The effects of suvorexant on sleep, stress, and cue-reactivity in methamphetamine use disorder

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Protocol Title: The effects of suvorexant on sleep, stress, and cue-reactivity in methamphetamine use disorder
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Study Coordinator: Jessica Vincent
Population: Participants with methamphetamine use disorder
Number of Sites: single site (BBSB)
Study Duration: 4 weeks

Project Summary:

Methamphetamine (MA) has re-emerged as the next substance use crisis in the United States. Unlike the opioid crisis, treatment of MA use disorder is significantly more challenging without an FDA-approved medication. Most of the candidate drugs tested to date focus on modulating monoaminergic pathways, yielding limited evidence of benefit. New interventions aimed at novel biological mechanisms are needed.

Converging evidence highlights the orexin system as a promising target for addressing key mechanisms in the recovery from substance use disorders, including regulating sleep architecture, buffering hyper-arousal and stress responses, and modulating reward processing and drug-motivated behaviors[1–5]. Activation of orexin (OX) receptors by psychostimulant drugs mediates arousal (OX_2R) and reward (OX_1R) functions and, by contrast, blockade of both receptors produces attenuation of these physiological and behavioral functions[6]. In preclinical animal models, selective OX_1 R /OX_2 R receptor antagonism has been shown to reduce MA self-administration and MA-induced reinstatement responding[7,8]. In humans with cocaine use disorder, we demonstrated that treatment with the FDA-approved dual orexin receptor antagonist suvorexant (SUVO) improved outcomes in relapse-related domains of sleep, stress, and cue reactivity[9]. Here, we propose to expand these promising findings by examining the effects of SUVO in humans with MA use disorder, an understudied clinical population for whom there is no currently approved treatment indication.

The primary goal of the study is to assess the effects of SUVO on physiological sleep (actigraphy, EEG) and self-reported sleep quality. We will also assess two other domains linked to the orexin system and commonly related to MA relapse including stress and cue reactivity/craving. Our overarching hypothesis is that treatment with SUVO will attenuate disruptions in sleep, stress, and cue reactivity/craving. By engaging these relapse-related target mechanisms, this work will provide critical proof-of-concept evidence for a subsequent R01. To that end, we will employ a within-subjects, two group cross-over design (N=12) and take a multimodal approach to assessing sleep, stress, and cue reactivity/craving. Participants will complete stress reactivity and electroencephalogram (EEG) laboratory tasks, self-report, and drug use measures after one week of SUVO, washout, and placebo (PL), order counterbalanced between groups. Participants will also wear an activity watch at night in order to have their sleep monitored via actigraphy.

Primary Hypotheses and Specific Aims:

Primary Aim 1: Determine the effects of SUVO on sleep, stress, and cue reactivity/craving

Hypothesis 1a: SUVO compared to placebo will improve sleep outcomes assessed by actigraphy (total sleep time, wake after sleep onset), self-report (Pittsburg Sleep Quality Index), and EEG (resting state alpha power);

Hypothesis 1b: SUVO compared to placebo will improve acute stress reactivity as measured by physiological responses (cold-pressor task induced cortisol and HR/BP) and subjective ratings (Visual Analog Scale; Depression Anxiety Stress Scale).

Hypothesis 1c: SUVO compared to placebo will reduce cue reactivity/craving as measured by LPP to methamphetamine images and self-report (Brief Substance Craving Scale).

Exploratory Aim 2: Evaluate the preliminary safety and side effects profile of SUVO.

Primary outcome measures: self-reported sleep, resting state alpha power, LPP, self-reported stress, and cortisol measured at each study visit after 1-week of SUVO, washout, and PL; total sleep time and wake after sleep onset measured nightly via actigraphy watch

Secondary outcome measures: methamphetamine use (TLFB and UDS) measured at each study visit after 1-week of SUVO, washout, and PL; side effects questionnaire, BDI, and CSSRS measured at each study visit after 1-week of SUVO, washout, and PL

Background and Rationale:

Public health significance of MA use disorder. MA use disorder 1) is surging in recent years, contributing to a massive (~180%) increase in overdose related MA deaths from 2015-2019[10], 2) presents a tremendous economic burden to society (likely >$48 billion/year)[11], and 3) leads to severe impacts on physical/mental health and social functioning[11].

The role of sleep, stress, and cue reactivity in addiction. MA use has marked effects on several interconnecting neurobiological processes such as sleep, stress, and cue reactivity. Chronic MA use and MA withdrawal is associated with poorer sleep quality[12]. Severe sleep disturbances can aggravate MA use disorder symptoms, such as drug craving and stress, and are commonly a large barrier to treatment success[2,12]. Similarly, stress is a critical part of the initiation and maintenance of addiction, e.g., use of substances to alleviate negative mood states[13,14]. Stress and anxiety are known to trigger cravings and use of drugs of abuse in turn activates stress pathways, which together can increase vulnerability to cue-induced relapse[15–17]. Cue reactivity is a hallmark feature of addiction, where previously innocuous stimuli become associated with drug reward and acquire incentive properties[18]. Cue-induced craving is central to addiction and can continue to occur during abstinence, triggering relapse[18]. Taken together, a medication targeting sleep, stress, and/or cue reactivity would be of interest in treating MA and other substance use disorders.

