Merck Investigator Studies Program (MISP) Protocol Template

Requirements for Submitting a Full Proposal

Section #1 - MISP Protocol Identification

Study Title:	Suvorexant and Trauma-related Insomnia (A placebo controlled trial with polysomnography)
Request Date:	6/22/15 Revised 9/17/18
Institution Name	Howard University
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Section #2- Core Protocol	
2.1 Objectives & Hypotheses	Disturbed sleep is one of the most common and distressing responses to exposure to severe trauma and can persist in many of those affected with and without accompanying posttraumatic stress disorder (PTSD). Insomnia is a risk factor for many of the conditions that are prevalent in trauma-exposed populations including PTSD, depression, and physical health conditions such as obesity, and cardiovascular disease. Trauma-related insomnia (TRI) is not typically differentiated in studies characterizing insomnia and its treatment, and insomnia accompanying PTSD has been shown to be relatively refractory to the treatments that are established for PTSD. Thus treatment of TRI presents an unmet need that has implications for the large and growing groups of people exposed to trauma in terms of relieving distress and preventing further psychiatric and medical morbidity. Most of the data on TRI comes from research on populations with PTSD. Difficulty initiating and maintaining sleep is designated as one of the heightened arousal symptoms of PTSD in the DSM. Sleep studies have suggested reduced slow wave sleep (SWS) in some PTSD populations and fragmented rapid eye movement (REM) sleep when PTSD is developing, and during its more acute stages. Suvorexant is a first in class orexin antagonist and is approved by the FDA for the indication of insomnia. Orexin antagonists dampen the activity of a specific arousal enhancing system in the brain during sleep. In rodent models suvorexant has been shown to enhance, and in healthy humans, to not affect slow wave and REM activity (in contrast with traditional hypnotics which can diminish both). Reducing arousal during sleep while maintaining REM and slow wave sleep is a promising profile for the treatment of TRI. We are therefore proposing a placebo controlled evaluation to assess the efficacy of suvorexant for treating TRI with and without PTSD and its tolerability in these populations. We will include polysomnography (PSG) in order to probe potential mechanisms and biomarkers predicting response. The proposed study will meet the objectives below and test the following hypotheses: Objective 1. To recruit a group of participants that meet criteria for insomnia and who identify a severely threatening event (DSM criterion A trauma) as a precipitant or a factor that significantly exacerbated their sleep disturbance; and to determine the frequency of PTSD diagnoses and symptoms among the recruited participants. Hypothesis 1) – Recruitment will reveal TRI to be a common condition that in approximately half of cases occurs absent PTSD. Objective 2. To evaluate the effectiveness and tolerability of suvorexant on insomnia and when present, associated PTSD symptoms and its effects on PSG measures in participants with TRI. Hypothesis 2a) Insomnia will improve, and nightmares and other PTSD symptoms will be reduced with suvorexant treatment compared with placebo. 2b) Improved sleep will be associated with reduced non-sleep related PTSD symptoms when present.

