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Treatment of comorbid sleep disorders and posttraumatic stress disorder in active duty military: Design and methodology of a randomized clinical trial

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ABSTRACT

Many individuals with posttraumatic stress disorder (PTSD) also suffer from insomnia and nightmares, which may be symptoms of PTSD or constitute partially independent comorbid disorders. Sleep disturbances are resistant to current treatments for PTSD, and those suffering from PTSD, insomnia, and nightmares have worse PTSD treatment outcomes. In addition, insomnia and nightmares are risk factors for depression, substance abuse, anxiety, and suicide. Cognitive-Behavioral Therapy for Insomnia and Nightmares (CBT-I&N) and Cognitive Processing Therapy (CPT) for PTSD are first line treatments of these conditions. CPT does not typically address insomnia or nightmares, and CBT-I&N does not typically address other symptoms of PTSD. There are limited

Abbreviations in paper and supplemental materials: 5HTTLPR, serotonin transporter gene; CAP, Consortium to Alleviate PTSD; CAPS-5, Clinician-Administered PTSD Scale for *DSM-5*; CBT-I&N, Cognitive-Behavioral Therapy for insomnia and Nightmares; CLOCK, circadian locomotor output cycles kaput; CPT, Cognitive Processing Therapy; CRP, C-reactive protein; *d*, Cohen's d (effect size); DoD, Department of Defense; DNA, deoxyribonucleic acid; *DSM-5*, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; ECG, electrocardiogram; EEG, electroencephalogram; EMG, electromyogram; EOG, electrooculogram; FoSI-SF, Fear of Sleep Inventory-Short Form; IE, independent evaluator; IL-1, interleukin-1; IL-6, interleukin-6; IL-10, interleukin-10; OSA, obstructive sleep apnea; PCL-5, PTSD Checklist for *DSM-5*; PE, Prolonged Exposure; PER3, period circadian clock 3; PHQ-9, Patient Health Questionnaire; PSG, polysomnography; PTSD, posttraumatic stress disorder; PROMIS, Patient-Reported Outcomes Measurement Information System; PVT, psychomotor vigilance task; REM, rapid eye movement; RNA, ribonucleic acid; rCSM, Reduced Composite Scale of Morningness; SCISD, Structured Clinical Interview for *DSM-5* Sleep Disorders; SNP, single nucleotide protein; TNF-α, tumor necrosis factor alpha; VA, Department of Veterans Affairses.

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scientific data on how best to provide these therapies to individuals suffering with all three disorders. This project aims to inform the most effective way to treat individuals suffering from PTSD, insomnia, and nightmares, potentially changing the standard of care. U.S. military personnel and recently discharged Veterans who served in support of combat operations following 9/11 aged 18–65 with PTSD, insomnia, and nightmares (N = 222) will be randomly assigned to one of the following 18-session individual treatment conditions delivered over 12-weeks: (1) 6 sessions of CBT-I&N followed by 12 sessions of CPT; (2) 12 sessions of CPT followed by 6 sessions of CBT-I&N; or (3) 12 sessions of CPT followed by an additional 6 sessions of CPT. All participants will be assessed at baseline, during treatment, and at 1-week, 1-month, 3-months, and 6-months posttreatment. The primary outcome will be PTSD symptom severity.

1. Introduction

In United States military personnel with posttraumatic stress disorder (PTSD), 93% report insomnia and 68% report nightmares [1], making sleep disturbance among the most common symptoms associated with PTSD [2,3]. Sleep disturbances often do not remit after PTSD treatment [1,4–7], with as many as 50–73% of service members continuing to report nightmares and insomnia [1]. In addition, baseline severity for insomnia and nightmares may predict more intractable PTSD, requiring more treatment sessions [5,8] and possibly additional treatment types.

Insomnia and nightmares negatively impact rapid eye movement (REM) sleep and slow wave sleep stages [9,10], important for learning, memory, emotional processing, and adaptation to stress. In this way, insomnia and nightmares may impede symptom reduction of PTSD treatments [11,12]. Furthermore, adequate sleep promotes extinction of conditioned fear in healthy humans [13,14]. Thus, improved sleep should result in more efficient cognitive and emotional processing of memories, thought to be one mechanism of action of PTSD treatments [15].

PTSD, insomnia, and nightmare disorders possess significant symptom overlap, and treating one may improve symptoms of the others. For instance, the symptoms and sequelae of PTSD (e.g., problems with concentration, diminished interest in significant activities, feeling detached or numb, persistent negative emotional states, irritable behavior and angry outbursts, suicidal ideation, suicidal behaviors, reduced quality of life, increased alcohol use, and substance abuse) are also common consequences for insomnia, nightmares and other sleep disorders [16]. It is highly plausible that comorbid PTSD and sleep disturbances have joint culpability in the severity of these common symptoms. Successfully treating insomnia and nightmares along with PTSD should improve both overall functioning and quality of life of service members with PTSD [5,17].

Cognitive-Behavioral therapies (CBT) for PTSD [18], insomnia [19], and nightmares [20] are considered first-line treatments of each condition. However, few studies have examined treatment approaches for comorbid sleep disorders and PTSD. One study examined the effectiveness of sleep-directed hypnosis compared to self-monitoring prior to starting Cognitive Processing Therapy (CPT) for PTSD in a sample of 108 women. They found sleep-directed hypnosis improved sleep but did not augment gains in PTSD treatment [21]. A pilot study of 22 veterans and active duty service members with combat-related PTSD found that adding CBT for insomnia and nightmares following evidence-based treatment for PTSD (Prolonged Exposure Therapy: PE) [22] resulted in large improvements in sleep and modest improvements in daytime PTSD symptoms compared to adding supportive care therapy. Studies are needed to replicate these findings, to determine how best to sequence PTSD and sleep treatments, and to determine if objective sleep biomarkers (e.g., duration, architecture, and continuity) change as a result of PTSD treatment and/or predict PTSD treatment outcomes. Studies with prospective assessment of objective sleep parameters such as REM onset, sleep duration, sleep fragmentation, and density are needed to adequately identify the role sleep may play in PTSD recovery.

2. Materials and methods

2.1. Research design

This study uses a three-arm randomized design (Fig. 1) to evaluate the efficacy of one of the following 18-session treatments delivered over 12 weeks:

- 6 sessions of Cognitive-Behavioral Therapy for Insomnia and Nightmares (CBT-I&N) followed by 12 sessions of CPT;
- 12 sessions of CPT followed by 6 sessions of CBT-I&N;
- 12 sessions of CPT followed by additional 6 sessions of CPT.

2.2. Research aims

The primary objective of this study is to determine if providing CBT-I&N and CPT for combat-related PTSD results in greater PTSD symptom reduction than CPT alone. The secondary objective is to determine if the sequencing of CBT-I&N, before or after CPT, results in differential effects on PTSD symptom reduction. The tertiary objective is to determine if genetic and sleep biomarkers predict PTSD symptom reduction as a result of CBT-I&N or CPT. Additional exploratory objectives include determining whether different treatments result in improvements in other domains commonly associated with sleep disorders and PTSD (e.g., cognitive function, suicidal ideation, substance abuse, depression, anxiety, relationships, sleep biomarkers and inflammatory biomarkers) and if changes in these domains mediate the links between treatment group and PTSD symptom reduction.

