EVALUATING THE ROLE OF THE OREXIN SYSTEM IN CIRDADIAN RHYTHMS OF SLEEP AND STRESS IN PERSONS ON MEDICATION-ASSISTED TREATMENTS FOR OPIOID USE DISORDER (IRB00223942; U01HL150835; NCT04287062)

Protocol

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1. Abstract

For individuals with moderate to severe opioid use disorder (OUD), medication-assisted treatments (MATs) such as buprenorphine, methadone, and extended-release naltrexone (XR-NTX) are the gold standard in initiating and maintaining long-term recovery. Still, many patients struggle with persistent sleep disturbance and stress reactivity in the early stages of recovery, which drive relapse behaviors. The scientific premise of this study is based on a rich preclinical literature demonstrating that increased orexin signaling disrupts sleep, increases stress via the hypothalamic-pituitary-adrenal axis (HPA-axis), and drives drug seeking behaviors in rodent models. The proposed study will determine whether the FDA-approved sleep medication, suvorexant (SUVO)—a dual orexin-receptor antagonist—improves sleep continuity and decreases diurnal measures of stress, and whether improvement of sleep/stress processes translates to improved OUD treatment outcomes including reduced opioid relapse. This study will recruit persons with OUD who have been abstinent from illicit opioids for at least 2 weeks, report sleep disturbance, and are utilizing a stable dose of buprenorphine, oral methadone, or XR-NTX (N=200). The study will consist of baseline measurements for 7 days (week 0) followed by randomization to either 20mg SUVO or placebo for an 8-week, double-blind randomized-controlled trial. Participants will undergo daily ambulatory monitoring of sleep and daytime activity throughout the study using wrist-worn actigraphy and electronic sleep diaries (weeks 0-8). Moreover, participants will undergo more intensive Data Bursts during study weeks 0 (baseline), 1, 4, and 8, which consist of four-times-daily ecological momentary assessments (EMA) of self-reported stress, craving, and affect, as well as diurnal salivary cortisol collection. Primary analyses 1 and 2 examine the effect of SUVO on total sleep time (TST), wake after sleep onset (WASO), and diurnal self-reported stress and separately in patients on MAT. Primary analysis 3 examines the effect of TST, WASO, and diurnal self-reported stress and salivary cortisol on opioid relapse, across MATs. Exploratory analyses include the effect of SUVO on opioid relapse and treatment retention, and the effect of MAT status on TST, WASO, and diurnal self-reported stress and salivary cortisol within the placebo condition. The proposed study will fill critical gaps in our understanding of the role of the orexin system in sleep disturbance and circadian rhythms of stress that impact OUD recovery.

2. Objectives

Primary Aims 1 and 2: Evaluate whether SUVO increases TST and decreases WASO (Aim 1), and decreases diurnal measures of stress (Aim 2) among participants on MAT. *Hypotheses. Relative to placebo, SUVO will increase TST, decrease WASO and decrease ambulatory measures of stress.* The Primary Outcomes for these aims are mean weekly TST and WASO in minutes, measured by actigraphy, and mean weekly diurnal self-reported stress, assessed via within-day area-under-the-curve (AUC) for Perceived Stress Scale (PSS-4) Total Score, in weeks 0 (baseline), 1, 4, and 8 of the study. Analyses: Mixed-effects models will be conducted for the entire sample and separately for each MAT group. The primary effect of interest in each model will be the Medication (SUVO vs. Placebo) X Time (Weeks 0 [baseline],1,4,8) interaction. Thus, we will regress the outcome (TST, WASO or PSS-4) on Medication, Time, and the Medication X Time interaction.

Primary Aim 3: Determine the association between sleep continuity, diurnal stress, and opioid relapse in both MATs, independent of the effect of SUVO. *Hypotheses. In patients on MATs, increased sleep continuity and decreased diurnal stress will be linearly associated with increased percent negative opioid urine drug screens over the course of the study.* The Primary Outcome for this aim is percent opioid negative urine drug screens in weeks 0-8. Analyses: In the first model, we will regress percent of opioid negative urines on TST, Time, and the interaction of TST X Time, along with the covariates. Separate models will be run substituting TST for WASO, PSS-4, and cortisol.

Exploratory Aim 1: Evaluate whether SUVO relative to placebo improves treatment outcomes in persons on MATs. The Primary Outcomes for this aim are percent opioid negative urine drug screens in weeks 1-8 and length of treatment retention in days. The secondary outcome is craving, assessed via mean weekly AUC VAS scores for "urge to use right now" in weeks 1-8. Analyses: To assess the effect of SUVO versus placebo on percent opioid negative urine drug screens or VAS craving, regardless of MAT group, a mixed effects model will be used with the Medication (SUVO vs. Placebo) X Time interaction as the primary effect of interest. For the effect of SUVO versus placebo on treatment retention, we will use interval censored survival analysis.

