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June 20, 2025

Re: NCT05076370

Attached please find the most recent protocol for the study, “Safety and Tolerability of Cannabidiol Among Persons with Opioid Use Disorder Receiving Methadone or Buprenorphine” (PI: De Aquino; NCT05076370).

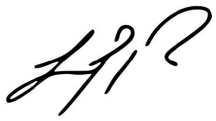
The goal of the study is to examine the safety, tolerability, and efficacy of oral cannabidiol (Epidiolex) as an adjunctive treatment for persons with comorbid opioid use disorder and chronic pain who receive opioid agonist maintenance treatment.

This human laboratory crossover study will include a total of 40 participants across two consecutive phases: One open-label phase including 6 participants (NCT05076370), and one placebo-controlled phase including 34 participants (NCT04587791). We obtained initial approval for the open-label study on 07/02/2020, and continuing reapproval for the placebo-controlled phase on 04/17/2025.

In the open-label phase, we administered single doses of 400 mg, 800 mg, and 1200 mg of CBD, across 3 test sessions, using a dose-escalation paradigm. The open-label phase will ensure the collection of critical safety data and inform the subsequent placebo-controlled phase. The placebo-controlled phase will administer placebo, 400 mg, 800 mg, and 1200 mg of CBD, across 4 test sessions, in a random order. This study is conducted at the VA Connecticut Healthcare System and at Yale University and has been approved by the Institutional Review Board of both institutions (VA Connecticut Healthcare Human Subjects Subcommittee and Yale University Human Investigation Committee).

Attached please find the up-to-date study protocol. If you have any questions, please do not hesitate to contact me at 203- 923-5711 Ext. 12916 or at the email address provided in this letter.

Sincerely,



Joao P. De Aquino, M.D.

A. PRINCIPAL INVESTIGATOR: Joao P. De Aquino, M.D.*

B. CO-INVESTIGATORS: Mehmet Sofuoglu, M.D., Ph.D.*, Mohini Ranganathan, M.D.*, Suprit Parida, M.D.*

Authorized Prescribers: Joao P. De Aquino, M.D., Mehmet Sofuoglu, M.D., Ph.D., Mohini Ranganathan, M.D., Suprit Parida, M.D., Julio Nunes, M.D.*, Scott Matthews, M.D.*

Research Personnel: Stephanie Dwy, R.N.*, Stacy Minnix, B.S.W.*, Christopher Cryan*, Julia Meyerovich, M.S.*, Rebecca Suh, B.A.*, Simon Asnes, B.S.*

* will have access to PHI and be able to obtain informed consent

C. TITLE: Cannabidiol Pharmacotherapy for Comorbid Opioid Use Disorder and Chronic Pain

D. PURPOSE:

The overarching goal of this study is to evaluate the potential of Cannabidiol (CBD) as an adjunctive treatment for comorbid opioid use disorder (OUD) and chronic pain. This is a randomized, placebo-controlled, crossover human laboratory study investigating the dose-dependent safety and acute effects of CBD on measures of pain and opioid craving in outpatients with OUD receiving medication-assisted treatment (MAT) with methadone or buprenorphine.

D.1. Hypothesis:

Treatment with CBD will be safe and well tolerated, and lead to improvement in vulnerability states that underlie the risk of relapse. Specifically, we hypothesize that:

a. *Primary Hypothesis:*
   - Acute administration of CBD will be safe and well-tolerated by people with comorbid OUD and chronic pain who are on opioid agonist maintenance. Safety will be thoroughly measured with the Systematic Assessment for Treatment Emergent Events (SAFTEE) for adverse effects, the Drug Effects Questionnaire (DEQ) for abuse potential, and the Continuous Performance Test (CPT) and the Hopkins Verbal Learning Test (HVLT) for cognitive effects of CBD.

b. *Secondary Hypotheses*:
   - Acute administration of CBD will lead to reduction of pain sensitivity, measured by assessments that include Quantitative Sensory Testing (QST) of thermal pain.
   - Reduction of cue-induced craving and attentional bias to opioid cues, measured by assessments that include a visual probe task and the Heroin Craving Questionnaire (HCQ-14).

c. *Exploratory Hypotheses*:
   - The above-mentioned effects will be influenced by the participants' biological sex.

E. BACKGROUND:

E1. The need to develop novel treatments for comorbid OUD and chronic pain. In the grip of the opioid crisis, it has been increasingly recognized that OUD and chronic pain have multiple points of interface. Growing evidence has shown that opioids increase pain sensitivity over time [1,2]. Opioid craving and chronic pain also share clinical features and neuroadaptive traces that promote frequent relapse [3]. Consequently, efforts to treat people with comorbid OUD and chronic pain have only been partially successful [4]. Particularly among this population, opioid agonist maintenance may provide limited pain and craving relief [5]. As result of inadequately treating these clinically relevant processes, the risk of relapse is increased.

While methadone is still a widely used medication for comorbid OUD and chronic pain, not only it is associated with pain hypersensitivity (hyperalgesia), but as a full opioid agonist, it causes dose-dependent gastrointestinal, cardiac, endocrine, and immune adverse effects – leading to lower quality of

life and high utilization of healthcare services [6-9]. Collectively, these challenges highlight the need for novel therapeutics that can be used alone or in combination with opioid agonists.

E2. The endocannabinoid (eCB) system as an emergent treatment target for comorbid OUD and chronic pain. The endogenous opioid and the eCB systems share signaling pathways central to pain control and reward [10,11]. Consistent with this notion, mounting preclinical data indicate that cannabinoids may curtail pain and opioid-seeking behavior. A meta-analysis of dozens of non-human primate and rodent studies showed that the opioid dose required to produce the same acute analgesic effect was up to 9.5 times lower, when co-administered with a cannabinoid agonist [12]. Further, convergent research shows that cannabinoids may reduce opioid self-administration in animals made opioid-dependent [13-15]. Importantly, these synergistic interactions between cannabinoids and opioids may be leveraged for treatment purposes, as their co-administration does not potentiate hypoactivity and respiratory depression [15].

E3. Scientific evidence vs. public opinion regarding the therapeutic efficacy of cannabinoids. To this date, 62% of U.S. states have authorized the use of cannabinoids for chronic pain [16]. A growing number of states have also added OUD to the list of qualifying conditions [17]. In stark contrast, treatment services for OUD and chronic pain often demand abstinence from cannabinoids as a sign of clinical stability [18]. Such discrepancy accentuates the need for high-quality clinical research. In healthy humans, a meta-analysis of experimental studies indicates that cannabinoids increase pain threshold and tolerability, likely by influencing affect-related pain modulation in the central nervous system [19]. Dysfunction in pain modulation is core feature of chronic pain, aggravating treatment refractoriness when OUD and chronic pain are comorbid [1,4,20-22]. Yet, in disproportion to the clinical significance of the problem, thus far all prior studies investigating the efficacy of cannabinoids for pain relief excluded people with OUD. Only two studies examined the effects of oral delta-9-tetrahydrocannabinol (THC), the main psychoactive component of cannabis, on people with chronic pain on long-term opioid analgesic therapy (LTOT) [23,24]. Although these studies suggested synergistic analgesia between opioids and THC, it is not clear if the results are generalizable to chronic pain patients with OUD. Further, there has been some concern about the use of THC, a compound with abuse potential, among individuals with OUD. Hence, nearly all the evidence on how cannabinoids affect people with OUD is observational, and the effects of cannabinoids in comorbid OUD and chronic pain remain to be studied systematically [25-29].

E4. Why Cannabidiol (CBD)? CBD is a non-addictive cannabinoid with a wide safety margin – an especially important consideration for people with comorbid OUD and chronic pain. In 2018, CBD received FDA approval for treating rare forms of epilepsy [30]. Since then, marked enthusiasm has mounted surrounding novel therapeutic applications, including chronic pain and OUD. CBD's anti-hyperalgesic and analgesic properties have been established across various preclinical models of pain (i.e., neuropathic, thermal, and inflammatory) [31-38]. Among the mechanisms proposed to account these properties is the suppression of brain- and spinal- mechanisms of central pain-sensitization [39-41]. CBD is also believed to enhance affect-related pain inhibition in key brain areas responsible for modulating pain [42]. Moreover, converging preclinical and human data indicate CBD's potential to reduce opioid craving and relapse [43,44]. In a human laboratory study involving recently abstinent people with OUD, oral CBD (400 or 800 mg) reduced cue-induced opioid craving, with large effect sizes [45]. Notably, cue-induced craving is a key mechanism in relapse that is not adequately treated by opioid agonist treatments [46]. Altogether, CBD's pharmacological profile draws attention as a compelling two-pronged strategy to improve the treatment of people with comorbid OUD and chronic pain, who are heavily represented in populations receiving methadone maintenance [47].

Although CBD has been safely co-administered with fentanyl in humans [48], it has not yet been given with methadone or buprenorphine. The high prevalence of chronic pain among people receiving methadone and buprenorphine maintenance, combined with the frequent and controlled dispensation, offers advantages in terms of participant safety, feasibility, and recruitment.

