Cover page

Oral Cannabidiol for Opioid Withdrawal
NCT04238754
June 28, 2021

JHM IRB - eForm A – Protocol

- **Use the section headings to write the JHM IRB eForm A, inserting the appropriate material in each. If a section is not applicable, leave heading in and insert N/A.**
- **When submitting JHM IRB eForm A (new or revised), enter the date submitted to the field at the top of JHM IRB eForm A.**

****

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.

Based on preclinical research and emerging human research, cannabidiol (CBD; a major constituent of the cannabis plant) is a promising pharmacotherapy for the treatment of opioid withdrawal. Most recently, CBD decreased cue-induced craving and anxiety (two common withdrawal symptoms) among abstinent heroin-dependent individuals relative to placebo. Despite promising data, there are no funded studies which are prospectively designed to rigorously test the ability of CBD to decrease opioid withdrawal symptoms. As of June 2018, Epidiolex, an oral formulation of plant-derived pure CBD, has been approved by the U.S. Food and Drug Administration (FDA) for treating severe forms of epilepsy and can be prescribed for other off-label indications. Epidiolex has a low side effect and high safety profile. Preclinical evidence has suggested that the cannabinoid system contributes meaningfully to the opioid withdrawal syndrome and withdrawal symptom severity. Given the recent FDA approval of Epidiolex, and a growing interest to develop existing pharmaceuticals to address issues related to OUD and its recovery, we are proposing a pilot study to examine the safety of Epidiolex in a human laboratory model of clinically relevant withdrawal. Results may be used to support an R01 grant application to more closely examine this hypothesis.

2. Objectives

The objective of this research study is to collect data to support a NIDA grant application. Data collected for this study will establish: (1) the safety of administering two dosing regimens of Epidiolex within our withdrawal paradigm and (2) the feasibility of our withdrawal paradigm for demonstrating clinically meaningful increases in withdrawal.

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

The increasing prevalence of opioid use disorder (OUD) is a public health crisis contributing to substantial economic and societal burden[1 2]. The treatment of OUD, even with the most efficacious interventions, is characterized with high rates of relapse (i.e., > 50% relapsed within 6 months of treatment initiation)[3]. Managing withdrawal is critical for ensuring successful treatment retention and outcomes [4-8]. Adjunctive pharmacotherapy is one way to address persistent opioid withdrawal symptoms and craving. Based on preclinical research and emerging human research, cannabidiol (CBD; a major constituent of the cannabis

plant) is a promising pharmacotherapy for the treatment of OUD. There is preclinical support that the endocannabinoid system is influential in the expression of opioid withdrawal[9]. Cannabinoid type 1 (CB1) receptors are co-localized with mu-opioid receptors and cannabinoid agonists and endocannabinoid catabolic enzyme inhibitors have all shown evidence for opioid withdrawal suppression[9-11].

Over the last 40 years, preclinical evidence has accumulated indicating that CBD can mitigate symptoms of opioid withdrawal and decrease opioid seeking behavior in rodent models[12-18]. In clinical research, retrospective analyses indicate that the use of cannabis products may be helpful for increasing opioid treatment retention[19-21]. Two human lab studies (N= 6 and n = 42) on this topic demonstrated that a single dose of oral CBD decreased cue-induced craving and anxiety (two common withdrawal symptoms) among recently abstinent heroin-dependent individuals relative to placebo[22 23]. In an effort to further characterize the clinical utility of CBD, we recently conducted a crowdsourcing survey study which determined that individuals with OUD with CBD use indicated that CBD helped mitigate the following opioid withdrawal symptoms: anxiety (76%), sleep problems (45%), restlessness (36%), and/or bone/muscle aches (36%).

Despite promising data, there are no funded studies which are prospectively designed to rigorously test the ability of CBD to decrease opioid withdrawal symptoms. As of June 2018, Epidiolex, an oral formulation of plant-derived pure CBD, has been approved by the U.S. Food and Drug Administration (FDA) for treating severe forms of epilepsy and can be prescribed for other off-label indications. In September of 2018, the DEA determined Epidiolex was a schedule V drug, further reducing barriers to conduct research with this promising pharmacotherapy. Epidiolex is remarkable for its wide safety profile alone and with opioids and its negligible abuse liability and is therefore appealing to use among high-risk clinical populations. Therefore, we plan to conduct a pilot study to establish the feasibility of our withdrawal paradigm and the safety of cannabidiol to treat withdrawal in a controlled setting. Within this context, we have incorporated two cue-attentional bias tasks which will allow us to identify the mechanisms by which CBD may reduce cue-induced craving and anxiety and whether changes in cue-reactivity influences suboptimal decision making. First, the visual probe task will expose participants to opioid-related and neutral cues and evaluate the role of these cues in attentional bias. This protocol will include two periods of exposure to opioid-related cues. Length of visual cue-exposure represent distinct assays for attentional bias; cues shorter than 200 ms measure automatic processing, cues longer than 500 ms measure controlled attention processing. Previous research has shown CBD influences automatic processing for cigarette-related cues but not controlled processing. To date, this effect has not been studied for opioid-related cues. The second cue-task will evaluate whether the presence of opioid-related cues influence decisions about money. This will allow us to evaluate whether CBD impacts not only influences cue-reactivity but also related suboptimal decision making. While participants complete this task, we will also collect eye tracking data using the Gazepoint eye tracking device, which tracks eye movement on a computer screen with a machine-vision camera. These data may support a larger NIH grant application to study the efficacy and mechanisms of cannabidiol to treat opioid withdrawal in a rigorously controlled lab study.

