework. AUD, alcohol use disorder. MH, mental health.

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 AND 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 and craving) have not been well established.[40 41] A priori power analyses (G*Power V.3.1) indicated that a sample of 44 participants would provide sufficient power to detect a medium (f=0.25) group by time interaction using repeated measures analysis of variance (ANOVA) (α=0.05, groups=2, repetitions=3, correlation=0.50). This study will be underpowered to detect small effects (n=260 participants for f=0.10); however, we will use multilevel modelling 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 (1) are veterans enrolled in the Addictions Treatment Programme at the Harry S. Truman Memorial Veterans' Hospital (Truman VA) in Columbia, Missouri; (2) meet DSM-5 criteria for moderate or severe AUD; (3) report substance use in the past 2 months; and (4) 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 min) at least three nights per week for at least 1 month, accompanied by daytime impairment.[42] Participants will be excluded if they (1) are unable to provide informed consent; (2) demonstrate cognitive impairment (defined as a Mini Mental Status Exam score below 26); (3) report continuous sobriety for more than 2 months at baseline; (4) report a manic episode or seizure in the past year (contraindications for CBT-I[43]); (5) have a severe psychiatric disorder that requires immediate clinical attention (eg, psychosis, suicidal ideation with intent and plan); or (6) 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

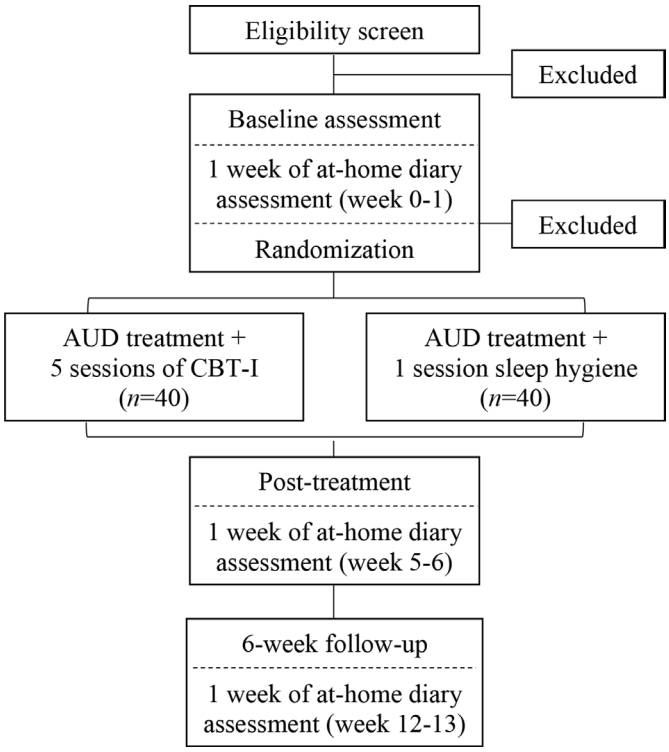

Figure 2 Participant flow diagram (n=80). AUD, alcohol use disorder; CBT-I, cognitive–behavioural therapy for insomnia.

in the programme'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 use a variety of evidence-based treatments for substance use disorders, including elements of CBT, mindfulness and motivational interviewing. The residential treatment programme 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 min) 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. Participants will complete a Timeline Followback (TLFB) 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 V.7.0.2 and a semistructured 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 (eg, mania, seizures and 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 apnoea in this population, individuals who meet all eligibility criteria but report symptoms of sleep apnoea will complete one night of holter monitoring (using an Evo Holter Recorder, SpaceLabs Healthcare) in their own beds to establish severity of sleep apnoea.[45]

The baseline period will include 1 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 three nights of sleep onset latency or wake after sleep onset of >30 min. 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.

Randomisation

Following the 7-day baseline period, eligible participants will be randomly assigned in a 1:1 ratio to either the CBT-I or SH 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. Randomisation 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 postassessment and follow-up assessment 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 (eg, iPhone, iPad, Android, PC and 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 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–behavioural therapy for insomnia

CBT-I will be delivered individually in 5 weekly 1-hour sessions. Study therapists will follow the 2014 CBT-I in Veterans manual developed by leading researchers in the behavioural sleep medicine field and currently being used throughout the VA.[43] Intervention components include (1) SH: 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 behavioural experiments.

