Cannabidiol Use to Reduce Cravings in Individuals with Opioid Use Disorder on Buprenorphine

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Detailed Protocol

Title: A single-arm, open-label feasibility pilot of cannabidiol as an adjunct to buprenorphine or methadone on cue-induced cravings among individuals with opioid use disorder

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I. Background and Significance:

Retention in medication treatment for opioid use disorder (OUD) decreases overdose mortality: Medication treatment for OUD with buprenorphine, methadone, or extended-release naltrexone reduces the risk for overdose by 70%.[1,2] As such, the current director of National Institute on Drug Abuse (NIDA) cites the increase in access to medications for OUD as one of the four central aims in reversing the opioid crisis.[3] However, treatment dropout rates remain unacceptably high—approximately 50% of patients will have discontinued treatment 6 months after initiation.[4] Therefore, there is a critical need to ensure patients not only have access to medications, but also are retained in treatment longer.

Cravings play a central role in OUD relapse and treatment discontinuation: There is a substantial body of research indicating that high rates of treatment discontinuation are due to the emergence of intense cravings to use illicit opioids in response to cues—which are reminders of the drug such as drug paraphernalia.[5–7] The brains of individuals with OUD are highly susceptible to experiencing strong cravings in response to environmental cues, and strength of the cravings correlates positively with the severity of the illness.[8–10] Even among individuals with OUD who have been abstinent for over a year, strong cravings can be elicited in response to cues.[11] Therefore, much of the research so far in improving treatment retention on medications for OUD have focused on helping patients learn how to avoid triggers and to manage their cravings if they do emerge.[12–14]

Psychosocial treatments as adjuncts to medications have not been as helpful as hoped: Interventions such as *cognitive-behavioral therapy* and *relapse prevention* teach skills to reduce exposure to cues and to learn how to manage cravings.[15] Unfortunately, in numerous randomized clinical trials among patients with OUD on buprenorphine, these treatments were less effective than one would hope for in improving treatment retention or suppressing the use of illicit opioids.[16] As such, there is a critical need to identify novel strategies that will improve retention in medication treatment for OUD.

Cannabidiol (CBD) has emerged as a possible adjunct to OUD treatment: CBD is a non-psychoactive and non-addictive constituent in marijuana. Both animal and human studies have identified that CBD possesses antiepileptic, anxiolytic, antipsychotic and other therapeutic properties, while producing minimal if any adverse effects.[17,18] While the mechanisms of action are being elucidated, CBD is an inverse agonist at the cannabinoid receptors and appear to target brain regions that mediate cue-induced cravings.[19] CB1 and CB2 receptors are densely located in striatal regions that mediate reward function, and also modulates serotonin and opioid receptors.[20] Cannabinoid receptors also modulate nociception, inhibit pro-inflammatory molecules, and display synergism with systems that influence analgesia such as the endogenous opioid system.[21] In animals, CBD administration blocks the reward-facilitating effects of morphine, reduces opioid withdrawal symptoms, and attenuates cue-induced relapse among abstinent

rats.[19,20,22] In 2018, CBD was approved by the FDA for the treatment of pediatric seizures, and reclassified as a Schedule V drug, opening up the path for human trials.

CBD reduces cue-induced cravings for individuals with OUD who are not taking any medications: To date, there are two double-blind, placebo-controlled randomized trials for CBD for OUD which have been published, but only among abstinent individuals not taking medications.[20,22] In both studies, either CBD (400mg or 800mg) or placebo were administered for 3 days, and the increase in cravings in response to heroin-related cues was measured. Results showed greater reduction in cue-induced cravings among those taking CBD compared to placebo, with minimal adverse effects. This adds to the growing body of data suggesting the relevance of CBD in modulating the attentional saliency of drug related cues which contribute to the risk for relapse.

