Study Name: Integrated CBT-I and PE on Sleep and PTSD Outcomes (Impact Study)
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2a. Research Plan

2a.1. Background and Significance

PTSD: Relevance to VA and to Treatment

The prevalence of posttraumatic stress disorder (PTSD) among Veterans is at least twice as high as in the general population.[1] Vietnam Veterans exhibit a lifetime prevalence of PTSD at approximately 30%.[2, 3] Estimates of PTSD among Iraq and Afghanistan combat Veterans (Operation Enduring Freedom, Operation Iraq Freedom, and Operation New Dawn; OEF/OIF/OND) suggest that nearly 17% of active duty and over 24% of reserve service members screen positive for PTSD approximately 6 months after their return.[4]

PTSD has been linked to poor health outcomes and is associated with enormous health care costs.[5] Several large-scale studies conducted with combat Veterans have compared those with and without PTSD, and found that Veterans with PTSD report significantly more chronic health conditions and generally poorer perception of physical health than their non-PTSD counterparts,[6-8] even when controlling for behaviors known to independently contribute to poor health outcomes such as smoking, alcohol use, deployment status, military status, and demographics.[9] PTSD is associated with increased risk of early mortality, attempted suicide, functional impairment, alcohol abuse and dependence, reduced quality of life, psychiatric comorbidity, and hospitalization.[9]

Prolonged exposure (PE) is an efficacious treatment for Veterans with PTSD that decreases avoidance of feared, but safe, cues to allow fear extinction and habituation to over-generalized feared stimuli.[10] Although PE is one of the best available treatments for PTSD, PE still has high partial and non-response rates with 25 to 45% of PTSD patients still meeting diagnostic criteria for PTSD at the end of treatment.[11] Given the high number of individuals who continue to have PTSD following PE, efforts to increase the efficacy of PE are critical. Independent comorbid disorders, such as insomnia, have been posited as one reason for the high non-response rates to PE. Examining how to increase efficacy of PE by focusing on comorbid insomnia offers a novel and logical approach to improve insomnia, PTSD, and quality of life outcomes.

Insomnia: Relevance to VA and to Treatment

Difficulty in sleep onset and maintenance is the most frequently reported symptom of the 17 symptoms of PTSD.[12] Among Veterans with PTSD, sleep disturbances are nearly universal with 70 - 91% of patients with PTSD reporting comorbid insomnia.[13-15] Veterans with PTSD show more trouble falling asleep, staying asleep, excessive daytime sleepiness and early morning awakenings than Veterans without PTSD.[15]

Insomnia has also been shown to have a deleterious effect on overall health and well-being. Insomnia contributes to prospective risk of major depression,[16-18] increased psychiatric symptoms and poor coping,[19] and is associated with physical health complaints as well as increased risk for hypertension, cardiovascular disease,[20] and immunosuppression.[21] Notable among those negative outcomes, insomnia is highly correlated with substance abuse, impaired daytime functioning, and suicide risk.[22]

Insomnia also has negative health consequences over-and-above the effects of PTSD. For example, sleep impairment accounted for a significant portion of the variance in physical health complaints even after controlling for other PTSD symptoms and depression.[23] The significant and chronic sleep loss commonly associated with PTSD contributes independently to additional negative health ramifications including pain disorders, asthma, and hypertension.[24, 25] Insomnia with PTSD is associated with a reduced capacity to carry out daily activities,[15, 26, 27] with functional impairment and reduced quality of life.[28-31] Overall, insomnia is associated with greater severity of PTSD symptoms and poorer quality of life and daily functioning.[32]

Trauma-Focused Treatment Does Not Resolve Insomnia

For some time it has been assumed that treatment of a “primary disorder” such as PTSD would be sufficient to alleviate comorbid sleep disturbances. However, even among responders to effective PTSD treatments such as PE, upwards of 70% still report clinically significant insomnia after treatment.[33-36] For example, Gutner[37] compared changes in insomnia symptoms across CPT to PE and found moderate to small effects for total insomnia scores, total sleep time and sleep efficiency, with sleep disturbance remaining at clinical levels even at long term follow-up in both treatment conditions. Research consistently suggests that insomnia is not adequately addressed by PTSD interventions.

Insomnia symptoms are often presumed to be symptoms of PTSD; however, there is increasing evidence that insomnia is an independent disorder. First, insomnia may precede PTSD.[38] Second, when insomnia initially occurs as a symptom of PTSD, it can become an independent disorder when the behavioral and cognitive responses to acute insomnia lead to perpetuating factors and conditioned arousal.[39] A Veteran suffering from PTSD may develop sleep disturbances following a traumatic incident or as the result of prolonged deployments

with lack of quality sleep on deployment (precipitating factor). The perpetuating factors that solidify and maintain insomnia are behaviors in response to poor sleep such as daytime napping, chronic worry about losing sleep, increased caffeine intake, or taking sleeping pills. Conditioned arousal of the bedroom may be a result of the PTSD (e.g., nightmares, having to check locks, hyperarousal) or the perpetuating behaviors lead to the repeated pairing of the bed with wakefulness and arousal. Thus, the perpetuating factors and conditioned arousal are often responsible for the maintenance of insomnia even after PTSD symptoms have been resolved.[35] Since trauma-focused treatments only affect the precipitating factors of insomnia, this indicates a need to separately and directly target the perpetuating factors and conditioned arousal that maintain insomnia.

Insomnia *May* Interfere with PE *Treatment* Mechanisms

There are converging lines of evidence suggesting that insomnia negatively affects the mechanisms involved with PE.[40-45] A defining feature of PTSD is that environmental cues during trauma are associated with the traumatic event, and these cues generalize and continue to evoke strong fear reactions and trigger avoidance responses long after the initial trauma has receded or in the presence of safe cues. Additionally, PTSD patients often have difficulty discriminating between threatening and safe environments, leading to hypervigilance symptoms.[46] PE is an efficacious treatment for Veterans with PTSD that decreases avoidance of feared, but safe, cues to allow fear extinction of over-generalized feared stimuli.[10] Through the process of repeated prolonged confrontation to trauma-related stimuli, habituation of emotional responses associated with the trauma occurs. During PE, fear reactions to such cues are reduced through extinction learning[40-45] and development of extinction memories.[47] Repeated exposure to these cues in a safe setting allows the feared cues to lose their predictive quality for danger (safety learning).[48, 49] Therefore, factors that impair the processes of PE, such as insomnia, may also reduce the effectiveness of PE.

Insomnia has been shown to disrupt sleep architecture including that of rapid eye movement (REM).[50] A growing body of research with animals and healthy humans shows that sleep, particularly REM sleep, serves an important role in the acquisition, recall, and generalization of extinction memories necessary for PE. It has been shown that stronger safety learning was associated with higher REM consolidation in healthy humans.[51] Additional research implicates REM sleep as a critical factor in the recall and generalization of extinction memories, which has been demonstrated in animal models[52] as well as in healthy humans.[45, 53, 54] REM fragmentation impairs consolidation of extinction memory, which implies the sleep symptoms of insomnia could potentially interfere with both natural extinction (thus maintaining PTSD) and treatment-induced extinction (thus reducing the effects of PE) of PTSD-related fear.[55] Sleep architecture, and REM sleep in particular, is disrupted by sleep difficulties in patients with PTSD.[51, 56] Together, these studies linking fragmented REM sleep to extinction memory and safety learning in animals and healthy control human subjects suggests a link between REM sleep and critical components of PE treatment (i.e., extinction memory and/or safety signal learning). To date, no studies have examined the relationship between *changes in sleep* on PE efficacy.

In addition to affecting safety learning and habituation, insomnia also affects emotional coping,[57] emotional processing,[58] and cognitive abilities[59] necessary for successful PTSD treatment. Individuals with insomnia have been shown to overly rely on emotion-oriented coping strategies and exhibit decreased emotional processing abilities that may account for the over-activation of anxiety when faced with feared stimuli or daily stressors. More effective involvement in emotion regulation and processing during exposure to fear-related cues would allow for more efficient processing of the feared stimuli (i.e., less reactivity in the Veteran's day to day life). Finally, PE requires processing alternative perspectives and shifting of beliefs about the trauma. Increased cognitive functioning (attentional control, working memory, processing speed) would increase effectiveness of processing necessary for successful PE. Taken together, addressing insomnia prior to trauma focused treatment offers a unique opportunity to potentially increase the effectiveness of processes necessary for successful PE.

