Role of the orexin receptor system in stress, sleep and cocaine use

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ABSTRACT

Preclinical research has established important functions for the orexin system in mediating arousal/sleep, stress, and cue-induced reinstatement of drug taking (e.g., relapse). The role of stress/anxiety and drug cue reactivity in human drug relapse is well established, but to date, the role of the orexin system in modulating these phenomena has not been examined in humans with substance use disorders (e.g., cocaine). The goal of the present first-in-human study will be to examine the effects of an orexin antagonist (suvorexant) on interactions among stress/anxiety, sleep, and drug-cue reactivity. We will utilize a battery of highly sensitive, drug-specific, laboratory measures of drug cue reactivity (a relapse risk model), and well-established metrics of stress/anxiety and sleep. We hypothesize that antagonism of the orexin system will attenuate the link between (1) stress/anxiety and drug cue reactivity, and (2) sleep and drug cue reactivity. These results will elucidate a unique biochemical mechanism for understanding relapse, and provide a potential medication target for relapse prevention

SCIENTIFIC IMPACT

Given the promising preclinical data on the orexin system in modulating sleep, anxiety, and drug cue reactivity, this research project has high translational scientific value. Several recent publications make a strong argument for the importance of the orexin system in addictions. This project is innovative in two important ways (a) use of a laboratory-based, multivariate measurement approach, and (b) it will represent a first-in-human substance abuser research study of the orexin system. Successful completion of this project is assured by a strong team of investigators, and a highly coordinated research team with a strong track record in addictions research, integrated via our UT-supported center of addictions research (CNRA). Confirmation of the study hypotheses will advance the field by (a) elucidating the role of the orexin system as a neurobiological factor in addiction, and (b) providing a target biochemical system for the development of pharmacotherapeutics.

Role of the orexin receptor system at the nexus of stress, sleep and drug abuse

PROPOSAL

Significance of the problem. Stimulant dependence continues to be a significant public health problem with no FDA-approved options to facilitate abstinence or prevent relapse. Of the stimulants, cocaine presents the largest burden to the healthcare and criminal justice systems in terms of mortality, morbidity, violent crime, and unemployment – and this trend has not declined significantly for decades [1-3]. Prevalence rates in North America approach 6.5 million users, 40% of whom meet diagnostic criteria for cocaine use disorder, or CUD [2,4]. CUD leads to persistent disruption of neurotransmitter function corresponding to a state of "allostatis" that manifests in cognitive deficits, compulsive drug use, loss of control over drug-taking, and repeated relapses despite the desire to quit [5]. Even current treatments are marked by high relapse rates [6,7], prompting a need for innovative and novel neurobiological research, and eventually new treatment options.

Stress/anxiety in addiction. Stress and anxiety contribute substantially to all phases in the development of SUD: from risk for binge use, to the onset of dependence, to triggering relapse. Importantly, stress and anxiety increase the magnitude of drug-cue reactivity, and serve as risk factors for both the initiation of substance use and addiction relapse [8-10]. The use of illicit substances to reduce physiological and psychological stressors has been extensively characterized across laboratory, clinical, and epidemiological domains [11-13]. Lifetime stress is significantly associated with cocaine use severity [14].

Sleep in addiction. Sleep architecture is disrupted in chronic stimulant use – including cocaine, including both slow-wave and REM sleep [15-18]. These alterations produce deficits in total sleep, and are associated with exacerbation in psychiatric symptoms and cognitive functions [18,19]. Importantly, there is a reciprocal relationship between cocaine use severity and sleep quality and duration, creating a viscous cycle of impaired sleep, increased stress, and increased risk for cocaine use [14,20,21]. Previous work revealed that the medication modafinil significantly reduced cocaine-free urines over 6-weeks, and increases in slow wave sleep time mediated the drug effect [19]. The foregoing suggests that medications that improve sleep quality can aid in reducing substance use, and sleep enhancement is a documented SUD treatment strategy [20].

Drug cue reactivity, addiction and relapse. Drug cue reactivity is a well-documented and robust predictor of relapse. This relationship has been established for a variety of abused drugs, including cocaine. Craving and attentional bias are two of the best-documented indices of reactivity to drug cues. Both cue-induced craving and attentional bias have been identified as factors in nearly every major drug of abuse, and both are predictive of relapse following treatment [22-26], including cocaine [27-31]. Indeed, physiological, neural, and attentional response to drug cues are now considered hallmark characteristics of addiction [32,33]. The neurobiological overlap and documented correlations between drug craving and attentional bias [34-36] are likely because they are measures of the same construct (cue reactivity) and are modulated largely by the same neurocircuitry. Both cue-induced craving and attentional bias are amenable to pharmacological modulation [37,38], supporting cue-reactivity as a relevant target for pharmacological interventions in CUD.