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: This study is a within-subject comparison of placebo and 800 mg of CBD. Participant will attend two residential sessions. Participants will receive active drug during one session and placebo on the other. The sequence of the sessions (Placebo, Active or Active, Placebo) will be randomized for all participants. Each of the two inpatient sessions will last 3-days /2-nights and will be scheduled at least one week apart. During the sessions, participant's will not take their regular daily methadone dose in order to produce an abstinence-induced withdrawal syndrome, which will allow

researchers to replicate realistic elevations in withdrawal symptoms under controlled laboratory conditions[23]. This inpatient study design will provide a mechanism for rigorously assessing the initial feasibility and safety of CBD to mitigate clinically-relevant opioid withdrawal symptoms among individuals with opioid use disorder. Participants will take the study drug (800mg CBD/20mL) once every 12 hours for a total of 4 doses. This dosing regimen has been selected based upon evidence that four doses are required for Epidiolex to reach steady-state levels and that this dosing regimen is well-tolerated (23). Following study drug administration, participants will complete standardized opioid withdrawal measures and a behavioral task that can assess whether CBD reduces opioid valuation. At the end of the study, participants will be provided with their routine dose of methadone and transitioned back into methadone treatment. This model is a scientifically rigorous and feasible way to conduct this initial assessment and will provide the efficacy and safety data necessary to support a more thorough examination of CBD for opioid withdrawal management. This provides an expedient and cost-efficient way to collect the data necessary to support a formal NIDA R01 grant submission.

Recruitment/Screening. Participants will be recruited through methadone clinics using our established and successful methods, and through respondent driven sampling. We will provide incentives ($10) to participants who refer a potential participant to the study who completes a screening visit. Individuals will complete a phone-screen for initial eligibility requirements and be invited for a remote consenting and screening visit. During the COVID-19 crisis, participants will be consented virtually. Participants will be able to review the consent form electronically using a secure IRB compliant method, and will be able to securely sign and submit the form after they have been provided ample time to read and ask questions related to the protocol. Participants will promptly receive an electronic form of the consent and can also receive a printed version via mail, at their request. Virtual consenting will follow IRB guidelines for virtual consenting procedures and will occur prior to any data collection.

When possible, we will use DocuSign, the Institution's approved and 21 CFR Part 11-compliant software, to obtain a secure electronic signature. Once the IRB approves this process, we will use the IRB-approved consent form(s) as the base for the DocuSign template. The IRB-approved document will not be altered other than to overlay locations where signatures, initials, dates or other DocuSign fields will be added to create the study-specific DocuSign template. We will send the consent to the participant via DocuSign, providing a participant-specific code in advance of sending the document via DocuSign, that will be required when the participant accesses and signs the consent. The consent discussion may take place via phone or video conference (e.g. Zoom). Participants will be given adequate time to consider the research study and ask questions prior to signing the consent form. When ready to sign, the participant will enter their code, verifying that the person signing the consent is the person that we spoke with previously, and sign the consent within the DocuSign system. Once the participant has electronically signed, the study team member obtaining informed consent will be notified that the electronic form is ready for his or her signature. Once signing is completed by all parties, both the study team and the participant can download the signed consent as a PDF. The study team will also have access to the audit log and the Certificate of Completion.

Self-report portions of the screen, including several questionnaires related to their medical and mental health and drug use history, will be done virtually (via phone or Zoom) with study staff. For persons who do not have access to phones or when participant privacy might be challenging (e.g., for persons without stable housing), we will conduct self-report portions of the screen in a private room at the BPRU with Zoom connection to study staff in another room, to minimize participant/staff interaction. If deemed eligible based on self-report and interviewer-based questionnaires, participants will be scheduled to complete a brief in-person medical assessment consisting of a blood draw that will be tested for medical eligibility and a medical history and physical. Participants will also provide a urine sample to be tested for

evidence of illicit opioid and other drug use and pregnancy (if applicable). Participants will also complete computerized tasks (e.g., Visual Probe Task and the Cue-concurrent Choice Task) to characterize baseline drug cue reactivity. Participants will sign a medical release which will allow research staff to contact the participant's provider to confirm (1) methadone maintenance dose and length of dose. All participants will be asked to sign a contraception contract in which they will agree to use an effective form of birth control for up to 30 days following the final session day.

Session Procedures.

Description of procedures to minimize risk during the COVID-19 pandemic for in-person sessions: It is not possible to conduct a portion of the screening and the inpatient protocol remotely due to the need to collect biological measures (e.g., blood, urine) for eligibility determination and to have continuous medical supervision and care during the supervised taper. However, there are specific safety procedures that will be put into place to minimize person-to-person contact in the context of the COVID-19 pandemic. First, during all in-person sessions, all participants will be required to wear a properly fitting face surgical grade mask while in the laboratory. The exception to this policy will be when the participant is alone in their residential room at the Clinical Research Unit (CRU) with nobody else present. Facemasks which meet these requirements will be provided to participants at no cost. Second, participants will be asked about potential COVID-19 symptoms upon arrival to each session and possible exposure to COVID-19. Any subject who arrives reporting symptoms indicative of COVID-19 per the JHU clinical screening algorithm will be required to return home and participation will be paused for at least 2 weeks after which a health care professional must clear a return to participation (e.g., with a negative COVID-19 test). Third, participants must adhere to the CRU policies for COVID-19 which are uploaded in the supplemental document section. This will be provided to participants at a screening visit and/or the first day of their enrollment into the residential portion of the study.

