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 laboratory study will evaluate whether a cannabinoid enhances the analgesic efficacy of an opioid in a clinical sample of chronic pain patients, laying the foundation for a larger clinical trial evaluating the utility of cannabinoids as potentially opioid-sparing adjuvants to chronic opioid therapy for pain. Heightened CNS processing, or central sensitization (CS), occurs across numerous chronic pain conditions and is an important treatment target in its own right. While cannabinoids show initial promise as treatments or adjuncts for some chronic pain conditions and pre-clinical data suggest effects on CS, little is known about the degree to which combining cannabinoids with opioids alleviates CS-mediated chronic pain. We propose a within-subject, single exposure, double-blind, placebo-controlled, human laboratory investigation of the extent to which a cannabinoid enhances opioid analgesia in a model chronic pain population (e.g., patients with knee osteoarthritis). Human laboratory studies are an ideal method for this initial evaluation because they provide the opportunity to tightly control study drug dosing and afford high sensitivity of measurements, and enable tight control of confounding variables that may otherwise exist in clinical treatment populations and could differentially impact outcomes. This approach will minimize the number of participants needed to determine whether a positive signal exists while permitting rigorous and elegant evaluation of the study aims. Primary study outcomes will include measures of clinical pain and central sensitization, physical function, drug effects (e.g., abuse liability, adverse events, cognitive performance), and pharmacokinetic analyses. The Aims will examine the magnitude and duration of cannabinoid/opioid combination in reducing clinical pain and central sensitization; the effects on physical functioning, adverse events and indices of abuse liability; and the pharmacokinetic and pharmacodynamics profiles for the individual and combined drugs. This study will provide the most systematic and rigorous evaluation of the potential for cannabinoids to enhance analgesic effects of opioids in human subjects to date, and will do so in a relevant and generalizable clinical pain population who has CS, which makes these results more directly relevant compared to studies conducted in healthy populations. These findings will be critical to informing the efficacy and safety profile for the advancement of opioid/cannabinoid combination regimens to clinical trials with chronic pain patients.

2. Objectives (include all primary and secondary objectives)

Aim 1: Evaluate the magnitude and duration of cannabinoid/opioid combination to reduce clinical pain and central sensitization. We hypothesize the cannabinoid/opioid combination will increase the

magnitude and duration of analgesia in clinical pain report (Hyp1) and QST-derived central sensitization (Hyp2), relative to each drug administered alone and relative to placebo.

Aim 2: Evaluate the degree to which physical functioning is altered by the cannabinoid/opioid combination. We hypothesize that the drug combination will improve physical function (Hyp3) relative to the drugs administered alone and placebo.

Aim 3: Compare the subjective, physiological, abuse liability, and cognitive effects of the cannabinoid, opioid, and combination. We hypothesize that cannabinoids will not increase adverse events (Hyp4), or abuse liability (Hyp5: ratings of positive drug effects) relative to opioids alone and that the cannabinoid (alone and in combination with opioids) will reduce neurocognitive performance (Hyp6), relative to the opioid alone and placebo.

Aim 4: Evaluate the pharmacokinetic and pharmacodynamic profile of the cannabinoid, opioid, and the combination in OA patients. We hypothesize that the combined dose will result in an altered pharmacokinetic (Hyp7) /pharmacodynamics profile (Hyp8) compared to either drug alone.

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 laboratory study is the first step in addressing an important and timely public health problem: Can cannabinoids enhance the analgesic efficacy of an opioid and ultimately reduce opioid dosing in people with chronic pain?

Effective adjuncts to opioid therapy are needed to address the critical public health problem of prescription opioid abuse. Chronic pain is a world-wide health problem and opioids are unanimously recognized as the most effective drugs for the relief of pain and suffering[1]. Opioid prescriptions for chronic pain conditions have increased despite serious consequences[2-4] and an epidemic of abuse, addiction, and accidental deaths[5] continues to escalate[6]. Undoubtedly, there is legitimate and necessary medical use of opioids to provide analgesia; yet there is a clear need for the clinical community to identify effective alternatives and adjuncts to opioid therapy that can serve as essential components of responsible pain management[7].

Opioids reduce pain at a cost. Opioids are the most effective analgesic for pain reduction and often become an integral component of treatment, yet result in myriad complications including escalating doses (tolerance), increased falls, constipation, respiratory depression/death, and hypogonadism[8-16]. Further, due to opioid-induced hyperalgesia, opioids often lose their effectiveness over time, which means that patients with chronic pain incur consequences of continued opioid use without increased pain relief and potentially increases in their pain. It is clear that reducing singular reliance on escalating doses of opioids for effective pain management is a significant public health need. The best evidence supports use of analgesic combinations that have different mechanisms of action[7].

Cannabinoids produce analgesia. Although not yet widely accepted as treatments or adjuncts for chronic pain, cannabinoids have shown initial promise for this indication in both preclinical and clinical studies[17-28]. A recent meta-analysis found moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain[8]. Specifically, cannabinoids reduce neuropathic pain[29-32] fibromyalgia pain[33;34] and pain from multiple sclerosis (MS)[35-40] as well as central pain in MS patients when used as an adjunct to current analgesics[41;42] measured out to two years without tolerance[43]. Recent reviews suggest that they can produce a reduction in opioid use, improve opioid pain relief, and reduce annual opioid overdose mortality by 25%[8]. The cannabinoid dronabinol is an FDA-approved synthetic THC analogue that is efficacious in reducing pain.

