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Effects of Sleep Disruption on Drug Response

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JHM IRB - eForm A – Protocol

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1. Abstract

- a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

This study will evaluate the effects of experimental sleep disruption (SD) on opioid response in patients with chronic low back pain (CLBP). The central scientific premise of the study is that SD may produce qualitative differences in opioid response that are relevant to opioid addiction risk among patients with CLBP. Opioid analgesics are commonly prescribed for CLBP patients despite clear evidence indicating that chronic opioid exposure increases risk for addiction. Our preliminary data show that SD acts on multiple mediators of opioid addiction, including positive affect and brain reward system function. However, no study has directly investigated the effect of SD on opioid abuse liability or opioid analgesia in patients with chronic pain, despite the fact that this patient group has an elevated risk profile. We propose a mixed between-within subjects study in patients with CLBP (N=60) and healthy controls (N=60), will receive one night of SD and one night of uninterrupted sleep (US), in random order. On the day after each sleep condition, we will evaluate the abuse liability and analgesic efficacy of hydromorphone, a common opioid analgesic with an abuse profile similar to heroin, in a placebo-controlled cumulative dose run-up paradigm. The findings from the proposed study will critically inform clinical decision making related to the use of opioids for patients with chronic pain.

2. Objectives (include all primary and secondary objectives)

Determining if SD alters opioid abuse liability and analgesic response in CLBP patients fills a critical knowledge gap with major implications for addressing the opioid abuse epidemic. The results of this overall line of research will critically inform clinical decision making related to the use of opioids for patients with chronic pain, and may lead to the development of novel interventions targeting sleep as a means to mitigating prescription opioid addiction risk.

Our first objective will be to demonstrate feasibility of the SD paradigm in CLBP patients. We have successfully executed similarly complex research designs in healthy subjects, but lack data in patients with chronic pain. This study will establish our ability to recruit CLBP patients for this project and safely execute the SD and opioid administration procedures in this clinical population.

Our second objective will be to evaluate whether SD alters opioid abuse liability in CLBP patients. The primary outcome of drug liking will be assessed in isolation, separate from the pain stimuli, on each assessment occasion; however, secondary analyses will explore whether the effects of SD on drug liking are different when it is assessed in isolation versus in the context of experimental pain stimuli.

Finally, we will evaluate whether SD alters opioid analgesia to laboratory-evoked pain in CLBP patients. Analgesia will be attenuated after SD compared to uninterrupted sleep.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

The U.S. is presently grappling with a nationwide ‘opioid epidemic’ characterized by widespread problematic use of prescription opioids, defined as misuse, abuse, and/or addiction^{1,2}. Approximately 25% of patients with chronic pain misuse prescription opioids and approximately 10% have opioid use disorder (OUD)³, compared to just 0.2% of the general population.⁴ These problems appear to be especially pronounced in patients with CLBP, who are more likely to misuse opioids than patients with other chronic pain diagnoses, such as arthritis.⁵ CLBP is the most common chronic pain disorder, with a point prevalence of between 12-33% in the U.S.⁶⁻⁸. Up to 66% of CLBP patients are prescribed opioids⁹, but multiple studies report that opioids do not relieve chronic pain¹⁰⁻¹², potentially increasing risk for opioid misuse. Given this risk profile, CLBP is an ideal condition in which to study predictors of iatrogenic opioid addiction.

Opioid sales increased approximately 400% between 1999 and 2010 in the U.S.¹³, with the majority of opioid prescriptions being for long-term opioid therapy treatment plans¹⁴. Over this time frame, problematic opioid use substantially increased, which has been linked to heroin initiation¹⁵ and a dramatically increased incidence of opioid overdose deaths.¹⁶ In 2015, opioid abuse problems cost the U.S. economy approximately \$504 billion¹⁷, which is 6 times higher than the previous estimate from 2013.¹⁸ Federal agencies, such as the Centers for Disease Control (CDC), have recently recommended that physicians be more circumspect in opioid prescribing to minimize patient risk. However, there are limited empirical data to inform physicians about how to identify patients who are increased risk of opioid addiction—particularly those who have no history of substance use disorder. **A critical next step in improving opioid prescribing practices is to identify easily observable predictors of opioid addiction risk that can be targeted for prevention in patients with chronic pain.**

The proposed study evaluates whether CLBP patients’ subjective responses to opioid administration are altered by SD. We focus on two outcome domains that are associated with increased risk for iatrogenic opioid addiction: opioid abuse liability (i.e., drug liking and valuation) and opioid analgesic efficacy. Higher opioid liking is the gold standard subjective assessment of likelihood to misuse or abuse opioids¹⁹, and it is therefore of interest to know which factors influence opioid liking in CLBP patients. Weak analgesic efficacy may also lead to opioid addiction by compelling patients to ask for and physicians to agree to escalating opioid dose strategies; in the long term, prolonged opioid exposure increases risk for addiction by altering opioidergic neurocircuitry in a manner that promotes drug-seeking behaviors.²⁰⁻²³ There are several reasons to explore the degree to which SD may increase the abuse liability and diminish the analgesic efficacy of opioids among CLBP patients, relative to healthy controls.

First, CLBP patients commonly experience disrupted sleep continuity²⁴⁻²⁷, so it is a clinically relevant target. Second, SD is easily observable and can be objectively tracked by physicians with actigraphy.²⁸ Third, SD and other sleep problems are common in people with opioid use disorders.²⁹⁻³¹ Fourth, our preliminary data suggest that experimental SD alters multiple putative intermediate mechanisms of opioid addiction, including positive affect, positive affective pain inhibition, and ventral striatum (VS) function. Fifth, SD is a reversible phenotype, which means that any effect SD may have on abuse liability or analgesic efficacy could potentially be remediated with pharmacological and non-pharmacological treatments. Finally, neuroimaging studies have shown that CLBP patients have altered reward system neurocircuitry relative to healthy individuals³². We expect that risk for problematic opioid use varies over the course of a CLBP disease trajectory, and that sleep-related problems could confer unique risk of developing OUD among those without a history of OUD or other substance use disorder. Although a portion of the population finds opioids aversive, a meta-analysis showed that 85% of chronic pain patients do not experience nausea, the most common negative side effect³³. Thus, our scientific premise is relevant to a substantial base of CLBP patients, including patients lacking a substance abuse history. Our preliminary data demonstrate that SD alters several intermediate mechanisms of OUD (e.g., positive affect, pain inhibition, and VS function). We now propose to investigate the direct effect of SD on opioid abuse liability and analgesia in CLBP patients (and healthy controls) who do not have a history of abusing opioids or other substances, and target this group because they are likely to be the most difficult to identify as “at risk” through current opioid risk screeners.

Major Gap in Knowledge: SD Effects on Opioid Abuse Liability in Chronic Pain. Other than a history of substance use disorder³⁴, there are few reliable person-level factors that have been identified as predictors of developing opioid addiction in patients with chronic pain. **To our knowledge, no study has rigorously evaluated SD as a predictor of opioid abuse liability among patients with chronic pain.** Our preliminary data and the extant literature suggest SD operates on many of the putative intermediate mechanisms thought to link initial opioid exposure to opioid addiction. Specifically, studies of total sleep deprivation and SD show that experimentally-induced sleep loss: a) reliably attenuates positive affect^{35,36}; b) increases impulsivity and risky decision making³⁷; c) alters dopamine signaling³⁸⁻⁴⁰; and d) alters the function of the mesolimbic reward system in response to rewards.^{41,42} Converging evidence from multiple preclinical and human neuroimaging labs suggests that individuals with CLBP may have abnormal dopaminergic and opioidergic signaling within the brain regions classically implicated in reward processing, such as the VS^{32,43-46}, leading to behavioral alterations that perpetuate pain and may increase opioid addiction risk. Our approach will address a critical gap in opioid addiction knowledge by directly testing how SD alters liking of and valuation for an exemplar opioid (hydromorphone), and whether such effects are more pronounced in CLBP patients than healthy controls.