The CRU policies stipulate that participants must remain in their residential rooms unless completing study related activities that must take place in another room (i.e., electrocardiograms). In order to address issues related to isolation or boredom, participants will have access to various recreational activities in their room including video games and stationary bicycling. Participants will also be allowed to bring materials from their home including books and magazines.

This will be a within subject comparison. Each participant will attend two 3-day inpatient sessions during which they will receive active drug during one session and placebo on the other. The placebo will be a flavor-matched cherry liquid syrup. 2 syringes of 10mL of Study Drug + Flavored syrup (4mL Epidiolex, 6mL flavored syrup per syringe) and 2 syringes of 10mL Placebo (flavored syrup) will be administered via the oral route under double-blind conditions. The sequence of the sessions (Placebo, Active or Active, Placebo) will be randomized and counter-balanced for all participants. Note that we do not anticipate safety issues with Epidiolex because of its extremely high safety profile. Participants will take the study drug once every 12 hours and will receive a total of 4 doses. This dosing regimen has been selected based upon evidence that four doses are required for Epidiolex to reach steady-state levels and that this dosing regimen is well-tolerated (23). Cannabidiol (Epidiolex) will be flavor-masked with cherry-syrup by our research pharmacy to ensure double-blind administration. Epidiolex dose and cherry syrup will be delivered in 2 x 10 mL oral syringes.

Eligible participants will attend two residential sessions that will last 3-days/2-nights. Study procedures will take place at the Behavioral Pharmacology Research Unit's Residential Research Unit (RRU) and the Clinical Research Unit (CRU); both located on the Johns Hopkins Bayview Medical Campus. Previous studies suggest this design will provide a sufficient observation period to produce abstinence-induced withdrawal (24). Patients will be instructed to arrive at the BPRU the morning of Day 1. Research staff will contact the participant's methadone prescribing clinic to confirm the participant did not receive their dose

that morning. After collecting vitals and testing a urine sample for pregnancy and to confirm abstinence from illicit drugs, participants will receive 50% of their prescribed methadone dose, which will be prepared by the BPRU pharmacy, to consume under staff observation at BPRU. This dose will produce modest suppression of participant opioid withdrawal for an acute period of time, which will provide an opportunity for them to become acquainted with the session procedures while still ensuring they will show prominent signs of withdrawal during the study period. Initial vitals and urine testing will take place at the BPRU. The participant then will be transferred to the CRU where they will remain until the end of the 3rd day. Participants will be assessed for symptoms of opioid withdrawal and complete measures of drug craving and anxiety periodically throughout Day 1. The first dose of study drug (placebo or Epidiolex) will be administered in the afternoon (e.g., 18:00 +/- 1:00 hour) on Day 1 at the CRU.

Participants will complete withdrawal ratings on a regular basis (e.g., every 4 hours) before and after study drug administration, except for when the participant is sleeping. This schedule will be based on the pharmacokinetic profile of CBD (21). Vital signs will also be measured every time withdrawal assessments occur (Figure 1).

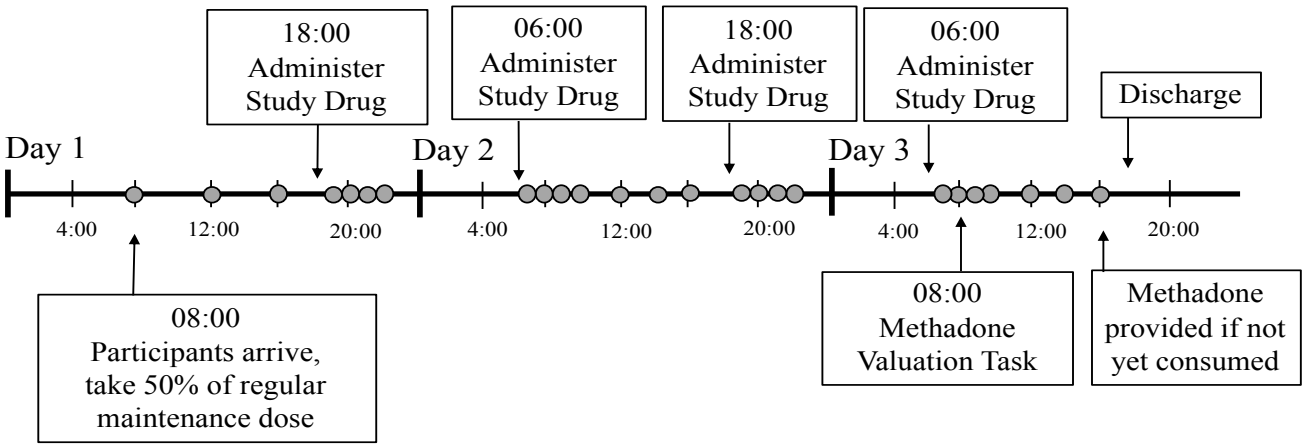

Figure 1. Timeline of inpatient session with approximate timing for study procedures. Gray circles indicate when measures of opioid withdrawal, craving, and anxiety are assessed.

On Day 3, participants will complete a cue-induced craving task and a Cue-concurrent Choice Task, and a Methadone Valuation Task described below. Withdrawal ratings will continue up to study discharge on Day 3 and acceptability ratings of the study drug will be collected prior to discharge. Participants will be discharged in the afternoon on Day 3, one hour after finishing the Methadone Valuation Task. At any point a participant can elect to resume regular methadone dosing and remain at the unit to complete study participation. However, participants who take their dose before beginning the Methadone Valuation Task he or she will not be able to participate in the Methadone Valuation Task. Finally, before participants leave, medical staff will collect a blood sample to be tested for liver enzyme levels. For an overview of study procedures, please reference Figure 1.