Novelty and promise of the orexin system. The orexins are a class of recently discovered amino acid peptides concentrated in the hypothalamus with projections widely distributed throughout the brain. Two orexin receptors (OXR1, OXR2) have been identified. The orexin system is neuromodulatory, increasing neural action potentials via the regulation of glutamate and GABA. Its primary role appears to be in *energy homeostasis* (e.g., arousal, vigilance). Accordingly, antagonism (blockade) of OXR1 and OXR2 promotes sleep [39,40]. In addition, there is strong preclinical and phase 1 evidence that orexin antagonists modulate three key cocaine-related variables documented above: sleep [39,40], stress/anxiety [41-43], reactivity to stimulant drug cues, including cocaine [44-47]. Only one approved FDA compound with specificity for the orexin receptor system (***suvorexant***) is currently available in the US market. It is indicated for treatment of insomnia. We propose that, due to the ability to regulate stimulant drug-cue reactivity, anxiety/stress, and sleep, suvorexant is an intriguing and potentially efficacious compound for the prevention of relapse in CUD.

Summary. Medications that attenuate drug cue reactivity (attentional bias, craving), reduce stress/anxiety, and enhance sleep quality may be effective pharmacotherapeutics for SUD. As these three factors all contribute to relapse, orexin receptor antagonists may be ideally suited to address the dynamic interaction of these factors, thereby helping in the prevention of relapse.

Overall Aim. According to the conceptual model posited in Figure 1, the overarching aim of this project is to conduct a first-in-human drug user study to examine the effects of the orexin antagonist suvorexant on drug-cue reactivity and its interactions with stress/anxiety and sleep.

HYPOTHESES and SPECIFIC AIMS

1. **Main effect:** To characterize the direct effect of suvorexant on drug cue reactivity. We hypothesize that suvorexant will significantly attenuate cocaine cue reactivity (attentional bias, craving).
2. **Stress/anxiety interaction:** To characterize the degree to which stress/anxiety mediates the effect of suvorexant on drug cue reactivity. We hypothesize an indirect effect of suvorexant on drug cue reactivity via stress/anxiety, such that attenuation of cocaine cue reactivity (attentional bias, craving) will be greater in those with larger reductions in stress/anxiety duration.
3. **Sleep interaction:** To characterize the degree to which sleep mediates the effect of suvorexant on drug cue reactivity. We hypothesize an indirect effect of suvorexant on drug cue reactivity via sleep, such that attenuation of cocaine cue reactivity (attentional bias, craving) will be greater in those with larger improvements in sleep duration.

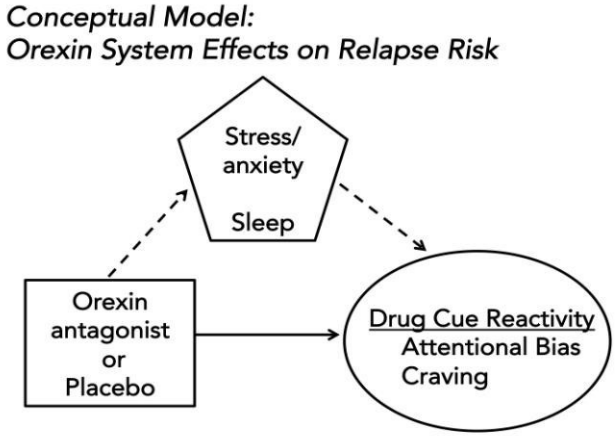

Figure 1. Summary of Conceptual Model

Research Plan

Our group at the University of Texas Center for Neurobehavioral Research on Addiction (CNRA) has developed, utilized, and validated laboratory models of drug relapse, allowing us to examine pharmacotherapeutic and cognitive-behavioral interventions for relapse prevention.

Study design. To accomplish the project aims, we will utilize a mixed-model experimental design, with a between-groups factor of dose (suvorexant vs. placebo) and a within-subjects factor of time. Subjects will receive suvorexant (**10 mg week 1, 20 mg week 2**) or placebo PO, once daily at 10 PM. Medication condition will be double-blind, with urn-randomized assignment to dose condition balanced by gender and severity of cocaine use. A summary of timelines and measures is shown in the Table below.