Major Gap in Knowledge: SD Effects on Opioid Analgesia in Chronic Pain. Very little is known about the effect of SD on opioid analgesia in patients with chronic pain. However, converging lines of evidence suggest that sleep loss in general, and SD in particular, alters opioidergic neurocircuitry in a manner that both increases pain sensitivity and decreases opioid analgesic efficacy. Following total sleep deprivation, rats exhibit brief periods of hyperarousal that are reversed by the opioid antagonist naloxone and enhanced by morphine.⁴⁷ Total sleep deprivation downregulates rats' μ and δ opioid receptors⁴⁸, the principal receptors involved in opioid analgesia, and diminishes the effects of morphine in the periaqueductal grey, impairing

descending analgesic effects in the rostral ventral medulla.⁴⁹ In humans, we know of only one published study showing that sleepiness is associated with decreased codeine analgesia; that study used healthy, pain-free volunteers and did not include an experimental manipulation of sleep.⁵⁰ Co-I Smith and colleagues⁵¹ reported that experimental SD impaired conditioned pain modulation in healthy females, a pain inhibitory process that is mediated by endogenous opioids^{52,53 53-55}. Those findings were recently replicated⁵⁶, and support several observational findings linking insomnia and SD to impairments in conditioned pain modulation⁵⁷⁻⁵⁹. However, they do not directly speak to the analgesic efficacy of exogenously administered opioids, leaving a critical gap in our ability to generalize those results to opioid prescribing practice.

Co-I Smith also leads an ongoing study that evaluates the effect of SD on analgesia to a single dose of morphine (.08 mg/kg) in healthy participants; preliminary analyses suggest the SD attenuates morphine analgesia at that dose. This study will expand on that preliminary finding by prospectively examining the effect of SD on opioid analgesic efficacy of an exemplar *short-acting* opioid, using a cumulative dose design that provides an opportunity to examine a full dose-effect curve in the context of SD vs. normal sleep. The doses are within the therapeutic range, making them ecologically valid, and the study will examine the relative differences that exist among chronic pain patients and healthy individuals, groups that differ at both neurobiological and behavioral levels, as well as males and females.

Major Gap in Knowledge: Sex Differences. It is not known whether CLBP patients respond to opioids differently as a function of sex. However, meta-analyses show that males are more likely to engage in risk taking and sensation seeking behaviors than females⁶⁰, and are more likely to misuse and become addicted to prescription opioids^{4,61}. Females may demonstrate greater analgesic responses to morphine than males under normal conditions.^{62,63} This effect is mediated by μ -opioid receptor availability, which is greater in females than males in the context of laboratory-induced pain.⁶⁴ In rats, descending brain stem pain inhibitory circuits that subserve conditioned pain modulation are sexually dimorphic such that females are more sensitive to the analgesic effects of a locally injected μ agonist.⁶⁵ Taken together, these data suggest that opioids may have different risk profiles for males and females in chronic pain. We will examine whether that is reflected in sex-specific responses to SD.

How Proposed Work Will Fill the Gaps. Our group's unique combination of expertise on chronic pain, sleep, and opioid behavioral pharmacology puts us in an ideal position to conduct the proposed rigorously controlled experiment to assess the effects of SD (versus uninterrupted sleep, within-subject) on the subjective effects of an exemplar opioid (placebo versus hydromorphone dose effect curve, within-subject), and the extent to which those effects vary as a function of CLBP (versus healthy controls, between-subject) and sex (between-subject).

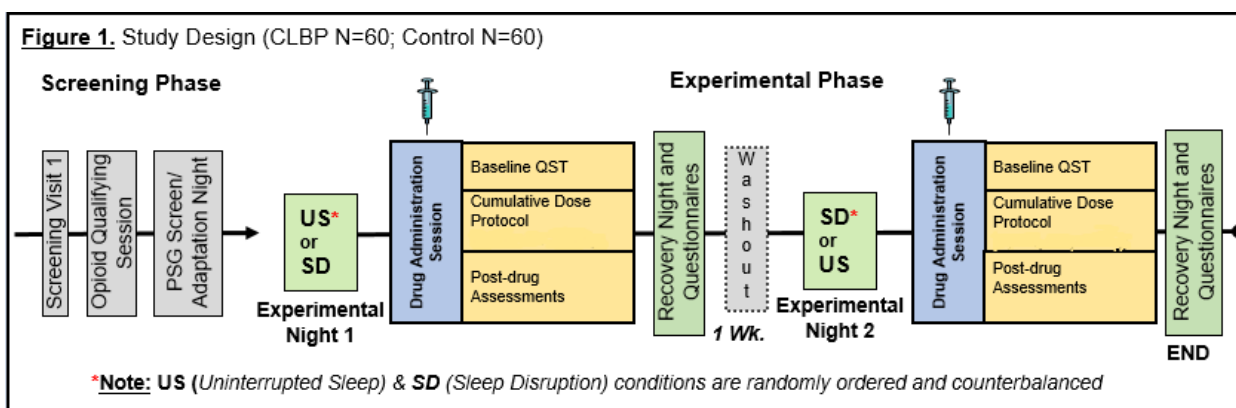
Contribution to the Field. If our study demonstrates that SD increases opioid abuse liability and reduces opioid analgesia in CLBP, we anticipate substantial ripple effects through clinical pain management practice. First, the results would encourage health care providers to thoroughly assess sleep prior to and during an opioid treatment regimen. Second, because SD is a malleable therapeutic target among patients with chronic pain⁶⁶, positive results from the proposed study would steer health care providers toward a strategy for intervention when elevations in risk are detected. Third, discovery of sex differences in the proposed effects would critically inform the implementation of an opioid risk decision tree for patients with CLBP. Fourth, CLBP is one of the most common chronic pain disorders^{67,68}, and its prevalence appears to be rising⁸, so our results will be generalizable to the greatest number of patients with chronic pain.

4. Study Procedures

- a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

Study Design Overview.

We propose a mixed between-within randomized crossover human-laboratory experiment that investigates placebo-controlled dose-response effects of hydromorphone on 1) abuse liability metrics (Drug Liking and Monetary Valuation) and 2) analgesia in response to laboratory-evoked standardized pain measures, across a range of clinically relevant doses after one night of uninterrupted sleep (US) and again after one night of sleep disruption (SD). We will recruit both CLBP patients (N = 60) and healthy controls (N = 60). The study team have extensive experience recruiting patients with chronic pain for complex longitudinal studies, including clinical trials^{69,70} and experimental studies⁷¹⁻⁷³, which we will draw upon to successfully recruit CLBP patients and execute the proposed protocol. **Figure 1** summarizes the study design.



Following initial screening, eligible participants will complete a qualifying session to verify that participants can detect and tolerate IM-injected hydromorphone. Eligible participants will complete a PSG screen/adaptation night, and will subsequently be randomized to the order in which they receive the sleep conditions (US-SF vs. SF-US). Each condition will consist of a standardized 8-hour overnight sleep (or sleep disruption) period and a next day 8-hr drug administration session; the two conditions will be scheduled at least 1 week apart to allow for resumption of normal sleep. The sleep conditions will use well-established procedures that we have used in several previous studies^{35,36,51,74}. The sleep conditions will take place in a monitored clinical research unit (CRU) at Johns Hopkins Bayview Medical Center. Drug administration sessions will begin in the morning (e.g., 8:30am, to control for circadian shifts) on the day after each sleep condition. Both sleep conditions will include a night of recovery sleep in the CRU, which will be followed by a brief assessment of questionnaires and quantitative sensory testing before the participant is discharged.

