Document Section Cover Sheet

Official Title: The Efficacy of Suvorexant in Treatment of Patients With Substance Use Disorder and Insomnia: A Pilot Open Trial

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Protocol Title:

The Efficacy of Suvorexant in the Residential Treatment of Patients with Substance Use Disorder and Insomnia: A Pilot Open Trial

Principal Investigator:

Name: Scott Bunce, PhD
Department: Psychiatry and Behavioral Health
Telephone: 215-510-8295 (cell)
E-mail Address: sbunce@pennstatehealth.psu.edu

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1.0 Objectives

1.1 Study Objectives

The literature supports the case for an open trial of suvorexant, an orexin 1 / 2 receptor antagonist, in patients in residential treatment for substance dependence disorders, who complain of sleep disturbance. The patients will be at least 5 days post-withdrawal, in order to minimize the residual sleep complaints associated with that phase of treatment. In previous, well-designed, placebo-controlled clinical trials in patients with insomnia (1), suvorexant has been shown to be efficacious compared with placebo. However, substance dependent patients with insomnia were not included in these studies. Although, as a new sleep medication, suvorexant has been placed in Schedule IV by the FDA, the drug has not been studied in the context of its potential abuse liability when administered at bedtime at the therapeutic dose among patients in residential treatment for substance dependence disorders. We will therefore incorporate a modified abuse liability protocol in this pilot study.

Importantly:
1. Data from animal models of opioid dependence suggest that orexins may be involved in reward seeking behavior, and that an orexin 1 receptor antagonist reduced heroin self-administration and cue-induced heroin seeking behavior in the rat (2).
2. Chronic stress and compulsive drug seeking are influenced by orexin transmission throughout the hypothalamic, extended amygdala, brainstem, and meso limbic pathways (3). These dysregulated states of hyperarousal may be normalized by an orexin 1 receptor antagonist
3. Finally, whereas the drug has been placed in Schedule IV by the DEA and the FDA, the FDA Briefing Document stated that "the potential abuse liability of suvorexant in patients with insomnia is considered to be low . . . suvorexant was not self-administered in non—human primates . . . Based on the outcome of these studies, there was no evidence that suvorexant has the potential for abuse or dependence" (1).

Hypotheses:
1. Relative to a baseline, patients being treated with suvorexant will experience an increase in total sleep time, fewer awakenings after sleep onset, and improved subjective sleep quality.
2. Relative to baseline, patients being treated with suvorexant are more likely to experience decreased total daily salivary cortisol over the course of 7 days of treatment.
3. Relative to baseline, patients being treated with suvorexant are more likely to report improved moods, and decreased ambient craving.
4. Patients being treated with suvorexant are not likely to endorse scale items associated with abuse liability 30 minutes after drug administration or the following morning.

1.2 Primary Study Endpoints

1) To determine if patients taking suvorexant will have improved sleep quality (increased total sleep time, fewer awakenings), as measured through, sleep wrist actigraphy, actigraphy logs, modified Pittsburgh Sleep Quality Index (PSQI), and modified Insomnia Severity Index (ISI).
2) To assess whether or not patients endorse scale items on a modified abuse liability assessment battery.
3) To determine if associations between daily reports of mood, stress, craving and sleep using Ecological Momentary Assessment (EMA data) change during the course of the study.
4) To determine if patients taking suvorexant will have a decrease in total daily salivary cortisol over the course of the study by collecting samples at five time points for two consecutive days at two different times in the study.

1.3 Secondary Study Endpoints

1) To assess reactivity of EMA ratings of craving and mood in response to naturally occurring stressors, determining if these associations change during the course of medication.

2) To use advanced statistical techniques to holistically characterize systemic dysregulation (including self-reported daily mood, stress and craving) and emerging patterns of re-regulation while taking suvorexant.

2.0 Background

2.1 Scientific Background and Gaps

It is now generally recognized that a number of factors contribute to the heightened risk of relapse in patients with substance use disorders (SUDs). These elements include, but are not limited to: 1) dysregulation of the HPA axis; 2) sleep complaints (including delayed sleep onset, time awake after sleep onset, total sleep time, and/or complaints of poor sleep quality); and 3) negative moods, ambient and cue-related craving and anhedonia (4-7). Persistent sleep disturbances following withdrawal from drugs of abuse are common and frequently continue over the course of a typical 28 to 30 days stay in residential treatment. Sleep abnormalities (8) have been associated with HPA axis dysregulation. Together, these findings suggest that complaints of insomnia in patients with alcohol or opioid dependence may represent an important but relatively untreated element in the complex neuropsychobiology contributing to risk of relapse.

2.2 Previous Data

The general study design of this research proposal builds on a NIDA funded study (Prescription Opioid Dependence: Physiology, Emotion & Treatment Outcome (R01 DA035240; STUDY 00044050)) that robustly predicted treatment outcomes in a cohort of patients with opioid dependence. Sleep complaints, and changes in daily and within day craving and mood and salivary cortisol over time, were assessed in a cohort of opioid dependent patients. In a subsample (n=13) of patients who remained in residential treatment for a period of 60 days; 5 relapsed while 8 remained abstinent 90 days after residential treatment discharge. These subjects were assessed for cortisol and sleep at two time points approximately 30 and 60 days following detox. Cortisol levels were assessed 5 times per day for two successive days during each data assessment period. There was no difference between those that relapsed or abstained during the initial assessment. However, cortisol levels were decreased in those that abstained and remained constant in those that relapsed after 60 days of treatment (P=0.007). Sleep was also objectively assessed with actigraphy across the full 12 day data collection period. Again, there was no difference between those that relapsed and those that did not during the first assessment period, but those that abstained demonstrated an increase in total sleep time while total sleep time in those that relapsed remained constant (P=0.048). In summary, an improvement in both cortisol and sleep during the 60 days of residential treatment was associated with abstinence of at least 90 days post discharge.

2.3 Study Rationale

Sleep complaints during the first weeks following detoxification should be considered a result of drug withdrawal, meeting the DSM-V criteria of substance induced sleep disorder- insomnia type (9). We can anticipate that HPA axis activation occurs in all phases of insomnia symptoms, i.e., substance induced sleep disorder – insomnia type, acute insomnia or chronic insomnia. Sleep complaints were common among opioid dependent patients in residential treatment for 30 days following medically assisted withdrawal in our NIDA-supported study (R01 DA035240; STUDY 00044050)). Patients who remained in residence for 60 days or more, showed either a worsening or an improvement in sleep symptoms. Individuals whose total sleep time increased over the 60-day period were more likely to remain abstinent following discharge than patients whose total sleep time decreased. At this juncture, there has been no systematic study on the effects of suvorexant on sleep complaints at any stage of recovery from opioid or alcohol dependence.