Hence, this study will entail a human laboratory study establishing the safety of CBD in people with comorbid OUD and chronic pain who are on methadone or buprenorphine. This study will assess the effects of CBD on key treatment targets – pain sensitivity and cue-induced opioid craving. In this

manner, this study will yield information not only on the safety of CBD, but also on CBD's optimal analgesic and anti-craving dose for OUD and chronic pain.

In summary, this study will evaluate the safety and efficacy of CBD for comorbid OUD and chronic pain, which cause extremely high morbidity and mortality nationwide. Since high pain sensitivity, cue-induced craving, and attentional bias for opioid cues increase the risk of relapse in this population, a human laboratory study will improve our understanding of the dose-related safety and efficacy of CBD to counteract these processes.

F. SIGNIFICANCE:

As outlined above, CBD has shown potential for improving several vulnerability states that underlie the risk of relapse. CBD's novel mechanisms of action as compared to the currently available drugs to treat OUD and chronic pain, and extremely favorable side effect profile, make it a compelling compound for investigation as novel agent to treat comorbid OUD and chronic pain – both to expand upon the currently available therapeutics and to limit the medical comorbidity associated with current therapies.

G. PARTICIPANTS:

An initial safety pilot phase will recruit six participants: three receiving treatment with methadone and three receiving treatment with buprenorphine. If the results of the pilot study support the safety of CBD administration in this clinical sample, 75 participants will be enrolled for the general study with comorbid OUD and chronic pain, for a total of 34 completers – 22 subjects (11 men and 11 women) receiving methadone and 12 subjects (6 men and 6 women) receiving buprenorphine. This number of enrolled participants is expected to account for both screen fails and dropouts. Both sub-studies will enroll participants who do not currently require an inpatient hospitalization.

G.1. Inclusion Criteria:

- Males and females, Veterans and non-Veterans, aged between 18 and 70 years old.
- Diagnosed with OUD and currently enrolled in methadone or buprenorphine maintenance treatment.
- Having chronic pain, uniformly operationalized as grade II (high-intensity) non-cancer pain for $\geq$ 6 months [49].
- Capable of providing informed consent in English.
- Compliant in opioid maintenance treatment and on a stable dose for four weeks or longer.
- Not meeting DSM-5 criteria for substance use disorders other than OUD or tobacco use disorder within the last 12 months.
- No current medical problems deemed contraindicated for participation by principal investigator.
- For women, not pregnant as determined by pregnancy screening; not breast-feeding; using acceptable birth control methods. Acceptable contraception for females includes oral contraceptives, contraceptive depot injections, contraceptive subdermal implants, intrauterine devices, or surgical contraception methods. Acceptable contraception for males includes condoms or surgical contraception methods.

G.2. Exclusion Criteria:

- Other current major psychiatric disorders deemed clinically unstable by the principal investigator, such as severe depression and/or active suicidal ideation.
- Having experienced major psychosocial stressors recently (≤ 6 weeks before enrollment), at the discretion of the principal investigator.
- Methadone dose under 30 mg or over 150 mg/day.
- Buprenorphine dose over 24 mg per day.
- Having received inpatient psychiatric treatment recently (≤ 60 days before enrollment).
- Candidates receiving products containing either THC or CBD will be excluded. All participants will be asked to abstain from cannabinoids. Prior to receiving the study medication on the first test session, participants' cannabinoid use will be assessed using a quantitative point-of-care

urine 11-nor-9-carboxy-THC concentration test with a cut-off of ≤ 50 mg/mL [146,147]. If a participant tests greater than ≤ 50 mg/mL, they will be asked to abstain for an additional 7 to 14 days. If 14 days after their initial THC concentration test the participant continues to test positive, they will not be allowed to participate in the study.

- A physician will carefully evaluate participants for use of over-the-counter or prescription psychoactive drugs known to affect pain threshold or pain tolerance (including NSAIDS, serotonin-norepinephrine reuptake inhibitors (SNRIs) (e.g. venlafaxine, duloxetine), gabapentinoids, tricyclic antidepressants (e.g., nortriptyline, amitriptyline), anticonvulsant medications (e.g., topiramate, carbamazepine)). Only participants who are on stable doses (i.e., consistent daily administration of the medication for at least three months at the same dose following the last dose change, either increase or decrease) of these medications, and whose dosing schedules allow participation in the study visits, thus excluding instances of single-dose or temporary dosing of the medication, will be eligible as determined by principal investigator. If possible, the morning dose will be administered after the study visit.
- Current, regular use of benzodiazepines, other prescription opioids, or platelet inhibitors (e.g., clopidogrel, apixaban, ticagrelor).
- Current weight of less of 60 kg.
- Allergy to sesame seed oil, which is an ingredient of the CBD formulation used.
- Serious medical or neurological illness or treatment for a medical disorder that could interfere with study participation as determined by principal investigator.
- Participants who have elevation of liver enzymes (ALT and/or AST) 2x above the normal limit or higher.

H. PRIVACY:

All information that is obtained from participants will be used for the specifically stated purposes that are described in this Project Description, and after approval by the HSS. The personal identifiers that are necessary for this research and that will be obtained are the following: Name, Medical Record Number, Age, Gender, Medical and Psychiatric History, and Laboratory Examination. The procedures for data collection and recruitment of participants, described elsewhere in the project description, are the least intrusive consistent with obtaining the information necessary to complete this project.

Mehmet Sofuoglu M.D., Ph.D., Joao P. De Aquino, M.D., and Ellen Mitchell R.N will review medical records to extract research information. All members of the research team will review, use, and record the minimum amount of information necessary to accomplish the goals outlined in the protocol. No study related procedures will invade into participant's privacy.

All members of the research team have been trained on HIC and VHA privacy regulations and policies and training are current. The data collected as part of this study may be made available to the VA, the US FDA, and NIDA. Participants are informed of these possibilities in the consent form. Demographic and outcome data described earlier will be collected as part of this study. Personnel listed on protocol will have access to data containing PHI. As noted above, limited PHI may be disclosed to the FDA, as required.

The settings in which informed consent discussions, other participant interviews or research procedures occur will provide the same privacy protections that would exist if these discussions, interviews, or procedures were carried out for required clinical care (private rooms, drawn curtains, etc.). The information will be used for this project, or disclosed to others, only as permitted by the Privacy Act, the HIPAA Privacy Rule, and VA policy.

The hardcopy data will be stored in locked file cabinets on the campus of VA Connecticut Healthcare System. Some electronic data including demographic data, screening data, laboratory data and RN/MD progress notes about each visit, etc. will be stored on the VA CPRS system.

I. SELECTION:

Participants will be recruited through the VA methadone and buprenorphine clinics, as well as through community (i.e., APT Foundation and New Era) and Opioid Treatment Programs. After the initial phone screening, potential participants will undergo a comprehensive evaluation, which will include medical, psychiatric, and drug use histories as well as physical, psychiatric, and laboratory examinations (see K.2. “Screening”).

If participants are noncompliant (i.e., repeated no-shows) participation will be terminated.

J. RECRUITMENT:

Potential participants will be identified through responses to flyers, web postings craigslist, as well as clinicaltrials.gov and BuildClinical. Furthermore, the research team will reach out to local mental health and substance use disorder treatment facilities – including local methadone and buprenorphine clinics – for patient referrals.

Participants will be asked to contact research staff through the advertisement methods listed above. If a participant responds to an advertisement, they will be contacting study staff. If a participant is referred from substance use disorder or mental health facility, research staff will require that the participant’s clinician contacts the participant first and then refers the participant to the research clinic. Participants known to us from participation in other studies who agreed to be re-contacted will also be contacted.

The PI and some co-investigators may provide clinical care to some potential participants and/or may work in the clinic where some potential participants are treated.

J.1. Build Clinical Screening: Build Clinical is an additional service that improves the predictability of recruitment. It involves operationalizing the study’s enrollment criteria in an online questionnaire, ahead of the phone screening. Build Clinical services have been successfully utilized by several investigatory at Yale and State of Connecticut Department of Mental Health and Addiction Services

J.2. Phone Screening: Participants who respond to the various recruitment strategies will be provided the Mental Illness Research, Education and Clinical Center (MIRECC) central recruitment telephone number to contact a member of the research team. At the first telephone contact, a brief telephone prescreening will be conducted with the verbal assent of the participant. The purpose of the prescreening is to save both potential participants and the research staff a considerable amount of time and effort. Participants find it quite burdensome to commit the time and effort for a face-to-face screening only to find out that they are ineligible for some obvious exclusion criterion e.g., age. At the very beginning of the telephone prescreening, potential participants will be first provided a summary of the studies they may be interested in. They will also be asked about allergies that may interfere with participation in the study (i.e., sesame allergies).

If a participant expresses an interest in participating in one of the studies, the participants will be told the following:

> “*We would like to ask you some general information to determine whether you might qualify for the study. This information will only be used to determine your eligibility to participate in research. This information will be stored in secure research files. If you do not want any information about you stored, we will terminate this interview now. If you agree to proceed ahead with this preliminary interview and seem to be eligible to participate in this study, we may invite you for a face-to-face meeting.*”

If they pass the initial brief screening for the study, they will then come into the clinic for a full screening evaluation. Upon arrival, the participants will be given the detailed consent form to read and will be asked questions to make sure that the participants understand the procedures and their rights and written informed consent will be obtained. Information collected during the phone screen will only be used if the participant continues to participate in the study.