The p-Site UVA School of Medicine, will assist with data processing and data analysis, and Dr. Finan will remotely interface with study participants (e.g., via phone or video conference) as needed. JHM will serve as the Coordinating Center and all participant recruitment, enrollment, consenting and study procedures will take place at the JHM site as described in the protocol. JHM IRB will serve as the single IRB of record for all domestic sites.

Screening Visit 1. At the screening visit, participants will complete a medical history and physical exam and provide a urine sample that tests negative for pregnancy and recent drug use. A complete blood count test will be performed to rule out infection, and hepatic and renal panels will be ordered to verify kidney and liver function. Subjects will also undergo a night of in-home sleep apnea monitoring to rule out sleep apnea. Subjects meeting diagnostic criteria⁷⁵ for sleep apnea (e.g. moderate to severe sleep apnea) will be ruled out and referred for clinical care. Urine and blood tests will be repeated each admission. An ECG will be administered to evaluate cardiac health. Subjects will complete questionnaires to verify eligibility criteria (see Screening Measures below). Additionally, subjects will be trained on how to complete a sleep diary and wear an actiwatch. Sleep diary, reports of daily stress¹²⁹, and actigraphy data will be collected over the subsequent week.

Screening Visit 2: Opioid Qualifying Session. Participants will undergo a qualifying session for hydromorphone to determine if they can differentiate hydromorphone from placebo. This is a recommended practice. This session will also allow us to exclude participants who experience adverse reactions at the lowest dose (0.14mg/70kg).

The qualifying session will last approximately 6 hours and participants will be provided with transportation before and after the session. Participants will provide a urine sample that tests negative for drug use and pregnancy to begin the session, and will receive a calorie-controlled breakfast before study procedures begin. Participants will then complete a baseline rating of pain severity and unpleasantness by quantitative sensory testing (QST) before receiving subcutaneous hydromorphone as part of a consecutive dose run-up procedure. Following baseline, up to four subcutaneous injections will be administered to participants in ascending order [0 (Saline), 0.14, 0.28, and .56 mg/ 70kg], separated by 60-90 minute inter-injection intervals. An abbreviated ~10-minute QST will be administered at baseline, 30, 90, 150, 210, and 270 minutes following the first injection. To minimize expectancy effects, participants will be blind to the order of placebo vs. drug, as well as the doses and dose order. This is a common procedure to reduce expectancy bias and one that is currently being utilized by Co-I Dunn in several ongoing studies. Participants will complete visual analog scale (VAS) ratings of Drug Effects item every 30 minutes. Participants will be excluded from primary study participation if they fail to identify drug effects or have serious adverse reactions to the lowest dose. Vital signs and respiration will be monitored throughout the session and participants who have fewer than 8 breaths per minute on 2 successive measurements will be excluded from further participation.

Experimental Sleep Procedures Overview.

All subjects will receive one polysomnography (PSG) adaptation night, one night of US and one night of SD, in randomized order. Each sleep condition will be followed by a recovery/monitoring night in the CRU. In total, there will be 5 nights spent in the CRU, divided into two stays of 3 nights (Adaptation night + Sleep Condition 1 + Recovery Night) and 2 nights (Sleep Condition 2 + Recovery Night), respectively. The two sleep conditions will be separated by at least 1 week. For as long as the IRB requires COVID-19 testing for protocols that include inpatient stays, we will adhere to the IRB policy and require written proof of a negative COVID-19 test within 72 hours of the inpatient admission.

SD will involve multiple forced nocturnal awakenings by research staff in the CRU at Johns Hopkins Bayview Medical Center, and sleep will again be monitored with PSG. Sleep conditions will be separated by at least one week. For females, a blood draw will be taken the evening

before each experimental session to quantify progesterone, which will be used as a covariate in analyses due to concerns that menstrual hormonal variation may influence opioid response^{76,77}. We will also track participants' estimations of sleep continuity and sleep quality with a daily sleep diary for one week prior to the initiation of the experimental protocol.

Nocturnal Polysomnography (PSG). PSGs will be conducted on all CRU overnight stays in private rooms. Lights out will occur at the subject's average bedtime per diary (verified, as needed, by actigraphy). Registered PSG technicians (RPSGT) will execute the PSG procedures according to standard technical guidelines. We will acquire electrophysiologic signals state of the art PSG equipment available at the CRU (e.g., Embla 7000). Respiratory function and effort will be measured via oronasal thermistor, nasal air pressure transducer, pulse oximetry, and abdominal and thoracic plethysmography belts. Following the adaptation night, some sensors (e.g., EMGs, respiratory sensors) may be removed for comfort during the US and SD nights. Records will be scored according to AASM guidelines, by an RPSGT and reviewed by a physician, board certified in sleep medicine. Both will be blind to study hypotheses.

Adaptation Night: Subjects will undergo a standard PSG, as described below, to rule out occult sleep disorders and provide an adaptation night. Subjects meeting ICSD criteria for a sleep disorder (e.g., sleep apnea) will be excluded from the study and referred for clinical care. A modified version of the Paced Auditory Serial Addition Task^{134, 135} (a mental math task) will be administered the next day (prior to sleep disruption) to assess affective and cardiovascular responses to acute stress.

Uninterrupted Sleep Condition. Subjects will be instructed to sleep for a period of 8 hours.

Sleep Disruption Condition. Subjects will undergo a series of forced nocturnal awakenings in a standardized SD protocol developed by our group^{36,51}, which serves as an experimental model of the type of partial sleep loss experienced by patients with chronic pain and insomnia. The night is divided into eight 1-hour intervals. One of the hour-long intervals is randomly determined to be a 60-min awakening, during which sleep is not permitted. The remaining seven, 1-hour intervals are subdivided into thirds (20-min period), and one 20-min period is randomly selected within each hour to be a forced awakening period. During assigned forced awakening periods, nursing staff awaken subjects and keep them awake for the entire interval. Subjects are asked to sit up in bed with the lights on to reduce the chance of microsleep. The maximum total sleep time targeted is 280 min. PSG monitoring is maintained for the entire sleep opportunity period. Subjects are not permitted to leave the inpatient unit during forced awakening periods and are under continuous nursing supervision/monitoring to ensure safety and protocol fidelity. Caffeine is not permitted while inpatient in order to maximize the effect of the SD paradigm, consistent with our prior work. An inpatient night of recovery sleep (ad libitum) will follow the daytime experimental procedures.

Experimental Opioid Procedures.

Drug Administration Sessions. Participants will be required to provide a urine sample that tests negative for drug use and pregnancy to begin each session. Participants will receive a calorie-controlled breakfast and participants who smoke will be permitted 1 cigarette before beginning the session and another every 2 hours. We will use a consecutive dose run-up paradigm after each sleep condition. The sessions, including post-administration assessment points, will last approximately 8-9 hours. Baseline assessments of pain severity and

unpleasantness will be assessed using quantitative sensory testing (QST; see below). Following the baseline pain assessment, double-blind doses of study medication will be administered via subcutaneous injection in an ascending design [0 (placebo), 0.14, 0.28, and .56 mg/ 70kg hydromorphone], each injection separated by 60-90 minutes. The Drug Effects VAS will be administered every 30 minutes during the drug administration period (0, 30, 60, 90, 120, 160, 180 minutes), and subsequently at 210, 240, 270, 300, 330, 360, 390, and 420 minutes. The QST procedures will be administered baseline (0 minutes), 30, 90, 150, 210, 270, 330, and 390 minutes. A blood draw will be taken after the peak dose, to be later analyzed to quantify hydromorphone metabolite. At 420 minutes, participants will complete the Drug versus Money Questionnaire that is modeled from the Multiple Choice Procedure, to indicate the dollar value they would place upon the cumulative dose, consistent with standard administration procedures for this measure.⁷⁸

Importantly, if it is determined in the opioid qualifying session that the participant cannot tolerate all of the doses, but they can tolerate at least one or two of the doses, the drug administration session will proceed according to the same assessment schedule (420 minutes), only with fewer doses administered.