Neuroadaptations that occur in the course of addiction disrupt the normal function of the HPA axis. The HPA axis is a major neuroendocrine system that controls reactions to stress and regulates many body processes, including sleep, mood, and emotions. When patients are withdrawn from drugs of abuse, they experience a cluster of symptoms, including diminished motivation for natural rewards (anhedonia), an increase in reward thresholds, hypersensitivity to stress, chronic irritability, emotional pain, dysphoria, and significant sleep disturbances. These symptoms have been described in the early stages of withdrawal from alcohol, opiates, cocaine, cannabis, stimulants, and polysubstance abuse, and are thought to significantly contribute to patient relapse. In numerous patients, these symptoms are present for several months following withdrawal, and many patients continue to complain of sleep disturbances even when utilizing currently available prescription and nonprescription sleep medications.

A medication that can improve sleep and normalize HPA axis function may help to alter mood and craving in patients with alcohol and/or opioid drug dependence. Suvorexant, an orexin 1/2 receptor antagonist, is a new type of sleep medication that works not only on the sleep response, but also on mood and emotion (1). Whereas orexin 2 receptors influence sleep, a compound that blocked orexin 1 receptors reduced heroin self-administration and cue-induced heroin seeking behavior in rats (2). Brain areas that are influenced by orexin transmission are involved in the regulation of responses to chronic stress and compulsive drug seeking (3). In summary, suvorexant may be a more efficacious medication for SUD patients with sleep disturbance, as it works on brain systems associated with mood and emotions, as well as sleep.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

1. Sex: male or female
2. Age: 21-64 (inclusive) years old
3. Caron Foundation residential alcohol or opioid dependent patients that have a history of daily or near daily substance use for the month prior to admittance.
   Group 1: At least 5 days post medically assisted withdrawal for alcohol dependence, and complain of problems falling asleep, remaining asleep after sleep onset, or poor sleep quality on current sleep medication (antidepressant/melatonin) for at least 3 days.
   Group 2: At least 5 days post medically assisted withdrawal for opioid dependence and complain of problems falling asleep, remaining asleep after sleep onset, or poor sleep quality on current sleep medication (antidepressant/melatonin)for at least 3 days.
4. Fluent in written and spoken English.

3.2 Exclusion Criteria

1. Patients who are concurrently receiving a psychoactive drug for the treatment of an Axis I disorder, but not including sedating antidepressants trazadone or mirtazapine that have been prescribed for the treatment of sleep disturbance.
2. Patients with current major depressive disorder greater than mild or moderate, schizophrenia, bipolar disorder, or a history of traumatic brain injury.
3. Patients with a history of narcolepsy or REM related phenomenon.
4. Patients with chronic respiratory problems including asthma, COPD, or other respiratory issues that can lead to sleep disturbances at night.
5. Patients with current suicidal ideation or a history of previous suicide attempts.
6. Patients with severe liver impairment.
7. Women who are pregnant or breastfeeding.
8. Patients who are severely obese.
9. Decisional impairment
10. Prisoners or under legal mandate.
11. On any medication that would interfere with study participation

12. Hypersensitivity to medications in the same class as suvorexant
13. Any chronic conditions or exclusionary criteria that would prevent participation in the study or lead to participant at risk of untoward effect because of participation in the study.

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

Subjects are free to withdraw at any time without any influence impacting their ongoing treatment. If a patient experiences side effects, these will be documented and reported to the FDA, as required.

3.3.2 Follow-up for withdrawn subjects

The primary reason for participant study withdrawal would be due to early discharge from the Caron treatment program prior to successful completion. There would be no follow up with these patients.

4.0 Recruitment Methods

4.1 Identification of subjects

Participants will be identified using two methods:

- The Caron based study coordinator will review the electronic medical records (EMR) of recently admitted patients and check for the inclusion/exclusion criteria
- Participants will also be identified through research flyers, which will be displayed in all units at the Caron Foundation. Interested patients will approach the Caron staff/counsellors who will in turn refer the subjects to the Caron based study coordinator. The Caron based study coordinator will check for inclusion/exclusion criteria by reviewing their EMR.

4.2 Recruitment process

Recruitment will use a two-step process:

- The Caron based study coordinator will complete a comprehensive REDCap screening and eligibility checklist to verify study eligibility based on established inclusion/exclusion criteria. It will be reviewed with the study coordinator at Hershey Medical Center (HMC) and the PI or his designee. If a Subject is deemed eligible to participate in the research based upon the preliminary assessment and if aggregable by the HMC coordinator and the PI of his designee, the Caron-based study coordinator will approach the participant to inquire about possible interest in the study. This study coordinator will review the study design, suvorexant information packet, and the inclusion/exclusion criteria with each prospective research participant.
- . Only subjects approved by the Hershey staff (study coordinator at Hershey Medical center and the PI or his designee) will be asked to review and sign an informed consent form if they wish to participate.

4.3 Recruitment materials

Flyers will be displayed on the treatment units at the Caron Foundation.

REDCap Screening Form (see the document “Screening Checklist” attached in CATS)

4.4 Eligibility/screening of subjects

In addition to the medical record review, participants may be asked questions designed to inform determination of eligibility from an additional screening script prior to signing the consent document .

5.0 Consent Process and Documentation

5.1 Consent Process

5.1.1 Obtaining Informed Consent

5.1.1.1 Timing and Location of Consent

Consent will be obtained on Day 0 (see study design) at the Caron Foundation by the Caron study coordinator after discussing the study in detail.

5.1.1.2 Coercion or Undue Influence during Consent

Subjects will be informed that participation is voluntary and that their decision to participate will not affect treatment at the Caron Foundation. The Caron-based study coordinator will comprehensively discuss the study with the patients, review consent documents, and answer all questions.

5.1.2 Waiver or alteration of the informed consent requirement

A waiver of consent is requested to review medical record information to determine preliminary eligibility to participate in the research.

