Cognitive Behavioral Therapy for Insomnia for Veterans with History of TBI

NCT02658669

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Study Protocol

Pre-study screening (15-30 minutes): Initial screening for interest and eligibility will take place in person or via telephone. Veterans will be given an overview of the study and, after providing verbal consent, will be screened with a questionnaire covering the major inclusion/exclusion criteria. Veterans who were not excluded based on the phone screening and who express interest in participating in the study will be invited to come to the VASDHS for continued evaluation of eligibility for participation in the study.

Baseline-Intake (2 hours): During the intake appointment, Veterans will first provide written informed consent *and* HIPAA consent and then be screened for sleep disorders using the Duke Structured Interview for Sleep Disorders. At this appointment, we will further confirm/document history of mild traumatic brain injury (mTBI) by noting number of mTBI events, type (blast/blunt/both), and duration of LOC and PTA for each event. At this visit all Veterans will be assessed on a battery of self-report questionnaires selected to evaluate global areas of functioning including sleep, fatigue, mood, PTSD, pain, post-concussive symptoms, and quality of life (see Table 2). We will also administer a neuropsychological assessment battery consisting of standardized measures with strong psychometric properties covering cognitive functions often impacted by mTBI, sleep disturbance, and/or depression. As part of this battery the Word Memory Test[46] (WMT) will be delivered to assess validity of neuropsychological results. Neuropsychological data of Veterans who fail effort testing will not be included in subsequent moderator analyses of impact of cognitive functioning on treatment outcomes. All assessments will be administered by a trained research assistant. At the conclusion of this appointment, Veterans will be given a sleep diary to compete for 7 days to prospectively record sleep measures (e.g., "lights out," time to fall asleep, time spent awake during the night, total sleep time, and "lights on"). After the baseline evaluation phase is completed, Veterans will be randomized into one of two treatment conditions (CBT-I or Sleep Education control).

Cognitive-Behavioral Therapy for Insomnia (CBT-I: 50-minute sessions): CBT-I treatments will be randomly assigned and will be conducted utilizing the VA Roll-out treatment manual. The standard approach to treatment involves 6 weekly sessions, and addresses several important concepts, including the underlying causes of insomnia, sleep restriction and stimulus control techniques, relaxation training, and relapse prevention. A significant emphasis is placed on using a case formulation to inform the treatment, and we will do that here, especially as it applies to how the Veteran's experience with mTBI informs the formulation. The session-by-session details are presented in Table 1 below.

Table 1. VA ROLL-OUT CBT-I TREATMENT PROTOCOL

Session	*Content*	*Homework*	*Measures / Handouts*
1	*Comprehensive assessment* *Goal setting* *Case conceptualization*	*Complete sleep diary*	*Case conceptualization form* *Sleep diary* *Insomnia Severity Index (ISI)*
2	*Review sleep diary* *Provide sleep education tailored to patient* *Introduce Stimulus Control (SC)* and Sleep Restriction Therapy (SRT)** guidelines and rationale anchored in sleep regulation* *Use cognitive therapy as needed* *Emphasize most relevant components and add components based on case conceptualization*	*Complete sleep diary* *Follow recommended times for getting into and out of bed* *Follow other relevant guidelines*	*Sleep diary* *ISI* *"A Guide to Overcoming Your Insomnia"* *Other relevant worksheets*
3	*Review sleep diary and adherence;* *Discuss adherence in relation to progress* *Modify Time in Bed (TIB) based on SRT* *Use cognitive therapy as needed* *Introduce relaxation when needed (unless already introduced in Session 2)*	*Complete sleep diary* *Follow recommended times for getting into and out of bed* *Follow other relevant guidelines (including relaxation home practice)*	*Sleep Need Questionnaire* *Sleep diary* *ISI* *Other relevant worksheets*

4 & 5	*Review sleep diary and adherence* *Discuss adherence in relation to progress* *Modify TIB based on SRT rules* *Use cognitive therapy as needed*	*Complete sleep diary* *Follow recommended times for getting into and out of bed* *Follow other relevant guidelines*	*Sleep Need Questionnaire* *Sleep diary* *ISI* *Other relevant worksheets*
6	*Review sleep diary and adherence* *Modify TIB based on SRT rules* *Develop continued care plan* *Develop a relapse prevention plan*	*Follow continued care and relapse prevention plans*	*Action Plan for Addressing Insomnia in the Future* *Sleep Need Questionnaire* *ISI*

*Sleep restriction therapy reduces nocturnal sleep disturbance primarily by restricting the time allotted for sleep each night so that, eventually, the time spent in bed closely matches the individual's presumed sleep requirement. This treatment typically begins by calculating the individual's average total sleep time from the sleep diary. An initial time-in-bed prescription is typically set at the total sleep time, however, is usually not set below 5 hours per night. On subsequent sessions the time in bed is titrated up or down in 20 to 30 minutes depending on sleep performance (sleep efficiency scores) over the past week.