Mon	Wed	Fri	Mon	Wed	Fri	Mon
1,4,5,6,7	1,2,3,4,5	1,2,3,4,5	1,2,3,4,5,6,7	1,2,3,4,5	1,2,3,4,5	1,2,3,4,5,6,7
Key: (1) Provide medication (MEMS bottle); (2) Compliance data for medication adherence (MEMS, pill count, riboflavin, text message); (3) Side effects data, med check, UA toxicology; (4) Sleep data; (5) stress /anxiety data; (6) acute stressor challenge (cold pressor); (7) Cue reactivity data						

Participants and setting. The study will test 30 current cocaine users (enroll 45 to complete 30), 19 to 55 years old, who meet current DSM-5 criteria for cocaine use disorder (CUD) of at least moderate severity (≥4 symptoms). Subjects meeting criteria for substance use disorders other than cocaine, marijuana, or nicotine will be excluded. Notably, because the study medication (suvorexant) is contraindicated with alcohol use, we will exclude subjects with alcohol use disorders (via screening at intake). We will also exclude those individuals who are drinking > 10 alcoholic drinks per week (NIAAA criteria problem drinking = at least 14 drinks per week), and who are unwilling to stop using alcohol in the evening for the two weeks of the study. We will exclude those who report binge drinking (NIAAA criteria = in < 2.5 hours, 5 drinks for men, 4 drinks for women).

Other exclusion criteria will include significant and unstable medical/ psychiatric disorders which might make participation hazardous; acute or chronic health conditions; and concomitant medication use contraindicated with the study medication (suvorexant). This will be accomplished via full medical evaluation at intake by Dr. Michael Weaver, M.D., CNRA Medical Director. The study will be conducted at the Neurobehavioral Research Laboratory at the CNRA, directed by Dr. Lane. Recruitment strategies will include local advertising in print media, public service announcements on radio, and referrals to CNRA in the Houston metropolitan area. Based on previous and current CNRA recruitment rates of participants with CUD, we expect to enroll 3-4 participants per month to meet recruitment goals.

Measurements

Cue reactivity: Attention bias (AB) task is a saccade-based eye-tracking measurement, developed by Dr. Lane to assess attentional bias to drug cues [48]. Eye movements (saccades) have advantages over other variables because they are directly observable, ecologically valid, and typically stable across repeated measures [49,50]. AB measures utilizing eye movements have produced moderate to robust effects for a broad class abused substances [51-53], including cocaine [34,48,54]. Using our drug specific anti-saccade task, the between-group effect size for anti-saccade error rates in the presence of cocaine cues was large: CUD vs. control Cohen's d_{av} = 0.6 [48].

Cue Reactivity: Cocaine Craving Questionnaire (CCQ, [55]) is self-report 14-item measure with five conceptual domains: Desire to Use, Intention to Use, Anticipation of Positive Outcome, Anticipation of Relief from Dysphoria, and Lack of Control over use. The measure is well validated and has been used in multiple studies of CUD [55,56].

Sleep: Misft Shine (Misfit © 2012). Sleep activity is monitored with a 3-axis accelerometer inside the watch device, using a general heuristic based on time and motion. The two primary data outcomes from sleep mode are total sleep and sleep quality (deep sleep duration). The device is waterproof and worn on the wrist 24 hrs per day. Data are downloaded to smartphone via Bluetooth.

Sleep: Pittsburg Sleep Quality Index (PSQI, [57]). The PSQI is an 18-item self-report measure of sleep, providing a well-validated and reliable measure of sleep quality, latency, duration, duration efficiency, and disturbance, and an overall summary. It has been used in several studies of individuals with SUD, including cocaine [21,58,59].

Stress/Anxiety: Cold Pressor Test (CPT). The CPT reliably increases activity of the sympathetic nervous system and the HPA axis, and produces reliable increases in heart rate and cortisol [75, 76]. Subjects are requested to submerge the dominant arm up to the wrist or elbow in ice-cold water (0° to 4° C) for as long as possible with a maximum of 90 seconds. The procedure activates afferent nerves and elicits a CNS stress response [75, 76, 77]. This procedure produces no lasting biological or psychological distress beyond the acute challenge period, and physiological effects return to baseline within 90 min [78]. In fact, the CPT is used to study pain in children [79], and is considered a noninvasive, exempt educational experimental activity by the IRB of the University of Texas-Austin [80]. It has been used extensively in cardiology, endocrinology, psychiatry, and psychology since 1940 as a challenge to the peripheral and central stress axis [75, 76].

Stress/Anxiety: DASS21 [60] is a 21-item self report questionnaire assessing the severity of clinically agreed upon core depression, anxiety, and stress symptoms. It is well validated in multiple languages and countries [61], and has been utilized in SUD treatment and withdrawal studies [62-64].