Participants who meet our respiration threshold at any point (e.g., <8 breaths per minute on 2 successive measurements) will not receive any additional injections and will remain in the unit under observation until agonist effects remit. This strategy ensures safety, and will not negatively impact primary analyses, which will focus on peak effect and do not rely on completion of the entire cumulative dose protocol.

Measures.

Screening Measures. Sleep continuity will be assessed with both a daily sleep diary⁷⁹ and actigraphy, as we do in all of our sleep studies. Additional sleep-related measures include the Epworth Sleepiness Scale⁸⁰ and the Athens Insomnia Scale⁸¹. CLBP diagnosis will be ascertained via physician confirmation and chronic pain status for healthy controls will be assessed with the Graded Chronic Pain Scale.⁸² Psychiatric history will be assessed with the computer adaptive testing for mental health (CAT-MH). The CAT-MH modules are accessed via www.CAT-MH.com, a password-protected website run by Psychiatric Assessments Inc. (PAI). There is a single Administrator log-in utilized by the research team to access the site. Each participant is assigned a four-digit subject ID, as well as a randomly generated log-in and password. The Research Assistant assigns the subject ID and log-in/password at the time of testing and notes this information in the Enrollment log or Visit Data Collection log, which links the patient code number with the CAT-MH subject ID. Using the tablet, the RA accesses the website and uses the newly assigned log-in and password to access CAT testing modules. The participant is handed the tablet to complete the computerized tests. Results of the testing modules are accessed by the Administrator log-in. No PHI is entered into the website. Substance use history will be assessed with the Mini International Neuropsychiatric Interview (MINI)⁸³. Smoking status will be assessed using tobacco measures from the Alcohol, Tobacco, and Other Substances Domain of the PhenX Toolkit⁸⁴, a catalog of recommended, standard measures that facilitates cross-study analysis.

Primary Outcome Measures. *Opioid abuse liability* will be assessed with visual analog ratings of “Drug Liking”. Primary ratings will be acquired at each time point prior to the administration of QST. Additional ratings will be collected immediately following each QST

assessment in order to assess Drug Liking ratings in the context of experimental pain. These will include “Liking due to Euphoria”, “Liking due to Feeling High”, and “Liking due to Analgesia (relief of pain).” These questions will provide a method of understanding whether drug liking is related to the hedonic value of the drug versus its analgesic effects, and whether that changes as a result of increased pain sensitivity following SD. The *Monetary Valuation* of hydromorphone will be assessed with the Drug or Money Multiple Choice Questionnaire⁷⁸. *Pain sensitivity* will be assessed with the 0-100 numerical rating scale.⁸⁵

QST: Heat Pain Threshold. At baseline, heat pain threshold (HPTh) will be assessed using an ascending method of limits paradigm. HPTh is a valid and reliable test of pain sensitivity.⁸⁶ The thermode is secured to the ventral medial forearm and the temperature is gradually increased (rate of rise = .5°C/sec) from a pre-set baseline (31°C), until the subject indicates when the stimulus “first feels painful” (threshold) by pressing a button, which stops and records the temperature. We will re-assess HPTh at each timepoint.

QST: Suprathreshold Tonic Heat Pain. Tonic thermal pain, via thermode applied to the ventral medial forearm, will be elicited at temperatures 1 and 2°C above each individual’s HPTh. These temperatures will be held tonically for 3 seconds, bilaterally. Pain ratings will be obtained following each stimulus and aggregated to create a suprathreshold heat pain index.

Design Note. We chose heat pain stimuli because they recruit endogenous opioids⁸⁷ and because responses to them are inhibited by exogenous opioids.⁸⁸⁻⁹⁰ Furthermore, suprathreshold pain stimuli are recommended for the evaluation of clinically relevant pain response⁹¹, particularly in the context of opioid administration designs.⁹² Our lab has substantial experience administering heat pain stimuli, both with healthy subjects undergoing experimental SF⁵¹ and patients with chronic musculoskeletal pain.⁷¹

Secondary Measures. Secondary measures of the response to hydromorphone include pupillary diameter response^{93,94}, and VAS ratings of Drug Effects, Good Effects, Bad Effects, Craving, and Nausea. Affective state will be assessed with the Positive and Negative Affect Schedule⁹⁵, the Snaith-Hamilton Pleasure Scale⁹⁶, and the BIS/BAS scale¹³⁶. Clinical pain will be assessed with the Brief Pain Inventory⁹⁷ and the 0-100 numerical rating scale. Pain catastrophizing will be assessed with the Pain Catastrophizing Scale.⁹⁸ The somatization scale of the Brief Symptom Inventory⁹⁹ will be administered to assess somatization. Additional QST measures of pressure pain threshold and cold water tolerance will be administered in order to evaluate analgesic effects across multiple sensory domains. Some of the QST measures may be administered simultaneously. Cognitive tasks will assess distraction, sustained attention/inhibitory control, the ability to categorize emotionally evocative facial expressions, affective and physiological reactivity to acute stressors, and decision making with respect to pain sensitivity and response to QST. Sleepiness and vigilance will be assessed with the Stanford Sleepiness Scale^{100,101} and the Psychomotor Vigilance Task¹⁰², respectively. Trait chronotype will be assessed with the Morningness-Eveningness Questionnaire.¹⁰³ Sleep architecture will be assessed via PSG. Among females, we will use the STRAW+10¹⁰⁴ at baseline to assess menopause stage, and will assess menstrual cycle information at each experimental visit. The Life Events Checklist¹³⁰ will be used to assess major life events that occurred within the past year and whether the events were appraised as stressful or positive. The Everyday Discrimination Scale¹³¹ will assess perceived discrimination across various domains of one’s identity (e.g., race, ethnicity, gender, sexual orientation, weight, etc). B-COPE¹³² will be used to measure various coping strategies that participants typically engage in when feeling stress. The Revised Adverse Childhood Experiences questionnaire will assess the occurrence of abuse and neglect before the age of 18¹³³.

A brief battery of primary (e.g., Multiple Choice Questionnaire; QST outcomes) and secondary (e.g., PANAS; SSS) measures, as well as an assessment of any adverse events will be administered in the morning following each Recovery Sleep night.

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

Participants will be enrolled in the study for approximately 3-9 weeks, with the possibility of a longer enrollment period if scheduling challenges arise. There are 4 total visits (Initial Screening Visit 1; Screening Visit 2 (Opioid Qualifying Session); Sleep Visit 3 (including Drug Administration); Sleep Visit 4 (including Drug Administration)). There is a minimum 1 week washout period between sleep conditions, and we anticipate requiring at least 1 week to schedule a participant for the first sleep/drug administration session after eligibility is determined in the opioid qualifying session. Given these considerations, 3 weeks is the expected minimum time to completion, and longer enrollment periods will be dictated by scheduling.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

Participants will be informed in the consent that the study drug will be hydromorphone, but they will be blind to the order of drug and placebo, as well as the dosing information. This is a common practice in laboratory-based studies of drug effects, a practice that Co-I Dunn and the BPRU faculty have followed for several years, and one that is recommended in peer-reviewed guidelines for abuse liability testing.¹⁰⁵ We will inform participants of the risks associated with hydromorphone in the consent form so they will be able to make an informed decision about study participation. Participants will receive double-blind doses of hydromorphone and placebo during the study to prevent expectancy effects and enable a rigorous evaluation of opioid administration on a variety of clinically-relevant outcome measures. Experimenters will also be blinded to the drug order and dosing information. Hydromorphone will be prepared by a research pharmacist for IM injection; placebo will be a volume-matched saline solution. A pharmacy technician with no participant interaction will prepare all medication doses.