Exploratory Aim 2: Determine the effects of MAT on TST, WASO, and diurnal measurements of stress in standard MAT treatment. Primary Outcomes for this aim are mean weekly TST and WASO in minutes, measured by actigraphy, mean weekly diurnal self-reported stress, assessed via within-day AUC for PSS-4 Total Score, and mean weekly diurnal salivary cortisol, assessed via within-day AUC for salivary cortisol (μg/dL), in weeks 0 (baseline), 1, 4, and 8 of the study. Analyses: This sub-analysis will be conducted only among participants assigned to Placebo. The primary effect of interest in each model will be the MAT Group (Buprenorphine vs. Methadone vs. XR-NTX) X Time (Weeks 0 [baseline],1,4,8) interaction. Thus, we will regress the outcome (TST, WASO, PSS-4, cortisol) on MAT, Time, and the MAT X Time interaction.

3. Background

The opioid crisis continues to devastate the lives of countless people and communities across the United States. More than 72,000 Americans died from drug overdose in 2017, the majority of which were opioid-related (National Center for Health Statistics, 2018). Chronic relapse is one of the defining features of OUD (Goldstein & Volkow, 2002; Volkow & Li, 2004), which is driven in part by negative reinforcement associated with opioid withdrawal (Dunn et al., 2018; Koob & Volkow, 2010; Koob, 2013) and post-withdrawal sequela (Koob, 2013; Volkow & Li, 2004). To address the high incidence of negative treatment outcomes for OUD, public health officials are advocating for the utilization of medication-assisted treatments (MATs) as a frontline approach to address the ongoing opioid crisis (Collins, Koroshetz, & Volkow, 2018; Volkow, Frieden, Hyde, & Cha, 2014). MATs consist of medications that act directly on the mu-opioid receptor coupled with counseling services to address the numerous behavioral manifestations of OUD. The full mu-opioid receptor agonist, methadone (Sees et al., 2000; Strain, Stitzer, Liebson, & Bigelow, 1993), and the long-acting mu-opioid receptor antagonist, XR-NTX (Krupitsky et al., 2011), are effective treatment options for OUD. Despite the clinical utility of these MATs, patients utilizing methadone or XR-NTX are still at high risk of opioid relapse, especially in the early stages of abstinence from illicit opioids (Connery, 2015). In the ongoing effort to mitigate this risk among persons with OUD, investigations into the putative mechanisms of opioid relapse in the context of MATs are desperately needed.

A recent FDA public meeting that included patients with OUD identified sleep disturbance as a primary contributor to treatment attrition (Food and Drug Administration, 2018). Moreover, there is a well-established link between both sleep and stress, as well as stress and negative treatment outcomes for OUD

(Koob, 2008; Sinha, 2007; Sinha, 2008). Little is known, however, regarding the role of sleep disturbance and dysregulated circadian rhythms of stress in persons in early OUD recovery, and how different forms of MATs might influence these processes. Despite a robust preclinical literature documenting the relationship between the orexin system and sleep, stress, and drug seeking behaviors, there is no published research on the role of the orexin system in the human experience of OUD recovery. SUVO is an ideal pharmacological probe of the orexin system in humans because it is FDA-approved and currently available on the market, has an excellent safety profile, and reliably improves sleep disturbance in other clinical populations (Sun et al., 2013; Sun et al., 2015).

4. Study Procedures

a. Study design:

PROJECT OVERVIEW: This U01 aims to evaluate the role of the orexin system in sleep disturbance and circadian rhythms of stress that might impact OUD relapse in persons on MATs. Assessment of intermediate sleep- and stress-related processes will be collected in real time over the course of an 8-week trial of SUVO versus placebo. We will enroll OUD patients with at least 2 weeks of opioid abstinence (N=200) and who are maintained on either buprenorphine, XR-NTX, or methadone. Within each MAT, we will randomize patients to either 20mg SUVO or placebo. Based on our extensive work with these MAT populations, we expect a 20% treatment attrition rate which will result in N=160 completers in the entire study. XR-NTX and buprenorphine patients will be recruited from and treated at Ashley Addiction Treatment. Methadone patients will be recruited from and treated at Addiction Treatment Services (ATS) at Johns Hopkins Bayview Medical Center or Man Alive Treatment. Participants utilizing any MAT may also be recruited from the community and conduct all study sessions at the Behavioral Pharmacology Research Unit (BPRU) at the Johns Hopkins Bayview Medical Center. University of Virginia will be involved as a p-site to allow for Co-I Patrick Finan to be involved with analysis of the study.

Following an initial screening visit, eligible participants will complete an ambulatory training session wherein they will be trained on procedures for daily actigraphy and sleep diary, as well as Data Burst collection of EMA and salivary cortisol (each described below). Participants will also receive basic training on sleep hygiene, which will include limiting daily caffeine, alcohol consumption, and nightly "screen time" (using smart phone or watching TV). Following the ambulatory training session, participants will undergo a 7-day Baseline ambulatory assessment period (week 0), which will include daily wrist actigraphy and electronic sleep diaries, as well as Data Burst activities (EMA to assess circadian rhythms of stress, craving, and affect, and diurnal salivary cortisol samples with ambulatory kits). After the baseline Data Burst, participants will be randomized to 20mg SUVO or placebo. Study drug will be distributed in a blister pack. Persons on SUVO will receive two 10mg SUVO capsules (20mg total) and persons on placebo will receive two weight/color matched placebo capsules. Individuals in both drug conditions will be allowed to self-titrate their dose, which (a) will improve medication adherence, (b) will account for individual differences in drug response throughout the study, and (c) is consistent with other sleep medication trials in OUD populations (Stein et al., 2012). At the end of each study week, participants will attend Weekly Safety and Outcome Sessions, which will be scheduled directly prior to or following daily treatment appointments at their respective treatment clinics, thus increasing participant attendance and study adherence. Weekly Safety and Outcome Sessions will include urine toxicology to assess relapse to opioids and other substances of abuse, self-reported substance use, abuse liability assessments, and evaluation of adverse events. Subjects will wear wrist actigraphs and complete daily diaries throughout the study. At Weeks 0, 1, 4, and 8, subjects will complete the expanded Data Bursts, which will include EMA and diurnal salivary cortisol assessments in addition to the actigraphy and daily sleep diaries. Final outcomes will be assessed following study week 8.

