PART B
STUDY DESCRIPTION

TITLE OF PROTOCOL	**Effects of the Orexin Receptor Antagonist Suvorexant on Sleep Architecture and Delirium in the Intensive Care Unit: a Randomized Controlled Trial**
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B1. PURPOSE OF PROTOCOL

The purpose of this randomized placebo-controlled trial is to evaluate the efficacy of postoperative oral suvorexant treatment on nighttime wakefulness after persistent sleep onset (WASO) among adult cardiac surgical patients recovering in the cardiac intensive care unit (ICU).

Primary objective
To evaluate the efficacy of postoperative oral suvorexant treatment on nighttime wakefulness after persistent sleep onset (WASO) among adult patients following cardiac surgery and recovering in the cardiac ICU. The primary hypothesis is that suvorexant compared with placebo decreases WASO, as measured by a specialized electroencephalogram (EEG), the SedLine monitor, during the first night in the cardiac ICU.

Secondary objectives
To evaluate the efficacy of postoperative oral suvorexant treatment on total sleep time (TST) as an additional measure of sleep maintenance. Secondary hypotheses are that suvorexant compared with placebo increases TST during the night of the sleep trial in the cardiac ICU.

Exploratory objectives
To determine the effect of postoperative oral suvorexant on postoperative delirium and delirium free days, to evaluate time to sleep onset (TSO) as a measure of sleep onset latency, and to explore patients' comorbidities, treatments, and conditions that may modify the sleep promoting effects of suvorexant in the ICU. We will test the exploratory hypotheses that:

- suvorexant compared with placebo decreases incidence of postoperative in-hospital delirium and increases delirium free days, as measured daily by the Confusion Assessment Method (CAM), CAM-ICU, and the Delirium Symptom Interview until hospital discharge (if CAM screening positive),
- suvorexant compared with placebo decreases TSO during the night of the sleep trial in the cardiac ICU,
- the effect of suvorexant will be modified by distinct perioperative factors leading to insomnia in the ICU, such as procedural severity, circadian disruption, and pharmacological treatment with centrally acting drugs.

B2. SIGNIFICANCE AND BACKGROUND FOR THE STUDY

Importance of study
Insomnia frequently occurs in patients admitted to an intensive care unit. ICU patients are exposed to circadian desynchronization phenomena similar to the experimental condition of a "constant routine", an established technique to assess human circadian rhythmicity and characterized by constant posture, temperature, dim light and noise, and feeding stimuli. Insomnia in the ICU can also be the consequence of a systemic stress response due to procedural pain and inflammation. In addition, centrally acting drugs given during anesthesia or for postoperative pain therapy could affect postoperative sleep in patients in the ICU [1]. Our data show that under these conditions, all patients demonstrate a severe impairment of sleep architecture [2]. Thus, it can be assumed that the majority of surgical ICU patients can be characterized as suffering from insomnia. As a consequence of the impaired sleep architecture, sleep promoting agents are frequently prescribed in ICU patients. In our hospital, patients who stay in the ICU for more than 48h often receive benzodiazepines (20%) and opioids (30%) during nighttime, which reduce REM sleep and have deliriogenic effects (see *Preliminary Data* below).

Background on suvorexant
Suvorexant is a sleep-promoting orexin receptor antagonist with FDA approval for the treatment of adult insomnia. In phase 3 clinical trials, suvorexant proved superiority over placebo in both measures of impaired

sleep onset and sleep maintenance in the elderly and non-elderly, objectively measured by polysomnography. Furthermore, suvorexant improved subjective outcomes of total sleep time, sleep onset latency, and impact of impaired sleep on daytime functionality [3]. Suvorexant is well-tolerated and its side effects are minor and related to the desired end-point [4]. Similar to the suvorexant filing studies, our outcomes will include objective measures of sleep maintenance (WASO, total sleep time) and onset (sleep onset latency) [5-7]. Subjective sleep quality will be assessed using the validated Richards-Campbell Sleep Questionnaire (RCSQ) [8, 9].

Assessment of sleep physiology

Due to the complex nature of sleep physiology, different methods of sleep assessment are required depending on the cohort to be studied. Questionnaires or sleep diaries are used to capture subjective quality and duration of sleep and serve as important screening tools. Objective measurements of sleep are achieved through EEG-monitoring. EEG-derived assessment of sleep differentiates wakefulness (stage 0), REM-sleep and non-REM-sleep (stages N1 to N3). Polysomnography (PSG), which combines EEG, measurement of eye movements, and electromyographic measurement of muscle activity, is considered the gold standard in determining sleep phases and diagnosing sleep disorders. A full PSG is, however, associated with discomfort and may affect the quality of sleep and the effectiveness of the sleep promoting agent, particularly in patients after surgery who are vulnerable to pain and agitation. A less invasive approach for the quantification of sleep is the SedLine® Brain Function Monitor, which consists of one disposable electrode with several sensors. Compared to polysomnography, the SedLine® Brain Function Monitor has a higher feasibility in collecting EEG measurements in challenging environments. The SedLine® monitor uses a symmetrical bilateral array of sensors that provides four-channel data. Bifrontal electrodes measure four channels of raw EEG with separate displays for locomotor EMG artifacts. The frontal electrode placements are similar to those recommended by the American Academy of Sleep Medicine [10].

