Official Title: Using Cannabinoids to Enhance Opioid Analgesic Effects in Humans

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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 systematically evaluate whether cannabinoids can enhance the analgesic efficacy of opioids, which will advance the use of cannabinoids for the treatment of acute and/or chronic pain. Chronic pain affects over 100 million Americans. Opioids are unanimously recognized as the most effective drugs for the relief of pain and suffering, but the US is now suffering from an epidemic of abuse, addiction and accidental deaths resulting from the increased sale and use of opioids. There is legitimate value in identifying adjuncts that might reduce reliance on opioids while maintaining adequate pain relief. Preclinical studies report that co-administering cannabinoids with opioid agonists significantly and reliably reduce the amount of opioids required for analgesia but this hypothesis has not been rigorously evaluated in humans. This proposal will evaluate the effect of dronabinol on opioid-induced analgesia. The study will enroll 60 healthy adults (30 men/women) to conduct a within-subject, dose-response evaluation of cannabinoids on the analgesic effect of hydromorphone (Dilaudid). Subjects will complete 5 experimental sessions that will occur at least once weekly and will enable subjects to admit themselves into a clinical research unit the night before the session to complete the study session. Subjects will receive a dose of hydromorphone (4mg, oral) and a double-blind oral dose of study drug or placebo the morning of each experimental session, and will undergo quantitative sensory testing (QST; a comprehensive pain testing battery), provide self-report ratings of drug effects, and complete a neurocognitive battery. QST testing will comprehensively and systematically measure pain sensitivity, and provide information on the full range of analgesic effects possible across a wide variety of pain measures, including threshold responses (thermal, pressure), temporal summation, cold pressor, conditioned pain modulation, and capsaicin sensitization. Primary outcomes will be magnitude and duration of pain as a function of study drug dose. Additional primary aims include proxy measures of abuse liability and neurocognitive performance. All measures will be assessed as a function of sex, due to substantial evidence that men/women differ with regard to pain perception, endogenous cannabinoid receptor density, and opioid response. We hypothesize that cannabinoids will shift the analgesic curve of hydromorphone and enhance analgesia effects. This will be the 1st human laboratory study to evaluate combinations of cannabinoids and opioids using QST, and results will identify whether a signal for this medication combination exists that should be advanced into randomized controlled trial evaluations with clinical pain populations. This study will also assess aspects that would impact drug development (abuse liability, neurocognitive impairment), as well as the effects of sex and cannabinoid type on outcomes. Results from this study will help advance the acceptance of cannabinoids from use with only treatment-

refractory pain conditions to widespread societal use for clinical pain.

2. Objectives (include all primary and secondary objectives)

1. **Primary Aim 1: Evaluate the magnitude and duration of combined dronabinol and hydromorphone to reduce pain sensitivity in a validated model of pain**. We hypothesize that the addition of a dronabinol to hydromorphone will result in a dose-dependent increase in the magnitude and duration of analgesia in patients undergoing a validated laboratory model of pain.
2. **Primary Aim 2: Evaluate the subjective responses to combinations of dronabinol and hydromorphone to determine the subjective, euphoric effects of the combination products**. We hypothesize that dronabinol will not increase the subjective ratings of positive drug effects or other proxy measures of abuse liability, relative to hydromorphone alone.

3. **Primary Aim 3**: **Evaluate the degree to which combining dronabinol with hydromorphone impacts neurocognitive performance**. We hypothesize that dronabinol may reduce neurocognitive performance at high doses, relative to hydromorphone alone, though the degree to which this may occur is unknown. This aim is critical for the advancement of potential opioid/cannabinoid combination products.

4. **Secondary Aim 1: Evaluate whether there are sex differences on study outcomes.** We hypothesize that dronabinol enhancement of hydromorphone-analgesia will be greater among female vs. male subjects.

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).

This study will systematically evaluate whether cannabinoids can enhance the analgesic efficacy of opioids, which will advance the use of cannabinoids for the treatment of acute and/or chronic pain.

Scope of the problem: Chronic pain affects over 100 million Americans - more than diabetes, heart disease, and cancer combined[1]. It exacts substantial suffering, physical disability, and is incredibly costly. Persistent pain profoundly impairs quality of life[2;3] and increases risk for medical[4] and psychiatric morbidity[5]. Medical providers have an obligation to treat their patient's pain and opioids are unanimously recognized as the most effective drugs for the relief of pain and suffering[6]. Opioids are the 3rd most widely prescribed category of medication in the US, however with increases in availability we have seen substantial increases in corresponding problems, most notably opioid-related overdose deaths. Accidental poisonings are now the leading cause of accidental death in adults aged 25-64[7], and 72% of overdose deaths involve opioid analgesics,[8] a higher prevalence than deaths from heroin and cocaine combined[9-11]. Improper use of prescription painkillers results in an estimated $72.5 billion annually in direct health care costs,[12] which does not include societal costs like social services, law enforcement, and lost productivity. The phenomena associated with high dosing, abuse, and addiction continues to challenge the clinical community and poses an important question to the scientific community – is there a method to enhance opioid prescribing requirements while maintaining adequate pain relief?