2.3. Research hypotheses

2.3.1. Hypothesis 1

Adding CBT-I&N to CPT will result in greater PTSD symptom reduction than CPT alone.

2.3.2. Hypothesis 2

Adding CBT-I&N before CPT will result in greater PTSD symptom reduction than adding CBT-I&N after CPT, because CBT-I&N will normalize sleep [23], allowing for more efficient cognitive and emotional processing of memories [15].

2.3.3. Hypothesis 3

Certain sleep disorder- and PTSD-related genes (e.g., period circadian clock 3 [PER3], circadian locomotor output cycles kaput [CLOCK], serotonin transporter [5HTTLPR]), along with disruptions to certain sleep stages (e.g., slow wave and REM) and/or sleep disorders (e.g., apnea) will predict worse PTSD and possibly worse insomnia and nightmare symptom reduction.

2.3.4. Exploratory hypotheses

Adding CBT-I&N to CPT will result in greater improvement in other domains commonly associated with sleep disorders and PTSD (e.g., cognitive function, suicidal ideation, substance abuse, depression, anxiety, relationships, sleep biomarkers and inflammatory biomarkers).

Adding CBT-I&N before CPT will result in greater gains than adding CBT-I&N after CPT. Gains in the above domains will partially mediate the PTSD symptom reductions.

2.4. Participants

Study participants will be 222 active duty military and recently discharged veterans living near Fort Hood and Killeen, Texas, with PTSD, insomnia, and nightmares who previously completed a military deployment in support of combat operations following September 11, 2001. All study procedures are approved and monitored by an Institutional Review Board at each study site as well as the US Army Medical Research and Materiel Command Human Research Protection Office.

2.4.1. Inclusion criteria

For study inclusion, research participants must meet the following criteria: be age 18–65; have chronic/persistent insomnia; have chronic/persistent nightmares; have PTSD; be active duty military or recently discharged veterans eligible for treatment at Carl R. Darnall Army Medical Center at Fort Hood; be willing to refrain from new behavioral health or medication treatment for issues pertaining to sleep, PTSD, or nightmares during participation in the study; and plan to be in the area for the 5 months following the first assessment.

2.4.2. Exclusion criteria

Exclusion criteria include the following: having been redeployed to home for fewer than 3 months; current suicide or homicide risk meriting crisis intervention; inability to speak and read English; moderate to severe brain damage; pregnancy; sleep efficiency $>$ 85%; serious mental health diagnosis (e.g., bipolar disorder or psychosis); or currently engaged in evidence-based psychotherapy for PTSD (i.e., PE or CPT), insomnia, or nightmares (i.e., CBT for insomnia and/or nightmares) by self-report or review of the medical record. Participants on active duty have the option of having the research staff notify their command to ensure that participants are afforded time to participate in the study.

2.5. Assessment procedures and measures

The measures and schedule of administration are listed in Table 1. This study is being supported by the Consortium to Alleviate PTSD (CAP), jointly funded and established by the Department of Defense (DoD) and Department of Veterans Affairs (VA). As part of the CAP, the study is administering the consortium's Common Data Elements [24]. The Supplemental Materials to this manuscript include detailed descriptions of measures being used exclusively in this study to address the exploratory hypotheses.

2.6. Screening

Interested individuals first complete a brief telephone screening, in which basic study inclusion and exclusion criteria are reviewed. Eligible individuals are then invited to attend an in-person meeting. Following

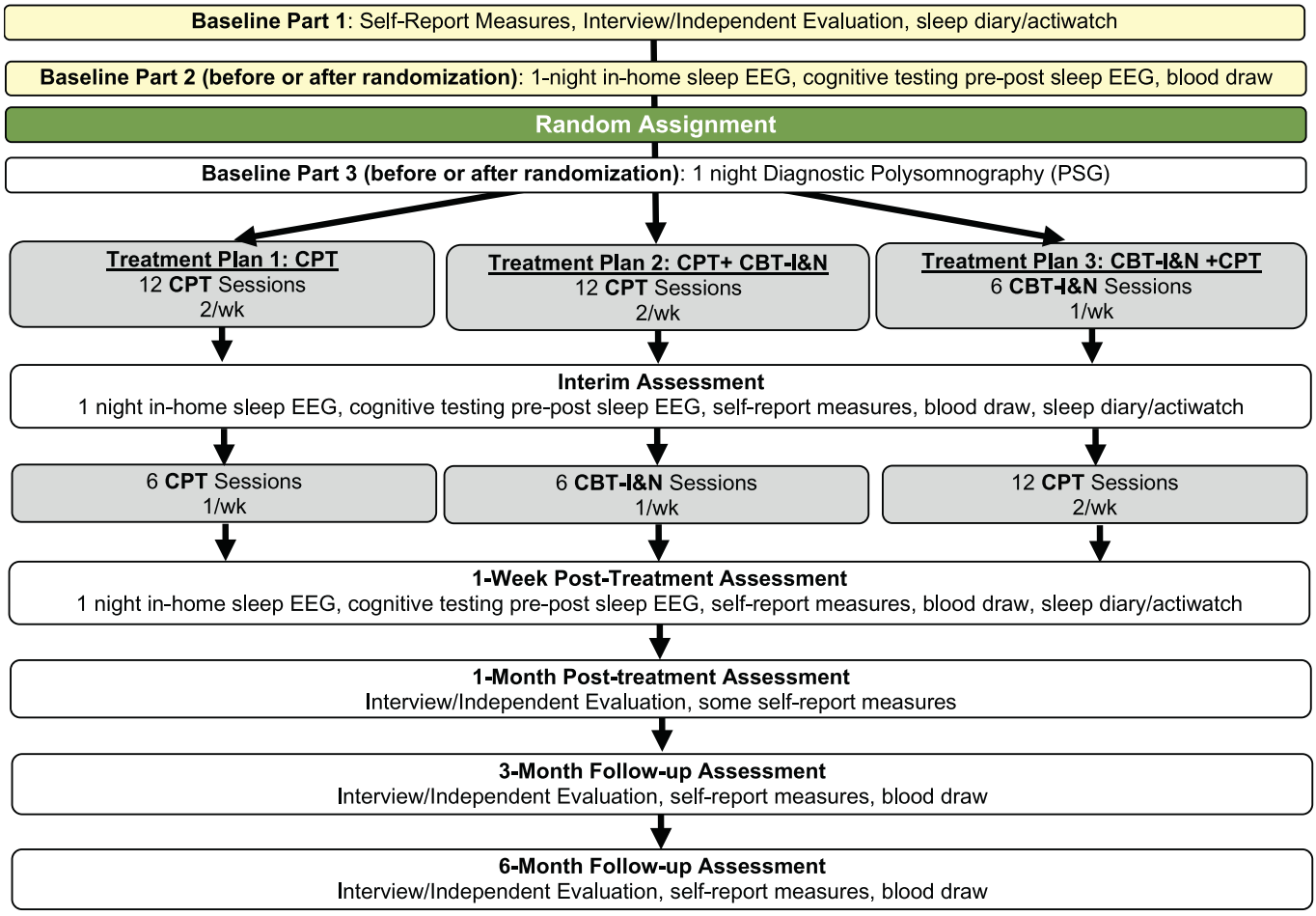

Fig. 1. Detailed design.