Insomnia is Not a First Line Focus in Treatment for PTSD

Difficulty in sleep onset and maintenance is the most frequently reported symptom of PTSD with as many as 90% of individuals with PTSD reporting insomnia.[13] Unfortunately, insomnia treatment is not a first line treatment with Veterans who have PTSD. Sleep disturbances in psychiatric patients are often labeled "psychiatric insomnia," which suggests that the insomnia is secondary to the psychiatric disorder.[60] As such, treatment is aimed at the "primary" disorder. However, treatment of the primary disorder does not consistently mitigate sleep disturbances during extended follow-ups in mental health patients.[61, 62] PTSD exemplifies this phenomenon because the diagnosis includes sleep related problems; however, insomnia rarely receives primary therapeutic attention.[63-66] Bradley Karlin, in Bridging the Gap in Delivery of Psychological Treatments for Posttraumatic Stress Disorder PTSD,[67] suggests that PTSD symptoms are only one part of the clinical picture and the focus

should expand to global quality of life. He suggested that sleep disturbances are often comorbid with PTSD and may be one of the ways to increase quality of life for Veterans; yet sleep is often not addressed in clinical PTSD practice. Focusing on insomnia in Veterans with PTSD treatment offers a novel opportunity to increase client-centered care by addressing Insomnia as a primary health complaint. This, in turn, can help increase the effectiveness of PE through increasing emotional coping, safety learning, habituation, and cognitive abilities. By addressing sleep as a primary complaint and increasing the effectiveness of PE, it is likely to enhance quality of life outcomes in Veterans.

Cognitive Behavioral Therapy for Insomnia is Effective for Improving Sleep

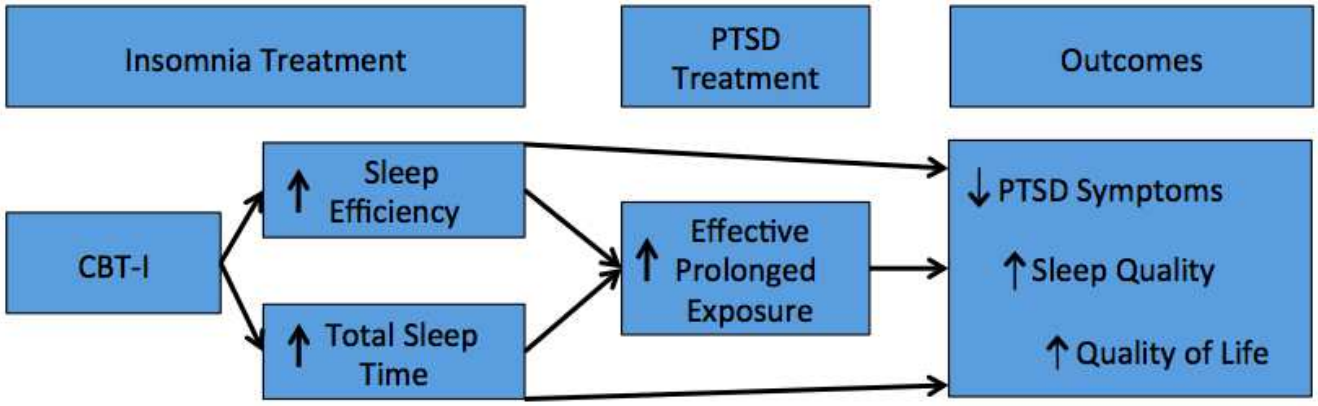
Cognitive behavioral therapy for insomnia (CBT-I) is the first line treatment of chronic and severe insomnia as recognized by the National Institutes of Health Consensus Statement, Academy of Sleep Medicine, and British Association of Psychopharmacology. CBT-I is a behavioral treatment with strong efficacy.[68-70] The current model for insomnia holds that insomnia occurs due to precipitating event(s) (e.g., trauma) acting upon individually defined trait factors such as personality traits or genetic predisposition, which in turn produce an acute sleep disturbance. Insomnia becomes chronic when it is reinforced over time by maladaptive coping strategies that result in conditioned arousal. Traditionally, insomnia has been viewed as a "secondary" ailment to the precipitating cause and/or a "symptom" of the primary illness. However, current clinical practice in the field of behavioral sleep medicine has moved toward identifying chronic insomnia as a comorbid illness,[71, 72] one that carries equal weight with the "primary" disorder in any treatment plan. This is reflected in the Insomnia Disorder diagnosis in the DSM-5.[73]

By offering integrated treatment of insomnia with comorbid PTSD, the outcomes for both may be significantly enhanced. While the most commonly employed treatment for chronic insomnia is prescription hypnotics, long-term use of these medications can result in dependence, side-effects, and loss of efficacy, and may be associated with increased risk of cancer and morbidity,[74] all causes for concern in the treatment of Veterans with *comorbid* PTSD. As a result of these concerns and as a result of recent scientific evidence demonstrating efficacy, CBT-I is now considered the first line treatment for chronic insomnia.[68] Empirical data have demonstrated that CBT-I is equally effective in the short-term treatment and is superior to pharmacologic treatment in the long-term management of insomnia.[75] CBT-I has also been shown to be preferential to combined treatments that include use of hypnotics.[76] As such, the Standards of Practice Committee of the American Academy of Sleep Medicine now advocates use of psychological and behavioral intervention in the treatment of both chronic primary insomnia and comorbid insomnia.[77]

CBT-I is an effective intervention for PTSD patients with comorbid insomnia. Several studies have examined CBT-I with participants with PTSD[78, 79] including Veterans.[80, 81] Results show that CBT-I is effective on improving indices of insomnia with large effect sizes (e.g., ES = 2.15 [80]). Given these findings, the next step in treatment outcome studies will be to examine the effects of CBT-I on PE outcomes and quality of life.

CBT-I is associated with objective changes in sleep architecture including increased and consolidated REM.[82] Consolidated *sleep* should directly influence better safety learning, faster extinction memory, *emotional coping and processing,* and increased sustained attention required of PE. Given insomnia's proposed influence on PE mechanisms, it is *expected* that treating insomnia prior to implementing trauma-focused treatments for PTSD will increase the efficacy of PTSD treatment (see Figure 1 for Full Model).

Figure 1. *Conceptual Model of CBT-I Integrated with PE*



***Novelty and* Significance for *Treating* Insomnia *Prior to* PTSD Treatment**

Insomnia is a primary complaint of Veterans with PTSD and yet is often overlooked in PTSD treatment in favor of trauma-focused treatment. This trial would be the first to examine insomnia treatment prior to engaging in evidence-based PE treatment. This application challenges and seeks to shift current clinical practice paradigms from PTSD only treatments to include insomnia intervention as a primary focus. This proposal is based on the evidence that untreated insomnia can persist for years, is independently associated with impaired health-related quality of life, and can exacerbate *daytime* PTSD symptoms. Importantly, there is increasing evidence that insomnia interferes with the mechanisms of PE *including safety learning, habituation, emotional coping, emotional processing, and cognitive functioning*. Given these factors, it is critical to *treat insomnia prior to PE*, and then *engage in trauma-focused treatment to maximize sleep, PTSD symptom*, and quality of life outcomes. By treating insomnia first, this study will: 1) increase client-centered treatment by addressing the number one subjective complaint among Veterans with PTSD; 2) enhance PTSD outcomes and *non-response rates* by addressing insomnia-related factors that interfere with PTSD treatment; 3) *act as a stepping stone and help to engage patients who are not initially willing to engage in trauma-focused PE; and 4) increase rehabilitation outcomes by addressing the two leading disorders that independently affect quality of life for Veterans. The proposed research project represents a unique opportunity to improve treatment and lead to better long-term rehabilitation outcomes for Veterans, furthering the VA's commitment to improving the mental health, recovery, and community reintegration of Veterans detailed in the 2014-2020 VHA Strategic Plan. Focusing on sleep prior to PTSD treatment offers a real and underutilized opportunity for recovery for many Veterans with PTSD.*