Impact of CBD on cue-induced cravings among individuals stabilized on buprenorphine is not known: A prior study of individuals with OUD who are receiving buprenorphine for detoxification (i.e. several days of tapering dose of buprenorphine) noted that participants remained highly reactive to cues.[8] Results from patients on long-term methadone treatment implies that cue-reactivity may decrease over time.[11,23] Given that long-term medication treatment remains the gold-standard approach, a critical question that remains unanswered is whether CBD can be used as an adjunct to buprenorphine treatment to reduce cue-induced cravings. If promising, the preliminary data will be used to seek NIDA R01 or R21 funding to conduct a placebo-controlled, double-blind, randomized clinical trial to examine the impact of CBD on cue-induced cravings among individuals with OUD taking medications. Longer-term, our goal is to examine the impact of CBD on treatment retention for OUD as an adjunct to medications in trials of longer duration. We will study the effectiveness of this approach with specific medical and psychiatric populations with OUD. If successful, this line of research has the potential to significantly impact clinical practice of treating OUD by providing a viable medication adjunct to existing evidenced-based therapies.

Individual differences in pain processing and central sensitization: Psychophysics, which is the careful and systematic testing of sensory processing in humans in a laboratory setting, with standardized equipment and protocols, has revealed important differences amongst individuals taking opioid analgesics, including higher pain sensitivity.[24–28] Specifically, central sensitization is a process by which the spinal nociceptive system responds to sustained noxious peripheral input by amplifying the transmission of this signal, and has proven to be an important mechanism in the development of chronic pain in preclinical research.[29–34] A clinical correlate of central sensitization is temporal summation of repetitive painful stimuli.[35] Importantly, variability in temporal summation, measured by the increase in pain sensation during a sequence of stimuli, is observed among individuals and groups and may indicate an individual's endogenous analgesic response.[36] Temporal summation has been shown to distinguish differences between low- and high- opioid users[37], and risk for opioid misuse.[38] By including a quantitative sensory testing (QST) assessment of both pressure pain threshold/tolerance and temporal summation of pain (TSP) in this study, we will gain valuable pilot data on: (1) how much patients with OUD on buprenorphine exhibit central sensitization, and how they may differ from chronic pain patients and healthy volunteers (from our other studies); and (2) how CBD impacts central sensitization, by performing a pair-wise comparison of temporal summation of pain of patients before and after they begin taking CBD.

II. Specific Aims:

Study Aim:
To determine the impact of CBD on cue-induced cravings among individuals with OUD on buprenorphine or methadone treatment.

- In a single-arm, open-label study, subjects will receive 600mg of oral CBD once daily for 3 consecutive days. Cue-induced cravings will be assessed before and after the intervention. We hypothesize that cue-induced cravings after CBD administration will be reduced by 50% compared to cue-induced cravings prior to the intervention.

III. Subject Selection:

The proposed study is a single-arm, open-label feasibility pilot. The study will enroll 12 adult subjects (including 2 pilot subjects) with OUD currently receiving treatment with buprenorphine or methadone.

Inclusion criteria:

- Diagnosis of DSM-5 opioid use disorder, severe
- Currently in treatment with methadone or buprenorphine

Exclusion criteria:

- Requiring level of care higher than outpatient treatment for alcohol, sedative/hypnotics, or stimulants
- Any current mood episode requiring level of care higher than outpatient treatment
- History of psychotic disorder
- Currently pregnant
- Hepatic liver enzymes greater than 3x upper normal limit
- Hypersensitivity to cannabinoids or sesame oil (CBD solution comes in sesame oil emulsion)
- Currently taking any medications with known significant pharmacokinetic interactions with CBD

IV. Subject enrollment:

Adults with a DSM-5 diagnosis of OUD and who are currently in treatment with buprenorphine or methadone will be recruited. Inclusion and exclusion criteria are listed above, which are designed to favor internal validity given the preliminary nature of this trial, and to recruit as homogenous of a group of subjects as possible. Patients with OUD at Brigham and Women's Hospital (BWH) and Brigham and Women's Faulkner (BWF) Addiction Recovery Program (ARP) will be recruited via Patient Gateway for possible inclusion. Subjects will also be recruited from the Partners Clinical Trials website, http://Rally.partners.org, as well as print advertisements and flyers, which will also be distributed to local methadone and buprenorphine clinics. Subjects will also be recruited via automated IRB-approved recruitment emails sent from their providers at BWH Bridge and/or BWFH ARP through the "Patient Gateway Blast." All study visits will be conducted at the BWH Center for Clinical Investigation. Study staff will perform a preliminary screen to establish suitability for the study. If suitable, a study staff will obtain informed consent and apply the inclusion and exclusion criteria. If the subject meets the full inclusion and exclusion criteria, the subject will be enrolled. Subjects will not be enrolled from among the Investigator's own patients as the Principal Investigator is no longer seeing any patients clinically.