Study staff will be included as Blinded Consent Designees with the appropriate forms included as supplemental documents.

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

N/A

e. Justification for inclusion of a placebo or non-treatment group.

Placebo is needed to control for potential expectancy effects.

f. Definition of treatment failure or participant removal criteria.

Participants will be removed from study participation if they ask to be removed, if they exhibit an allergic reaction or serious adverse event to the study drug, if they fail to comply with the requirements of the study, or if new information becomes available that suggests that continued study participation may put them at increased risk of adverse events.

- g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

Participants are not treatment-seeking and do not have any underlying medical condition that would warrant continued treatment with the study drug upon completing the study. Participants will be informed they can agree to begin the study now and withdraw later without any penalty. Participants who request to discharge from the study prior to completing the study will be assisted with contacting medical professionals upon request from the participant.

5. Inclusion/Exclusion Criteria

General Inclusion Criteria. 1) 18-60 year olds; 2) less than 2 servings/day of caffeinated beverages or willing to discontinue 3 days prior to admission; 3) any prior history of opioid use.

CLBP-Specific Inclusion Criteria. In addition to the general inclusion criteria, participants in the CLBP group must: 1) have a physician-confirmed diagnosis of CLBP; 2) report low back pain on average at least 3/10 pain intensity on a majority of days over the past 3 months.

General Exclusion Criteria. 1) BMI >40; 2) significant medical or psychiatric morbidity within 6 months or lifetime history of bipolar disorder, psychotic disorder, seizure disorder, opioid use disorder; 3) clinically significant abnormal complete blood count or comprehensive metabolic profile; 4) current or recent (prior 6 months) renal or hepatic disease, or obstructive sleep apnea; 5) current use of opioids or benzodiazepines any purpose; 6) positive toxicology screen for opioids, stimulants, or recreational drugs; 7) pregnancy or lactation; 8) significant preadmission psychological distress (T-scores >64 on the Brief Symptom Inventory¹⁰⁶ global scales); 9) previous adverse reactions to opioids; 10) serious or significant adverse events associated with any dose, including placebo, and/or failure to detect hydromorphone (<20 Drug Effect VAS and <5% pupil diameter change; both conditions must be met at every dose to be exclusionary); 11) A QTc interval of more than 450msec or clinically significant ECG findings. 12) Any medication, medical condition or behavior observed during participation that the investigators determine could compromise the integrity or safety of the study.

Healthy Control and CLBP-Specific Exclusion Criteria. In addition to the general exclusion criteria, healthy controls will be excluded if they report current medical / psychiatry history; report acute painful injury (within 3 months); have a diagnosed chronic pain disorder. CLBP participants will be excluded for the presence of any comorbid idiopathic or rheumatic chronic pain condition.

6. Drugs/ Substances/ Devices

- a. The rationale for choosing the drug and dose or for choosing the device to be used. Hydromorphone is an ideal medication for this study. It is a short-acting synthetic opioid with strong affinity for the μ -opioid receptor, and powerful analgesic properties--approximately 7-8 times that of morphine.¹⁰⁷⁻¹¹⁰ It is commonly used for post-operative pain relief^{111,112}, and is also prescribed for patients with CLBP.¹¹³ There have been several cumulative dosing studies of hydromorphone that have demonstrated safety and

tolerability.^{114,115} The cumulative dosing strategy is essential to minimize the number of study visits (and, thus, participant burden) while providing an opportunity to assess a full dose-effect curve, so the use of a short-acting opioid with established safety and tolerability is a critical component of our study design. The abuse liability of hydromorphone has been established.¹¹⁶ Finally, hydromorphone has been shown to produce analgesia to noxious thermal stimuli¹¹⁷, which will serve as our primary pain stimuli from which to evaluate the effects of SD on opioid analgesia.

- b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

Hydromorphone hydrochloride is a pure mu opioid agonist that can be administered in oral, rectal, intramuscular (IM), or intravenous (IV) formulations for the indication of acute and/or chronic pain. We have chosen to administer hydromorphone through IM in this study to facilitate a cumulative dosing scheme in a single day's session, which is essential to minimize participant burden while providing an opportunity to assess a full dose-effect curve. The half-life of hydromorphone is 2.5-3 hours, with peak analgesic effect occurring between 8 – 20 minutes after intravenous injection¹¹⁸ and slightly more delayed for IM injection¹¹⁹. The cumulative dose of hydromorphone will therefore, be .98 mg/70 kg. The doses were selected because they have been previously shown to be safe and tolerated in a cumulative dose run-up study involving healthy participants¹¹⁴, and are within the range of clinically relevant doses for acute analgesia.¹²⁰ There is no apparent effect of sex on the pharmacokinetics of hydromorphone.

- c. Justification and safety information if non-FDA approved drugs without an IND will be administered.
N/A

7. Study Statistics

- a. Primary outcome variables.

- 1) Opioid abuse liability
- 2) Monetary valuation of hydromorphone
- 3) Pain sensitivity (i.e., analgesia)

- b. Secondary outcome variables.

- 1) Pupillary diameter response
- 2) VAS ratings of Drug Effects, Good Effects, Bad Effects, Craving, and Nausea.
- 3) Positive and negative affect
- 4) Clinical pain
- 5) Pressure pain threshold
- 6) Cold water tolerance

- 7) Sleepiness and psychomotor vigilance
- 8) Sleep architecture

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

Using distributions and residuals from our parent study of SD and morphine administration, we ran Monte Carlo simulations with 1000 bootstraps to estimate sample size needed for the proposed analyses. With 60 subjects each in the CLBP and healthy control groups (Total N = 120), we are powered at 80% to observe a 5.24 (SE = 1.96) point (on 101-point Liking scale) greater increase in opioid liking, among CLBP patients compared to controls following SD relative to US (Aim 1). This small effect is similar in size to that reported by Lydon-Staley et al.¹²¹ in an analysis of daily self reports of sleep quality and opioid craving ($d = .13$). We expect our manipulation to produce stronger effects, but are powering the study to detect even a small effect. Sex-based comparisons (Aim 3) will halve our sample size for the primary contrasts, which will be restricted to males vs. females within the CLBP group. We are powered at 80% to observe a 7.76 (SE = 2.78) point greater increase in opioid liking among males with CLBP (N = 30) compared to females with CLBP (N = 30), following SD. A difference of that magnitude is comparable to those observed in our preliminary data in response to morphine at a single dose. In the proposed study, we will measure responses to multiple doses of hydromorphone in a cumulative dose paradigm, and therefore will have greater power to detect peak response changes across the range of doses administered.

Our preliminary effect sizes (derived from preliminary analysis described in Figure 4 above) indicate that a single dose of morphine resulted in a 65% reduction in cold pain tolerance in healthy subjects, and that SD attenuated that degree of analgesia by approximately 50%. Based on those parameters, we ran Monte Carlo simulations designed to power the Sleep Condition X Drug effect and the Group (CLBP vs. Healthy) X Sleep Condition X Drug effect for heat pain analgesia (Aim 2), assuming a 65% analgesic effect under uninterrupted sleep across subjects. With 60 participants in each group (CLBP vs. Healthy) we are powered at 80% to detect a group difference in pain ratings of 10.17 (on 101-point numerical rating scale), reflective of peak post-drug analgesia (i.e., lowest post-drug pain rating across doses). Thus, assuming an intercept of 60 (on 101-point scale) and a 65% analgesic effect under normal sleep, we are powered at 80% to observe 17% lower analgesic efficacy (i.e., pain sensitivity following drug relative to placebo) among CLBP patients (N = 60) vs. Healthy Controls (N = 60) following SD compared to US. Within the CLBP group, we are powered at 80% with 30 subjects per sex to observe 23.3% lower analgesic efficacy in males than in females following SD.