Sleep hygiene (SH)

Participants in both conditions will review a one-page handout on SH with a trained study therapist. Interactions last 15–30 min (depending on the number of questions participants ask), and this is the only intervention that participants assigned to the SH 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. On completion of the study, SH 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 counselling psychology. Consistent with recommendations

for clinical trials,[46] treatment integrity will be assessed at the point of (1) delivery, (2) receipt and (3) enactment. In terms of treatment delivery, study therapists will undergo 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 behavioural 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 summarise and ask questions about the rationale for various recommendations throughout treatment, and they will be asked to review and record the most helpful things they learnt 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, with regard 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 sessions 3 and 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 five-item treatment credibility questionnaire[47] assessing the extent to which (1) treatment techniques appeared to be a logical treatment for insomnia; the participant (2) liked and (3) had confidence in his/her therapist; (4) the participant had confidence that the treatment would work; and (5) 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 SH and all five sessions of CBT-I will indicate retention in the SH and CBT-I conditions, respectively.

Treatment satisfaction

The eight-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 use.[49] All items are scored 1–4, 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 seven-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 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 labelled 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 and 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'. 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

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[62]	Total scores range from 0 to 80, with higher scores indicating more severe PTSD symptoms.
Depression symptoms (past 2 weeks)	Patient Health Questionnaire[63]	Total scores range from 0 to 27, with higher scores indicating more severe symptoms of depression.
Anxiety symptoms (past 2 weeks)	Generalised Anxiety Disorder[64]	Total scores range from 0 to 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 to 30, with higher scores indicating stronger past-week alcohol craving.
Negative emotionality		
Negative affect (current)	Positive and Negative Affect Schedule[66]	Negative affect subscale scores range from 10 to 50, with higher scores indicating more extreme negative affect (measured "right now").
Emotion regulation (past month)	Difficulties in Emotion Regulation Scale[67]	Total scores range from 36 to 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[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'[72] syntax.[72]
Impulsivity (current)	UPPS-P Impulsive Behaviour Scale (20 item)[73]	Total scores on the negative urgency, lack of perseverance, lack of premeditation, sensation seeking, and positive urgency subscales

AUD, alcohol use disorder; CBT, cognitive–behavioural therapy; DSM-5, *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition; PTSD, post-traumatic stress disorder.

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.

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 (eg, 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 modelling to compare conditions at post-treatment and 6 weeks. We chose multilevel modelling over other statistical approaches (eg, ANOVA) 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 hypothesised 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 randomised 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 confounding variables at baseline and control for these when necessary. These include alcohol use severity, insomnia severity and course (eg, persistent vs episodic), hours of addiction treatment engagement, treatment history, other substance use, use of sleep aids (eg, 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 CIs for indirect effects, with 5000 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 modelling 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 AND 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 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 (1) compelling evidence from this or another study of a serious adverse effect of CBT-I that has potential to over-ride benefit, (2) 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 (3) low probability of addressing study aims within a feasible time frame. Audits are conducted randomly.

Dissemination

The results of this trial will be disseminated widely to enhance the impact of preliminary findings, and deidentified 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 programmes.[60]

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Contributors All authors contributed to the conceptualisation and design of the study. MBM drafted the initial proposal, with input from all authors. MBM, KC, JM and JEMcG drafted screening and assessment procedures, which were reviewed and finalised in collaboration with JM. KC, BB, CMcC and JTA refined procedures for treatment delivery and integrity. JM and MBM drafted the statistical analysis plan. MBM drafted the manuscript, which all authors reviewed and revised.