Methadone Valuation Task: The morning of Day 3, participants will complete baseline withdrawal ratings and be presented with the opportunity to take 50% of their usual methadone maintenance dose or earn money. For every 60 minutes up to 14:00 that the participant does not take the dose, they will earn a small amount of money (Total potential earnings= $100). At the end of the period, all participants who have not yet requested their methadone dose will receive it. All Day 3 methadone doses will be 50% of the participant's prescribed dose. Participants will be required to remain on the unit under observation until

17:00 to provide sufficient opportunity for peak effects of methadone to occur. At that time, all participants who show no signs of respiratory distress (SP02<96, respiration rate <8 breaths per minute) and feel safe to leave will be discharged.

All participants will be required to stay in the unit until 17:00, to prevent them from selecting methadone in order to end the study prematurely and to provide an opportunity for withdrawal to decrease in severity before they leave. The purpose of this task is to assess the objective, behavioral economic value the participant places on methadone as a withdrawal-relieving medication following accumulated exposure to Epidiolex vs. placebo. We have developed this task by translating preclinical methodology and we will use this opportunity to determine whether this task is an appropriate method to include in a formal R01 application.

Visual Probe Task: The effects of CBD on attentional bias to opioid-related cues will be evaluated with a visual probe task. In the task, a series of opioid (target) and composition-matched neutral (non-target) images are shown. Each trial begins with a fixation point before presenting a pair of images then appears on the left and right of the screen for either a short (e.g., 200 ms) or long (e.g., 500 ms) duration to assess automatic orientating and controlled attention processing, respectively. Image pairs are replaced by a probe (an arrow pointing upwards or downwards) in the location of either the neutral or opioid-related image. The probe remains on screen until the participant responds to identify the probe orientation (upwards or downwards) by pressing one of two appropriate response keys as quickly and accurately as possible (defined as a 'correct trial' if a correct response was made). Probes replace the opioid-related and neutral images equally often. The position of image type, probe location and stimulus duration is counterbalanced. Trials are displayed in a single block with each pair presented eight times, producing both critical and neutral trials. The task begins with four buffer trials. Trial order is randomized each time the task is run.

Cue-concurrent Choice Task: The effects of opioid-related cues on concurrent choice will be evaluated using a cued concurrent choice task. Participants will be instructed that they will be asked to make choices about different amounts of money that they would like to earn. Participants will be instructed that they should consider the choices carefully because they will randomly receive five of the monetary outcomes they chose. This task consists of a series of trials in which concurrent choice is evaluated between two monetary values (e.g., $0.10 versus $0.05). Each concurrent choice is immediately preceded by two visual stimuli presented side-by-side. On opioid trials, one image is opioid-related and the other is a paired neutral image. Opioid-related images include depictions of prescription pills or heroin and/or related drug paraphernalia. Paired neutral images are chosen to match the number of objects, color, and size of opioid images. On neutral filler trials, both images are unrelated to opioids or opioid paraphernalia (e.g., furniture pieces). All trials begin with a fixation point presented for 1000 ms in the center of the screen. The two visual stimuli then replaced the fixation point and are displayed for 2000 ms. Finally, a monetary value appears below each image and participants are instructed to select the monetary reinforcer they want to receive. Participants will receive their money choices from 20 random trials which could earn them an additional $5. Potential earnings will be explained prior to starting the task to increase engagement with the task.

Methadone Reinduction: At the end of the Methadone Valuation Task, all participants who have not yet requested the methadone dose will receive their dose. All Day 3 methadone doses will be 50% of the participant's prescribed dose. Participants will be required to remain on the unit under observation until 17:00 to provide sufficient opportunity for peak effects of methadone to occur. At 17:00, all participants who show no signs of respiratory distress (SP02<96, respiration rate <8 breaths per minute) and feel safe to leave will be discharged. Any participant who is unable to leave will be observed until he/she is safe ot

leave or will be readmitted to the CRU one additional night. Participants will be expected to return to routine care upon methadone reinduction and study discharge.

Diet Considerations: All participants will receive a calorie-controlled, low-fat, caffeine-free diet and grapefruit juice will not be permitted at any time. Food restrictions will be in place for 1 hour before and after study drug dosing to promote consistency in absorption across administrations and individuals.

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

The study consists of one screening visit and, if eligible, two 3-day/2-night inpatient sessions scheduled approximately 1 week apart.

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

All participants will receive placebo during one of the residential sessions to provide the most rigorous test of our study hypothesis that CBD will reduce the severity of some opioid withdrawal symptoms. This within-subject design will allow us to collect the strongest data with the smallest possible sample size.

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

Routine Care will be suspended for the purpose of causing spontaneous withdrawal to assess the primary study outcome. Participants will be returned to routine dosing upon completion of the residential study session.

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

A placebo control will be used to rigorously assess the study hypotheses.

f. Definition of treatment failure or participant removal criteria.

Participants will be removed from the study if they withdraw consent or are unable to tolerate the study procedures or medication. We will remove participants if they become noncompliant with study tasks or if information emerges that suggests the study procedures or drugs are contraindicated in the study sample.

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

Study participation will suspend standard of care treatment while participants are completing the inpatient study sessions. Upon discharge, and in the case of the study ending prematurely, treatment as usual will resume as it was prior to the study session. Participants will be fully informed about the study design so they can make an informed decision regarding their participation.