5.2 Consent Documentation

5.2.1 Written Documentation of Consent

The consent process will be documented in writing with the long form of consent documentation:

- The current IRB approved consent form will be obtained.
- We will verify that we are using the most current IRB-approved version of the study specific consent form and that the consent form is in language understandable to the subject.
- A copy of the consent form will be provided to the subject. Whenever possible the consent form will be provided to the subject in advance of discussion.

5.2.2 Waiver of Documentation of Consent (Implied consent, Verbal consent, etc.)

The study team intends to potentially ask subjects eligibility questions prior to written consent. The study team will obtain verbal consent from the participant to ask questions detailed in the additional screening script.

5.3 Consent – Other Considerations

5.3.1 Non-English Speaking Subjects

Not applicable.

5.3.2 Cognitively Impaired Adults

5.3.2.1 Capability of Providing Consent

Not applicable.

5.3.2.2 Adults Unable To Consent

Not applicable.

5.3.2.3 Assent of Adults Unable to Consent

Not applicable.

5.3.3 Subjects who are not yet adults (infants, children, teenagers)

5.3.3.1 Parental Permission

Not applicable.

5.3.3.2 Assent of subjects who are not yet adults

Not applicable.

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☒ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☒ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure

Information is included in the "Confidentiality, Privacy and Data Management" section of this protocol.

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

Upon study completion, all electronic patient research information will be deleted from all research sources. Any hard copy patient information collected for research will be placed in one of HMC's patient information bins to be shredded in compliance with HIPAA regulations and PSU research document retention policies.

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

Information must be obtained from the subject's electronic medical record at Caron during recruitment to determine eligibility and, in some cases, to confirm information discussed with the subject in regard to their medical history.

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

The waiver is requested only for recruitment to determine subject eligibility to ensure that no medical conditions that fall into the exclusion criteria are present and would thus preclude enrollment. This waiver will minimize the enrollment of subjects' who may ultimately fail to meet the study inclusion/exclusion criteria.

6.3 Waiver or alteration of authorization statements of agreement

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted uses and disclosures according to federal regulations.

The research team will collect only information essential to the study and in accord with the 'Minimum Necessary' standard (information reasonably necessary to accomplish the objectives of the research) per federal regulations.

Access to the information will be limited, to the greatest extent possible, within the research team. All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

7.0 Study Design and Procedures

7.1 Study Design

Open label, pilot observational study of suvorexant, an orexin 1 / 2 receptor antagonist, for the treatment of sleep disturbance in patients in residential treatment for opioid or alcohol use disorder.

7.2 Study Procedures

When a medication is studied for a new indication, or in a new population, it is common (in clinical neuropsychopharmacology) to conduct the first study in an open trial. We plan to study two groups of patients in an open 7-day trial of 20 mg suvorexant HS, following a two-day baseline during which patients will be taking a previously prescribed sleep medication (i.e. trazodone, mirtazapine, or melatonin) before switching to suvorexant. The study design includes a combination of assessments, and the collection of biological samples. Participants will be enrolled in the study for a total of 10 days (9 nights). Table 1 references the daytime questionnaires and procedures, and Table 2 represents the night questionnaires and procedures. Night is considered to be the time after the patient takes the medication. In our study, the night falls after the day.

Table 1. Daytime questionnaires and procedures.

Study Day	0	1	2	3	4	5	6	7	8	9
Consent and Screening (Form 90 AI/DI, MINI Screen/MINI 7.0.2, HAM-D)	X									
EMA		X	X	X	X	X	X	X	X	X
Modified ISI	X									X
Modified PSQI	X									
*DNA Collection**	X									
Cortisol Collection		X	X					X	X	
Abuse Liability Battery – Morning			X						X	

Table 2. Night questionnaires and procedures.

Study Night	0	1	2	3	4	5	6	7	8
Suvorexant			1	2	3	4	5	6	7
*Baseline***	X	X							
Suvorexant Administration			X	X	X	X	X	X	X
Actigraphy/Logs	X	X	X	X	X	X	X	X	X
Abuse Liability Battery - Night		X						X	
Observer Rated Questionnaire		X						X	

*Optional saliva for patients with opioid use disorder only
**Current medicine regime including antidepressants/melatonin

Abbreviations: EMA, ecological momentary assessment; ISI, Insomnia Severity Index; PSQI, Pittsburgh Sleep Quality Index.

7.2.1 Consent and Screening: Study Day 0

After signing the informed consent document, the Caron based study coordinator will complete a comprehensive screening assessment with each participant to further evaluate their eligibility in the study. The comprehensive screening assessment includes questionnaires to evaluate psychiatric comorbidities, sleep quality, depression and previous drug/alcohol use. The screening assessment questionnaires will be administered to the patients by the Caron based study coordinator on paper/ electronic tablet using the REDCap software. The screening questionnaires will include:

• The M.I.N.I International Neuropsychiatric Interview (M.I.N.I. 7.0.2; if applicable) (10) which provides psychiatric diagnosis.

• The Hamilton Depression Rating Scale (HAM-D; 11) will be used to provide a continuous measure of depressive symptomatology and severity.
• The Form 90-AI or Form 90-DI (12) will be administered to assess recent and lifetime history of drug and alcohol use, respectively. Recent substance use will document the 90 days prior to residential treatment admittance.
• The Pittsburgh Sleep Quality Index (PSQI; modified) (13) will be used to document the subjective severity of sleep complaints.
• The Insomnia Severity Index (ISI; modified) (14) will measure insomnia related symptoms. This assessment will also be administered on Study Day 9.
The study coordinator at Caron will also provide the patient with an actigraph, sleep log and EMA smartphone which the patient will return after completing the study.

Optional Research: Participants who are being treated for opiate dependence will be asked if they would like to give a DNA sample from saliva using an Oragene collection kit to be used for DNA extraction. This is not mandatory. The samples will be stored at Department of Psychiatry, Penn State Hershey Medical center until the end of the study. When the study is complete, the samples will be shipped to Dr. David J. Vandenbergh at University Park who will process the data for genotyping. He will purify the DNA from the saliva in his laboratory. Genotypes will be established from approximately 5 million sites in the genome. Candidates for single genes to study include the opioid receptor genes and the alcohol dehydrogenase genes. He will include these new genes in the analyses of the relation between suvorexant and opioid use. In addition to testing for genotype (the bases present in DNA), he will test for patterns of DNA methylation, which is an underpinning of epigenetics.