Data Analytic Strategy.

All models will control for age, race, body mass index, and clinical pain levels, as these variables may influence pain sensitivity. Additionally, medications and CLBP subtypes will be classified and included as covariates. Secondary covariates, including affective state, clinical pain, sleepiness, and psychomotor vigilance will also be tested in all models and retained if significant. Additionally, sleep variability assessed through diary and actigraphy between admissions will be covaried in all models. Models will test for order effects for sleep condition. Tests will be two-sided and the threshold for statistical significance will be set at $\alpha = .05$.

Primary Analyses: Linear mixed-effects modeling will be the primary analytic technique. Similar models will be built for each aim, with the within-subject factor of Sleep Condition included as the primary fixed effect in all models. Between-subject covariates will be tested as conditional interaction effects with Sleep Condition. A random intercept will be included in all

models. For **Aim 1 (opioid abuse liability)**, Drug Liking VAS scores across measurement occasions will be inspected with spaghetti plots to determine if there is random variation in the slope of time (e.g., 0-420 mins post-exposure) that should be included in primary models. The primary effect of interest will be the Sleep Condition X Drug Condition interaction, with planned pairwise comparisons evaluating differences in Peak Hydromorphone Liking between SD and normal sleep. Monetary Valuation of hydromorphone will be assessed once for each drug condition, per convention⁷⁸, and differences will be evaluated in a separate model with the Sleep X Drug Condition interaction. These models will be re-run including healthy controls and a separate interaction term (Group X Sleep Condition X Drug Condition) will evaluate whether CLBP patients differ from healthy controls in opioid abuse liability.

For **Aim 2 (analgesic response)**, separate models will test changes in HPT_h and suprathreshold heat pain from baseline (pre-drug) to 420 minutes post-exposure. Random variation in pain ratings across time points will be evaluated and, if appropriate, a random slope for time will be included in models. An index of change from baseline (pre-injection) to peak analgesia (post-injection) will serve as the primary outcome. The fixed interaction effect of Sleep Condition X Drug Condition will be the primary test of interest, again with planned pairwise comparisons evaluating differences in Peak Analgesia between the SD and normal sleep conditions. As with Aim 1, a Group X Sleep Condition X Drug Condition will also be evaluated to detect differences between healthy controls and CLBP patients on analgesic response.

For **Aim 3 (sex differences)**, the primary models for Aims 1 and 2 will be re-run with Sex as a cross-level interaction term. Thus, for these models, the Sex X Sleep Condition X Drug Condition interaction will be the primary effect of interest. There are no clear preliminary data to guide directional hypotheses regarding whether sex differences would emerge in different patterns between CLBP and healthy controls, so those tests (Sex X Group X Sleep Condition X Drug Condition) will be considered exploratory.

Secondary Analyses: We will assess whether clinical pain in CLBP patients increases following SD, and whether such increases mediate or moderate the effects of SD on primary outcomes. We will also test the extent to which SF-induced reductions in SWS and/or positive affect mediate or moderate the effects on primary outcomes. It will also be of interest to explore whether the effects of SD on VAS Drug Liking ratings for euphoric or analgesic reasons differ between groups or sleep conditions.

d. Early stopping rules.

If a participant experiences a serious side effect that seems to be related to the study drug, s/he will be discontinued from the study. If clinically indicated, the participant will be referred to the Johns Hopkins Bayview Medical Center (JHBMC) Emergency Department for further treatment. BPRU and the CRU have policies in place to ensure safety of all participants and staff, and some policies may lead to administrative discharge of a participant, and therefore, discontinuation from the study. Participants who do not abide by the BPRU policies and procedures, or who demonstrate behaviors abusive of staff or other participants may be discontinued from the study. Intercurrent illness or condition changing participant risk may result in medical discharge from the study.

Stopping criteria for the study: In addition, the committee of investigators convened to uphold the Data and Safety Monitoring Plan will review of the risks-benefits ratio of the study. At mid-point during enrollment this panel will be provided with a report of adverse events and

participant outcome data (subjective response to hydromorphone) by unlabeled sex groups (A vs. B). This information will be used to assess whether the risks reported are considered to be of unusual magnitude or frequency across any specific group, and to determine whether the study should be ended prematurely due to participant safety concerns or because a result has been unequivocally demonstrated. It is unlikely that such a small study would be interrupted because of a large rate of adverse events, particularly given the established safety of this medication and our experience at administering this drug, however we will ensure that a qualified panel of reviewers makes this decision.

The following specific stopping rules have been requested by the FDA:

Subject Stopping Rules:

- 1) Any serious adverse event (SAE) related to study participation
- 2) Significant respiratory depression judged to be a serious adverse event
- 3) Administration of naloxone to reverse opioid agonist effects during study session
- 4) Subject rescinds informed consent/requests study discharge
- 5) Subject is withdrawn from study by the Investigator

Study Stopping Rules:

- 1) Any SAE related to study participation that emerges at an unexpectedly high frequency
- 2) Administration of naloxone occurs at an unexpectedly high frequency

8. Risks

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

Possible risks are reviewed below for each aspect of the proposed studies. All of the methods and interventions have been performed previously on humans.

Sleep Disruption. The most common risks associated with sleep deprivation include: sleepiness, poor concentration, slowed reaction times, irritability, negative mood, and a diminished capacity to operate a motor vehicle or perform work. Sleep deprivation lowers seizure threshold, and rarely, may trigger manic episodes in individuals with bipolar disorder. There are no documented risks unique to the sleep disruption protocol, relative to other total sleep deprivation protocols.

Hydromorphone Administration: The primary risk to the participant is associated with effects of hydromorphone administration during the controlled laboratory sessions. Hydromorphone hydrochloride is a pure mu opioid agonist that can be administered in oral, rectal, intramuscular (IM) or intravenous (IV) formulations for the indication of acute and/or chronic pain. We have chosen to administer hydromorphone IM because we have extensive experience administering hydromorphone in all formulations^{122,123}, and know that it will produce reliable and consistent results that will aid interpretation of outcomes. When administered IM, hydromorphone effects will be detectable in 15 minutes and effects may last 4-5 hours. Hydromorphone was also strategically selected as the exemplar opioid for this study because it is not subject to differences in CYP metabolic enzymes and therefore will not require us to screen out individuals with recent exposure to CYP inhibiting or inducing medications, or to analyze and statistically control for CYP metabolic profiles in individual subjects. Further, in contrast to morphine, hydromorphone

also *does not* produce a localized adverse effect when administered IM. We have selected doses of hydromorphone that are in the range of common dosing for chronic pain, which increases the clinical relevance and direct application of these study results into clinical practice, and because it will produce a moderate analgesic effect following pain testing. This is an important feature because too strong a dose of an opioid analgesic could make it difficult to observe differences in opioid analgesia between sleep conditions. By selecting a moderate dose of hydromorphone, we will be able to evaluate shifts in the analgesic curve that occur as a function of sleep disruption. There is also no apparent effect of sex on the pharmacokinetics of hydromorphone, which will permit an evaluation of sex differences in the effects of sleep disruption on the subjective responses to hydromorphone.