**Stimulus control therapy is based on the assumption that both the timing (bedtime) and sleep setting (bed/bedroom) are associated with repeated unsuccessful sleep attempts and, over time, become conditioned cues for arousal that perpetuate insomnia. As a result, the goal of this treatment is to re-associate the bed and bedroom with successful sleep attempts. In practice, this therapy requires instructing the patient to: (a) go to bed only when sleepy; (b) establish a standard wake-up time; (c) get out of bed whenever awake for long periods; (d) avoid reading, watching TV, eating, worrying and other sleep-incompatible behaviors in the bed/bedroom; and (e) refrain from daytime napping.

Sleep Education Control Condition (50 minute sessions): The sleep education control condition used in this study is matched for number of sessions and length of sessions, however the content is modified to exclude the active components of standard CBT-I treatment. The sleep education control sessions focus on review of sleep diaries, providing information on relationship between sleep disturbance and mTBI, presentation of sleep hygiene education, and reviewing daily stressors that may impact sleep (see Table 2 below).

Table 2. SLEEP EDUCATION CONTROL CONDITION PROTOCOL

Session	***Content***	***Homework***	***Measures / Handouts***
1	*Veteran check-in* *Provide information on relationship between sleep disturbance and TBI* *Description of sleep management*	*Complete sleep diary*	*Sleep diary* *Insomnia Severity Index (ISI)*
2	*Veteran check-in* *Review sleep diary* *Present sleep hygiene education*	*Complete sleep diary*	*Sleep diary* *ISI*
3	*Veteran check-in* *Review sleep diary* *Present sleep hygiene education*	*Complete sleep diary* *Change one aspect related to sleep hygiene*	*Sleep diary* *ISI*
4	*Veteran check-in* *Review sleep diary* *Review stressors related to sleep*	*Complete sleep diary* *Change one aspect related to sleep hygiene*	*Sleep diary* *ISI*
5	*Veteran check-in* *Review sleep diary* *mTBI education*	*Complete sleep diary* *Change one aspect related to sleep hygiene*	*Sleep diary* *ISI*
6	*Veteran check-in* *Review sleep diary* *Review techniques learned and strategies used over past five weeks of sleep education sessions*	*Complete sleep diary*	*Sleep diary* *ISI*

Post-treatment Assessment: In the week following completion of the final treatment module, Veterans will be given a sleep diary to fill out for 7 days to prospectively assess sleep at post-treatment. At the end of the post-treatment evaluation week Veterans will return to the VASDHS to turn in the diary and will at this time be administered the same battery of clinical assessments originally given during the baseline evaluation visit.

1-Month Follow-up: 30 days following completion of post-treatment assessment Veterans will be contacted and asked to participate in a 1-week follow-up assessment of their sleep and functioning. For follow-up Veterans will be given a sleep diary to fill out for 7 days to prospectively assess sleep at post-treatment. At the end of the sleep tracking week Veterans will return to the VASDHS to turn in the diary and will at this time be administered the same battery of clinical assessments originally given during the baseline and post-treatment evaluation visits. At the conclusion of this session the Veteran will have completed participation in the study.

Statistical Analysis

Specific Aim 1: To determine the efficacy of CBT-I relative to a Sleep Education control in Veterans with insomnia following mTBI.