	2c) Suvorexant will be well tolerated by the participants. 2d) Sleep latency and wake after sleep onset (WASO) will be reduced with suvorexant treatment compared with placebo. 2e) (exploratory hypothesis) When reduced at baseline (i.e. SWS below 100 minutes and mean REM segment duration below 15 minutes) SWS and the duration of continuous segments of REM sleep will increase with suvorexant compared with placebo.
2.2 Background & Rationale, Significance of Selected Topic & Preliminary Data	<u>Trauma-Related Insomnia (TRI)</u> Insomnia is a common sequela of trauma exposure. In a review of studies of populations exposed to disasters, "trouble sleeping" was the most common symptom reported, especially from studies where sampling occurred within 4 months.[1] Findings from the Millennium Cohort Study indicated that military personnel who had been deployed to Afghanistan and/or Iraq were 14 – 29% more likely to report insomnia symptoms compared with those who had not been deployed, and 27% of the post-deployment personnel reported insomnia symptoms that were at least moderately severe.[2] Krakow and colleagues[3] found that 99% of 78 treatment seeking evacuees of the Cerro Grande Fire met criteria for "psychophysiological" insomnia. Rates of insomnia for veterans and civilians with PTSD, have ranged from 70 to 91%.[4-6] When both have been reported, the rates for insomnia in trauma exposed populations exceed those for PTSD (e.g. PTSD rates for the Millennium Cohort were estimated at 5%,[2] in the group recruited by Krakow et al. the rate for PTSD was 59%[3]). In our recent report of 136 urban young adult African Americans, 83% were trauma exposed, 16% met full criteria for current PTSD, and 43% exceeded a recommended threshold score for diagnosing insomnia (Insomnia Severity Index score of 10 or greater[7]).[8] TRI may often endure when other PTSD symptoms have remitted. For example, Zayfert and DeViva[9] reported that 48% of patients who achieved remission of PTSD following CBT developed for PTSD continued to experience insomnia indicating that Further evidence that TRI represents an important treatment need comes from an analysis by the applicant and collaborators of a state Medicaid data base which revealed that over half of patients with a PTSD diagnosis taking psychopharmacologic medications were receiving various hypnotics.[10] <u>Polysomnographic findings in TRI</u> Studies with objectively recorded sleep in TRI have generally been in the context of PTSD. A meta-analysis of PTSD sleep studies published in 2007 by this application's co-PI revealed "lighter sleep" in terms of reduced SWS and increased stage 1 as well as increased frequency of eye movements during REM sleep (REM density).[11] Much of the focus of such research has been on REM sleep. This interest was initially inspired by hypothesized abnormalities of REM sleep based on the occurrence of recurring nightmares that (to varying degrees), replicate past (traumatic) experiences.[12] Dreams most commonly arise from REM sleep and do not normally represent unaltered memories of specific events.[13,14] More recently investigators have postulated that REM sleep (when not disrupted) provides conditions that are conducive to reducing the affective intensity of trauma memories and

facilitating their integration into overall autobiographical memory.[15]

Studies have not found consistent alterations in the latency to, or amounts of, REM sleep with PTSD. The increased REM density that was confirmed in the aforementioned meta-analysis[11] has also been reported in association with trauma exposure absent PTSD.[16] In this study that uniquely reported PSG findings from the early aftermath of trauma the length of uninterrupted segments of REM sleep were shorter among the injured patients developing PTSD.[16] Of all of the PSG measures examined, this index of REM sleep fragmentation also demonstrated the strongest correlation with insomnia symptoms (i.e. stronger than the correlations with total sleep duration or WASO).[16] Reduced and fragmented REM sleep was also noted anecdotally in a report of sleep in association with acute combat fatigue.[17] Symptomatic awakenings in PTSD, with and without nightmares, have been shown to be preceded by, and thus could be considered to disrupt REM sleep.[18,19] Such awakenings have been noted to occur less frequently in laboratory settings than in naturalistic environments and laboratory sleep studies of PTSD have not consistently demonstrated reduced or fragmented REM sleep. Our recent report provides some perspective on this apparent inconsistency in documenting an inverse relationship between several indices of REM duration and continuity and the duration of PTSD. This report also noted that the tendency for REM sleep to be suppressed or disrupted with PTSD of less chronic duration is also consistent with the overall findings in the literature.[20] Thus, while reducing insomnia and improving sleep is an important goal for distressed trauma-exposed individuals, maintaining the continuity of REM sleep may be of particular significant to interventions applied within a few years of trauma exposure in alleviating insomnia symptoms.

Rationale for suvorexant

Orexin antagonists are a new class of therapeutic agents that are promising for diminishing arousal to maintain overall sleep and specifically REM sleep. Orexin is implicated in coordinating brain stem centers that initiate and maintain states of arousal and are deficient in narcolepsy, a disorder with excessive and disinhibited REM sleep.[21] The Merck product suvorexant is a dual orexin receptor antagonist and the first and to date only FDA approved agent from this class.[21] Results of the 2, pivotal 3 month trials involving over 2000 patients[22] have been reported as well as a 1 year trial where 522 patients received suvorexant.[23] Suvorexant has shown consistent efficacy in reducing insomnia, and in reducing WASO and latency to persistent sleep in people with primary diagnoses of insomnia. It has also been well tolerated with somnolence being the most common adverse effect, endorsed by 7% of insomnia patients receiving approved doses versus 4% of those receiving placebo. Only 3% of trial participants receiving suvorexant discontinued treatment due to adverse effects which was comparable to the rate for those receiving placebo. Of note, despite targeting a system that is implicated in narcolepsy, there were no incidences of cataplexy observed in these clinical trials. Orexin antagonists have been shown to increase REM and SWS in animal models, however, in healthy humans (without disturbed sleep) there were no significant changes in the amount of REM sleep nor changes in the distribution of spectral EEG frequencies within each sleep stage.[21] Based on