A trial in subjects who underwent simultaneous PSG and SedLine monitoring demonstrated similarity of PSG and SedLine data including typical sleep architecture with an initial descent from lighter to deeper sleep stages at sleep onset, a concentration of deep sleep (stage N3) in the early portion of the night, a concentration of REM in the later portion of the night, and a number of transitions between sleep stages and awakenings that are within the normal range [11]. This group further successfully performed sleep monitoring in an ICU setting using the SedLine monitor demonstrating its feasibility and good tolerance in a similar study cohort [11].

There is some evidence suggesting that typical EEG patterns usually associated with sleep may be absent in ICU patients (atypical sleep), while EEG during behaviorally confirmed wakefulness may also be abnormal (pathological wakefulness) [12], which cannot be differentiated by conventional assessment of sleep. Recently, an EEG-derived index, the odds-ratio product (ORP) has been proposed, allowing off-line assessment of atypical sleep and pathological wakefulness [13, 14].

In addition, skin temperature recordings (which are already part of the standard operating protocol in the ICU) will provide information about patients' circadian function.

Delirium in the ICU

Delirium is a syndrome of acute organ dysfunction occurring in up to 50% of ICU patients [15], which carries financial and societal burdens due to its association with increased morbidity, mortality, and prolonged hospital stays. The occurrence of ICU delirium predicts a 3 to 13-fold rise in the likelihood of death within one year after adjusting for severity of illness, coma, sedatives, and other relevant covariates [16]. Delirium is usually multifactorial, and sleep deprivation is a contributing mechanism.

It has been reported that suvorexant may have preventive effects on postoperative delirium [17]. However, the published evidence is poor, since sleep in those studies was not formally assessed using objective methods and subjective assessments failed to identify an effect of suvorexant on sleep onset or maintenance. Also, the incidence of delirium was surprisingly low in this study (< 10 percent), and no patient in the intervention group developed delirium [17]. These are surprising findings which are at odds with the sound biological concepts and results of published, carefully conducted studies. It is frankly hard to believe that suvorexant given at a dose that does not improve sleep quality eliminates delirium in the ICU. The effect of suvorexant on postoperative delirium in the intensive care unit in patients after cardiac surgery were analyzed and recently published [18]. The authors reported that following routine use of suvorexant 20 mg, only one patient out of 36 presented with postoperative delirium, as compared to 11 of 52 patients prior to the introduction of suvorexant. The small

sample size and insufficient confounder control limit the value of this study. In addition, sleep was not quantified - so as of today, it is unclear as to whether the observed, numerical reduction in postoperative delirium rate by suvorexant is the consequence of improved sleep quality.

Assessment of delirium

In this study, delirium will be assessed daily using the Confusion Assessment Method (CAM) or CAM-ICU for reintubated patients [19]. The CAM is a standardized tool for screening purposes based on the four core features of delirium: acute onset and fluctuating course, inattention, disorganized thinking, and altered level of consciousness. The CAM is implemented into routine clinical practice at our institution. In addition, to verify the CAM screening results in CAM-positive patients we will perform the Delirium Symptom Interview, a diagnostic set of tests evaluating attention, orientation, and memory [19]. We have recently conducted and published a randomized clinical trial investigating effects of intravenous acetaminophen on postoperative delirium at our institution, which successfully utilized the same methods of outcome assessment [19]. Given the importance of insomnia and delirium in the ICU, there is a need for a well-designed study that examines the effects of suvorexant on sleep and delirium in critically ill patients. Our study will inform the effect size calculation for those future trials.

Preliminary data

Sleep in the ICU

We recently studied sleep in ICU patients using polysomnography during the night after extubation. We observed a severe disruption of sleep architecture: on average, study patients slept less than 4.5 h, predominantly in non-REM sleep stage 1 and non-REM sleep stage 2. Only 10% of patients reached REM sleep. Sleep cycles were fragmented with a high number of arousals from sleep [2]. Thus, the cohort studied here meets the insomnia criteria independently of any pre-admission diagnosis of insomnia.

To estimate the need for treatment of insomnia in our institution, we analyzed the sedative medication given during nighttime at the intensive care units at BIDMC in patients who stayed in the ICU for more than 48 h during the year 2017. **Figure 1** shows that about one third and one fifth of patients receive opioids and benzodiazepines during nighttime, respectively.

Delirium in the ICU

Based on our study conducted in a similar cohort [19], we expect an incidence of delirium of 28.3% with an average of 20-25 delirium free days during the hospital stay. We further examined our data obtained in the cardiovascular ICU and found that the incidence of delirium was similar for patients undergoing isolated coronary artery bypass graft (44/179, 24.6%) and coronary artery bypass with aortic (8/32, 25.0%) or other (2/9, 22.2%) cardiac valve replacement surgery.