***Novelty and* Significance for Integrated Insomnia and PTSD Treatment**

Beyond the benefits of treating insomnia prior to PE, integrating treatment of CBT-I *and* PE (CBTI-PE) offers several novel advantages *that can further maximize quality of life outcomes for Veterans*. *Integrated treatment* has the potential to benefit outcomes for Veterans with PTSD by: 1) allowing patients to address both symptoms of insomnia and PTSD within a shortened timeframe, 14 weeks, versus 20 weeks if the treatments were offered sequentially; 2) increasing continuity by allowing patients to work with a single provider; 3) addressing two disorders together that, while independent, influence each other; and 4) decreasing the risk of attrition between referral clinics and waitlists. *Evidence for integrated PTSD treatments and comorbid disorders is still in its infancy. However, the PTSD and substance use literature shows that both clinicians and patients have reported a preference for integrate treatment.*[83, 84]

Significance and Relevance to VA Patient Care Mission and Advancement of Clinical Practice

The proposed research plan aims to directly address *three* notable limitations within the current state of PTSD research. These include: 1) the need to identify methods to improve concernedly high partial and non-response rates of even the most effective treatments for PTSD such as PE; 2) limited attention thus far to insomnia as an independent disorder from PTSD that often does not improve with trauma-focused treatment and may negatively affect PTSD treatment outcomes; 3) limited *focus on one of the primary complaints of Veterans (i.e., insomnia).* The proposed study will examine Veteran recovery using multi-modal assessment including structured interviews, self-report measures, and *actigraphy watches*. This multi-modal approach will advance the literature with translational and integrated framework to further our understanding of PTSD recovery *and rehabilitation outcomes*.

Among Veterans with both insomnia and PTSD, addressing insomnia with integrated CBTI-PE represents a logical, innovative, and empirically-informed method for augmenting existing treatments and optimizing global *quality of life* outcomes. The proposed research is well aligned with the VA's emphasis on evidence-based treatment and is directly relevant to Veterans' health in three key ways. First, this treatment directly addresses the call for "Bridging the Gap" of services for PTSD[67] and providing comprehensive care to Veterans with PTSD by focusing on sleep complaints. Insomnia is a primary health complaint and is independently linked to impaired quality of life (e.g., disruption in major social and occupational responsibilities and suicidal ideation). Findings from the proposed study will help direct VA resources to improve mental health treatment by focusing on insomnia as a treatment goal. Second, findings from the proposed study will determine the malleability of mechanisms (e.g., Total sleep time, Sleep efficiency) that can be targeted to improve recovery outcomes among this vulnerable population and to inform future treatment development and research. Understanding the role of sleep as a mechanism of change for PE will allow for further refinement of treatment and will provide information to drive future research. Ultimately, this line of research can reduce risk of chronic impairment and potentially free up resources to treat new incidences of PTSD. Third, Veterans are often uncomfortable seeking psychotherapy due to stigma regarding PTSD, but they will seek treatment for sleep problems that are often perceived as medical problems rather than mental health related concerns. Therefore, offering sleep treatments

may be an acceptable "stepping stone" before starting trauma-focused treatment. This aspect of treatment should help support a Veteran's self-efficacy and provide encouragement to complete homework assignments, practice skills, and participate actively in future treatments even when faced with potentially difficult concepts and issues in the course of therapy.

2a.2 Preliminary studies

Below we summarize studies that have generated support for the current study as well as pilot data to support the feasibility and early efficacy for integrated treatment. These studies reflect our experience with PTSD, insomnia, and co-occurring disorders.

Study 1: Manual Testing of Integrated CBT-I and PE (CBTI-PE). Data were collected on *three* Veterans who have successfully finished the CBTI-PE protocol; *two* more Veterans are currently in progress. We learned from the *three* Veterans who completed the protocol that: 1) they could tolerate CBTI-PE as indicated by successfully completing treatment; 2) they reported before and after treatment that the protocol was logical, credible, and expected to see improvement on both PTSD and insomnia indices; and 3) showed objective decreases in insomnia and PTSD symptoms as well as increases in total sleep time and sleep efficiency from pre- to post-treatment. All PTSD, depression, *and insomnia* symptom decreases from pre- to post-treatment are considered clinically significant changes. Running these pilot participants through the CBTI-PE protocol has also allowed us to identify and address obstacles that may occur in the proposed CDA-2. Overall, this pilot study gave evidence that it is possible to recruit our target population of Veterans into CBTI-PE, that we can successfully adhere to and complete the protocol, and that the intervention is *very* promising in *reducing* PTSD and insomnia symptoms. Comparing pre- to post CBT-I plus PE score, *on average, there was a 30 point decrease in PTSD symptoms, 15 point decrease in the ISI, an 18% increase in sleep efficiency, and 83 more minutes of sleep* (see Table 1 and Figure 2).

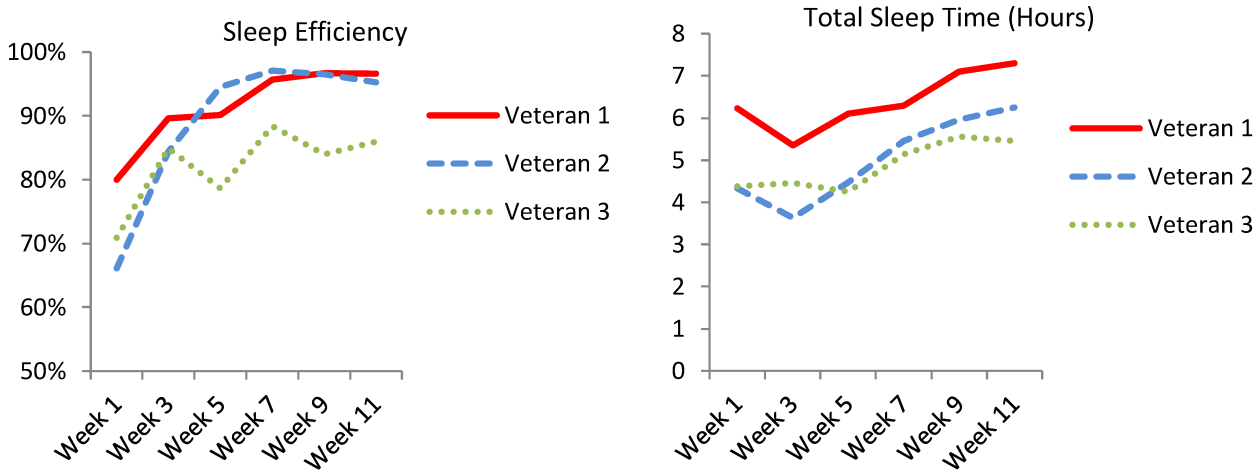


Figure 2. Sleep Diary Indices

Table 1. Means and SDs of *Pre and Post Study Variables (N = 3)*

	Pre Tx Means (SD)	Post Tx Means (SD)	Paired Sample t-test	Effect Size
***Basic* Variables**				
Number of Sessions		12 (2)		
Age		33.33 (7.23)		
Treatment Credibility				
Therapy Credibility (CEQ)	85%	93%		
Expectancy of Success (CEQ)	81%	90%		
PTSD Symptoms				
PTSD symptoms (PCL-5)	45.67 (12.50)	15.33 (8.62)	$t(2) = 4.15$, $p = .05$	$r = 0.95$ *
Sleep Variables				
Insomnia (ISI)	19 (5.29)	6 (7.21)	$t(2) = 3.25$, $p = .08$	$r = 0.92$
Sleep efficiency (sleep diaries)	73.30% (8.65)	91.07% (6.24)	$t(2) = -4.21$, $p = .05$	$r = 0.95$ *
Total Sleep Time (sleep diaries)	304.67 (61.21)	387.57 (47.69)	$t(2) = -4.75$, $p = .04$	$r = 0.96$ *
Actigraphy Watch Variables				
Sleep efficiency	76.33%	84.33%	$t(2) = -0.73$, $p = .54$	$r = 0.46$
Total Sleep Time	325.78 (79.30)	362.18 (38.26)	$t(2) = -0.94$, $p = .45$	$r = 0.55$
Depression Symptoms				
Depression (PHQ-9)	15.00 (5.19)	5.00 (3.46)	$t(2) = 2.00$, $p = .18$	$r = 0.82$

Note: SE = sleep efficiency; TST = total sleep time; CEQ = credibility/expectancy questionnaire; ISI = insomnia severity index; PCL-5 = PTSD Checklist DSM 5; PHQ - 9 = Patient health questionnaire.