Table 1
Schedule of measures at each assessment time-point.

	Baseline	During Tx	Interim	1-Wk post	1-Mo post	3-Mo post	6-Mo post
Demographic information							
1. Demographics & military service characteristics	X						
PTSD measures							
2. Clinician administered PTSD scale [58]	X				X	X	X
3. PTSD checklist for *DSM-5* [59]	X	X[1, 2]	X	X[3]	X[3]	X[3]	X[3]
4. Deployment risk and resilience inventory - combat experience and postbattle experience sub-scales [60]	X						
5. Life events checklist-5 [61]	X		X	X	X	X	X
Sleep Measures							
6. Structured clinical interview for *DSM-5* sleep disorders [62]	X					X	X
7. Sleep diary	X	X[2]	X	X			
8. Insomnia severity index [63]	X	X[1, 2]	X	X[3]	X[3]	X[3]	X[3]
9. Trauma-related nightmare survey[4] [64]	X		X	X[3]	X[3]	X[3]	X[3]
10. Fear of sleep inventory-short form [65]	X		X	X		X	X
11. PROMIS sleep disturbance, sleep-related impairment [66,67]	X		X	X		X	X
12. Reduced composite scale of morningness [68]	X		X	X		X	X
Biomarker measures							
13. Actigraphy	X		X	X			
14. Polysomnography (PSG)/sleep EEG	X[5]		X	X			
15. Genetics	X[6]		X[6]	X[6]		X[6]	X[6]
16. Inflammatory	X[6]		X[6]	X[6]		X[6]	X[6]
Neuropsychological measures							
17. Cognitive functioning battery	X[7]		X[7]	X[7]			
Health measures							
18. Health questionnaire	X				X	X	X
19. History of head injuries [69,70]	X			X		X	X
20. Patient health questionnaire-15 [71]	X		X	X		X	X
21. Veterans RAND 12-item health survey [72]	X		X	X		X	X
22. Fagerström test for nicotine dependence [73]	X		X	X		X	X
23. Fagerström test for nicotine dependence – smokeless tobacco version [74]	X		X	X		X	X
Other psychosocial measures							
24. Mini international neuropsychiatric interview [75] - Mania Module	X						
25. Patient health questionnaire-9 [76]	X	X[1, 2]	X	X[3]	X[3]	X[3]	X[3]
26. Depressive symptom index – suicidality subscale [77]	X	X[1, 2]	X	X	X	X	X
27. Self-injurious thoughts and behaviors interview [78]	X				X	X	X
28. Generalized anxiety disorder screener [79]	X		X	X		X	X
29. Dimensions of anger reactions-5 [80]	X		X	X		X	X
30. Alcohol use disorders identification test [81]	X						
31. Quick drinking screen - self-report version [82]	X		X	X		X	X
32. Brief inventory of psychosocial functioning [83]	X		X	X		X	X
33. Ten-item personality inventory [84]	X			X		X	X
Therapy process measures							
34. Credibility expectancy scale [85]		X[8]					
35. Homework compliance		X[9]					
36. Independent evaluator blind form					X	X	X

Abbreviations: DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; EEG, electroencephalogram; mo, month; post, posttreatment; PTSD, post-traumatic stress disorder; PROMIS, Patient-Reported Outcomes Measurement Information System; Tx, treatment; wk., week.

[1] Also given once weekly during the course of Cognitive Processing Therapy (CPT).

[2] Also given once weekly during the course of Cognitive-Behavioral Therapy for Insomnia and Nightmares (CBT-I&N).

[3] Included in the abbreviated assessment battery that could be administered over the phone at the posttreatment assessments if the participant no longer lived in the area.

[4] An abbreviated version was given at the interim, posttreatment, and all follow-up assessments.

[5] At baseline, participants received diagnostic PSGs as well as sleep EEG PSGs.

[6] Drawn between 1200 and 1600 on day sleep the EEG equipment returned.

[7] PVT was given pre-sleep EEG; retrospective memory task was completed pre- (learning) and post-sleep EEG (recall and recognition) along with prospective memory; Stroop and Trail Making tasks were completed between 1200 and 1600 after blood draw.

[8] Given between first and second session of each treatment module.

[9] Given at each session.

informed consent, a baseline assessment is conducted in three parts over several, separate days.

2.6.1. Baseline assessment

2.6.1.1. Baseline part 1. Participants first complete self-report questionnaires and undergo a diagnostic interview for PTSD, insomnia, and nightmares. Participants who meet study diagnostic criteria are then given an actigraph to wear and a sleep diary to complete over the next week to confirm the insomnia interview diagnosis. Upon return of the actigraph and sleep diary and verification of sleep efficiency <85%, participants are scheduled for Baseline Part 2. Participants with sleep efficiency >85% will be excluded and referred for treatment.

2.6.1.2. Baseline part 2. Participants will undergo one night of ambulatory, in-home sleep polysomnography (PSG) monitoring to document sleep architecture. In the evening prior to the start of the PSG, the participant will complete cognitive testing and be fitted with the ambulatory PSG monitor at the study offices. The participant will then be sent home to sleep as normal. The PSG equipment will be returned the next day at which time blood will be drawn for genetic and inflammatory cytokine analyses. Blood draws will occur between noon and 4 p.m. to control for circadian rhythm fluctuations. The cognitive testing will be repeated as described in the Supplemental Materials.

2.6.1.3. Baseline part 3 (which could occur before or after randomization). Participants will be referred to the Sleep Disorders Center at Carl R. Darnall Army Medical Center for a clinically indicated, diagnostic PSG test to diagnose underlying sleep disorders, such as sleep apnea or periodic limb movement disorder, which could aggravate insomnia, nightmares, and PTSD. Baseline Part 3 could occur before or after randomization because it could take several weeks for a participant to be seen in the Sleep Disorders Center and we do not want to delay the start of treatment as part of this study. If participants received a diagnostic PSG in the previous 2 years, a referral is not necessary.

Participants diagnosed with untreated sleep disorders, such as obstructive sleep apnea (OSA), periodic limb movement disorder, nocturnal seizures, or a parasomnia (e.g. sleepwalking, confusional arousals, nocturnal eating and drinking syndrome), will be seen for clinical care at the sleep center. In cases of OSA, compliance data on the first 30 days on continuous positive airway pressure (CPAP; i.e., standard care for OSA) will be obtained to be used as a predictor of outcomes.

2.7. Random assignment

Neither Baseline 2 nor Baseline 3 assessments are needed to determine participant eligibility; therefore, eligible participants are randomized using a randomization list generated by the biostatistician using randomly permuted blocks of 3, 6, and 9. This is done to ensure equal numbers of participants in each of the three treatment groups as the study progresses as well as to make anticipation of group assignment nearly impossible and to reduce the potential for bias.

2.8. Study interventions

2.8.1. PTSD Treatment

This study employs individual CPT for PTSD [25]. Randomized clinical trials, meta-analyses, and research reports have identified CPT as one of the most effective treatments for PTSD [26]. CPT has been disseminated across the DoD [27] and VA [28]. The version of CPT validated in this population consists of 12 twice-weekly, 1-h sessions [29,30]. In the CPT-only group, participants receive an additional six weekly sessions. During these sessions, they continue practicing skills learned in the 12-session protocol or continue to work on problematic beliefs that have not been resolved using appropriate worksheets.