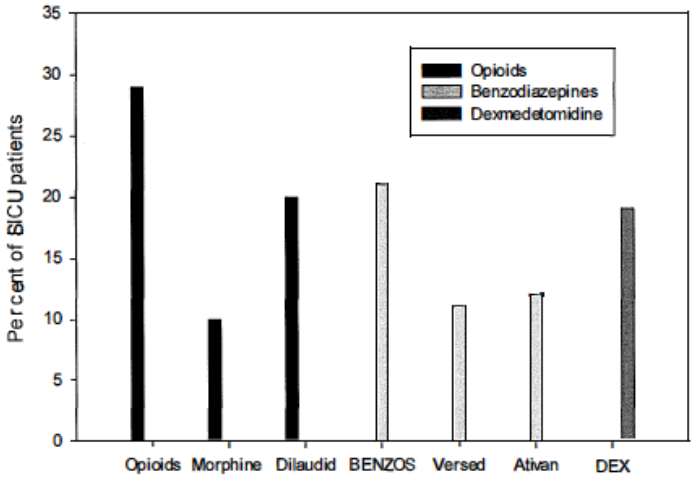

Figure 1. Administration of sedatives and opioids during nighttime (6 PM - 6 AM) in ICU patients admitted to Beth Israel Deaconess Medical Center (BIDMC) ICU for more than 48h in 2017.

B3. DESCRIPTION OF RESEARCH PROTOCOL

A. Study Design – Overview, Methods, Procedures

Study design & overview

- This is a single-center, randomized, double-blind, placebo-controlled trial expected to enroll 120 subjects. Participants will be enrolled preoperatively and randomized in a 1:1 ratio to receive suvorexant or placebo. Prior to randomization, informed consent will be obtained from all participants. The patient is first asked to report information about their sleep using the Richards-Campbell Sleep Questionnaire (RCSQ).Patients will be asked to complete a sleep questionnaire for at least one night before surgery or, if possible, daily, starting 3 days before surgery.The questionnaire will be performed online in RedCap; patients will be emailed a link to the survey. If patients do not have access to an internet-enabled device, they will be handed the RCSQ on paper and asked to complete it before surgery. The intervention (study drug) will be applied for 7 nights starting the night after postoperative extubation in the ICU. Primary and secondary outcomes will be assessed once during the night of the sleep trial in the ICU. The sleep trial will take place during the first night after extubation if the patient has been extubated before 7pm. If patient is extubated after 7:00 pm study medication will be administered the night after extubation only if still in ICU.

Exploratory outcomes will be assessed from day of extubation until hospital discharge. An outline of the study procedures is provided in **Figure 2**.

Screening Tests

After obtaining informed consent (approach detailed in section A6), authorized members of the study team will conduct screening assessments.

1. Confusion Assessment Method (CAM): Trained assessors will administer the CAM to enrolled participants to identify those with delirium. Patients identified as CAM positive will be excluded.
2. Montreal Cognitive Assessment (MoCA): Trained assessors will administer the MoCA to enrolled participants to identify those with undiagnosed, early stage cognitive decline. Patients with a MoCA score below 23 points will be excluded. The test ranges from 0 [worst] to 30 [best], with 26 and above typically considered "normal" range.

Randomization and blinding

After postoperative extubation, eligible patients will be randomly allocated in a 1:1 ratio to receive either suvorexant 20 mg or placebo. If extubation is planned outside of research pharmacy hours, randomization and drug preparation will take place in coordination with research and hospital pharmacy in accordance with their policy. Randomization will be performed by computer-generated variable block size random allocation stratified by duration of perioperative anesthesia and sedation, using a cut-off value of 420 minutes of perioperative sedation (i.e. duration of anesthesia and postoperative sedation of equal to or over 420 minutes). The allocation sequence will be provided to the research pharmacy. To achieve blinding, the study drug and placebo will be delivered in the form of non-identifiable pills, containing either the active ingredient suvorexant, or lactose. Individual patients' drug bottles will be labeled with randomization numbers. Randomization number-specific codebreakers, prepared by the research pharmacy, will contain information about a patient's treatment allocation in a sealed envelope and will be kept in the patient's study record. If unblinding procedures are necessary for clinical reasons, the clinical team will be able to contact a member of the research team with access to the codebreaker at any time by pager or phone. The codebreaker envelope is only to be opened with PI approval as instructed on the envelope. The PI will immediately inform the research pharmacy and study team of any unblinding procedures. Delivery of research medication to the patient care area will take place per pharmacy guidelines. Disposal of any unused study medication will be done per pharmacy guidelines.