Study 2: Prolonged Exposure with Veterans with Comorbid PTSD and SUDs in a Residential Substance Use Treatment Program (SARRTP; Norman, S., Davis, B., **Colvonen, P.,** et al., *in press*, 2015)
This study represents taking an idea from design to dissemination. As a co-investigator on the study, *Dr. Colvonen is* tracking Veterans who are a part of a PTSD track on a residential substance use treatment unit, examining baseline, post-treatment, and three-month follow-up on substance use, PTSD symptoms, and other psychosocial measures of health and quality of life. A sub-group of Veterans on the SARRTP unit went through PE and were compared to Veterans who received treatment as usual (TAU*). Dr. Colvonen used mixed model procedures*[85-87] *to analyze the data. This approach takes into account all the obtained data and missingness for participants with missing data, reducing the analytic problem presented by missing data for intent-to-treat analyses. Main fixed effects were condition (PE vs. TAU) and time, with Condition by Time as the interaction factor. Several random factor models using slope and intercept were tested and found that only using a random intercept model fit the data best (as indicated by Log Likelihood). Results showed* that PE was not only well tolerated and effective, but also showed greater reductions in PTSD symptoms than Veteran who went through TAU. The treatment gains of the PE group continued through 3 months follow-up.

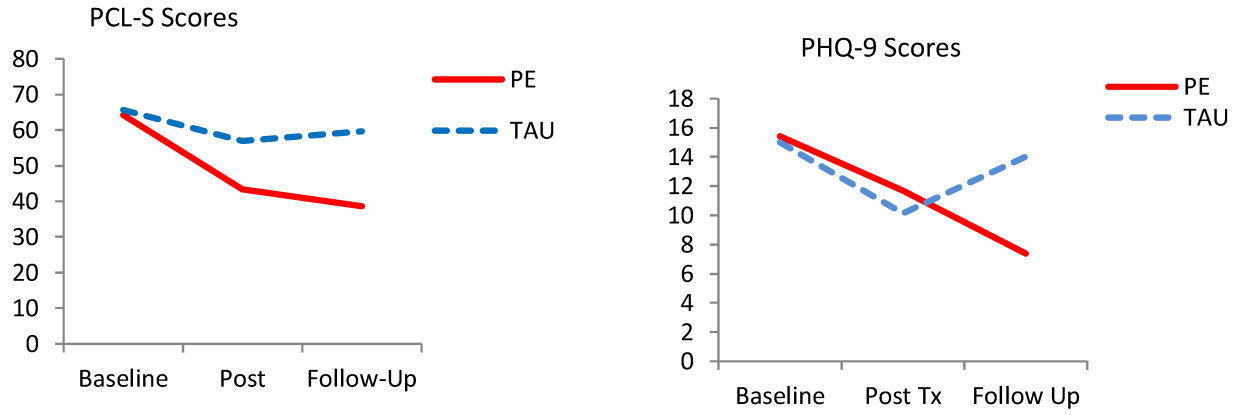


Figure 3. Observed PHQ-9 and PCL-S Scores over time, stratified by Group (PE and TAU).

Study 3: Prevalence and Mental Health Correlates of Insomnia in First-Encounter Veterans.
(Jenkins, M., **Colvonen, P.,** Norman, S., Afari, N., Allard, C., Drummond, S., 2015)

We examined the relationship between military sexual assault (MST) and insomnia and found that first-encounter Veterans with MST showed higher rates of insomnia than first-encounter Veterans without MST. To our knowledge, this is the first study to examine the prevalence of insomnia in Veterans with MST. The present study with a large community sample of first-encounter Iraq and Afghanistan Veterans documented higher rates of moderate and severe insomnia in Veterans with MST than in those without reported MST. Insomnia was more prevalent than depression, hypomania, PTSD, and substance misuse in both the full sample of Veterans and the MST subsample. These findings confirm previous suggestions that Veterans are a vulnerable group when it comes to sleep disturbance and is highly comorbid with MST. We suggest that routine insomnia assessments, referrals, and treatment to providers who can provide evidence-based insomnia treatments are crucial to increasing global functioning and client center care.

Study 4: Examining the Differential Relationship of Alcohol Use and PTSD on Insomnia in a Veteran Sample. (Colvonen, P., Straus, L., Drummond, S., & Norman, S., manuscript in progress). We examined the relationship of alcohol use (AU) and PTSD on insomnia severity. Participants were 46 Veterans with PTSD and alcohol use disorder consented for a longitudinal treatment study (Age = 40.78±10.97; 89.1% male). We examined: 1) the independent relationship of percent of days drinking in the last 90 days (%AU) and PTSD on insomnia; 2) the differential relationship of %AU and PTSD on insomnia; 3) the interaction of %AU and PTSD on insomnia. We found that both PTSD and percent of days drinking in the last 90 days associated with insomnia severity when examined in the same regression, suggesting two independent relationships to insomnia; the interaction effect was not significant. Given insomnia can influence daytime PTSD symptoms and drinking relapse, and insomnia frequently does not decrease after PTSD and AUD treatments, addressing insomnia directly may be an important factor for comorbid PTSD and AUD treatments. Overall, furthering our understanding of the relationship between insomnia, AUD, and PTSD will benefit global treatment outcomes for Veterans.

Study 5: Examining the Relationship between PTSD Symptom Clusters and Insomnia Symptoms in a Veteran Sample with Comorbid AUDs. (**Colvonen, P.,** Straus, L., Bogner, B., Norman, S., & Drummond, S., manuscript in progress). We examined the relationship of clinician administered PTSD scale (CAPS) symptom clusters, controlling for alcohol use in the past 90 days, on sleep variables. When the CAPS was broken into symptom clusters, hyperarousal accounted for the relationship to the ISI and approached significance with sleep latency. Avoidance PTSD symptoms associated with wake after sleep onset. The relationship between overall PTSD severity and insomnia severity was most accounted for by hyperarousal. PTSD hyperarousal also associated with trouble falling asleep; being on guard and being aroused by sounds in the night may partially account for trouble with sleep latency. PTSD avoidance was related to wake after sleep onset suggesting that avoiding memories and reminders of the trauma event may manifest itself with middle of the night awakenings. Given the cross sectional data, it is also feasible that wake after sleep onset leads to higher daytime avoidance. These findings suggest a strong and possibly bidirectional feedback loop between PTSD symptom clusters and insomnia.

Conclusions and considerations from our preliminary work. Several conclusions can be drawn from our preliminary work. First, as seen in also seen in the extant literature, PTSD is highly comorbid with other disorders (e.g., insomnia and SUDs) that affect course and treatment outcome. Second, interventions that include exposure to a traumatic memory are an effective way to intervene on PTSD symptoms and we found such an intervention to be acceptable to pilot participants with PTSD and comorbid insomnia. Third, sleep disorders are highly prevalent in Veterans with PTSD. As presented in the background section, the next theoretical step in PTSD treatment research is to understand whether exposure therapy that is integrated with insomnia treatment has additive value above PTSD treatment alone. Our research team is ideally suited to carry out this work based on our clinical and research experiences. The research team has a strong background in sleep and PTSD research and treatment, *in mentoring postdocs to independent research careers*, and large-scale randomized controlled trials (RCTs). Our preliminary work supports that we have the theoretical and logistical experience to carry out the proposed work.

2a.3 Research Design and Methods

Design framework. This proposed study will be a Stage 2[88] RCT comparing CBT-I integrated with PE (CBTI-PE) to a non-active sleep education component and PE (Hygiene-PE) for the treatment of male and female

Veterans with comorbid insomnia and PTSD. 90 Veterans will be enrolled through the PTSD, MST, sleep, and primary mental health treatment programs at the VASDHS. Assessments will occur at baseline, 6-weeks, post-treatment, and 3-month follow-up. All procedures will be for research purposes. Phase I start-up activities will include finalizing procedures, hiring and training research staff and therapists, and setting up of data entry and management procedures with the statistician. Phase II includes participant recruitment, enrollment, and treatment. Methods and procedures are consistent with CONSORT guidelines for conducting and reporting RCTs.[89] We will aim to recruit 2-3 participants per month for this study. Dr. Norman's Merit has recruited 4-6 participants per month with a more restricted inclusion and exclusion criteria, thus a minimum of 2-3 participants per month is feasible. Data entry and management will begin immediately after enrollment starts with preliminary statistical analyses in the second year and continuing through the end of the study. The end of Phase II will include writing a Merit grant proposal to further examine PTSD and insomnia treatment to include other highly prevalent comorbid disorders (e.g., substance use disorders) and to explore the biological mechanisms of change (i.e., fear habituation, safety learning, and executive functioning). Phase III Dissemination includes assessments, data analyses, manuscript writing, and presentations to the scientific and clinical community. See Table 2 for timeline of major project goals during the award period.