For this study, methadone treatment will be standardized, such that patients will have their dose stabilized between 60-130mg, with no more than +/-10% dose change thereafter in response to clinical indicators such as relapse. Participants enrolled at ATS will conduct study sessions either at ATS or in the Behavioral Pharmacology Research Unit (BPRU), which is in the same building as ATS. Participants at Man Alive will conduct study sessions at either Man Alive or the BPRU. Individuals recruited from other community providers will conduct study sessions at the BPRU, and will sign a medical release form so that the study team can confirm their methadone dosing and other medical history information to confirm study eligibility.

Screening Visit: Participants meeting initial eligibility criteria derived from the electronic medical record will be invited for a screening visit, which will occur in dedicated lab space at each respective site. After undergoing informed consent, participants will then complete a series of measures to establish study eligibility, including demographic and drug use history via the Addiction Severity Index (McLellan, Cacciola, & Zanis, 1997), Fagerstrom Nicotine Dependence Questionnaire (Bierut et al., 2007), and Caffeine Intake Questionnaire (Song et al., 2008), sleep quality via the Pittsburg Sleep Quality Severity Index (PSQI) (Buysse, Reynolds III, Monk, Berman, & Kupfer, 1989) and medical history via assessment of past and current medications and medical conditions, and mental health and current depressive symptoms via standard assessments of psychiatric functioning including the MINI International Neuropsychiatric Interview (Lecrubier et al., 1997), the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960), the Beck Anxiety Inventory (BAI) (Beck, Epstein, Brown, & Steer, 1988), and the Columbia Suicide Severity Rating Scale (CSSRS) (Posner et al., 2008). Participants will also provide a urine sample that will be tested for evidence of opioid and other drug use, and pregnancy (when applicable). Participants will undergo one night of sleep testing using the WatchPat (Kinoshita et al., 2018) or Nox T3 device to screen for possible central or obstructive sleep apnea, which will be used to rule out (AHI>30) and stratify (AHI <15 or >15) participants; participants will undergo another night of sleep testing via WatchPatTM or Nox T3 during the first four weeks of the study to ensure that central and/or obstructive apnea does not worsen. SUVO does not worsen sleep apnea or cause respiratory depression, however it does not treat these conditions either.

Ambulatory Training Session: Participants who consent to study participation and meet eligibility criteria will participate in a brief training session that acclimates them to study procedures involving ambulatory monitoring (wrist actigraphy, daily sleep diaries, EMA to assess diurnal changes in stress, craving, and affect, and diurnal salivary cortisol samples with ambulatory kits).

Randomization: Following the baseline Data Burst, participants within each MAT will be randomized to either 20mg SUVO or placebo. Randomization will utilize a minimization procedure to balance groups by (1) sex (M/F), (2) age (<35 or >35), (3) race (black/African American or other), (4) PSQI (<13 or >13), (5) BMI (<30 or >30), (6) AHI (<15 or >15).

Daily Study Activities: Following the Ambulatory Training Session, participants will wear a wrist actigraph (24 hours/day; 7days/week) and complete a sleep diary every morning for the remainder of the trial.

- Wrist Actigraphy. Participants will wear a triaxial accelerometer (GT0X Link Wrist Actigraphy, Actigraph LLC) on their non-dominant wrist at all times. Wrist-worn actigraphy has been validated against PSG and provides an acceptable alternative measure of sleep continuity (Ancoli-Israel et al., 2015; Sadeh, Hauri, Kripke, & Lavie, 1995). Actigraphy will provide the primary assessment of the primary sleep continuity outcomes TST and WASO.
- Daily Sleep Diaries. Participants will be asked to document perceived sleep continuity and quality each morning (Buysse, 2005). This method is a gold standard assessment of sleep continuity, and is commonly used to verify actigraphic assessments (Carney, et al., 2012). Diaries will be completed

on participants' smartphones via the mEMA application, a flexible mobile survey platform (Metricwire, Inc).

Data Burst Activities: Diurnal measures will occur in Week 0 (baseline), and Weeks 1,4, and 8.