Study interventions

Suvorexant 20 mg or placebo will be administered p.o. once a day at 9:00 pm for a maximum of 7 days starting the night after extubation in the ICU. A one-hour window (9:00 pm-10:00 pm) to administer the drug will ensure protocol adherence in case of delays in drug administration. Prior to every study drug administration, the Richmond Agitation-Sedation Scale will be assessed. In case of RASS < -1, the study drug will not be administered on that same day. The study drug will be discontinued:

1. After 7 consecutive doses following extubation; or

2. At hospital discharge (if less than 7 days after extubation); or
3. At ICU discharge, if patient showed signs of airway obstruction during sleep; or
4. At ICU discharge or after a maximum of 3 consecutive doses, whichever occurs sooner, if strong inhibitors of CYP3A (e.g. digoxin, diltiazem, verapamil) are co-administered; or
5. In the event of early termination: subject withdrawl of consent, investigator withdrawal for toxicity or other reasons.

Rescue medications
If deemed necessary by the treating clinicians, sleep promoting rescue medications may be administered. First choice rescue medication will be melatonin (to be administered no earlier than 3 hours after study drug administration). If this is insufficient, a benzodiazepine may be added for treatment of insomnia (no earlier than 2 hours after melatonin administration). Melatonine and benzodiazepines are drugs of choice for the treatment of insomnia. Haloperidol may be given for agitation, and oxycodone (or dilaudid as second line choice) may be given for pain control as deemed necessary by the primary care team. Dexmedetomidine will not be given to any patient enrolled in the study. Dexmedetomidine will not be used since there is some evidence suggesting that Dexmedetomidine has preventive effects on postoperative delirium [20, 21]. All patients will receive usual supportive care as per the treating physicians and standard practice.

Questionnaires/Assessments

- Richards-Campbell Sleep Questionnaire (RCSQ): The RCSQ is a validated instrument for assessing sleep and evaluates subjective perceptions of depth of sleep, time to sleep onset, number of awakenings, time spent awake, and overall sleep quality. Each of these five items is assessed using visual analogue scales (each from 0 [worst value] to 100 [best value]). The participant will be asked to use a slider to mark the answer on the scale in the electronic version of the questionnaire or mark an "X" on the paper version.
- Montreal Cognitive Assessment (MoCA): The MoCA Test is a validated tool to quickly assess a patient's cognitive health and detect cognitive impairment. The assessment consists of a one-page test and evaluates several cognitive domains: Short-term memory, visuospatial abilities (clock-drawing), executive functions (trail-marking), attention, language, abstraction, and orientation. The score point values range from 0 [worst] to 30 [best], with 26 and above typically considered "normal" range.
- Confusion Assessment Method (CAM): The CAM is a standardized screening tool used for identification of delirium symptoms. It consist of two parts: Part one screens for overall cognitive impairment, while part two focuses on the 4 features found to have the greatest ability to distinguish delirium from other types of cognitive impairment. Those features of delirium include acute onset and fluctuating course, inattention, disorganized thinking, and altered level of consciousness. The CAM-ICU (a modified version of the CAM for use in ICU patients) includes both brief cognitive testing and the CAM algorithm to screen for delirium.
- Delirium Symptom Interview (DSI): The Delirium Symptom Interview is a standard cognitive assessment assessing areas such as disorientation and perceptual disturbance. The instrument can be administered on a daily basis to track symptoms over time. Each item is scored as present or absent and subscores are created for each assessed area.

Figure 2. Illustration of study procedures

Study endpoints

1. Primary outcome: duration of nighttime wakefulness after persistent sleep onset (WASO) during the first night in the cardiac ICU.
2. Secondary outcome: total sleep time (TST) during the night of the sleep trial in the cardiac ICU.
3. Exploratory outcomes:
    a) incidence of postoperative in-hospital delirium
    b) number of delirium free days,
    c) time to sleep onset (TSO) during the night of the sleep trial,
    d) effect modification by distinct perioperative factors leading to insomnia in the ICU, such as procedural severity, patients' comorbidities, circadian disruption, and pharmacological treatment with centrally acting drugs.

The following baseline variables will be collected: Clinical and demographic variables will be collected including age, gender, body mass index, type and severity of chronic lung disease, ASA class, history of obstructive sleep apnea, smoking history, hypertension, coronary artery disease, heart failure, cerebrovascular accident or neurologic dysfunction, chronic kidney disease, diabetes mellitus, Charlson comorbidity index and Procedural Severity Score. Additionally, to track other important intraoperative and postoperative factors related to overall patient outcome, we will record administrative, demographic, clinical and billing data including: vital signs, medications administered, length of operation, type of operation, duration of mechanical ventilation, duration of bypass time, total blood loss, blood transfusion, postoperative complications, ICU length of stay prior to drug administration.
We will also record nursing-patient interactions (e.g. intravenous line placement, IV flushing, blood sampling, turning/positioning of patients, wound care, breathing treatments, medication administrations, vital sign checks, neurological checks, point-of-care glucose measurements, and patient-initiated contacts).