J.3. Face to Face Screening: This will include written informed consent followed by screening procedures. Please see screening section under research plan for more details.

J.4. Consent Procedures: Potential participants will be invited to meet with the research staff, who will fully explain the risks and procedures as outlined in the consent form. After reviewing this information and answering questions, informed consent will be obtained from all participants. A copy of the consent form will be provided to all participants. After signing the consent form, participants will proceed with screening. Once all screening procedures have been collected, research staff as well as the principal investigator will review all relevant information and determine, based on the inclusion and exclusion criteria, if the participant will be enrolled in the study and continue with the remaining study procedures. Participants already on pharmacotherapy specified in the protocol will continue use of the medications while participating in the current study. Participants will not be taken off their current medications for participation in this study.

K. RESEARCH PLAN:

K.1. Study design: This project will consist of 2 sub-studies.

K.1.1. Pilot safety data sub-study: The first study will be a pilot study in which 6 participants (3 receiving methadone, and 3 receiving buprenorphine) will receive ascending doses of CBD, to determine its safety and tolerability of this medication. Participants will be stratified based on whether they are receiving methadone and buprenorphine. This open-label phase will inform the conduction of the general study. Participants will be receiving either buprenorphine (up to 24 mg/day sublingual tablets) or methadone from their designated opioid treatment program and will thereby be at steady state at enrollment. Participants will receive consecutive doses of 400 mg, 800 mg, and 1200 mg, over a total of 3 test sessions, with at least 72 hours of interval between each test session, using a dose-escalation paradigm.

If we encounter no clinically significant sedation or serious adverse events during the test session, participants will be eligible to receive the next CBD dose – at least 72 hours later. Clinically significant sedation will be defined as Agitation and Calmness Evaluation Scale (ACES) scores of 7 (marked calmness) or higher at any point during the session, or no return to baseline – assessed with vital signs, Mini Mental Status Exam (MMSE), and a field test – 3 hours after the administration of buprenorphine, or 4 hours after the administration of methadone. Serious adverse events will be defined in accordance with FDA guidelines. If 2 participants experience clinically significant sedation, defined as above, or serious adverse events, study enrollment will be stopped until the Data Safety Monitoring Board (DSMB). examines the findings. Randomization to distinct doses of CBD, using the general study design described below, will not occur before the safety data is analyzed, in consultation with the DSMB.

K.1.2 General study: This is a double-blind, randomized, placebo-controlled, cross-over human laboratory study. Thirty-four male and female participants with OUD on MAT will be asked to arrive at approximately the same time each morning, coordinating with attendance at their opioid maintenance clinic. Participants will be stratified based on whether they are receiving methadone or buprenorphine. This will ensure that the safety and efficacy of CBD can be tested in each arm. On test days, all participants will be asked to refrain from caffeine, nicotine, and will be fasting on the test days. A study nurse will confirm with their respective program that participants did not receive either methadone or buprenorphine that morning and will call the program when testing is complete to permit dispersal of that day's methadone or buprenorphine dose. Participants will undergo a variety of cognitive and self-report measures, as well as assessments to confirm restraint from illicit drug use and lack of adverse effects of medication. Participants are asked to have blood draws during testing session, but this is optional. Participants who give permission to have this blood drawn will have an IV placed will have it placed the morning of each test session. If a subject chooses not to have an IV, only safety bloods will be drawn. Prior to their daily methadone or buprenorphine dose and thus at trough plasma levels of opioid, participants will receive CBD (400 mg, 800 mg, 1200 mg) or placebo, over a total of four sessions. Subsequently, all participants will undergo laboratory testing of measures relevant to vulnerability to relapse, including physiological, subjective, and cognitive outcomes. Participants will be observed for at

least 6 hours after the administration of CBD/placebo, and for 2 hours after the administration of buprenorphine/methadone. In case participants experience any sedation beyond these time points, observation will continue, —consistent with procedures in our research clinic (HSS #JD002). The order of study medication administration will be counterbalanced to reduce perceived bias of study participants and staff.

Justification for not requiring blood testing during test sessions: The primary aim of our study is to establish the safety and analgesic and craving suppression efficacy of cannabidiol (CBD) among persons with opioid use disorder who are receiving opioid agonist therapy. Our study was designed to look at pharmacodynamic effects of CBD in this population, rather than to investigate the relationship between pharmacokinetic and pharmacodynamic effects of CBD. Accordingly, drug levels are an exploratory outcome.

While the blood collection does not represent a “critical data point” of this study, collecting these data in a subset of participants will allow establishing the feasibility of conducting adequately powered pharmacokinetic studies — a next logical step of our research.

In conducting this work, we observed that, since a substantial proportion of our participants have a history of intravenous drug use, obtaining an intravenous line can often be challenging and may require multiple attempts that can produce participant discomfort. Therefore, by giving the participants the choice of opting out of this procedure, we will reduce participant burden without compromising the scientific aims of the study.

K.2. Screening (Pilot and General Studies): At the screening session, the following procedures will take place:

1. The participant will receive a full, written explanation of study procedures and sign a consent form. Any questions will be answered, and a physician or nurse will be available to answer any medical questions.
2. Participants will be evaluated with a detailed medical and psychiatric history.
3. Complete physical examination (including vital signs, height, weight and abdominal circumference).
4. Laboratory tests, including standard screening blood tests (CBC with differential and platelet count, electrolytes, creatinine, BUN, liver enzymes, TSH), a urinalysis, urine toxicology use, urine pregnancy test (for premenopausal females), and electrocardiogram (EKG).
5. Participants will complete several questionnaires pertaining to personality.
6. IQ will be measured at screening using the Wechsler Test of Adult Reading or a comparable IQ measurement tool.

The screening process will take approximately 2 hours.

K.3. Consenting (Pilot and General Studies): Participants who meet entry criteria will be invited to meet with the research staff, who will fully explain risks and procedures as outlined in the consent form. After reviewing this information and answering questions, informed consent will be obtained from all participants. A copy of the consent form will be provided to all participants.

The consent process is a multistep process, whereby information about the risks and benefits of the study will be provided to potential participants across several sessions. The number of sessions over which this information will be provided will depend on how well the participant understands and retains the information. The process begins with the participant initiating contact via telephone. The research staff will provide a brief description of the study following which the participant is screened by a member of the research team. Thereafter, potentially eligible candidates are scheduled for a face-to-face interview. Participants will also be informed of all potential risks of participation. Participants will be required to read the informed consent form and the investigator will additionally describe the risks and discomforts.

To ensure that the study participant understands the study, the participant will be asked questions about the study procedures and the risks associated with participation. If any concern arises that the study participant did not fully understand the study, the PI may decide that the participant is not suitable for

participation. This process generally takes about one hour. If the participant is still interested after all questions have been answered, the PI or staff member consenting, will ask the participant to sign the informed consent form. Participants will be informed that they can decline to participate in the study without penalty and given the opportunity to withdraw from the study prior to analysis of their data. Following the resolution of any questions, the participants will be asked to sign the consent form if he/she agrees to participate.

Great care will be taken to ensure that the participant is able to give informed consent. If any concern arises that the study participant did not fully understand the study, the principal investigator may decide that the participant is not suitable for participation.

This process will involve careful explanation of the consent form by a member of the research staff. Non-research clinicians will be involved in the process when available.

K.4. Justification of Cannabidiol Dose and Administration (Pilot and General Studies): FDA-approved Cannabidiol, produced under Current Good Manufacturing Practice (cGMP), will be obtained from G.W. Pharmaceuticals, as “Epidiolex”. The bioavailability of oral CBD is 13-19% and the elimination half-life is 56-61 hours [50]. CBD is metabolized primarily in the liver, through the enzymes CYP3A4, UGTA7, UGTA and UGT2B7 isoforms [51,52]. Importantly, CBD has a wide safety margin and was well-tolerated when co-administered with fentanyl, a high-potency opioid, in humans [48]. The product will be stored in the VACHS research pharmacy as per package instructions. The research pharmacy will prepare CBD oil-based solutions and matching placebos, which will be administered by mouth by the study physician or nurse. CBD will be administered 24 hours after the last methadone/buprenorphine dose. A new IND is being pursued specifically for this project.

CBD is a non-rewarding compound with a wide safety margin [30]. Further, CBD has been shown to produce central effects including hypnotic, anticonvulsive, anxiolytic and neuroprotective effects [53]. CBD has been found to be a potent non-competitive inhibitor at CB-1 and CB-2 receptors [54] in addition to an allosteric modulator at kappa-opioid receptors, normalizing glutamatergic impairments induced by heroin self-administration [43]. Moreover, CBD has been used in large clinical trials investigating its antipsychotic potential without significant adverse events [55,56].