- Ecological Momentary Assessments (EMA). Momentary self-report assessments of perceived stress, and other time-varying covariates related to opioid abuse (e.g., craving, positive and negative affect, pain) will be prompted multiple times daily via the mEMA smartphone application. Prompts will be pseudo-randomly delivered within each day (Finan, Tennen, Thoemmes, Zautra, & Davis, 2012; Finan, Quartana, & Smith, 2013; Finan & Garland, 2015). The Metricwire mEMA software interfaces with a smartphone and has features which ensure data integrity and optimize compliance. Automatic reminders will be delivered when subjects fail to complete assessments after initial prompts. Customized, real time reports will be generated, highlighting extreme values and/or noncompliance, which may require follow-up by the investigative team. The data are secure, backed up, and meet HIPAA and other regulatory requirements.

- Salivary Cortisol. Salivary cortisol will be collected during each Data Burst using Salivette collection tubes (Sarstedt Inc.). Participants will return salivary cortisol tubes at the Weekly Safety and Outcome session, and study staff will immediately store samples in a -20° Celsius deep freezer (although samples are stable at room temp for up to 2 weeks). Samples will be processed via Enzyme-Link Immunosorbent Assay (ELISA), which has an inter- and intra-assay coefficient of variance of less than 10%, to determine secondary measures of systemic cortisol at each time point. Diurnal salivary cortisol is a reliable measure of HPA-axis function that affects the sleep-wake cycle (Edwards, Evans, Hucklebridge, & Clow, 2001).

Weekly Safety and Outcome Assessments: Each week, participants will attend a lab session in a dedicated research space housed within their respective clinics (either Ashley Addiction Treatment, BPRU, Man Alive, or ATS). During the session, patients will be assessed for drug use via urine toxicology and self-report, abuse liability of study drug and illicit opioids, and medication safety (e.g., adverse event reports) and satisfaction. Mental health outcomes include depressive symptoms assessed via the HAM-D, anxiety symptoms via the BAI, and suicidal thoughts/behaviors via the CSSR, and questions on emotional coping. Secondary sleep measures such as risk for apnea and daytime sleepiness will be monitored via the Stop-Bang Questionnaire (Chung et al., 2016) and Epworth Sleepiness Scale (Johns, 1991), respectively. Patients with Chronic Pain will complete the Brief Pain Inventory (Cleeland & Ryan, 1994), the Graded Chronic Pain Scale (Von Korff et al., 1990), Short Form McGill Pain Questionnaire, and Pain Catastrophizing and Pain Resiliencee Scale (Sullivan et al., 1995). At the end of the session, participants will be given a refill of their study medication.

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

The maximum study duration for participants will be nine weeks. The entire study will be conducted during routine outpatient treatment at Ashley Addiction Treatment in Bel Air and Elkton, MD, Man Alive Inc. in Baltimore, MD, Addiction Treatment Services at the Johns Hopkins Bayview Medical Center in Baltimore, MD, and for participants recruited from other community providers, at the Behavioral Pharmacology Research Unit at Johns Hopkins Bayview Medical Center in Baltimore, MD. Each participant will attend a screening session, ambulatory monitoring training session, and nine weekly safety and outcome sessions, for a total of 11 study visits. The entire study will take place over a four year period.

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.

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

Routine care for sleep disturbance during OUD recovery includes medications such as trazodone, which are not FDA approved for sleep (but commonly used), in lieu of benzodiazepines that might be abused. Participants currently taking benzodiazepines for sleep disturbance will not be included in this study, and participants will be asked to cease all prescribed and over the counter sleep medications for the duration of the study, to avoid potential confounds and adverse events. SUVO is an ideal medication for sleep disturbance in this population. 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. 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.

The aftercare plan for each individual will be decided by the treatment facility, independent of the research study. Early exit from this study will not affect patient care or continuation of MAT.

5. Inclusion/Exclusion Criteria

Inclusion Criteria:

- Between the ages of 21-65, inclusive.
- Past 30-day sleep disturbance as evidenced by a Pittsburgh Sleep Quality Index Total Score $\geq$5.
- Enrolled in either outpatient methadone-maintenance, buprenorphine-maintenance, or XR-NTX treatment for OUD.
- Willingness to be maintained on a protocolized dose starting between 60-130mg methadone or 380mg XR-NTX for the duration of the study.
- At least 2 weeks of continuous abstinence from illicit opioids as evidenced by self-report and urine drug screens collected as part of routine care.
- Willing to comply with the study protocol, which will include weekly study visits, daily actigraphy and EMA.
- Use of birth control throughout study.

- Have no clinically significant chronic medical disorders or conditions that are judged by the investigators to prevent participation.

Exclusion Criteria:

- Serious mental illnesses that are unstable and could affect study participation (thought disorders, hallucinations, delusions, thoughts of harm to self/others).
- Current moderate to severe substance use disorder other than OUD.
- Current illicit stimulant use, including cocaine and methamphetamine.
- Pregnant as verified by urine testing, or breast feeding.
- Have a known allergy to the study medications.
- Past 30-day prescribed use of SUVO.
- Current use of a benzodiazepine or other schedule IV medication for insomnia.
- Use of CYP3A inhibitors.
- Current narcolepsy, sleep paralysis, or restless leg syndrome as assessed by medical history
- Apnea-hypopnea index [AHI] > 30.
- Use of glucocorticoid medications and any medication that would alter the HPA axis.
- Past 30-day suicidal behavior as assessed by the Columbia Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2008).
- Current use of continuous positive airway pressure (CPAP) device for sleep apnea.
  Have circumstances that would interfere with study participation (e.g., impending jail; severe clinical issues).