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REFERENCES

1 Chaudhary NS, Kampman KM, Kranzler HR, *et al*. Insomnia in alcohol dependent subjects is associated with greater psychosocial problem severity. *Addict Behav* 2015;50:165–72.
2 Brower KJ, Aldrich MS, Robinson EAR, *et al*. Insomnia, self-medication, and relapse to alcoholism. *Am J Psychiatry* 2001;158:399–404.
3 Kolla BP, Schneekloth T, Mansukhani MP, *et al*. The association between sleep disturbances and alcohol relapse: a 12-month observational cohort study. *Am J Addict* 2015;24:362–7.
4 Cucciare MA, Darrow M, Weingardt KR. Characterizing binge drinking among U.S. military veterans receiving a brief alcohol intervention. *Addict Behav* 2011;36:362–7.
5 Fortier-Brochu E, Morin CM. Cognitive impairment in individuals with insomnia: clinical significance and correlates. *Sleep* 2014;37:1787–98.
6 Soehner AM, Harvey AG. Prevalence and functional consequences of severe insomnia symptoms in mood and anxiety disorders: results from a nationally representative sample. *Sleep* 2012;35:1367–75.
7 Sandru C, Voinescu BI. The relationship between emotion regulation, dysfunctional beliefs about sleep, and sleep quality - An exploratory study. *Journal of Evidence-Based Psychotherapies* 2014;14:249–57.
8 Baum KT, Desai A, Field J, *et al*. Sleep restriction worsens mood and emotion regulation in adolescents. *J Child Psychol Psychiatry* 2014;55:180–90.
9 Fairholme CP, Nosen EL, Nillni YI, *et al*. Sleep disturbance and emotion dysregulation as transdiagnostic processes in a comorbid sample. *Behav Res Ther* 2013;51:540–6.
10 Pickett SM, Barbaro N, Mello D. The relationship between subjective sleep disturbance, sleep quality, and emotion regulation difficulties in a sample of college students reporting trauma exposure. *Psychol Trauma* 2016;8:25-33.
11 DeMarce JM, Gnys M, Raffa SD, *et al*. Dissemination of cognitive behavioral therapy for substance use disorders in the Department of Veterans Affairs health care system: description and evaluation of veteran outcomes. *Subst Abus* 2021;42:168–74.
12 Brower KJ. Assessment and treatment of insomnia in adult patients with alcohol use disorders. *Alcohol* 2015;49:417–27.
13 Anton RF, O'Malley SS, Ciraulo DA, *et al*. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the combine study: a randomized controlled trial. *JAMA* 2006;295:2003–17.
14 Miller WR, Walters ST, Bennett ME. How effective is alcoholism treatment in the United States? *J Stud Alcohol* 2001;62:211–20.
15 Brower KJ, Perron BE. Sleep disturbance as a universal risk factor for relapse in addictions to psychoactive substances. *Med Hypotheses* 2010;74:928–33.
16 Smith N, Hill R, Marshall J, *et al*. Sleep related beliefs and their association with alcohol relapse following residential alcohol detoxification treatment. *Behav Cogn Psychother* 2014;42:593–604.
17 Kolla BP, Schneekloth T, Biernacka J, *et al*. The course of sleep disturbances in early alcohol recovery: an observational cohort study. *Am J Addict* 2014;23:21–6.
18 Chakravorty S, Chaudhary NS, Brower KJ. Alcohol dependence and its relationship with insomnia and other sleep disorders. *Alcoholism: Clinical and Experimental Research* 2016;40:2271–82.
19 Vengeliene V, Noori HR, Spanagel R. Activation of melatonin receptors reduces relapse-like alcohol consumption. *Neuropsychopharmacology* 2015;40:2897–906.
20 Brower KJ, Myra Kim H, Strobbe S, *et al*. A randomized double-blind pilot trial of gabapentin versus placebo to treat alcohol dependence and comorbid insomnia. *Alcohol Clin Exp Res* 2008;32:1429–38.
21 Anton RF, Myrick H, Wright TM, *et al*. Gabapentin combined with naltrexone for the treatment of alcohol dependence. *Am J Psychiatry* 2011;168:709–17.