Central sensitization (CS) heightens clinical pain. A growing literature indicates that heightened CNS processing, or CS, occurs in chronic pain conditions and is an important treatment target[48]. CS is characterized by a rewiring of pain transmission that initiates and/or maintains pain chronicity and heightens pain in a number of clinical pain disorders, including osteoarthritis[48]. CS results from alterations in CNS neurons, increasing afferent nociceptive input and uncoupling pain from the presence, intensity, or duration of peripheral stimuli. In humans, CS manifests as hyperalgesia, allodynia, and spreading of pain. It is a marker for pain chronification[48;49] and can be reliably assessed in laboratory

studies through application of noxious stimuli[48]. Knee osteoarthritis (KOA) is one of the leading causes of pain and impairment in physical function in the U.S.[50-54] and a growing literature, including our own work[48], documents enhanced central pain processing at both affected and non-affected (distal) anatomical sites[55-59]. This augmented CNS processing[55;57] and deficits in endogenous pain inhibition[60-62] are associated with clinical pain[57] and reduced physical function; we and others have suggested that CS may be a more important mechanism of clinical pain amplification in KOA than radiologic features[60;63].

Human laboratory measures of CS predict clinical outcomes. Subjects who rate calibrated noxious laboratory stimuli as most painful[64;65], who show the greatest CNS sensitizability[66] and the least endogenous pain inhibition[67], report the most frequent, disabling daily pain complaints. Human experimental pain models link animal and clinical pain studies, and quantitative sensory testing (QST) has specifically been recommended for testing analgesic compounds, and noted as "ideally suited" in proof-of-concept and dose finding studies[68]. Variability in psychophysical pain responses is common and strongly parallels the variability in clinical pain[69-74]. QST is responsive to drug effects in mechanistic studies[75-77], and predict opioid analgesia[78-83], correlate with opioid dosing in chronic pain patients[13;84], are responsive to analgesics[82;85;86], and are frequently used to determine analgesic efficacy[77;87]. We propose to focus our testing on two CS-specific tasks, Conditioned Pain Modulation (CPM), and Temporal Summation (TS). **CPM** refers to the phenomenon whereby one longer-lasting noxious stimulus inhibits the pain produced by a 2nd brief noxious stimulus (i.e., counter-conditioning)[88]. Generally, responses to the brief noxious stimulus are reduced during concurrent administration of the other stimulus to a distant body site, with the magnitude of the reduction (decreased sensitivity) serving as a measure of the efficacy of central inhibitory, analgesic systems[67]. These effects are not simply diversion of attention[88;89]; CPM serves as an indirect index of endogenous opioid function[90-97]. **TS** refers to the enhancement of pain caused by repeated noxious stimulation; animal studies have shown that it involves sensitization of 2nd-order dorsal horn neurons (called wind-up) in the spinal cord[98-100]. In humans, TS is thought to reflect endogenous pain-modulatory processes arising from supraspinal structures[5] and like CPM, TS has also been implicated in pathophysiologic models of chronic pain[101].

Central pain agents can inhibit hyperalgesia and CS. Both opioids and cannabinoids have central effects, some of which are complementary. Because cannabinoids modify and mediate the actions of NMDA receptors[102;103] which attenuates CS in preclinical models of chronic pain[26;104], we believe that cannabinoids may substantially inhibit CS maintained pain in KOA. Additionally, some chronic pain conditions characterized by CS are hypothesized to have an underlying clinical endocannabinoid deficiency that could be rectified through cannabinoid administration[105]. No studies to date have examined cannabinoids for CS-mediated pain. The proposed design (using QST) provides a systematic and rigorous model for evaluating these effects in a relatively opioid inexperienced clinical population (KOA). While KOA is a peripheral disease, central mechanisms underlie symptom expression[107] and central pain agents may be useful in treating KOA hyperalgesia.

Combination therapies may provide synergistic effects. Cannabinoids modulate the function of opioids[108]. There is substantial preclinical evidence in rodents[119-122] and primates[123-125] that the combination of cannabinoids and opioids is extremely effective, with up to a 20-fold increase in efficacy, and the combination may circumvent the development of tolerance compared to either drug alone[109]. However, these non-human animal results require systematic and rigorous evaluation in human subjects. In healthy participants, THC produced an additive analgesic effect when combined with morphine on a measure of electrical sensitivity[110]. Among patients, the single Phase I study of which we are aware reported decreased pain intensity and increased satisfaction following oral administration of 10-20mg of dronabinol relative to placebo in patients using their typical, prescribed dose of opioids[111]. 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[111]. In a Phase II study, average daily and worst pain significantly decreased following low and medium dose Nabiximols (cannabinoid spray) compared to placebo in daily sustained release fixed dose opioid therapy for opioid refractory cancer pain patients[112]. No human studies to date

have used QST to rigorously evaluate the combination of cannabinoid/opioid-induced analgesia or laboratory measures of CS.