5. Inclusion/Exclusion Criteria

Inclusion Criteria:

- Aged 18-55
- Medically cleared to take study medication
- Are not pregnant or breast feeding

- Willing to comply with the study protocol
- Provides urine that tests positive for methadone
- Maintained on 40-120 mg of daily methadone with no dose changes in the past 2 weeks (verified through a medical release with the participant's provider)

Exclusion Criteria:

- Meet DSM-5 criteria for past year alcohol/substance use disorder other than opioid use disorder
- Previous adverse reaction to a cannabinoid product
- Urine sample that tests positive for drug other than methadone
- Self-report any illicit drug use or cannabinoid 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 events
- Past year suicidal behavior as assessed via the Columbia Suicide Severity Rating Scale
- History of seizure disorder
- Past 14 day use of any of the following contraindicated medications:
    - Clobazam, Valporate
    - Moderate or strong inhibitors of CY3A4 or CYPC19 (with the exception of methadone)
    - Strong CYP3A4 or CYP2C19 inducers
    - UGT1A9, UGT2B7, CYP1A2, CYP2C8, CYP2C9, CYP2C19 substrates (with the exception of caffeine).
    - CNS depressants that are contraindicated with Epidiolex
- Breathalyzer that tests positive for alcohol prior to session admission
- Self-reported consumption of grapefruit juice within 24 hours of session admission
- Have a history of clinically significant cardiac arrhythmias or vasospastic disease
- Have circumstances that the study investigators believe are contraindicated with study participation and/or would interfere with study participation (e.g., impending jail).
- Moderate-severe hepatic impairment as indicated by ALT or AST levels > 3x ULN and/or Bilirubin levels >2x ULND as evidenced by a blood test.

6. Drugs/ Substances/ Devices

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

Study Drugs: Cannabidiol and Methadone

a. *Cannabidiol (Epidiolex)* has been strategically chosen for this study because it is a widely-used, commercially-available Schedule V cannabinoid medication that is currently indicated for seizure control in persons with Lennox-Gastaut syndrome and severe infantile myoclonic epilepsy, but which could be prescribed off-label for the adjunctive treatment of clinical pain. **Epidiolex is the only FDA-approved formulation of cannabidiol and we are proposing to administer 800 mg**. Epidiolex has been administered safely to individuals with polydrug use in single doses up to 4500mg and in healthy participants in single doses up to 6000mg [24,25]. In open-label clinical trials among individuals with epilepsy and tuberous sclerosis complex patients, Epidiolex was well tolerated at doses up to 50 mg/kg/day (3500 mg/day in a 70 kg person) for a 3-month period[26,27]. Doses up to 1500mg twice daily were well tolerated among healthy adult participants for a 7-day period[25]. Epidiolex is an oral solution that will be purchased commercially, the research pharmacy will prepare the dose and a flavor-matched control for placebo dosing. A recent pharmacokinetic study reported that a 200mg dose of Epidiolex, administered orally, reached peak concentrations in 2-3 hours and had a half-life of 8-9 hours. It is highly lipophilic and subject to extensive first-pass metabolism via the CYP 1A1, 2D6, and 2C9 pathways, which yields an active

metabolite (7-OH-CBD). 7-OH-CBD is believed to contribute to cannabidiol's efficacy for seizure control and has a half-life of 13.3 hours, with no evidence of psychoactive effects[(143)].

Epidiolex is an oral solution that will be purchased commercially, and our research pharmacy will prepare the dose and a flavor-matched control for placebo dosing. A recent pharmacokinetic study reported that a 750mg dose of Epidiolex, administered orally, reached peak concentrations in 5-6 hours after administration. The same study reported that a 1500mg dose of Epidiolex, administered orally, reached peak concentrations 6-7 hours after administration. CBD is highly lipophilic and subject to extensive first-pass metabolism via the CYP 1A1, 2D6, and 2C9 pathways, which yields an active metabolite (7-OH-CBD). 7-OH-CBD is believed to contribute to cannabidiol's efficacy for seizure control and has a half-life of 13.3 hours, with no evidence of psychoactive effects.

b. Methadone Hydrochloride Oral Solution will be administered to participants at their prescribed dose or less for its indicated use (maintenance therapy for opioid use disorder). Using our standard procedure, we will procure the participant's written permission to contact his or her provider to confirm (1) the participant's enrollment in a methadone maintenance program for opioid dependence, (2) the participant's daily dose of methadone and (3) the length of time the participant has been maintained on their current dose. Methadone will be administered in a way that is within the participant's normal dosing regimen with the exception that we will be administering it at our residential research unit and that one dose will be less than what is normally prescribed (Day 1), another dose will be omitted (Day 2) and the final dose may be delayed (Day 3). Methadone is a commercially-available Schedule II medication that is currently indicated for management of pain, detoxification treatment of opioid addiction and maintenance treatment of opioid addiction.

Following oral administration, the bioavailability of methadone ranges between 36 to 100% and peak plasma concentrations are achieved between 1 and 7.5 hours. Published reports indicate that after multiple dose administration the apparent plasma clearance of methadone ranged between 1.4 and 126 L/h, and the terminal half-life (T1/2) was highly variable and ranged between 8 and 59 hours in different studies[28,29]. Methadone undergoes hepatic N-demethylation by cytochrome P450enzymes, principally CYP3A4, CYP2B6, CYP2C19 and to a lesser extent by CYP2C9 and CYP2D6. Since methadone is lipophilic, it has been known to persist in the liver and other tissues. The slow release from the liver and other tissues may prolong the duration of methadone action despite low plasma concentrations.

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.