7.2.2 Study Days 0-9

Sleep data: Sleep disturbances are common among actively-using opiate and alcohol dependent individuals, severe during the withdrawal phase, and are considered as a long-term risk factor for substance abuse relapse. Chronic insomnia is associated with increased cortisol levels over a 24-hour period. Sleep disturbances and HPA axis activation are expected to be strongly correlated; normalization of HPA axis is predicted to be associated with normal sleep.

The collection of both objective and subjective sleep data and subjective non-sleep activity data will allow an assessment of the validity of the subjective and objective estimates of sleep quality in the effectiveness of suvorexant administration. Sleep data will be collected in 3 ways:

1) Objective wrist actigraphy sleep measurements will be collected nightly (Study Nights 0 to 8)
2) Subjective sleep and activity data will be obtained the following morning using actigraph logs and EMA survey questionnaires (Study Days 1 to 9). Subjective sleep data will include time to bed, estimated time to fall asleep, night-time awakenings, wake-time in the AM, and quality of sleep.
3)
4) Standardized measures of sleep quality will be collected. Subjects will complete a modified version of the PSQI at baseline. We will use a modified version of the ISI to measure subjective sleep at baseline (Day 0) and on completion of the study (Day 9) to determine the improvement in sleep quality over the study period.

EMA Daily Diary Data Collection: Ecological momentary assessment (EMA) data refers to the intensive measurement of intra-individual processes in real context (i.e., ecological) and in real

time (i.e., momentary). In the proposed study, such data will be collected via Motorola Droid smart phones that are programmed to elicit the participants' response four times per day, during each of the 9 full study days (Study Days 1 to 9), resulting in approximately 36 assessments per individual. Instructions on how to use the smart phone for the EMA surveys, and what to do if a survey is missed, will be provided verbally on Day 0 to the participant using an approved EMA script. EMA survey administration times will be established to occur at 4 specific time points on a daily basis in order to take advantage of the highly structured patient schedule, maximize compliance, and reduce patient burden. Using the data collection paradigm developed for the National Study of Daily Experiences as a framework (12), EMA surveys will be administered in the morning, early afternoon, late afternoon and evening with minor fluctuations in collection times being adjusted to accommodate specific treatment unit schedules. Research staff will contact the participant using Passport, an in-house simple message system (SMS) used to contact patients while they are at Caron, to remind them to take the EMA surveys. Passport communication does not extend outside of the Caron Treatment Center. EMA reminders will be sent twice daily, at approximately 11 am and 4 pm. If an EMA survey is missed, paper versions of the surveys are provided to the participant to fill out retroactively.

Multiple domains of affect will be drawn from the Extended version of the Positive and Negative Affect Scale and assessed on a daily basis at the four established collection times (PANAS-X; 15). Items included will cover the circumplex spectrum, and include hostility, guilt, sadness, stress, anxiety, fatigue, and happiness. Similarly, formatted items will be used to assess the occurrence and degree of participants craving (16) within each of the 4 EMA surveys. In addition to items inquiring about mood, stress, and craving, the morning assessment will include subjective items related to sleep. These sleep items will record estimated time to fall asleep, night-time wakenings, quality of sleep, daytime sleepiness, and the nightly experience of dreams that involve alcohol/drug content. Two identical and brief mid-day surveys will inquire about mood, stress, and craving using repeated items as described above. The evening survey will expand upon the repeated measures of mood, stress, and craving to capture aspects of late day experience such as 12 Step meeting attendance and patient perceptions about their day. Thus, our study will be able to capture both the variability in affect/craving and the temporal ordering of stressors and affect necessary to characterize within-day reactivity as well as changes observed in subjective and objective indices of sleep associated with suvorexant administration.

The smart phones that will be used for EMA data collection will have a security application installed that prevents user access to all other applications that are not associated with survey data collection. Smart phones will not be activated on a cellular network resulting in the disabling of voice, text, and internet functions. Research staff will use brief in-person meetings (every other day) as a means to ensure devices are being charged, build rapport, answer participant questions, monitor compliance, and to manually download data for backup storage on the RAs laptop and then uploaded to a secure server, Virtual COLO, at University Park in State College, PA. The server has all of the latest security updates applied as well as the physical security of the data center itself. The only people with access to the server are James Mundie, Tim Brick, and Zita Oravecz. Access to the web-facing application is controlled by CoSign (The standard university login system). Only encrypted communications are used to and from the device, and there is only access to the database through the localhost. The database containing user responses will be backed up periodically (hourly).

Diurnal cortisol: (Study Days 1,2,7,8) Saliva will be collected for cortisol measurement at 5-time points for two consecutive days at two different periods in the study, i.e. 8:00 AM before breakfast, 12:00 PM before lunch, 3:00 PM, 6:00 PM and 9:00 PM. The research staff will visit with the participant at approximately 3 PM (Day 0, 6, 9), 8 AM and 3 PM (Days 1, 2, 7, 8) to

provide fresh cortisol collection kits needed for the next collection and to collect provided saliva samples. Instructions on how to provide saliva samples will be given to the participant on Day 0. Specimens are collected using a cotton swab kit (Salivette, item #51.1534). It has been demonstrated that five samples are adequate to examine circadian variation of cortisol secretion. Cortisol levels will be determined using a commercially-available, high-sensitivity salivary cortisol enzyme immunoassay kit (Catalog # 11-CORHU-E01-SLV; Alpco, Salem, New Hampshire) designed to standardize the measurement of salivary cortisol across research and biomedical laboratories. Saliva cortisol assaying will be done by a certified lab technician in the research laboratory at the Penn State College of Medicine.

7.2.3 Abuse liability: Study Nights 1, 7, and the days following it (Study Days 2 and 8)

Abuse liability will be assessed with a modified protocol which includes the abuse liability battery morning, abuse liability battery night and the observer rated questionnaire. It is based on questions used in previous studies of abuse liability (17). The abuse liability –night battery will be completed by each research participant 30 min after medication administration on study Nights 1 and 7. The abuse liability battery – morning will be completed the morning after drug administration on study Day 2 and 8. The abuse liability battery- morning and night has the same questions related to drug liking, drug value questionnaire, drug effects questionnaire except that there are additional questions asking to categorize the medication effect to one of the seven classed of psychoactive substances on the abuse liability battery-night . The observer rated assessment will be completed by the medication nurse as described below. Our primary measures of abuse liability on the abuse liability battery- morning, night and the observer rated assessment will include the following 5 measures:

1. Drug Liking, with questions asking 1) if the drug made them feel high/euphoric, and if they liked the euphoric effect; 2) if the drug made them sleepy, and/or if they liked the sleep effects, or 3) if they disliked the effects of the drug. Each question is scored on a 5-point Likert scale.
2. A three-item Drug Value questionnairewill ask participants 1) if they would use the drug to get high; 2) whether they thought that the drug might be addicting; 3) if they would buy the drug illegally to get high.
3. The Drug Effect questionnaire, (DEQ) will be used to evaluate how strong a drug effect was felt on a 5-item response scale, ranging from No Drug Effect to Very Strong Effect.
4. To further measure abuse liability, patients will also be asked to categorize the drug effect according to one of 7 classes of psychoactive medications. It will be administered on the abuse liability battery – morning on the morning of Study Day 2 and 8.
5. The Observer-Rated assessment (ORA) will be completed by the medication nurse on the evening of Study Day 1 and 7, 30 min after drug administration.