Objective measurement of critical processes. Research suggests that subjective measures may not capture the substantial heterogeneity in risk for relapse[19], especially in persons with substance use disorders, who may lack insight[20]. Further, despite longstanding debate in the literature, there is no accepted self-report measure of craving. Recognizing these limitations, the current study will take a multi-modal approach to measuring relevant constructs related to use and relapse[21]. First, sleep measurement will be enhanced by leveraging actigraphy methods in addition to self-reported sleep[22]. While including a neuroimaging measure during sleep is out of the scope of the current study, waking effects on sleep disruptions will also be assessed with resting state electroencephalogram (EEG). For stress, salivary cortisol and heart rate/blood pressure assessments will be taken before and after induction of stress with the cold pressor task. Finally, cue reactivity and craving will be assessed both with self-report and the late positive potential (LPP), an EEG component that reflects the motivational relevance of a stimulus[23–25].

Orexin system as a novel target for MA treatment. One system that has been neurobiologically linked to regulating these processes is the orexin system. Orexins are a class of amino acid peptides that are sourced in the hypothalamus for which two receptors have been discovered (OX_1R, OX_2R). Orexins are neuromodulators: they exert their effects through regulation of GABA and glutamate. While the orexin system is widely known for regulating appetite[26] and arousal/sleep[27,28], it has widespread connections throughout the brain and is now known to modulate a wide variety of other behaviors including stress, reward-seeking behaviors, and reactivity to reward cues[29]. Critically, recent evidence indicates that selective OX_1R/OX_2R receptor antagonism reduced MA self-administration/MA-induced reinstatement responding[7,8] as well as blocked MA-induced hyperarousal and sleep impairment in preclinical studies[30]. While pharmacological interventions in animal models studies show promise, medication development for MA use disorder has largely failed[31,32]. However, there is one FDA-approved orexin compound indicated for the treatment of insomnia: Suvorexant (SUVO), a dual orexin receptor antagonist. *FDA-approval of suvorexant for the treatment of insomnia helps pave the way for rapidly advancing the development of orexin-based therapies for the treatment of MA use disorder and other addictions.* In the current study participants will receive SUVO and placebo in a cross-over design, have their sleep measured via actigraphy, undergo an EEG assessment, and complete laboratory tasks to assess stress and MA cue reactivity.

Methods:

Overall study design. We will use a two-group cross-over design. Each group will complete three conditions, each lasting one week. 12 participants will be randomized to one of the two groups. Group one (n=6) will receive one-week placebo, one-week washout, and one-week SUVO. Group two (n=6) will receive one-week SUVO, one-week washout, and one-week placebo. During the washout period, the participants will not receive any pills. Eligibility criteria and baseline measures will be collected on Day 0 before the start of week one. Participants will come to the clinic once a week on Monday for 4 weeks. On Day 1 (Monday) of the first week, the participants will receive their medication and actigraphy watches. Each following Monday, they will complete self-report and drug use measures, as well as the laboratory tasks (cold pressor and EEG). Table 1 outlines the schedule of assessments. We will aim to enroll a total of 16 participants to complete 12, with dropouts being replaced, if possible.

Participants, Recruitment, and Setting. The participants will consist of non-treatment-seeking individuals meeting DSM-5 criteria for MA use disorder. All participants will be between the ages of 18- [illegible] and fluent in English.

Individuals will be excluded if they meet the following criteria: presence of an alcohol use disorder (AUD), reporting binge drinking (>7 drinks for women and >14 drinks for men), greater than mild substance use disorder on any other illicit drug; any medical conditions contraindicating SUVO (e.g., severe pulmonary disease, severe cardiovascular disease or clinically abnormal ECG, severe liver or kidney disease, seizure disorder, or sleep disorder – particularly narcolepsy); currently taking medications with known drug interactions with SUVO (e.g., MAO inhibitors, anticonvulsants, haloperidol, phenothiazines, anesthetics, and any sedative); pregnant or breast feeding; current DSM-5 psychiatric disorder or neurological disease requiring on-going treatment that would make participation unsafe; history of seizure disorder; head injury with loss of consciousness in the last 5 years. Eligibility criteria will be assessed at baseline and will be conducted by licensed counselors and the medical director (Dr. Weaver). The study will be conducted at the Center for Neurobehavioral Research on Addiction (CNRA), where the PI (Dr. Webber) and Co-Is (Drs. Schmitz, Lane, Suchting) have experience conducting treatment and laboratory-based studies in substance use populations. Recruitment will follow typical CNRA protocols, including local advertising in print/radio, recruitment companies (Build Clinical/TrialFacts) and referrals from prior CNRA studies and the Houston area. Data analyses will be performed by Dr. Robert Suchting, a biostatistician also affiliated with the CNRA, with expertise in the application of quantitative methods to investigate experimental and clinical outcomes related to EEG, sleep, and psychostimulant use[9,23].

