MEDICAL MANAGEMENT OF SLEEP DISTURBANCE DURING OPIOID TAPERING (IRB00198426; UG3DA048734-01; NCT03789214)

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1. Abstract

This study will evaluate whether a dual orexin-receptor antagonist approved by the FDA for sleep disturbance, suvorexant (SUVO; Belsomra®), will increase total sleep time in patients with opioid use disorder (OUD) undergoing supervised withdrawal. The scientific premise of this study is based on substantial preclinical and human literature demonstrating that opioids modify the sleep-wake cycle. *Acute* doses of opioids disrupt sleep in animal and human models, and *chronic* opioid exposure produces persistent sleep disturbance in both animal and human models. In humans, chronic opioid use is associated with development of hypoxemia, sleep apnea, and disruptions in the hypothalamic-pituitary-adrenal axis in a manner that impairs sleep. These data are consistent with the fact that many OUD patients report substantial sleep disturbance. SUVO treats sleep disturbance by antagonizing the "wake cycle". In addition there is a substantial preclinical literature shows that orexins influence the mesolimbic reward system that is broadly implicated in addiction. Interactions between the orexin and opioid systems suggest the orexin system could exert a clinically meaningful impact on the course of OUD.

This study is designed as a dose-finding study of SUVO compared to placebo. Briefly, OUD patients seeking supervised withdrawal will be admitted into a clinical research unit and stabilized onto buprenorphine before being randomly assigned to study condition. All participants will then undergo a routine buprenorphine taper, followed by a post-taper phase. Participants will be randomized to receive either placebo, SUVO 20mg, or SUVO 40mg and we hypothesize that one or both doses of SUVO will improve total sleep time relative to placebo. The dose of SUVO identified as most efficacious in this study will be used in a subsequent study. This study is supported by power analyses that were conducted for both Aims 1 and 2. Primary outcomes of this study include total sleep time as measured via an ambulatory electroencephalography (EEG) device, wrist actigraphy, and self-reported sleep as well as abuse liability measures of SUVO. Participants will be referred to ongoing treatment following completion of the study and will be provided with opioid overdose education and Narcan as an additional prevention measure.

2. Objectives (include all primary and secondary objectives)

- Primary Aim 1: Evaluate whether 20mg and 40mg suvorexant, relative to placebo, improves total sleep time among patients undergoing routine opioid withdrawal, assessed via (a) EEG, (b) actigraphy, and (c) self-report.

- Primary Aim 2: Evaluate the abuse liability of 20mg SUVO versus 40mg SUVO relative to placebo using self-report ratings, and secondary measures that include a hypothetical purchase task and drug ratings.
- Secondary Aim 1: Evaluate whether 20mg SUVO and 40mg SUVO decreases self-reported measures of drug effects and craving, opioid withdrawal, concomitant medication use, and self-reported stress; decreased diurnal salivary cortisol and serum cortisol/adrenocorticotropic releasing hormone; and improves treatment retention relative to placebo.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Significance: OUD is a significant public health problem. More than 72,000 Americans died from drug overdose in 2017, the majority of which were opioid-related (Dunn et al., 2013). Individuals who are physically dependent on opioids experience an array of extremely aversive withdrawal symptoms upon opioid-removal, and most opioid treatment approaches are explicitly designed to minimize withdrawal severity. Thus, investigation into opioid withdrawal symptom management is critical for improving OUD treatment outcomes and has broad implications for many thousands of patients. For instance, the majority of the >500,000 people who sought OUD treatment from state-certified addiction treatment facilities in 2016, received supervised opioid withdrawal treatment (also known as detoxification) (Substance Abuse and Mental Health Services Administration, 2016). Below we summarize the limited available literature on this topic to demonstrate that (a) sleep is directly impaired by opioids, (b) the orexin system may underlie sleep disturbance in persons with OUD, and (c) the dual-orexin receptor antagonist SUVO is an ideal medication to treat sleep disturbance in persons withdrawing from opioids.

Sleep is directly impaired by opioids: There is a substantial preclinical and human literature demonstrating that opioids modify the sleep-wake cycle. Acute doses of opioids disrupt sleep in animal (Cronin, Keifer, Baghdoyan, & Lydic, 1995; Gauthier, Guzick, Brummett, Baghdoyan, & Lydic, 2011; Moreton, Roehrs, & Khazan, 1976; Watson, Lydic, & Baghdoyan, 2007) and human models (Dimsdale, Norman, DeJardin, & Wallace, 2007; Howe, Hegge, & Phillips, 1980; Kay, 1975a; Kay, Eisenstein, & Jasinski, 1969), and chronic opioid exposure produces persistent sleep disturbance in both animal (Robert, Stinus, & Limoge, 1999; Young, Moreton, Meltzer, & Khazan, 1975) and human (Dunn, Finan, Tompkins, & Strain, 2018; Kay, 1975b) models. In humans, chronic opioid use is associated with development of hypoxemia, sleep apnea (Charpentier, Bisac, Poirot, Vignau, & Cottencin, 2010; DeVido, Connery, & Hill, 2015; Farney et al., 2013; Mogri, Desai, Webster, Grant, & Mador, 2009; Peles, Schreiber, Hamburger, & Adelson, 2011b; Schwarzer, Aichinger-Hinterhofer, Maier, Vollert, & Walther, 2015; Wang et al., 2005) and disruptions in the hypothalamic-pituitary-adrenal (HPA) axis (Bunce et al., 2015) in a manner that impairs sleep. We know of only two studies that have empirically examined methods for improving sleep in OUD patients; these studies reported no benefit of electrostimulation or acute doses of methadone among patients being withdrawn from opioids (Gossop & Bradley, 1984) or the non-benzodiazepine trazodone in patients maintained on methadone (Stein et al., 2012b). Despite the lack of data, patients undergoing supervised withdrawal who experience sleep disturbance may first be prescribed hydroxyzine, then trazodone, and finally an antipsychotic such as quetiapine (Seroquel) (Pinkofsky et al., 2005).