these data we predict that suvorexant will not precipitate REM sleep-related parasomnias in the proposed target population but rather will consolidate fragmented REM sleep periods that have been observed in the earlier stages of PTSD. This would be similar to the effects seen for the alpha 1 adrenergic antagonist prazosin, an agent that targets central noradrenergic arousal promoting mechanisms and has been shown to reduce the severity of nightmares and related sleep disruption with PTSD. Specifically, the only study that monitored EEG sleep found lengthened discreet REM sleep periods with increases in the amount of REM sleep that were proportionate to the increases in overall sleep time. Prazosin, however, did not reduce time to fall asleep in this study.[24] Given the data from animals and that the absence of changes was in healthy volunteers, we hypothesize that suvorexant will also enhance SWS when it is deficient at baseline.

Summary of Significance

Insomnia is quite common among those exposed to trauma. PTSD usually features insomnia symptoms and insomnia precipitated or exacerbated by trauma is also common absent a PTSD diagnosis. TRI does not appear to respond well to previously available treatments. Fragmented patterns of REM sleep have been observed during the development of PTSD and within several years of its onset. Suvorexant is promising for maintaining overall sleep and REM sleep that is being disrupted by heightened arousal. In addition to proposing a placebo-controlled evaluation of efficacy and tolerability of suvorexant for TRI we further propose utilizing PSG to potentially elucidate physiological biomarkers of treatment response. Given the rising toll of trauma this proposal is a timely response to Merck's call for proposals for "clinical studies exploring the investigational use of suvorexant in key insomnia subpopulations."

2.3 Study Design

A double-blind placebo-controlled 6-week trial of suvorexant 10 – 20mg for trauma related insomnia (with and without PTSD) with polysomnography

2.4 Study Flowchart

(Visits)	Prescreen	Screen	Baseline	Med Week 1	Med Week 2	Med Week 3	Med Week 6	Post-Rx Week1
Phone screen	X							
Physical		X						
Wt. & Vital Signs		X		X	X	X	X	X
DSISSD and SCID		X						
LEC		X						
CAPS			X			X	X	
ISI			X			X	X	X
Sleep Diaries			X (1 week)	X		X	X	X(1week)
PSG			XX			X		
AE				X	X	X	X	X

2.5 Study Procedures	Participants *Recruitment:* We will recruit 90 adults with the expectation of retaining 70 (see power analysis). Participants will be between the ages of 18 to 55 with insomnia and trauma exposure (see below). Recruitment will occur over a 2 1/2 year period with the expectation of recruiting 3 per month and having 2 months for start-up and 6 months for final data analysis and preparing presentations and manuscripts. We will utilize advertisements including 10 radio and 10 newspaper ads in the Washington Post Express at early and other strategic times during study recruitment. We will also continue to employ recruitment methods that have been successful for our program in recruiting participants with trauma-related symptoms including posting flyers on the Howard University campus and in strategic locations in the Washington DC community, and referrals from prior participants. Those who meet initial criteria by phone or on-site screening will be invited to the Clinical Research Unit (CRU) for further screening and informed consent. We will recruit men and women. This study will be open to all ethnic and racial groups; however, with the study location of Howard University in urban DC we anticipate that many of the recruited participants will be from minority groups. *Screening Procedures:* Participants will initially be screened over the phone with a preliminary checklist of inclusion and exclusion criteria as well as be further informed regarding the purpose and goals for the study. Those who remain interested and appear to meet study criteria will be invited for the screening evaluation at the Howard University CRU. (See study flow chart.) *Inclusion criteria and justification:* Physically healthy young to middle-aged adults (age 18-55) who report on screening and are confirmed by a clinical interview to meet the Diagnostic and Statistical Manual of Mental Disorders – 5th Edition (DSM-5) criteria for primary insomnia and Criterion A (exposure to a traumatic event) for PTSD.[25] insomnia symptoms must have started or worsened after the exposure to the index trauma. We anticipate that approximately half of the recruited sample will meet criteria for PTSD thus enabling comparisons between those with TRI present or absent PTSD. *Exclusion criteria:* 1. Psychiatric disorders other than insomnia, PTSD and specific phobias; including bipolar and psychotic disorders and meeting criteria for DSM-5 moderate alcohol or drug use disorders within the past year. 2. Diagnosis of a sleep disorder other than insomnia including PSG findings of apnea/hypopnea or periodic limb movement indices > 10/hour;