Potential to combine cannabinoids with opioids for pain relief: Population based studies in fibromyalgia, arthritis, muscular sclerosis and spinal cord injury have all described cannabis use for pain relief [13]. Currently, 12-15% of the population uses medicinal cannabis and the most commonly cited reason is for chronic pain[14]. A systematic review reported that >80% of trials demonstrated a significant analgesic effect of cannabinoid relative to placebo[15] and the endocannabinoid system (ECS) offers a strong mechanistic rationale for the pain reducing actions of cannabinoids[16]. Further, there is now substantial preclinical evidence in rodents[119-122] (Cichewicz, Martin, Smith, & Welch, 1999; Finn et al., 2004; Smith, Cichewicz, Martin, & Welch, 1998; Welch & Stevens, 1992; Williams et al., 2006) and primates[123-125] that cannabinoids and opioids, *when administered together*, are extremely effective in reducing pain, with up to a 20-fold increase in efficacy, suggesting that these two medications may have a *synergistic effect on pain*. The CB1 receptor is located in regions of the peripheral and central nervous system where pain signaling is mediated, including the dorsal horn of the spinal cord, PAG, thalamus, and cortical regions associated with central pain processing, including the anterior cingulate cortex, amygdala and the prefrontal cortex[17]. CB2 receptor modulation also decreases pro-inflammatory mediators in a manner that may contribute to antinociceptive effects and improve endogenous neuroinflammatory properties that play an important role in pain perception[18]. However, the synergistic combination of co-administering cannabinoids with opioid agonists has not ever been rigorously evaluated in human subjects and the degree to which non-human animal results will generalize to human subjects is unknown. The only

Phase I study, of which we are aware, evaluating this concept reported that patients who received 10-20mg of dronabinol with their stable and normally prescribed dose of opioids experienced decreased pain intensity and increased satisfaction relative to placebo[19]. A Phase II study found that titrated dronabinol in chronic pain patients receiving a stable dose of opioids conferred significant pain relief, reduced secondary problems associated with pain, and increased ratings on a self-report satisfaction scale (0-10) compared to baseline[19].

QST measurement of pain: Chronic pain is conceptualized as a disease of the nervous system that involves varying degrees of peripheral input and dysregulation of central nociceptive modulatory systems[20;21], which are frequently assessed with laboratory measures. Due to the potential confounding of disease-specific factors, such as severity and duration, differences in pain management and systemic inequalities, as well as the potential issue of opioid-induced hyperalgesia, systematic quantitative sensory testing (QST, in which the noxious stimuli are rigorously calibrated and standardized) in healthy individuals is of great value to elucidate sensory characteristics[22-25]. Human experimental pain models link animal and clinical pain studies, and has specifically been recommended for testing analgesic compounds, and noted as "ideally suited" in proof-of-concept and dose finding studies[26]. These experimental designs allow for precise control over the nature of the noxious stimuli applied to the nervous system and are crucial in examining and understanding the underlying mechanisms that account for physiological pain sensitivity and pain perception in clinical pain reports. That is, physically identical stimuli can be applied to all subjects, permitting the study of drug effects in the experience of pain and minimizing confounding by individual differences in the noxious stimuli that produce the pain experience. Such variability in psychophysical pain responses strongly parallels the variability in clinical pain in many samples[27-32] (i.e., subjects who are most pain-sensitive in the laboratory also report the most intense or frequent clinical pain). The use of QST to evaluate drug effects on pain responses is well-established, sensitive and frequently used in mechanistic studies[33-35]. A number of studies have shown strong cross-sectional associations between QST and clinical pain responses in healthy[29;36-38] and chronic pain patients[39-43]. More importantly, many studies have shown that QST responses predict post-surgical pain[44-48] and treatment outcomes[49;50] as well as correlate with changes in clinical pain[51-54]. QST is also predictive of opioid analgesia[55-60], and opioid dose consistently correlates with multiple QST measures in chronic pain patients[61;62]. In addition, basal opioid receptor binding is significantly associated with QST[63]. Elevated pain sensitivity profiles, established using QST, is also observed in chronic pain patients at risk for opioid misuse[64]. Importantly, both static (measures including threshold and tolerance) and dynamic (methods that probe central pain systems) QST are responsive to the influences of analgesics[59;65;66] and are frequently used to determine analgesic efficacy[35;67]. Hydromorphone, which is identified in the current application, specifically produces potent and dose-dependent analgesic effects on pain reported during QST[68] and significantly suppresses secondary hyperalgesia and acute thermal nociception[69]. As shown in our preliminary studies, we are experienced in quantifying opioid effects on QST using these methods (see Figure 1). We do not know of any studies that have used QST to rigorously evaluate cannabinoid-induced analgesia.

Conclusion: This will be the 1st human laboratory study to evaluate combinations of cannabinoids and opioids on a comprehensive and validated quantitative sensory testing battery, and the results of this study will identify whether a signal for this medication combination exists that should be advanced into randomized controlled trial evaluations with clinical pain populations. This study will also assess aspects that would impact drug development (abuse liability, neurocognitive impairment) and the effect of participant sex on outcomes. The ultimate goal of this research will be to determine which medication/dose combinations may exert strong analgesic effects, while minimizing abuse liability and cognitive deficits, in order to advance these medications into clinical trials for the treatment of chronic pain. This is a logical first step towards evaluating combined cannabinoid/opioids treatments for chronic pain, and will provide data necessary to support numerous evaluations of combination treatments for this population.

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).

Project Overview: This study will enroll 100 healthy adults, and will aim to complete 60 (30 men, 30 women) participants. Participants will conduct a within-subject evaluation of the degree to which the FDA-approved cannabinoid dronabinol (Marinol) enhances the analgesic effect of the prototypic opioid hydromorphone (Dilaudid). Subjects will complete a Screening visit to establish study eligibility and 5 experimental sessions. Experimental sessions will occur approximately once weekly and will permit subjects to admit themselves into the clinical research unit the night before the session if interested. Subjects will be provided with taxi service to and from the session. Subjects will receive a dose of hydromorphone (4mg, oral) and a double-blind oral dose of study drug or placebo the

morning of each experimental session, and will undergo QST measures of laboratory evoked pain, provide self-report ratings of drug effects, and complete a neurocognitive battery. The order of sessions will be randomized with the exception of Session 1, which will always be active hydromorphone + placebo to ensure the participant has a safe response to hydromorphone before proceeding into the remaining sessions.

Subject Recruitment: Subjects will be recruited from the greater Baltimore area using established recruiting resources and media advertising, including newspaper, radio, and website listings. We also have an extensive list of potential study volunteers who have given permission to call them regarding potential study participation. All interested individuals will first complete a phone screen to establish initial study eligibility and individuals who pass will be invited for an in-person screening during which final study eligibility will be determined.