The orexin system may underlie sleep disturbance in persons with OUD: Orexinergic neurons are located in the lateral hypothalamus and activate a "wake cycle" that suppresses sleep. In addition to their well-known association with sleep, a substantial preclinical literature shows that orexins influence the mesolimbic reward system that is broadly implicated in addiction. Interactions between the orexin and opioid systems suggest the orexin system could exert a clinically meaningful impact on the subjective experience of opioids. A recent study in postmortem human brains found that long-term heroin users had 54% more orexinergic neurons than age/sex matched healthy adults, suggesting that chronic opioid exposure is associated with increased orexin signaling (Thannickal et al., 2018). The proposed study is

significant because it targets a modifiable aspect of OUD (sleep) linked to a neurotransmitter system (orexin) that promotes drug craving and motivation to seek drug.

The dual-orexin receptor antagonist SUVO is an ideal medication to treat sleep disturbance in persons withdrawing from opioids: Suvorexant (SUVO; Belsomra®) is a dual orexin receptor antagonist that is FDA-approved for insomnia. In contrast to benzodiazepines and other sleep aids that promote sleep through sedation, suvorexant SUVO prevents onset of the wake cycle. In clinical trials SUVO significantly increases sleep time, even among otherwise treatment-resistant patients. One within-subject, double-blind cross-over study reported SUVO improved ratings of sleep efficiency, wake after sleep onset, and latency to persistent sleep, as rated by PSG, over a 4-week period (Herring et al., 2012). A subsequent large-scale, Phase III randomized, controlled, double-blind trial reported significant improvements in subjective and PSG ratings of sleep relative to placebo (Herring et al., 2016a). Fewer people on SUVO, relative to other sleep aids, experience next-day sedation (Gotter et al., 2013). Because of this, SUVO has been suggested as a treatment for alcohol use disorder, however there is no controlled research in any substance use disorder population regarding the potential benefit of SUVO for drug or alcohol treatment (Campbell, Marchant, & Lawrence, 2018).

SUVO acute dosing studies have repeatedly shown that sleep architecture changes following a single SUVO dose (Herring et al., 2016b; Sun et al., 2013), and that beneficial clinical outcomes are evident within 1 week (the earliest time point assessed; (Herring et al., 2016a; Herring et al., 2016b). These data suggest that SUVO has a quick onset of action, and are supported by a recent review/meta-analysis of 37 available studies that found SUVO to improve sleep (Kishi, Matsunaga, & Iwata, 2015). EEG analyses have further revealed that, in contrast to the other common sleep aids gabapentin, zolpidem (Ambien), and trazodone (Oleptro), SUVO did not confer negative collateral effects on other transmitter systems (Ma et al., 2014; Snyder et al., 2016). The focused effect of SUVO on the orexin system may contribute to its impressive safety profile; clinical trials and meta-analyses report SUVO is well-tolerated and produces a low rate (<5%) of adverse events (Herring et al., 2016a; Herring et al., 2016b; Kishi et al., 2015), even following 1 year of chronic treatment (Michelson et al., 2014). Examination of SUVO effects on respiration among patients with and without sleep apnea showed no impairment in respiration or SpO2 levels, even when administered at doses twice what is recommended for clinical care (Sun et al., 2016; Uemura et al., 2015). Although SUVO was designated a Schedule IV substance by the DEA based on a study comparing 2-7.5 x the maximum dose of SUVO versus 1.5-3 x the maximum dose of zolpidem (Ambien), the abuse liability ratings from SUVO did not change in a dose-dependent manner (unlike zolpidem). In that study, SUVO also produced lower levels of feeling “high”, and fewer abuse-related adverse events (e.g. euphoric mood) than zolpidem. These data, combined with the absence of reports that SUVO is being diverted or abused, suggest the abuse liability of SUVO is lower than comparable Schedule IV substances. No studies have evaluated SUVO’s profile of effects in OUD patients (Pinkofsky et al., 2005).

Summary: This study is significant not only because it evaluates the efficacy of SUVO for sleep disturbance in OUD patients, but also because sleep disturbance during supervised opioid withdrawal is pronounced and there is a dearth of indicated, effective pharmacotherapies.

4. Study Procedures

a. Study design:

Screening Visits: Participants will be recruited from the community via flyers, newspaper postings, and other media outlets. Screening visits will take place on the Behavioral Pharmacology Research Unit at the Johns Hopkins Bayview Medical Center. Individuals will complete a phone-screen to assess for initial eligibility and will be invited for a clinic-based visit to confirm final eligibility. During this visit, participants will first review an informed consent form with a staff member and discuss the study before

providing voluntary informed consent to participate. Participants will then complete a series of measures to establish study eligibility, including a demographics questionnaire, self-reported opioid use and withdrawal, a past 30-day timeline follow back for drug and alcohol use, assessments of DSM-5 drug and alcohol use disorders, the Stop-Bang questionnaire assessment of sleep apnea, psychiatric functioning (MINI International Neuropsychiatric Interview [Sheehan et al., 1998]), and the Columbia Suicide Severity Rating Scale (Posner et al., 2011). Participants will provide a blood sample that will be tested for complete blood count and comprehensive metabolic panel, provide a urine sample that will be tested for evidence of opioid and other drug use, and pregnancy (when applicable). Either during the Screening or admission day, participants will complete a medical history and physical examination with qualified medical staff to determine final study eligibility. The physical examination will include an electrocardiogram (ECG) to determine if the participant has any heart abnormalities, and the Brief Pain Inventory to quantify current chronic pain issues (Cleeland et al., 1994). Opioid withdrawal scales will be collected at the end of the Screening visit to help confirm opioid physical dependence.

