Study Protocol

Official Title: Can Blocking the Orexin System Enhance Sleep's Benefits to Therapeutic Exposure for PTSD?

NCT number: NCT02849548

Date of the Document: July 7,2016

Approach

Study Team: The highly qualified interdisciplinary study team has significantly contributed to the proposal and will continue to guide the candidate. Thomas Mellman, M.D., primary mentor, is an expert in sleep, PTSD, and pharmacological trials for PTSD and insomnia and advises on all aspects of the clinical trial. Larry Sanford, Ph.D., co-mentor, contributes his expertise in neurophysiology and animal models of PTSD and sleep and advises on all aspects of the animal pilot study. Patrick Forcelli, Ph.D., co-mentor, contributes his expertise in neurophysiology and optogenetic methods and supervises the implementation of the animal pilot study. John Kwagyan, Ph.D., collaborator, contributes his expertise in biostatistics. Akihiro Yamanaka, Ph.D., consultant, contributes his expertise in optogenetic manipulations of orexin neurons using transgenic mice.

Clinical Study Approach: AIM 1: *To examine effects of pharmacologically blocking the orexin system after WNE on sleep, PTSD symptoms, and intersession habituation.*

Participants: Participants will be physically healthy adults (1:1 gender ratio) (age 18 – 55) who meet DSM-5 criteria for PTSD[57] with index trauma exposure within the previous 5 years. Justifications for this include a greater likelihood of remembering the details of the event and our prior finding indicating changes in sleep characteristics over the duration of PTSD.[58] Exclusion criteria include: 1) medical or psychiatric conditions that require consistent use of medication, except for hormonal contraceptives; 2) medical condition that affects sleep; 3) inability to remember most details of the index event; 4) body mass index ≥ 40 (due to very high comorbidity rates of sleep apnea[59]); 5) diagnosis of a sleep disorder other than insomnia including PSG findings of apnea/hypopnea index > 10/hour; 6) consumption of more caffeine than 5 cups of coffee/day equivalent; 7) smoking > 20 cigarettes/day; 8) habitual bedtimes after 2AM, habitual rise times after 9AM, or habitual napping > 1 hour/day; 9) moderate or severe alcohol or drug use disorders within the past year; 10) positive urine toxicology for illicit drugs including cannabis; 11) a diagnosis of psychotic disorders, bipolar disorder, or depression that preceded the onset of PTSD; 12) suicidal ideation with intent to act or with specific plan and intent in the past 6 months [Type 4 – 5 ideation on the Columbia Suicide Severity Rating Scale (C-SSRS)] or history of a suicide attempt; 13) completion of exposure-based therapy targeting the index trauma; 14) pregnancy or breast feeding (All female participants will be required to complete an urine pregnancy test. Sexually active female participants will be required to use a medically acceptable form of birth control); 15) known sensitivity or allergy to an orexin receptor antagonist; and 16) limited ability to read or write English.

Design and Overview (Table 3): This is a randomized, double-blind, placebo-controlled trial examining the effects of suvorexant (Merck & Co., Kenilworth, NJ), a dual orexin receptor antagonist that is FDA approved for insomnia, on sleep and PTSD symptom reduction following WNE. We will employ our successful recruitment strategies, including flyers, outreach activities, and referral from previous participants. Potential participants will initially be screened over the phone or in person, and those who meet initial criteria will be invited to the Clinical Research Unit (CRU) at Howard University to complete a consent procedure, questionnaires, a clinical interview, a physical examination, and urine tests. Participants who meet the selection criteria will be invited to complete two pairs of 30-minute WNE sessions and four overnight PSG recordings [screening, baseline, between WNE sessions (twice)]. Both pairs of WNE sessions will occur at 8PM and 8AM in the following morning with intervening sleep. The second pair will occur one week after the first pair. Four WNE sessions are