3. Consistent (daily) use of medication other than medications taken for blood pressure or nonnarcotic medications for pain and/or inflammation, or medical conditions that compromise sleep;
4. Caffeine use exceeding 5 cups of coffee per day or its equivalent;
5. Habitual bedtimes after 3AM, habitual rise times after 10AM, or habitual napping > 1hour/day;
6. Pregnancy or breastfeeding, or expecting to conceive while in study (sexually active women will be required to use a medically acceptable form of birth control);
7. Positive urine toxicology.

Procedures

Medication:

After the baseline screening, participants will be randomly assigned to either the suvorexant or placebo group, and suvorexant or placebo will be administered to be taken one hour before bedtime. Randomization will be stratified for the presence or absence of PTSD (full or subthreshold) and gender. Medication will be managed by the research pharmacy and provided to the participant by CRU nursing staff with instructions for use. In case of a missed appointment they will receive a 15 day supply except for between treatment week 3 and week 6 when they will receive a 4 week supply. Initial dosing will be 10 mg. At week one, Dr. Mellman or a study clinician in consultation with Dr. Mellman, will determine whether to increase to 20 mg. based on tolerance of the medication and persistence of symptoms. If there are no, or only negligible, side effects and insomnia symptoms remain present then the dose will be increased. If tolerability is compromised by the dose increase the study clinician will have the option of reducing back to 10 mg if done at or before the week 2 study visit. Dose increases can be deferred until week 2 but after this visit medication dose will be held constant until the end of the study. Participants will discontinue medication after the week 6 study visit. At the final follow-up 1 week later clinical assessment will inform the study clinician's recommendation for further treatment including possible resumption or initiation of suvorexant. At each medication study the coordinator or research nurse will conduct a pill count and review diaries to determine adherence. They will also query for potential adverse events including a list of the most common adverse effects reported in the suvorexant trials[22,23] will be queried as well as any events suggestive of parasomnias or narcolepsy phenomena (see Assessments below).

Assessments:

The following diagnostic and outcome assessments will be performed by research staff members blind to participants' treatment condition.

(Diagnostic)

Duke Structured Interview Schedule for DSM-IV-TR and International Classification of Sleep Disorders 2nd edition (ICSD-2) Sleep Disorder Diagnoses (DSISSD)[26] – A widely used semi-structured interview designed to assess sleep disorder diagnostic status. We will use this interview to evaluate the presence of insomnia and to rule out insomnia that is accounted for by a mental disorder other than PTSD, medical conditions, and substance use, parasomnias, narcolepsy, and circadian rhythm sleep disorders. This interview will establish the onset and course of insomnia, with in conjunction with the information from the LEC and CAPS (see below) will determine the criteria for "trauma-related."

Structured Clinical Interview for DSM-V (SCID)[27] The SCID is semi-structured diagnostic interview that assesses the DSM diagnostic criteria for psychiatric disorders and is considered the "gold standard" for assessing mental disorders. A modification will be utilized in order to screen for excluded and establish allowable comorbid conditions.

Life Event Checklist (LEC),[28] is an inventory of lifetime exposure to traumatic events that lists 15 of the more common categories of trauma experiences and asks for endorsement of whether they occurred directly to the person or were witnessed and the age of exposure.

The Clinician Administered PTSD Scale (CAPS)[29] will be administered to further assess the details of trauma exposure, and (past week) PTSD severity, and lifetime diagnostic criteria. The CAPS evaluates the frequency and intensity of each of the 17 symptoms of PTSD and is considered a gold standard for assessment of the diagnosis and severity of PTSD.

*(*Assessments used for outcomes)

Insomnia Severity Index (ISI)[30] The ISI is a seven-item measure used to evaluate insomnia severity for the past two weeks. Items are scored on a 5-point scale and a total score is obtained by summing the seven items, with higher scores indicating greater insomnia severity. A cutoff score of 10 has been determined to be optimal for detecting insomnia in population samples. The ISI is also validated as an outcome measure for insomnia treatment studies and is widely used for that purpose.