Summary. Developing effective adjuncts to opioid therapy for chronic pain management will address a life-threatening public health problem that has reached epidemic proportions. Cannabinoids are a logical adjunct to effective opioids due to preclinical findings and their potential effects on CS, which heightens pain, increases chronification, and likely contributes to pain-related disability. Studying KOA patients in the laboratory provides an excellent model for establishing initial efficacy and safety of combination dosing, addressing important questions about the magnitude and duration of analgesia, effects on physical function and other clinical parameters, while also addressing key questions about pharmacokinetics and pharmacodynamics. *The ultimate goal of this research is to determine whether the drug combination exerts analgesic effects on CS, clinical pain and physical functioning 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/opioid treatments for chronic pain and foundational in supporting numerous future evaluations of combination treatments for various pain populations.*

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 to study the separate and combined effects of the FDA-approved cannabinoid dronabinol (Marinol) and the prototypical opioid hydromorphone (Dilaudid). Following telephone and screening to establish study eligibility, a cohort of **n=100** adults with knee osteoarthritis (KOA) will complete four different within-subject experimental sessions. Participants will complete one of two Phases, receiving either a 4mg or 2mg dose of hydromorphone. Randomization will be split equally across the two Phases. During each session, participants will complete baseline QST, questionnaires, and a neurocognitive battery. Oral hydromorphone will be administered in the first session. Subsequent sessions will consist of 1 of 3 conditions, and session order will be randomized and counter-balanced. Conditions will be 1) placebo; 2) oral dronabinol (10mg); and 3) combined hydromorphone and dronabinol (10mg). Measures will be repeated throughout the session to fully characterize the drug effects. Participants and staff will be kept blinded to the study medications under investigation, and participants will be informed in the consent form they may receive a combination of FDA-approved stimulants, benzodiazepines, opioids, cannabinoids, over-the-counter medications or placebo, though the participants will not actually be receiving stimulants, benzodiazepines, or over-the-counter drugs. All participants will be provided with transportation to and from the experimental sessions. Primary outcomes are measures of clinical pain, central sensitization, physical function and drug effects/adverse events. A subset of participants will undergo blood draws for pharmacokinetic (pK) profile. This will be voluntary and should aid recruitment as those that do not want an IV will still be allowed to participate in the study. We will aim to recruit 30 participants that volunteer to undergo IV/blood drawing procedures in order to characterize pK.

Phase 1: The initial Phase of this project will include hydromorphone at a dose of 4mg.
Phase 2: The second Phase of this project will include hydromorphone at a dose of 2mg in order to evaluate drug effects at a reduced opioid dose.

Recruitment. We will recruit subjects utilizing multiple strategies successfully implemented by our research groups, including via recruitment flyers, brochures and posters posted throughout Johns Hopkins affiliated hospitals and community, print and electronic media, Trialfacts, website postings, and radio advertisements. We also have a list of over 400 previous KOA study volunteers who have given permission to call them regarding potential future study participation – we will send these previous participants a letter introducing the study. Participants will also be recruited directly through flyers, brochures or posters at the Department of Orthopedic Surgery clinics, who sees high volumes of KOA patients; an initial search of

their electronic medical record identified over 3000 Hopkins patients who have been diagnosed with KOA. These flyers/brochures/posters will invite interested individuals to call the study coordinator or complete an online initial assessment of eligibility. Our co-investigators may also refer patients to the study. Additionally, we will offer $25 to our participants who refer someone to the study that is eligible. We expect the overall sample to be ≥50% female,[113] and expect a diverse socioeconomic background representative of Baltimore.

In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for in person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participant's risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

Screening. Telephone Screening: Following completion of an initial phone screening, eligible participants will be scheduled for additional Screening. **Screening:** Screening will be used to obtain informed consent, and establish preliminary study eligibility. Screening may occur in-person or as a combination of virtual/in-person. Subjects will review and sign an informed consent document with a study staff member to begin the Screening visit. Virtual consenting will follow IRB guidelines for virtual consenting procedures and will occur prior to any data collection. Subjects will provide a urine sample that must test negative for illicit drugs and pregnancy (for premenopausal females), will complete a battery of measures to establish study eligibility prior to being scheduled for their first experimental session. Training for the QST protocol prior to study sessions will be completed during in-person screening activities where possible. We may also collect a saliva sample for future analyses for those that consent to this portion of the study, once allowed. Medical eligibility will be determined based on ECG, a blood sample to analyze hepatic, hematologic, and chemistry functioning, a history and physical, and a knee x-ray occurring prior to medication administration at the first Experimental Session. Eligible individuals will be asked to complete pain diaries over the course of the study to evaluate clinical pain between sessions.

Randomization: The BPRU pharmacy has no subject interaction and will manage drug randomization/ blinding.