Screening Visit: Subjects will complete a brief phone screen to determine initial eligibility and will be invited to complete an in-clinic screen. Subjects will review and sign an informed consent document with a study staff member to begin the Screening visit. Subjects will provide a urine sample that must test negative for illicit drugs and pregnancy (for females), and will then complete a battery of measures to establish study eligibility. Medical eligibility will be determined by medical staff and will consist of an ECG, a blood sample to analyze hepatic, hematologic, and chemistry functioning, and a medical history and physical, which will occur prior to any drug administration.

Experimental Sessions: Upon final eligibility confirmation, subjects will complete 5 experimental study sessions. The sessions will be conducted on a closed research unit and subjects will be permitted to stay the night before the session on a clinical research unit. We have chosen to not conduct the entire study using a continuous inpatient design because we want to impose a minimum 7-day wash-out period between opioid exposures so that any acute tolerance that may have developed to the hydromorphone dose has time to dissipate and so that dronabinol, which has an elimination half life of 19-36 hours, has sufficient time to be excreted between drug administrations.

Subjects may either arrive at the BPRU in the early evening prior to an experimental session or the morning of the session. They will be required to provide a urine sample that tests negative for illicit drugs and pregnancy prior to admission. Female subjects will be asked to provide a blood sample that will be tested for progesterone, which will serve as an index of menstrual cycle status. Progesterone analysis is a rigorous method for assessing hormonal cycle that will enable us to statistically control for the influence of hormone status on QST and response to medications. Subjects will then be admitted to the research unit.

The morning of each experimental session, the subject will receive a calorie-controlled breakfast each morning. Following breakfast, subjects will complete a baseline rating of QST and self-report measures (from which all subsequent ratings will be compared for data analysis purposes). An oral capsule containing either study drug or placebo will then be administered and hydromorphone (4mg oral in four sessions and a placebo oral dose in one session) will be administered. The time of drug administration will be selected to enable both dronabinol and hydromorphone to exert peak effects at the same time. Subjects will complete QST (see below) and self-report measures at regular intervals following study drug administration. Self-report measures will include specific opioid agonist and antagonist effects, to assess whether cannabinoids are exerting an effect on a particular category of opioid agonist symptom, and will capture whether any negative effects (e.g., nausea) occur as a function of the cannabinoid dose. Frequent collection will enable evaluation of time to peak drug effects, duration of effects, and general time course of effects and is a widely used and accepted approach in laboratory studies of drug effects. During the final assessment each day, subjects will complete a Drug vs. Money Questionnaire to indicate the dollar value they would place upon the drugs received[98]. This is a well-accepted proxy measure of abuse liability. Study staff will document adverse events throughout the study and any subject who experiences a strongly unpleasant effect of the medications will be able to end participation. Any subject who is experiencing strong agonist effects at the end of the session will be provided overnight accommodation in the CRU; based on our experience we expect this to be minimal and are budgeting for 10% of sessions to have a 2nd night.

Quantitative Sensory Testing (QST) Measures of Laboratory Evoked Pain: Subjects will complete a state-of-the-art quantitative sensory testing (QST) battery, which will comprehensively and systematically measure pain sensitivity. This approach will provide information regarding the full range of analgesic effects possible, across a wide variety of psycho-physiologically-mediated, experimentally-induced measures of pain perception. Subjects will complete a baseline QST session prior to study drug administration on each experimental session day, and will complete the pain testing battery at regular intervals during the experimental session day. Each administration of the QST battery will take 20-30 minutes. The QST battery will consist of threshold and tolerance, temporal summation, and conditioned

pain modulation (CPM) tests. The threshold responses will be conducted in randomized and counter-balanced order, and conditioned pain modulation will always occur last.

Threshold Responses will be assessed using thermal and pressure stimulation. *Thermal threshold:* All contact heat stimuli will be delivered using a peltier-element-based stimulator (Medoc, Israel). Two trials of heat pain threshold will be administered using an ascending method of limits paradigm. The thermode will gradually increase in temperature (rate of rise = .5°C/sec) from a pre-set baseline (31°C), until the subject indicates when the stimulus "first feels painful" (threshold, HPTh) and presses a button (which terminates the procedure) indicating that the pain is intolerable (tolerance, HPTo). *Pressure threshold*: A pressure algometer will be utilized to assess responses to pressure stimulation at a variety of anatomical sites in a randomly determined order. The pressure algometer (Somedic; Sweden) uses a rubber probe covered with 1mm polypropylene material; pressure at the site is gradually increased at a steady rate. Subjects indicate when the stimulus is first perceived as painful, which terminates the application. The algometer produces a sensation of localized pressure; technicians will place the probe of the algometer in the center of each muscle group or anatomic site when delivering the mechanical stimuli. Thirty-second inter-stimulus intervals will be maintained for all stimuli. Each trial will be averaged together to result in one HPTh, HPTo, and PPTh measure.

Temporal Summation (TS) of Pain will be assessed in 2 ways, using repetitive thermal stimuli and repetitive punctuate stimuli. Sequences of 10 heat pulses will be applied using the Medoc. (Note: within each 10-pulse sequence, the temperature of each phasic stimulus is the same). Within each sequence, successive thermal pulses at a given temperature will be delivered for a duration of approximately 0.5 sec each, with an approximately 2.5-sec inter-pulse interval. Subjects will verbally rate the perceived intensity of each thermal pulse on a 0-100 rating scale and may terminate the procedure at any time. Windup is measured as the differences between the highest rated thermal stimulus and the 1st thermal stimulus.[99]

Mechanical Temporal Summation will be studied using punctate stimulators (a set of weighted pinprick stimulators with fixed stimulus intensities (flat contact area of 0.2 mm diameter) that exert forces of 8- 512 mN). The probes are applied perpendicular to the skin. We will apply both single stimuli and 10-stimulus trains at 1HZ, and will record the subjects pain rating (0-100). Single pinprick stimuli are alternated with the trains of 10 stimuli. The mean pain rating of 10-stimulus trains divided by the mean pain rating to single stimuli is then calculated as a ratio.[100]