Buprenorphine Induction and Stabilization: Participants will be inducted onto buprenorphine prior to beginning the buprenorphine taper. Induction may occur up to 3 weeks prior to admission to the CRU. Participants will be required to show evidence of opioid withdrawal (as per ratings on the COWS) and will receive incremental doses of buprenorphine throughout the day, up to a maximum of 16mg of buprenorphine on the induction day. The induction protocol will be conducted as clinically indicated, based upon medical team recommendations. To increase comfort during the induction, the medical team may administer the PRN concomitant medications that are approved for the taper protocol as well as clonidine. Participants may then be maintained on buprenorphine as an outpatient for up to 3 weeks before CRU admission. Briefly maintaining participants on buprenorphine will enable the study to retain participants between Screening and CRU admission, as the CRU has restricted access for protocols requiring weekend coverage. Participants who are maintained on buprenorphine as an outpatient will receive blister packages of sublingual buprenorphine for outpatient administration and may receive up to 24mg/day (beginning the day after induction) during this period. During the stabilization period between Screening and Admission, participants will be required to visit the clinic on a weekly basis to exchange blister packages. Participants may receive assistance (e.g., bus tokens) from the study to help facilitate transportation to the BPRU on those days. Any participant receiving >16 mg as an outpatient will be transitioned to 16mg on the CRU admission day. Participants who are inducted onto buprenorphine on the CRU admission day will follow an identical induction procedure and will only receive up to 16mg.

Clinical Research Unit (CRU): Following confirmation of eligibility, participants will be admitted onto a residential CRU that is located on the Bayview Medical Campus. Participants will reside on the CRU for up to 11 days (10 nights) and will be allowed to smoke cigarettes ad libitum in a designated smoking area during their stay. Female participants will provide a sample of blood upon admission that will be analyzed for levels of progesterone and estrogen.

Brief Sleep Hygiene Education: During stabilization, staff will conduct a brief educational session with participants to provide information regarding appropriate sleep hygiene (Doshi et al., 2017) . This session will ensure all participants have the same understanding of healthy sleep behaviors before the taper begins, to minimize the impact that differences in sleep hygiene has, and better isolate the impact of SUVO on study outcomes.

Overdose Education: During the stabilization period, participants will also complete a brief opioid overdose prevention computerized education session (developed by Co-I Dunn under NIDA R21DA035327).

Randomization to Group: Participants will be stratified into experimental group based on (a) baseline Pittsburg Sleep Quality Index (PSQI) (<5/≥5) , (b) peak SOWS ratings during buprenorphine induction (≤10/>10), (c) buprenorphine stabilization dose (<16mg/16mg), and (d) sex (M/F). Randomization will occur via a minimization procedure to balance the distribution of these characteristics

across the experimental groups. Study pharmacist staff, who have no direct participant contact, will oversee randomization and dispensing of study medications.

Taper Phase (4 days): Participants will undergo an open-label, step-wise buprenorphine taper. An open-label phase is necessary because buprenorphine placebo tablets/filmstrips are not available; however, this open-label design feature is of value because it increases the overall generalizability of the study results. **Post-taper Phase (4 days):** Participants will continue study participation for four days (three nights) following buprenorphine discontinuation, to capture the full course of opioid withdrawal.

Study Medications*:* Double-blind study medication dosing will begin on the evening before Taper Day 1. Study medications will either be 20mg SUVO, 40MG SUVO, or placebo, which will be administered prior to bedtime. Though participants will be reminded to practice good sleep hygiene, no contingencies or consequences will be associated with their sleep behavior. This is because our extensive experience suggests that participants who are unable to sleep at night will attempt to sleep during the day; all sleep attempts will be captured by wrist actigraphy and nightly questionnaires and evaluated as outcome data. Placing contingencies on sleep parameters (such as no day-time sleeping) could also prompt attrition.

Upon study completion, participants will be discharged with referral to ongoing OUD treatment and will be provided with take-home dose of intranasal naloxone (Narcan, Adept Pharmaceuticals).

Follow-up: Participants will also complete a follow-up visit approximately 5-10 days after study discharge, during which outcomes including adverse events, suicidality and depressive symptoms, need for additional OUD treatment referral, past 7-day day sleep, and illicit drug use (as assessed via self-report and a urine sample) will be collected.

Study Measures

Objective Sleep Measures:

Sleep Profiler™ Wireless EEG Monitor: The Sleep Profiler™ (Advanced Brain Monitoring, Inc.) is an unobtrusive wireless EEG device that was designed for patients to use in their home sleep environment without the assistance of a professional technician. We will train our research staff and the CRU nursing staff to assist participants with application of the device nightly so we may ensure good measurement fidelity throughout the study. The Sleep Profiler™ runs on a continuous charge for approximately 16 hours and provides three channels of frontal EEG, a pulse rate, and a sensor to detect head movement. The device is lightweight (2.5 oz) and utilizes three proprietary, pre-gelled, self-adhesive, snap electrodes. It can be comfortably applied and strapped to the forehead in 5 minutes and features a built-in impedance check to protect against poor connections, which audibly prompts the user to reaffix the electrodes when impedance is high. Participants will begin wearing the Sleep Profiler™ on Stabilization day 1, which will familiarize participants with the product before they experience withdrawal, and provide baseline data for statistical comparison. Participants will be instructed to affix the Sleep Profiler after receiving their dose of study medication and to remove it upon waking every morning.