2.8.2. Sleep treatment

This study employs a six-session weekly CBT-I&N protocol to address nighttime symptoms of PTSD. The CBT-I&N protocol is a combination of a CBT-I protocol that has been validated in this population [31–34] and a trauma-focused version of Imagery Rehearsal Therapy called Exposure, Relaxation, and Rescripting Therapy [35] that is identified as an approach that can be used for the treatment of PTSD-associated nightmares by the American Academy of Sleep Medicine [20] and that has been piloted in a military population [36].

2.8.3. Therapist training, certification, and supervision

Therapists are required to attend a 2-day workshop in CPT and a 1-day workshop in CBT-I&N. They then treat at least two non-study patients under supervision and meet therapy fidelity requirements prior to treating consented study participants. Video recordings of treatment sessions are reviewed regularly by designated supervisors to ensure fidelity and to discuss during weekly supervision meetings.

2.8.4. Treatment adherence and competence

Therapist treatment adherence and competence is determined by independent raters who are trained in both CPT and CBT-I&N and who are not otherwise involved in the project. All sessions are video recorded, and 10% are randomly selected for review using standardized treatment fidelity rating scales. Patient treatment adherence is captured at each session on a homework review form, where the therapist rates, on a scale from 0% to 100%, the extent to which participants adhered to each treatment recommendation or homework assignment.

2.9. Statistical power

Sample size calculations were made using RMASS2 power software for longitudinal data [37] to ensure sufficient power to answer the secondary hypothesis that adding CBT-I&N before CPT will result in greater PTSD symptom reduction than adding it after CPT. This was done because this important pairwise comparison is a less powerful analysis than the overall three-group comparison. Using a repeated measures (pretreatment and posttreatment assessments) design and assuming medium effect of Cohen's $d = 0.50$, power = 0.80 at $p = .05$ (two-sided type I error) and allowing for 25% attrition at posttreatment, $n = 74$ per group (total $N = 222$) is needed. The test of the overall three-group main effect will have power of 0.88 or more to detect a medium effect ($d = 0.50$). There is no universally applicable algorithm for determining this threshold value across outcome domains, but leaders of the field recommend the medium effect size ($d = 0.50$) as a reasonable estimate of "the threshold below which clinicians are unlikely to be interested in the effect." [38] It is notable that $d = 0.50$ is equivalent to a Number Needed to Treat (NNT) of 3.6, which closely approximates the NNT = 3.1 that Rosenthal et al. [39] reported as being associated with effectiveness of psychotherapy [40]. In composite data from 159 patients enrolled in two recent clinical trials of CPT by our group [41], the standard deviation of pre-post change was 20. The study was thus powered for a difference in change scores of more than 10 points on the PCL-5 which is frequently cited as representing a clinically significant value [42].

2.10. Statistical analysis plan

To test the *primary hypothesis* that adding CBT-I&N to CPT is more effective at reducing CPT symptoms than simply adding more sessions of CPT, the *primary analysis* will compare results of the two groups that received CBT-I&N (CBT-I&N + CPT and CPT + CBT-I&N) to the group that received CPT-only in a repeated measures mixed effects regression model with PTSD severity (scores on the PTSD Checklist for *DSM-5* [PCL-5]) as the outcome variable assessed at baseline, throughout treatment, 1-week posttreatment and 1, 3, and 6 months following the completion of treatment. To test the *secondary hypothesis* that providing CBT-I&N before CPT (CBT-I&N + CPT) will be more effective in reducing PTSD symptoms than providing it after CPT (CPT + CBT-I&N), the *secondary analysis* will compare the two groups that received CBT-I&N to each other (CBT-I&N + CPT vs. CPT + CBT-I&N) using the same repeated measures mixed effects regression model design as proposed for the primary hypothesis. Both of the above tests will be repeated using data from all follow-up assessments to assess durability of gains. To address concerns about Type I error, principal analyses will be restricted to stated primary hypotheses and outcome variables, with exploratory analyses identified as such. All tests will be two-tailed at alpha = 0.05.

2.10.1. Additional analyses

Several additional analyses will also be performed. A series of mixed effects regression analyses will be performed using the Insomnia Severity Index, sleep diaries, actigraphy, and other variables of interest that have significant overlap (e.g., suicidal ideation, substance abuse, depression, anxiety, and inflammation [e.g., CRP, IL-1, IL-6, IL-10, TNF-α]) with the dependent variable of PTSD severity (PCL-5 scores). In addition, logistic regression analyses will be performed using the treatment group membership as the predictor variable and response and remission status (using Clinician Administered PTSD Scale for *DSM-5*) as the dependent variables. Again, tests will be repeated for data from all posttreatment assessments to assess durability of gains. Finally, baseline characteristics (e.g., gender, ethnicity, disease severity, comorbidities, sleep architecture and disorders, and genetic biomarkers) and treatment fidelity (e.g., therapist and patient adherence) will be added to the analysis with their interactions with treatment to explore their roles as predictors of treatment outcome or moderators of treatment effects [43].

Survival analysis will be used to model time to all-cause discontinuation, censoring participants who complete all scheduled sessions and using last session attended as time to dropout (or time to stopping in the study due to military reasons such as deploying, changing stations, or separating from the military). Differences between treatment arms will be evaluated with the log-rank test. To assess the possible impact of attrition on outcome analyses, participants with usable outcome data will be compared to intentional dropouts on baseline characteristics and clinical status up to the time of dropout using multiple logistic regression. If these analyses suggest that sampling bias due to dropout is an issue, supplementary propensity-weighted analyses will be done [44,45]. This method estimates the likelihood of dropping out and uses these estimates to weight the scores of those remaining to assess the biasing effects of dropout.

3. Discussion

There is limited scientific research on how best to provide cognitive-behavioral therapies for individuals suffering from a combination of PTSD, insomnia, and nightmares. This is an important question for the scientific community and for DoD and VA clinicians providing care to the nation's service members. The current approach (comparing 18 sessions of CBT-I&N + CPT to 18 sessions of CPT + CBT-I&N to 18 sessions of CPT-only) is the most rigorous and efficient design to answer our two primary questions: "Does adding CBT-I&N to CPT improve PTSD symptom reduction?" and "Does ordering/sequencing of the CBT-I&N and CPT result in differential improve PTSD symptom reduction?" Our measurement plan provides a state-of-the-science assessment of PTSD, insomnia, and nightmares and also assesses for several innovative and potentially groundbreaking biomarkers that may provide important insights into the treatment of PTSD, insomnia, and nightmares. In addition, we are examining the potential for secondary benefits of treatment on co-occurring problems (e.g., cognitive function, suicidal ideation, substance abuse, depression, anxiety, relationships, sleep biomarkers and inflammation).

3.1. Rationale for using CBT-I&N + CPT

A strong argument can be made that sleep disturbances should be treated before PTSD [46–48]. Sleep disturbances appear to undermine PTSD treatments [9–12]. Improving sleep first could alleviate sleep deprivation, which in turn would be expected to improve cognitive functioning and emotional regulation, thereby helping the patient to better process the trauma. In addition, receiving treatment for sleep disturbance may be less stigmatizing than receiving treatment for PTSD, making active duty military and veterans more likely to seek this treatment. Receiving treatment for sleep disturbance first might demystify the therapy process, build confidence in behavioral therapy, and allow for an easier transition and more confidence in PTSD treatments [49]. This sequence also allows the opportunity for patients with PTSD to quickly realize improvements in sleep and to develop rapport with a provider prior to processing trauma-related material as a part of the PTSD treatment. Among service members who screened positive for both insomnia and PTSD at Fort Hood [31,32], 65% opted to enter treatment for insomnia prior to entering treatment for PTSD.