Table 1. Schedule of Assessments

	0 (Intake)	1 (PL or SUVO)							2 (washout)							3 (PL or SUVO)							4 (Final)
Study Day	M-F	M	T	W	R	F	S	S	M	T	W	R	F	S	S	M	T	W	R	F	S	S	M
Consent and Baseline Screening (UDS, SCID, ASI, KMSK, TLFB, physical/ psychiatric eval)	x																						
Receive Study Medication (SUVO or PL)		x	x	x	x	x	x	x								x	x	x	x	x	x	x	
Medication Compliance		x	x	x	x	x	x	x								x	x	x	x	x	x	x	x
Actigraphy		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Self-report Sleep, Stress, Craving, MA use (PSQI, ISS, PROMIS-SF, DASS, VAS, BSCS, BDI, TLFB), and UDS									x							x							x
Laboratory Tasks (Cold Pressor, EEG)									x							x							x

SCID - Structured Clinical Interview for DSM-5**, ASI** - Addiction Severity Index[33]; **KMSK** - Kreek-McHugh-Schluger-Kellogg scale[34]; **TLFB** - Timeline Followback[35]; **PSQI** – Pittsburg Sleep Quality Index; **ISS** – Insomnia Severity Index; **PROMIS-SF** – Patient Reported Outcomes Measurement Information System Short Form Sleep Disturbance; **BDI –** Beck's Depression Inventory; **DASS** – Depression Anxiety Stress Scale[36]; **VAS** – Visual Analogue Scale of Stress[37]; **BSCS** – Brief Substance Craving Scale[38].

Payment and Compensation. Participants will receive $40 for the baseline evaluation. As methamphetamine users tend to live further outside the city, we are budgeting extra for bus/parking validation/rideshare options, up to $30 per visit. Participants will receive $50 for each laboratory visit (3 visits total) and a completion bonus on their final visit for $50. If medication compliance is reached, participants will receive an extra $10 at each clinic visit (for more information see Medication Compliance).

Baseline Screening. As a part of the CNRA general evaluation protocol (HSC-MS-0322), participants will receive a full physical and psychiatric evaluation on the first day including: a medical-history questionnaire, physical examination, urine drug screen (UDS), pregnancy test, blood draw, and ECG. Clinicians will administer the SCID, the ASI, the KMSK, and TLFB to assess current diagnoses, severity, chronicity, and daily use of MA (Table 1). UDS will be used to assess eligibility and substance use at baseline as well as on EEG testing days. It will also be used to assess medication compliance.

Medication. Suvorexant (Belsomra®) is a dual orexin receptor antagonist and an FDA-approved medication for the treatment of insomnia. Prior research in humans indicates it is safe in human populations[39–42]. While this would be the first study assessing SUVO in MA users, a prior study from our group indicated that SUVO was safely administered to individuals with cocaine use disorder[9]. Our prior study used a conservative 2-week dose titration schedule (Week 1: 10mg; Week 2: 20mg), with no serious adverse effects reported or observed. In the current study, participants will receive 20mg of SUVO for 7 days, the highest allowed FDA dose. Study medication will be compounded by CNRA pharmacists using size 00 capsules. Each dose will contain 20mg (active medication) or 0mg (placebo) of suvorexant, 25mg of riboflavin, and cornstarch filler. The half-life is about 12 hours on average and steady-state plasma concentrations occur in 3 days with daily administration[43]. Due to the hypnotic [illegible] the drug participants will be

directed to take the medication at 10:00PM.

Medication Compliance. Because SUVO will be administered in the evening at 10:00 PM, compliance is a high priority. Compliance will be assessed with CAROMA (cell-phone assisted remote observation of medication adherence)[44]. Participants record short videos of themselves taking the medication and send it to the CNRA study cell phone or save the videos to show study staff in person. Riboflavin will be added to medication capsules and urine ultraviolet fluorescent tests will be conducted at the weekly clinic visit to assess compliance. Text-based medication reminders with required text replies (Y/N) will also be used. If CAROMA, pills count, riboflavin readings, and text replies agree, then participants will be paid $10 per visit for compliance. Payments are adjusted downward if the measures do not agree[9]. Specifically, if compliance is reached for 7 days, then the participant will receive the full $10, up to 6 days: $7, up to 4 days: $5, up to 2 days: $3, less than 2 days: $0.

Measures.

Sleep (Actigraphy). Sleep will be monitored using an activity tracker watch (FitBit Charge 5, FitBit Inc., San Francisco, CA). Fitbits demonstrate superior accuracy and sensitivity with minimal bias compared to other models[45]. The Charge 5 is the most recent model. Data will be downloaded via the FitBit app onto an IRB-approved and HIPA compliant research iPad. The following outcome measures will be calculated: total sleep duration and wake after sleep onset, two outcomes that are considered good indicators of sleep quality[46].

Sleep (Resting State EEG). Resting state EEG will be collected on test days to assess the waking effects of sleep quality. The primary outcome variable will be alpha power (8-12 Hz), which reflects a state of eyes closed wakeful rest[47,48]. Decreasing alpha during eyes closed is an indicator of entry into early sleep stages when drowsy[49]. As such, eyes closed alpha power is decreased after sleep deprivation and negatively correlated with sleepiness[50–53]. Importantly, differing results can be observed for eyes open and eyes closed conditions[51], with more alpha during eyes open indicating sleepiness (which is the opposite to eyes closed). Therefore, both eyes open and eyes closed conditions will be measured and analyzed separately. Resting alpha power will be collected at each test day. See *EEG Protocol* for details.