Stress/Anxiety: VAS-Stress: current stress level is ranked on a 0 – 10 visual analog scale (0 = no stress, 10 = extreme stress) cued by the question "Please rate your current stress level". We have utilized this measure in previous studies of stress and SUD in our lab [48,65].

Medication compliance. Because the medication must be taken in the evening, compliance is a high priority. Accordingly, we will use a four-level approach to measurement of compliance: (1) Medical Event Monitoring System (MEMS, Aprex Corp.) bottles, (2) pill counts, (3) riboflavin markers, and (4) text reminders / replies. Text-based reminders to take the medication will be enabled via using a HIPAA secure texting service (Talksoft ©), used broadly in medical settings. Participants will be prompted each night at 10 PM to take their medication, and instructed to text back "yes" when they have taken their medication. Compliance-based payment contingencies (M, W, F): 4/4 = 100%, 3/4 = 75%, 2/4 = 50%, etc. These contingencies produce high compliance based on previous work in our laboratory using similar designs, where compliance rates averaged near 90% [66,67].

Data Analyses. We will use multilevel modeling to evaluate cue reactivity (attentional bias, craving) as a function of suvorexant, time, and the interaction of suvorexant x time. Hypothesis evaluation will utilize both Frequentist and Bayesian methods. Power and sample size focus on the effect of suvorexant on drug cue reactivity (AB, CCQ). From a Frequentist perspective, assuming a correlation of r = 0.5 between measurement points and alpha = 0.05, a sample of N=30 participants will provide 80% power to detect a moderate effect (Cohen's f= .0.24) for the interaction if treatment and time. For Bayesian analyses, multilevel priors will be vague and neutral: coefficients ~Normal (mean = 0, variance = $1x10^6$), level 1 variance ~ Gamma (shape=.001, scale=.001), level 2 variances ~ Uniform (0,100). Frequentist statistical models will utilize traditional mediation analyses as recommended by Baron and Kenny [68], which permits unbiased OLS estimates appropriate for this experimental design and sample size [69], and which we have utilized in previous published research [70]. Bayesian statistical models will utilize path analysis (BSEM) to evaluate the mediating effects of stress/anxiety (biological and subjective-rated) and sleep (biological and subject-rated) for the effects of suvorexant on drug cue reactivity. An example of a mediation analysis using Bayesian SEM may be found Arbuckle [71]. Uncertainty surrounding the Bayesian estimate for the indirect effect employs the posterior distribution of the parameter (i.e. the product coefficient): a density denoting the probability that different values of the parameter obtain given the observed data. This approach may be particularly important for evaluating more complex mediation models (e.g. multiple mediators, latent variables) in the context of small sample sizes. Use of the MCMC (Monte Carlo Markov Chain) approach in Bayesian analyses has demonstrated superior small sample performance relative to maximum likelihood-based approaches in continuous, normally distributed data [72]. These properties are likely due to the MCMC approach's lack of reliance on large sample size assumptions [73]. BSEM prior specification will adapt recommendations from Muthén and Asparouhov [74].

Subject Payment. The payment schedule is detailed below. Subjects will be paid the medication compliance, study visit bonus, and participation earnings at the end of each experimental day (M, W, F). Subjects will receive an additional bonus ($50) for completing of the study. Total possible payment for meeting all study requirements and collecting all bonus payments will be $337.

Medication compliance. $2 for each metric: 1) Medical Event Monitoring System (MEMS) bottle opening, (2) pill counts (empty bag), (3) positive riboflavin markers, and (4) text reply to reminder. Absence of each will result in payment not being earned for that specific metric. Total possible payment = $8 per day X 14 study days = **$112**. *Study visit bonus*. $10 for on time arrival and providing an alcohol-free breath sample and urine sample. Total possible payment = $10 per day X 7 visit days = **$70**. *Participation*. Total possible payment = $15 per day X 7 visit days = **$105**. Completion bonus **$50**.

Subject participation requirements. Subjects must take the medication as close as possible to 10:00 PM each evening, and reply "yes" to the medication text prompt (texts will be sent at 15-minute intervals from 9:45 PM to 10:30 PM). On M, W, F over 2 consecutive weeks (see Study Design), subjects will visit the lab at 10 AM. At every visit, they will provide the following: medication update (MEMS bottle), side effects data questionnaire, med check up with nurse, UA fluorescence and toxicology, sleep data (wrist monitor and sleep questionnaire), and stress/anxiety questionnaires. The visit will take approximately 1 hour. In addition, on each Monday (day 1, 7, and 14) subjects will complete: (1) the cold pressor test (with cardiovascular measures and saliva sample for cortisol level), (2) the saccade-based attentional bias test, and (3) the cocaine cue reactivity questionnaire. On these three study days, the visit will take approximately 2 hours.