Abuse Liability Battery Scope (Detailed)

Study Day	**1, 7**	**2, 8**
Night/Day	**Night**	**Day**
Onset/Morn	**O**	**M**
Measures		
DLQ	X	X
DVQ	X	X
DEQ	X	X
Categorize		X
O-RA	X	

O = Onset of Action (30 min after taking medication); M = Morning; DLQ = Drug Liking Questionnaire; DVQ = Drug Value Questionnaire; DEQ = Drug effects questionnaire; Categorize; O-RA = Observer-Rated Assessment

7.2.4 Suvorexant: Study Nights 2-8

Patients will participate in an open 7-day trial of 20 mg suvorexant at night.

7.3 Duration of Participation

Participants will be enrolled in the study for a total of 9 days.

7.4 Test Article(s) (Study Drug(s) and/or Study Device(s))

7.4.1 Description

Subjects will continue on their current off label sleep medication including trazodone, mirtazapine or melatonin for the initial two nights of the study period and then on the study medication, suvorexant for 7 nights.

Trazodone is a sedative triazolopyridine antidepressant, used for the treatment of depression and insomnia because it possesses antidepressant and also anxiolytic and hypnotic activities (18,19). When prescribed as a hypnotic, it is habitually used at low-doses (i.e., 50-150 mg daily at bedtime). The effects of trazodone on sleep have been evaluated in a variety of subjects, including patients with insomnia, depression, substance dependence and normal controls. In general, most studies with Insomnia have shown that trazodone improves subjective and objective sleep. In substance dependent patients, it has shown mixed results, with some studies improving sleep (20,21) and others not in substance dependent subjects (22).

Mirtazepine is an antidepressant used in the treatment of depression and off label for the treatment of Insomnia. It acts by increasing the central noradrenergic and serotonin levels by antagonism of pre synaptic α 2 adrenergic inhibitory auto receptors. Mirtazepine also has potent anti-histaminergic effect at lower doses of 7.5 to 15 mg and hence is used off label for the treatment of insomnia in general population and in substance use disorder subjects (23).

Melatonin is a hormone produced by the pineal gland. Exogenous melatonin is available over the counter in 1 to 20 mg dosage. It is an agonist on melatonin 1, 2 and 3, which improves sleep and stabilizes circadian rhythms. It is found to be efficacious in the treatment of insomnia in the general population (24) but has shown mixed results in the treatment of insomnia in substance use disorders (25).

The sleep medication, suvorexant, has been placed in Schedule IV by the FDA and DEA, and is approved for treatment of Insomnia. The form of the drug will be a 20 mg capsule (1). The drug, to be administered for seven nights under supervision of a nurse, will help determine overall sleep quality, levels of cortisol, and potential abuse liability. The dosage of 20mg was chosen following a recommendation by the lead investigator of the Phase-3 clinical trial for suvorexant performed by Merck. It has been suggested that the difference in side effects between 10 and

20mg is minimal. It has also been suggested that 10mg would have similar effects to a placebo, and that the higher dose of 20mg will be necessary.

7.4.2 Treatment Regimen

During the 9 day study period, subjects will be on their current dosage of medication prescribed by the Caron Foundation physician including trazodone, mirtazapine or melatonin for two nights followed by 7 suvorexant trial. Participants will be administered one 20 mg suvorexant capsule per night for 7 nights. In total, participants will receive 1 capsule per night for a total of 7 nights. There will be no dose adjustments during this trial. All capsules will be taken orally.

7.4.3 Method for Assigning Subject to Treatment Groups

Since this is an open medication trial, there will be no randomization process for assigning treatment to the research subjects stratified by alcohol dependence or opioid dependence.

7.4.4 Subject Compliance Monitoring

Medication compliance will be monitored and documented by the nursing staff at the Caron Foundation during the study. Any compliance issues will be documented and reported to the physician at Caron immediately by the nursing staff at Caron, and Dr. Scott Bunce will also be notified within 12 hours. A modified abuse liability assessment will also be administered on the evening of Study Night 1 and 7 as well as the following morning (Study Day 2 and 8). On the evening of Study Nights 1 and 7, nursing staff at Caron will complete an observer-rated form 30 minutes after medication administration, to further validate subjective patient reports assessing abuse liability and adverse effects.

7.4.5 Blinding of the Test Article

Not applicable.

7.4.6 Receiving, Storage, Dispensing and Return

7.4.6.1 Receipt of Test Article

The drug capsules will be ordered and received by Synergy Pharmacy, an off-site pharmacy that works with Caron. The Pharmacy will order the medication after receiving a scanned signed informed consent from Caron. The capsules will be ordered in blister packs that contain 7 capsules. These blister packs will be labeled according to FDA and Penn State Pharmacy guidelines.

7.4.6.2 Storage

The storage of the medication will be at the medical detox unit at the Caron Foundation. In this unit is a locked room (nurses station) that contains a locked medication cart, with a locked drawer where the medication will be stored. Therefore, the medication will be double locked. Only ‘charge nurses’ will have access to the medication. Since the medication does not need to be refrigerated, it will be stored at room temperature in the medication cart. In addition to the study medication, the nurses will also have access to a log containing participant names, in order to observe patient compliance and to perform the appropriate abuse liability questionnaires on the evening of Study

Night 1,7. This log will also be kept with the medication in the locked room at the medical detox unit.

7.4.6.3 Preparation and Dispensing

The drug will be ordered by the medical staff at Caron and stored in the medical unit. Caron Foundation nursing staff will administer medication, one capsule per night for 7 nights, and will be overseen by the Foundation's medical staff. As mentioned in section 7.4.6.2, the nursing staff will keep a log of subject names to ensure compliance.