The oral doses of CBD administered in this study will range from 400 mg to 1200 mg. Relatively low doses (400 mg) of oral CBD had anti-craving efficacy and were well-tolerated by people with OUD [45]. Hence, 400 mg will be the lowest dose used in this proposal involving people with comorbid OUD and chronic pain. In preclinical studies, the doses of CBD required to inhibit pain were between 10 and 50 mg/kg [31-38,42]. Even though CBD was safe and well tolerated in doses up to 4500 mg in adults (FDA Briefing Document, April 19, 2018, NDA 210365 Cannabidiol), the maximum recommended dose approved by the FDA is 20 mg/kg daily [57]. The highest dose used in this study will be below maximum dose recommended by the FDA (up to 1200 mg in this study, compared to 1400 mg in a 70 kg or 155 lb person). Although higher doses can be used, this is a reasonable first step. Similarly, since CBD has never been administered to people comorbid OUD and chronic pain who are on opioid agonist maintenance, single doses in an open-label, dose-escalation paradigm will be used an initial safety procedure in pharmacotherapy development. The open-label, pilot safety phase will inform the doses used in the general study.

Although the half-life of CBD is up to 61 hours, its pharmacodynamic effects are short-lived, so that the interval of 72 hours between test sessions is not expected to generate carryover effects. First, Hurd and colleagues did not find carryover effects when administering 400 mg or 800 mg of CBD to recently abstinent persons with OUD, with intervals of 3-4 days between each test session [45]. Notably, as in the current protocol, the first 2 of the 4 test sessions in this study were conducted following a single-dose of CBD [45]. Second, the lack of carryover effects after a 72-hour interval is consistent with local experience conducting Phase 1 and Phase 2 human laboratory studies involving the administration of cannabinoids. For instance, Skosnik and colleagues studied individual and interactive effects of THC and CBD among healthy humans, with an interval of 72 hours between each test session [58]. Third, other lines of evidence support the notion of a non-linear relationship between the clinical and pharmacokinetic effects of CBD –

such that the pharmacokinetics of CBD can vary widely, often without alteration in clinical effects. For instance, administering CBD with food may alter its pharmacokinetics, without significant change in its clinical effects: Among adults with epilepsy, in the fed state, the average Cmax of CBD was 14 times higher, and the AUC0 - ∞ was 4 times higher, compared to the unfed state; conversely, the antiseizure, neuropsychological, and safety profile of CBD remained unchanged in both conditions [59]. Fourth, the relationship between the clinical – or pharmacodynamic – effects of drugs and their pharmacokinetic properties are often non-linear. This is especially true for highly lipid soluble drugs like cannabinoids, including THC and CBD. For example, although THC metabolites stay in the organism for several days or weeks – THC's elimination half-life ranges from 25 to 36 hours –, clinical effects like analgesia or sedation last only several hours.

As a result, cannabinoids like THC and CBD are often administered twice daily when used clinically, rather than once every 3 to 4 days, as if the pharmacokinetic and clinical effects were linear. We have an ongoing randomized, placebo-controlled, within-subject human laboratory study administering single doses of oral THC (10 mg or 20 mg) to persons with opioid use disorder treated with methadone, also has an interval of 72 hours between test sessions.

The latter study has been recently reviewed and approved by the VA HSS (MS0056) and the Yale IRB (Protocol # 2000027065; NCT04025359). Fifth, prior studies conducted at our center suggest that a longer interval is likely to increase attrition of the study population – persons with comorbid opioid use disorder and chronic pain –, such that data collection may be compromised. Finally, we are considering the pharmacokinetic effects of CBD on the main study outcomes, as exemplified by the repeated measurements of CBD and opioid levels in our protocol. Notably, both the FDA and NIDA are in accordance with the proposed interval of 72 hours.

For the general study Research Pharmacy will create a randomization sheet for this general study. Both the research team and participants will be blind to the randomization.

An Environmental Assessment is not required because the action requested qualifies for a categorical exclusion per 21 CFR 25.31(e). To the applicant's knowledge, no extraordinary circumstances exist per 21 CFR 25.15(d).

K.5. Placebo (General Study): The study interventions include CBD (open-label safety phase); and CBD or placebo (general study, following the safety phase). The container in which the study medication and placebo are dispensed will be labeled according to 21 CFR 312.6. "Caution: New Drug--Limited by Federal (or United States) law to investigational use." This study will recruit individuals receiving opioid agonist MAT. This study will not interfere with standard of care and will be in addition to treatment as usual. Safety assessments will be done in person during the scheduled experimental sessions. Furthermore, participants will be encouraged to remain compliant with their regular treatment sessions and medications.

K.6. Outcome Measures (Pilot and General Studies):

Data Collection Methods (General Study): In order to enhance the reliability of the data collection and analysis process, the web-based software toolset REDCap (Research Electronic Data Capture) will be utilized in this study. REDCap is a secure, web application designed for electronic collection, management, and storage of clinical research data. The system includes features for HIPAA compliance including real-time data entry validation (e.g., for data types and range checks), a full audit trail, user-based privileges, de-identified data export mechanism to numerous statistical packages (e.g., SPSS, SAS, Stata, and R), and integration with the institutional Active Directory. REDCap is also compliant with FDA requirements, and hence is the ideal system of this FDA-supervised study (see Section M.4 for details). Notably, REDCap@Yale is being used in VA HSS-approved protocols (e.g., HSS #1586389), and the version of REDCap used in the current study has several additional layers of safety, due to is compliance with FDA requirements (please see section M.4. for details).

Following informed written consent, participants will be assigned a unique study ID, which will be used across all REDCap surveys during both screening and experimental sessions. Once in the database,

participants will only be able to complete surveys via a scannable QR code provided by a research assistant. All REDCap data collection will be done on Yale-managed iPads. Only personable identifiable information (PII) (e.g.) email, age in years, and sex/gender) will be collected, no personal health information (PHI) will be entered into REDCap. Assisted by study staff, participants will have the option of using a study-specific email, rather than their personal email.

The option to use traditional paper-survey's will be provided if participants prefer not to use computerized behavioral data collection.

Experimental Session Measures

Safety Assessments

Screening for alcohol intoxication: Before the start of each session, participants will be screened for alcohol intoxication by clinical examination (e.g., neurological exam and field test) and laboratory assessment (urine ethyl glucuronide testing). The use of breathalyzers will be limited due to the risk of exposure to SARS-CoV-2 through aerosols.

Systematic Assessment of Side Effects (SAFTEE): To monitor adverse events from the study medications, the SAFTEE will be administered before and after each experimental session. This is a symptom checklist [60] that has been used successfully in our previous studies to assess possible side effects of study medications. It includes information regarding severity of any presenting side effects, as well as the course of action taken by study staff in response.

Vital Signs: Heart rate, respiratory rate, blood pressure and pulse oximetry will be monitored throughout the session.

Neuropsychological battery: For cognitive performance, we chose tests that are likely to be sensitive to CBD's effects in our patient sample, such as the Continuous Performance Test (CPT) and the HVLT (Hopkins Learning Verbal Test). *Continuous Performance Test* (*CPT)* – will assess attention, concentration, and working memory. The outcomes will be percent correct responses and reaction time [61]. *Hopkins Verbal Learning Test (HVLT)* – will measure verbal memory. The outcome will be delayed recall [62]. Both the CPT and HVLT have been used to measure cognitive performance in prior studies with CBD [45,63].

Opioid Withdrawal Symptom Checklist (OWSC): This instrument will measure opioid withdrawal symptoms [64].

Drug Effects Questionnaire (DEQ): Participants will rate the following items from "not at all" to "extremely" on a 100-mm scale: "alert," "calm," "confused," "depressed," "confused," "high," "anxious," "sedated," "tired," "social," "self-confident," "talkative," "hungry," "feeling the drug strength," "feel good drug effects," "feel bad drug effects," and "want more drug." These items are commonly used to assess effects of drugs [65].

Mini Mental Status Examination (MMSE): The Mini-Mental State Examination (MMSE) or Folstein test is a 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment [66].

Agitation Calmness Evaluation Scale (ACES): The ACES consists of a single item that rates overall agitation and sedation at the time of evaluation, where 1 indicates marked agitation; 2, moderate agitation; 3, mild agitation; 4, normal behavior; 5, mild calmness; 6, moderate calmness; 7, marked calmness; 8, deep sleep; and 9, unarousable. The ACES is a well-validated instrument to assess sedation and has been used in various clinical trials [67,68].

Field Test: The field test will consist of a finger-to-nose test; a walk-and-turn test; a Romberg test. During the *finger-to-nose test*, participants will be asked to bring tip of the index finger up to touch the tip of the nose while his/her eyes are closed and his/her head is tilted slightly back, six times – three with each hand. During the *walk and turn test*, participants will be asked to take nine heel-to-toe steps along a straight line. After taking nine heel-to-toe steps, participants will then be directed to turn on one foot

and return in the same exact manner in the opposite direction. During the *Romberg test,* participants will be asked to stand with their feet together, head tilted back, and eyes closed for 30 seconds. The study physician will look for clues of changes from baseline, such as any loss of psychomotor coordination, loss of balance, eyelid/body tremors, muscle tone, and ability to follow directions.

Positive and Negative Affect Schedule (PANAS): This is a 20-item, widely used measure of momentary mood states, has been found to be sensitive to the mood-altering effects of several substances [69].