Cannabidiol: Cannabidiol is a constituent of the cannabis plant that is being actively investigated for efficacy in a wide range of potential indications (including anxiety and alcohol/substance use disorders, as evidenced by clinicaltrials.gov entries) because of its unique pharmacological mechanisms of action. Specifically, it acts as an inverse agonist on the cannabinoid CB1 and CB2, as a 5-HT1a agonist, as a positive modulator of the transient receptor vallinoid-1 (TRPV1) receptor, and as an allosteric modulator of the mu and delta opioid receptors[10 11]. The only empirical human studies that have examined the effects of cannabidiol in the context of opioid use reported that cannabidiol can reduce opioid craving and associated anxiety in persons with opioid use disorder. There is preclinical support that the endocannabinoid system is influential in the expression of opioid withdrawal. Cannabinoid type 1 (CB1) receptors are co-localized with mu-opioid receptors and cannabinoid agonists and endocannabinoid catabolic enzyme inhibitors have all shown evidence for opioid withdrawal suppression[9 11]. Furthermore, over the last 40 years, preclinical evidence has accumulated indicating that CBD can mitigate symptoms of opioid withdrawal and decrease opioid seeking behavior in rodent models. Together these data suggest that CBD warrants further examination as a legitimate treatment for opioid withdrawal symptoms. Safety studies have demonstrated

that CBD is well-tolerated in combination with the highly potent opioid fentanyl among individuals with a history of opioid use disorder[28]. Finally, unlike some other cannabinoids, cannabidiol is believed to be relatively void of euphoric and psychoactive effects, as evidenced by an abuse liability examination that reported therapeutic (750mg) and supratherapeutic doses (1500mg and 4500mg) demonstrated little to no signal for abuse potential relative to alprazolam and dronabinol comparators[24].

Epidiolex will be administered via the oral route, which is the FDA-approved route of administration.

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.
Feasibility:

- Number of participants who complete the study as intended
- Peak change in withdrawal scores (Subjective Opiate Withdrawal Scale; SOWS[29]) during abstinence-induced withdrawal- this will provides evidence that withdrawal will be sufficiently quantifiable to use this model to examine Epidiolex suppression of withdrawal in a large-scale R01-type trial.

Safety:

- Frequency of Adverse Events (excluding symptoms of opioid withdrawal) reported under each condition (0, 800mg CBD)
- Number of participants whose AST/ALT levels >3xULN at the end of the session according to a blood test at the end of the active drug condition

Initial Efficacy:

- Efficacy will be assessed by comparing the following outcomes between the active (CBD) and placebo-dosing sessions:
    - Withdrawal symptom suppression, measured through daily self-report ratings of withdrawal on the SOWS, evaluated as Total score and individual scores. Scores will be evaluated using area-under-the-curve for each day as well as peak daily rating.
    - Number of 30-minute intervals for which the participant selected money over methadone during the methadone evaluation task

b. Secondary outcome variables.
Acceptability:

- Percent of participants who would recommend their medication to a family member or friend trying to taper down from opioid medications
- Visual analog ratings of the degree to which the medication suppressed opioid withdrawal symptoms
- Participant rating of medication acceptance on a 5-point acceptance rating scale
- Attentional bias measured by the visual probe task and the cue-concurrent choice task

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

This is a within-subject pilot study to support an R01 trial. Results will be primarily evaluated descriptively because the study will not be sufficiently powered or designed for formal between-group testing. Outcomes described above will be used as preliminary data within an R01 application.

d. Early stopping rules.

Participants will be discharged from the study if they leave the residential unit against medical advice, request to be removed from the study, express suicidal thoughts, are noncompliant with study tasks, or if new information becomes available to suggest this study may cause them more than minor harm.

The study will be stopped if any of the following criteria are met: 1) participant death during participant or 2) five participants have AST/ALT values 3X ULN at the end of the study relative to baseline (collected at screening) levels.

8. Risks

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

Risks Associated with Cannabidiol: Cannabidiol has few contraindications. It should not be administered to persons with known sensitivity to cannabidiol. Epidiolex is extensively metabolized by the liver, therefore persons with moderate-severe hepatic impairment (defined in the FDA product label as ALT or AST levels >3x ULN and/or Bilirubin levels >2x ULN) who might have different plasma concentrations of Epidiolex as a result of liver impairment will also be excluded. Epidiolex has been reported to produce somnolence or sedation in up to 32% of patients (compared to 11% of patients receiving placebo) and this may be further exacerbated in persons who are taking other CNS depressants. The FDA also recommends that persons receiving any antiepileptic drug, of which Epidiolex is one, be screened for suicidal behaviors prior to beginning drug administration. Additional side effects reported in clinical trial examinations of Epidiolex for seizure indications in adult and child populations include decreased appetite, diarrhea, weight decrease, gastroenteritis, lethargy, fatigue/malaise, insomnia, irritability/agitation, drooling, gait disturbance, rash, hypoxia, and infections. A determination of the safety of CBD during pregnancy has not yet been made.

Risks Associated with Methadone: The risks associated with methadone are well known and it is notable that we will not be administering any dose of methadone that is higher than the dose the participant already receives as part of his or her routine methadone maintenance treatment. The potential acute side effects of methadone relevant to our protocol include constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, and abdominal pain. Like other opioids, methadone is contraindicated in patients with respiratory depression or acute bronchial asthma or hypercarbia.

Both methadone and Epidiolex are metabolized by CYP3A4. Although methadone will not be co-administered with Epidiolex, it is possible that methadone may still be undergoing metabolization early in the study because of its long half-life. We will monitor for any adverse events and believe there will be little risk of negative interactions because Epidiolex will be titrating up as methadone plasma levels are decreasing. The most likely effect is that participants will experience a more delayed onset in withdrawal from methadone, which we will be able to visualize as a result of our placebo control condition.

b. Steps taken to minimize the risks.