Sleep (Self-Report). The PSQI is a well-validated and reliable measure of sleep quality[54–56]. We will use the total summary score of the 18-items as the main outcome variable. We will also use the ISS[57] and PROMIS[58]-SF as secondary self-reported measures of sleep.

Stress (Physiological). The cold pressor task will be used to induce and measure the stress response. The cold pressor task reliably activates the sympathetic nervous system and the HPA axis which is observed by increases in heart rate, blood pressure, and cortisol[59–62]. HPA-axis activation during the CPT can be increased by incorporating a social evaluative component. These will include 1) a study member dressed in a white labcoat and taking notes on a clipboard; and 2) a webcam and monitor showing the participant's face (no recording will actually be taken). Participants will be informed that their facial expressions will be assessed during the CPT. The addition of these social components during the CPT has been demonstrated to selectively activate the HPA-axis and significantly increase salivary cortisol levels[63]. During the CPT, participants will submerge their dominant arm in an ice-water bath for up to 2 minutes. Physiological measures of stress reactivity will include HR, BP, and salivary cortisol consistent with previous studies from our group[37,64]. Saliva samples will be collected before and after in swabs using the Cortisol-Salivette® system (Sarstedt) and measured using the Cortisol ELISA Kit (Enzo Life Sciences), per manufacture instructions. Subjective stress will be assessed before and after using a single-item VAS question (see below) and HR/BP will also be collected before during and after the CPT.

Stress (Self-Report). Subjective stress levels will be assessed with the DASS-21[36], a validated and reliable measure of core symptoms associated with depression, anxiety and stress. We will also use a Visual Analogue Scale (VAS) ("Please rate your current stress level": 0=no stress, 10=extreme stress) to assess current subjective stress levels[37]. These measures will be collected on each test day prior to the laboratory tasks.

Cue Reactivity/Craving (LPP). The late positive potential (LPP) is an event-related potential component thought to reflect the motivational relevance of visual stimuli[25,65]. The LPP to drug images is enhanced in drug users compared to controls, is correlated with craving, and tracks with abstinence [66–68], thus serving as an objective measure of cue reactivity/cue-induced craving. EEG will be collected on test days prior to the cold pressor task. The Picture Viewing Task will be used to elicit the LPP. Suvorexant might lead to decrease drug use through reducing reactivity toward drug cues. Therefore, the picture viewing task will provide this neural assessment of cue reactivity. In the task, the participants view images in four categories, pleasant, unpleasant, methamphetamine, and neutral. The other image categories are necessary, so that we can ensure the brain reactivity is specifically in response to drug images and not just salient images. This is a standard task used in the EEG literature and a meta-analysis s[illegible] drug users have an increased

response to drug images with a large effect size[69].

Cue Reactivity/Craving (Self-Report). The Brief Substance Craving Scale (BSCS) will be used to assess current MA craving[38]. The BSCS will be assessed on each test day prior to laboratory tasks.

Safety/Side Effects. A 31-item questionnaire will be administered on each test day to assess side effects and adverse events. The Colombia Suicide Severity Rating Scale (CSSRS)[70] and Beck's Depression Inventory (BDI)[71] will be administered at each visit per NIH guidelines. Breath alcohol concentration will also be assessed at each visit to assess for current intoxication.

EEG Protocol. On EEG days, participants will be seated comfortably in front of a monitor, fitted for the EEG cap, and the electrodes will be prepared with conductive gel. EEG will be collected using a 64-channel actiCAP electrode cap, amplified with BrainAmp MR and digitized using Brain Vision Recorder (Brain Products, Munich). The EEG machine is situated within the CNRA on the first floor of the Behavioral and Biomedical Sciences Building. Before collection, impedances will be maintained below 50 k(OHM), as suggested by the manufacturers. The sampling rate will be 250 Hz and data will be filtered with .1 Hz high-pass and 100 Hz low-pass filters. Resting State EEG. Resting state EEG will be collected prior to the Picture Viewing Task (below). We will collect resting EEG for 3 minutes with eyes opened and 3 minutes with eyes closed. Picture Viewing Task. The Picture Viewing task will be used to elicit the LPP, reflecting the motivational salience of a stimulus. During this task, participants are asked to view a slideshow of images including pleasant, unpleasant, neutral, and MA-related images. EEG Data Reduction. Data reduction will be performed with Brain Vision Analyzer 2, MATLAB, and BESA. Resting state data will be analyzed using the fast-Fourier transform. The primary outcome of interest will be alpha power (8-12Hz) although other frequencies will also be explored. Picture Viewing Task data will be segmented (200 ms pre-stimulus to 1000 ms post-stimulus) by the following conditions: unpleasant, pleasant, methamphetamine, and neutral images. The LPP will be defined as the mean amplitude between 400-800ms post stimulus over an ROI of central-parietal electrodes used in prior reports[23].