Sleep diary - Participants will complete our standard sleep diary each morning throughout this trial. The diary includes questions about bedtime, final awakening time, sleep onset latency (SOL) estimate, the number of awakenings, and duration of each awakening, overall sleep satisfaction, morning restfulness, adherence/non-adherence to the study medication regimen, nightmare frequency, and content of nightmare. Estimated total sleep time (TST) and wake after sleep onset (WASO) for each night will be calculated using information provided in the diary.

One week CAPS nightmare item and total score minus sleep items.

Adverse Event Screening At each medication visit participants will be queried regarding the presence of any new symptoms or concerns. We will specifically query the adverse effects that occurred at a frequency that exceeded placebo in either the 3 month pivotal trials[22] or the 1-year study[23] including somnolence, fatigue, dry mouth, dyspepsia, and peripheral edema. We will also specifically query the pre-specified events of interest for those trials including suicidal ideation, complex sleep-related behaviors (e.g. getting food during the night and not remembering it), sleep onset or off-set hallucinations, sleep paralysis, and falls. Excessive daytime sleepiness will be assessed by administering the Epworth Sleepiness Questionnaire.[31] Weight and vital signs will be obtained at each study visit. At the post-treatment visit specific inquiry will also include the occurrence of common medication withdrawal symptoms such as dizziness, shaking, nausea, and muscle tension as well as re-assessment of insomnia and sleep patterns for that period.

Polysomnography (PSG):

PSG collection includes a standard electroencephalogram (EEG) montage with two central, frontal, and occipital leads, two electrooculograms, chin and limb electromyograms, and an electrocardiogram (ECG). Recordings will be conducted using an Embla (Denver, CO) Titanium unit in the CRU. Screening for sleep disordered breathing and limb movements will be performed using the screening night data. Visual scoring of sleep records from a computer monitor will be done following the American Academy of Sleep Medicine (AASM) Manual, Version 2.0.[32] The REMLogic software (Embla) will calculate sleep parameters including TST, SOL, WASO, the percentage of each sleep stage, and mean duration of continuous REM segment. Calculation of REM segment length used our previous criteria[16] of at least two epochs of consecutive REM sleep with no more than one 30-sec epoch of non-REM sleep interruption. The sleep parameters for baseline will be obtained from the second night recording after an accommodation recording that will also screen for apnea will be used in data analysis. Respiratory strain gauge, nasal air flow, and oximetry monitors will be included on the first but not subsequent nights. Participants will be instructed to go to bed near their habitual bedtimes and will wake up naturalistically. PSG will be done prior to medication and after 3 weeks of medication treatment to allow for stable dosing.

Summary of changes (9/17/2018)

1. Allowing ongoing use of medications for blood pressure and non-narcotic medications for pain and/or inflammation.
   Pg 2, exclusion criteria #3 of consent
   Pg 7, first line also #3 in protocol