Protection against Epidiolex risks: We have experience in the administration of study medications in laboratory settings and therefore anticipate few problems. Participants 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. We will also conduct psychiatric screening during the Screening session to ensure that patients with current or history of psychiatric events, namely history of suicidality, 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. Both methadone and Epidiolex are metabolized by CYP3A4. Although methadone will not be co-administered with Epidiolex, it is possible that methadone may still be undergoing metabolization early in the study because of its long half-life. We will monitor for any adverse events and believe there will be little risk of negative interactions because Epidiolex will be titrating up as methadone plasma levels are decreasing. The most likely effect is that participants will experience a more delayed onset in withdrawal from methadone, which we will be able to visualize as a result of our placebo control condition.

Protection Against Methadone Risks*:* Our group has experience in the administration of methadone and other opioids in laboratory settings and anticipate few problems. Importantly, we will not administer methadone in amounts greater than what is normally prescribed to the participant. All drug administration will take place at the residential research unit under supervision of medical and research staff.

c. Plan for reporting unanticipated problems or study deviations.

All study events will be monitored during weekly meetings between the study investigators and we will follow all IRB guidance and recommendations regarding the reporting of unanticipated problems of study deviations. All such problems and deviations will be documented and if they do not meet the criteria for immediate reporting, they will be submitted to the IRB as part of the continuing review (or when otherwise requested).

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

Participants are all receiving methadone for the purpose of OUD outside of the study activities, and we do not believe this study poses any legal risks associated with breach of confidentiality.

e. Financial risks to the participants.

Participants will not incur any cost for study participation. All study medications will be provided to them at no cost.

9. Benefits

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

There is no direct benefits to participants for participating in the study. This information will be used to support a NIDA-grant application that will help launch Co-I Bergeria's research career. In addition, this information has incredible value for society, by evaluating improved methods

for managing withdrawal we will be able to provide empirical information to help inform providers as to whether CBD is an appropriate treatment resource. This is also important because CBD is widely-endorsed as providing therapeutic benefit but there is little-to-know empirical support for this approach. Thus, our data will be among the first to provide insight into the safety profile and potential efficacy of combining CBD with methadone in persons with OUD.

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 completing the screening visit. Participants will be paid $900 for study participation ($450/session), up to $5 for the cue-concurrent choice task at the end of each session, and will have the opportunity to earn an additional $100 in the behavioral task at the end of each session, for a total potential earning of $1140. This compensation is consistent with our previous studies. Participants will be compensated using reloadable credit cards that do not permit money to be withdrawn from ATMs so will not receive cash payments.

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 costs will be paid for by the study.