3.2. Rationale for using CPT + CBT-I&N

A strong argument can also be made for treating PTSD before treating sleep disturbances. There are several reasons. First, it is possible that the hyperarousal symptoms of PTSD might undermine efforts to treat sleep. Second, sleep difficulties can be conceptualized as symptoms of PTSD, rather than comorbid disorders that will improve during PTSD treatment. It may be more efficient (in terms of time and expense) to treat residual sleep problems after treating PTSD [50–52]. Third, treating sleep disturbances first would delay addressing trauma-related material. If the patient decides to focus on sleep first, this could potentially be avoidance of discussing the trauma. Fourth, treating sleep disturbances after treating PTSD could still improve overall PTSD outcomes by addressing residual insomnia or nightmares. Finally, treating insomnia and nightmares after PTSD may address PTSD symptoms that are related to sleep problems, including concentration, irritability, and anhedonia. As a result, many therapists may be reticent to treat sleep before PTSD [53] without an evidence base to guide them. All of these reasons make it important to test the efficacy of CPT + CBT-I&N against both CPT-only and CBT-I&N followed by CPT.

3.3. Rationale for using CPT-only

The CPT-only group serves as a control to help determine if there are any benefits of adding CBT-I&N. There are strong data indicating that additional CPT sessions beyond the standard 12 sessions results in additional decreases in PTSD [54]. We considered a variety of options to control for time, therapist contact, expectancy, and non-specific treatment effects, including a monitor-only control, treatment as usual, or a sleep treatment placebo. However, each of these had significant drawbacks, primarily being an inactive control. This could be considered unethical, particularly when working with an active duty population.

3.4. Why not just use a two-group design such as CPT + CBT-I&N vs. CPT-only or CBT-I&N + CPT vs. CPT + CBT-I&N?

We considered comparing only two groups but decided the current, three-group comparison design was preferable because it allowed us to answer both the questions: "Does adding CBT-I&N result in greater PTSD symptom reduction than CPT alone?" and "Does sequencing of PTSD and sleep treatment result in differential effects on PTSD symptom reduction?" This design also optimizes power by allowing us to combine the CBT-I&N groups while also controlling for therapist contact, expectancy, specific and non-specific treatment effects and time compared to the CPT only condition. Performing two separate studies would increase expenses by at least 25%.

3.5. Why not integrate CPT and CBT-I&N?

There are significant drawbacks to attempting to integrate CPT and CBT-I&N. First, PTSD and sleep treatments are contextually different, and both have considerable homework assignments that are essential for improvements. Simultaneous treatments would potentially double the burden for fully employed individuals who are already experiencing significant distress related to PTSD, insomnia, and nightmares. The integration of CPT and CBT-I&N treatments increases risk for fatigue, reduced adherence to treatment, and/or dropout. Secondly, it takes approximately 6 weeks for the full benefit of the sleep therapies to take effect. Therefore, offering treatments simultaneously could increase

burden to participants while potentially limiting the benefit of either treatment.

3.6. Why not use PE instead of CPT?

We appreciate that some of the basic research on sleep disturbance and PTSD focuses on constructs more closely related to PE than CPT (e.g., extinction). However, research has shown that CPT is as effective as PE in treating PTSD [55]. Finally, CPT consists of 60-min sessions, whereas PE consists of 90-min sessions, so it is easier to match for session length across phases and arms of the trial when using CPT. The nightmare treatment uses similar themes as CPT to guide the rescripting element of treatment, so it may promote skill transfer between the two treatments.

In summary, the current study intends to advance science by examining the following: (1) the best method of treating the 68%–93% of PTSD patients who suffer with comorbid insomnia and nightmares [2,56,57], 2) the potential mechanisms of treatment that independently affect PTSD, insomnia, and nightmares; and (3) sleep-related genetic and inflammatory biomarkers as potential predictors, mediators, and/or outcomes of the different treatments. No fully powered clinical trial has attempted to determine if sequencing the treatment for insomnia or nightmares before or after evidence-based treatment of PTSD improved PTSD recovery above and beyond additional PTSD treatment alone. In addition, no other study has so comprehensively assessed sleep (subjective and objective) along with genetic and inflammatory biomarkers as potential predictors, mediators, and/or outcomes within or between the different sleep *and* PTSD treatments. This single study will be the first to assess the following questions:

1. Does treating insomnia and nightmares with CBT improve short- and long-term PTSD outcomes and reduce relapse in active duty military personnel and recently retired veterans?
2. If treating sleep improves PTSD outcomes, should sleep be treated first or second?
3. Do sleep and/or genetic biomarkers predict improve PTSD symptom reduction?
4. Does CBT-I&N or CPT-alone alter methylation of certain genes or sleep biomarkers (e.g., architecture)?
5. Do changes in gene methylation or sleep biomarkers mediate PTSD symptom reduction?
6. Does CBT-I&N or CPT-alone improve levels of inflammatory biomarkers?

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Disclaimer

The views expressed in this article are solely those of the authors and do not reflect an endorsement by or the official policy of the U.S. Army, the Department of Defense, the Department of Veterans Affairs, or the U.S. Government.

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Appendix A. Supplementary data