2. No longer restricting the time from the trauma and onset of symptoms
   Pg 6 of the protocol

2.6 Study Duration	Three years – 2 months preparation, 30 months to recruit 3 participants per month except December, 4 months for final data analyses, presentation and manuscript preparation Estimate the length of time (e.g., number of days, weeks, months) required to recruit patients and complete the study.
2.7 Statistical Analysis and Sample Size Justification	The data will be analyzed by the Investigator and Co-investigator. Main outcomes will be ISI, CAPS nightmare frequency and total score, diary and PSG sleep latency and WASO at week 3 and for non-PSG variables Med week 6. We will also explore effects on REM and SWS and their relationships to other study outcomes. An alpha level of .05 (one-tailed) will be applied in testing Hypotheses 2a), 2b), 2d), and 2e). Initially, data will be pre-screened for errors, outliers, normality of distributions, and any necessary modifications, such as transformation of variables and/or elimination of cases, will be conducted. Our initial objectives are descriptive. We will generate frequencies of types of trauma exposures associated with insomnia and the rates for PTSD diagnoses and sub-diagnostic threshold PTSD symptoms in the recruited study population (**Objective 1**) and the frequency of adverse events (**Objective 2**). The latter will be descriptively contrasted to the extant data for suvorexant from the insomnia registry trials as a guide to planning future trials including dosing. ***Hypothesis 2a) Insomnia will improve, and nightmares and other PTSD symptoms will be reduced with suvorexant treatment compared with placebo:*** We will compare baseline characteristics of the treatment groups using independent samples *t*-tests for continuous variables or chi-square tests for categorical variables. If a significant group difference is found in some of the variables, the variable(s) will be included in subsequent analyses as a covariate(s). We will perform 2 (Group) x 3 (Time: baseline, Med week 3, and week 6) mixed ANOVAs or ANCOVAs [if there is a covariate(s)] to compare the changes in ISI scores, nightmare frequency, and CAPS scores, separately, between the two groups. ***Hypothesis 2b) Improved sleep will be associated with reduced non-sleep PTSD symptoms:*** Correlation coefficients between baseline – Med week 6 changes in sleep measures (e.g., ISI scores and nightmare frequency) and changes in the CAPS scores excluding two sleep-related items will be computed. In addition, we will exploratively examine if there is an interaction with treatment condition by performing regression analyses in which CAPS scores will be predicted by changes in sleep measures, treatment condition, and a Sleep measure X Treatment condition interaction. ***Hypothesis 2d) Sleep latency and wake after sleep onset (WASO) will be reduced with suvorexant treatment compared with placebo::*** We will perform 2 (Group: suvorexant vs. placebo) x 2 (Time: Baseline and Med week 3) mixed ANOVAs or ANCOVAs [if there is a covariate(s)] to compare the changes in PSG measured sleep latency and WASO between the suvorexant and placebo groups. ***Exploratory hypothesis 2e) When reduced at baseline (i.e., SWS below 100 minutes and mean REM segment duration below 15***

	minutes), SWS and the duration of continuous segments of REM sleep will increase with suvorexant than placebo: Participants with reduced baseline SWS (below vs. above 100 minutes) and mean REM segment duration (below vs. above 15 minutes) will be included in the analyses. 2 (Group) x 2 (Time: Baseline and Med week 3) mixed ANOVAs or ANCOVAs will be performed to compare treatment changes in SWS and REM segment duration between the suvorexant and placebo groups. Power Considerations: G*Power 3.1 [33] was used to conduct power analysis. **Power analysis for Hypothesis 2a)** is based on the effect size estimated using findings of Herring and colleagues'[22] placebo controlled trial of suvorexant in adults with insomnia. **Since there are no data for suvorexant on trauma related nightmares and PTSD symptoms, we also used** Taylor and colleagues'[24] placebo controlled trial of prazosin in civilian outpatients with PTSD, sleep disturbances, and nightmares. Taylor et al. found a large-size effect of prazosin on changes in trauma-related nightmare severity compared with placebo (*d* = 0.96 or f = 0.48) and PTSD severity (d =0.79 or f = 0.40) and a medium-size effect on changes in trauma-related insomnia symptoms severity (*d* = 0.50 or f = .25). Herring and colleagues found a small-size effect of a 1-month suvorexant treatment (20mg for nonelderly and 15mg for elderly) on insomnia severity measured by the ISI (d = 0.39 or f = 0.20). To detect an f = 0.20 Group x Time interaction effect in the proposed mixed ANOVA with 80% power, a total of 42 participants are needed. **Power analysis for Hypothesis 2b)** is based on the effect sizes estimated using Krakow and colleagues' findings[34] from their study examining effects of cognitive behavioral therapy for nightmares and insomnia in crime victims with PTSD. They found correlations between changes in nightmare frequency, insomnia severity, and sleep quality and changes in overall PTSD symptom severity ranging from *r* = .37 to .40. A sample size of 43 will allow for detecting similar size effects with 80% power. **Power analysis for Hypothesis 2d)** is based on findings from the aforementioned Herring and colleagues' study. They found that effects of suvorexant on sleep latency and WASO were f =0.17 and 0.31, respectively. To detect an effect size of 0.17 using the proposed mixed ANOVA with 80% power, a total of 70 participants are needed. **Power analysis for Exploratory hypothesis 2e)** is based on findings from the aforementioned Taylor and colleagues' study. They found that the effect of prazosin on mean REM period duration was f = 0.50. Using the proposed mixed ANOVA, a total of 16 participants will allow for detecting a large size within-between interaction effect (*f* = 0.50) with 80% power.
2.8 Specific Drug Supply Requirements	The study will require suvorexant 10 and 20 mg and placebo 10 and 20 mg in coded pill containers. It will be stored and managed by the Howard University Hospital Research Pharmacy.