Data Analytic Strategy:

Overview. Analyses will primarily rely on generalized linear modeling (GLM) for cross-sectional analyses and generalized linear mixed modeling (GLMM) for longitudinal analyses. This approach allows for various outcome distributions and multilevel data. All models will account for repeated observations with via the best-fitting structure of level-2 intercepts/slopes. We will aim to collect full data on 12 participants. Other participants who drop out or are withdrawn will be excluded from analyses, depending on how much data we are able to collect. If only a few data points are missing, generalized linear mixed modeling will natively handle missing outcome data. GLMM natively handles missing data by allowing unequally spaced observations between participants; any other issues related to missing data will be handled via explicit modeling of missingness or imputation. Analyses will be performed in R[72] via packages lme4[73], rstan[74], and brms[75]. **Confounders:** Preliminary data analyses will inspect relationships between sample characteristics, predictors, and outcomes via GLMM. Variables that demonstrate a relationship with both the predictor and outcome in a model meet criteria for being potential confounders[76,77] and yield models with and without covariate adjustment. We report the simpler model if inferences are not affected by these covariates and report both models otherwise. **Inference:** Analyses will be run in parallel frequentist and Bayesian models. Frequentist results yield the probability of the data (or data more extreme), given the null hypothesis, while Bayesian results directly yield the probability of an alternative hypothesis[78,79]. Weakly informative priors will be used for all Bayesian analyses in order to emphasize the influence of the present data. **Multiplicity:** All *a priori* frequentist models will be evaluated at the α=0.05 (two-tailed) significance level, and will employ false discovery rate (FDR) to control for Type I error across any *post hoc* analyses. Bayesian models will be evaluated via PP threshold guidelines in the literature[80,81] suggesting that PP = 75% to 90% indicates moderate evidence, PP = 91% to 96% indicates strong evidence, and PP = 97% or above indicates very strong to extreme evidence. **Assumptions:** Posterior predictive checking, scale reduction factors ("rhat"), and effective sample size will be used to evaluate Bayesian assumptions. Evaluation for frequentist models will use graphical evidence and statistical tests.

Specific Hypothesis Testing.

Aim 1: GLMM for repeated measures will separately model each outcome measure as a function of treatment condition, with Level-2 effects included for best fit. Outcomes will include measures of sleep (H1a: actigraphy; self-report sleep quality; EEG), acute stress reactivity (H1b: physiological responses; subjective ratings) and cue reactivity/craving (H1c: LPP to methamphetamine images; self-report craving)

Aim 2: Descriptive statistics will evaluate the frequency of adverse events (AEs) and severe adverse events (SAEs) between and within conditions. Logistic regression will evaluate presence (vs. absence) of specific AEs as a function of condition.

Sample Size and Power.

The current study is primarily concerned with deriving a preliminary range of plausible effect sizes for the effect of treatment; as such, power estimates are provided here purely as due diligence. Frequentist estimates rely on G*Power 3.1.9.7 and focus on a simplified model predicting the effect of treatment on one given normally-distributed outcome. Assuming two-sided alpha = 0.05, N = 12, 3 total measurements, a correlation among repeated measures of r = 0.15, the current proposal has 80% power to detect an effect size Cohen's f = 0.59. Notably, Bayesian inference will provide probabilistic estimates of the effect of treatment irrespective of sample size.

Protection of Human Subjects:

Recruitment and Informed Consent

The study will be conducted at the Center for Neurobehavioral Research on Addiction (CNRA), where the PI (Dr. Webber) and Co-Is (Drs. Schmitz, Lane, Suchting, Weaver) have experience conducting treatment and laboratory-based studies in substance use populations. Recruitment will follow typical CNRA protocols, including local advertising in print/radio, recruitment companies (Build Clinical/TrialFacts) and referrals from prior CNRA studies and the Houston area. We will also recruit from the Department of Psychiatry Recruitment Registry: HSC-MS-23-0768. Our study and contact information will be shared with potential subjects that are on the psychiatry waitlist via the Department of Psychiatry website or e-mail blasts. Individuals who call for information will be given a brief description of the study. Those interested will then be asked to answer questions about their current substance use. A trained research assistant will conduct this telephone-screening interview. Eligible subjects will be scheduled for an in-person intake visit at the CNRA, first floor BBSB. The first intake appointment will begin with the presentation of the informed consent form. The consent form will detail the requirements of study participation (e.g., # of visits, type of data collected, time commitment, etc.).

Subjects will be told that the purpose of the study is to evaluate the effects of medications on human behavior related to mood, sleep, and methamphetamine cravings/use. Information about the components of the experimental procedure will be explained. Details of the random assignment procedure (placebo or active dose) will be explained. Subjects will be informed of their attendance expectations. Other information on the consent form will include a full description of study requirements, reimbursement, risks, benefits, alternatives, and the role of the local IRB. All questions will be answered before written consent is requested. All research conducted in our laboratory and the CNRA has prior approval from the Committee for the Protection of Human Subjects (CPHS) of the University of Texas Health Science Center - Houston.