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 medication for this study as previous clinical trials demonstrated that SUVO improves sleep architecture after a single dose (Herring et al., 2016; 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., 2016a). This study will use the highest FDA-approved dose (20mg) although participants will have the option each night to receive half the dose of SUVO (10mg) if they experience negative side-effects and/or would prefer a lower dose. Participants will be given their medication dose in two weight and color-matched capsules, containing either two 10mg SUVO (20mg dose), or two placebo capsules.

Acetazolamide: Both SUVO and placebo capsules will also contain 15mg acetazolamide. The 15mg dose is non-active (therapeutic dosing starts at 250-500mg), however acetazolamide is easily detectable in urine samples and is used in this study only to track medication adherence. This technique has been used in other studies (Hampson et al., 2016).

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 5, 10, 15 and 20mg dose; we requested guidance from the FDA as to whether this study would require an IND and the FDA requested that we *do not* submit an IND. Suvorexant has a broad therapeutic window, and persons with OUD might have increased orexin signaling, as evidenced by postmortem studies reporting 54% more orexinergic neurons in the lateral hypothalamus of persons with OUD compared to healthy controls.

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., 2016a; 2016b).

Acetazolamide: The only purpose for acetazolamide in this study is to easily track medication adherence. NIDA developed an assay to detect acetazolamide in urine samples (Hampson et al., 2016), which will be used in this study to confirm that participants are taking either active SUVO or placebo regularly.

7. Study Statistics

a. Primary outcome variables.

Sleep Continuity: Total Sleep Time (TST) is calculated from actigraphy and sleep diaries as the total number of minutes spent asleep between the time in bed and the time out of bed each night. Wake after sleep onset (WASO) is a sleep continuity measure used to index sleep maintenance problems and poor sleep consolidation. WASO will be calculated from actigraphy and sleep diaries as the total number of minutes spent awake after sleep onset and before the final awakening. Other secondary sleep continuity measures include sleep onset latency (in minutes), sleep efficiency (ratio of time asleep vs time in bed), and the circadian measure of sleep midpoint (median time between sleep initiation and final awakening). For study aims, sleep measures will be averaged by study week to provide a robust and granular appraisal of sleep over time.

Self-reported Stress: Diurnal fluctuations in self-reported stress will be captured via EMA using the Short-Form Perceived Stress Scale (PSS-4) (Schlotz, Yim, Zoccola, Jansen, & Schulz, 2011). The PSS-4 is a 4-item measure of the degree to which individuals appraise certain situations as stressful. Items are rated on a 5-point Likert scale and will be adapted for the micro-longitudinal time frame of EMA, consistent with prior studies (Dunton et al., 2018; Gidlow, Randall, Gillman, Silk, & Jones, 2016). For study aims, four daily PSS-4 Total Scores will be transformed into area-under-the-curve (AUC) scores and averaged across Data Burst weeks. In addition to the PSS-4, Visual Analogue Scales of "Stress" will be used, with "0" equating to "not at all" and "100" equating to "extremely".

Biological Measurement of the Hypothalamic-Pituitary-Adrenal axis (HPA-axis): Diurnal fluctuations of the HPA-axis will be collected in study weeks 0,1, 4, and 8 to enhance the primary assessment of perceived stress gathered through the EMA. Within-Data Burst diurnal salivary cortisol will be calculated by deriving an AUC score representing diurnal HPA-axis function.

Treatment Outcomes: Urine drug screens for opioids and other illicit substances including cocaine, amphetamines, benzodiazepines, and marijuana will be collected at weekly study sessions and monitored via clinic electronic health records. Treatment adherence to counseling sessions and

treatment retention will be collected via clinic electronic health records and through self-report at weekly study sessions.

b. Secondary outcome variables.

Ecological Momentary Assessments (EMA) Craving and Affect: Self-reported opioid craving is a key antecedent of relapse, and is optimally assessed through EMA in close-to-real time(Huhn et al., 2016; Preston & Epstein, 2011; Preston et al., 2018). Participants will be asked to rate the frequency of cravings (number of episodes or continuous), the mean intensity of craving, and the degree to which they have an urge to use illicit opioids *right now* on a 0-100 point visual analogue scale (VAS), with 0 being "Not at All" and 100 being "Extremely". Affective state will be assessed with a selection of items from the Positive and Negative Affect Schedule (Watson, D. & Clark, 1999), which have been commonly deployed in EMA protocols involving patients with SUDs and/or sleep disturbance (Buysse et al., 2007; Lydon-Staley et al., 2017; Steptoe, Gibson, Hamer, & Wardle, 2007).

Abuse Liability Assessments: Medication and opioid abuse liability will be assessed in study weeks 1, 4, and 8.