Cold Pressor Testing and CPM: A series of procedures designed to elicit and measure endogenous inhibition of pain will be applied. In the present protocol, subjects will undergo a series of cold pressor tasks (i.e., the conditioning stimuli) consisting of immersion of the hand for up to 1 minute in a circulating cold water bath. During hand immersion, pressure responses or temporal summation will be re-assessed while subjects' hands remain in the cold water. Subjects may remove their hand at any time. Two minutes after finishing the first immersion, subjects will re-immerse their hand in the water, and one of these tests will be re-assessed, each separated by 2 min and identical to the first 2 trials (the tests will be conducted in random order). A CPM Index is quantified as the average percent change (across trials) in PPTh or TS during the cold pressor tasks relative to baseline ratings [(PPTh or TS during cold pressor/PPTh or TS prior to cold pressor)*100.[101] One final cold-water immersion will be performed at the conclusion of the CPM procedures. This will involve a typical cold pressor task, using immersion of the hand until the subject's tolerance is reached, with a 5-minute uninformed time limit.

Capsaicin: Capsaicin sensitization procedures similar to well established protocols developed by Peterson and colleagues will be utilzed[70]. Heat will be delivered using, a computer driven, peltier device, heating element (Medoc TSA II). The procedure involves a 35 minute sensitization period (conducted during the baseline period) with a 1.25inch^2 treatment site on the non-dominant, ventral forearm. The thermode will be heated to 45°C for 5 minutes and pain ratings will be collected every one minute on the 0-100 rating scale. An open square raised adhesive frame (internal dimensions same as thermode, to reduce leakage beyond the site) will then be applied and capsaicin cream (10%)[71] will be spread onto the skin and permitted to absorb for 30 minutes. This induces mild-moderate (48.25±27.93), but well tolerated pain. Capsaicin is then removed and the heat pain threshold and mechanical temporal summation (described above) will be conducted again in the area. The treated skin will be re-kindled for each of the additional QST sessions each session by heating the treatment site with the thermode at 40°C for 5 min. Following each rekindling episode, heat pain threshold and mechanical temporal summation as well as measurement of secondary hyperalgesia will be conducted. The area of secondary hyperalgesia will be quantified with a von Frey hair by stimulating along eight linear paths around the treated site. Stimulation starts well outside the hyperalgesic area, and continues towards the treated skin area until the subject reports a change in sensation. The border is marked on the skin with a pen and traced to acetate paper, which is subsequently measured. Studies have demonstrated excellent test-retest stability in 2° hyperalgesia measurements over rekindlings[72;73;73] and the procedure

is ideal for including in paradigms with repeated testing as the rekindlings allow for rapid evaluation of capsaicin sensitization (which typically necessitates at least 30min each).

Additional Study Measures: Study measures comprise both pharmacologically and qualitatively nonspecific measures (e.g., any drug effect) and qualitatively specific measures (e.g., liking, good effects, bad effects), that are considered the gold standard method by consensus panels and the FDA for detecting drug effects (Comer et al., 2012). We will also conduct comprehensive neurocognitive testing, using a standard battery that is regularly used by our group at BPRU in studies assessing both opioid and cannabinoid effects.

Study Measures to Establish Eligibility and Characterize Sample:

- BPRU Demographic Questionnaire: A questionnaire designed by us to document standardized demographic items (e.g., age, gender, marital status).
- Alcohol/Drug subscale of the Addiction Severity Index: A 31-question subscale to assess past 30 day and life-time use of drugs, history of treatment, and interest in treatment. Subscales provide a measure of severity.
- MINI International Neuropsychiatric Instrument: A standardized semi-structured diagnostic interview assesses participants for evidence of psychiatric disorders. The MINI will be used to verify that participants do not meet DSM-5 dependence on alcohol and/or drugs.
- Brief Pain Inventory (BPI): A 9-item widely-used, standardized, self-report measure to characterize the presence and severity of pain, as well as the interference of pain in every-day activities. The BPI has been modified to be appropriate for self-administration.
- Fagerström Test for Nicotine Dependence (FTND): A 6-item measure to determine presence of smoking and severity of nicotine dependence.
- Beck Depression Inventory (BDI): The BDI-II is a 21-item self-report measure of depressive symptoms.
- Beck Anxiety Inventory (BAI): The BAI is a 14-self-report measure of anxiety symptoms.
- Barratt Impulsiveness Scale: A 30-item, widely used measure of impulsivity that will provide a self-report comparison to the delay-discounting test of impulsivity.
- The Positive and Negative Effect Scale (PANAS): A 20-item self-report measure to characterize positive and negative emotional responses to pain.
- Pain Catastrophizing Scale (PCS): A 14-item self-report measure to characterize the emotional response to pain, with particular emphasis on anxiety and/or fear of pain.
- PROMIS Global Health Scale: A 10 item-self report measure of quality of life.
- Distress Tolerance Scale: A 15-item self-report measure of tolerance to distressing situations.
- Discomfort Intolerance Scale: A 7-item self-report measure of tolerance to distressing situations.

Session Measures:

- Clinical Opiate Withdrawal Scale: A widely used, 11-item observer-rating of opioid withdrawal symptoms.
- Vital Signs: We will assess blood pressure, pulse, respiration, and oxygen saturation.
- Pupillary Diameter: Pupil size will be assessed using an electronic Neuroptics Pupilometer
- Visual Analog Rating Scales: Participants will rate the subjective reports of drug effects items on a scale of 0 (none at all) to 100 (strongest possible), including items such as good effects, bad effects, high, withdrawal, sick, like how I feel, nausea, sedation, feel sleepy.
- Opioid Agonist/Antagonist Rating Scale: This questionnaire assesses positive and negative effects of opioids.
- Drug vs. Money Questionnaire: This questionnaire is a frequently used measure to assess relative monetary value of a drug and is being used to assess relative reinforcing effects of the drug compared to hypothetical monetary values.