Table 2. Timeline of Major Goals

Year	1				2				3				4				5			
Quarter	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Activity	Startup		Clinical Trial														Dissemination			
Finalize procedures																				
Hire and train staff																				
Recruit/Enroll																				
Collect Data																				
Clinical Trial																				
Merit Application																				
Data Analysis																				
Dissemination																				

2a.3.a. Study Settings

All work will be carried out in the PTSD outpatient clinic of the VASDHS. Dr. Angkaw (co-mentor) is the Director of the PTSD clinic and shows a long-standing ability to recruit patients to participate in research (see Letter of Support). The staff at the PTSD clinic includes clinical psychologists, social workers, program assistant, and trainees (psychiatry residents, psychology interns and postdoctoral fellows, and social work interns). As observed in past VA-funded projects of the mentors of this proposal, the close proximity between study personnel and the treatment program (located on the grounds of the San Diego VA) facilitates communication and adherence to project procedures and thus, increases the overall feasibility of the proposed work.

2a.3.b. Recruitment Procedures

Recruitment will target Veterans with PTSD and comorbid insomnia in the outpatient PTSD clinic, MST clinic, and sleep clinic at VASDHS. In fiscal year (FY) 2013, over 21,000 Veterans sought mental health services at the VASDHS. In the FY 2013 and 2014 the PTSD clinic had 2,089 consults with 699 Veterans who showed up for three or more appointments. The MST and interpersonal trauma (IPT) clinic had 1,407 consults in FY 2013 and 2014 with 374 Veterans who showed up for three or more appointments. We have recruitment support from each clinic along with institutional support from VASDHS and the Center of Excellence for Stress and Mental Health (CESAMH; see Letter of Support). Staff in each clinic will provide a descriptive study flyer to patients newly accepted and enrolled into the outpatient PTSD program, with a diagnosis of insomnia and PTSD (based on information collected through intake). Individuals reporting interest in the study will be asked for verbal consent to be contacted by the research coordinator. In addition, informational flyers will be posted throughout the clinics with telephone number listed for interested participants to call. The research coordinator will contact prospective participants to provide an explanation of study procedures and to complete a phone-based screening. The research assessor will schedule a lab-based baseline screening visit should the individual meet basic eligibility requirements.

We will aim to recruit 2-3 participants per month for this study. Dr. Norman's Merit has recruited 4-6 participants per month with a more restricted inclusion and exclusion criteria, thus a minimum of 2-3 participants per month is feasible. Additionally, Dr. Norman's Merit is recruiting Veterans with active AUD, which we exclude for, eliminating any conflict of recruitment. The size of the proposed recruitment sample was estimated based on: (1) power analyses (see Planned Data Analysis 2a.3.j); (2) mentor experiences conducting research with similar screening procedures, designs and populations and in similar treatment settings; and (3) attrition rates reported in the literature in PTSD treatment. Based on mentors' experiences and estimates in the literature, we expect to phone screen approximately 200 Veterans to obtain *100* individuals for baseline assessment. We anticipate that 33% of Veterans will not meet inclusion/exclusion criteria following baseline assessment, resulting in 90 Veterans getting randomized to treatment. A conservatively estimated total recruitment sample of 90 will allow for up to 25% attrition, resulting in a final sample size of approximately 52 Veterans at follow-up. 52 Veterans at follow-up conservatively allow adequate power to examine all study aims.

2a.3.c. Participants

A total sample of *90* male and female Veterans with a diagnosis of insomnia and PTSD will be recruited at VASDHS.

2a.3.d. Inclusion/Exclusion Criteria.

Inclusion criteria are: a) Over the age of 19 years old; b) Diagnosis of PTSD; c) Meet diagnostic criteria for insomnia; d) Enrolled at the VASDHS and living within 50 miles of the respective facility; and e) English literacy.

Exclusion criteria are: a) Unmanaged psychosis or manic episodes in past year; b) Substance/alcohol use disorder in past 6 months; c) Diagnosed (previously or by our study screen) and untreated sleep disorder other than insomnia (Sleep disorders diagnosed, but stably treated, such as obstructive sleep apnea treated with CPAP, will be allowed); d) Participation in concurrent psychotherapies targeting PTSD; Veteran can be reassessed after their PTSD treatment concludes, Veterans who are engaged in treatment for non-PTSD symptoms (e.g., 12-step programs) will be eligible; e) Severe medical or psychiatric illness that would make it difficult to regularly attend psychotherapy sessions or participate fully in the study; and f) History of moderate to severe cognitive impairment.

2a.3.e. Participant Retention

The retention component of the study is informed by recommended strategies in the literature[90] and the training team's wealth of experience running similar studies. Throughout the course of the study simultaneous strategies will be employed at the management, staff, and participant levels to maintain participant contact and to maximize fidelity to the training protocol.

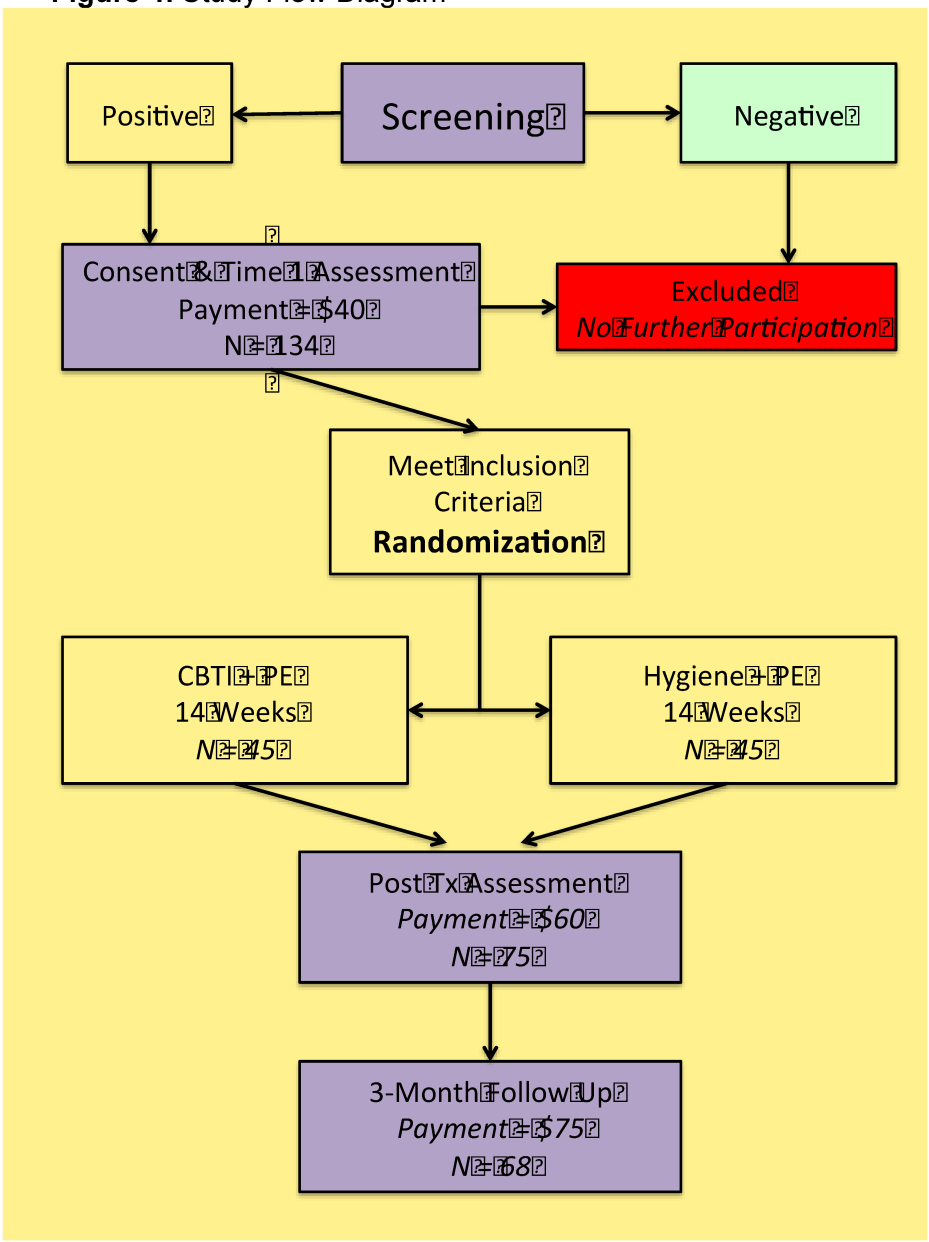
Tracking, General Contact, Check-ins: Throughout the course of the study simultaneous strategies will be employed at the management, staff and participant levels to maintain participant contact and to maximize fidelity to the training protocol. First, during the initial screening assessment a Locator Form[91] will be completed for each participant that includes: (1) home address, (2) email address, (3) home/work /cell phone numbers, (4) employment or school information, and (5) contact information for two additional individuals to be used if contact with the participant is lost. Tracking information will also be collected and updated at all follow-up interview points. Based on strategies successfully employed by Dr. Norman's (mentor) research team, additional methods to help reduce attrition will include specialized cards (e.g., birthday cards) which will includes a change of contact information form and a toll free number of the study center for subject-initiated contact.[92] A reminder call will be placed the day prior to participants' scheduled in-lab assessment. Research staff will mail a reminder to participants one week prior to their follow-up appointment. Therapists will be trained to check-in each session with the Veterans to facilitate adherence to the training protocol so that participants may derive maximal benefit.