Wrist Actigraphy: Participants will wear a triaxial accelerometer (Actigraph wGT3X-BT, Actigraph, LLC) on their non-dominant wrist for the entire duration of study enrollment. Wrist-worn actigraphy has been validated against PSG and provides an acceptable alternative measure of sleep continuity.

Self-report Sleep Measures: Additional self-report measures of sleep will be collected as part of the Primary Study Aims to corroborate quantitative analyses and increase the breadth of sleep data available. These will include measures such as:

1. *Stanford Sleepiness Scale* (Hoddes et al., , 1973) : A 7-point scale, which is a widely-used self-report measure of daytime sleepiness that will be collected on a daily basis.

2. *Daily Sleep Diary*: Participants will be asked to document perceived sleep continuity and quality each morning. This method is widely used as an adjunct to objective measures of sleep (Carney et al., 2012) .
3. *Pittsburg Sleep Quality Index (PSQI;* (Carpenter & Andrykowski, 1998) *):* The PSQI is a widely-used self-reported measure of sleep quality and disturbance over the previous 30 days. It will be used at screening (past 30 day version) and on the final day of this study (related to study days only).

Abuse Liability Measures: Medication abuse liability will be assessed as Primary Aim 3 and will include measures such as:

1. *Study Drug Abuse Liability Ratings:* The abuse liability of the blinded study drug will be assessed each morning during the taper and post-taper phases by asking participants to rate questions pertaining to drug liking and drug effects on a 0-100 point visual analogue scale, as well as the perceived street value of the study drugs.
2. *Hypothetical Opioid Purchase Task:* This is a validated method for assessing the abuse liability of opioids as well as other drugs of abuse (Aston, Metrik, & MacKillop, 2015; Jacobs & Bickel, 1999; Kiselica, Webber, & Bornovalova, 2016) .

Opioid Withdrawal Measures: Withdrawal symptom severity will be evaluated daily, using measures such as:

1. *Visual Analog Ratings*: Self-report ratings of drug effects that include withdrawal, nausea, sick, like how I feel, sleepiness, quality of sleep, and pain will be collected on a 0 (not at all) to 100 (extremely) scale.
2. *Subjective Opiate Withdrawal Scale (SOWS)* (Handelsman et al., 1987) : A 16-item widely-used self-report measure that rates opioid withdrawal symptoms on a 4-point Likert scale.
3. *Clinical Opiate Withdrawal Scale (COWS)* (Wesson & Ling, 2003) : An 11-item scale that includes some self-report items (e.g., muscle aches, nausea) and observer-rated measures of opioid withdrawal rated on unique ordinal scales.

Secondary Study Outcomes: These measures are a comprehensive range of pharmacologically specific and general questions, and are the FDA standard for the measurement of drug effects in humans. We will use measures such as:

1. *Vital Signs*: Physiological measurements of blood pressure, pulse, respiration, and oxygen saturation will be measured several times daily.
2. *Pupil Diameter*: Physiological measure of autonomic nervous system activity that is a hallmark metric of opioid withdrawal. Will be assessed several times daily using a hand-held, ambulatory pupilometer (Neuroptics; Irvine CA).
3. *Retention in Treatment*: Retention will be evaluated as number days completed (continuous) and being present on the final day of the study (yes/no).
4. *Opioid agonist/antagonist scale:* A 37-item self-report measure of opioid effects on a 5-point Likert scale.

Drug Specific Measures: Secondary aims will assess a variety of domains related to the study medication using measures such as:

1. *Drug Identification*: Upon study discharge, participants will indicate whether they believe they are receiving SUVO or placebo.
2. *Drug Satisfaction*: Upon study discharge, participants will be asked whether they would recommend the study medication (yes/no) to a family or friend experiencing sleep impairment while withdrawing from OUD.
3. *Adverse Event Ratings:* We will follow standard FDA guidelines regarding recording of adverse events and will document all events on a daily basis. AEs will be summarized descriptively by severity and relatedness.

4. *Neurocognitive Test Battery*: Participants will complete a daily battery of cognitive tests to assess whether the study medication and/or sleep impairment is associated with changes in cognitive function and psychomotor agility during the course of withdrawal. The battery will consist of the Circular Lights test of fine motor movement, the Psychomotor Vigilance Task, the Digit Symbol Substitution Task (DSST) measure of psychomotor speed/pattern recognition, and the N-back measure of working memory. These tests were selected because they can be completed quickly, are not prone to practice effects, produce robust, reliable results, and have not been aversive to previous patients during opioid withdrawal.
5. *The Hamilton Depression scale (HAM-D)*: The HAM-D is a structured clinical interview that will be used multiple times throughout the study to provide a continuous measure of depressive symptomatology (Hamilton, 1960).

Stress and Craving Measures: Several brief and validated measures (such as those below) will be used to inform potential mechanism underlying effects and whether prospective studies to examine these effects more thoroughly are warranted.

1. *Visual Analog Ratings*: Self-report ratings of opioid craving (e.g. How much do you want to use right now? How much do you want to avoid using right now? How much control would you have over using if someone offered you opioids right now?) and stress (e.g. How stressed do you feel right now? How much is opioid withdrawal contributing to your stress?)
2. *Diurnal Cortisol*: Salivary cortisol will be collected several times daily. Diurnal cortisol is a measure of HPA-axis function that affects the sleep-wake cycle (Edwards, Evans, Hucklebridge, & Clow, 2001) .
3. *Additional HPA-axis Measures:* One blood sample will be taken during the stabilization, withdrawal, and post-withdrawal periods to measure change in adrenocorticotropic hormone to cortisol ratios. These measures have been associated with treatment outcomes in other substance using populations including cocaine use disorder (Sinha, Garcia, Paliwal, Kreek, & Rounsaville, 2006) .

b. Study duration and number of study visits required of research participants.