Its reliability and validity have been extensively evaluated (Ref). The PANAS consists of 20 emotion words, with 10 loading on the Positive Affect factor and 10 on the Negative Affect factor (10). Sample words for Positive Affect include “alert”, “inspired”, and “enthusiastic”. Sample words for Negative Affect include “distressed”, “upset”, and “guilty”. Participants rate the degree to which they endorse each item on a rating scale (1 = very slightly or not at all; 5 = extremely). Items are then totaled to create a score for each factor: Positive Affect and Negative Affect. Higher scores represent greater endorsement of the construct. High levels of The PANAS will be used during each session and at each weekly outpatient session to measure the effects of CBD on mood.

Pain Assessments

Brief Pain Inventory – Short Form (BPI-SF): The BPI-SF is a self-report questionnaire that assesses severity of pain, impact of pain on daily function, location of pain, pain medications, and amount of pain relief in the past 24 hours or the preceding week [70]. It will be used during screening and before experimental sessions.

Quantitative Sensory Testing (QST) of Thermal Pain: This is a reliable, dynamic, and computerized method of quantifying distinct mechanisms of the pain experience, measuring top-down pain inhibition and bottom-up pain facilitation (**Figure 4**). QST measures are sensitive to the effects of cannabinoids [73], important biomarkers of chronic pain, and predictors of the pain treatment response [74,75].

Conditioned Pain Modulation (CPM): CPM measures top-down pain inhibition, by leveraging the “pain inhibits pain phenomena”. Higher CPM reflects supra-spinal pain modulation [76].

Temporal Summation of Pain (TSP): TSP involves the repeated administration of noxious stimuli, indexing bottom-up pain facilitation [77]. Higher TSP indicates the increased firing of ascending pre-synaptic neurons, reflecting mechanisms of central sensitization.

Pain Visual Analog Scale (VAS): The pain VAS will be used by participants as a secondary rating scale for pain severity before, during, and after pain testing. This scale contains a horizontal line, anchored by verbal descriptors of “no pain” and “pain as bad as it could be”. Participants will place a vertical line at the point that best indicates their present pain [79].

Pain Catastrophizing Scale (PCS): This is a 13-item self-report scale to measure pain catastrophizing. Each item is rated on a 5-point scale: 0 (Not at all) to 4 (all the time). It contains three subscales: magnification, rumination, and helplessness [80].

Craving and Attentional Bias Assessments

Heroin Craving Questionnaire (HCQ-14): This instrument will measure cue-induced urges to use heroin, which are highly relevant for persons with comorbid OUD and chronic pain receiving opioid agonist maintenance [45,81].

Opioid Attentional Bias (AB): The primary AB measure will be a visual probe (VP) task [60]. VP tasks rely on a tendency for individuals to respond faster to probes (e.g., small dots) when they are presented in an attended region of a visual display[61]. In the task used in this study, a drug-related word is presented next to a neutral word for 500 milliseconds. Subsequently, a probe (e.g., a dot) replaces the drug word or the neutral word. The participant’s task is to indicate the location of the probe as quickly as possible by pressing one of two buttons on the mobile device. Faster responses when the probe replaces the drug word is interpreted as an AB to drug cues. A drug Stroop task will also be used to assess generalization of training effects to a second AB measure. Drug Stroop tasks are a form of emotional

Stroop widely used in addiction studies[79]. Longer latency to name the color of a word when it is a drug word compared to when it is a neutral word is indicative of an AB to drug words. For all AB tasks, opioid words will be presented in separate blocks in counterbalanced order. As in our Preliminary Studies, neutral words are common indoor/ household (e.g., couch) and outdoor items (e.g., fence) equivalent to the cocaine (e.g., smoke) and opioid words (e.g., smack) in length and frequency of use in the English language. For opioid words, we focused on both heroin and prescription opioid medications. Immediately before and after the opioid dot probe task participants will be asked estimate *cue-elicited craving* with a VAS. The difference of these ratings will be used to index cue-elicited craving.

Intake and Follow-up Measures

Timeline Follow-Back Assessment Method (TLFB): Drug use for the past 30-day period prior to study, participation and throughout the period of study participation will be obtained using this self-report measure. Participants are given a blank calendar covering the specified time interval and are asked to retrospectively reconstruct their drug use over that time interval. The process is facilitated by establishing anchor points (e.g., holidays, anniversaries, major national events, etc.). It can be scored to provide the number of days on which various levels of drug use occurred. The time-line method has good test-retest reliability and good validity for verifiable events. It has been used in numerous studies to assess substance use.

Childhood Trauma Questionnaire (CTQ): This is one of the most sensitive tools for quantifying early maltreatment, and it measures five categories of childhood maltreatment: Emotional, Sexual and Physical Abuse (EA, SA and PA), and Emotional and Physical Neglect (EN and PN) [82]. Scores on the CTQ, specifically, correlate with both the onset and course of mental illness, As well as the structure, function and connectivity of critical brain regions associated with resilience and vulnerability to life stressors (i.e., amygdala). This outcome measure will be included in the intake session because of the potential role of trauma as moderator of the cannabinoid and opioid response [83].

Hamilton Depression Rating Scale (HDRS) [84]: The HDRS is the one of most widely used clinician-administered depression assessment scale. The original version has 17 items pertaining to symptoms of depression experienced over the past week. This instrument will be used to assess depressive symptoms during screening. Candidates who meet criteria for severe depression will be excluded and referred for treatment.

Columbia Suicide Severity Rating Scale (C - SSRS) [85]: The C-SSRS is a measure used to identify and assess individuals at risk for suicide. Participants with active suicidal ideation will be excluded from the study and referred for treatment.

K.7. Biological Specimen Collection / Phlebotomy (Pilot and General Studies): Biological specimens will be collected at baseline for safety/routine lab work, as well as to examine the effect of administration of CBD on serum methadone/buprenorphine levels, since these drugs are CYP450 3A4 substrates [52] (**Table 2**). Further, we will collect potential biomarkers, including cytokines (TNF-alpha, IL-6, and IL-10) and endocannabinoid levels (e.g., 2-Arachidonoylglycerol and anandamide) for exploring the relationship between cannabinoid therapeutics, analgesia, and opioid-mediated inflammation. Your information or biospecimens collected as part of the research, even if identifiers are removed, will not be used, or distributed for future studies.

There will be a total of five blood draws in this study, one at screening and four at each test session. Over the course of the study, less than 175 ml (3/4 of a cup) of blood will be drawn. Participants may choose to not have blood draw during the testing sessions, and therefore not have an IV catheter placed. Those who choose not to have an IV placed during the test sessions, will have just safety bloods drawn 80ml (1/3 of a cup) over the course of four test sessions. Notably, the amount of blood drawn at screening and on each of the study visit is well within the Red Cross blood standards.

K.8. Schedule of Study Visits (Pilot and General Studies): Participants will have the following visits (**Table 1A and 1B**):

Table 1A. Experimental Design for the Pilot Study				
Day 0	Day 1	Day 4	Day 7	Day 14
IS Lab Assessments	ES	ES	ES Lab Assessments	FU

Day 0: Screening.
Day 1: First experimental session, where the first dose of study medication will be administered, and laboratory experiments will be conducted.
Day 4: Second experimental session.
Day 7: Third experimental session.
Day 10: Follow-up telephone contact.

Table 1B. Experimental Design for the General Study					
Day 0	Day 1	Day 4	Day 7	Day 10	Day 17
IS Lab Assessments	ES	ES	ES	ES Lab Assessments	FU

Abbreviations: *IS*: Initial Screening; *ES*: Experimental Session; *FU*: Follow-up telephone contact

Day 0: Screening.
Day 1: First experimental session, where the first dose of study medication will be administered, and laboratory experiments will be conducted.
Day 4: Second experimental session
Day 7: Third experimental session.
Day 10: Fourth experimental session.
Day 17: Follow-up telephone contact.

Table 2. Schedule of Events During the Experimental Sessions* (72 hours apart)	
Timepoint	**Measures and Events**
Baseline	VS, physical exam, ACES, MMSE, field test, Lab Assessments, EKG, SOWS, breathalyzer, urine drug testing, plasma opioid (methadone/buprenorphine) level, TLFB, SAFTEE, DEQ, CPT, HVLT, PANAS, AB, HCQ-14, PCS
0 min *	Cannabidiol (400, 800, 1200 mg) or placebo* administration
30 min	VS, SOWS, DEQ, PANAS
60 min	VS, DEQ, PANAS
90 min	VS, SOWS, cue session, AB, HCQ-14, pain measures plasma drug levels (blood)
120 min	VS, DEQ, PANAS, pain measures
150 min	VS, SOWS, DEQ, PANAS, pain measures
180 min	VS, DEQ, PANAS, CPT, HVLT
210 min	VS, SOWS, DEQ, PANAS, pain measures, methadone/buprenorphine administration
240 min to 420 min (buprenorphine) or 480 min (methadone)	VS, DEQ, PANAS, SAFTEE, HCQ-14, Plasma opioid and CBD levels, safety bloods and Lab Assessments (Day 10) Safety monitoring: VS, MMSE, ACES, field test hourly for at least 2 hours after the administration of methadone/buprenorphine → discharge if VS, MMSE, ACES are back to baseline
Follow-up	Safety follow-up by phone 8 hours after the administration of methadone/buprenorphine

***** The same schedule of events (Table 2) applies to the pilot study and the general study, except for time point 0 minutes. The difference is that in the pilot study, participants will receive 400 mg of CBD on the first test session,

800 mg in the second test session, and 1200 mg in the third test session, using dose-escalation and stopping criteria described in this protocol (Section K.1. subsection K.1.1). Conversely, the general study will have a randomized, placebo-controlled design, so participants will be assigned to CBD (400 mg, 800 mg, 1200 mg CBD) or placebo in a random order (Section K.1, subsection K.1.2.).