Experimental Sessions. Upon eligibility confirmation, subjects will complete four experimental study sessions (Table 1a or 1b). Sessions will begin at approximately 0800 and subjects will be asked to refrain from eating prior to the session in order to control dietary intake on the day of testing. Following provision of a negative urine sample for illicit drugs and pregnancy and consumption of a calorie-controlled breakfast (whether eaten in-person or the participant follows instructions and guidelines to eat at home), for those in the pK group, an intravenous line will be established on the non-dominant arm. After 15 minutes of rest, the first 10-14mL blood draw will be taken for those in the pK group. At

Table 1a. Phase 1. Study Drug Dosing
Subjects complete each condition

Condition	Hydromorphone (Oral)	Dronabinol (Oral)
1	4mg	0 (placebo)
Randomized Order		
2	0 (placebo)	0 (placebo)
3	0 (placebo)	10mg
4	4mg	10mg

approximately 0930 participants will complete baseline QST, physical functioning measures, and self-report measures (see below). The second 10-14mL blood draw (for those in the pK group) will be collected and then two oral capsules containing either active drug or placebo (randomized in sessions 2-4) will be administered at approximately 1100. Briefly, subjects will complete QST, physical functioning, cognitive testing, self-report, and vital sign measures (as well as blood draws for those in the pK group) 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. 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 drug received[98,] which 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, or wishes to discontinue for any reason will be able to end participation at any time. Any subject who is experiencing strong agonist effects at the end of the session will be provided overnight accommodation in the Clinical Research Unit (CRU; which is located on our campus and with whom we have frequent collaborations); based on our experience we expect this to be rare and are budgeting for 20% of sessions to undergo a one-night CRU stay.

Table 1b. Phase 2. Study Drug Dosing
Subjects complete each condition

Condition	Hydromorphone (Oral)	Dronabinol (Oral)
1	2mg	0 (placebo)
Randomized Order		
2	0 (placebo)	0 (placebo)
3	0 (placebo)	10mg
4	2mg	10mg

Measures

Pilot testing indicates it takes approximately one hour to complete the assessment battery (see Table 2).
Pain Testing: Subjects will complete quantitative sensory testing (QST) to comprehensively and systematically measure general pain sensitivity and central sensitization. This approach will provide data 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 the pain testing battery will be repeated approximately every 90 mins. The QST battery consists of threshold and tolerance, and 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 a thermode that gradually increases in temperature from a pre-set baseline (31ºC) 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*: Pressure pain thresholds (PPTh) will be determined at each of the following sites on both sides of the body using a pressure algometer (SBmedic; Sweden): the medial fat pad of the knee, patella, trapezius, and thumb. Pressure at the site is gradually increased at a steady rate and stopped when the subject indicates the stimulus is first perceived as painful. Thirty-second inter-stimulus intervals will be maintained. Trials will be averaged for one HPTh, HPTo, and PPTh measure.

Temporal Summation (TS) of Pain will be assessed using thermal stimuli (TTS) and repetitive punctuate stimuli. Sequences of 10 heat pulses are applied and the temperature of each phasic stimulus remains the same. Within each sequence, successive thermal pulses 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. TTS is measured as the differences between the highest rated thermal stimulus and the 1st stimulus[57;67]. Mechanical Temporal Summation (MTS) will use a set of weighted pinprick stimulators 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 subject's pain ratings (0-100). Single pinprick stimuli are alternated with trains of 10 stimuli. The difference between the pain rating to the train of stimuli and the single stimuli is then calculated as MTS[118].

Capsaicin: Capsaicin sensitization procedures similar to our frequently used and well-established protocols, originally developed by Peterson and colleagues, will be utilzed[70]. Heat will be delivered using the Medoc. The procedure involves a 35-minute sensitization period (conducted during the baseline period) with a 1.25inch^2 treatment site on the ventral forearm. The thermode will be heated to between 38-45°C (depending on the sensitivity of participants) 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 timepoint by heating the treatment site with the thermode at between 38-45°C (again depending on sensitivity) for 5 min. Following each rekindling episode, heat pain threshold and mechanical temporal summation as well as measurement of flare and secondary hyperalgesia will be conducted. The area of flare (redness around the capsaicin site) will be traced to acetate paper. The area of secondary hyperalgesia will be quantified with a probe or 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^o 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).

Cold Pressor Testing and CPM: A series of procedures designed to elicit and measure endogenous inhibition of pain will be applied. Subjects will undergo a series of cold pressor tasks (i.e., the conditioning stimuli) consisting of immersion of the hand 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 (pressure response or temporal summation) will be re-assessed, each separated by 2 min (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[119]. 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.

CS: Temporal summation measures, CPM, and after-sensation responses to these measurements will be combined to create the CS index for use in statistical analyses for which we have previously published[57].
Physical Performance Measures will objectively assess physical functioning. Patient self-report of activity relates only modestly to performance measures on standardized physical tests[120-125] and physical performance under the effects of the drugs administered here are an essential test of the real-world applicability of administering such analgesic combinations in the natural environment. This set of tests will involve a Timed Up and Go (TUG) test. Stair climb (which includes hand rails) and a three-Minute Walk (3MW) test, all commonly used measures of KOA physical function[126]. The TUG test measures the time it takes a subject to rise from a standard chair, walk 3m, and then return to sitting in the same chair. In the 3MW test, subjects are asked to cover as much distance as possible in 3 minutes while walking laps on a standardized indoor course. Each test will be conducted at baseline and at projected peak effect to avoid participant fatigue.