Computer-based Cognitive Tests:

- Divided Attention Task (DAT): Participants simultaneously perform two different simple tasks based on visual stimuli presented on a computer screen. This task is computer based.
- Digit Symbol Substitution Task (DSST): Participants must hand type patterns presented to them on a computer screen for 90 seconds
- Paced Auditory Serial Addition Task (PASAT): Participants are provided a string of single digit numbers on the computer and must add the total of the prior to integers presented and respond by selecting the answer using the computer mouse on the screen.

Participants will also be asked to provide an optional blood sample that will be banked with the Genetic Resources Core Facility. Samples will be analyzed at a later date and governed by a separate hypothesis-driven IRB protocol. Genetic sample collection will be optional and will not impact primary study eligibility.

Optional Hair Analysis Substudy: Participants will be asked whether they would like to participate in a hair sampling substudy. The study will be considered optional to prevent disinterest in hair sampling from negatively impacting recruitment for the primary study. The rationale for this substudy is that hair analyses are emerging as an important method for detecting drugs use. This study can contribute valuable information to efforts to refine hair analyses because it administers drugs that have known abuse potential in a controlled manner and at known and uniform dose levels. The study PI has been asked by a NIDA Program Officer to collect hair samples from willing participants to be analyzed by the Neuroproteomics and Neurometabolomics Center at Northwestern University. Samples will be used to improve Maldi Sampling Techniques, to determine the degree to which accurate identification and quantification of levels of opioid and cannabinoid exposure in hair samples from individuals who are biologically confirmed to have no extra-study drug use is possible. Participants who are enrolled in the parent study will be asked about interest in this substudy and consented into the substudy via an oral consent procedure. The substudy will collect a hair sample at the beginning and end of the 6-week participation period. Samples will be collected via the commercially available Hair Test Collection Kit from Therapak and coded by participant ID numbers so that no PHI will be shared with the Center. Samples will be sent annually to the Center for analyses.

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

Participants will complete a Screening visit and 5 experimental session visits. Though sessions are expected to occur once weekly (for 5 weeks) participants will be able to extend sessions to greater than once per week if necessary, to accommodate potential scheduling barriers.

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

Participants and staff will be blinded to the doses of study medications being administered at each study visit. This will allow a rigorous test of the study hypotheses by not biasing participants or staff towards differential pain ratings.

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.

We have included placebo control conditions for each study drug, to assist with interpretation of the study results. Since this study will recruit healthy individuals and we will not be removing access to a known treatment, we believe that inclusion of the placebo conditions poses low risk to participants.

f. Definition of treatment failure or participant removal criteria.

Participants will be removed from the study if they remove their consent to participate, become pregnant, refuse to adhere to the study session schedule, or if it becomes clear that their continued participation could put them at increased risk (e.g., develop a chronic pain condition that requires treatment, onset of a medical/psychiatric disorder). These decisions will be made in conjunction with the BPRU medical team.

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

5. Inclusion/Exclusion Criteria

Inclusion Criteria:

- Aged 18-75
- Urine sample tests negative for common illicit substances of abuse, including cannabis
- Medically cleared to take study medications

- Are not pregnant or breast feeding
- Willing to comply with the study protocol.

Exclusion Criteria:
- Meet DSM-5 criteria for alcohol/substance use disorder
- Taking opioids for pain
- Previous adverse reaction to a cannabinoid product
- Prescribed and taking stimulants or benzodiazepines
- Answer "yes" to item 1 of the Brief Pain Inventory indicating chronic pain
- Self-report any illicit drug use in the past 7 days
- Presence of any clinically significant medical/psychiatric illness judged by the investigators to put subject at elevated risk for experiencing an adverse event
- History of seizure disorder
- Have a known allergy to the study medications or sesame seed oil
- Taking medications contraindicated with hydromorphone or dronabinol
- Have a history of clinically significant cardiac arrhythmias or vasopastic disease
- Have an abnormal and clinically-significant ECG
- Failure to discriminate between hydromorphone and placebo in the Screening 2/Qualifying session.

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

Study Drugs: Hydromorphone and dronabinol will be over-encapsulated by our research pharmacy and administered orally.

Study Drug Dosing		
Condition	Hydromorphone Oral	Dronabinol Oral
Nonrandomized		
1	4mg	Placebo
Randomized		
2	4mg	2.5mg
3	4mg	5mg
4	4mg	10mg
5	placebo	placebo
Session 1 will be nonrandomized and used as a safety screening day. Sessions 2-5 will be randomized and counter-balanced across participants.		

Hydromorphone (Dialudid) is a potent mu-opioid agonist that we have extensive experience administering in controlled laboratory settings. Hydromorphone is not subject to differences in CYP metabolic enzymes (in contrast to other opioids such as oxycodone) and therefore will not require us to screen out individuals with recent exposure to CYP inhibitors/inducers, or to analyze/statistically control for CYP metabolic profiles. We have selected a 4mg oral hydromorphone dose for this study because we have data from another ongoing study (IRB00047423) indicating it produces a mild-moderate effect (versus a ceiling or floor effect) and will therefore allow us to visualize changes as a function of the dronabinol. 4mg oral hydromorphone is also a dose that is commercially available and regularly prescribed for analgesia, which increases the clinical relevance of this study. Based on clinical experience, we expect it to produce a moderate analgesic effect on pain. This is an important feature because too strong a dose could overwhelm the cannabinoid effect and prevent us from effectively evaluating the study hypotheses. A moderate dose of hydromorphone will better enable us to evaluate shifts in the analgesic curve as a function of the study drug, and provide a stronger assessment of whether cannabinoids will enhance the analgesic effect of hydromorphone.