K.9. Sample Size Determination and Power Analysis (General Study): There are no preliminary data on the effects of CBD on individuals with OUD who are receiving MAT, to calculate the sample size for this study. In a recent human laboratory study, CBD, compared to placebo, blocked cue-induced craving with large effect sizes [45,86] . To detect a more conservative (d=0.64) difference in the attentional bias, craving and pain sensitivity paradigm used, using a within-subject design, given $\alpha = 0.05$ and $\beta = 0.2$ (80% power), 34 subjects will be required for the general study. We expect this sample size will also allow us to detect CBD-induced changes in cue-induced craving. To achieve this sample size, considering a historical attrition rate of 25%, we will expect to enroll a total of 46 participants (30 methadone and 16 buprenorphine).

K.10. Data Analysis Methods (Pilot and General Studies): To preserve the blind, a data entry operator will enter all study data into an electronic database using double data entry procedures. The data will first be scanned for potential outliers and influential observations using graphical and statistical tools. All outcomes will be summarized descriptively and assessed for normality prior to analysis using normal probability plots and Kolmogorov test statistics. Transformations or nonparametric analyses will be performed as necessary. All tests will be two-sided and considered statistically significant at alpha=.05. All analyses will be performed using SAS, version 9.3 (SAS Institute Inc., Cary, NC).

Aim #1: To determine the safety of acute CBD administration (400 mg, 800, 1200 mg) to people with OUD and chronic pain who are on opioid agonist maintenance. Hypothesis #1: Acute CBD administration will be safe and tolerable. Safety of CBD will be assessed with: the SAFTEE for adverse events; the DEQ items “I like the drug effect” and “I want more of the drug I received” for abuse potential; and by percent correct responses/reaction time in the CPT, and delayed recall in the HVLT, for cognitive performance. All safety outcomes will be tabulated, and descriptive analyses will be conducted. Dose conditions will be compared with regards to the frequency and severity of adverse events, abuse potential and cognitive effects. The PI, in consultation with the DSMB, will determine the dose with the best safety profile.

Aim #2: To determine if CBD (400, 800 mg, 1200 mg) vs. placebo reduces pain sensitivity and attentional bias for opioids and cue-induced craving, elicited by visual probes. Hypothesis #2: The CBD dose required to reduce pain sensitivity and cue-induced craving will be between 400 and 1200 mg. We will fit separate mixed-effects models for each outcome measure. The models will include the within-subject factor drug (CBD 400 mg, 800 mg, 1200 mg or placebo), time of assessment, and interaction between these terms. We will also consider order effects for experimental session day (1, 2, 3 or 4) and several different correlation structures for the repeated measures within individuals and will select the best fitting one based on Schwartz Bayesian information criterion. We will also explore the effects of potential covariates including sex, cannabis use frequency, opioid withdrawal severity, plasma opioid levels, and affective states. SAS PROC MIXED will be used for the mixed-model analyses [87].

Exploratory Aims: Linear mixed models will be used to assess sex differences, and if CBD is more effective than placebo in the exploratory outcomes.

L. RISKS AND BENEFITS (Pilot and General Studies):

***L.1. Risks*:** The risks associated with this study include those related to:1) Cannabidiol administration, 2) psychiatric evaluation and study assessments, 3) phlebotomy, 4) loss of confidentiality and privacy,

L.1.1 Cannabidiol Administration: CBD has been shown to be safe and well-tolerated in doses up to 750 mg, 1500 mg, and 4500 mg in adults (FDA Briefing Document, April 19, 2018, NDA 210365 Cannabidiol). Doses even up to 6000 mg, investigated in healthy individuals, resulted in no severe effects [50]. However, the FDA maximum recommended dose is 20mg/kg daily [57]. Although methadone,

buprenorphine, and CBD are CYP450 3A4 substrates, CBD was safe and well tolerated when co-administered with intravenous fentanyl, a high-potency synthetic full opioid-agonist [48]. Participants receiving medications that may have clinically significant interactions with CBD (e.g., platelet inhibitors, other prescription opioids, or benzodiazepines) will be excluded.

The highest dose of CBD used in the proposed studies is still below the maximum FDA approved dose. An open-label, dose-escalation phase will be conducted to establish the safety of CBD administration in this clinical population. The most common adverse reactions (10% or more for CBD and greater than placebo) are: somnolence, decreased appetite, diarrhea, transaminase elevations, fatigue, malaise, and asthenia, rash, insomnia, sleep disorder, poor-quality sleep, and infections. However, the extent to which CBD effects are perceived as unpleasant depends on the context and route of administration, and can be reduced by using the oral route, and preparing individuals in advance for the possible responses.

Using our open-label, dose-escalation paradigm, we collected safety data of three different doses of CBD (400 mg, 800 mg, and 1200 mg) among 4 participants receiving a mean methadone dose of 91.2 mg (SD=10.31). There was no evidence of sedation, which was thoroughly measured with the ACES, MMSE, and a field test. Notably, unlike methadone, buprenorphine is a *partial* opioid agonist; therefore, the risk of sedation following the administration of CBD is expected to be lower when given with buprenorphine than with methadone. Please see DSMB report attached for details.

L.1.2. Psychiatric Evaluation and Study Assessments: Participants will undergo a Structured Clinical Interview for DSM-5 conducted by a research assistant and a psychiatric and medical evaluation during screening. The diagnostic interviews may cover issues, which are stressful to a person, for example, questions regarding the experience of paranoid thoughts or social isolation. Thus, they may experience some distress during these interviews. During the laboratory assessments, study participants may experience transient increase in craving and level of pain or become tired or frustrated. They will be encouraged to take breaks if they wish to do so. It is also possible that some individuals may experience discomfort during the interviews, when they are asked to talk about their psychiatric symptoms. Participants may feel bored, tired, exhausted, discouraged, or distressed by the questionnaires or testing. During the QST laboratory assessments of Study 1, study participants may experience a transient increase in thermal pain, opioid craving, or overall discomfort.

L.1.3. Phlebotomy: Blood will be drawn weekly during the study to monitor medication levels as well as safety labs. Blood will be drawn on four occasions during the test sessions using an IV line. There are usually no serious medical problems with blood drawing, but there may be pain at the venipuncture site or bruising or infection may occur. These risks can be minimized by having these procedures performed by experienced personnel using good clinical technique. Approximately one ounce of blood will be drawn during the initial screening. In addition, blood will be sampled during study for plasma drug levels and safety bloods. Additionally, the amount of blood drawn at screening and on each of the study visit will be approximately 30cc which is within the Red Cross blood standards.

L.1.4. Loss of Confidentiality and Privacy: Participation in any research study may involve the risk of loss of confidentiality or privacy. Overseeing agencies may inspect records, and future investigators may use data. Additionally, no protected health information will be collected or stored in the REDCap database. Only PII (e.g., email) is necessary in order to enroll participants into the REDCap system. No PHI will be collected or stored in REDCap. Access to study data in REDCap will be restricted to the members of the study team with authentication through University NetID credentials.

The REDCap@Yale database and web server are housed on secure platforms that are backed up daily. REDCap@Yale meets the security standards for use with high-risk data as set forth by the Yale Information Security Office. REDCap@Yale is also compliant with FDA requirements (please see Section M.4 for details). All participant information will be kept confidential and only members of the investigative team with appropriate HIC and HIPAA training will have access to the study data. Information that could be used to identify participants individually will be stored on the VA encrypted investigators drive. Only authorized research staff will have access to this information. As with all paper records containing identities, containing identities will be stored in locked cabinets, and will be available only to authorized staff. Data will be maintained and secured in locked file cabinets or password

protected on the VA investigator drive. A numbering code will be used to assign a unique identifier to each participant. A certificate of confidentiality (CoC) has been issued for this study, as it is funded by the National Institute of Health. Notably, the CoC is issued as a term and condition of the award, rather than as a physical certificate.

L.2. Risk/Benefit Ratio: The potential risks for study participation are moderate because both proposed studies include the administration of CBD, which is not an approved an approved pharmacotherapy for OUD or chronic pain. Additionally, one of the proposed studies involves temporarily inducing pain and opioid craving, although in a controlled human laboratory environment. The proposed studies have a favorable risk: benefit ratio because they may lead to new treatment approaches for patients with OUD and chronic pain. These studies will be the first step in establishing the risks and benefits of cannabinoid-based interventions for comorbid OUD and chronic pain, paving the way for future investigation aimed at reducing the adverse consequences of opioid agonist treatment, such as respiratory depression – a strategy that holds promise for saving lives. Finally, since several U.S. states are authorizing the use of cannabinoids as adjunctive or substitutes for opioid agonist treatment, high-quality, experimental data collected in the proposed studies will contribute to evidence-based decision-making to guide patients, healthcare providers and future policy makers.