Self-report Pain Measures: Subjects will complete the Western Ontario McMaster Universities Osteoarthritis Scale (WOMAC, 3.1[127]), the Brief Pain Inventory (BPI[128;129]), and a visual analog scale (VAS; 0-10 rating of pain) of their current clinical pain at multiple points within each session. The

WOMAC is comprised of 24 items and is a well-validated[130], widely-used measure that yields three indices specific to osteoarthritis (pain, disability, and joint stiffness), which are also sensitive to treatment[131]. The BPI is the most widely-used, best-validated "generic" pain measure for assessing chronic nonmalignant pain[128;129] and includes two primary dimensions: pain severity and interference with activity[132]. These measures will provide both "disease-specific" and "generic" indices of pain and pain-related physical dysfunction.

Pharmacological Measures of Drug Effects: The measures of drug effects comprise both pharmacologically and qualitatively nonspecific measures (e.g., any drug effect) and qualitatively specific measures (e.g., liking, good effects, bad effects); the gold standard method by consensus panels and the FDA for detecting drug effects.[133] We will also measure vital signs (e.g,. blood pressure, heart rate, respiration) and pupil diameter as physiological responses to the study drugs. Neurocognitive testing, using a standard battery will also be conducted and is considered critical before any additional drug development for opioid/cannabinoid combination therapies could proceed. Neurocognitive performance (5 minute) assessments will assess aspects of cognitive/ psychomotor functioning known to be sensitive to the acute effects of marijuana and relevant to functioning in the workplace and/or in operating a motor vehicle or heavy machinery. All subjects will be trained on the performance tasks to a stable baseline level during one of the screening session. Tasks include: 1) Divided Attention Task (DAT): subjects simultaneously perform two different simple tasks based on visual stimuli presented on a computer screen; 2) Digit Symbol Substitution Task (DSST): subjects must hand type patterns presented to them on a computer screen for 90 seconds; and 3) a computerized version of the Paced Auditory Serial Addition Task (PASAT): subjects 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. A circular lights task will also be included where participants touch areas that light up on a board. This takes about one minute to complete. These tests have been selected because they capture a wide range of cognitive abilities and do not require substantial time for completion (so they will not interfere with additional study requirements). Co-I Vandrey uses these tasks in laboratory examinations of oral, smoked, and edible cannabinoids, which will aid with interpretation.

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 drug 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 study will be asked about interest in this substudy and consented into the substudy via an additional signature on the consent form (similar to consenting to be contacted for future research). The substudy will collect a hair sample at the beginning and end of the 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.

Optional Saliva Sample: A saliva sample will be collected for genetic analyses. These samples will be provided for DNA analysis of genetic variability that may explain individual differences in the perception and experience of pain. In recent years, it has become clear that people differ widely in their experience and report of pain-related processes, exhibiting profound variability in their sensitivity to noxious stimuli, susceptibility to acute and chronic clinical pain, and responses to analgesics (Edwards 2005;Fillingim

2005). Currently, many pain research laboratories are exploring the associations of common genetic variants in humans with pain sensitivity or clinical pain conditions by evaluating common single nucleotide polymorphisms (i.e., sites in the genome where the DNA sequences of many individuals differ by a single base) located on pain-relevant genes (Diatchenko, Slade et al. 2005;Diatchenko, Nackley et al. 2006). For example, genetic variability at sites coding for a particular opiate receptor are primary candidates for genetic influences on pain since this receptor is the principal site of action for both endorphins and exogenous opioids (Lotsch, Skarke et al. 2004).

At present, the field of human pain genetics is in its infancy; a handful of putative pain-relevant polymorphisms have been identified, but positive findings have often failed to replicate, and new polymorphisms are expected to be identified over the next several years (Edwards 2006). Thus, we will evaluate several current candidate pain genes, and will also store participants' samples for future evaluation as more information becomes available regarding which polymorphisms are likely to play a role in shaping individual differences in the perception and experience of pain. The SNPs that we will evaluate based on the current literature are in the genetic regions coding for the Catechol-O-Methyltranferase gene, the mu opioid receptor gene, the delta opioid receptor gene, and the interleukin-1 and interleukin-6 genes.

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

Participants will complete one screening visit and four experimental session visits.

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

Participants and staff will be blinded to both the drugs and 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. This is an essential component of the study. As described, we will inform participants that they may receive a combination of FDA-approved stimulants, benzodiazepines, opioids, cannabinoids, over-the-counter medications or placebo, though the participants will not actually be receiving stimulants, benzodiazepines, or over-the-counter drugs.

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 a placebo control condition to assist with interpretation of the study results. Since this study will not be removing access to a known treatment, we believe that inclusion of the placebo condition 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 another chronic pain condition that requires treatment, onset of a medical/psychiatric disorder). These decisions will be made in conjunction with the study 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.

Because we will only be delivering study medications for assessment during visits and will not ask participants to stop taking their routine medications, there will be no need to taper the use of study medications or continue to monitor drug effects once participants are released.

5. Inclusion/Exclusion Criteria

Inclusion Criteria: 1) Age 45 or older, 2) meet the American College of Rheumatology criteria for knee OA, 3) report an average pain level of ≥3/10, 4) not have taken any opioid medications for the past 30 days, 5) provide a urine sample that tests negative for illicit drugs and pregnancy, 6) be medically eligible to take study medications, 7) patients taking NSAIDs or acetaminophen must be on a stable dose for 30 days, 8) be fluent in English, and 9) willing to comply with the study protocol. We will enroll ≥50% women because there is substantial evidence that men/women differ with regard to pain perception, endogenous cannabinoid receptor density, and response to opioids and will use sex as a covariate in analyses.