Data Safety Monitoring Plan

E1. Human Subjects Involvement and Participant Characteristics

The study will test 30 current cocaine users (enroll 45 to complete 30), 19 to 55 years old, who meet current DSM-5 criteria for cocaine use disorder (CUD) of at least moderate severity (≥4 symptoms). Subjects meeting criteria for substance use disorders other than cocaine, marijuana, or nicotine will be excluded. Notably, because the study medication (suvorexant) is contraindicated with alcohol use, we will exclude subjects with alcohol use disorders (via screening at intake). We will also exclude those individuals who are drinking > 7 alcoholic drinks per week, and who are unwilling to stop using alcohol in the evening for the two weeks of the study. Other exclusion criteria will include significant and unstable medical/ psychiatric disorders which might make participation hazardous; acute or chronic health conditions; and concomitant medication use contraindicated with suvorexant (e.g., medications with sedative properties). This will be accomplished via full medical evaluation at intake by Dr. Michael Weaver, M.D., CNRA Medical Director. The study will be conducted at the Neurobehavioral Research Laboratory at the CNRA, directed by Dr. Lane. Recruitment strategies will include local advertising in print media, public service announcements on radio, and referrals to CNRA in the Houston metropolitan area. Based on previous and current recruitment rates of cocaine treatment-seeking men and women for studies at the CNRA, we expect to enroll 3-4 participants per month to meet recruitment goals. Subjects will be required to participate for 2 days (intake, screening) + 2 weeks (formal experimental study), coming to the CNRA lab M, W, F.

Research data will be collected at scheduled time points during intake, baseline, experimental conditions, and end-of-study. Urine assays will assess recent cocaine use as urine benzoylecgonine < 300 ng/mL confirmation.

Demographic characteristics of cocaine-dependent patients recruited into treatment studies show a mean age of 41 years, 83% are male, 15% Caucasian, 75% African-American, 10% Hispanic. Men and women of all ethnic backgrounds will be recruited to participate. It is anticipated that the subject demographic profile will closely mirror the larger population from which they are recruited, however, because we are recruiting non-treatment seekers, we expect to a broader range of subjects to select from and anticipate a 70% / 30% male/female subject distribution. Efforts will be made to increase the percentage of women in the study. These efforts will include (1) having the outreach coordinator present educational material and referral information at women's clinics in the greater Houston area.

Children (defined here per NIH guidelines as 19-21 years old) will be included in this research. The incidence of severe cocaine use disorder is relatively small in the population of youth less than 18 years old. From a safety perspective, risks of exposure to the proposed study medication in substance dependent children 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.

Exclusion criteria will include: (1) current DSM-IV diagnosis of any psychoactive substance dependence other than cocaine, marijuana, or nicotine; (2) have a DSM-IV axis I psychiatric disorder or neurological disease or disorder requiring ongoing treatment and/or making study participation unsafe; (3) significant current suicidal or homicidal ideation; (4) medical conditions contraindicating administration of suvorexant (e.g., severe pulmonary disease, severe cardiovascular disease or clinically abnormal EEG, severe liver or kidney disease, seizure disorder, or sleep disorder – particularly narcolepsy); (5) taking medications known to have significant drug interactions with the study medication(s) (e.g., MAO inhibitors, anticonvulsants, haloperidol, phenothiazines, anesthetics, and all sedatives); (6) currently or recently (last 3 months) treated for substance use [other than cocaine or nicotine] or another psychiatric condition; (7) conditions of probation or parole requiring reports of drug use to officers of the court; (8) impending incarceration; (9) pregnant or nursing for female patients; (10) inability to read, write, or speak English [required for lab tasks and psychometric scales]; (11) unwillingness to sign a written informed consent form; (12) subjects with alcohol use disorders or are drinking > 7 alcoholic drinks per week. All subjects who are excluded will be given referral information to other local treatment programs.

E2. 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 intake, 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., 10500), under which all information collected will be filed. All materials will be obtained for the specific purposes of this research.

E3. Potential Risks

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.

Risks for Behavioral and Psychometric Testing. Behavioral tests are administered via custom written computer programs that track subject's eye movements. This testing could produce frustration or fatigue if subjects have trouble with acquisition or mastery of the task or concentrating eye gaze for 10-12 minutes. Items on certain psychological/psychiatric questionnaires and interviews might be perceived as personally discomforting to some subjects. While subjects may be uncomfortable reporting these issues, the risks of serious sequelae are extremely low.