V. Study procedures:

Overall approach: After obtaining informed consent, participants will complete the baseline assessments as outlined in **Table 1**. The subject will then be scheduled for their study visits 2 and 3.

Schedule of visits and assessments:

The blood and urine samples (see **Table 1**) collected during the Baseline Visit 1 and Post-Exposure Visit 3 will be used only for inclusion/exclusion purposes. Specifically, participants who are currently pregnant (as confirmed by the pregnancy test), have hepatic liver enzymes greater than three times the upper normal limit (as confirmed by the liver function tests, or LFTs), or who are not taking their buprenorphine as clinically prescribed (as confirmed by the urine toxicology) will be excluded. Other inclusion/exclusion criteria not dependent on blood and urine samples are detailed elsewhere in this protocol. Baseline measures and the pre-exposure cue-induced cravings, anxiety, and pain assessments will both be conducted before the CBD administration. The first oral CBD administration will occur during Visit 2, following the pre-exposure assessment. Participants will be instructed to take the second and third oral CBD doses at home, and will be asked to complete a drug diary which will also assess general craving and adverse effects. Participants will be asked to take their regular dose of sublingual buprenorphine at their regular time, and to return to the BWH Center for Clinical Investigation for Visit 3 following their last home administration of oral CBD. Follow-up assessments, including post-exposure cue-induced cravings, anxiety, and pain assessments, will occur after administration of CBD. During Visits 2 and 3, general craving, anxiety, and pain scales will also be administered before the cue-reactivity paradigm. There will also be continuous physiological monitoring (vital signs: heart rate, blood pressure, respiration rate, oxygen saturation, and temperature) during Visits 2 and 3. Table 1 summarizes the schedule of visits and assessments.

	Baseline	Pre-exposure + open-label CBD 600mg (dose 1)	Open-label CBD 600mg (doses 2 and 3)		Post-exposure
Study visit number	1	2	Home administration	Home administration	3
Psychiatric History Self-Report					
Pregnancy test					
PHQ-9					
GAD-7					
BPI					
LFTs					
PANAS					
COWS					
Urine toxicology					
Cue-induced craving, anxiety, and pain scales					
General craving, anxiety, and pain scales			Drug diary	Drug diary	
Adverse effects			Drug diary	Drug diary	
Physiologic monitoring (vital signs)					
Quantitative Sensory Testing (QST)					
TLFB					

Table 1: Schedule of visits and assessments

MINI=Screening instrument for psychiatric diagnoses; PHQ-9=Patient Health Questionnaire 9-item; GAD= Generalized Personality Disorder 7-item; BPI=Brief Pain Inventory; LFT=Liver function test; PANAS=Positive and Negative Affect Schedule; COWS=Clinical Opioid Withdrawal Scale; TLFB=Timeline Followback

Cannabidiol:

Subjects will receive 600mg of oral CBD for 3 days in an open-label fashion. Cannabidiol will be provided using Epidiolex™ oral solution 100mg/mL. Drug will be procured by the BWH Investigational Drug Services (IDS) pharmacy. The first dose will be administered at the BWH Center for Clinical Investigation during Visit 2 following the pre-exposure cue-induced cravings assessment, while doses 2 and 3 will be self-administrated at home. The CBD will be repacked in pre-drawn syringes for the subjects to self-administer at home. Cannabidiol will be stored at room temperature (68 to 77 F) in its original bottle and in an upright position. Once opened, Cannabidiol has a shelf life of 84 days.