Assessment of study endpoints

Primary outcome

Sleep and wakefulness will be measured by electroencephalogram (EEG) using a SedLine® Brain Function Monitor during the night of the sleep trial. EEG data will be exported from the SedLine device at the end of the study using an encrypted portable USB storage drive. Data will immediately be transferred to a firewall-protected network drive and deleted from the portable storage. EEG data will be stored on firewall-protected computers as described in detail in section B8. EEG data will be analyzed using dedicated computer software and scored independently by two researchers, blinded to treatment assignment, who will be trained accordingly by a sleep medicine consultant. In case of disagreements between the two researcher's assessments, a sleep medicine consultant will be involved in the scoring. Sleep staging for single channel EEG will then be performed visually with 30 second epoch windows, according to Rechtschaffen & Kales criteria and in accordance with AASM guidelines and differentiated into sleep (REM stage or non-REM stages N1 to N3) and wakefulness (stage 0) [22]. The SedLine Monitor will allow for exclusion of motion-related artifacts by simultaneously capturing EMG signals. A wrist actigraphy will also be used to detect movements during sleep to help trace motion related EEG artifacts more precisely.

Continuous EEG measurements in the ICU may sometimes be prone to artifacts due to electrical interferences arising from devices such as ventilators and infusion pumps, or agitated patients [23]. Therefore, we will also utilize heart rate, respiratory rate and blood pressure reading which are routinely recorded via electronic medical record in the patients enrolled.

Additionally, EEG band power analysis will be performed using fast Fourier transformation (FFT). Briefly, FFT will be performed on all artifact-free EEG epochs visually scored as nonrapid eye movement (NREM) sleep during the entire recording. The average EEG power will be calculated for β (12–30Hz), α (8–13 Hz), θ (4–8

Hz), and δ (0.5–4 Hz) frequency bands for each individual patient.

The primary outcome will be Wakefulness After persistent Sleep Onset (WASO). WASO will be defined as the duration of wakefulness after the onset of persistent sleep in the observation period between 10 PM (Lights-Off) to 6 AM (Lights-On) in minutes [24]. Onset of persistent sleep will be defined on the EEG as the first epoch of 10 consecutive minutes of sleep (REM or non-REM Stages 1, 2, 3 or 4) after Lights-Off. Wakefulness will be defined as any epoch of Stage 0.

Secondary outcome

Secondary outcomes will include total sleep time (TST) measured during the night of the sleep trial by using electroencephalography (EEG), in analogy to the primary outcome.

Exploratory outcomes

Time to sleep onset (TSO) during the night of the sleep trial will be assessed using electroencephalography.

Subjective sleep quality will be assessed by applying the Richards-Campbell Sleep Questionnaire (RCSQ). The RCSQ is a validated survey instrument for assessing sleep quality in critically ill patients based on a five-item, visual analogue scale (each from 0 [worst value] to 100 [best value]) [8]. The scale evaluates perceptions of depth of sleep, sleep onset latency, number of awakenings, time spent awake, and overall sleep quality.

Delirium

Incidence of postoperative delirium and delirium-free days during the hospitalization (capturing days in the ICU and on the hospital ward) will be assessed. Delirium assessments will be performed daily until hospital discharge using the Confusion Assessment Method (CAM) or CAM-ICU [19]. Assessments will be performed by nursing staff as part of routine clinical care, or a research team member trained in the survey administration methodology and blinded to treatment assignemnent. The CAM is a standardized screening tool used for identification of delirium symptoms through a diagnostic algorithm based on 4 cardinal features of delirium, namely acute onset and fluctuating course, inattention, disorganized thinking, and altered level of consciousness. The CAM-ICU, which is routinely performed in the ICU, includes both brief cognitive testing and the CAM algorithm to screen for delirium. For CAM-positive patients, the Delirium Symptom Interview, a standard cognitive assessment consisting of tests of attention, orientation, and memory will be performed by a research team members trained in the survey administration methodology and blinded to treatment assignement to verify the CAM screening results.

Variability in response to suvorexant treatment

We will determine whether the effect of suvorexant are modified by the following patient, procedure, and anesthesia-related factors: subjective TST during the nights prior to surgery measured by RCSQ, , cardiovascular function impairment (norepinephrine equivalent dose), duration of mechanical ventilation, total propofol dose since skin incision, and markers of pain intensity such as total opioid dose since skin incision for up to 48 hours postoperatively and numeric rating scale (NRS) pain scores (scale from 0 [no pain] to 10 [worst pain]) [23] obtained by nursing staff blinded to treatment allocation on each evening before study drug administration for 7 days. To account for surgical complexity as a marker of postoperative stress response, we will further include duration of bypass time, total blood loss, and the Procedural Severity Score for mortality (PSS mortality).

B. Statistical Considerations

Sample Size Justification

We will consider a 30 minute difference in WASO as clinically meaningful, with a standard deviation (SD) of 45 minutes [24]. Accordingly, we expect that a sample size of 50 subjects per group will provide us with >90% power to detect this difference between treatment groups, using a two-sample t-test with 2-sided α=0.05. As for the exploratory outcome, we may see a difference of 3 delirium-free days (this assumption is based on findings observed with early mobilization by us in a similar cohort [25]) between groups with a SD of 5 days. The given sample size of a total of 100 patients will yield a power of 84.4% to detect a difference in the exploratory

outcome. To account for drop-out, we plan to enroll up to 120 patients to achieve our desired sample size of 100 completed participants.