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References

[1] K.E. Pruiksma, D.J. Taylor, J.S. Wachen, J. Mintz, S. Young-McCaughan, A. L. Peterson, J.S. Yarvis, E.V. Borah, K.A. Dondanville, B.T. Litz, E.A. Hembree, P. A. Resick, on behalf of the STRONG STAR Consortium, Residual sleep disturbances following PTSD treatment in active duty military personnel, Psychol. Trauma 8 (6) (2016) 697–701.
[2] M.M. Ohayon, C.M. Shapiro, Sleep disturbances and psychiatric disorders associated with posttraumatic stress disorder in the general population, Compr. Psychiatry 41 (6) (2000) 469–478.
[3] J.A. Brownlow, G.C. Harb, R.J. Ross, Treatment of sleep disturbances in post-traumatic stress disorder: a review of the literature, Curr. Psychiatry Rep. 17 (6) (2015) 41.
[4] S.E. Larsen, C. Fleming, P.A. Resick, Residual symptoms following empirically supported treatment for PTSD, Psychol. Trauma 11 (2) (2019) 207–215.
[5] P.J. Colvonen, L.D. Straus, C. Stepnowsky, M.J. McCarthy, L.A. Goldstein, S. B. Norman, Recent advancements in treating sleep disorders in co-occurring PTSD, Curr. Psychiatry Rep. 20 (7) (2018) 48.
[6] P.P. Schnurr, C.A. Lunney, Residual symptoms following prolonged exposure and present-centered therapy for PTSD in female veterans and soldiers, Depress. Anxiety 36 (2) (2019) 162–169.
[7] P.L. Haynes, I. Skobic, D.R. Epstein, S.E. Emert, S. Parthasarathy, S. Perkins, J. Wilcox, Cognitive processing therapy for posttraumatic stress disorder is associated with negligible change in subjective and objective sleep, Behav. Sleep Med. 18 (6) (2020) 809–819, https://doi.org/10.1080/15402002.2019.1692848.
[8] G. Belleville, S. Guay, A. Marchand, Persistence of sleep disturbances following cognitive-behavior therapy for posttraumatic stress disorder, J. Psychosom. Res. 70 (4) (2011) 318–327.
[9] J. Backhaus, K. Junghanns, J. Born, K. Hohaus, F. Faasch, F. Hohagen, Impaired declarative memory consolidation during sleep in patients with primary insomnia: influence of sleep architecture and nocturnal cortisol release, Biol. Psychiatry 60 (12, 2006) 1324–1330.
[10] P. Simor, K. Horváth, F. Gombos, K.P. Takács, R. Bódizs, Disturbed dreaming and sleep quality: altered sleep architecture in subjects with frequent nightmares, Eur. Arch. Psychiatry Clin. Neurosci. 262 (8) (2012) 687–696.
[11] M.P. Walker, E. van der Helm, Overnight therapy? The role of sleep in emotional brain processing, Psychol. Bull. 135 (5) (2009) 731–748.
[12] L.D. Straus, S.B. Norman, V.B. Risbrough, D.T. Acheson, S.P. Drummond, REM sleep and safety signal learning in posttraumatic stress disorder: a preliminary study in military veterans, Neurobiol. Stress 9 (2018) 22–28.
[13] E.F. Pace-Schott, M.R. Milad, S.P. Orr, S.L. Rauch, R. Stickgold, R.K. Pitman, Sleep promotes generalization of extinction of conditioned fear, Sleep 32 (1) (2009) 19–26.
[14] L.D. Straus, D.T. Acheson, V.B. Risbrough, S.P. Drummond, Sleep deprivation disrupts recall of conditioned fear extinction, Biol. Psychiatry 2 (2) (2017) 123–129.
[15] E.B. Foa, M.J. Kozak, Emotional processing of fear: exposure to corrective information, Psychol. Bull. 99 (1) (1986) 20–35.
[16] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders (DSM-5®), American Psychiatric Pub, Arlington, VA, 2013.
[17] E. Koffel, I.S. Khawaja, A. Germain, Sleep disturbances in posttraumatic stress disorder: updated review and implications for treatment, Psychiatr. Ann. 46 (3) (2016) 173–176.
[18] S.P. Cahill, B.O. Rothbaum, P.A. Resick, V.M. Follette, Cognitive-behavioral therapy for adults, in: E.B. Foa, T.M. Keane, M.J. Friedman, J.A. Cohen (Eds.), Effective Treatments for PTSD: Practice Guidelines from the International Society for Traumatic Stress Studies, Guilford, New York, 2009.
[19] T. Morgenthaler, M. Kramer, C. Alessi, L. Friedman, B. Boehlecke, T. Brown, J. Coleman, V. Kapur, T. Lee-Chiong, J. Owens, J. Pancer, T. Swick, Practice parameters for the psychological and behavioral treatment of insomnia: an update. An American Academy of Sleep Medicine report, Sleep 29 (11) (2006) 1415–1419.
[20] T.I. Morgenthaler, S. Auerbach, K.R. Casey, D. Kristo, R. Maganti, K. Ramar, R. Zak, R. Kartje, Position paper for the treatment of nightmare disorder in adults: an American Academy of Sleep Medicine position paper, J. Clin. Sleep Med. 14 (06) (2018) 1041–1055.
[21] T.E. Galovski, J.M. Harik, L.M. Blain, L. Elwood, C. Gloth, T.D. Fletcher, Augmenting cognitive processing therapy to improve sleep impairment in PTSD: a randomized controlled trial, J. Consult. Clin. Psychol. 84 (2) (2016) 167–177.
[22] E.M. Walters, M.M. Jenkins, C.M. Nappi, J. Clark, J. Lies, S.B. Norman, S. Drummond, The impact of prolonged exposure on sleep and enhancing treatment outcomes with evidence-based sleep interventions: a pilot study, Psychol. Trauma 12 (2) (2020) 175–185.

[23] K. Cervena, Y. Dauvilliers, F. Espa, J. Touchon, M. Matousek, M. Billiard, A. Besset, Effect of cognitive behavioural therapy for insomnia on sleep architecture and sleep EEG power spectra in psychophysiological insomnia, J. Sleep Res. 13 (4) (2004) 385–393.

[24] B.J. Barnes, C. Presseau, A.H. Jordan, N.K. Kline, S. Young-McCaughan, T. M. Keane, A.L. Peterson, B.T. Litz, and the Consortium to Alleviate PTSD, Common data elements in the assessment of military-related PTSD research applied in the consortium to alleviate PTSD, Mil. Med. 184 (5–6) (2018) e218–e226.

[25] P.A. Resick, C.M. Monson, K.M. Chard, Cognitive Processing Therapy for PTSD: A Comprehensive Manual, Guilford Publications, New York, NY, 2016.

[26] Institute Of Medicine, Treatment of Posttraumatic Stress Disorder: An Assessment of the Evidence, The National Academic Press, Washington, DC, 2008.

[27] Center for Deployment Psychology, Evidence-based Workshops for Military & Civilian Providers, 2011.

[28] B.E. Karlin, J.I. Ruzek, K.M. Chard, A. Eftekhari, C.M. Monson, E.A. Hembree, P. A. Resick, E.B. Foa, Dissemination of evidence-based psychological treatments for posttraumatic stress disorder in the Veterans Health Administration, J. Trauma. Stress. 23 (6) (2010) 663–673.

[29] P.A. Resick, J.S. Wachen, J. Mintz, S. Young-McCaughan, J.D. Roache, A.M. Borah, E.V. Borah, K.A. Dondanville, E.A. Hembree, B.T. Litz, A.L. Peterson, on behalf of the STRONG STAR Consortium, A randomized clinical trial of group cognitive processing therapy compared with group present-centered therapy for PTSD among active duty military personnel, J. Consult. Clin. Psychol. 83 (6) (2015) 1058.

[30] P. Resick, J. Wachen, K. Dondanville, K. Pruiksma, J. Yarvis, A. Peterson, J. Mintz, and the STRONG STAR Consortium, A randomized controlled trial comparing group with individual cognitive processing therapy in active duty military seeking treatment for PTSD, JAMA Psychiatry 74 (2017) 28–36.

[31] D.J. Taylor, A.L. Peterson, K.E. Pruiksma, W.J. Hale, S. Young-McCaughan, A. Wilkerson, K. Nicholson, B.T. Litz, K.A. Dondanville, J.D. Roache, E.V. Borah, A. Brundige, J. Mintz, on behalf of the STRONG STAR Consortium, Impact of cognitive behavioral therapy for insomnia disorder on sleep and comorbid symptoms in military personnel: a randomized clinical trial, Sleep 41 (6) (2018). https://doi.org/10.1093/sleep/zsy069.

[32] D.J. Taylor, A.L. Peterson, K.E. Pruiksma, S. Young-McCaughan, K. Nicholson, J. Mintz, and the STRONG STAR Consortium, Internet and in-person cognitive behavioral therapy for insomnia in military personnel: a randomized clinical trial, Sleep 40 (6) (2017). https://doi.org/10.1093/sleep/zsx075.