The entire study will consist of one screening visit and a residential stay over the course of 11 days and 10 nights. All study activities will take place at the BPRU and the Bayview CRU.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

The only blinded medication in this study is SUVO. Since this is the medication of interest, participants will be blinded to ensure study rigor and assess the utility of SUVO to treat sleep disturbance compared to placebo. The buprenorphine taper and concomitant medications will not be blinded in order to mimic the real-world experience of supervised opioid withdrawal and increase ecological validity.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

Routine care for sleep disturbance during opioid withdrawal includes medications such as trazodone, which are not FDA approved for sleep (but commonly used). SUVO is an ideal medication for sleep disturbance in this population. Participants currently taking benzodiazepines for sleep disturbance will not be included in this study. Study participation will be stopped if participants opt out or if study physicians determine that it is unsafe for participants to continue in the study (at any time, including in serious adverse events).

e. Justification for inclusion of a placebo or non-treatment group.

Placebo sleep medication will be utilized to rigorously assess the efficacy of SUVO in OUD patients undergoing supervised withdrawal. This is necessary for the scientific integrity of the study. Patients

experiencing persistent sleep disturbance might experience discomfort, but will not be at increased risk for serious adverse events.

f. Definition of treatment failure or participant removal criteria.

Participants will be removed from the study if they opt out or if the medical team determines it is not safe to continue in the study or if they request to discharge from the study. Additional stopping rules will include not abiding by study policies and procedures, or engaging in behaviors towards staff or other participants that are abusive. Finally, development of an intercurrent illness or condition that changes the participant's risk profile may result in a medically-related discharge from the study.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

Upon study completion, participants will be discharged with referral to ongoing OUD treatment. We have relationships with several local treatment providers and participants will be referred to a treatment that best matches their recovery goals. As a safety measure, participants will complete an overdose prevention training module prior to randomization and be discharged with internasal naloxone (Narcan).

5. Inclusion/Exclusion Criteria

Inclusion Criteria:

- Aged ≥18 years old
- Meets DSM-5 criteria for OUD with evidence of physical dependence on opioids.
- Provides a urine sample that tests positive for opioids.
- Seeking treatment to stop using illicit opioids.
- Willing to comply with the study protocol.
- Have no clinically significant chronic medical or surgical disorders or conditions that are judged by the investigators to prevent participation.

Exclusion Criteria:

- Seeking or currently enrolled in methadone or buprenorphine maintenance treatment for OUD
- Pregnant or breast feeding.
- Have evidence of physical dependence on alcohol or benzodiazepines that requires medical detoxification.
- Have a known allergy to the study medications.
- Past 30-day prescribed use of suvorexant or benzodiazepines for the indication of insomnia.
- Current use of an SSRI or MAO inhibitor for depression or insomnia, or other medications that are contraindicated with suvorexant.
- Current narcolepsy, restless leg syndrome, or sleep paralysis.
- High risk for current sleep apnea as assessed via the Stop Bang questionnaire.
- Current major depressive disorder.
- Past year suicidal behavior as assessed via the Columbia Suicide Severity Rating Scale
- Severe hepatic or renal impairment, defined as:
    - AST or ALT >3x ULN.
    - Total Bilirubin >2x ULN.
    - Creatinine >1.5x ULN.
- Have circumstances that would interfere with study participation (e.g., impending jail).

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

Suvorexant (SUVO): SUVO is FDA-approved for the treatment of insomnia and is an ideal candidate for evaluation because it is intended for PRN administration, improves sleep architecture after a single dose (Herring et al., 2016b; Sun et al., 2013) , and does not cause a withdrawal syndrome after abrupt discontinuation even when it has been administered chronically for several weeks (Herring et al., 2016b). This study utilizes two doses of SUVO (20 and 40mg) to evaluate which dose has a superior risk/benefit profile, although we do not anticipate a high rate of adverse events for either dose. The most effective dose can then be used in future clinical trials as well as in practice for the treatment of sleep disturbance during opioid withdrawal. Participants will be given their medication dose in two weight and color-matched capsules, containing either two 20mg SUVO (40mg dose), two 10mg SUVO (20mg dose), or two placebo capsules. As an added precaution, participants will be allowed to reduce their dose from two to one capsule (representing a 50% dose decrease) if they experience negative side-effects and would prefer a lower dose.

Buprenorphine: Buprenorphine is FDA-approved for the treatment of OUD and it will be used according to that indication in this study. The buprenorphine stabilization and taper will be open label. Participants will be stabilized on buprenorphine for a maximum 3 week period before study admission, and will then complete a 3-day stabilization period (e.g., 8-16mg/day) and a 4-day step-wise taper. These approaches are standard clinical practice. This study utilized the open label taper approach in order to increase ecological validity of the supervised withdrawal paradigm.