Exclusion Criteria: Individuals who 1) have cognitive impairment preventing completion of study assessment procedures, 2) meet current DSM-5 criteria for alcohol/substance use disorder, 3) meet criteria for lifetime history of opioid use disorder, 4) have taken stimulants, benzodiazepines, TCA, venlafaxine or duloxetine in the past seven days, 5) have a history of clinically significant cardiac arrhythmias or vasospastic disease, or an abnormal and clinically-significant ECG, 6) have history/current evidence of significant medical/ psychiatric illness that elevates risk for experiencing an adverse event (including current suicidal ideation), 7) have a known allergy to the study medications, or 8) are pregnant or breastfeeding. Additional exclusion criteria due to their effects on pain responses include 10) current peripheral neuropathy, 11) presence of Raynaud's phenomenon, 12) active vasculitis or severe peripheral vascular disease, 13) current infection, 14) confirmed diagnosis of periodic limb movement disorder or restless legs syndrome, 15) systemic inflammatory or autoimmune disorders such as rheumatoid arthritis, lupus, etc., 16) seizure disorder, or 17) have a chronic pain condition that produces pain greater than their KOA.

6. Drugs/ Substances/ Devices

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

We have strategically selected hydromorphone and dronabinol for this study, both drugs will be encapsulated by the BPRU pharmacy to ensure double-blind administration, and placebo will consist of lactose or another benign weight-matched filler. See Table 1 above for drug dosing details.

i. *Hydromorphone (Dilaudid)* 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 so will not require us to screen out individuals with recent exposure to CYP inhibitors/inducers, or to analyze/ statistically control for CYP metabolic profiles. The two (2 and 4 mg) oral doses of hydromorphone are commercially-available and regularly used for analgesia, which increases the clinical relevance of these results. We expect both doses of hydromorphone to exert a moderate analgesic effect on pain, which is an important feature because too strong a dose could overwhelm the cannabinoid effect and prevent us from effectively evaluating the study aims. Including both a low and moderate dose will provide an elegant assessment of whether a cannabinoid will produce an additive, synergistic, or no effect on the analgesic profile of hydromorphone.

ii. *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) and 10mg dose of dronabinol in this study,** which is 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.

Pharmacokinetic (pK) Analyses: Blood samples, drawn on a subset of participants, will enable direct comparison of serum drug levels with outcomes for the study aims (e.g., analgesia and physical functioning, subjective and observer- rated effects, abuse liability measures, and cognitive performance). We have chosen to sample pK at numerous timepoints to examine whether the duration of effects changes as a function of drug administration and determine whether behavioral changes following hydromorphone/dronabinol co-administration result from pharmacological enhancement or whether co-administration modifies the metabolic profile of either drug in such a way that it changes their duration of action. pK analysis is considered critical for this initial stage of evaluating drug-drug interactions[135] and will directly inform decisions regarding specific opioid/cannabinoid dose combinations that may be most appropriate to advance into clinical trials for the treatment of pain.

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 hydromorphone because we have extensive experience administering hydromorphone in all formulations [96; 109-117], and know that it will produce reliable and consistent results that will aid interpretation of outcomes. Hydromorphone was also 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. There is also no apparent effect of gender on the pharmacokinetics of hydromorphone. We have selected a low and mid-level dose because they are within the range of doses approved by the FDA. They are also sensitive to the QST tests we have proposed, and we therefore believe both 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 10 mg, 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 more likely than nabilone to be prescribed in practice due to cost. We believe this approach will yield data that can be instantly utilized by pain treatment specialists, which increases the generalizability of our study approach.

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:

Aim 1: Evaluate the magnitude and duration of cannabinoid/opioid combination to reduce clinical pain (Hyp1) and central sensitization (Hyp2). Hyp1 (pain VAS) and Hyp 2 (CS) will be analyzed using repeated 2-factor (Drug x Time) models that examine linear and quadratic effects as well as duration and magnitude, and direct and interaction effects. If large variation exists across subjects at baseline, then raw data will be transformed to change-from-baseline and analyzed in drug condition by time models. A secondary outcome will be peak change from baseline, analyzed as a function of Drug (1-factor model).

- **Aim 2: Evaluate the degree to which physical functioning is altered by the cannabinoid/opioid combination**. Hyp3 will be assessed using the TUG and 6MWT. Time to complete the TUG task will be the primary outcome and will be evaluated using 2-factor (Drug x Time: Pre to Peak) models.