Financial Incentives: Participants will be compensated for their time after each completed assessment. Veterans will receive *$40* for the first in-person assessment, *$60* for the post-treatment assessment, and *$75* for the follow up assessment (Total possible = *$175*).

2a.3.f. Data Collection Procedures (See Figure 4 for Study Flow Diagram)

Data will be collected at screening, baseline, post-treatment, and follow-up assessment. During each assessment, the research assessor will assess for any major changes in health (e.g., overnight hospitalizations), possible adverse events, suicidal ideation, and general well being. Therapists will also assess for clinically significant worsening during therapy sessions. Any exacerbation of symptoms will be reported and discussed with the supervising investigator so that appropriate action can be taken if necessary. Data collection staff and intervention staff will be strictly separate. The research assessor will be trained prior to Veteran assessment through a minimum of two assessments for each measure and then be observed for a minimum of two assessments. Dr. Angkaw (mentor) is a CAPS-5 trained assessor. Additionally, the research assessor will be tested for reliability (once every six months), and participate in weekly staff meetings to address questions. Training is also provided on common issues associated with self-report measures.

Figure 4. Study Flow Diagram



Screening (30 minutes): Following oral consent, potential participants will undergo a telephone screening that takes approximately 30 minutes to complete. The research coordinator will schedule a lab-based screening visit should the individual meet basic eligibility requirements. The screening is intended to detect clinically significant insomnia and PTSD symptoms.

Consenting Protocol. Post screening, all eligible patients will be offered participation in an IRB approved research protocol for the treatment of insomnia and PTSD. The voluntary nature of the study will be emphasized. If participants choose not to participate in the study, they will still receive treatment as usual from the referring clinic.

Baseline Assessment (2-3 Hours): Baseline assessment consists of screening items from the Duke Structured Interview for Sleep Disorders and the clinician administers PTSD scale (CAPS-5). 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, and quality of life (see Table 2 for measures). All assessments will be administered by a condition-blind trained research assessor.

If the Veteran meets eligibility criteria based on baseline assessment, the Veteran will then be randomized into either CBTI-PE or the control condition Hygiene-PE. 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”) and be given an actigraph (a wrist watch device) which they will wear continuously for the 7-day baseline evaluation.

Treatment Randomization: Following baseline assessment, participants will be randomized to the intervention (CBTI-PE) or control condition (Hygiene-PE). A computer-generated randomization sequence will be provided by our statistical expert Dr. Shahrokh Golshan (consultant), and held by a colleague not otherwise involved with the study. Randomization will be stratified by gender to ensure a balanced number of males and females are in each treatment group.

Bi-Weekly Assessment *(approximate time = 10 minutes):* During treatment, brief self-report assessments will be given every other week when the patient arrives for therapy to track quality of life, sleep, and PTSD symptoms. Additional measures will include adherence to assignments and satisfaction with treatment.

Post-treatment Assessment *(approximate time = 2 hours)*: 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. Patients will also wear an actigraph during the post-treatment week so as to provide objective measures of sleep to compare with the subjective sleep diary reports. At the end of the post-treatment evaluation week Veterans will return to the VASDHS to turn in the diary and actigraph and will at this time be administered the same battery of clinical assessments originally given during the baseline evaluation visit.

3-Month Follow-Up Assessment *(approximate time = 2 hours)*: Veterans will return to VASDHS to do the same battery of clinical assessments they completed at baseline and post-treatment. At the conclusion of the assessment, Veterans will have completed the study. Veterans who are randomized to the control condition and who are interested in receiving the standard CBT-I treatment will be provided with CBT-I treatment at the completion of their participation in the study.

Merit Pilot Data (N = 8) Evaluation of Objective PSG Assessment of Sleep (4 Overnights total): *PSG will be assessed in a small sample of Veterans pre- and post treatment* of CBT-I *and PE in order to gather pilot data necessary for the next step in the proposed line of research and give the PI experience with using PSG in research*. *PSG will help inform the mechanisms (specifically REM consolidation) through which sleep affects PE treatment.* The first night of PSG will be used to adapt the Veteran to the sleep laboratory environment and to screen for sleep disorders other than insomnia and will not be used for data analysis. The second night of PSG will be used to acquire objective measures of sleep and will be used in data analysis. For the overnight sleep evaluation subjects will go to bed and be awakened at their habitual sleep and wake times. The recording montage will consist of a minimum 10 electrophysiologic signals. The basic montage includes 2 electrooculograms (EOGs) referenced to a single mastoid, 6 EEGs referenced to linked mastoids [F3, F4, C3, C4, O1 and O2], a bipolar mentalis electromyogram (EMG), and an electrocardiogram (ECG). Several measures, in addition to our core montage, will be obtained. These include: 1 channel of nasal/oral airflow and 2 channels of leg-related motor activity (right and left tibial EMGs). The airflow and tibial data are used to detect obstructive sleep apnea (OSA) and periodic limb movements (PLMs), respectively. The second PSG night will be used to characterize subjects’ sleep. The montage will be the same as for the first night except OSA and PLMs will not be measured. The PSG will be used to assess standard sleep continuity parameters (e.g., sleep latency, wake after sleep onset, total sleep time, sleep efficiency, and number and length of nocturnal awakenings) and sleep architecture parameters (e.g., time spent in each sleep stage), as well as to characterize sleep microarchitecture (e.g., spectral analytic measures of EEG frequency components of sleep).

2a.3.g. Treatment Overview, Fidelity, and Safety
Treatment Overview.

Active Sleep Treatment (CBT-I): CBT-I will be conducted utilizing the VA Roll-out treatment manual. Training in the manualized treatment will be provided by Dr. Gehrman (Mentor). The standard approach to treatment involves 7 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 PTSD informs the formulation (e.g., hypervigilance). The core components of CBT-I include sleep restriction and stimulus control.

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 not set below 5 hours per night. On subsequent sessions the time in bed is titrated up or down in 15 to 20 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.

PTSD Treatment (Prolonged Exposure): Treatment guidelines for PTSD[93] supports exposure therapy as an evidence-based treatment. PE uses repeated exposure (in-vivos and imaginal) to habituate to feared response to stress-provoking situations. By staying in a safe, but distress-producing situation, one is able to have a corrective experience, learn that the situation is not as fearful or dangerous as imagined, and learn that they are able to handle their distressing feelings. With repeated exposures to the situation, the anticipatory, initial, and maximum levels of distress will decrease, and the length of time that it takes to habituate to the situation will decrease. Specifically, PE, the most investigated exposure therapy for PTSD, includes: (a) an overview of treatment, review PTSD symptoms, and teach breathing skills; (b) present the rationale for exposure therapy (i.e., anxiety is reduced by habituation to feared stimuli); (c) in-vivo exposures (in real life) help patients to stop unhealthy avoidance behaviors and to habituate to stimuli that frequently cause PTSD symptoms; and (d) imaginal exposures where patients are asked to express images, thoughts, and feelings related to their worst traumatic memory, repeatedly, with the therapist.