Risks for Cold Pressor Test. 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 from placing the hand and wrist in ice water (0° Celsius) for 90 seconds.

Risks for Physical Examination. There is a slight risk of bruising and infection in the blood draw procedures. This draw and the intake screening and physical exam are part of the CNRA General Evaluation protocol, and are approved under protocol HSC-MS-05-0322 and detailed therein.

E4. Adequacy of Protection Against Risks

Procedures to Minimize Drug-Related Risks.

We will screen very carefully for alcohol use and depressive symptoms. It will be made explicit that participants are not to drink alcohol in evening. We will use the Alcohol Use Disorders Identification Test (AUDIT) score and our mental health counselors SCID-screeners to enroll only those with low risk for alcohol abuse. Subjects will report no current depressive symptomatology (Beck Depression

Inventory, or BDI < 15), with no past depressive episodes or suicidal ideation. 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 AUDIT score, intake self-report, or breath alcohol, or indication of increase in depressive symptomatology / 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. Pregnancy and 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, although it should be noted that in our cocaine use disorder population, we rarely encounter obese patients.

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, first 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). The large majority of our cocaine use disorder subjects use the METRO system, thus driving hazards are expected to be rare. However, 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.

For the cold pressor task, participants will be told that if the level of pain is too uncomfortable, they should remove the hand immediately and not wait to the end of the 90 sec test period. 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. Because there are no sustained effects of cold water, if a participant cannot sustain the immersion for 90 sec on one test day, it will not preclude repeated testing on other lab test days (the cold pressor test will be repeated 3 times).

Other Protections Against Risk. 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 using MEMS caps, 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.

For all three experiments included in this project, 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.

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., 3200), 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.

Recruitment and Informed Consent. Participants will be self-referred in response to various study advertisements via newspaper (Grensheet, Houston Press) and radio. All CNRA recruitment materials have been approved by CPHS for ongoing studies over the past 5 years. 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 substance abuse (cocaine users). 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.

E5. Potential Benefits of the Proposed Research to the Subject and Others

All services provided in these studies will be free. The studies should help compliment and advise clinical research focused on stopping cocaine use, preventing relapse, and improving cognitive and behavioral functioning related to impairment following cocaine abuse. Subjects will be told if unusual information is discovered during the study that will make a difference in treatment for this or other

problems. By taking part in this research subjects may help themselves toward recovery and others with similar problems.

Subject Payment. The payment schedule is detailed below. Subjects will be paid the medication compliance, study visit bonus, and participation earnings at the end of each experimental day (M, W, F). Subjects will receive an additional bonus ($50) for completing of the study. Total possible payment for meeting all study requirements and collecting all bonus payments will be $337.

Medication compliance. $2 for each metric: 1) Medical Event Monitoring System (MEMS) bottle opening, (2) pill counts (empty bag), (3) positive riboflavin markers, and (4) text reply to reminder. Absence of each will result in payment not be earned for that specific metric. Total possible payment = $8 per day X 14 study days = $112. *Study visit bonus*. $10 for on time arrival and providing an alcohol-free breath sample and urine sample. Total possible payment = $10 per day X 7 visit days = $70. *Participation*. Total possible payment = $15 per day X 7 visit days = $105. Completion bonus $50.

E6. Importance of the Knowledge to be Gained.

Research participation may assist non-treatment seeking subjects in abstaining from cocaine during study, and via study completion protocol, bring them into contact with treatment resources at our research center and in the community. Cocaine dependence 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 cocaine use. Suvorexant (and orexin agonists more broadly), may help reduce sleep disruptions and anxiety, and attenuate craving and biased attention toward drug cues – 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 cocaine dependence. 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.

E7. Inclusion of Women and Minorities

Women, minorities, and children will be included at minimum to the extent they are reflected in this cocaine-dependent population. In previous cocaine clinical studies at the Treatment Research Clinic (TRC), the percentage of females and males is approximately 20% and 80% respectively. We will continue recruitment efforts to achieve a 50-50 balance and thus permit meaningful analyses by sex across groups. One effort will be to have the TRC outreach coordinator present educational material and referral information at women's clinics in Houston and the surrounding communities. In the past this has helped to enhance recruitment of women with cocaine dependence.