[33] D.J. Taylor, A.L. Peterson, J.L. Goodie, E. Grieser, A.S. Hryshko-Mullen, A. Rowan, A. Wilkerson, K.E. Pruiksma, J.R. Dietch, B. Hall-Clark, B. Fina, Cognitive-Behavioral Therapy for Insomnia in the Military: Therapist Guide, University of Arizona, Tucson, AZ, 2019. https://insomnia.arizona.edu/cbti-m.

[34] D.J. Taylor, A.L. Peterson, J.L. Goodie, E. Grieser, A.S. Hryshko-Mullen, A. Rowan, A. Wilkerson, K.E. Pruiksma, J.R. Dietch, B. Hall-Clark, B. Fina, Cognitive-Behavioral Therapy for Insomnia in the Military: Patient Guide, University of Arizona, Tucson, AZ, 2019. https://insomnia.arizona.edu/cbti-m.

[35] J.L. Davis, Treating Post-Trauma Nightmares: A Cognitive Behavioral Approach, Springer Publishing Co, New York, NY US, 2009.

[36] K.E. Pruiksma, D.J. Taylor, J. Mintz, K.L. Nicholson, M. Rodgers, S. Young-McCaughan, B.N. Hall-Clark, B.A. Fina, K.A. Dondanville, B. Cobos, S. Wardle-Pinkston, B.T. Litz, J.D. Roache, A.L. Peterson, on behalf of the STRONG STAR Consortium, A pilot randomized controlled trial of cognitive behavioral treatment for trauma-related nightmares in active duty military personnel, J. Clin. Sleep Med. 16 (1) (2020) 29–40, https://doi.org/10.5664/jcsm.8116.

[37] D. Hedeker, R.D. Gibbons, C. Waternaux, Sample size estimation for longitudinal designs with attrition: comparing time-related contrasts between two groups, J. Educ. Behav. Stat. 24 (1) (1999) 70–93.

[38] H.C. Kraemer, J. Mintz, A. Noda, J. Tinklenberg, J.A. Yesavage, Caution regarding the use of pilot studies to guide power calculations for study proposals, Arch. Gen. Psychiatry 63 (5) (2006) 484–489.

[39] R. Rosenthal, R.L. Rosnow, D.B. Rubin, Contrasts and Effect Sizes in Behavioral Research: A Correlational Approach, Cambridge University Press, 2000.

[40] H.C. Kraemer, D.J. Kupfer, Size of treatment effects and their importance to clinical research and practice, Biol. Psychiatry 59 (11, 2006) 990–996.

[41] P.A. Resick, J.S. Wachen, K.A. Dondanville, S.T. LoSavio, S. Young-McCaughan, J. S. Yarvis, K.E. Pruiksma, A. Blankenship, V. Jacoby, A.L. Peterson, J. Mintz, for the STRONG STAR Consortium, Variable-length Cognitive Processing Therapy for Posttraumatic Stress Disorder in Active Duty Military: Outcomes and Predictors, Submitted for publication, 2020.

[42] B.M. Byllesby, B.D. Dickstein, K.M. Chard, The probability of change versus dropout in veterans receiving Cognitive Processing Therapy for posttraumatic stress disorder, Behav. Res. Ther. 123 (2019) 103483.

[43] H.C. Kraemer, G.T. Wilson, C.G. Fairburn, W.S. Agras, Mediators and moderators of treatment effects in randomized clinical trials, Arch. Gen. Psychiatry 59 (10, 2002) 877–883.

[44] K. Hirano, G.W. Imbens, G. Ridder, Efficient estimation of average treatment effects using the estimated propensity score, Econometrika 71 (2003) 1161–1189.

[45] P.R. Rosenbaum, D.B. Rubin, The central role of the propensity score in observational studies for causal effects, Biometrika 70 (1983) 41–55.

[46] V.I. Spoormaker, P. Montgomery, Disturbed sleep in post-traumatic stress disorder: secondary symptom or core feature? Sleep Med. Rev. 12 (3) (2008) 169–184.

[47] B. Krakow, R. Schrader, D. Tandberg, M. Hollifield, M.P. Koss, C.L. Yau, D. T. Cheng, Nightmare frequency in sexual assault survivors with PTSD, J. Anxiety Disord. 16 (2) (2002) 175–190.

[48] C.S. Ulmer, J.D. Edinger, P.S. Calhoun, A multi-component cognitive-behavioral intervention for sleep disturbance in veterans with PTSD: a pilot study, J. Clin. Sleep Med. 7 (1) (2011) 57–68.

[49] J.L. Baddeley, D.F. Gros, Cognitive behavioral therapy for insomnia as a preparatory treatment for exposure therapy for posttraumatic stress disorder, Am. J. Psychother. 67 (2) (2013) 199–210.

[50] D. Forbes, A.J. Phelps, T. McHugh, Treatment of combat-related nightmares using imagery rehearsal: a pilot study, J. Trauma. Stress. 14 (2) (2001) 433–442.

[51] D. Forbes, A.J. Phelps, A.F. McHugh, P. Debenham, M. Hopwood, M. Creamer, Imagery rehearsal in the treatment of posttraumatic nightmares in Australian veterans with chronic combat-related PTSD: 12-month follow-up data, J. Trauma. Stress. 16 (5) (2003) 509–513.

[52] J.C. DeViva, C. Zayfert, W.R. Pigeon, T.A. Mellman, Treatment of residual insomnia after CBT for PTSD: case studies, J. Trauma. Stress. 18 (2) (2005) 155–159.

[53] C. Zayfert, J.C. DeViva, Residual insomnia following cognitive behavioral therapy for PTSD, J. Trauma. Stress. 17 (1) (2004) 69–73.

[54] T.E. Galovski, L.M. Blain, J.M. Mott, L. Elwood, T. Houle, Manualized therapy for PTSD: flexing the structure of cognitive processing therapy, J. Consult. Clin. Psychol. 80 (6) (2012) 968.

[55] P.A. Resick, P. Nishith, T.L. Weaver, M.C. Astin, C.A. Feuer, A comparison of cognitive-processing therapy with prolonged exposure and a waiting condition for the treatment of chronic posttraumatic stress disorder in female rape victims, J. Consult. Clin. Psychol. 70 (4) (2002) 867–879.

[56] K.E. Pruiksma, D.J. Taylor, J.S. Wachen, J. Mintz, S. Young-McCaughan, A. L. Peterson, J.S. Yarvis, E.V. Borah, K.A. Dondanville, B.L. Litz, E.A. Hembree, P. A. Resick, On behalf of the STRONG STAR Consortium, Residual sleep disturbances following PTSD treatment in active duty military personnel. Psychol. Trauma 8 (6) (2016) 697–701, https://doi.org/10.1037/tra0000150.

[57] T.C. Neylan, C.R. Marmar, T.J. Metzler, D.S. Weiss, D.F. Zatzick, K.L. Delucchi, R. M. Wu, F.B. Schoenfeld, Sleep disturbances in the Vietnam generation: findings from a nationally representative sample of male Vietnam veterans, Am. J. Psychiatry 155 (7) (1998) 929–933.

[58] F. Weathers, B. Litz, T. Keane, P. Palmieri, B. Marx, P. Schnurr, The PTSD checklist for DSM-5 (PCL-5), Scale Available From the National Center for PTSD. www.ptsd.va.gov, 2013.