M. SAFETY

M.1. Protection of Participants (Pilot and General Studies):

M.1.2. Screening: Participants will be recruited exclusively from OTPs, which provide both psychiatric and addiction treatment. The screening process has been optimized to reduce the risk of participating in the study. Participants with a clinically unstable psychiatric disorder, including severe depression and/or active suicidal ideation, or any recent psychosocial stressor that might increase the level of risk of taking part, will be excluded. This assessment will be stringently made using the stated inclusion/exclusion and, where stipulated, the discretion of the primary investigators in discussion with the study physician. All participants will undergo a Structured Clinical Interview for DSM-5 conducted by a research assistant, screening bloodwork will be draw, a urine test will also be collected to test for drugs and pregnancy, and a psychiatric evaluation (including psychiatric history, drug use history, the physical examination, and the laboratory studies) by a specialized addiction psychiatrist with experience in treating individuals with OUD.

M.1.3. Study Visits: Participants' comfort with all study procedure will be monitored throughout the study. Participants will be informed that they can withdraw (themselves and their data) without justification at any time. Subjects who choose to have an IV placed will have it placed the morning of each test session. Those who choose not too or an IV couldn't be placed a nurse or phlebotomist will only draw safety bloods during each test session. A member of the research team will be present with the participants during all the testing.

All equipment adheres to local institutional safety standards. A physician will remain on hand with access to a crash cart with emergency medications if necessary.

After testing, study staff will inquire after the participant's general wellbeing. A physician will conduct a thorough assessment before participants are discharged.

Participants who experience elevation of liver enzymes above 3x the normal limit or significant sedation will have their individual participation terminated. In the event we encounter these adverse events in more than 3 participants, we will consult with the DSMB overseeing this study. The DSMB will independently review the safety data and make recommendations.

Participants will be reminded not to drive before each test session, they must confirm transportation prior each test session.

Study staff will check medications for potential pharmacokinetic interactions before each dose session. Participants will be asked to inform study staff if new medications for pain are started. If other prescription opioids, benzodiazepines, or platelet inhibitors are started, their participation in the study will

be discontinued. If participants require a dose increase in their opioid agonist treatment during the study, their participation will be discontinued.

The QST tasks employed in this protocol have been safely and widely used. While thermal testing induces pain, risks to the individual are minimal because: 1) the pain in transient and subsides immediately after the stimulus is withdrawn; 2) the level of pain experienced by participants will be below their tolerance level. Further, risk of thermal injury is reduced by: 1) the built-in shutdown system in the stimulator that prevents the delivery of prolonged or high-intensity stimuli; 2) the lock out of the stimulus above 47 °C; 3) the electronic thermometer that measures the temperature at the surface before and during each use. Notably, participants will be instructed that they may stop any procedure at any time, with no adverse consequence. Before discharge, the study physician will evaluate participants for any residual discomfort.

Required private identifiable information about individuals will be collected by the research staff and be used for research purposes and charting after consent is obtained. This information includes the results from laboratory tests for blood and urine, EKG and physical examination results. Study team members will collect required research data through study procedures as outlined in this protocol and record it in confidential research records and protected computer files. Data will be stored at the VA in a manner that is compliant with HIC regulations. All information obtained in this research study will be kept confidential and only be made available to the investigators. In all records of this research study, participants will be identified by a unique identifier number code known only to researchers working directly on this protocol. These codes will not be derived from participants PHI (e.g., name, date of birth etc.). A master list of participant names along with unique identifier number will be kept in a locked cabinet in the in Building 36 and the electronic records will be kept in VA intranet (investigator-drive).

Procedures to ensure confidentiality follow the regulations and policies of the VA Connecticut Healthcare System. If the results of this research study are reported in any scientific meetings or literature, participants will not be identified by name or photograph. Records will be maintained according to FDA Good Clinical Practice guidelines to ensure protection of confidentiality and security of records. The Human Studies Subcommittee (HSS), which approves the completion of this study, may inspect study records. All protected health information collected specifically for this research will be secured in the manner described above. The data will be stored in a secure location- we anticipate that the data will be stored for at least 10-15 years.

If participants report any threats of violence to a child or elderly person, this will be reported to the Department of Health and Human Services. Threats of violence to self or others will be assessed by the principal investigator who will determine appropriate reporting procedures. Furthermore, positive HIV, hepatitis B, or C results will be reportable to the Connecticut Department of Public Health.

Participants will be closely monitored for worsening of symptoms or side effects. They will be provided with a 24-hour access to study personnel to discuss any concerns. Participants will be given a wallet card indicating they are taking experimental medication and directions for how to determine what they are taking in case of an emergency.

Evidence of clinical worsening will be assessed as operationalized for clinical trials conducted by our group and approved by the HSS. Clinical emergence will include:

1. Emergence of new SI/HI or SI/HI with intent
2. Significant worsening not otherwise specified by the patient’s clinician or PI

These factors will result in the participant discontinuing from the study.

The research team of the New England MIRECC will work closely with clinicians at the VA Hospital and other treatment facilities in the community, and routinely communicate with them. In regard to this study, communication with the outpatient psychiatrist is as follows:

1. During screening, study staff confirm the study criteria and participant participation with the participant’s primary clinician (verbally/written).

2. As notified to the patient during consent, all concerns will be immediately communicated to the primary clinician and will be documented (verbally/written).

3. Additionally, the participant's primary clinician is updated each week via the research clinical notes.

4. Please note, if the participant meets one of the criteria for discontinuation, this will be communicated verbally with the participant's primary clinician and will be documented in the participant's chart. The study team will closely coordinate the stabilization of the patient (including inpatient hospitalization if needed) and transfer of care to outpatient treatment as has been previously successfully done in other studies.

M.2. Data Safety and Monitoring Plan (Pilot and General Studies): This is a moderate risk study, and no serious adverse events are expected. The safety data is reviewed after every test day, during weekly research team meetings, and will be suspended or modified if indicated. The principal investigator will conduct a data and safety review at least quarterly and at any time a serious adverse event occurs. During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification, continue, or close enrollment.

In accordance with FDA guidelines, an adverse event is defined as "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related". An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study medication and does not imply any judgment about causality.

A mild adverse is defined as one that results in transient discomfort, not requiring intervention or treatment; does not limit or interfere with daily activities (e.g., insomnia, mild headache).

A moderate adverse is defined as an event that is sufficiently discomforting so as to limit or interfere with daily activities; may require interventional treatment.

A severe adverse is defined as an event that leads to incapacitating with inability to work or perform usual activity; or events that result in significant symptoms that prevent normal daily activities and may require invasive intervention.

An adverse event or suspected adverse reaction will be considered "serious" if: Death, a life-threatening adverse event, inpatient hospitalization, or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Adverse events will be graded in severity as follows:

- **0** No adverse event or within normal limits
- **1** Mild adverse event
- **2** Moderate adverse event
- **3** Severe adverse event
- **4** Serious adverse event

Severe and serious adverse events will be reported to the Human Investigation Committee (HIC) within 24 hours. Other adverse events will be reported to the HIC in a timely manner, using the following predefined causal relationships:

i. Definite: Adverse event(s) will clearly be related to investigational agent(s) or other intervention
ii. Probable: Adverse event(s) will likely be related to investigational agent(s)
iii. Possible: Adverse event(s) may be related to investigational agent(s)
iv. Unlikely: Adverse event(s) will doubtfully be related to investigational agent(s)

v. Unrelated: Adverse event(s) will clearly not be related to the investigational agents(s)

Serious unanticipated adverse events will be reported immediately to the VA Connecticut Healthcare System institutional review boards and any appropriate funding and regulatory agencies. Serious anticipated adverse events will be reported immediately to the institutional review boards and others whenever their magnitude or frequency exceeds expectations.
Adverse events will be reported to the HIC, HSS and any appropriate funding and regulatory agencies. The investigator will apprise fellow investigators and key study personnel of all serious and unanticipated adverse events that occur during the conduct of this research project. Adverse events will be graded as per HIC policy.

The PI will evaluate all adverse events and determine whether the adverse event affects the risk/benefit ratio of the study and whether modifications to the protocol or consent form are required. A summary of the adverse events will be reported to the institutional review boards periodically or, at minimum, when re-approval of the protocol is sought. The summary will include number of participants enrolled and a summary of graded adverse events to date. Adverse events will also be reported to NIDA through the Serious Adverse Event Tracking and Reporting System (SAETRS).

M.3. Data Safety Monitoring Board (DSMB) (Pilot and General Studies): A Data Safety Monitoring Board has been assembled for this study. Un-blinded safety data will be provided to the committee for monitoring. DSMB reports will be provided to the HIC. Any serious, unanticipated, and related adverse events will be reported to the VA-HSS. DSMB reports will also be sent to NIH/NIDA.

M.4. Loss of Confidentiality (Pilot and General Studies): There is a risk of loss of confidentiality in this study. All participant information will be kept confidential and only members of the investigative team with appropriate HIC and HIPAA training will have access to the study data. Data will be maintained and secured in locked file cabinets or password protected electronic media. A numbering code will be used to assign a unique identifier to each participant. A certificate of confidentiality (CoC) has been issued for this study, as it is funded by the National Institute of Health. Notably, the CoC is issued as a term and condition of the award, rather than as a physical certificate.