The ethnic representation has been 67% Black, 25% White, and 8% Hispanic. In the absence of data on the prevalence of cocaine dependence disorder in the Houston area, we cannot define ethnic base rates. The medical center environment is not known to be uniquely avoided by any particular ethnic group and patients view it as favorable and neutral. Nevertheless, we are prepared to implement recruitment procedures to ensure a more diverse patient population. These procedures include: 1) Targeted advertising in newspapers which serve minority communities (e.g., Hispanic or Latino communities). 2) Distribution of flyers and notices in neighborhoods known to have a high minority population. 3) Engaging in outreach activities on an ongoing basis, e.g., contacting church and community leaders in the Hispanic communities to provide educational material about cocaine dependence and its consequences; providing contact information to aid in referrals to our clinic (see **Core** for additional details).

E8. Inclusion of Children

Children (age 18-21years) will be included in this research. The incidence of severe cocaine abuse/dependence is relatively small in the population of youth less than 18 years old. From a safety perspective, risks of exposure to the proposed study medication in substance-dependent children 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.

E9. Data and Safety Monitoring Plan (NIH/NIDA specific issues)

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 physician, use of standardized assessments, continued medical monitoring during the study, procedures to monitor medication compliance (MEMS caps, texts). As PI, Dr. Lane 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 2016. 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, the Monitoring Committee, and to the NIDA. 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.

E10. Specific Issues: NIDA / NACDA Guidelines on Administration of Drugs to Human Subjects.

Risk/Benefit. These issues are described in sections **E1 through E6**. As noted above, the potential for advances in scientific and treatment domains related to addiction are considerable. Based on the qualifications and long history of work in this area by the investigative team and the careful screening and monitoring for subject safety, we feel there is a favorable balance of potential benefit against risk.

Data Safety Monitoring Board is described in **E9**.

Informed Consent is described in section **E4**.

Subject Selection is described in section **E1**.

Confidentiality is described in section **E4**.

Medical and Psychological Screening and Services are described in sections **E1, E4, and E9**, as well as sections **D1 and D2** of the application.

Administration of Drugs to Individuals Who Have Never Used Drugs. Study drugs will not be

administered to subjects who have never used drugs. By definition all subjects will be individuals with substance use disorder (cocaine). Most of our subjects with cocaine use disorders also have an extensive history of use of other illicit drugs.

Involvement of Individuals Currently Addicted to Drugs and/or Are Frequent Drug Abusers. We have taken into consideration the need to assess the participant's ability to provide informed consent (via use of screening and the Shipley-2 aptitude assessment). While these are non-treatment seeking individuals, a serious and concerted effort will be made to link these individuals to drug abuse treatment. At study end, subjects will receive a follow up medical examination and a session with a licensed counselor in our treatment research clinic, who will provide information about treatment options and referrals. As described thoroughly in D1, D2, E1 and E4 we have rigorous medical examination and screening procedures to assure the absence of any medical or mental condition for which further drug exposure would be contraindicated. Our procedures do not entail exposure to higher doses, rates of administration, or new route of administration than they would normally encounter by under usual circumstances. If subjects have participated in prior clinical drug intervention trials at our treatment research clinic, a complete list of drugs and dosing protocols will be reviewed and kept in his/her evaluation record. Subjects using any current CNS active medications will be excluding from testing and rescheduled (if medication use was idiosyncratic, e.g., OTC for recent cold or headache) or excluded (if medication use is regular or for a chronic condition). In particular, we will exclude those with alcohol use disorders or who report frequent alcohol consumption (> 7 time drinks per week), as suvorexant is contraindicated with alcohol due to potentially dangerous interactions with regard to sedative effects.

Administration of Drugs to Incarcerated Individuals. Individuals who are currently on parole or probation with random drug testing by court officers, or who are currently incarcerated, will be excluded

Administration of Drugs to Individuals with Mental Disorders. Individuals with DSM-IV Axis - I mental disorders other than SUD will be excluded.

Drug Doses and Routes of Administration. The proposed doses in these experiments (10 mg, 20 mg) have all been safely given to human subjects in previous laboratory experiments and clinical trials. Standard routes of administration (PO capsules) will be used. No doses will be given outside the range of those already administered to humans in previous studies and indicated in the prescribing information in the investigator's brochure.

Prior and Current Drug Treatment Status. All subjects in the proposed experiments will be non-treatment seeking. Although appropriate measures for help with addiction will be provided at study end, where subjects will receive a follow up medical examination and a session with a licensed counselor in our treatment research clinic, who will provide information about treatment options and referrals.

Prior and Current Treatment Experience. If subjects have participated in prior clinical drug intervention trials at our treatment research clinic, a complete list of drugs and dosing protocols will be reviewed and kept in his/her evaluation record. Subjects using any current CNS active medications will be excluding from testing and rescheduled (if medication use was idiosyncratic, e.g., OTC for recent cold or headache) or excluded (if medication use is regular or for a chronic condition).