Concomitant Medications: Consistent with standard clinical practice treatment, the following concomitant medications will be available to patients upon request: ibuprofen, acetaminophen, loperamide, milk of magnesia, and simethicone. Clonidine may be provided during the induction period only. Concomitant medications introduce a necessary confound in opioid withdrawal research because they reduce the withdrawal symptom severity that is being evaluated as part of the primary study outcomes. However, our considerable experience with opioid withdrawal studies suggests that provision of some additional supportive medications is necessary to prevent treatment attrition. Following randomization to experimental group, patients will not receive additional sleep aids or clonidine. Concomitant medication use will be PRN and compared across groups as an outcome.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

Suvorexant (SUVO): Suvorexant is approved by the FDA for the indication of insomnia at a 10mg and 20mg dose, so an IND will be requested from the FDA for the doses (20mg, 40mg) proposed in this trial. The proposed 40mg dose is being evaluated because suvorexant has a broad therapeutic window, persons with OUD might have increased orexin signaling, as evidenced by postmortem studies citing 54% more orexinergic neurons in the lateral hypothalamus of persons with OUD compared to healthy controls, and because sleep disturbance during opioid withdrawal is severe and- as of yet- no sleep-promoting pharmacotherapies have been shown to be effective in human opioid withdrawal studies.

Suvorexant has been examined in humans at doses up to 240mg and has been shown to produce minimal side effects (Belsomra product label). Several phase III trials have been conducted to support suvorexant's approval. The first trial evaluated 10mg, 20mg, 40mg, 80mg doses (active N=243, placebo N=249) in persons with insomnia and reported dose-dependent effects on outcomes, with 10mg doses producing minimal improvement relative to placebo and higher doses producing larger magnitude improvements on numerous objective sleep measures (Herring et al., 2012). However, inspection of the data suggested that, whereas large differences existed between the 10, 20, and 40mg doses, only small improvements were gained by increasing the dose beyond 40mg to 80mg. A subsequent phase III trial in persons with insomnia reported that suvorexant 40mg (N=322) relative to placebo (N=162) was effective at reducing insomnia and

produced a low rate of adverse events (69% vs. 64%, respectively) and SAEs (5% vs. 7%, respectively) following 1 year of continuous dosing (Michelson et al., 2014). Two final phase III trials were conducted in persons with insomnia to further examine the effectiveness of the 20mg (N=493) and 40mg (N=770) suvorexant doses relative to placebo (N=767). Participants used suvorexant daily for 3 months, and results showed dose-dependent improvements in numerous objective sleep outcomes relative to placebo and a low rate of SAEs (0.6%, 0.8%, 2.1% for the 20mg, 40mg, and placebo doses, respectively) (Herring et al., 2016). The NDA for suvorexant indicates that Merck intended to request the 40mg dose be approved, but decided to reduce the dose range to 10mg and 20mg because the FDA had just published concerns about next-day somnolence related to the sleep aid zolpidem (Ambien), which is not an orexin-antagonist. Thus, the FDA was not asked to rule on the safety or efficacy of 40mg suvorexant. Existing data support the evaluation and safety of the 40mg dose. This approach will help ensure that any lack of therapeutic benefit was not due to suvorexant doses that are below the therapeutic threshold in this population. This strategy is consistent with seminal trials evaluating suvorexant, and will also provide an opportunity to determine whether suvorexant may confer beneficial effects on other opioid-related outcomes, such as drug craving.

7. Study Statistics

a. Primary outcome variable.

The first primary outcome for this study will be total sleep time during opioid withdrawal as determined by EEG, and supplemented by actigraphy and self-report.

The second primary outcome for this study is abuse liability, which will be assessed via next day measures of Drug Liking measured on a 0-100 point VAS.

b. Secondary outcome variables.

(1) Secondary outcomes from the Sleep Profiler EEG will include measures of sleep continuity and architecture
(2) Secondary actigraphy outcomes will include sleep and activity-related outcomes
(3) Secondary self-report sleep ratings will include self-reported sleep measures
(4) Opioid withdrawal severity, assessed via the subjective opiate withdrawal scale.
(5) Other secondary outcomes include a hypothetical purchasing task, other self-report VAS measures of abuse liability (e.g. drug effect, good effect, bad effect, perceived drug value), self-reported measures of drug craving, VAS opioid withdrawal, stress; diurnal cortisol; vital signs; and retention in treatment.

c. Statistical plan including sample size justification and interim data analysis.

Power Analyses: In order to support the planned 2 and 3 group analyses (comparing 20mg SUVO, 40mg SUVO, and placebo), we used G-power to derive sample sizes from previously reported effect sizes in clinical trials on SUVO and hypothetical opioid purchase task data; both displayed large effect sizes (≥0.70). A total sample size of 36 participants (12 per group) would provide 95% power to detect an effect size of 0.70 for difference in total sleep time (Primary Aim 1) and difference in the opioid demand curve (Secondary Aim 1). A study on the abuse liability of SUVO, zolpidem, and placebo in non-OUD patients (Schoedel et al., 2016) reported a medium to large effect size on drug liking (0.45), suggesting a total sample size of 34 would provide 90% power to detect an effect size of 0.45 for Primary Aim 2. To protect against participant drop out, we are proposing to enroll 15 participants per medication group (total N=45).

Analyses: All Primary Outcomes (total sleep time, opioid withdrawal severity, and abuse liability) will be compared as a function of group (20mg SUVO, 40mg SUVO, and placebo; or SUVO [collapsed] vs placebo) and phase (taper vs. post-taper), as well as group by day (7 nights) using 2-factor Proc Mixed analyses with Tukey posthoc testing. Both peak values and Area-under-the-curve (AUC) values of total sleep time, SOWS scores, and Drug Liking

will be derived for (a) the entire study, (b) the taper period, and (c) the post-taper period. These outcomes will be compared as a function of group and group x phase using independent groups t-tests and ANOVAs with Tukey post-hoc for pairwise comparisons. If data does not meet ANOVA assumptions, mixed model regressions will be used.