Data Analysis
The statistical analyses will be initiated by blinded study team members supervised by a BIDMC statistician. All study personnel will be blinded to the treatment group of the subject, except the investigational pharmacist. For the purpose of the final analysis, unblinding will be performed by the statistician and the research team. The research database will not be unblinded until the medical/scientific review has been completed, protocol violations have been identified (if appropriate), and data collection has been declared as complete.

All analyses will be conducted by research staff supervised by a BIDMC statistician and performed in Stata (StataCorp LP, version 13.0 or higher) and Rstudio (Rstudio.INC, Boston, MA,Version 1.1.4638). All personnel involved in data analyses will be blinded to intervention group assignment. A two-sided P value of <0.05 will be considered statistically significant.

Primary and secondary analyses
The primary and secondary analyses will be by intention-to-treat and will compare WASO and TST between patients receiving suvorexant or placebo. Baseline characteristics of the two groups will be presented descriptively. Normally distributed continuous variables will be expressed as means and standard deviations, non-normally distributed variables as medians and interquartile ranges, and categorical variables as frequencies and percentages. We will calculate the standardized differences of baseline characteristics between the two groups. To determine whether times of WASO and TST differ between treatment groups, we will analyze our data using a Student's t test, or Mann-Whitney-U test, as appropriate.

Exploratory analyses
Time to sleep onset (TSO)
To determine whether times to sleep onset differ between treatment groups, we will analyze data using a Student's t test, or Mann-Whitney-U test, as appropriate.

Delirium
To determine whether incidence of postoperative delirium and delirium free days differ between treatment groups, we will analyze data analogously to the primary and secondary analyses.

Variability in response to suvorexant treatment
To determine whether there is an association between each of the previously described potential confounders and TST during the night of the sleep trial, we will use logistic regression models. Subsequently, we will evaluate a potential interaction between any statistically significant predictor of TST and suvorexant treatment on total sleep time.

Safety
Incidences of serious and non-serious adverse events will be compared between the two groups using a Chi-Square test. Specific comparisons will further include somnolence, fatigue, headache, dry mouth, cough, and upper-respiratory infections as well as abnormal thoughts and behaviors, hallucination, memory loss, anxiety, sleep paralysis, and lower-extremity weakness.

Multiplicity
As this study tests a single pre-specified primary endpoint, no adjustment for multiplicity will be required for the primary outcome. Effects on secondary endpoints will be assessed after appropriate corrections for multiple endpoints have been applied. We will adjust the level of significance for secondary endpoints using Bonferroni's adjustment.

C. Subject Selection

Inclusion criteria:

1. Age 60 years or older
2. Undergoing elective cardiac surgery [coronary artery bypass graft surgery with or without aortic and/or mitral valve replacement ,isolated valve surgery] requiring cardiopulmonary bypass, who are expected to be transferred to the ICU postoperatively

Primary Exclusion criteria:

1. Preoperative left ventricular ejection fraction of less than 30%
2. Renal failure (creatinine >2 mg/dl or dialysis dependence)
3. Liver failure (CHILD-Pugh score> 6)
4. Coma (RASS<-1)
5. Signs and symptoms of delirium and agitation at time of enrollment (CAM-ICU positive)
6. Montreal Cognitive Assessment (MoCA) below 23 at time of consent
7. Psychiatric or neurologic diseases (including chronic benzodiazepine use, bipolar disorder, psychotic disorder, posttraumatic stress disorder, requirement of prophylactic psychiatric medication, evidence of acute depression on screening visit, preexisting cognitive impairment, Alzheimer disease, Parkinson's disease, medications for cognitive decline, history of recent seizures (within 1 year prioir visit), alcoholism or documented history of alcohol abuse, and narcolepsy)
8. Severe sleep apnea requiring home CPAP treatment
9. Morbid obesity (BMI >40)
10. Known or suspected pregnancy (there are no adequate and well-controlled studies of suvorexant in pregnant women. Based on animal data, Suvorexant may cause fetal harm).
11. Patients with known hypersensitivity to study medications
12. English language limitations (Sleep assessment and delirium assessment tools are only validated in English)
13. Patients enrolled in other interventional studies which could confound the primary endpoint.

Participants who do not speak English will be excluded because of their inability to complete the cognitive assessments, which have been extensively validated in English. Adult patients unqualified or incapable of giving legal consent will be excluded. Secondary exclusion criteria after enrollment will include massive intraoperative hemorrhage, postoperative respiratory failure,loss of enteral access and signs and symptoms of delirium and agitation at time of study drug initiation (CAM ICU positive) . An overview of eligibility criteria is provided in **Figure 3**.

Gender and Racial Distribution of Subjects
We anticipate that our study population will reflect the normal distribution of race and gender of patients presenting for cardiac surgeries at BIDMC.