[59] F. Weathers, D. Blake, P. Schnurr, D. Kaloupek, B. Marx, T. Keane, The Clinician-administered PTSD Scale for DSM-5 (CAP-5), Instrument available from the National Center for PTSD at, www.ptsd.va.gov, 2013.

[60] D.S. Vogt, S.P. Proctor, D.W. King, L.A. King, J.J. Vasterling, Validation of scales from the deployment risk and resilience inventory in a sample of operation Iraqi freedom veterans, Assessment 15 (4) (2008) 391–403.

[61] F.W. Weathers, D.D. Blake, P.P. Schnurr, D.G. Kaloupek, B.P. Marx, T.M. Keane, The Life Events Checklist for DSM-5 (LEC-5), Instrument available from the National Center for PTSD at, www.ptsd.va.gov, 2013.

[62] D.J. Taylor, A.K. Wilkerson, K.E. Pruiksma, J.M. Williams, C.J. Ruggero, W. Hale, J. Mintz, K. Maarczyk-Organek, K.L. Nicholson, B.T. Litz, S. Young-McCaughan, K. A. Dondanville, E.V. Borah, A. Brundige, A.L. Peterson, on behalf of the STRONG STAR Consortium, Reliability of the Structured Clinical Interview for DSM-5 Sleep Disorders Module, J. Clin. Sleep Med. 14 (03) (2018) 459–464.

[63] C.M. Morin, Insomnia: Psychological Assessment and Management, The Guilford Press, New York, NY, 1993.

[64] C.C. Cranston, K.E. Miller, J.L. Davis, J.L. Rhudy, Preliminary validation of a brief measure of the frequency and severity of nightmares: the Trauma-related Nightmare Survey, J. Trauma Dissoc. 18 (1) (2017) 88–99.

[65] K.E. Pruiksma, D. Taylor, C. Ruggero, A. Boals, J. Davis, C. Cranston, J. Deviva, C. Zayfert, A psychometric study of the Fear of Sleep Inventory-Short Form (FoSI-SF), J. Clin. Sleep Med. 10 (5) (2014) 551.

[66] D.J. Buysse, L. Yu, D.E. Moul, A. Germain, A. Stover, N.E. Dodds, K.L. Johnston, M. A. Shablesky-Cade, P.A. Pilkonis, Development and validation of patient-reported outcome measures for sleep disturbance and sleep-related impairments, Sleep 33 (6) (2010) 781–792.

[67] L. Yu, D.J. Buysse, A. Germain, D.E. Moul, A. Stover, N.E. Dodds, K.L. Johnston, P. A. Pilkonis, Development of short forms from the PROMIS™ sleep disturbance and sleep-related impairment item banks, Behav. Sleep Med. 10 (1) (2012) 6–24.

[68] C. Randler, Validation of the full and reduced Composite Scale of Morningness, Biol. Rhythm. Res. 40 (5) (2009) 413–423.

[69] K.A. Schwab, G. Baker, B.J. Ivins, M. Sluss-tiller, W. Lux, D. Warden, The Brief Traumatic Brain Injury Screen (BTBIS): investigating the validity of a self-report instrument for detecting traumatic brain injury (TBI) in troops returning from deployment in Afghanistan and Iraq, Neurology 66 (5) (2006) A235.

[70] K.A. Schwab, B. Ivins, G. Cramer, W. Johnson, M. Sluss-Tiller, K. Kiley, W. Lux, D. Warden, Screening for traumatic brain injury in troops returning from deployment in Afghanistan and Iraq: initial investigation of the usefulness of a short screening tool for traumatic brain injury, J. Head Trauma Rehabil. 22 (6) (2007) 377–389.

[71] K. Kroenke, R.L. Spitzer, J.B. Williams, The PHQ-15: validity of a new measure for evaluating the severity of somatic symptoms, Psychosom. Med. 64 (2) (2002) 258–266.

[72] L.E. Kazis, D.R. Miller, J.A. Clark, K.M. Skinner, A. Lee, X.S. Ren, A. Spiro III, W. H. Rogers, J.E. Ware Jr., Improving the response choices on the veterans SF-36 health survey role functioning scales: results from the Veterans Health Study, J. Ambulat. Care Manag. 27 (3) (2004) 263–280.

[73] T.F. Heatherton, L.T. Kozlowski, R.C. Frecker, K.O. Fagerstrom, The Fagerström test for nicotine dependence: a revision of the Fagerstrom Tolerance Questionnaire, Br. J. Addict. 86 (9) (1991) 1119–1127.

[74] J.O. Ebbert, C.A. Patten, D.R. Schroeder, The Fagerström test for nicotine dependence-smokeless tobacco (FTND-ST), Addict. Behav. 31 (9) (2006) 1716–1721.
[75] D.V. Sheehan, Y. Lecrubier, K.H. Sheehan, P. Amorim, J. Janavs, E. Weiller, T. Hergueta, R.W. Baker, G.C. Dunbar, The Mini-International Neuropsychiatric Interview (M.I.N.I): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10, J. Clin. Psychiatry 59 (Suppl. 20) (1998) 22–33.
[76] K. Kroenke, R.L. Spitzer, J.B. Williams, The Phq-9, J. Gen. Intern. Med. 16 (9) (2001) 606–613.
[77] G.I. Metalsky, T.E. Joiner Jr., The hopelessness depression symptom questionnaire, Cogn. Ther. Res. 21 (3) (1997) 359–384.
[78] M.K. Nock, E.B. Holmberg, V.I. Photos, B.D. Michel, Self-injurious Thoughts and Behaviors Interview: Development, Reliability, and Validity in an Adolescent Sample, 2007.
[79] R.L. Spitzer, K. Kroenke, J.B. Williams, B. Löwe, A brief measure for assessing generalized anxiety disorder: the GAD-7, Arch. Intern. Med. 166 (10, 2006) 1092–1097.
[80] R. Novaco, Dimensions of Anger Reactions, University of California, Irvine, CA, 1975.
[81] T.F. Babor, J.C. Higgins-Biddle, J.B. Saunders, M.G. Monteiro, Audit, The Alcohol Use Disorders Identification Test (AUDIT): Guidelines for Use in Primary Care, 2nd ed., World Health Organization, 2001.
[82] L.C. Sobell, S. Agrawal, M.B. Sobell, G.I. Leo, L.J. Young, J.A. Cunningham, E. R. Simco, Comparison of a quick drinking screen with the timeline followback for individuals with alcohol problems, J. Stud. Alcohol 64 (6) (2003) 858–861.
[83] B.P. Marx, Development & Validation of a PTSD-related Impairment Scale, DTIC Document, U.S. Army Medical Research and Material and Materiel Command, Fort Detrick, MD, 2013, https://apps.dtic.mil/dtic/tr/fulltext/u2/a585414.pdf.
[84] S.D. Gosling, P.J. Rentfrow, W.B. Swann, A very brief measure of the Big-Five personality domains, J. Res. Pers. 37 (6) (2003) 504–528.
[85] G.J. Devilly, T.D. Borkovec, Psychometric properties of the credibility/expectancy questionnaire, J. Behav. Ther. Exp. Psychiatry 31 (2) (2000) 73–86.