Secondary outcomes from the Sleep Profiler EEG may include measures of sleep continuity (sleep latency, sleep efficiency [total sleep time/time spent in bed], wake after onset [WASO], number of awakenings) and architecture (time spent in stage 1, stage 2, stage 3, and rapid eye movement [REM] sleep). (b) Secondary actigraphy outcomes may include wake after sleep onset (WASO), time spent napping, number of naps, and total activity. (c) Secondary self-report ratings may include subjective WASO, VAS sleepiness and quality of sleep, and Stanford Sleepiness Scale score. **Analyses**: All outcomes will be compared as a function of group (20mgSUVO, 40mg SUVO, and placebo) and phase (taper vs. post-taper), as well as group by day (7 nights) using 2-factor Proc Mixed analyses with Tukey posthoc testing. Area-under-the-curve (AUC) values for the entire study and the taper and post-taper periods will then be derived and compared as a function of group and group x phase using independent groups t-tests and ANOVAs with Tukey post-hoc for pairwise comparisons. If data does not meet ANOVA assumptions, mixed model regressions will be used.

Secondary actigraphy outcomes may include wake after sleep onset (WASO), time spent napping, number of naps, and total activity. Secondary self-report ratings may include subjective WASO, visual analogue scale (VAS) sleepiness and quality of sleep, and Stanford Sleepiness Scale score. All outcomes will be compared as a function of group (20mg SUVO, 40mg SUVO, and placebo) and phase (taper vs. post-taper), as well as group by day (7 nights) using area-under-the-curve (AUC). The taper and post-taper periods will then be derived and compared as a function of group and group x phase using independent groups t-tests and ANOVAs with Tukey post-hoc for pairwise comparisons. If data does not meet ANOVA assumptions, mixed model regressions will be used.

Secondary measures will be additional ratings on the hypothetical purchase task, SOWS and VAS ratings of opioid withdrawal, VAS ratings of abuse liability, self-reported craving, self-reported stress, perceived drug value, and diurnal salivary cortisol (measured via AUC values and mean daily cortisol) and cortisol/ACTH ratios. Purchase task data will be fit to opioid demand curves for comparison. **Analyses:** All outcomes will be compared as a function of group (20mg SUVO, 40mg SUVO, and placebo) and phase (taper vs. post-taper), as well as group by day (7 nights) using area-under-the-curve (AUC). The taper and post-taper periods will then be derived and compared as a function of group and group x phase using independent groups t-tests and ANOVAs with Tukey post-hoc for pairwise comparisons. If data does not meet ANOVA assumptions, mixed model regressions will be used. Exploratory analyses will include linear and multivariate regression models to examine the relationship between measures of sleep, stress, opioid withdrawal, and craving. Logistic regression will be used to examine the relationship between sleep, stress, opioid withdrawal, and craving on the likelihood of treatment attrition.

d. Early stopping rules.

Patients will discontinue their study participation if they request to be discharged, have a serious adverse event, or if the study physicians decide it is in the patient's best interest to be removed from the study. All patients will be discharged with naloxone, opioid overdose education, and referral to outpatient OUD treatment.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

1. Risk associated with suvorexant (Belsomra®): Suvorexant is a Schedule IV dual orexin antagonist that is FDA-approved for the treatment of insomnia. Suvorexant is 82% bioavailable and has a Tmax of 2 hours. Tmax can be delayed by food though this does not impact the Cmax. It is extensively metabolized by the liver through CYP3A enzymes. The elimination half-life is 12 hours, and it is excreted through both renal (23% unchanged) and fecal (66%) means. Suvorexant is contraindicated with other CNS depressants and alcohol and strong CYP3A inhibitors. It is rated pregnancy category C, indicating insufficient data available to make determination for human subjects. Suvorexant is contraindicated in patients with narcolepsy, patients with recent suicidal behavior, or patients with severe hepatic impairment. There is no evidence of potential overdose and a toxic dose has not been established. Clinical trials that administered up to 240mg of suvorexant reported no overdose effects, though there was a dose-dependent increase in the frequency and duration of next day somnolence. As per product label, most common side effects are sleepiness/drowsiness (7% of people), headache (7%), dizziness (3%), diarrhea (2%), dry mouth (2%), upper respiratory infection (2%), abnormal dreams (2%), and cough (2%). Serious adverse effects include sleep paralysis (7%), somnolence (7%), and worsening of depression or suicidal ideation.

2. Risks associated with buprenorphine/naloxone**:** Participants in this study will be maintained on buprenorphine/ naloxone briefly before beginning a 4-day buprenorphine/naloxone taper. Buprenorphine is Schedule III FDA-approved medication that is approved for the indication of opioid withdrawal treatment. Participants in this study will receive the generic sublingual tablet version of this product (which also has naloxone). Buprenorphine is partial opioid agonist/antagonist at the opioid mu/kappa receptors (respectively), has a low ceiling on its agonist effects, and a slow dissociation from the receptors that results in a 26-hour elimination half-life. There is nothing experimental about the use of buprenorphine/naloxone use in this study. All participants will receive the same buprenorphine/naloxone detoxification schedule, and the highest potential dose (24mg) is well below what can be administered for use on a daily basis (32mg). Buprenorphine/naloxone has very few contraindications, and is not recommended for patients with respiratory distress (such as acute or severe bronchial asthma, or respiratory depression), patients with a known allergy to buprenorphine, or patients with history of cardiac problems such as long QT syndrome or severe hypotension. It is contraindicated for use with the opioid antagonist naltrexone or other opioid agonists. It is rated in pregnancy category C, therefore all women who are pregnant or breastfeeding will be excluded from study participation. Buprenorphine/naloxone's noted side effects are minimal and rare (hyperhidrosis 14%, abdominal pain 11%, constipation 12%, nausea 15%, headache 37%, insomnia 14%) and overlap significantly with known opioid withdrawal symptoms (e.g., abdominal pain, nausea).