Dronabinol (Marinol) has been strategically chosen for this study because it is a widely-used, commercially-available Schedule II cannabinoid medication that is currently indicated for nausea and vomiting, and anorexia in AIDS patients, **but which could be prescribed off-label for the adjunctive treatment of clinical pain.** Dronabinol is a synthetic delta-9-tetrahydrocannabinol (THC) product (the primary psychoactive compound in cannabis sativa (marijuana)), and thus has generality with other THC compounds (such as smoked or edible marijuana products). When administered orally (as proposed here), dronabinol reaches peak concentrations in 2-4 hours and is 90-95% absorbed but, due to extensive first-pass metabolism, is only 10-20% bioavailable. It is excreted in fecal (35-50%) and renal (10-15%) waste. The elimination half-life is biphasic, with an initial half-life of 4 hours and a terminal half-life of 25-36 hours, and an active metabolite (11-hydroxy-delta-9-THC) is produced. There is no current evidence that dronabinol is differentially affected by P450 status. Dronabinol is sold commercially in 2.5mg, 5mg, and 10mg dose ranges. **We have chosen to administer a 0 mg (placebo), 2.5mg, 5mg, and 10mg, dose of dronabinol in this study,** which are within the range currently prescribed for chemotherapy-induced nausea and vomiting and AIDS-

related anorexia, and therefore will have direct clinical applicability. Dronabinol will be purchased as a capsule and will be over-encapsulated by our research pharmacy to ensure double-blind administration procedures. Placebo doses will consist of lactose or another benign weight-matched filler.

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: 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 4mg oral hydromorphone for the study sessions because we have ongoing experience with this dose in another IRB approved study (PI Dunn, IRB_00047423) and we have observed that it produces the effect intended for investigation in this study; namely, that it produces a mild-moderate effect that will better position this study to evaluate whether dronabinol can increase or decrease drug effects.

Hydromorphone was strategically selected for this study 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. Both doses of hydromorphone are within the range that is commercially available, which increases the clinical relevance and direct application of these study results into clinical practice, and our data indicates 4mg oral hydromorphone will produce a moderate analgesic effect following pain testing. This is an important feature because too strong a dose of an opioid analgesic could overwhelm the cannabinoid effect and prevent us from effectively evaluating the study hypotheses. By selecting a dose of hydromorphone that produces a moderate effect, we will be able to evaluate shifts in the analgesic curve that occur as a function of dronabinol, which will allow us to better determine the degree to which dronabinol can augment the analgesic effect of hydromorphone. There is also no apparent effect of gender on the pharmacokinetics of hydromorphone.

We have selected hydromorphone for this study because it is a prototypical opioid with a known safety profile and because we have extensive experience administering this drug in oral preparations. We have selected a mid-level dose because it is within the range of doses approved by the FDA. It is also sensitive to the QST tests we have proposed, and we therefore believe it will provide an ideal opportunity to evaluate whether the curve of hydromorphone is shifted as a function of dronabinol administration.

Dronabinol: Dronabinol is a schedule II drug that is being administered at 2.5mg, 5 mg, and 10 mg doses in this study, which is consistent with the range approved by the FDA for therapeutic use in patients with chemotherapy-induced nausea and vomiting, and loss of appetite in patients with advanced HIV (AIDS). Dronabinol is also used off label for the treatment of Gilles de la Tourett's syndrome, general loss of appetite (related to cancer), spasticity from Multiple Sclerosis, treatment refractory and postoperative nausea and vomiting, and treatment refractory pruritus. When administered orally (as proposed here), dronabinol reaches peak concentrations in 2-4 hours and is 10-20% bioavailable. It is subject to extensive first-pass metabolism and is excreted in fecal (35-50%) and renal (10-15%) waste, with an elimination half-life of 19-36 hours.

We have selected oral dronabinol because it is FDA approved for pain conditions, and we have selected to administer the full range of FDA approved doses to best understand the dose at which any change in opioid analgesic effect may emerge. We believe this approach will yield data that can be instantly utilized by pain treatment specialists, which increases the generalizability of our study approach.

Capsaicin: 10% capsaicin topic cream will be applied as part of the standardized quantitative sensory testing battery. This is a conventional pain testing technique. For application, a piece of thick, non-porous adhesive dressing with a $1.25inch^2$ opening will be applied to the skin at the location of intended application. The area will be marked with a pen or sharpie for later visualization. A 0.35g application of 10% capsaicin cream will be applied inside this opening and evenly spread on the skin. The area will then covered by Tegaderm transparent dressing and the capsaicin cream will be permitted to absorb into the skin for 30 minutes. Capsaicin will then be removed from the skin using alcohol prep pads.

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

7. Study Statistics

a. Primary outcome variable:

- **Primary Aim 1:** The primary outcome will be the area under the curve of each QST procedure, which will provide an assessment of the mean duration and magnitude of the drug effect. Primary outcomes will be tested with repeated two-factor (Drug Condition x Time) models to examine main and interaction effects for all raw data as designed. If there is large variation across subjects at the baseline timepoint, the raw data will be transformed as a change from baseline and analyzed in drug condition by time models. Statistical analyses will be conducted using multilevel analyses with an autoregressive covariance structure using SAS PROC MIXED Software[131]. These analyses will permit an examination for effects of drug condition and time effects associated within the course of the study. Interpretation of drug condition main effects and interactions will rely on Tukey post-hoc tests. This aim will also assess frequency of adverse events as a function of study drug.

Specific outcome variables for the QST procedures will be as follows:

a. Heat Pain Threshold and Tolerance: HPTh and HPTo in ºC (both in normal and capsaicin treated skin)
b. Pressure Pain Threshold: PPTh in kilopascals
c. Thermal and Mechanical Temporal Summation: Verbal pain ratings (both in normal and capsaicin treated skin for MTS)
d. Conditioned Pain Modulation: The index score of CPM:PPTh and CPM:TS (compared to baseline) for each dose
e. Cold Water Tolerance: Time to tolerance (compared to baseline) for each dose.

- **Primary Aim 2:** The Drug vs. Money questionnaire will be compared across dose conditions, using peak monetary rating for each dose as the primary outcome. Within-subject changes, as a function of dose, will be analyzed using a repeated measures analysis of variance (ANOVA).