- **Aim 3: Conduct a direct comparison of the subjective, physiological, abuse liability, and cognitive effects of the cannabinoid, opioid, and combination.** Hyp4 (adverse events) will be assessed by summing the mean number of related mild, moderate, and severe adverse events (separately) and using 1 factor models to assess a main effect of Drug. Hyp5 (abuse liability) will be assessed using the Drug vs. Money questionnaire and changes in VAS ratings using 2-factor models (Drug x Time). Hyp6 will evaluate changes in neurocognitive performance, including study session number as a covariate to control for practice effects, using 2-factor (Drug x Time) analyses. Secondary outcomes for this hypothesis will be analysis of peak change from baseline for the cognitive outcomes, analyzed using 1-factor (Drug) ANOVAs to evaluate a main effect of drug.
- **Aim 4: Evaluate the pharmacokinetic (pK) and pharmacodynamic (pD) profile of the cannabinoid, opioid, and the combination in OA patients.** Hyp 7 (pK) will be assessed by evaluating Cmax (maximum concentration) and Tmax (time to maximum concentration) as a function of Drug condition using 1-factor models. We will also examine linear and quadratic effects to evaluate the time course of concentration. Linear and quadratic effects will be modeled for Hyp8 (pD) and analyzed by evaluating VAS and physiological ratings, transformed to change from baseline, evaluating area under the curve and peak change from baseline to identify main effects of the Drug condition. We will then conduct multivariate regression analyses to evaluate the degree to which the Cmax and Tmax correlate with pharmacodynamic outcomes, including abuse liability ratings, VAS ratings of drug effects, and cognitive testing outcomes.

Statistical analyses will be conducted separately by Phase and use multilevel analyses with an autoregressive (AR1) or compound symmetry (CS) covariance structures (as appropriate for the data set) using SAS PROC MIXED[137]. Interpretation of drug condition main effects and interactions will rely on Tukey post-hoc tests. Statistical significance will be set at $p < 0.05$.

Expected Outcomes: We expect that dronabinol will enhance hydromorphone-induced analgesia to both clinical and laboratory-evoked pain. Our comprehensive battery of rigorous, testing procedures provides an opportunity to test effects on multiple mechanisms of experimentally-induced pain. We also expect improvement in physical functioning under combined dosing, and that the addition of the cannabinoid will not significantly increase the overall abuse liability or adverse event profile. We do suspect the cannabinoid may have cognitive effects (though the degree to which this may happen is not clear).

b. Secondary outcome variables.

Demographic and drug use characteristics 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.

This will be the first study to examine interactions between cannabinoids and opioids on clinical and laboratory-evoked measures of pain in a population who has chronic pain and central sensitization. The study uses a within-subject, placebo-controlled design and no data exist upon which to generate a power analysis. We have selected two primary outcomes for the measurement of analgesia: measures of conditioned pain modulation and time to hand withdraw latency in a cold presser test.

Mr. Paul Nuzzo, a biostatistician with extensive experience analyzing within-subject laboratory tests of drug effects, conducted a revised power calculation based on new literature that employs methods similar to those of this study (Cooper et al., 2018). Sample size estimates were premised with a power of 0.8, alpha =0.05 and calculated effect sizes (Cohen, 1988). These analyses suggests a sample size ranging from 10-15 individuals would be sufficient to detect large effect sizes. Because one of our aims focuses on a sex-comparison, we originally planned to double our enrollment. Thus, our sample of 64 completers (32/sex) will yield sufficient power to evaluate direct effects of study condition on CPM and cold presser in both Phases, even at small effect size levels, and will also be sufficient to identify between-session differences on pK results[140].

d. Early stopping rules.

The safety of participants is the highest priority. 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 exposed to the cannabinoid dronabinol who were also undergoing opioid withdrawal (of which increased heart rate and blood pressure is a known symptom). This group differs from our target population in many ways, however out of an abundance of caution in these early studies, we will use this experience to inform our safety criteria. 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 building, 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 CMBR/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.

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 in oral formulation because it has a slower onset and lower magnitude of effects. Co-I Dunn is currently administering hydromorphone in a dose and formulation identical to what is proposed here to opioid-naïve participants as part of a NIDA-funded R01 and has not observed any moderate effects or any serious adverse effects (IRB00047423). When administered orally, hydromorphone effects are detectable in 15 minutes and can last 4-5 hours, which provides adequate time to assess the effects of dronabinol on opioid analgesic function. 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. There is also no known effect of gender on the pharmacokinetics of hydromorphone.

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. The BPRU has extensive experience administering hydromorphone to opioid naïve individuals and employs well-established and rigorous eligibility criteria to ensure that individuals who may be more prone to experiencing opioid-induced side effects will not be admitted into the study.

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 a dose that has been demonstrated to be safe and tolerable in similarly opioid inexperienced participant populations, 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 closely 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. 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. Opioid-Cannabinoid Interactions: There are limited data available to indicate whether there are consistent opioid-cannabinoid interactions on physiological outcomes. One study that was published in 1975 evaluated combinations of delta-9 THC (which is present in smoked marijuana and dronabinol) and the opioid oxymorphone reported that the combination of drugs decreased CO_2 slope and increased tachycardia, though heart rate increased generally following exposure to delta-9 THC141. A second, more recently published study reported that a 40mg dose dronabinol that was administered to participants undergoing opioid withdrawal (as a method of minimizing the withdrawal syndrome) also produced tachycardia142. This effect was eliminated once the dose of dronabinol was reduced to 30mg. We do not believe this will be a problem for this study. The second study only reported negative effects when dronabinol was administered at the highest dose approved for human consumption by the FDA (40mg) and the effect was completely eliminated once the dose was marginally reduced. In addition, this study enrolled patients who were opioid dependent and withdrawing from opioids, and increases in heart rate and blood pressure are well-recognized symptoms of the opioid withdrawal syndrome. Thus, though we have presented these studies to be transparent, we do not believe their results will necessarily generalize to our patient population. We have listed our protections against risk in the following section.