Selection Criteria

Eligible participants will:

1. Be between the ages of 18 and 65 years old
2. Meet DSM-5 criteria for methamphetamine use disorder
3. Be fluent in English and able to understand the consent form

Participants will be excluded if they:

1. Have an alcohol use disorder or report binge drinking (>7 drinks for women and >14 drinks for men)
2. Have a greater than mild substance use disorder on any other illicit substance
3. Have any medical conditions contraindicating SUVO (e.g., severe pulmonary disease, severe cardiovascular disease or clinically abnormal ECG, severe liver or kidney disease, seizure disorder, or sleep disorder – particularly narcolepsy)
4. Are currently taking medications with known drug interactions with SUVO (e.g., MAO inhibitors, anticonvulsants, haloperidol, phenothiazines, anesthetics, and any sedative)
5. Are pregnant or breast feeding
6. BMI > 30 (women only)
7. Have a current DSM-5 psychiatric disorder or neurological disease requiring on-going treatment that would make participation unsafe
8. Have history of seizure disorder

9. Have a head injury with loss of consciousness in the last 5 years

Assessment of Criteria

Eligibility will be carefully assessed in person at the CNRA. Participants will receive a full physical and psychiatric evaluation on the first day including: a medical-history questionnaire, physical examination, urine drug screen, pregnancy test, and ECG. SCID-5 will be conducted by licensed counselors and the physical examination will be performed by medical director (Dr. Weaver, M.D.).

Sources of Materials

We will obtain information about subjects from structured interview evaluations, physical examinations, self-report measures, and computerized behavioral tasks. This information will be collected at specified time points during the study phases of eligibility/baseline assessment, experimental testing, and end-of-study. The biological specimens obtained from all subjects will include urine, saliva for cortisol assessment, and breath samples for alcohol detection. Individuals who volunteer to participate will be assigned a subject number (e.g., 15000), under which all information collected will be filed. All materials will be obtained for the specific purposes of this research.

Potential Risks

Study Medication (suvorexant). Suvorexant (BELSOMRA®) is an orexin receptor antagonist indicated for the treatment of insomnia, characterized by difficulties with sleep onset and sleep maintenance. Recommended dose is 10 mg, 1x per night taken within 30 minutes of going to bed, with at least 7 hours of planned time before awakening. If the 10 mg dose is well tolerated but not optimally effective, it can be increased but not to exceed 20 mg once daily. Medication is taken PO, with dosage in tablets of 5, 10, 15, and 20 mg. Contraindicated in patients with narcolepsy. Precautions include daytime somnolence; dose-related risk of impaired alertness and motor coordination, including impaired driving; patients taking 20 mg should be cautioned against next-day driving; nighttime "sleep-driving" and other complex behaviors while out of bed and/or not fully awake; worsening of depression or suicidal thinking; compromised respiratory function; sleep paralysis, hypnagogic/hypnopompic hallucinations. Risk of the above symptoms increases with use of CNS depressants and alcohol. In obese women (BMI > 30), there is increased risk of exposure-related adverse effects. Belsomra® is a schedule-IV compound with mild/modest abuse-potential in the same class as existing sleep medications and anxiolytics. The most common adverse reactions include somnolence and slowed motor coordination. Not recommended for use in patients taking strong CYP3A inhibitors, efficacy may be reduced, or for patients with severe hepatic impairment. Based on animal data, Belsomra® may cause fetal harm.

Psychometric Testing. Items on certain psychological/psychiatric questionnaires and interviews might be perceived as personally discomforting to some subjects.

Actigraphy. Participants may experience mild discomfort while acclimating to wearing the device during sleep.

EEG Task. The EEG may lead to redness or skin irritation where the sensors are placed. This will almost always disappear after a few hours. The images that the participants will view will contain sexual and violent images (including erotic scenes and mutilated bodies) and may upset some participants. Viewing drug images can induce craving.

Cold Pressor Task. Individuals with cardiovascular disorders and neurological disorders should not participate. This information will be obtained during medical screening. Due to individual variation in pain and cold sensitivity, for some subjects the cold water may become too painful to sustain immersion for 90 seconds. There are no lasting effects (physical or physiological) from placing the hand and wrist in ice water (0° Celsius) for 90 seconds.

Psychiatric/Physical Examination. There is a slight risk of bruising and infection in the blood draw procedures. Disclosing mental health information during the clinical interview can be uncomfortable for some participants.

Confidentiality. There is always a risk of loss of confidentiality when participating in research.

Adequacy of Protection Against Risks

Study Medication (suvorexant). We will screen very carefully for alcohol use and suicide symptoms. It will be made explicit that participants should not drink alcohol for the duration of the study. We will use the mental health counselors SCID-screeners to enroll only those with low risk for alcohol abuse. The Columbia Suicide Severity Rating Scale (CSSRS) will be administered at each visit (see additional details below), as per NIH/FDA guidelines. Indication of regular alcohol use by SCID, intake self-report, or breath alcohol, or indication of increase in suicidality as measured by the CSSRS will result in study stopping (see details below). Will exclude for any patients taking CYP3A inhibitors; patients with severe hepatic impairment; and women who are or become pregnant. Pr d drug tests are administered.

on via urinalysis on lab testing days. Women of childbearing capacity must be taking one form of birth control. We will exclude for women with BMI > 30 to decrease risk of side effects.