Primary outcome (cue-induced cravings):

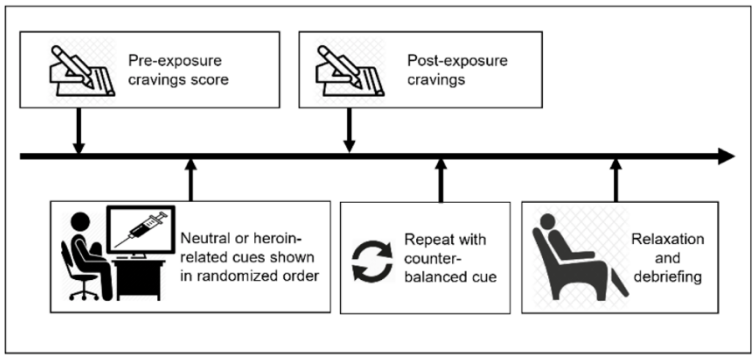

Figure 1: Cue-induced craving assessment

The cue-induced cravings, anxiety, and pain assessment will be conducted before and after the CBD administration. Subjects will be shown both heroin-related and neutral images on a computer screen using a standardized protocol used in previous studies (Figure 1).[8] The order in which the cues will be presented will be randomized and counter balanced. Subjects will rate their cravings, anxiety, and pain on a visual analog scale of 0 to 10. The images will not be repeated to limit habituation to the visual cues. Instead the images will be similarly matched, and utilize images that have evoked strong responses in prior studies.[8] The cue exposure procedure will end with a standardized relaxation and debriefing exercise. It is important to note that cue-exposure is a safe paradigm for studying craving in this population when employing debriefing procedures.[39]

Cue-induced craving procedure: Participants will be presented with a series of 20 heroin-specific or neutral images. Images will be presented on a computer using a timed stimulus presentation on Microsoft PowerPoint. Participants will view both presentations (heroin-specific and neutral) for one minute each, and after presentation of all images will complete the paper-and-pencil ratings of opioid craving, anxiety, and pain scales. This task is anticipated to take between 10-15 minutes to complete, depending on participant speed of responding. Participants will complete a standardized relaxation procedure after completion of the cue-reactivity test.

Quantitative Sensory Testing (QST) Procedure: QST consists of two parts: 1) Pressure pain threshold and tolerance, determined by a pressure algometer; 2) Temporal summation, measured using repeated mechanical pinprick.

1) *Pressure pain threshold*: Pressure algometry is the most commonly used test for static mechanical pressure sensation in the skin and in deep tissues. Pressure algometers deliver a firm and quantifiable pressure through a flat base applied to the skin. The electronic pressure algometer that we will use (Wagner Instruments) is a hand-held algometer utilizing a pressure-sensitive strain gauge, covered by a 0.5 cm^2 circular probe. The probe is covered with a soft polypropylene disk, to avoid injury to the skin. The pressure applied through the probe is transduced, amplified, and converted to electrical reading on a digital display. The pressure will be slowly increased (1 lb/s) and the participant will be asked to note when they first feel pain and when they want the pressure to stop , which will be recorded as the pressure pain threshold and tolerance, respectively.[40] This process will be repeated on the trapezius and the forearm, alternating between sides of the body with 20 seconds between measurements.

2) *Temporal summation testing methods*: Mechanical pinprick pain will be assessed in a similar manner to our previous studies,[26,41] using standardized weighted pinprick applicators similar to those described by Rolke et al,[42] using a range of forces (128 mN, 256mN and 512mN) which result in a painful sensation in most subjects.[43] First, a single stimulation of the lower force pinprick will be applied to the dorsal aspect of the index finger between the first and second interphalangeal joints of each hand while resting palm down on a flat surface such as a table or armrest, and then rated by the subject on

a scale of 0-10. The weight probe that induces at least some pain, but not more than 3/10 pain will be determined, and this probe used for repeated testing. After a break of at least 10 seconds, a train of 10 stimuli will be applied at the same spot, at a rate of 1 stimulation/second. The subject will rate pain on a scale of 0-10 after the first, fifth and tenth stimulus, then rate any ongoing pain 15 seconds after cessation of the last stimulus (painful aftersensations). Temporal summation will be calculated as the change in pain score between the highest and lowest pain ratings in a train.