22 Siebern AT, Manber R. New developments in cognitive behavioral therapy as the first-line treatment of insomnia. *Psychol Res Behav Manag* 2011;4:21–8.
23 Smith MT, Perlis ML, Park A, *et al*. Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. *Am J Psychiatry* 2002;159:5–11.
24 Germain A, Richardson R, Moul DE, *et al*. Placebo-Controlled comparison of prazosin and cognitive-behavioral treatments for sleep disturbances in US military veterans. *J Psychosom Res* 2012;72:89–96.
25 Talbot LS, Maguen S, Metzler TJ, *et al*. Cognitive behavioral therapy for insomnia in posttraumatic stress disorder: a randomized controlled trial. *Sleep* 2014;37:327–41.
26 Edinger JD, Olsen MK, Stechuchak KM, *et al*. Cognitive behavioral therapy for patients with primary insomnia or insomnia associated predominantly with mixed psychiatric disorders: a randomized clinical trial. *Sleep* 2009;32:499–510.
27 Germain A, Richardson R, Stocker R, *et al*. Treatment for insomnia in combat-exposed OEF/OIF/OND military veterans: preliminary randomized controlled trial. *Behav Res Ther* 2014;61:78–88.
28 Edinger JD, Sampson WS. A primary care "friendly" cognitive behavioral insomnia therapy. *Sleep* 2003;26:177–82.
29 Karlin BE, Trockel M, Spira AP, *et al*. National evaluation of the effectiveness of cognitive behavioral therapy for insomnia among older *versus* younger veterans. *Int J Geriatr Psychiatry* 2015;30:308–15.
30 Finan PH, Buenaver LF, Runko VT, *et al*. Cognitive-Behavioral therapy for comorbid insomnia and chronic pain. *Sleep Med Clin* 2014;9:261–74.
31 Smith MT, Huang MI, Manber R. Cognitive behavior therapy for chronic insomnia occurring within the context of medical and psychiatric disorders. *Clin Psychol Rev* 2005;25:559–92.
32 Arnedt JT, Conroy D, Rutt J, *et al*. An open trial of cognitive-behavioral treatment for insomnia comorbid with alcohol dependence. *Sleep Med* 2007;8:176–80.
33 Arnedt JT, Conroy DA, Armitage R, *et al*. Cognitive-Behavioral therapy for insomnia in alcohol dependent patients: a randomized controlled pilot trial. *Behav Res Ther* 2011;49:227–33.
34 Currie SR, Clark S, Hodgins DC, *et al*. Randomized controlled trial of brief cognitive-behavioural interventions for insomnia in recovering alcoholics. *Addiction* 2004;99:1121–32.
35 Trockel M, Karlin BE, Taylor CB, *et al*. Effects of cognitive behavioral therapy for insomnia on suicidal ideation in veterans. *Sleep* 2015;38:259–65.
36 Chakravorty S, Morales KH, Arnedt JT, *et al*. Cognitive behavioral therapy for insomnia in Alcohol-Dependent veterans: a randomized, controlled pilot study. *Alcoholism: Clinical and Experimental Research* 2019;28:1244–53.
37 Miller MB, Donahue ML, Carey KB, *et al*. Insomnia treatment in the context of alcohol use disorder: a systematic review and meta-analysis. *Drug Alcohol Depend* 2017;181:200–7.
38 Kwako LE, Momenan R, Grodin EN, *et al*. Addictions Neuroclinical assessment: a reverse translational approach. *Neuropharmacology* 2017;122:254–64.
39 Koob GF, Colrain IM. Alcohol use disorder and sleep disturbances: a feed-forward allostatic framework. *Neuropsychopharmacology* 2020;45:141–65.
40 Miró E, Lupiáñez J, Martínez MP, *et al*. Cognitive-Behavioral therapy for insomnia improves attentional function in fibromyalgia syndrome: a pilot, randomized controlled trial. *J Health Psychol* 2011;16:770–82.
41 Barnes CM, Miller JA, Bostock S. Helping employees sleep well: effects of cognitive behavioral therapy for insomnia on work outcomes. *Journal of Applied Psychology* 2017;102:104–13.
42 Edinger JD, Bonnet MH, Bootzin RR, *et al*. Derivation of research diagnostic criteria for insomnia: report of an American Academy of sleep medicine work group. *Sleep* 2004;27:1567–96.
43 Manber R, Friedman L, Siebern AT. *Cognitive behavioral therapy for insomnia in veterans: therapist manual*. Washington, DC: U.S. Department of Veterans Affairs, 2014.
44 Sobell LC, Sobell MB. *Timeline follow-back users guide*. Toronto: ARF, 1996.
45 Stein PK, Pu Y. Heart rate variability, sleep and sleep disorders. *Sleep Med Rev* 2012;16:47–66.
46 Lichstein KL, Riedel BW, Grieve R. Fair tests of clinical trials: a treatment implementation model. *Advan Behav Research and Therapy* 1994;16:1–29.
47 Borkovec TD, Nau SD. Credibility of analogue therapy rationales. *J Behav Ther Exp Psychiatry* 1972;3:257–60.
48 Larsen DL, Attkisson CC, Hargreaves WA, *et al*. Assessment of client/patient satisfaction: development of a general scale. *Eval Program Plann* 1979;2:197–207.