- **Primary Aim 3:** Neurocognitive tests will be compared as a function of study drug dose, using study session number (1-6) as a covariate to control for practice effects. Specific outcome measures will include:

a. Divided Attention Task (DAT): Accuracy with which they perform the two tasks
b. Digit Symbol Substitution Task (DSST): Accuracy, total number of patterns completed in allotted time
c. Computerized version of the Paced Auditory Serial Addition Task (PASAT): Summed of correct trials

b. Secondary outcome variables.

Demographic and drug use characteristics, including a positive signal (defined as >20 points rating from baseline on VAS rating of Drug Effect from Session 1), that are hypothesized a priori to be associated with outcomes (e.g., Body Mass Index) will be compared across sex groups and significant differences will be included as covariates in the subsequent analyses. All analyses will be repeated and sex (male/female) will be added as a factor to the analyses.

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

Since this will be the first study to examine the effect of cannabinoids on opioid-induced analgesia using a within-subject laboratory model of pain, there are no data available upon which a power analysis may be directly based. Therefore, we have used G-power to estimate our sample size. We estimate that a within-subject comparison using peak change from baseline as the primary outcome measure and comparing 6 medication conditions will yield power of 0.95 to detect a main effect at even a low effect size (0.2) by enrolling a sample size of 45. For each study, we are proposing to enroll 60 subjects to ensure we will have 50 study completers, and we will enroll equal quantities of men and women to examine sex-based differences in responding. This approach will result in an overall completion sample of 50 per study, with subsamples of 25 per group, which is consistent with other within-subject evaluations of drug effects. This sample size has been powered to support within-subject effects of study drug and between-subject effects of sex on study outcome measures.

d. Early stopping rules.

The safety of participants is a priority of BPRU. The largest potential risk of this study is cardiovascular in nature. This notion is based upon the results of a published study that reported an increase in heart rate and blood pressure

among patients undergoing opioid withdrawal (of which increased heart rate and blood pressure is a known symptom) and who received a dose of dronabinol (40mg) that is double the highest potential dose proposed here (20mg). These effects were diminished when the dronabinol dose was reduced to 30mg (132). Though we do not believe this study completely corresponds to our laboratory design, which is enrolling healthy individuals who are not otherwise predisposed to elevated blood pressure and heart rate and who are receiving doses of dronabinol that are lower than those administered in the prior study, we are sensitive to this potential outcome. To address this, we will monitor vital signs at all study data collection time points and will follow procedures that we have developed and successfully used in previous studies that administered drugs (e.g., cocaine) with known cardiovascular risks. Specifically, if a participant's parameters reach these thresholds, then a study physician, who will always be available via telephone, will be contacted and consulted to determine the appropriate course of action.

- Systolic blood pressure: $\geq$180mm Hg
- Diastolic blood pressure: $\geq$120mm Hg
- Heart Rate: $\geq$ submaximal heart rate (220 – [age x 0.85)].

Appropriate courses of action may include observing the participant until the parameters return to normal or transferring the participant to the Emergency Department (ED). Our research unit, which is the location in which all study sessions will be conducted, is located across the street from the Johns Hopkins Bayview Medical Center (JHBMC) ED. Participants who can walk will be escorted to the ED by a study staff member. If there is any question in a participant's ability to walk safely then 911 will be called to have an ambulance dispatched for the participant.

Additional stopping rules will include not abiding by the BPRU policies and procedures, or engaging in behaviors towards staff or other participants that are abusive. Finally, development of an intercurrent illness or condition that changes the participants risk may result in medical discharge from the study.

8. Risks

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

a. 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 an identical participant population, 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, and participants will be monitored throughout the study session, up to 8 hours, by trained staff who will have access to the opioid antagonist naloxone to reverse the opioid agonist effects. Hydromorphone has no known interactions with dronabinol.

b. Dronabinol: The FDA identifies the following adverse effects of dronabinol: cardiovascular (hypertension, hypotension, palpitations, tacharrhythmia, vasodilation); dermatologic (flushing); gastrointestinal (abdominal pain, nausea, vomiting, xerostomia); neurological (amnesia, ataxia, confusion, coordination problem, dizziness, somnolence, vertigo), and psychiatric (anxiety, delusion of persecution, depersonalization, depression, disturbance in thinking, euphoria, hallucinations), though it should be noted that the adverse effects were collected from studies of patients undergoing chemo therapy or with advanced HIV, which may have decreased their threshold for experiencing negative effects. Dronabinol is listed as pregnancy category C, meaning that preclinical studies have revealed adverse effects on the fetus but that no controlled human studies have been conducted to assess this risk (pregnancy or breast-feeding will be an exclusion criterion). The only absolute contraindication of dronabinol is allergy or hypersensitivity to cannabinoids or sesame oil. Dronabinol has moderate – severe interactions with breast cancer resistance protein inhibitors (topotecan, ataluren), and has moderate interactions with the antiretroviral protease inhibitor ritonavir (Norvar), which is used to treat HIV and AIDS.

c. Capsaicin: Capsaicin is the main ingredient in hot peppers, and is used as an over the counter drug for the treatment of pain. The dose of capsaicin we are using is higher than what is available over the counter, although it is less than half of the dose in a single habanera pepper. Capsaicin does cause pain, like a hot pepper may do when it is eaten. Capsaicin may produce some local redness and swelling that will disappear within a day. The area of skin where the capsaicin is applied could be sensitive for up to 48 hours. Capsaicin may cause a burning feeling in the eyes or other areas of the body if accidentally rubbed onto other skin areas.

d. Chance That Participants May Begin Abusing Opioids or Cannabinoids Following Exposure to Study Drugs: There is a small but potential risk that exposing non-drug abusing individuals to doses of hydromorphone or cannabinoids may elicit reinforcing effects that could precipitate subsequent drug-use behavior. Enrolling non-drug users into controlled laboratory studies is a conventional strategy that has been used extensively to evaluate the abuse liability potential of numerous drugs of abuse both within our laboratory and by other laboratories.

e. Discomfort from Pain Testing: Participants will likely find the pain testing procedures uncomfortable for a brief period of time. This effect is expected to be transient and to produce only mild levels of discomfort.