3. Risk associated with opioid withdrawal: It is expected that participants will experience some level of opioid withdrawal as part of this study. Symptoms of opioid withdrawal include nausea, diarrhea or stomach cramping, muscle aches and pains, yawning, sweating, pupil dilation, minor increases in blood pressure, and runny nose/tearing eyes.

4. Risk of opioid overdose: Patients are at an increased risk of experiencing an opioid overdose whenever their tolerance to opioids has decreased. This includes completion of an opioid detoxification (or leaving prison/jail). The reason for this increased risk is really related to patient knowledge of how their tolerance contributes to their opioid use, and patients who are not aware that their tolerance has decreased and relapse to opioids by using the same dose they were using before they entered treatment are most susceptible to an opioid-related overdose. 5. Risk associated with clonidine: Patients may receive clonidine during the induction period only to assist with the transition from illicit opioids to buprenorphine/naloxone. Clonidine will be administered per clinical recommendation and this study expects to use it in only a very small number of patients. The largest risk associated with clonidine is hypotension (experienced in 44.8% of patients). Up to 38% of patients may also experience symptoms related to sedation, fatigue, and/or. Fewer than 10% of patients experience symptoms related to GI upset (nausea, constipation), insomnia, respiratory, neurologic, or psychiatric complications. Clonidine has few contraindications, however given that it

reduces blood pressure will not be administered to participants whose blood pressure is <80/60, however we expect this to be rare because hypertension is a symptom of opioid withdrawal.

b. Steps taken to minimize the risks.

Adverse events will be assessed daily. The safety of participants is a priority of our research unit. The largest potential risks to participants on SUVO are worsening of depression and/or sleep paralysis. We will exclude any participant with current major depressive disorder, past year suicidal behavior, or self-reports of current sleep paralysis. Medical team members will be consulted about adverse events and we will follow all reporting guidelines. In the event of an SAE, appropriate courses of action may include observing the participant until the parameters return to normal or transferring the participant to the Emergency Department (ED). Our research unit, the location in which all study sessions will be conducted, is located across the street from the Johns Hopkins Bayview Medical Center (JHBMC) ED. Participants who can walk will be escorted to the ED by a study staff member. If there is any question in a participant's ability to walk safely then 911 will be called to have an ambulance dispatched for the participant.

Given the small sample size, the relatively short study duration, and the fact that medications are being administered as clinically-indicated, we are not planning an interim analysis.

c. Plan for reporting unanticipated problems or study deviations.

Adverse events may be identified by a member of the research staff, the Principal Investigators, or study co-investigators. The PI will be responsible for consulting a medical team member about adverse events The PI and research staff will meet on a weekly basis to review safety monitoring data and adverse events and to ensure that any safety concern has been addressed by medical staff and has been recorded appropriately.

All SAEs will be reported to the JHM IRB within 3 working days after a study PI learns of the event. In addition, the study PI will notify the study co-investigators, the NIDA Program Official, and the FDA (if applicable). The PI will coordinate dissemination of subsequent information obtained relating to the death (e.g., autopsy report, hospital records, toxicological analyses).

The Johns Hopkins IRB will be provided with an annual summary of AEs and SAEs as part of the continuing review**.** If any SAEs requires a change to the protocol or consent form, the PI will make those changes promptly and submit the revised documents to the JHM IRB and appropriate other agencies.

Important adverse events that are unanticipated, including pregnancy, will be reported to the Johns Hopkins IRB within 10 working days. If the important adverse events requires changes to the protocol or consent form, the PI will make those changes promptly and submit the revised documents to the IRB and appropriate other agencies.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Consistent with these regulations a signed authorization will be obtained that informs each subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

e. Financial risks to the participants.

There are no financial risks to the patient.

9. Benefits

a. Description of the probable benefits for the participant and for society.

This study will increase our understanding of the association between sleep and opioid withdrawal symptoms, the degree to which sleep impairment contributes to opioid treatment outcomes, and the degree to which a novel FDA-approved medication (suvorexant) with low abuse liability, high safety profile, and immediate onset of action has on sleep impairment during opioid withdrawal. This will be the first study to examine this medication in opioid use disorder (OUD) patients, the first to examine any sleep pharmacotherapy with OUD patients during a withdrawal procedure, and the first to use a rigorous unobtrusive, wireless, objective EEG monitor to collect sensitive objective data regarding sleep continuity and architecture. These results will be rigorous and transparent and will advance our understanding of the role sleep may play in OUD and the value of evaluating the orexin system's role in OUD more broadly, to ultimately provide an empirically-supported way to address the opioid epidemic.

10. Payment and Remuneration

a. Participants will earn $30 for the screening visit. Participants who complete the study will earn $100 per day for a total of $1100. Participants will also earn an adherence bonus of $30/day (up to $300) for wearing the wireless EEG device throughout the night. The total maximum payment is $1430 (See Payment Table).

Payment Schedule	**Daily Payments**	**EEG Bonus**
Screen	$30	-
Day 1	$100	-
Day 2	$100	$30
Day 3	$100	$30
Day 4	$100	$30
Day 5	$100	$30
Day 6	$100	$30
Day 7	$100	$30
Day 8	$100	$30
Day 9	$100	$30
Day 10	$100	$30
Day 11	$100	$30
Follow-up	$30	-
Total	**$1160**	**$300**
Maximum Payment		**$1460**

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

The participants in this study will not pay for any aspect of study participation. All study medications, residential treatment costs, and staff support is paid through the NIHA grant **UG3DA048734-01.**

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