Administration of any drug involves some risk because it is not always possible to predict individual response to drugs. The most likely risk in this study is that subjects will experience side-effects of the drugs that may be unpleasant. Common side effects of hydromorphone are light-headedness, dizziness, sedation, nausea, vomiting, sweating, flushing, dysphoria, euphoria, dry mouth, and pruritus. Less frequently observed side effects are weakness, headache, agitation, tremor, uncoordinated muscle movements, alterations of mood (nervousness, apprehension, depression, floating feelings, dreams), muscle rigidity, paresthesia, muscle tremor, blurred vision, nystagmus, diplopia and miosis, transient hallucinations and disorientation, visual disturbances, insomnia, increased intracranial pressure, flushing of the face, chills, tachycardia, bradycardia, palpitation, faintness, syncope, hypotension, hypertension, bronchospasm and laryngospasm, constipation, biliary tract spasm, ileus, anorexia, diarrhea, cramps, taste alteration, urinary retention or hesitancy, antidiuretic effects, urticaria, other skin rashes and diaphoresis. Side effects of hydromorphone are generally temporary, dissipate within several hours, and are dose-dependent. Thus, participants may only experience side-effects occasionally during the research study. Serious potential adverse effects of hydromorphone administration that are possible but extremely unlikely to be encountered in this study are respiratory depression and loss of consciousness. The FDA has identified the following conditions as increasing the risk for respiratory depression or other serious side effects following hydromorphone administration: patients with status asthmaticus; chronic obstructive pulmonary disease; reduced respiratory function; high blood pressure; impairment of hepatic, pulmonary or renal functions; myxedema or hyperthyroidism; adrenocortical insufficiency; gall bladder disease; acute alcoholism; history of convulsive disorders; history of head injury; currently taking sedatives, hypnotics or phenothiazines; and sulfite allergy. Mean exposure to hydromorphone is also increased 4-fold among patients with hepatic impairment and 3-fold among patients with renal impairment. Therefore, to further reduce the risk serious side effects, we will exclude any potential participant who exhibits one or more of these conditions.

The most serious potential adverse event following hydromorphone administration is opioid agonist overdose, which is characterized by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and sometimes bradycardia and hypotension. In serious overdosage, particularly following intravenous injection, apnea, circulatory collapse, cardiac arrest and death may occur. We believe the risk of overdose in this study to be low for the following reasons: we have extensive experience in the administration of hydromorphone, we have chosen doses that have been demonstrated to be safe and tolerable in adults, we will exclude any individual who has a medical condition that may increase the risk for respiratory depression and/or other adverse events, all medication doses will be administered by a trained research nurse, a study physician

will be on-call and on campus during all drug administration sessions, and participants will be monitored by trained staff who will have access to the opioid antagonist naloxone to reverse the opioid agonist effects. Additional protections against the risk of hydromorphone side effects, including overdose, are discussed in the Protection Against Risks section.

Quantitative Sensory Testing (QST). Participants will likely find the QST procedures uncomfortable for a brief period of time. This effect is expected to be transient and to produce only mild levels of discomfort.

Acute Laboratory Stressor. Participants will likely experience psychological stress and negative emotions while performing these tasks; however, it is unlikely to exceed the level of stress experienced in daily life. Although uncommon, participants may experience clinically significant levels of anxiety (e.g., crying) during the tasks.

Questionnaires. Participants may become fatigued or bored with the questionnaires or uncomfortable answering questions on the questionnaire.

Venipuncture & Blood Draws. Temporary discomfort, bruising, inflammation, infection, or bleeding at the venipuncture site, or light-headedness from the blood draws may occur. If light-headedness occurs the participant will be monitored by the research personnel and not released until it has resolved.

Urine Sample: There are no known risks to collecting a urine sample.

Ambulatory Sleep EEG: There are minimal risks associated with routine ambulatory sleep EEG testing. Very rarely, individual may experience a mild allergic reaction to electrode placement.

Outcome of Test Results. Participants may feel psychological stress or anxiety due to the outcome of tests, such as if urine pregnancy test is positive.

b. Steps taken to minimize the risks.

All research personnel will be fully trained in the protection of human subjects as required by the Johns Hopkins. Any modification to the protocol, consent form, or study forms will be submitted to the Johns Hopkins IRB. Unexpected departures from the protocol will be reported to the PI and the Co-Is. If the departure becomes planned or routine, it will be considered a modification to the protocol and reported to the Johns Hopkins IRB. Medical coverage is always available and an emergency cart is available onsite. If any participant is in need of emergent medical care, a study physician will immediately assess the needs of the participant, manage their care, and/or refer them for further care to Johns Hopkins or an appropriate community referral as needed. We will also ensure that participants are aware of their right to stop any procedure they find too uncomfortable. Specific protections against risks are outlined below.

Sleep Disruption. Because sleep deprivation lowers seizure threshold, and may trigger manic episodes in individuals with bipolar disorder, individuals with these conditions are excluded as described. Because sleep deprivation is a stressor that can impact mood, we exclude subjects

with major psychopathology or acute psychological distress. All subjects undergoing experimental sleep disruption procedures will remain under surveillance on the clinical research unit (CRU). To prevent accidents that might be caused by drowsiness or disruption of daily activities following discharge, subjects will be offered a recovery night of sleep in the CRU following the night of Forced Awakenings. Subjects who refuse a recovery night will be required to obtain a ride or take a taxi home (at the study's expense), will be instructed not to drive or operate heavy machinery for 24 hours, and will sign a document indicating they understand these risks. We have successfully employed these procedures in several prior studies.

Hydromorphone Administration. We have extensive experience in the administration of hydromorphone and other opioid agonists in controlled laboratory settings and therefore anticipate few problems. Any individual who may be prone to the risks associated with hydromorphone will be excluded from participating. Although research staff and participants will be blinded to the dosing information, both groups will be informed of the potential side effects and risks associated with the study drug administration. Participants will be free to discontinue study participation at any time without consequence. The doses of hydromorphone that will be administered are consistent with clinical care for the treatment of pain. Further, the Qualifying Session provides us a unique opportunity to assess for sensitivity to hydromorphone, and any participant who shows intolerance to hydromorphone during the Qualifying Session will be excluded from the primary study. Great care has been taken in selecting the appropriate drug doses to ensure hydromorphone is well-tolerated and safe for our participants and participants will also be able to discontinue study participation at any time.

The most serious risk associated with hydromorphone administration is respiratory depression. We believe this risk is minimal in this study for several reasons. First, we are administering doses that have previously been shown to be safe in humans^{114,115}, and have extensive experience administering this drug at controlled levels in healthy controls. Second, we have developed several standard criteria that are followed by nursing staff and research personnel to monitor participants who have been provided with a study medication. All nursing and research staff are informed of these standards, and a list of these standards is posted in each testing room. The standards are as follows: If respiratory rate drops below 12 breaths/minute and is accompanied by sedation, participants are prompted verbally to breathe. In our experience, verbal and physical stimulation is often sufficient to prompt breathing and restore a normal respiratory rate. If respiratory rate drops further and/or if oxygen saturation rates fall below 90% saturation, then patients are monitored carefully. Specifically, they will be accompanied continuously by a medical and/or nursing staff member, evaluated by a staff physician, and are given supplemental oxygen at 2L/min via a nasal cannula (available on site in the exam testing room) if deemed necessary by the physician. If clinical evaluation determines that a participant's sedation level is increasing, the opioid antagonist naloxone can be promptly administered via intramuscular or intranasal route to produce an immediate reversal of opioid effects. There have been very few incidents throughout our >15 year experience administering opioid agonists to human participants in controlled laboratory conditions that have necessitated actual intervention (oxygen and/or naloxone), however our equipment and medical/nursing staff are always prepared for this possibility. We feel these procedures will sufficiently protect participants from possible adverse and serious adverse events. Finally, we will submit an annual review of study-related adverse and serious adverse events to the Johns Hopkins IRB and an independent group of

consultants who will serve as our data safety monitoring board for evaluation (this is described in more detail in the Data Safety and Monitoring Plan below).