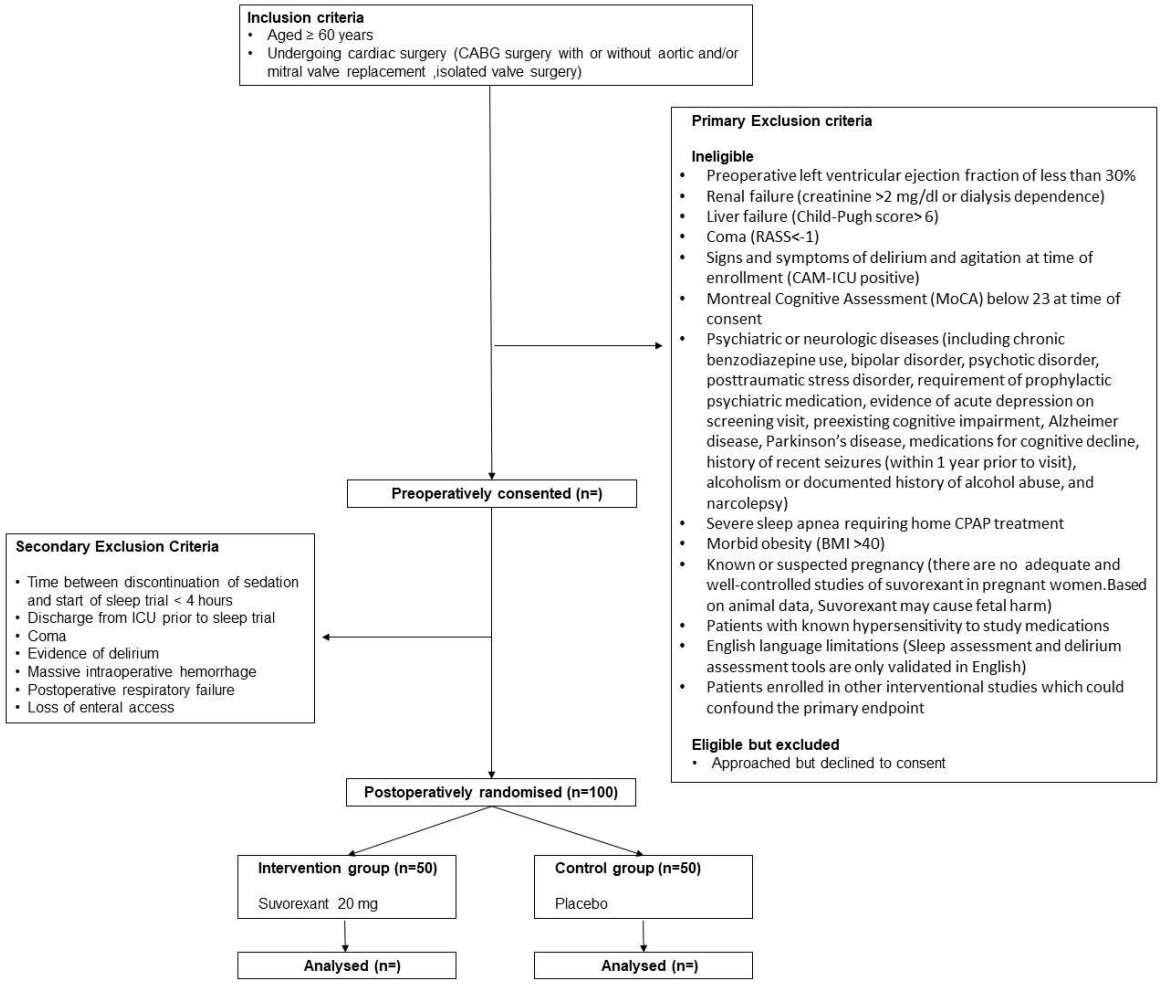

Figure 3. Flowchart of study cohort. Abbreviations: CABG: coronary artery bypass graft; EF: ejection fraction; ICU: intensive care unit.

B4. POSSIBLE BENEFITS

It is not possible to predict whether there will be direct benefit to the individual subject by participating in this study. However, based on our review of the literature, it is not unreasonable to assume that the administration of suvorexant could result in a lower incidence of impaired sleep onset and sleep maintenance in ICU patients. Suvorexant may also improve the subjective outcomes of total sleep time, sleep onset latency and impact of impaired sleep on daytime functionality.

B5. POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO

The following includes descriptions of reasonably foreseeable risks or discomforts associated with participation in this study.

Risks associated with the administration of suvorexant
Suvorexant is well-tolerated and its side effects are minor and related to the desired end-point: drowsiness, abnormal thoughts and behavior, memory loss, temporary inability to move or talk (sleep paralysis), or temporary weakness in the legs [4]. It must be noted that in a highly monitored ICU environment, all of these side-effects can be quickly diagnosed and treated if necessary. Suicidal ideations, a side effect of unknown frequency, will be assessed and managed in accordance to BIDMC policy 1600-3 (Management of the Suicidal Patient Being Cared for on the Inpatient Units and in ED).

Risks associated with EEG measurements
There are no physical risks associated with EEG recordings using the SedLine monitor. The electrodes are generally well-tolerated, but the patient may still experience discomfort from the electrodes applied to the forehead for the duration of the recording. In case of patient discomfort, the study team will do their best to make the patient feel more comfortable.