In addition to the rigorous screening criteria for inclusion. At the end of each experimental day, cardiovascular measures will be taken and the subject will be evaluated for signs of impairment or side effects, by a research assistant and then by the research nurse, medical director, or PI. The assessment battery includes subjective effects questionnaire, nystagmus, touching nose, balance, and walking a straight line). If cardiovascular measures are normal, within the range of pre-dose levels, and the subject is determined to be unimpaired, the subject will be released. If any signs of intoxication are detected, participants will be required to remain at the experimental site until such symptoms are no longer observed.

In the event of either an unexpected adverse event or a prolonged period of intoxication, we have several measures in place. First, Dr. Weaver (CNRA medical director) has clinical experience and training in emergency medicine. Thus, a physician will be in the immediate vicinity of laboratory at all times. Offices and clinical space are within 100 feet of the lab. Collaborating MDs can be paged at any time during the day. Second, Ben Taub Hospital, a level 5 emergency medical center is located just minutes away from BBSB. Finally, in the event of extended sedation, intoxication, or impairment, in which any subject does not appear clear-headed, feeling well, and in full control of his or her behavior, two steps will be taken. First, the subject will remain in the lab until such time that the primary or a co-investigator deems that it is safe for him or her to leave (e.g., passing the sobriety test described above). In the event of extended impairment, we will arrange (and pay for) a taxi service to drive the subject back to his/her home rather than having to use METRO. We will administer the Columbia Suicide Severity Rating Scale (CSSRS screening version) at each visit to assess suicidality and depressive symptoms, consistent with current FDA best practices. If the screening indicates change in suicidal ideation, we will administer the full version. If suicidality is judged to clinically significant as per CSSRS scoring criteria, we will (1) report the event to CPHS within 48 hours; (2) remove the patient from the study; (3) make a referral to either the BBSB outpatient mood disorders clinic or UT HCPC, depending on consultation from Dept of Psychiatry outpatient faculty at BBSB.

The following procedures will be taken to safeguard against adverse medication events: (1) careful initial intake evaluation to determine eligibility based on inclusion/exclusion criteria; (2) thorough physical evaluation prior to treatment, consisting of physical examination, standard laboratory tests, electrocardiogram, toxicology screen, pregnancy test, and vital signs; (3) repeated tests during treatment; (4) daily monitoring of pill taking via CAROMA, returned pill counts, and self-report; (5) weekly review of adverse events and medication compliance; (6) regular evaluation by the study physician (Dr. Weaver). Specific criteria will be used to exclude potential subjects for whom any of the study medications is contraindicated. Any abnormal physiological, psychological, or behavioral event will be evaluated and, if indicated, will result in the subject's removal from the study.

We will use an Adverse Event Log (AEL) based on NIDA SAFTEE procedures. The AEL will record the duration, severity, and frequency or any adverse events, signs, and symptoms. An evaluation will be made as to the event's relationship to the study drug(s), scaled as unrelated, unlikely, possible, and probable. The AEL will be included in the report to DSMB.

Subjects will be monitored regularly for compliance with the study requirements, including the dosing regimen and breath alcohol testing upon arrival at the laboratory each day of testing. Written and verbal information about the medication will be given to all participants. This information will remind the subject to: (1) take food shortly after medication if needed to relieve gastric irritation; (2) inform the treatment research clinic nurse or physician of any over-the-counter and prescription medication taken, especially: cough medication, diarrhea medication, narcotic medication; (2) notify treatment research clinic nurse or physician of any side effects that persist or worsen. The study physician, nurse, and PI will review cases involving clinical deterioration of increased symptomatology or substance abuse. Appropriate actions will be taken, including study termination with proper referral.

Behavioral and Psychometric Testing. The participants do not have to answer any questions they do not feel comfortable answering and can not take part in the study.

EEG Task. Participants will be shown example images during the consent process and will be told they can stop viewing the images at any time. Those who think they will be affected by the pictures (erotic, mutilations, and drug-related images) can choose to not participate.

Cold Pressor Task. Participants will be told that if the level of pain is too uncomfortable, they should remove the hand immediately. Each participant will be able to test the water temperature for 10 sec prior to beginning the procedure. These details are presented in the informed consent document.

Psychiatric/Physical Examination. Our experienced phlebotomist will t[illegible]; any precautions to

prevent unnecessary bruising during venipuncture. All risks and protections are discussed further in the general evaluation of eligibility protocol (HSC-MS-0322).

Confidentiality: Confidentiality will be protected in several ways. All information collected solely for research purposes will be kept in locked, restricted access files. Individual subject information will be transferred to outside sources only with the express written request of the subject. Subjects will receive a copy of their signed consent form. All personnel associated with this grant have successfully completed ethics training in the Protection and Welfare of Human Participants, and certification is on file at the Health Science Center CPHS and office of sponsored projects. All intake and experimental data that are collected will be uploaded onto a laboratory database, computers dedicated to data storage and management. These computers are protected by password. All data will be treated as confidential information. All data including urine samples, medical and psychiatric intake exams, and behavioral and drug administration data – will be obtained solely for research purposes. All individuals who elect to participate and sign the informed consent agreement will be assigned a subject number (e.g., 15000), which will serve as that subject's identifier (rather than name or SS#). A log book and electronic database that connect participants' identifying information with subject number are kept in a locked file cabinet and room and password protected, respectively.