Hypothesis 1a: Veterans treated with CBT-I will experience significant improvement in the primary outcome of sleep efficiency when compared to Veterans treated with Sleep Education. Sleep efficiency scores will be derived from the Veteran's sleep diaries by averaging nightly sleep efficiencies for each 1-week (seven day) period of time. Sleep efficiency data will be collected for 1-week intervals at multiple study time points including: 1) baseline/pre-treatment, 2) for each week during treatment sessions 1-6, and 3) at post-treatment. Analyses of this data will be conducted using a Random Regression Model, a generalized linear model described by Gibbons et al.[64], Hedeker et al.[65], and Laird et al.[66]. The random effects method has several advantages over more traditional analytic approaches such as a change score, end-point, or repeated measures ANOVA. This method allows the inclusion of subjects with missing data or those who were terminated early in the study, without relying on data imputation procedures. This method provides an estimate of the individual variability around the population trend, the variability of the individual intercepts (baseline values) and slopes (changes across time), and the correlation between them. The model will include a random intercept, a random effect for assessment time, and fixed effects for comparison groups and group-by-time interaction. A fully saturated treatment by time model will be utilized for inference. Co-variance structure will be chosen based on Akaike's Information Criterion (AIC). Random group level treatment effects will also be evaluated for importance based on the model AIC. This allows for any group level effects to be incorporated into the model. Denominator degrees of freedom will be calculated using the Kenward-Roger small sample correction. Data will be analyzed from all randomized subjects using all available data collected at baseline, during treatment, and at post-treatment.

> Independent variables: Treatment group (CBT-I versus Sleep Education control) and Time (Baseline, Treatment Weeks 1-6, Post-treatment).
>
> Dependent variables: Insomnia severity.

Hypothesis 1b: Veterans treated with CBT-I will report significant improvement on secondary outcome measures of depression, PTSD, and global functioning and disability when compared to Veterans treated with Sleep Education. Analyses of this data will be conducted using the Random Regression Model for assessments conducted at baseline, mid-treatment (treatment Session 3), and at post-treatment using a similar methodology as described for hypothesis 1a. Bonferroni adjusted alphas will be used.

> Independent variables: Treatment group (CBT-I versus Sleep Education control) and Time (Baseline, Mid-treatment [Session 3], Post-treatment).
>
> Dependent variables: Depression (PHQ-9), PTSD (PCL-S), and global functioning and disability (World Health Organization Disability Assessment Schedule 2 [WHODAS-2]).

Specific Aim 2: Examine sleep efficiency as a mediator of distal effects of CBT-I on symptoms of comorbid depression and PTSD, and global functioning and disability.

Hypothesis 2: Veterans demonstrating improvement in sleep efficiencies will also show improvements in comorbid depression, PTSD, and global functioning and disability. The dependent or outcome measures will be evaluated throughout the study and will be used as repeated measures for all the available time points. For this hypothesis, we will use the same mixed model procedure identified in Hypothesis 1a and 1b. To test for mediation, we will utilize the analytic strategy described by Krull and MacKinnon[67,68]. In this approach, four conditions must be met: a) a significant relationship between the independent variable (i.e., intervention condition) and the dependent variable, b) a significant relationship between the independent variable (i.e., intervention) and the proposed mediator (sleep efficiency), c) a significant relationship between the mediator (sleep efficiency) and the outcome measures, and d) the relationship between the independent variable (intervention) and outcome measures must be significantly lower after controlling for the mediator. To test for significant mediation, we will conduct a Sobel test[69]. We will also use the formula provided by MacKinnon and Dwyer[70] to determine the percentage of the intervention condition to primary outcome path that was accounted for by change in the mediator.

Independent variables: Treatment group (CBT-I versus Sleep Education control)

Dependent variables: Depression (PHQ-9), PTSD (PCL-S), and global functioning and disability (World Health Organization Disability Assessment Schedule 2 [WHODAS-2]).

Mediator: Sleep efficiency.

Specific Aim 3: Examine the effects moderator variables on CBT-I treatment outcomes

Hypothesis 3: We anticipate that several post-concussive factors such as depression, PTSD, and physical pain may moderate treatment outcomes whereas other factors such as global functioning and disability, neuropsychological functioning, and medication use will not moderate treatment outcomes. The rationale for this hypothesis comes from published work suggesting psychopathology and pain may play a significant role in maintenance of post-concussive symptoms (such as sleep disturbance) in patients with history of TBI[21] thereby potentially impacting CBT-I treatment outcomes. Conversely, factors such as neuropsychological functioning, disability, and medication use have not been previously demonstrated to impact and/or moderate CBT-I treatment outcomes in a significant manner. These positional moderators will be explored by adding one outcome at a time to the Random Regression Model.

Independent variable: Treatment group (CBT-I versus Sleep Education control).

Dependent variable: Sleep efficiency.

Moderators: Depression (PHQ-9), PTSD (PCL-S), global functioning and disability (World Health Organization Disability Assessment Schedule 2 [WHODAS-2]), pain (BPI), neuropsychological functioning, and medication use (e.g., hypnotics, SSRIs).