7.4.6.4 Return or Destruction of the Test Article

Final reconciliation of the medication will take place at the Caron Foundation, if appropriate. The Caron Foundation performs these procedures according to DEA regulations. Non-controlled substances are stored in locked medical bins, which are then shipped to a company that will safely destroy the medication. Controlled substances are placed in medical bags where a charcoal-like liquid is added to make the medication 'inactive'. After this procedure, the medication can then be thrown into the trash. Patients who do not complete the entire study will have their medication destroyed via Caron's established medication disposal protocols. Patients will then be redirected to their doctors to discuss any outstanding sleep issues.

7.4.6.5 Prior and Concomitant Therapy

The subjects recruited will be current patients in a residential facility for the treatment of alcohol or opioid dependence. Since the doctors at Caron will be approving patient eligibility, they will know current and past patient medication regimes. Subjects may be taking concomitant medicines/therapies for various reasons at the treatment center. The pharmacy staff at Caron will also know which medications may not be permitted to take with the medication during the study, due to potential counteracting affects. Patients who are concurrently receiving a psychoactive drug for the treatment of an Axis I disorder excluding sedating antidepressants that have been prescribed for the treatment of sleep disturbance, will be excluded, as described in section 3.2.

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

The total sample size will consist of 36 participants stratified by alcohol (n=22) or opioid dependence (n=14). This sample size of convenience is expected to yield 10 evaluable data sets from the opioid group and 15 evaluable data sets from the alcohol group for statistical analysis.

8.2 Sample size determination

The purpose of this pilot study is to determine the feasibility of the study and explore the hypotheses of interest. A sample size of 10 in the opioid group and 15 in the alcohol group will be sufficient to provide meaningful assessment of the study outcomes. The findings from this study will be used to plan a future study.

8.3 Statistical methods

The primary analyses will be mostly descriptive. Summary statistics and graphical methods will be used to examine the distribution of the data. Any potential outliers or leverage points of concern will be evaluated. The outcomes of interest will be summarized and plotted over time for each study group to explore the effect of treatment. Linear or generalized linear mixed effects models will also be used to evaluate the patterns of changes in study outcomes after the treatment of insomnia. Subjects with missing data can be incorporated in the mixed model analysis when data are missing at random. Adverse events and medication compliance will be documented and summarized.

A priori hypotheses derived from the literature as well as from our previous data will be tested separately in alcohol use disorder and opioid use disorder using paired Student's t-tests for pre-post medication contrasts. Specific hypotheses are that both objective measures (sleep actigraphy measures of total sleep time, number of awakenings) and subjective measures of sleep (PSQI, sleep quality) will improve over the course of 10 days on suvorexant. EMA measures of negative mood are expected to decline, and positive moods are expected to increase from baseline to Day 10.

9.0 Confidentiality, Privacy and Data Management

9.1 Confidentiality

Refer to the Data Plan Review Form.

10.0 Data and Safety Monitoring Plan

10.1 Periodic evaluation of data

Our data and safety monitoring plan will be under the jurisdiction of the PI, Dr. Scott Bunce. For this study, the main source of adverse events will be medication related. A potential adverse event includes a breach of data confidentiality. According to the Penn State College of Medicine IRB's Standardized Operation Procedure "Reporting and Review of Unanticipated Problems Involving Risks to Participants or Others", all participants and research staff who have direct interaction with the participant or with the confidential data of the participant, will be instructed to report any unexpected discomforts or any potential breach of confidentiality of participant's data to the Principal Investigator responsible for the related components of data collection involved. Within 12 hours of any reported event, the PI will gather detailed information on the episode (See 19.2). If the event is considered to be an unexpected adverse event or a serious adverse event (SAE) it will be reported promptly to the IRB. The IRB will conduct its independent review and decide whether the episode represents an unexpected problem or an SAE. After a confirmed episode of an unexpected adverse event or SAE, the IRB will decide what, if any, corrective action is required. A summary of all events will also be reported to the IRB at the time of annual review.

10.2 Data that are reviewed

Data that will be reviewed include any reported side effects, adverse events (see below) or complications from the study.

Adverse event: Any untoward or unfavorable medical occurrence associated with the subject's participation in the research, whether or not considered related to the study intervention.

Serious adverse event: Any event temporally associated with the subject's participation in research that meets any of the following criteria:

- Results in death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);

- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in a persistent or significant disability/incapacity;
- Results in a congenital anomaly/birth defect;
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the participant's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse); or
- Results in a severely debilitating situation for the subject, such as psychological distress, financial hardship or damaging impact on social standing or employability.

Unexpected adverse event: A adverse event is considered "unexpected" if it is not listed in the general investigational plan or protocol; or is not listed at the specificity or severity that has been previously observed and/or specified.

10.3 Method of collection of safety information

Data will be collected during study procedures and through reports from staff and participants.

10.4 Frequency of data collection

The principal investigator , Dr. Scott Bunce will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study intervention(s); and 3) if the adverse event meets the criteria for a *serious adverse event*. The PI, Dr. Scott Bunce, will consult the study physician Dr. Adam Scioli as needed.

10.5 Individuals reviewing the data

All participants and research staff who have direct interaction with the participant or with the confidential data of the participant, will be instructed to report any unexpected discomforts or any potential breach of confidentiality of participant's data to the reference physician and Principal Investigator responsible for the related components of data collection involved.

10.6 Frequency of review of cumulative data

Not applicable.

10.7 Statistical tests

Not applicable.

10.8 Suspension of research

The report of a serious adverse event.

11.0 Risks

Medication: Suvorexant is a new class of approved hypnotic drug that acts as an orexin 1 /2 receptor antagonist, suppressing wakefulness. It has been approved for the treatment of insomnia in adults at a dose of 10 or 20 mg – for complaints related to sleep onset and/or sleep maintenance. Adverse reactions which were reported to the FDA included central nervous system depression, amnesia, hallucinations, complex sleep – related behavior,

exacerbation of symptoms of depression, suicidal ideation and potential substance abuse, and impaired next day mental alertness. Common, but less serious, reactions included somnolence, headache, dizziness, abnormal dreams, diarrhea, cough, sleep paralysis, and cataplexy like symptoms (1).