Women of childbearing potential will not be excluded from these experiments.

Pregnant Women will be excluded from these experiments, and urine pregnancy testing will be performed at each visit to the research center (3 to 5 days per week).

Special Considerations Across the Lifespan. Individuals under the age of 19 will be excluded from this research due to risks and unknown effects of these drugs in adolescents, and ethical concerns of administering drugs of abuse to individuals this age. Additionally, individuals this age may be in school,

which would preclude the normal daytime participation time. We will also exclude individuals over age 55, as elderly subjects also constitute a vulnerable population with regard to drug effects. Additionally, changes in anatomy and physiology in the elderly that may alter the metabolism and short and long-term effects of drugs, compromising both safety and scientific validity.

Study Personnel Training and Experience. All medical and psychiatric screening and interviews will be conducted by trained clinicians, who are first trained by experienced SCID interviewers using standardized training videotapes from Biometrics Research, NY. 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. CNRA pharmacists will carry out preparation of medication; distribution of medication by research assistants will follow after training has been conducted by the PI (Lane).

Infection Risk Reduction Counseling and Testing. As described in sections D1, D2, E1 and E4, we recognize these risks and have included the necessary tests and precautions for disease transmission and infection risk (HIV, tuberculosis (TB), hepatitis, syphilis). HIV counseling will be made available as deemed appropriate by medical personnel in the treatment research center.

Safety of Research Participants Outside of the Research Site. These issues are addressed in section **E4.** They are repeated here for clarity. In addition to the screening criteria for inclusion, each visit to the laboratory will include a full side effects profile. Additionally, subjects will be evaluated for signs of impairment or side effects, first by a research assistant and then by a PI and CNRA research nurse. The assessment battery includes subjective questionnaire, nystagmus, touching nose, balance, and walking a straight line. If the subject is determined to be unimpaired, s/he will be released promptly. If any signs of sedation or other impairment 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 heavy sedation, we have several measures in place. First, Dr. Weaver (CNRA medical director) is a licensed MD with clinical experience and training in emergency medicine. Thus, a physician will be in the immediate vicinity of laboratory. Offices and clinical space are contiguous to the lab. Second, Ben Taub Hospital, a level 5 emergency medical center is located less then 5 minutes away from our building. Finally, in the event of extended sedation 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 PI, medical director, or research nurse deems that it is safe for him or her to leave (e.g., passing the test described above). Second, if necessary, we will arrange for a taxi service to drive the subject back to his/her home.

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 (including exclusion for alcohol use disorder or frequent regular use); (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 using MEMS caps, returned pill counts, and self-report; (5) weekly review of adverse events and medication compliance; (6) 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.

For this project, 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, scaled as unrelated, unlikely, possible, and probable. The AEL will be included in the report to DSMB. Relevant information is also included in section **E9.**

Referral to Treatment. As noted above, at study end subjects will receive a follow up medical examination and a session with a masters-level licensed counselor or RN in our treatment research

clinic, who will provide information about treatment options and referrals. If depression or suicidal ideation is measured at risk during the study, participation will be terminated and appropriate referrals made (see above).

Incomplete Disclosure. We have no elements of deception in this project, other than withholding of dose information to subjects about dose contents on days of testing (e.g., suvorexant or placebo). However, informed consent documents will contain full disclosure of the drug that may be received during the course of the experiments, along with potential side effects. No information about study risks will be withheld from subjects.

Payment for Participation in Research. Subjects will be paid daily for attendance and for performance on the behavioral tasks, and a bonus at the end of the study for completion. Subjects will be paid the medication compliance, study visit bonus, and participation earnings at the end of each experimental day (M, W, F). Subjects will receive an additional bonus ($50) for completing of the study. Total possible payment for meeting all study requirements and collecting all bonus payments will be $337. *Medication compliance*. $2 for each metric: 1) Medical Event Monitoring System (MEMS) bottle opening, (2) pill counts (empty bag), (3) positive riboflavin markers, and (4) text reply to reminder. Absence of each will result in payment not be earned for that specific metric. Total possible payment = $8 per day X 14 study days = **$112**. *Study visit bonus*. $10 for on time arrival and providing an alcohol-free breath sample and urine sample. Total possible payment = $10 per day X 7 visit days = **$70**. *Participation*. Total possible payment = $15 per day X 7 visit days = **$105**. Completion bonus **$50**.

F. Vertebrate Animals

Not applicable.

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