f. Breach of Confidentiality: Although staff members are highly trained to maintain participant confidentiality, there is always a risk that some of the confidential information collected could be revealed to people who are not involved in the research study. This could be embarrassing to the participant if the participant preferred to keep his or her study participation secret, or if sensitive information became known to an individual outside the study. We have an extensive history of conducting research among substance abusers and have instituted several practices to prevent a breach from confidentiality from occurring (see below); thus, we believe this risk to be minimal.

b. Steps taken to minimize the risks.

a. Protection Against Hydromorphone Risks: 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 exact medication provided, 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 dose of hydromorphone that is being administered is consistent with clinical care, and is a medium level dose 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 a mid-level dose and have extensive experience administering

this dose 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 breath. 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 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 is always prepared for this possibility. We feel these procedures will sufficiently protect participants from possible adverse and serious adverse events.

b. Protection Against Dronabinol Risks: The majority of risks that are known to occur following dronabinol administration are psychiatric in nature. These risks are recognized as being transient and readily reversible. To mitigate these risks, we will exclude participants who endorse having previously experienced negative effects to cannabinoid products. We will also conduct psychiatric screening during the Screening session to ensure that patients with current or history of psychiatric events are excluded from study participation. Further, all participants will be informed about the potential side effects of the study medications and will be permitted to end study participation at any time if they experience negative events, with no consequences. Finally, we are providing participants with taxi service to and from the study sessions to ensure no persistent drug effects will impact their driving. We are also budgeting for the potential for a participant to stay the night at the CRU following study drug exposure. Based on our previous experience, we expect this to be a rare occurrence but are prepared to make that option available as needed.

c. Protection Against Risks That Participants May Begin Abusing Opioids or Cannabinoids Following Exposure to Study Drugs: 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[126]. 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[127]. 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[128]. 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[129]. 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[130]. 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 with recreational histories of drug abuse will not be associated with future drug use behavior.

Participants will also not be informed about the specific medication they are receiving, which is a common procedure used by our research unit to minimize bias in responding. This procedure also makes it difficult for the

participant to seek out drugs they may have found reinforcing during the study session, thus further minimizing the opportunity for study participation to increase risk of non-study drug abuse.

d. Protection Against Risks of Discomfort from Pain Testing: It is likely that participants will experience some acute and transient discomfort from the pain testing session, however we will work to mitigate that risk as much as possible. First, participants will be informed of the pain testing procedure during the informed consent and will be able to make an informed decision regarding their study participation. Second, we chose standardized pain tests that are known to produce short-lived effects and thus are unlikely to produce any residual pain. Third, the measures rely on the participant ending the pain testing procedure as an outcome measure, which means that all participants are encouraged to remove themselves from the painful stimulus at any time and that they are in control of the magnitude and duration of pain they experience. Fourth, we will enforce an upper limit on both pain measures to prevent any tissue damage from occurring (e.g., hand cannot be in cold presser task for >150 seconds). Fifth, 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 24 hours by study staff and will have access to medical care and concomitant medications to treat residual pain if necessary. We will also document and review all adverse events reported from the pain testing session and will follow any recommendations they may have regarding the cessation of pain testing.

e**. Specific Protection Against Risks with Capsaicin:** Capsaicin is being used to induce mild pain/discomfort and is a primary outcome of the study. We will ensure that all participants are informed about the discomfort associated with capsaicin so they may make an informed decision regarding their study participation. One of the primary risks of capsaicin is that it could be accidentally transferred to another part of the body. To prevent this from happening, we will make sure the exposure site is well-marked and that all residual topical cream is removed with alcohol pads once the cream has been mostly absorbed. We will also be able to apply ice to the exposure site to reduce any persistent discomfort associated with capsaicin.

f. Protection Against Risks Associated with Breach of Confidentiality: To protect confidentiality, all research participants will be assigned unique participant identification codes that will be used on all study–related forms and online websites. Documents that include the participants' full names (e.g., signed informed consent forms) will be stored in an independent binder, consistent with FDA Good Clinical Practice Guidelines, and will be kept in a locked room. Confidential information will never be shared with anyone outside of the research program without the explicit written permission of the research participant. Only selected designated staff members will be approved to share confidential information after explicit written permission is obtained from the participant and the participant will be able to revoke written permission at any time. In accordance with IRB requirements, all research staff will be formally trained in these procedures. No identifying participant information will be used in written reports, manuscripts and/or conference presentations

c. Plan for reporting unanticipated problems or study deviations.

All adverse events will be reported to the IRB and other relevant agencies (e.g., FDA, NIDA) as required. 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. It is possible that participants' urine samples may test positive for the study drugs for up to 1 week after each session. To mitigate any potential negative impact this may have on participants, we will inform them of this potential risk in the ICF so they may make an informed decision regarding their participation despite this potential consequence, and will provide any interested participants (who sign a release of information) with a letter signed from the study investigator stating that their urine sample may be positive for drugs that can be considered abusable for up to 7 days following a study session.

e. Financial risks to the participants.

None.

9. Benefits

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

There is no direct benefit of this study to the participant. However, this study will provide the first empirical evidence in humans of the magnitude and duration by which cannabinoids may enhance opioid analgesic effects, using a standardized quantitative sensory testing (comprehensive pain testing) battery. This information will advance the use of cannabinoids from treatment-refractory conditions to more wide-spread use for pain treatment. A positive result will provide new medication targets and will help lead efforts to reduce societal reliance upon opioids for the treatment of pain. Reduced availability of opioids will lead to reductions in use/abuse and related problems (risky injection behavior, opioid overdose).

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.

Participants will receive $30 for the Screening Visit, and will receive payments in an escalating fashion to promote study retention. Specifically, participants will earn $150/Session 1, $200/Session 2, $250/Session 3, $300/Session 4, and $350/Session 5. Total possibly study-related earnings will be $1,280.

Participants will be offered $25 for each hair sample provided, for a total of $50 for the optional substudy.

11. Costs

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

All study related procedures will be paid by a National Institute on Drug Abuse grant; participants will not incur any direct cost for study participation.

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