Suvorexant should not be used concurrently with alcohol or a CNS depressant. Suvorexant should not be given to patients who have a hypersensitivity to drugs of the same class. Suvorexant should not be given to patients with narcolepsy, to patients with major depression or impaired respiratory function. The drug should be used with caution in patients with a history of alcohol or drug abuse; but, complaints about insomnia are highly prevalent in this group of patients – and insomnia is strongly associated with risk of relapse following a period of abstinence. While the patients in the proposed study will have a history of current alcohol or drug dependence, they are all in residence in a treatment facility where they will be closely monitored. We will be employing a modified abuse liability protocol to assess the relative risk of developing some form of dependence on suvorexant. Importantly, neither tolerance nor withdrawal effects were observed with suvorexant in the pre-marketing studies. Suvorexant was not self-administered in non-human primate models.

As per the exclusion criteria, we will not be including pregnant or nursing female patients or patients with a current or history of major psychiatric disorder including depression, schizophrenia, or bipolar disorder; and, we will be excluding patients with current suicidal ideation and/or a past history of suicidal behavior.

Actigraphy: There is no known risk to wearing the wrist actigraphs. A minor skin rash may develop from the wristband, but this risk is very slight.

Questionnaires: The interviews and forms are routine, standardized forms for sleep research and psychology research. They pose no known risks, although certain questions may be mildly upsetting because they may probe sensitive psychological areas and others inquire about family history of medical and psychological illness or alcohol and substance use. Appropriate referrals are offered if areas of concern arise in the course of collecting this information. Research participants are free to skip any questions that make them uncomfortable.

Loss of confidentiality: The main risk of allowing us to obtain limited health information for research is a potential loss of privacy.

12.0 Potential Benefits to Subjects and Others

12.1 Potential Benefits to Subjects

Sleep quality may improve (total sleep time, less frequent awakenings) over the course of the study.

12.2 Potential Benefits to Others

The results of this study may guide future treatment of insomnia in patients with opioid and alcohol dependency.

13.0 Sharing Results with Subjects

Not applicable. We will not be sharing results with participants or others.

14.0 Subject Stipend (Compensation) and/or Travel Reimbursements

Patients who are research participants will receive a $10 gift card for each day in the study. Upon completion of the entire medication period, they will get a bonus of a $50 gift card. The total amount they will receive for completing the entirety of the study will be $150 in gift cards.

Although the institutional standard now is to provide payment via Greenphire clincard, the population for this study are patients in a residential treatment center for substance use disorder. Compensation for participation in the study is given in the form of Target gift cards as alcohol or tobacco cannot be purchased at Target and Greenphire clincards could be used at vendors that sell alcohol and tobacco. As such, the study team has received an exception from the controller's office to continue using gift cards (approved 08/08/2020).

15.0 Economic Burden to Subjects

15.1 Costs

Not applicable. Participants will not be responsible for any costs related to participation in the research.

15.2 Compensation for research-related injury

Not applicable. There are no plans for HMC/PSU to provide financial compensation or free medical treatment for any research-related injury.

16.0 Resources Available

16.1 Facilities and locations

Recruitment and study procedures will be performed at the Caron Foundation, a treatment facility in Wernersville, PA.

16.2 Feasibility of recruiting the required number of subjects

Based on our previous studies at the same treatment center, we were able to recruit 80 patients with opiate dependence within 19 months, resulting in an average of 4 patients per month. We had similar results for our alcohol study.

We will be recruiting from all units at Caron.

OUD: During a recent census, there were 31 patients on the Men's Primary Care Unit, 9 patients on the Women's Primary Care Unit, 3 on the Young Adult Female Unit, 13 on the Young Adult Men's Unit, 3 on the Grand View Manner Unit, and 13 on the Health Care Professionals Unit that had a primary diagnosis of OUD (not including Heroin). Ten (10) patients had a diagnosis of OUD only (9 Male, 1 Female); the remaining patients had a history of at least one other co-morbid SUD (e.g., cannabis, alcohol, cocaine) (47 Male, 14 Female). The men ranged in age from 18-69; the women from 18-59. Duration of Opioid use ranged from several months to 30+ years. Throughout April-June 2017, the Caron Treatment Center admitted (in those selected units) 71 patients with a diagnosis of OUD (approximately 23 patients/month).

AUD: During the most recent census, there were 63 patients on the Men's Primary Care Unit, 33 patients on the Women's Primary Care Unit, 6 on the Young Adult Female Unit, 24 on the Young Adult Men's Unit, 19 on the Grand View Manner Unit, and 11 on the Health Care Professionals Unit that had a primary diagnosis of AUD. A total of 74 patients had a diagnosis of AUD only (46 Male, 28 Female); the

remaining patients had a history of at least one other co-morbid SUD (e.g., cannabis, opiates, cocaine). The men ranged in age from 19-68; the women from 21-61. Duration of alcohol use ranged from several months to 30+ years. Throughout April-June 2016, the Caron Treatment Center admitted (in those selected units) 156 patients with a diagnosis of AUD (approximately 52 patients/month).

Not all patients will qualify or consent to be in the study. Our goal is to finish recruitment within a 1-year time period.

16.3 PI Time devoted to conducting the research

The PI will be able to devote 50% of time to conducting and completing the research, considering outside responsibilities.

16.4 Availability of medical or psychological resources

Medical and/or psychological resources will be primarily available at the Caron Foundation through their counselors and medical staff. However, the PI, Scott Bunce is a fully trained and licensed psychologist, will also be available for consultation with participants should any participant request one; and, will be on-call 24/7 if there are any complaints, questions, or concerns about the research, in regards to the study medication.

16.5 Process for informing Study Team

The research team will be given specific duties to conduct the research study. The study coordinators will be provided with training to conduct the screening process (obtain informed consent, and to oversee patient self-reports on the M.I.N.I 7.0.2, HAM-D, Form 90AI or DI, PSQI and ISI), and instruct participants on how to use the actigraphs, cortisol tubes and smart phones that are used to collect the EMA data. Staff members and nurses at Caron will be instructed on medication distribution and abuse liability procedures.

17.0 Other Approvals

17.1 Other Approvals from External Entities

The Caron Foundation has granted approval to use their facility to conduct research.