Analysis of Risk/Benefit Ratio
Given the minor side effects associated with the study drug and the minimal risks associated with the study interventions, the risk/benefirt ratio is favourable. Results from this study may improve the treatment of insomnia in ICU patients and consequently reduce the aforementioned negative effects of insomnia, which would outweight the minimal risks.

B6. RECRUITMENT AND CONSENT PROCEDURES

Recruitment
Eligible participants will be identified on the medical or surgical floors, at pre-admission testing clinic appointments, or in the cardiac catheterization lab with all inclusion and exclusion criteria assessed at this time. Members of the study team will screen operating room schedules, patient medical records and appointment schedules for the presence of inclusion or exclusion criteria to determine eligibility for enrollment. A secure screening and enrollment log will be kept. If a patient is deemed a potential candidate, they will be approached for informed consent by authorized team members.

Consent
Once a patient is found eligible and after notifying the clinical care team, authorized study team members will obtain written informed consent from all participants prior to surgery and initiation of study procedures. Consent will be obtained by trained study staff with doors closed/curtains drawn to assure patient privacy. Trained study team members will introduce the study to the prospective participant. The study physician will be present to answer questions, describe the study, and sign the consent form with participants. All study procedures including associated risks and benefits will be explained in detail. All questions asked by subjects will be answered. Subjects will be informed that participation is voluntary and that they can withdraw consent at any time. Study staff will conduct a screen for comprehension and capacity during the consent conversation. Methods include asking questions such as: “we’re asking you to make an important choice. I need to check if we’ve done a good job explaining everything. May I ask you a few questions? What condition have you been treated for? What are the researchers trying to find out? What would you do as part of the study?” If a patient is not able to answer the screening questions comfortably or if any doubt about a patient’s competency to sign the consent form arises, the patient will not be enrolled in the study. The original signed consent form will be stored in the study binder. We will provide a copy of the consent form to the patient. Another copy will be stored in the patient´s medical record. The study team undergoes standardized, rigorous training regarding the informed consent process for research.

Subject Protection
It is not expected that vulnerable subjects will be candidates for participation in this study. To avoid potential coercion, informed consent will be obtained by a study physician who is not the primary care provider for the patient. Subjects will be informed that participation is voluntary and that they can withdraw consent at any time

and will be given enough time to review risks benefits, ask questions and decide whether they wish to participate in the study. It will be clearly stated that the subjects' decision to participate or refrain from participation in the research study will not affect the performance or outcome of their clinical care.

B7. STUDY LOCATION

Privacy

All study interaction will take place in private settings with curtains/doors closed so as to provide privacy and comfort for the subject.

Physical Setting

Enrollment will take place at Beth Israel Deaconess Medical Center. Study procedures will take place in the BIDMC ICUs and wards, with the exception of the preoperative sleep assessments that patients will record at home. Data collected will be housed on password-protected BIDMC network servers behind institutional firewalls. Paper recorders will be kept in locked filing cabinets/offices.

B8. DATA SECURITY

Data will be stored and maintained securely on password-protected servers in the BIDMC network. Paper records will be stored in locked cabinets. A study ID number will be assigned to each patient. Data will be uploaded, stored and maintained on the secure Research Electronic Data Capture (REDCap). Medical Record Numbers, fiscal numbers, or patient names will not be entered into REDCap. The study team will be responsible for all data entry and quality control activities.

We will retain information on patients who are screened but excluded from the trial for the purpose of populating a CONSORT diagram at the time of results publication (see **Figure 3**). Only the minimum amount of data necessary will be stored.

A crosswalk linking patient identifiers to study ID number will be maintained by the PI. Limited information will be retained on patients who are prescreened and do not qualify, or who are approached and declined, for the purposes of generating a CONSORT diagram at the conclusion of the trial (see **Figure 3**).

All study staff undergo formal training in proper research procedures, good clinical practice and application of HIPAA privacy laws.

De-identified final results will be included in the results registry data bank at www.clinicaltrials.gov in accordance with current regulations. Progress reports will be provided to Merck in accordance with the terms of the fully executed Clinical Trial Agreement and any other relevant contracts.

B9 Multi-Site Studies

Is the BIDMC the coordinating site? ☐ Yes ☐ No

Is the BIDMC PI the lead investigator of the multi-site study? ☐ Yes ☐ No

N/A (single center study)

B10 Dissemination of Research Results

Study participants will be thanked for their participation throughtout the study. Results arising from this study will be published in a peer-reviewed medical journal, as well as presented at both national and international conferences. Study participants will be acknowledged as a group in those publications for their contribution and time. There is no plan to share study results with participants at the conclusion of the trial. Because study results are likely to be published a few years after a given subject's participation, it is not feasible to send subjects follow-up with the published results. We are concerned that mailing the published manuscript and an additional thank-you note years after participation risks violating subject privacy, as mailing addresses are increasingly likely to change with passing time. It is out of the scope of this study to continue tracking mailing addresses after completion of enrollment since this is not a longitudinal study.

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