1. *SUVO Abuse Liability Ratings:* The abuse liability of the blinded study drug will be assessed by asking participants to rate "drug liking", "high", "good effects", and "bad effects", on a 0-100 point VAS, with 0 being "None" and 100 being "Extremely". Participants will also report the perceived street value of the study drug. These subjective drug effect ratings are considered by the FDA to be the gold standard for assessing abuse liability (Huhn, Andrew S. et al., 2019; Tompkins, Lanier, Harrison, Strain, & Bigelow, 2010).
2. *Hypothetical Opioid Purchase Task:* This is a validated method for assessing the abuse liability of drugs of abuse (Jacobs & Bickel, 1999; Kiselica, Webber, & Bornovalova, 2016). The task captures how a participant's illicit opioid consumption may change as a function of escalating price (Hursh & Silberberg, 2008), which will determine whether inhibition of the orexin system might reduce the perceived value of illicit opioids as an underlying mechanism of drug craving.

Drug Specific Measures: Secondary aims will assess a variety of domains related to SUVO.
1. *Drug Identification*: At each weekly session, participants will indicate whether they believe they are receiving SUVO or placebo to confirm whether the study medications are subjectively detectable.
2. *Adverse Event Ratings:* We will follow standard FDA guidelines regarding adverse events. Participants will be able to self-report adverse events through the mEMA application and via a study contact number, if warranted. In addition, study staff will use an FDA standard assessment of AEs at each weekly session. AEs will be summarized descriptively by severity and relatedness.

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

Statistical Plan: A priori covariates include: depressive symptoms, anxiety symptoms, duration of illicit opioid abuse, other current illicit drug use, and MAT stabilized dose (within the methadone group), as each has been linked to MAT treatment outcomes (Huhn et al., 2019; Lofwall, Brooner, Bigelow, Kindbom, & Strain, 2005; Strain et al., 1993). The sample will be controlled on age, race, and sex, through randomization, so those variables will not be covaried. Unexpected group differences in a patient characteristics will also be considered as covariates. Sex is an important biological variable in sleep and opioid treatment studies. In addition to stratifying the sample by sex, we will perform secondary analyses directly comparing outcomes as a function of sex. Missing data will be handled by restricted maximum likelihood. If the missing-at-random assumption is violated, we will consider multiple imputations. We will

use mixed effects modeling as the primary analytic strategy across endpoints. We will perform intent-to-treat analyses, using mixed-effects models to account for random variation in intercepts, control for autoregression, and include all available data points (Mallinckrodt et al., 2003). Mixed-effects linear growth models will be fit with restricted maximum likelihood estimates and include a random intercept, and a set of fixed effects (i.e., predictor/s, covariates, and interaction terms). The random intercept will effectively control for random variation in treatment outcomes at baseline. The growth term, "Time", will represent each of the discreet assessment points in each analysis (Week 0 [baseline], and Weeks 1,4, and 8). Time will be tested as a random slope to account for random variation in response trajectory, and retained for primary models if it significantly improves model fit, as determined with a likelihood ratio test (Stram & Lee, 1994). In preliminary analyses, we will evaluate autocorrelation in the primary endpoints and will model an autoregressive 1 (AR1) variance-covariance matrix.

Power Analysis and Sample Size: For Aims 1 and 2, the effect of SUVO versus placebo is based on previous clinical trials of 10 or 20mg SUVO versus placebo and our preliminary data on sleep and stress outcomes in OUD patients. For sleep outcomes, previous studies report f effect sizes $\geq$0.50 for TST and WASO(Herring et al., 2012; Herring et al., 2016), suggesting that a total sample size of 54 would provide 95% power to detect a significant effect at $p<0.05$. For stress outcomes, an effect size of .41 was derived from our preliminary data on salivary cortisol, suggesting that a total sample size of 79 would provide 95% power to detect a significant effect at $p<0.05$. For Aim 3, an effect size of 0.51 was derived from our preliminary data on TST and opioid relapse, suggesting that a sample size of 53 would provide 95% power to detect a significant effect at $p<0.05$. Similarly, an effect size of 0.49 was derived from our preliminary data on salivary cortisol and opioid relapse, suggesting that a sample size of 56 would provide 95% power to detect a significant effect at $p<0.05$. The highest N needed for these aims is 79; to account for treatment attrition, we will recruit at least 100 participants to achieve 80 completers.

STUDY AIMS

Primary Aims 1 and 2: Evaluate whether SUVO increases TST and decreases WASO (Aim 1), and decreases diurnal measures of stress (Aim 2). *Hypotheses. Relative to placebo, SUVO will increase TST and decrease WASO (Aim 1) and decrease ambulatory measures of stress (Aim 2).* The Primary Outcomes for these aims are mean weekly TST and WASO in minutes, measured by actigraphy, and mean weekly diurnal self-reported stress, assessed via within-day AUC for PSS-4 Total Score, in weeks 0 (baseline), 1, 4, and 8 of the study. Analyses: Mixed-effects models will be conducted for the entire sample and separately for each MAT group. The primary effect of interest in each model will be the Medication (SUVO vs. Placebo) X Time (Weeks 0 [baseline],1,4,8) interaction. Thus, we will regress the outcome (TST, WASO or PSS-4) on Medication, Time, and the Medication X Time interaction.