17.2 Internal PSU Committee Approvals

Check all that apply:

☐ Anatomic Pathology – Hershey only – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of HRP-902 - Human Tissue For Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ Animal Care and Use – All campuses – Human research involves animals and humans or the use of human tissues in animals

☒ Biosafety – All campuses – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Clinical Laboratories – Hershey only – Collection, processing and/or storage of extra tubes of body fluid specimens for research purposes by the Clinical Laboratories; and/or use of body fluids that had been collected for clinical purposes, but are no longer needed for clinical use. Upload a copy of HRP-901

- Human Body Fluids for Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ Clinical Research Center (CRC) Advisory Committee– All campuses – Research involves the use of CRC services in any way.

☐ Conflict of Interest Review – All campuses – Research has one or more of study team members indicated as having a financial interest.

☐ Radiation Safety – Hershey only – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload a copy of HRP-903 - Radiation Review Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ IND/IDE Audit – All campuses – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☒ Scientific Review – Hershey only – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Hershey Cancer Institute Scientific Review Committee is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website at: http://www.pennstatehershey.org/web/irb/home/resources/investigator

18.0 Multi-Site Research

18.1 Communication Plans

Not applicable.

19.0 Adverse Event Reporting

19.1 Adverse Event Definitions

For drug studies, incorporate the following definitions into the below responses, as written:	
Adverse event	Any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related
Adverse reaction	Any adverse event caused by a drug
Suspected adverse reaction	Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than "adverse reaction". • *Reasonable possibility.* For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.
Serious adverse event or Serious suspected adverse reaction	Serious adverse event or Serious suspected adverse reaction: An adverse event or suspected adverse reaction that in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-

	threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
Life-threatening adverse event or life-threatening suspected adverse reaction	An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator (i.e., the study site principal investigator) or Sponsor, its occurrence places the patient or research subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that had it occurred in a more severe form, might have caused death.
Unexpected adverse event or Unexpected suspected adverse reaction.	An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure, general investigational plan, clinical protocol, or elsewhere in the current IND application; or is not listed at the specificity or severity that has been previously observed and/or specified.

For device studies, incorporate the following definitions into the below responses, as written:	
Unanticipated adverse device effect	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

19.2 Recording of Adverse Events

Subjects will be routinely questioned about adverse events from nursing staff at Caron during each nightly administration (all 9 nights of the study). Information will also be collected through the modified abuse liability assessment where patients will be given the Drug Effect questionnaire, administered 30 minutes after drug administration, and the next morning, to be used to evaluate how strong a drug effect was felt on a 5-item response scale, ranging from No Drug Effect to Very Strong Effect. This assessment will be administered in the evening of Study Night 1, as well as the morning of Study Day 2. Nursing staff will also complete an observer-rated questionnaire 30 minutes after drug administration on Study Night 1 and 7.

All adverse events should be reported immediately and will be addressed by the physician and other staff at Caron. The staff at Caron will then complete a Suvorexant Adverse Reaction Documentation form. All forms will be sent to and reviewed by the PI on our study team, Dr. Scott Bunce. In the event of a serious or life threatening adverse reaction, Caron medical staff will be immediately informed and address the situation. Dr. Scott Bunce will be contacted within 12 hours. Subjects are also encouraged to call the PI (with the assistance of the staff at Caron), Dr. Scott Bunce at 215- 510- 8295 (cell) if they have questions, complaints or concerns about the research or believe they may have been harmed by being in the research study.

All adverse events (serious or non-serious) and abnormal test findings observed or reported to study team believed to be associated with the study drug(s) or device(s) will be followed until the event (or its sequela) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms

- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy
  NOTE: Simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.
- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study
- The test finding is considered an adverse event by the investigator.

19.3 Causality and Severity Assessments

The investigator will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study drug(s) or device(s); and 3) if the adverse event meets the criteria for a serious adverse event.

If the investigator's final determination of causality is "unknown and of questionable relationship to the study drug(s) or device(s)", the adverse event will be classified as associated with the use of the study drug(s) or device(s) for reporting purposes. If the investigator's final determination of causality is "unknown but not related to the study drug(s) or device(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

19.4 Reporting of Adverse Reactions and Unanticipated Problems to the FDA

19.4.1 Written IND/IDE Safety Reports

Not applicable.

19.4.2 Telephoned IND Safety Reports – Fatal or Life-threatening Suspected Adverse Reactions

Not applicable.

19.5 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

19.6 Unblinding Procedures

Not applicable.

19.7 Stopping Rules

In the event of an adverse reaction, the participant will consult with the nursing and doctoral staff at Caron to determine if they should continue with study. If deemed appropriate, participants will be removed from the study. If this event occurs, or the patient refuses to continue with the study, they will consult their doctors, and the medication will be properly destroyed, as described in section 7.4.6.4.

20.0 Study Monitoring, Auditing and Inspecting

20.1 Study Monitoring Plan

20.1.1 Quality Assurance and Quality Control

The study will be monitored by Clinical Trial Monitoring Team from the Department of Public Health Sciences at Penn State Hershey College of Medicine.

Staff within the Department of Public Health Sciences will be monitoring the study for protocol compliance, data quality, and regulatory compliance. This will include reviewing the informed consent process and completed forms, verifying the presence of essential documents in the study regulatory binder, completing source document verification for data entered into REDCap, ensuring the study is implemented as planned, reviewing adverse events and the reporting of serious adverse events, and ensuring that all data quality rules have been executed and resolved and all data queries are resolved and closed.

The monitor will create a detailed report following each scheduled monitoring session to forward to the PI and will verify that proposed action items are addressed and completed. The monitoring will occur at regular intervals as specified in the monitoring plan developed by Public Health Sciences and PSU Sponsor Investigator.

20.1.2 Safety Monitoring

The Principal Investigator will confirm that all adverse events (AE) are correctly entered into the AE case report forms by the coordinator; be available to answer any questions that the coordinators may have concerning AEs; and will notify the IRB, FDA, sponsor and/or DSMB of all applicable AEs as appropriate. All assessments of AEs will be made by the PI, a licensed medical professional.

The Research Coordinator will complete the appropriate report form and logs; assist the PI to prepare reports and notify the IRB, FDA and/or DSMB of all Unanticipated Problems/SAE's.

The Monitor will confirm that the AEs are correctly entered into the case report forms. The Monitor will also confirm that the adverse events are consistent with the source documents and are reported to the appropriate regulatory bodies as required.

Under the direction of Dr. Bixler, in his role as Vice Chair for Research, the research coordinator will ensure that all data is collected and analyzed appropriately.

21.0 Future Undetermined Research: Data and Specimen Banking

Not applicable.

22.0 References

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