Integrated Treatment (CBTI-PE): The integrated treatment uses the core components of CBT-I[94] and PE,[95] with the goal of enhancing both insomnia and PTSD outcomes. Integrated treatment will be delivered in 14 90-minute weekly sessions. CBTI-PE (see Table 3 for full outline of protocol) starts with VA rollout CBT-I for the first 3 weeks with a focus on the effects of PTSD on insomnia. PE protocol (psychoeducation) begins on week 4 of treatment and both treatments overlap till week 6 when CBT-I ends and the active treatment of PE begins (i.e., imaginal and in-vivo exposures). However, CBT-I sleep diary review and sleep time adjustment will continue till the end of treatment to increase adherence to the sleep schedule. The timing of integrated treatment will allowing appropriate time for CBT-I to influence sleep efficiency before PE exposures start. Final session 14 includes reviewing goals from treatment, discussing progress and concrete skills to be used post-treatment, and discussing relapse prevention and handling reemergence of insomnia or PTSD symptoms. The integrated manual was developed and piloted with two subjects (see Preliminary Studies 2a.2) diagnosed with comorbid insomnia and PTSD at the VASDHS.

Table 3. CBTI-PE Protocol

Week	Content	Home Work
1	**General:** Establish rapport; motivational enhancement for Insomnia and PTSD treatment; review goals for Insomnia and PTSD **CBT-I:** Psychoeducation about insomnia; review 4-Factor Model of Insomnia and PTSD; review the theoretical model of treating insomnia first **PE:** N/A	-Track sleep with sleep diary
2	**CBT-I:** Review sleep diary; problem solve any difficulties in completing diaries; conduct psych-education about sleep restriction therapy; conduct breathing retraining technique (both sleep and PTSD) **PE:** N/A	-Track sleep with diary -Adhere to sleep restriction bedtime and wake time
3	**CBT-I:** Review sleep diary; problem solve any difficulties in completing diaries or adhering to sleep restriction therapy; review stimulus control therapy; modify Time in Bed (TIB) based on sleep efficiency (SE) **PE:** N/A	-Track sleep with diary -Adhere to sleep restriction schedule and stimulus control

4	**CBT-I:** Review sleep diary; problem solve any difficulties in completing diaries or adhering to sleep restriction therapy or stimulus control; review sleep hygiene; modify TIB based on SE **PE:** Discuss psychoeducation about PTSD; review rationale for exposures; normalizing avoidance	-Track sleep with diary -Adhere to sleep restriction schedule and stimulus control
5	**CBT-I:** Review sleep diary; problem solve any difficulties in completing sleep assignments; teach strategies to reduce the effects of stress on sleep; modify TIB based on SE **PE:** Review common reactions to trauma; administer trauma interview	-Track sleep with diary -Adhere to sleep restriction schedule and stimulus control
6	**CBT-I:** Review sleep diary; problem solve any difficulties in completing sleep assignments; review thoughts about insomnia; modify TIB based on SE **PE:** Discuss rationale for exposure; introduce subjective units of distress (SUDS); create in-vivo hierarchy	-Track sleep with diary -Adhere to sleep restriction schedule and stimulus control -Start In-vivo exposure
7	**CBT-I:** Review sleep diary; problem solve any difficulties in completing sleep assignments; modify TIB based on SE **PE:** Review in-vivo exposures; conduct first imaginal exposure; process imaginal exposure	-Track sleep with diary -Adhere to sleep restriction schedule and stimulus control -Continue In-vivo exposures -Listen to Imaginal exposure tape
8-13	**CBT-I:** Review sleep diary; problem solve any difficulties in completing sleep assignments; modify TIB based on SE **PE:** Review in-vivo exposures; continue in-vivo and imaginal exposures; focus in in-vivo on both reducing avoidance and increasing healthy interactions	-Track sleep with diary -Adhere to sleep restriction schedule and stimulus control -Continue In-vivo exposures -Listen to Imaginal exposure tape
14	**General:** Review goals from treatment, discuss progress, and concrete skills to be used post-treatment **CBT-I:** Discuss relapse prevention and handling reemergence of insomnia **PE:** Final imaginal exposure; discuss how to handle reemergence of PTSD symptoms	N/A

Control Non-Active Sleep Treatment (Sleep hygiene education). We have included a non-active control arm to allow for the dose response of CBTI-PE to just PE alone. The non-active sleep control condition used in this study is a manualized protocol developed by Dr. Gehrman (Mentor) for use in his ongoing HSR&D funded Merit Award examining the efficacy of CBT-I delivered via telemedicine (see Table 4 for weekly Hygiene protocol). The protocol is matched to CBTI-PE 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 reviewing sleep diaries, providing information on relationship between sleep disturbance and PTSD, presentation of sleep hygiene education, and reviewing daily stressors that may impact sleep. Dr. Gehrman (mentor) showed in a recent trial that sleep hygiene had no effect on insomnia; the pre- to post-treatment means (SD) on the Pittsburgh Sleep Quality Index in participants randomized to the proposed non-active intervention were 12.9 (3.3) and 11.8 (3.8), respectively ($p > 0.05$). In addition, patients rated the treatment as having high credibility, suggesting that this treatment condition was successful as a non-active treatment. Following completion of participation, enrollees in the sleep hygiene education group will be offered a clinical referral to the Sleep program at the VASDHS for CBT-I.

Table 4. Hygiene-PE Protocol

Week	Content	Homework
1	**General:** Establish rapport; motivational enhancement for Insomnia and PTSD treatment; review goals for Insomnia and PTSD	-Track sleep with sleep diary

	Sleep Education: Review psychoeducation about insomnia; provide information on relationship between sleep disturbance and PTSD **PE:** N/A	
2	**Sleep Education:** Veteran check-in; describe sleep management and sleep hygiene **PE:** N/A	-Practice good sleep hygiene
3	**Sleep Education:** Veteran check-in; review change(s) to sleep hygiene, review daily stressors related to sleep **PE:** N/A	-Practice decreasing stress related to sleep
4-14	**Start PE protocol**	

Fidelity of Treatment. We will measure treatment fidelity in several ways. First, in addition to training that both therapists will undergo in preparation for the study, study therapists will receive monthly consultation from Dr. Gehrman (mentor) for CBT-I. Second, therapist will receive weekly consultation from Dr. Angkaw (mentor) for PE. Third, therapists will have a checklist to guide them in conducting the CBTI-PE and Hygiene-PE protocols. Fourth, all sessions of both interventions will be audio recorded, and a random sample of 10% of recording from each randomized group will be reviewed and rated. Ratings will incorporate use of standard checklists to document presence of all program elements and absence of extraneous elements. We will define therapist adherence as 90% adherence to the items on the weekly checklist. Sub-threshold adherence ratings will include extra training and increased oversight of sessions.

2a.3.h. Limitations to the proposed procedures and alternative approaches

A) The first design consideration involved moving the CBT-I component at the end of evidence-based PE only if insomnia symptoms did not dissipate post-treatment. However, given the possible effects of fragmented sleep on the mechanism of PE (extinction and safety learning), it is critical that CBT-I should precede PE.

B) The second design consideration focused on limiting the study to CBT-I in a sample comorbid with PTSD. However, in a recent paper, Talbot and colleagues[79] ran an RCT examining CBT-I in a comorbid PTSD and insomnia sample. They found that CBT-I was an effective intervention for insomnia. As such, our study is the next step in treatment outcome studies examining the effects of CBT-I on PE outcomes.

C) We discussed limiting the age range from 19 – 60 to avoid confounds of naturally occurring sleep changes with aging. However, due to the effectiveness of CBT-I and PE in older adults,[78] and not wanting to limit access to older era Veterans, we decided to include Veterans over 60 years old.

D) We considered using a PE only group as the control group. The benefit of this would be to compare a "pure" PE treatment to the integrated treatment. However, this design would not account for the dose response in number of extra sessions in integrated treatment.