Primary Aim 3: Determine the association between sleep continuity, diurnal stress, and opioid relapse in both MATs, independent of the effect of SUVO. *Hypotheses. In patients on MATs, increased sleep continuity and decreased diurnal stress will be linearly associated with increased percent negative opioid urine drug screens over the course of the study.* The Primary Outcome for this aim is percent opioid negative urine drug screens in weeks 0-8. Analyses: In the first model, we will regress percent of opioid negative urines on TST, Time, and the interaction of TST X Time, along with the covariates. Separate models will be run substituting TST for WASO, PSS-4, and cortisol.

Exploratory Aim 1: Evaluate whether SUVO relative to placebo improves treatment outcomes in persons on MATs. The Primary Outcomes for this aim are percent opioid negative urine drug screens in weeks 1-8 and length of treatment retention in days. The secondary outcome is craving, assessed via mean weekly AUC VAS scores for "urge to use right now" in weeks 1-8. Analyses: To assess the effect of SUVO versus placebo on percent opioid negative urine drug screens or VAS craving, regardless of MAT group, a mixed effects model will be used with the Medication (SUVO vs. Placebo) X Time interaction as the primary

effect of interest. For the effect of SUVO versus placebo on treatment retention, we will use interval censored survival analysis.

Exploratory Aim 2: Determine the effects of MAT on TST, WASO, and diurnal measurements of stress in standard MAT treatment. Primary Outcomes for this aim are mean weekly TST and WASO in minutes, measured by actigraphy, mean weekly diurnal self-reported stress, assessed via within-day AUC for PSS-4 Total Score, and mean weekly diurnal salivary cortisol, assessed via within-day AUC for salivary cortisol (μg/dL), in weeks 0 (baseline), 1, 4, and 8 of the study. Analyses: This sub-analysis will be conducted only among participants assigned to Placebo. The primary effect of interest in each model will be the MAT Group (Methadone vs. Buprenorphine vs. XR-NTX) X Time (Weeks 0 [baseline],1,4,8) interaction. Thus, we will regress the outcome (TST, WASO, PSS-4, cortisol) on MAT, Time, and the MAT X Time interaction.

d. Early stopping rules.

Patients will discontinue their study participation if they request to be discharged, have a serious adverse event, or if the treatment facility decides it is in the patient's best interest to be removed from the study. All patients will be encouraged to continue treatment following the study.

8. Risks

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

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.

Risks associated with methadone dosing: Methadone dosing will be protocolized in this study such that patients maintained on 60-130mg will be enrolled and dose increase or decrease will be restricted to <=10% of the initial dose, and dose adjustment will only occur in consultation with clinical staff at Addiction Treatment Services, Man Alive, or the participants community provider. Methadone is a Schedule II mu-opioid receptor agonist that is FDA-approved for the treatment of opioid use disorder. Methadone is 41-99% bioavailable through oral consumption, and has a Tmax of 2-2.8 hours. It is extensively metabolized by the liver through CYP3A4, CYP2B6, and CYP2D6 enzymes. The elimination half-life is 15-55 hours, and it is excreted through both renal and fecal means. It is used in specialty clinics for pregnant women, although fetal risk cannot be ruled out. Common adverse effects include hypotention, diaphoresis, constipation, nausea, vomiting, asthenia, dizziness, lightheadedness, and sedation. Serious adverse effects include decreased vascular flow, prolonged QT interval, Torsades de pointes, adrenal insufficiency, hypoglycemia, anaphylaxis, respiratory acidosis, respiratory arrest, respiratory depression, drug dependence, and serotonin syndrome. Methadone is contraindicated with acute bronchial asthma,

hypercarbia, hypersensitivity to methadone, paralytic ileus, respiratory depression, and gastrointestinal obstruction.

b. Steps taken to minimize the risks.

Protection against risks for suvorexant: We will conduct a thorough medical screen to ensure that participants with medical contraindications or who are taking contraindicated medications (including strong CYP34A inhibitors or CNS depressants such as alcohol, bromazepam, tapentadol, and flibanserin), patients with narcolepsy, current and major psychiatric illness (such as major depression) or past 30-day suicidal behaviors are excluded for participating. Participants will be provided the maximum FDA-approved dose (20mg) but will be permitted to reduce the dose to 1 capsule a day (representing a 10mg dose, which is the initial FDA-recommended dose for treatment of insomnia). All participants will be informed they can refuse doses at any point and we will track participant acceptance (e.g., in terms of adherence with dosing schedule) of the medication as part of the study. Given that suvorexant can cause next-day drowsiness, participants will be explicitly instructed not to drive or operate heavy machinery under any circumstances within 8 hours of taking suvorexant, or if they continue to feel drowsy or have cognitive difficulties after 8 hours post suvorexant dosing. Participants will also be instructed to contact the study team if drowsiness or cognitive difficulties persist for longer than 8 hours after dosing. All participants will be asked to plan alternative transportation strategies if needed. In addition, to protect against the risk of worsening sleep apnea, central and obstructive apnea will be assessed via the WatchPat or Nox T3 following the screening session, then again in the first 4 weeks of the study. A study physician will determine if worsening apnea is potentially related to study drug, and if so, whether the participant should be removed from the trial.