1. Birnbaum HG, White AG, Schiller M, et al. Societal costs of prescription opioid abuse, dependence, and misuse in the United States. *Pain medicine (Malden, Mass)* 2011;12(4):657-67. doi: 10.1111/j.1526-4637.2011.01075.x [published Online First: 2011/03/12]
2. Han B, Compton WM, Blanco C, et al. Prescription Opioid Use, Misuse, and Use Disorders in U.S. Adults. *Annals of internal medicine* 2018;168(5):383-84. doi: 10.7326/l17-0700 [published Online First: 2018/03/07]
3. Lee JD, Nunes EV, Jr., Novo P, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. *Lancet (London, England)* 2018;391(10118):309-18. doi: 10.1016/s0140-6736(17)32812-x [published Online First: 2017/11/19]
4. Gowing L, Ali R, White JM. Buprenorphine for the management of opioid withdrawal. *The Cochrane database of systematic reviews* 2009(3):Cd002025. doi: 10.1002/14651858.CD002025.pub4 [published Online First: 2009/07/10]
5. Northrup TF, Stotts AL, Green C, et al. Opioid withdrawal, craving, and use during and after outpatient buprenorphine stabilization and taper: a discrete survival and growth mixture model. *Addictive behaviors* 2015;41:20-8. doi: 10.1016/j.addbeh.2014.09.021 [published Online First: 2014/10/06]
6. Whitley SD, Sohler NL, Kunins HV, et al. Factors associated with complicated buprenorphine inductions. *Journal of substance abuse treatment* 2010;39(1):51-7. doi: 10.1016/j.jsat.2010.04.001 [published Online First: 2010/08/05]
7. Magura S, Nwakeze PC, Demsky SY. Pre- and in-treatment predictors of retention in methadone treatment using survival analysis. *Addiction* 1998;93(1):51-60. [published Online First: 1998/06/13]
8. Gossop M, Marsden J, Stewart D, et al. Outcomes after methadone maintenance and methadone reduction treatments: two-year follow-up results from the National Treatment Outcome Research Study. *Drug and alcohol dependence* 2001;62(3):255-64. [published Online First: 2001/04/11]
9. Dunn KE, Huhn AS, Bergeria CL, et al. Non-Opioid Neurotransmitter Systems that Contribute to the Opioid Withdrawal Syndrome: A Review of Preclinical and Human Evidence. *The Journal of pharmacology and experimental therapeutics* 2019 doi: 10.1124/jpet.119.258004 [published Online First: 2019/08/09]
10. Bloomfield MAP, Hindocha C, Green SF, et al. The neuropsychopharmacology of cannabis: A review of human imaging studies. *Pharmacology & therapeutics* 2019;195:132-61. doi: 10.1016/j.pharmthera.2018.10.006 [published Online First: 2018/10/23]
11. Kathmann M, Flau K, Redmer A, et al. Cannabidiol is an allosteric modulator at mu- and delta-opioid receptors. *Naunyn-Schmiedeberg's archives of pharmacology* 2006;372(5):354-61. doi: 10.1007/s00210-006-0033-x [published Online First: 2006/02/21]
12. Bhargava HN. Effect of some cannabinoids on naloxone-precipitated abstinence in morphine-dependent mice. *Psychopharmacology* 1976;49(3):267-70. [published Online First: 1976/09/29]
13. Markos JR, Harris HM, Gul W, et al. Effects of Cannabidiol on Morphine Conditioned Place Preference in Mice. *Planta medica* 2018;84(4):221-24. doi: 10.1055/s-0043-117838 [published Online First: 2017/08/10]
14. Chesher GB, Jackson DM. The quasi-morphine withdrawal syndrome: effect of cannabinol, cannabidiol and tetrahydrocannabinol. *Pharmacology, biochemistry, and behavior* 1985;23(1):13-5. [published Online First: 1985/07/01]
15. Katsidoni V, Anagnostou I, Panagis G. Cannabidiol inhibits the reward-facilitating effect of morphine: involvement of 5-HT1A receptors in the dorsal raphe nucleus. *Addiction biology* 2013;18(2):286-96. doi: 10.1111/j.1369-1600.2012.00483.x [published Online First: 2012/08/07]
16. de Carvalho CR, Takahashi RN. Cannabidiol disrupts the reconsolidation of contextual drug-associated memories in Wistar rats. *Addiction biology* 2017;22(3):742-51. doi: 10.1111/adb.12366 [published Online First: 2016/02/03]
17. Ren Y, Whittard J, Higuera-Matas A, et al. Cannabidiol, a nonpsychotropic component of cannabis, inhibits cue-induced heroin seeking and normalizes discrete mesolimbic neuronal disturbances. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 2009;29(47):14764-9. doi: 10.1523/jneurosci.4291-09.2009 [published Online First: 2009/11/27]
18. Russo EB, Burnett A, Hall B, et al. Agonistic properties of cannabidiol at 5-HT1a receptors. *Neurochemical research* 2005;30(8):1037-43. doi: 10.1007/s11064-005-6978-1 [published Online First: 2005/11/01]
19. Socias ME, Wood E, Lake S, et al. High-intensity cannabis use is associated with retention in opioid agonist treatment: a longitudinal analysis. *Addiction* 2018;113(12):2250-58. doi: 10.1111/add.14398 [published Online First: 2018/09/22]
20. Scavone JL, Sterling RC, Weinstein SP, et al. Impact of cannabis use during stabilization on methadone maintenance treatment. *The American journal on addictions* 2013;22(4):344-51. doi: 10.1111/j.1521-0391.2013.12044.x [published Online First: 2013/06/26]
21. Bisaga A, Sullivan MA, Glass A, et al. The effects of dronabinol during detoxification and the initiation of treatment with extended release naltrexone. *Drug and alcohol dependence* 2015;154:38-45. doi: 10.1016/j.drugalcdep.2015.05.013 [published Online First: 2015/07/19]

22. Hurd YL, Yoon M, Manini AF, et al. Early Phase in the Development of Cannabidiol as a Treatment for Addiction: Opioid Relapse Takes Initial Center Stage. *Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics* 2015;12(4):807-15. doi: 10.1007/s13311-015-0373-7 [published Online First: 2015/08/14]
23. Hurd YL, Spriggs S, Alishayev J, et al. Cannabidiol for the Reduction of Cue-Induced Craving and Anxiety in Drug-Abstinent Individuals With Heroin Use Disorder: A Double-Blind Randomized Placebo-Controlled Trial. *The American journal of psychiatry* 2019;176(11):911-22. doi: 10.1176/appi.ajp.2019.18101191 [published Online First: 2019/05/22]
24. Schoedel KA, Szeto I, Setnik B, et al. Abuse potential assessment of cannabidiol (CBD) in recreational polydrug users: A randomized, double-blind, controlled trial. *Epilepsy & behavior : E&B* 2018;88:162-71. doi: 10.1016/j.yebeh.2018.07.027 [published Online First: 2018/10/05]
25. Taylor L, Gidal B, Blakey G, et al. A Phase I, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose, Multiple Dose, and Food Effect Trial of the Safety, Tolerability and Pharmacokinetics of Highly Purified Cannabidiol in Healthy Subjects. *CNS drugs* 2018;32(11):1053-67. doi: 10.1007/s40263-018-0578-5 [published Online First: 2018/10/31]
26. Devinsky O, Marsh E, Friedman D, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. *The Lancet Neurology* 2016;15(3):270-8. doi: 10.1016/s1474-4422(15)00379-8 [published Online First: 2016/01/03]
27. Thiele EA, Marsh ED, French JA, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet (London, England)* 2018;391(10125):1085-96. doi: 10.1016/s0140-6736(18)30136-3 [published Online First: 2018/02/06]
28. Manini AF, Yiannoulos G, Bergamaschi MM, et al. Safety and pharmacokinetics of oral cannabidiol when administered concomitantly with intravenous fentanyl in humans. *Journal of addiction medicine* 2015;9(3):204-10. doi: 10.1097/adm.0000000000000118 [published Online First: 2015/03/10]
29. Handelsman L, Cochrane KJ, Aronson MJ, et al. Two new rating scales for opiate withdrawal. *The American journal of drug and alcohol abuse* 1987;13(3):293-308. doi: 10.3109/00952998709001515 [published Online First: 1987/01/01]