REDCap is 21 CFR Part 11 ready, which means that REDCap meets the technical software specifications that are required by the FDA. Further, REDCap has a number of data security and protection features including: 1) Authentication uses the Yale Active Directory encrypted with Kerberos via SLDAP, such that user passwords are never stored locally, and password strength and expiry meet Yale University IT security policies; 2) role-based security with individualized access and permissions; built-in data validation and data cleaning; 3) all web-based communications are protected by the Yale enterprise firewall and encrypted with TLS; 4) secure configuration, Ubuntu CIS (Center for Internet Security), that conforms to best practice and compliance standards; 5) daily back-ups and incremental snapshots ensure against the possibility of data loss or corruption. REDCap instance is located on an internal OSUWMC network. Remote access to this network can be obtained over an encrypted VPN tunnel (AnyConnect). This VPN uses Protocol: DTLS and Cipher: RSA_AES_128_SHA1. Background checks are performed on all staff that are on the network or obtaining VPN access. Moreover, access to study data in REDCap will be restricted to the members of the study team with authentication through Yale University NetID credentials. REDCap is already being used in VA HSS-approved protocols (e.g, HSS #1586389).

M.5. Psychiatric Evaluation and Study Assessments (Pilot and General Studies): It is worth noting that our participants will be recruited exclusively from OTPs, which provide both psychiatric and addiction treatment. Participants will be seen every 3 days for 4 experimental sessions. Before each experimental session, participants will be required to refrain from consuming alcoholic beverages and drugs during study participation, which will be verified by urine drug screening and breathalyzer measurements before the sessions. If results indicate non-adherence with these study procedures, the session will be rescheduled. Repeatedly non-adherent participants will be discharged from the study. Since our participants are provided with a light snack before each test session, and a small meal at the

end of each test session, we ask our participants to not eat after midnight on the day of your test sessions. However, you can drink your usual amount of coffee or caffeinated beverage before each test session.

A physician and a member of the research team will be present with the participants during all the testing, monitoring participants' comfort with all study procedures, using equipment that adheres to local institutional safety standards. Participants will be informed that they can take breaks or withdraw (themselves and their data) from the study without justification at any time. After testing, study staff will inquire about the participant's general well-being. Participants will be made aware that, if they experience a clinically significant worsening of mood symptoms, or if active suicidal ideation emerges, they will be escorted to the nearest psychiatric emergency room.

A physician will conduct a thorough evaluation before discharge after each experimental session. Participants may be observed until craving subsides. In the event participants test positive for non-medical substance use or breathalyzer indicate recent alcohol use, the experimental sessions will be rescheduled until clinical stability is ensured. Regular treatment with opioid agonists will be continued during the study. One week after completing the four experimental sessions, participants will be contacted by telephone for another safety follow-up.

M.6. CBD Administration (Pilot and General Studies): The doses selected for this study are within the FDA-approved range and we expect them to be safe and well tolerated. CBD has been safely co-administered with opioid agonists with much higher potency than methadone/buprenorphine, such as fentanyl [48]. Participants will be thoroughly assessed at each study visit for the development of adverse effects, abuse potential and cognitive deficits. Symptoms of OUD will also be assessed.

A research addiction psychiatrist will perform a comprehensive evaluation if participants state that they noticed a worsening of symptoms or adverse effects. Notably, a pilot study will be conducted to establish the safety of CBD administration in this clinical population. Results from this pilot study will inform the conduction of the general study.

M.7. Risks of Blood Draws (Pilot and General Studies): Due to the risks associated with phlebotomy procedures, participants who have donated blood within eight weeks to the present study will be excluded. Participants will be told that they should not give blood for at least eight weeks.

N. INFORMED CONSENT (Pilot and General Studies):

The informed consent form (see attached), which will be given to the participating participants, explains all the information pertaining to this study such as the objectives of the study, all the procedures, risks and benefits, confidentiality, safety measurements, payment, and other aspects of the study. Understanding of the information is verified using a questionnaire (see attached).

O. CONFIDENTIALITY (Pilot and General Studies):

All participant information will be kept confidential and only members of the investigative team with appropriate HIC/HSS and HIPAA training will have access to the study data. A numbering code will be used to assign a unique identifier to each participant. This study will be conducted with support from the National Institute of Drug Abuse (NIDA), under an IND issued by the US FDA.

Therefore, data collected as part of this study may be made available to the VA, the US FDA and NIDA. Participants are informed of these possibilities in the consent form.

Demographic and outcome data described earlier will be collected as part of this study. Personnel listed on protocol will have access to data containing PHI. As noted above, limited PHI may be disclosed to the VA and the FDA, as required.

The hardcopy data will be stored in locked filing cabinets on the campus of VA Connecticut Healthcare System. Some electronic data including demographic data, screening data, laboratory data and RN/MD progress notes about each test day etc. will be stored on the VA CPRS system. All phone screen

information obtained will be stored behind the VA firewall. Other outcome data in electronic format will be stored either on 1) a limited access computer encrypted using VA approved encryption software, 2) a VACHS server, or 3) any other server that is approved by VACHS. If data is stored on a computer using VA encrypted software, those data will be backed up on a backup device that will be stored in a locked cabinet in Building 36 and encrypted using VA approved encryption software.

Data will be shared with employees at the VA not listed on this protocol and other collaborators not listed above. However, if this occurs, data will be *stripped of PHI* before it is shared. For example, *data stripped of PHI* will be shared with statisticians, laboratory personnel who conduct assays and others.

P. LOCATION OF STUDY (Pilot and General Studies):

The study will be conducted at the VA Connecticut Healthcare System, West Haven Campus.

Q. COMPENSATION TO PARTICIPANTS (Pilot and General Studies):

All participants will be compensated with cash or checks for their participation. They will receive $50 for the initial screening and $200 for each of the test sessions and $20 dollars for transportation for each test session. Compensation of an additional $20 will offered if participants need to return to the clinic for additional procedures. Finally, upon study completion, participants who referrer other candidates will also be compensated $20 for each referred candidate who is enrolled in the study.

Participants will be compensated only for the visits they participate in. If a study visit is cancelled because the participant fails to follow pre-visit restrictions such as refraining from illicit drugs, alcohol, and caffeine, then they will not be compensated for that day.

Costs for Participation (Economic Considerations): Participants will not be charged for any aspects of this study.

R. FUNDING SOURSE (Pilot and General Studies):

NIH (grant 1K23DA 052682-01, PI: De Aquino) and the VISN-1 MIRECC will fund both sub-studies in this protocol. CBD and placebo will be provided by Greenwich Biosciences.

S. DURATION (Pilot and General Studies):

Expected duration of the study of the pilot study will be of 6-8 months. The expected duration of the general study will be of approximately 30 months.

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Consent Questionnaire

This is a questionnaire to help us to test your understanding of the study protocol. For you to qualify for this study, you will need to pass this test. To pass this test, you will need to score at least a 75% and also get all three questions underlined.

You will have only 2 chances to take this test. Incorrect answers on your first attempt will tell us those parts of the study you did not understand well, so that we can go over the consent form again with you. If you answer more than 5 questions wrong at your first attempt, you will not be considered for this study.

1. Will you need to stop taking your medications (methadone or buprenorphine) as part of this study?

Yes No Maybe I can't decide

2. What medications might you receive?

Cannabidiol Prozac Paxil Ativan

3. Will you be able to choose what medication that you may receive in this study?

Yes No Maybe I can't decide

4. During the study, will you or the study doctor or the research team know exactly which study medication you are on?

Yes No Maybe I can't decide

5. Could your symptoms get temporarily worse during this study?

Yes No Maybe I can't decide

6. Will blood be drawn for this study?

Yes No Maybe I can't decide

7. Can the study medication have side effects?

Yes No Maybe I can't decide

8. Name at least 2 side effects of the study medication:

_____ _____

9. Once you start the study, are you free to stop at any time?

Yes No Maybe I can't decide

10. What would happen to your regular treatment if you dropped out of the study?

a. Treatment with regular clinician will end b. Treatment with regular clinician will continue c. Don't know

11. Will you be hospitalized for this study?

Yes No Maybe I can't decide

12. Will you get paid for taking part in this study?

Yes No Maybe I can't decide

_____/ _____

Signature *Date*

WALLET CARD (1D)

IMPORTANT

The holder of this card is participating in a clinical study with an investigational drug called ***cannabidiol,*** as an adjunctive treatment for opioid use disorder.

Treatment Period:

From: _____

To: _____

EMERGENCY CONTACT

If this participant presents to you for treatment, please contact the research clinic below and ask for the cannabidiol (CBD) study:

Doctor: Joao P. De Aquino, M.D.

Phone: 203-932-5711 x1-2916 HSS# 1584988

Doctor: Mehmet Sofuoglu, M.D., Ph.D. HIC# 2000029286

Phone: 203-932-5711 x1-4809 .

24 Hour Emergency: 203-974-7560 .

Dial 0 for the operator and ask that the on-call research psychiatrist be paged.