Protection against risk for methadone: Methadone dose will be held between the initial dose of 60-130mg +/- 10% dose adjustment if deemed necessary by clinical staff at Addiction Treatment Services. Man Alive, or other community provider. Since methadone dosing will be managed by the medical team(s) at these facilities and will stay well within the normal range, the risks associated with this study are not different than usual care. Nonetheless, adverse events will be closely monitored and patients experiencing adverse events will be referred back to their treatment provider for additional dose adjustment if deemed medically necessary. Serious adverse events will result in admission to the Emergency Department at Johns Hopkins Bayview Medical Center, which is across the street from the study site, or whichever hospital closest to the participant at the time or the potential serious adverse event.

Participant adverse events (AEs) will be monitored and documented at weekly study sessions and on a daily basis if participants initiate contact regarding an adverse event. Participants will be able to self-report adverse events daily via ecological momentary assessments and in depth at weekly study sessions. Participants will also be provided a 24 hour contact number for adverse events or serious adverse events, which will enable sensitive detection of these events in real time. Events will be documented on a standardized form that adheres to FDA standards for adverse event reporting. Specific information to be documented is the event, the system affected, the start and stop date/time, the perceived relationship to the study (possible, probable, definitely, or unrelated), the severity (mild, moderate, severe), and the expectedness (expected, unexpected) of the event. We will also document whether concomitant medications were self-administered in response to the event (and the associated medication, dose, route, start and stop date/time, and outcome), whether the event resolved by study discharge, and whether the event met the criteria for a serious adverse event. All events will be documented by trained staff members or clinical research unit nursing staff and will be disclosed to the study PIs and medical team members daily via daily memos (confidential emails that are sent each night to the study team via secure email system). Events will be discussed by the team at weekly study meetings or more frequently as needed. Any event that exceeds an *a priori* safety threshold, that is unexpected or of unexpected severity, or for which the participant expresses concern, will result in the staff member contacting a medical team member immediately via phone for a consultation. Staff will be instructed to document all adverse reports.

We will minimize risk of breach of confidentiality by de-identifying data stored in the master data set. All other medical care will be managed as usual by the treatment clinics. This study will monitor adverse events associated with the research protocol, which could include psychological distress associated with questionnaires.

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 NHLBI 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.

Method for ensuring that all sites have the most current version of the protocol and are aware of protocol amendments: JHU faculty and staff will manage and implement all study tasks at all study sites. JHU faculty and staff will have direct access to the study protocol through eIRB, will be verbally informed of protocol amendments at weekly study meetings, and will receive written notification of protocol amendments. Ashley Addiction Treatment and Man Alive staff who are not approved in the JHU eIRB system will not perform study-related tasks, however Ashley Addiction Treatment and Man Alive staff who have medical monitoring responsibilities for patients in the study will be notified of protocol amendments via email within 5 business days of IRB approved amendments. Participants recruited from the community will sign a medical release of information and the study team will only contact community providers to obtain inclusion/exclusion criteria during screening, and for methadone-maintained participants, to check that the dose of methadone has stayed within the +/-10% range for the duration of the study.

Plan for collecting and managing data and reporting protocol events from all participating sites: All data collection and weekly study tasks will be managed by JHU faculty and staff at all study sites, including Ashley Addiction Treatment, ATS, and Man Alive. JHU faculty and staff will perform study sessions with patients directly at each site (Ashely Addiction Treatment, ATS, Man Alive, or for individuals recruited from the community, BPRU). All data will be maintained on JHU computers only. Medical and clinical staff at all sites will have PI contact information to report any adverse events or protocol deviations that are not collected by JHU faculty and staff.

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 role of the orexin system in sleep and circadian rhythms of stress in persons in OUD recovery who are utilizing either methadone or XR-NTX. While this study is designed to answer mechanistic hypotheses, positive results might also suggest that suvorexant is a safe and effective sleep medication for persons with OUD, which would support the use of this FDA-approved and widely available medication.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

b. Participants will earn $30 for the screening visit. Participants will earn $20 for the attending the ambulatory training session, $15 per session in weeks 0-8. Attending the screen and all study sessions will result in payment total of $185. Participants will also earn an adherence bonus of $5/day for taking medication, wearing actigraph, and completing daily diaries (up to $35/week or $315 for the 9-week study). Participants will earn an additional $100/week for four data burst weeks if they complete ≥80% of daily EMA and salivary cortisol collection, for a total of $400. Finally, participants can earn up to $100 in device return payments; $20 after screen, $20 after week 2 and $60 at the final session. The total maximum payment is $1000 (See Payment Table).

Payment Schedule

	Weekly Session Payments	Daily Bonus ($5/day)	Data Burst Bonus	Device Return Payments
Screen	$30	-	-	-
Ambulatory Training Session	$20	-	-	$20
Week 0 (baseline)	$15	$35	$100	-
Week 1	$15	$35	$100	-

Week 2	$15	$35	-	-
Week 3	$15	$35	-	$20
Week 4	$15	$35	$100	-
Week 5	$15	$35	-	-
Week 6	$15	$35	-	-
Week 7	$15	$35	-	-
Week 8	$15	$35	$100	$60
Total	**$185**	**$315**	**$400**	**$100**
Maximum Payment		**$1000**		

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.

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