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. Pressure Pain Testing: There is a slight chance of mild transient bruising associated with use of the algometer. In our experience, this is quite rare (< 5 % of cases). Thermal Pain testing: There is a very small chance that the heating device might produce a burn, but the risks associated with the relatively small amount of heat applied to the skin (maximum of 122 degrees Fahrenheit or 51 degrees Celsius) are very low. The Medoc device has safety features built into both the hardware and software. The risks associated with use of this equipment are less than those associated with common household appliances. Punctuate Probe Pain Testing: There is a very slight chance that the probe might superficially puncture the skin for individuals with "thin skin." 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. Cold Water Testing: There are no significant risks from immersion of a hand in cold water. Participants are informed that they can stop testing whenever they would like to do so. We have used the proposed laboratory pain procedures in a number of previous studies with healthy adults and chronic pain patients, including patients with KOA. No serious adverse effects were ever reported.

f. Blood draws: For participants that volunteer to undergo this part of the project, some discomfort may be associated with the drawing of blood samples, and there is a very small chance that phlebotomy may cause hematoma, infection, anemia and minor pain at the puncture site. However, these procedures are routinely performed without incident in medical settings.

g. Knee X-Rays: Knee X-rays expose participants to very low amounts of radiation. Knee x-rays will be conducted for research purposes in the current study, even though it is a procedure that would potentially be part of routine clinical care. The benefits of knee x-rays usually outweigh the minimal risk. Of note, our study physician will review incidental findings following the initial read by Dr. Auster and we will follow-up with participants/their providers as appropriate.

h. Physical Functioning Tasks: Minimal risks are associated with the 3 minute walking task, stair climb and timed up and go task. Participants may become fatigued or experience mild discomfort when completing the tasks.

i. Hair Testing: A small amount of hair will be cut from the head (not pulled). This is of minimal risk to participants.

j. 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. Hydromorphone will always be administered along with placebo in the first session, which will provide a valuable opportunity to exclude from further participation any participant who experiences untoward effects (e.g., nausea, vomiting) resulting from that dose of hydromorphone. 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.

To protect against risks of increased heart rate and tachycardia following co-administration of opioids and cannabinoids we will require all participants to be in good cardiovascular health prior to study enrollment (evidenced by a clean ECG, reviewed by a study physician). During sessions, all participants will be attached to a vital signs monitor and will have vital signs collected at 15 minute intervals for the first 2 hours to ensure safety. The risk of an opioid/cannabinoid interaction will only occur during a single study session, however since staff and participants will be blind as to the timing of that session, we will employ this monitoring schedule for all sessions. We will review data following completion of 5 participants and if it becomes evident that tachycardia is occurring regularly during any sessions, we will reevaluate the dose of study drugs being administered. However we believe that any changes to our dosing strategy are highly unlikely and this monitoring schedule will ensure participant safety during study participation.

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 all pain measures to prevent any tissue damage from occurring (e.g., hand cannot be in cold pressor task for >300 seconds). Fifth, participants will be informed that they can revoke their consent to participate in the pain testing at any time without penalty. Specific to capsaicin- 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. Finally, the participants will be monitored 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 IRB all adverse events reported from the pain testing session and will follow any recommendations they may have regarding the cessation of pain testing. Across hundreds of research participants with various conditions, we have had no adverse events deemed greater than mild (even this level AE occurs in < 1/100 cases) related to the use of these devices.

e**. IV Placement and Blood Draws:** These procedures are routinely performed without incident in medical settings and will be performed by a certified phlebotomist. Additionally, these procedures will only occur in a subset of participants that volunteer to undergo these procedures and can be stopped at any time without penalty.

f. Knee X-Rays: The X-rays will be read by a radiologist from the Division of Radiology within the Russell Morgan Department of Radiology, JHU. If they occur, incidental findings will be communicated to the study investigators who will communicate the result to the subject and an appropriate referral will be made if clinically indicated.

g. Physical Functioning Tasks: Minimal risks are associated with the 3 minute walk test, stair climb and timed up and go task, as these activities are part of everyday activity for most people. Should participants feel pain and be unable or unwilling to continue, they are instructed that they may stop at any time.

h. 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 in OA patients, 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.

This study is moderately intense so, given the older age (45+) of the population and the multiple drug and pain testing exposures, we have set compensation accordingly. Based on our extensive experience, remuneration will need to compensate for lost workdays and other inconveniences and will need to be high enough to encourage continued retention so that we are able to complete the study in the proposed period of time. Subjects will earn $100 for the in-person screening visit, and $150 for completing the first, $200 for the second, $250 for the third, and $325 for the fourth experimental session. For subjects that choose to participate in the blood drawing aspect of the study, an additional $100 will be earned for each session. Participants will be offered $25 for each hair sample provided, for a total of $50 for the optional substudy. We frequently use this approach to compensate subjects for individual sessions AND study completion, and found it to successfully promote retention in studies over multiple weeks.

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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