2.9 Adverse Experience Reporting	We will use the methods specified in the protocol and will adhere to the Model Study Agreement.
2.10 Itemized Study Budget	Budget on Merck Template is included.
2.11 References	1. Green BL. Disasters and posttraumatic stress disorder. In: Davidson JRT, Foa EB, eds. *Posttraumatic stress disorder: DSM-IV and beyond.* Washington, DC: American Psychiatric; 1993:75-98. 2. Seelig AD, Jacobson IG, Smith B, et al. Sleep patterns before, during, and after deployment to Iraq and Afghanistan. *Sleep*. 2010;33(12):1615-1622. 3. Krakow B, Haynes PL, Warner TD, et al. Nightmares, insomnia, and sleep-disordered breathing in fire evacuees seeking treatment for posttraumatic sleep disturbance. *J Trauma Stress*. 2004;17(3):257-268. 4. Neylan TC, Marmar CR, Metzler TJ, et al. Sleep disturbances in the Vietnam generation: Findings from a nationally representative sample of male Vietnam veterans. *Am J Psychiatry*. 1998;155(7):929-933. 5. Ohayon MM, Shapiro CM. Sleep disturbances and psychiatric disorders associated with posttraumatic stress disorder in the general population. *Compr Psychiatry*. 2000;41(6):469-478. 6. Leskin GA, Woodward SH, Young HE, Sheikh JI. Effects of comorbid diagnoses on sleep disturbance in PTSD. *J Psychiatr Res*. 2002;36(6):449-452. 7. Morin CM, Belleville G, Bélanger L, Ivers H. The insomnia severity index: Psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep*. 2011;34(5):601-608. 8. Mellman TA, Hall Brown TS, Kobayashi I, et al. Blood pressure dipping and urban stressors in young adult African Americans. *Ann Behav Med*. in press. 9. Zayfert C, DeViva JC. Residual insomnia following cognitive behavioral therapy for PTSD. *J Trauma Stress*. 2004;17(1):69-73. 10. Mellman TA, Clark RE, Peacock WJ. Prescribing patterns for patients with posttraumatic stress disorder. *Psychiatr Serv*. 2003;54(12):1618-1621. 11. Kobayashi I, Boarts JM, Delahanty DL. Polysomnographically measured sleep abnormalities in PTSD: A meta-analytic review. *Psychophysiology*.

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	disorder: A placebo-controlled study. *Biol Psychiatry*. 2008;63(6):629-632. 25. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders.* 5th ed. Washington, DC: American Psychiatric Association; 2013. 26. Edinger JD, Wyatt JK, Olsen MK, et al. Reliability and validity of insomnia diagnoses derived from the duke structured interview for sleep disorders. *Sleep*. 2009;32(suppl):A265. 27. First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured clinical interview for DSM-IV-TR axis I disorders, research version, patient edition.* New York: Biometrics Research; 2002. 28. Gray MJ, Litz BT, Hsu JL, Lombardo TW. Psychometric properties of the life events checklist. *Assessment*. 2004;11(4):330-341. 29. Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS. The development of a clinician-administered PTSD scale. *J Trauma Stress*. 1995;8(1):75-90. 30. Bastien CH, Vallières A, Morin CM. Validation of the insomnia severity index as an outcome measure for insomnia research. *Sleep Med*. 2001;2(4):297-307. 31. Johns MW. A new method for measuring daytime sleepiness: The Epworth Sleepiness Scale. *Sleep*. 1991;14(6):540-545. 32. American Academy of Sleep Medicine. *The AASM manual for the scoring of sleep and associated events: Rules, terminology and technical specifications version 2.0.* American Academy of Sleep Medicine; 2012. 33. Faul F, Erdfelder E, Buchner A, Lang A. Statistical power analyses using G* power 3.1: Tests for correlation and regression analyses. *Behav Res Methods*. 2009;41(4):1149-1160. 34. Krakow B, Johnston L, Melendrez D, et al. An open-label trial of evidence-based cognitive behavior therapy for nightmares and insomnia in crime victims with PTSD. *Am J Psychiatry*. 2001;158(12):2043-2047.
2.12 Publication Plan	We plan to submit at least 2 manuscripts close to the end of the funding period to SLEEP and Journal of Traumatic Stress.
2.13 Curriculum Vitae	Included