We will assess vital signs during drug administration in the following manner: Thirty minutes after the first injection, and every 30 minutes thereafter (until 420 minutes after the first injection; 240 minutes after the last injection), vital signs [respiratory rate, pulse, oxygen saturation (spO2), and blood pressure] will be monitored. If any of the *a priori* thresholds for any vital sign is breached, we will wait 5 minutes and re-assess vital signs. If vital signs return to acceptable levels, resume planned monitoring protocol (every 30 minutes). If any vital sign is consistently beyond the *a priori* threshold in 2 consecutive measurements, study-related activities will cease, the medical monitor will be notified and will evaluate the patient, vital signs monitoring frequency will increase to every 5 minutes, and pulse oximetry will be maintained continuously. The thresholds are as follows:

Respiratory Rate: <8 breaths/minute

Pulse: >110 or <50 BPM

spO2: <90

Blood Pressure: Systolic >170 or < 90 mmHg

Protection Against Chance that Participants May Begin Abusing Opioids Following Exposure to Hydromorphone: Another concern is the possibility that exposure of participants with no histories of drug abuse to drugs in our research setting might in some way increase the likelihood of these individuals to begin abusing illicit drugs when they return to the community. The Johns Hopkins IRB closely monitors this issue, and has repeatedly concluded that administering drugs that have reinforcing effects to individuals who do not abuse drugs is not associated with an increased propensity to begin abusing drugs. Administering drugs that may have reinforcing effects to non-dependent users has substantial precedent in laboratory examinations of drug effects, and we have a rich and extensive history of utilizing this practice. Several research studies that have directly examined the association between study-related drug administration and subsequent drug use behavior have failed to demonstrate that controlled, laboratory drug exposure increases the risk for developing future dependence. For example, authors of a recent study that administered methamphetamine to a sample of non treatment-seeking drug abusers reported no difference between-group differences in drug use behaviors, assessed via the Addiction Severity Index, at a 6-month follow-up assessment.¹²⁴ Second, a systematic follow-up study reported that alcohol-dependent volunteers randomly assigned to laboratory studies either involving or not involving experimental alcohol consumption have not differed in their follow-up outcomes.¹²⁵ Third, a recent study concluded that investigational administration of intravenous cocaine to intravenous inexperienced cocaine users did not increase the risk of recreational intravenous use.¹²⁶ Fourth, a study conducted by our research team administered cocaine and/or opioids to participants with histories of drug abuse and observed no significant changes in number of days of reported drug use, dollar amounts reported spent for various drug classes, or any increases in Addiction Severity Index domain scores at a one month follow-up.¹²⁷ Finally, the College on the Problems of Drug Dependence, a prestigious international association of drug dependence researchers, supports the practice of enrolling non treatment-seeking individuals into drug abuse liability evaluation studies. Specifically, the College on Problems of Drug Dependence reported that exposure of drug abusers to abused drugs in a controlled research setting does not enhance the desire of an individual to use drugs, worsen addiction, or make addiction more difficult to treat.¹²⁸ Overall, given the substantial data available in the literature

and our own laboratory experience, we feel confident that administration of small quantities of psychoactive drugs to individuals without recreational histories of drug abuse will not be associated with future drug use behavior.

Quantitative Sensory Testing: It is likely that participants will experience some acute and transient discomfort from QST, however we will work to mitigate that risk as much as possible. First, participants will be informed of the QST procedure during the informed consent and will be able to make an informed decision regarding their study participation. Second, we will use standardized QST procedures with which we have extensive experience, and that are known to produce transient effects that are unlikely to produce any residual pain. Third, the equipment used for thermal stimuli has an upper limit (51°C) at which the system will automatically shut down to prevent tissue injury. Fourth, participants will be informed that they can revoke their consent to participate in the pain testing at any time without penalty. Finally, the participants will be monitored throughout the duration of their outpatient visits by study staff and will have access to medical care and concomitant medications to treat residual pain if necessary. We will also document and submit to our DSMB all adverse events reported from the QST session and will follow any recommendations they may have regarding the cessation of QST.

Acute Laboratory Stressor. Participants will likely experience psychological stress and negative emotional reactions in response to the stress task. However, participants' negative reactions to the task typically abate within 10 minutes of completing the task. To facilitate this process, all participants will be debriefed on the true purpose of the task and informed that their performance was not truly being evaluated. In the unlikely situation that a participant demonstrates clinically significant levels of anxiety (*e.g.*, crying) during the laboratory stressor, the task will be stopped immediately, and the participant will be debriefed on the true nature of the task.

Questionnaires. Participants will be offered breaks if fatigued or bored. Participants will also be instructed that they do not need to disclose any information that may be too uncomfortable and of their right to stop the questionnaire.

Venipuncture & Blood Draw. If bleeding at the venipuncture site occurs, a bandaid will be offered and applied. If light-headedness occurs the participant will be monitored by the research personnel and not released until it has resolved. Additionally, nursing staff and study staff will be trained according to best practices for biohazard safety to ensure the safe and proper handling of blood and disposal of venipuncture materials. The PI is required by the IRB to register the study and the research staff for biohazard safety approval.

Urine Sample. There are no known risks to collecting a urine sample. Strict confidentiality of the sample and results will be maintained.

Ambulatory PSG: To protect against adverse effects all equipment will be tested prior to use in order to ensure it is functioning properly. All devices are approved by bioengineers for safety and proper functioning before approval of any research protocol by Johns Hopkins' IRB. Devices touching participant's skin are sterilized before and after use with an appropriate agent. All participants will also be provided with the research team's contact telephone number and

instructed to report any side effects immediately. In the event that a participant experiences an allergic reaction to the electrode gels/paste, a study physician will evaluate the condition. If the side effect is deemed not medically urgent nor emergent, side effects will be evaluated and managed by a study physician and referred to Johns Hopkins or an appropriate community referral as needed. If the side effect is deemed medically urgent or emergent by either the participant or research staff, participants will be instructed to present or be transported to the nearest emergency room.

Test Results. Urine pregnancy testing results will be shared with participants. The PI or the study physician will discuss any positive pregnancy test results directly with the participant and make appropriate referrals or recommendations for further medical care as warranted. Abnormal labs will also be shared with participants along with recommendations for follow-up care.

Confidentiality. Every effort will be made to prevent a breach of confidentiality. In accordance with HIPAA regulations, all potential participants will be fully informed of their rights pertaining to disclosure of patient health information. The proposed research will be subject to the rules of confidentiality maintained at Johns Hopkins Medical Institutions. Confidentiality will be maintained by assigning participants a study number and numerically coding all data. All research documents and data will be kept in locked filing cabinets or controlled access, password-protected databases housed behind the JHU firewall. Only summaries of group data, without any individual identification, will be reported in any publications or presentations.

- c. Plan for reporting unanticipated problems or study deviations.

All adverse events will be reported to the IRB and other relevant agencies as required and as described in the DSMP. The Principal Investigator and Co-investigators are responsible for reporting such events.

- d. Legal risks such as the risks that would be associated with breach of confidentiality.

Although there is always a small risk that confidentiality will be breached, we believe this risk to be very minimal with the current study.

- e. Financial risks to the participants.

None.

9. Benefits

- a. Description of the probable benefits for the participant and for society.

All participants will receive a sleep apnea and insomnia evaluation at no cost. All individuals will be informed of any disorders identified and referred for appropriate clinical care. The knowledge to be gained regarding the effects of sleep disruption on opioid abuse liability and opioid analgesia will yield potential benefits to those who have CLBP, and to society as a whole.

10. Payment and Remuneration

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

All participant payments, including general participation remuneration, are detailed in Table 1.

Table 1	Payment
Screening Visit 1	\$25
Qualifying Session	\$150
Sleep Diary and Actigraphy	\$125
Adaptation Night	\$100
Uninterrupted Sleep, Sleep Disruption, and Recovery Nights, and associated daytime procedures	\$200 x4
TOTAL	\$1200

In addition, we will offer participants a bonus of \$25.00 for referring a participant who completes the first two visits of the study. We will cap this bonus up to 5 people or a maximum of \$125.00 in additional compensation.

11. Costs

Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

There are no costs to the participants.

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