Potential Benefits of the Proposed Research to the Subject and Others

This study should help compliment and advise clinical research focused on stopping methamphetamine use, preventing relapse through improvement in relapse-related constructs (e.g., sleep problems, stress, and cue-reactivity). Subjects will be told if unusual information is discovered during the study that will make a difference in treatment for this or other problems.

Subject Payment

Participants will receive $40 for the baseline evaluation. As methamphetamine users tend to live further outside the city, we are budgeting extra for bus/parking validation/rideshare options, up to $30 per visit. Participants will receive $50 for each laboratory visit (3 visits total) and a completion bonus on their final visit for $50. If medication compliance is reached, participants will receive an extra $10 at each clinic visit.

Importance of Knowledge to be Gained

Research participation may assist non-treatment seeking subjects in abstaining from MA during study, and via study completion protocol, bring them into contact with treatment resources at our research center and in the community. MA use disorder is marked by repeated relapse, leading to devastating consequences on a personal and societal level. Currently, there is no medication that has been shown to be broadly effective in reducing MA use. Suvorexant (and orexin agonists more broadly), may help reduce sleep disruptions and attenuate stress and craving – helping to reduce risk of relapse. This experiment will compliment and provide valuable information to our ongoing and future addiction work, and contribute to the knowledge base in the treatment of MA use disorder. Our procedures have been designed to minimize the probability of risks. Our research center has an excellent track record in conducting human psychopharmacology experiments and clinical trials with the utmost attention to safety.

Inclusion of Women and Minorities

We aim to enroll nearly 50/50% male/female representation. In our prior study recruiting methamphetamine users, we enrolled a sample consisting of ~40% female. We will employ targeted advertising strategies to achieve gender representation in the proposed study as needed, including distribution of educational material and referral information at women's clinics in Houston and the surrounding communities (e.g., Passages for Women, Saving Grace Women's Home, Sober Living for Women). Also informed by our prior study, we expect the minority distribution to be approximately 12% Hispanic/Latino, with the racial breakdown being 12% Black/African American, 71% White, and 17% Other or more than one race.

Inclusion of Children

Children (age 18-21years) will be included in this research. From a safety perspective, risks of exposure to the proposed study medication in children with MA use disorder have not been established. The safety and efficacy of the proposed study medication should be established in adults first, before conducting this type of treatment research in children.

Data Safety and Monitoring Plan

1. The Principal Investigator will be responsible for knowing the policies of the local IRB (the UT – Houston Committee for the Protection of Human Subjects, CPHS). The PI will adhere to CPHS policies and maintain accurate documentation of CPHS correspondence and reports (e.g., annual report). The PI is responsible for documentation and handling of all possible study-related adverse events. The Treatment Research Clinic (TRC) within our Center for Neurobehavioral Research on Addictions (CNRA) has longstanding data collection and safety monitoring systems in place that will be available for the proposed study. These include staff training, weekly audit of data collection/entry, medical screening with results reviewed by on-site nurse and/or physician, use of standardized assessments, continued medical monitoring during the study, procedures to monitor medication compliance (CAROMA). As PI, Dr. Webber will assure that the above systems are in place and functioning properly during the study.

2. A Monitoring Committee will provide additional, independent oversight of data related to subject safety. This committee will perform the following activities: (a) review the research protocol and plans for data and safety monitoring; (b) evaluate study progress, including data quality, participant recruitment rates, retention rates, outcome and adverse experience data, and risk versus benefit profile; (c) make recommendations to the PI for a discontinuation of study medication for an individual patient based on adverse experiences; (d) make recommendations to terminate the study because of safety concerns; and (e) protect the confidentiality of the data and the results of monitoring. The Committee will be blind to study medication, unless they believe that termination of the trial is warranted. This committee meets annually to review all CNRA studies, and this present study will be added to the DSMB review in 2023. The DSMB report is submitted annually to CPHS.

3. Adverse events (AE) will be reported to the UT-CPHS on an annual basis. Serious adverse events will be reported immediately (verbally within 24 hours) to the UT-CPHS and the Monitoring Committee. A written report will follow as soon as possible but in no more than three days. The written report will be in the format required by the local IRB and will contain information regarding the date of the AE, description of the AE, severity rating (Grade 1 to 4), assessment of cause, whether the AE indicates an increased risk for current or future subjects, and whether changes to the informed consent form are necessary.

4. We will also use an ongoing Adverse Event Log (AEL) based on NIDA SAFTEE procedures. The AEL will record the duration, severity, and frequency or any adverse events, signs, and symptoms. An evaluation will be made as to the event's relationship to the study drug(s), scaled as unrelated, unlikely, possible, and probable. The AEL will be included in the report to DSMB.

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