Table 3. Study Design

Day	1	2	3	4	5	11	12	18
Consent; Questionnaires	X							
Physical exam	X							
Vital signs	X				X		X	
Urine tests	X							
CAPS (lifetime & past month)	X							
SCID	X							
CAPS (past week)				X		X		X
C-SSRS	X			X		X		X
Alertness scale			X		X		X	
Adverse event assessment	X			X	X	X	X	
WNE (AM)					X		X	
WNE (PM)				X		X		
Suvorexant or placebo				X		X		
PSG		X screen	X baseline	X		X		

needed because the majority of participants in the preliminary study did not achieve remission until after completing the second pair of WNE. Participants will be stratified by gender and randomly assigned to either suvorexant or placebo. After the 1st evening WNE, a 10 mg tablet of suvorexant or placebo will be administered orally 30 minutes before bedtime. If the medication is well tolerated, the dose will be increased to 20 mg at the 2nd administration after the 3rd WNE. The recommended dose is 10mg, and the maximum recommended dose is 20mg.[60] The 1-week CAPS will be administered before the 1st and 3rd sessions and at 1-week follow-up.

Feasibility: The primary mentor's lab has been successfully recruiting, on average, one trauma-exposed participant/week. A pilot study will be conducted during the current KL2 to address potential barriers for recruitment and retention of participants. In the R21 funded study, approximately a half of participants met inclusion criteria and completed at least first two WNE sessions (Fig. 2). Therefore, we expect to enroll 140 participants during the 40-month K01 recruitment period (3.5/month), and ~70 of them would complete at least first two WNE sessions. Based on the previous retention rate, we estimate that 54 participants (27 in each group) would complete the entire protocol. Reasons for dropouts from the R21 study included time conflicts and a family emergency. No participants reported distress related to WNE as a reason for withdrawal.

Assessment: Screening and self-report measures. The initial phone screening will include questions about excluded conditions, trauma exposure, and PTSD symptoms (using the Primary Care PTSD screen,[61] a 4-item screener). The questionnaire package includes a demographic questionnaire, the Life Event Checklist (LEC) [55] to determine the most stressful event (the index trauma), and a sleep questionnaire developed in the mentor's lab to assess habitual sleep schedule and signs of possible narcolepsy.

Medical/physical tests. Vital signs, height, and weight will be measured, and a physical examination will be performed by a physician or a nurse practitioner. Urine toxicology screening (all participants) and a urine pregnancy test (all female participants) will be conducted by a nurse at the CRU.

Clinical interviews. Structured interviews will be conducted by clinically trained staff and will be reviewed weekly in a consensus conference with the candidate (a licensed psychologist) and the primary mentor (a board certified psychiatrist). The CAPS[55] will be administered to assess current (past month and past week) and lifetime PTSD diagnosis and severity associated with the index trauma. The Structured Clinical Interview for DSM-5 (SCID)[62] will be administered to assess current and lifetime psychiatric diagnoses and confirm inclusion criteria. The C-SSRS[63] will be administered at the initial visit to assess suicidal ideation and behaviors in lifetime and past 6 months and at subsequent visits to assess any changes since the previous visit. The PI will be immediately notified if a participant indicates concerning suicidal ideation or behaviors.

Sleep recordings. PSG recordings in the CRU will use a Natus/Embla (Pleasanton, CA) Titanium PSG unit including two central, frontal, and occipital EEG leads, two electrooculograms, chin and limb electromyograms, and an electrocardiogram. Participants will be instructed to go to bed at their habitual bedtime and wake up at 8 AM. Screening for sleep disordered breathing will be performed using the screening night data. Visual scoring of sleep records will be done following the American Academy of Sleep Medicine Manual, Version 2.3.[64] We will calculate standard PSG sleep parameters including total sleep time, WASO, the percentage and the duration of each sleep stage, and REM density using the REMLogic software (Natus/ Embla). Sleep changes from baseline to post-WNE will be computed by subtracting baseline measures from respective measures obtained during sleep following the 1st and 3rd WNE sessions.

Alertness visual analogue scale (VAS). Participants will complete an alertness VAS upon awakening in the morning after PSG recordings. The VAS is a 100 mm horizontal line with a label "very sleepy" on the left end and "very alert" on the right end. Participants will be place a

slash mark on the scale to indicate their alertness at the moment. A morning WNE session will not begin until the participant's alertness level reaches the level he/she indicated in the morning after the baseline PSG recording.