49 Kelly PJ, Kyngdon F, Ingram I, *et al*. The client satisfaction Questionnaire-8: psychometric properties in a cross-sectional survey of people attending residential substance abuse treatment. *Drug Alcohol Rev* 2018;37:79–86.
50 Morin CM, Belleville G, Bélanger L, *et al*. The insomnia severity index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep* 2011;34:601–8.
51 Schutte-Rodin S, Broch L, Buysse D, *et al*. Clinical guideline for the evaluation and management of chronic insomnia in adults. *Journal of Clinical Sleep Medicine* 2008;04:487–504.
52 Miller WR, Tonigan JS, Longabaugh R. The Drinker Inventory of Consequences (DrInC): An instrument for assessing adverse consequences of alcohol abuse (Project MATCH Monograph Series). In: *Us department of health and human services pHs*. Rockville, MD: National Institute on Alcohol Abuse and Alcoholism, 1995.
53 Alterman AI, Cacciola JS, Ivey MA, *et al*. Reliability and validity of the alcohol short index of problems and a newly constructed drug short index of problems. *J Stud Alcohol Drugs* 2009;70:304–7.
54 Kwako LE, Schwandt ML, Ramchandani VA, *et al*. Neurofunctional domains derived from deep behavioral phenotyping in alcohol use disorder. *American Journal of Psychiatry* 2019;176:744–53.
55 Graham JW, Olchowski AE, Gilreath TD. How many imputations are really needed? some practical clarifications of multiple imputation theory. *Prev Sci* 2007;8:206–13.
56 Hallgren KA, Witkiewitz K. Missing data in alcohol clinical trials: a comparison of methods. *Alcohol Clin Exp Res* 2013;37:2152–60.
57 Mackinnon DP, Lockwood CM, Williams J. Confidence limits for the indirect effect: distribution of the product and resampling methods. *Multivariate Behav Res* 2004;39:99–128.
58 Hayes AF. *Introduction to mediation, moderation, and conditional process analysis: a regression-based approach*. New York, NY: Guilford Press, 2013.
59 Fritz MS, Taylor AB, MacKinnon DP. Explanation of two anomalous results in statistical mediation analysis. *Multivariate Behav Res* 2012;47:61–87.
60 Karlin BE, Cross G. From the laboratory to the therapy room: national dissemination and implementation of evidence-based psychotherapies in the U.S. department of Veterans Affairs health care system. *Am Psychol* 2014;69:19–33.
61 Carney CE, Buysse DJ, Ancoli-Israel S, *et al*. The consensus sleep diary: standardizing prospective sleep self-monitoring. *Sleep* 2012;35:287–302.
62 Bovin MJ, Marx BP, Weathers FW, *et al*. Psychometric properties of the PTSD checklist for diagnostic and statistical manual of mental Disorders-Fifth edition (PCL-5) in veterans. *Psychol Assess* 2016;28:1379–91.
63 Delgadillo J, Payne S, Gilbody S, *et al*. How reliable is depression screening in alcohol and drug users? A validation of brief and ultra-brief questionnaires. *J Affect Disord* 2011;134:266–71.
64 Spitzer RL, Kroenke K, Williams JBW, *et al*. A brief measure for assessing generalized anxiety disorder. *Arch Intern Med* 2006;166:1092–7.
65 Flannery BA, Volpicelli JR, Pettinati HM. Psychometric properties of the Penn alcohol craving scale. *Alcohol Clin Exp Res* 1999;23:1289–95.
66 Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psychol* 1988;54:1063–70.
67 Bjureberg J, Ljótsson B, Tull MT, *et al*. Development and validation of a brief version of the difficulties in emotion regulation scale: the DERS-16. *J Psychopathol Behav Assess* 2016;38:284–96.
68 Basner M, Mollicone D, Dinges DF. Validity and sensitivity of a brief psychomotor vigilance test (PVT-B) to total and partial sleep deprivation. *Acta Astronaut* 2011;69:949–59.
69 Dinges DF, Powell JW. Microcomputer analyses of performance on a portable, simple visual RT task during sustained operations. *Behav Res Methods Instrum Comput* 1985;17:652–5.
70 Schmiedek F, LÃ¶vdÃ©n M, Lindenberger U. A task is a task is a task: putting complex span, n-back, and other working memory indicators in psychometric context. *Front Psychol* 2014;5.
71 Kirby KN, Petry NM, Bickel WK. Heroin addicts have higher discount rates for delayed rewards than non-drug-using controls. *J Exp Psychol* 1999;128:78–87.
72 Gray JC, Amlung MT, Palmer AA, *et al*. Syntax for calculation of discounting indices from the monetary choice questionnaire and probability discounting questionnaire. *J Exp Anal Behav* 2016;106:156–63.
73 Cyders MA, Littlefield AK, Coffey S, *et al*. Examination of a short English version of the UPPS-P impulsive behavior scale. *Addict Behav* 2014;39:1372–6.