E) The fifth design consideration was whether to exclude substance/alcohol use disorders in past 6 months. Because it would be difficult to discern the effects of sleep on PTSD if SUD and AUDs were included, we decided to exclude moderate to severe SUDs from this trial. However, in future studies we will recruit individuals with SUD and AUDs to understand how to improve treatment outcomes in commonly comorbid disorder with PTSD. We will permit nicotine, caffeine, alcohol, and marijuana use during the study.

F) Substantial consideration was given to the acceptable use of medications in the study and the potential impact these medications might have on primary outcome measures. Based on the CBT-I treatment literature, we made a determination that we would include participants who take prescription and over-the-counter sleep medications including benzodiazepines, trazodone, hypnotics (e.g., zolpidem). We made this decision on the grounds that a) a high percentage of Veterans with sleep complaints will be on one or more of these medications and it would be difficult to recruit participants by excluding all those taking sleep medications, b) there is no direct evidence that use of hypnotics will adversely affect the planned interventions, and c) if patients met eligibility for the study, then it is likely that the medications alone were not satisfactorily controlling symptoms (i.e., insomnia). Additionally, research suggests that even in cases where medication taper or discontinuation is not feasible, CBT-I may still result in treatment benefits during acute therapy.[96] Despite the variable effects of SSRIs on sleep, we will allow Veterans taking these medications into the study. We will allow use of prazosin for control of nightmares in Veterans with PTSD. Our general approach, therefore, will be to allow for prescription medication use provided that participants are on a stable medication regimen for at least one month prior to enrollment in the study and do not plan to start, stop, or change dosage during the study (changes during the study will be noted). Note that since we will track medication use during the study, we will be able to examine the potential moderating influence of medications on treatment outcomes.

2a.3.i. Measures (see Table 5 for schedule of assessments)
A multi-modal method of assessment will be utilized to measure all variables. This will include the use of self-report questionnaires, clinical interviews, and *actigraphy watches*. The primary outcome of interest will be reduction in PTSD symptoms, increase in SE, and quality of life at follow-up. Other outcomes include depression symptoms, other covariates that affect PTSD and sleep (e.g., pain), and predictors of outcomes such as process variables and affect.

Primary Outcome Measures.

PTSD: The Clinician-Administered PTSD Scale DSM 5 (CAPS-5)[97, 98] is the gold-standard, semi-structured interview that corresponds to DSM-5 criteria for PTSD. The CAPS-5 shows strong reliability and validity.

Sleep: Daily Sleep Diary. Patients will complete a daily sleep diary throughout the course of treatment (14 weeks) and for one week prior to the follow-up assessment. The sleep diary includes typical subjective measures (bed time, sleep latency, number and duration of awakenings, wake time, total time in bed, sleep quality) and two calculated variables (total sleep time and sleep efficiency). Daily sleep diaries are commonly used in studies and treatment of insomnia. The primary outcomes measure of the sleep diary will be sleep efficiency.

Quality of Life: World Health Organization Quality of Life-BREF (WHOQOL-BREF)[99] comprises 26 items, which measure the following broad domains: physical health, psychological health, social relationships, and environment. It shows strong validity and reliability.

Other PTSD and Sleep Assessments.

The PTSD Checklist (PCL-5)[100] is a 21-item self-report measure of PTSD symptoms with good psychometric properties. The PCL-5 maps directly onto DSM-V diagnostic criteria.

Insomnia Severity Index (ISI)[62] is a widely used measure of insomnia with well-established reliability and validity. The ISI consists of seven items, three of which assess severity of insomnia (i.e., degree of difficulty falling asleep, staying asleep, and waking too early). The remaining questions tap satisfaction with sleep pattern, effect of sleep on daytime and social functioning, and concern about current sleep difficulties.

Pittsburgh Sleep Quality Index (PSQI)[101] is a 19-item self-report assessment of sleep quality and degree of sleep difficulties over the past month. We will also administer the PTSD Addendum for the PSQI. This validated measure assesses sleep disruptive behaviors common to PTSD patients and those with chronic nightmares.

Pre-sleep arousal scale (PSAS)[102] is a self-administered measure in which participants rate the intensity of experienced arousal for somatic (8 items) and cognitive (8 items) subscales. The PSAS shows strong internal consistency and reliability. This measure will help control for the hyperarousal seen in PTSD.

Actigraphy. Participants will wear an actigraph for 7 days prior to the start of treatment (week 0) and one week prior to the start of imaginal exposures (week 6), post-treatment, and the 3-month follow-up assessments. Actigraphy-measured SE and Sleep Percent are the primary variables. The former provides an overall measure of the response to CBT-I, while the latter provides an indication of sleep consolidation and abnormal motor activity during sleep. The actigraphy watch variables use the daily sleep diary for interpretation. *The Actiwatch is a wrist-worn device that measures body movements and light. It is lightweight (17.5 g) and worn like a wristwatch. The methodology is commonly used to record sleep/wake patterns over several days and has strong agreement with polysomnography in validation studies.[103] These data will provide standard sleep parameters: total sleep time, sleep efficiency, number of nocturnal awakenings, and length of awakenings.*

Duke Structured Interview for Sleep Disorders (DSISD)[104] is a clinician-administered assessment used for diagnosing sleep disorders based on DSM and ICD criteria. For the current study, the DSISD will be used to assess for presence and severity of sleep symptoms at screening.

Nox T3 recorders. Nox T3 recorders are a portable sleep monitoring system that can accurately diagnose obstructive sleep apnea (OSA). It has a simple and easily monitor hook ups the that patients can use on their own at home. The Nox T3 will give an accurate Apnea Hypopnea Index (AHI) per hour to diagnose OSA.

Other Measures

Patient Health Questionnaire (PHQ-9)[105] *is a 9 item questionnaire based directly on the diagnostic criteria for major depressive disorder as outlined by the DSM and will be used to assess the severity and frequency of mood symptoms..*

The World Health Organization Disability Assessment Scale (WHODAS 2.0)[106] is a 36-item questionnaire that assess functional impairment across 5 subscales: cognitions (understanding and communicating), mobility, self care getting along with others, household responsibilities, work responsibilities, and community participation.

The Client Satisfaction Questionnaire (CSQ)[107] is an 8-item self-report scale measuring satisfaction with treatment. It has excellent internal consistency and correlates with therapists' estimates of client satisfaction. This instrument will be used to measure participants' satisfaction with the interventions.

Pain Disability Questionnaire (PDQ)[108] is a 15-item questionnaire for assessing pain-related functional disability that separately evaluates the Functional Status Component and a Psychosocial Component. Pain is an important variable to control for as it may affect both insomnia and PTSD. The psychometric properties of the PDQ are excellent, demonstrating strong reliability, responsiveness, and validity, sufficient to study longitudinal change.

The Difficulties in Emotion Regulation Scale (DERS)[109] is a 36-item self-report questionnaire that measures emotion dysregulation by assessing individuals' abilities regarding the following dimensions: 1) awareness and understanding of emotions; 2) acceptance of emotions; 3) ability to engage in a goal-directed behavior and refrain from impulsive behavior when experiencing negative emotions; and 4) access to emotion regulation strategies that are perceived as effective.

Medications Use Interview: All participants will complete a standard interview regarding recent medication use. Additionally, participants will be instructed to bring in the names and dosing schedule of all medications they are currently being prescribed.

Pilot Data Measures (N = 8)

Polysomnography (PSG) is used to capture standard sleep architecture variables (NREM Stages N1, N2, N3 and REM sleep) as well as track other sleep disorders, such as obstructive sleep apnea.

Table 5. *Proposed measure timeline*

	Baseline	**Week 6**	**Post**	**3-month**	**Bi-Weekly**
Primary Outcomes Measures					
CAPS-5	X		X	X	
Sleep Diary (SE)					X
WHOQOL-BREF	X	X	X	X	
Other PTSD and Sleep Measures					
PCL-5					X
Actigraphy Watch	X	X	X	X	
Pre-Sleep Arousal	X	X	X	X	
ISI					X
PSQI	X	X	X	X	
DSISD	X				
Nox 3	X				
Other Measures					
Medications	X		X	X	
Pain Index	X	X	X	X	
CSQ					X
DERS	X	X	X	X	
PHQ-9					X
WHODAS 2.0	X	X	X	X	
Pilot Data Measures (N = 8)					
PSG	X		X		