Adverse event assessment. Participants will be queried regarding the presence of any symptoms or concerns before and after the medication administration.

Pulse rate. The pulses will be continuously recorded during the 5-min baseline and the 30-min WNE through a finger pulse transducer of the PowerLab system (ADInstruments, Colorado Springs, CO). Data will be visually inspected using the LabChart software (ADInstruments), and segments with artifacts will be excluded. The average pulse rates for the 5-min baseline and each 2-minute epoch during WNE will be computed. A baseline-corrected highest average pulse rate for each session will be computed by subtracting the session's average baseline pulse rate from the highest average pulse rate in the session. The baseline correction will be performed to correct for circadian influences on pulse rates.[65-67]

Study Medication: Suvorexant, a dual orexin receptor antagonist, is the first and only FDA-approved agent in this class for treatment of insomnia. Over 2,000 patients with insomnia have been exposed to suvorexant in one 4-week Phase IIB, two 3-month Phase III, and one 1-year Phase III trials.[48,49,68] Suvorexant (both 10 mg and 20 mg) reduced PSG-measured WASO and increased total sleep time, sleep efficiency, and REM sleep on the first night and at 4-week follow-up. In the largest trial, 20 mg (non-elderly)/15 mg (elderly) suvorexant increased SWS on the first night in patients with insomnia, and the effect was greater with a higher dose, 40/30 mg.[50] No gender differences were found in its effects on self-reported or PSG outcomes or its safety.[48,60,69] The most common adverse effect was somnolence which occurred in 7% of insomnia patients receiving 20/15 mg, daily for 3 months compared with 3% receiving placebo. Other adverse events included nasopharyngitis (5%) and headache (7%), although these rates were comparable to the rates for those receiving placebo. Only 3% of the 3-month trial participants receiving suvorexant discontinued treatment due to adverse effects, which was comparable to the rate for those receiving placebo. The recommended dose is 10 mg, once daily, and the maximum recommended dose is 20 mg. The prescription information provided by Merck instructs to take the medication within 30 minutes of going to bed and stay in bed for at least 7 hours.[60] Given that suvorexant's effects on SWS were stronger with the higher doses, in this study, the dose will be increased from 10 mg at the 1st administration to 20 mg at the 2nd administration if the participant tolerated the lower dose well. The 2nd dose will remain at 10 mg if the participant had mild to moderate sedation in the morning after the 1st administration. If the participant had significant adverse events (that is rare), he/she will not have the 2nd administration. The CRU nurse and the study staff will monitor participants' alertness level in the following morning, and those who remain at a low alertness level will be prohibited from driving themselves.

Study Medication Administration: Participants will be stratified for gender and randomly assigned to either suvorexant or placebo before the 1st WNE. Suvorexant or placebo will be administered orally after the 1st and 3rd WNE, 30 minutes before the participant's habitual bedtime. If the participant well tolerates 10mg, the dose will be increased to 20mg at the 2nd administration. Participants will have continuous access to research nurses during the sleep recording. In the following morning, a nurse will assess possible adverse effects.

Written Narrative Exposure (WNE): We will use a procedure similar to the one used in the R21 study. Sessions will begin at 8PM and approximately 8AM. The morning sessions will not start until the participant's alertness level reaches the level he/she indicated in the morning after the baseline PSG recording. The participant will sit at a desk in a private room with a facilitator, and a pulse transducer will be attached to the distal of the middle finger of his/her non-dominant hand placed on the desk. After a 10-minute acclimatization period, a 5-minute baseline pulse recording will begin. At the end of the baseline, the facilitator will provide instructions to write in as much detail as possible about his/her index trauma including what

happened, how s/he felt, and what s/he perceived and thought and to use the entire 30 minutes. The facilitator will also instruct the participant to orally report an overall level of distress on a scale from 0 – 100 [subjective units of distress scale (SUDS)] at baseline, every 10 minutes, and at the end of the writing period. The facilitator will remain in the same room during the writing to obtain SUDS scores and to assist and encourage the participant if necessary. At the end of the writing period, if warranted, the facilitator will instruct the participant in relaxation techniques for ≤10 minutes. Participants will not be dismissed until distress is minimal.