Alternative approach for temporal summation of pain assessment: Tonic, deep-tissue, mechanical stimulation will be applied using a rapid cuff inflator (Hokanson) wrapped around the leg, centered around the middle of the gastrocnemius muscle in a similar manner to our previous studies. Pressure will then be increased at approximately 5-10 mmHg/s, at which time participants will be asked to note when they first start feeling pain and then when they feel as though the pain is a 4/10. At this point the cuff will be deflated. Participants will be given a 30 second break. The cuff will be re-inflated to this previously identified pressure and held for two minutes (or until participant asks to stop), at which point the cuff will be deflated. Participants will be asked to rate their pain every 30 seconds, as well as to rate any painful after sensations after cuff deflation. Temporal summation will be calculated as the change in pain score between the highest and lowest pain ratings in the 2 minutes.

Figures 2 and **3** below summarize the schematic order of Visit 2 (Pre-exposure) and Visit 3 (Post-Exposure), respectively.

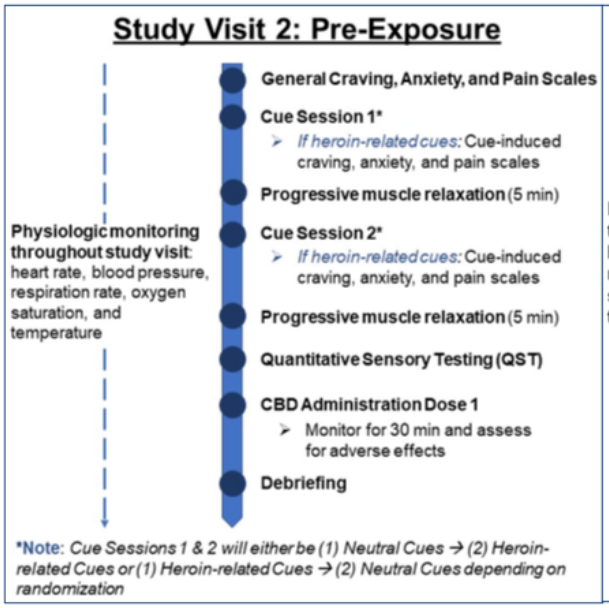

Figure 2: Study Visit 2 Schema

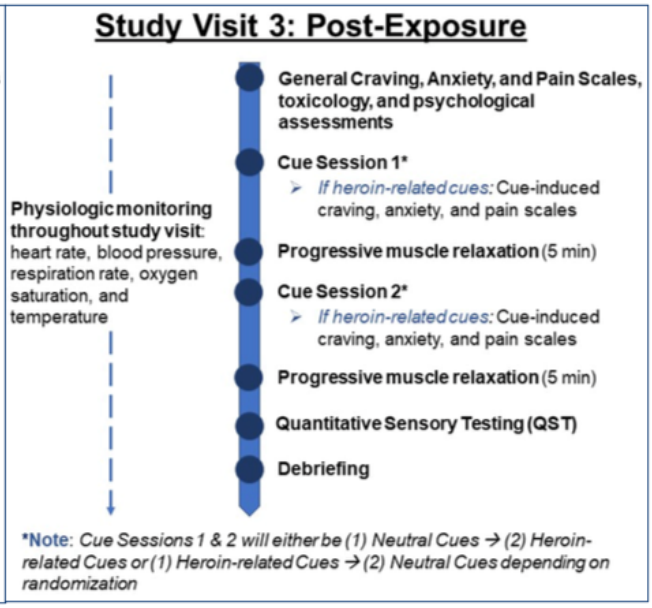

Figure 3: Study Visit 3 Schema

Compensation: Participants will be reimbursed for travel/parking, $100 for completing the baseline visit, $50 for completing visit 3, and $100 for completing visit 3 ($250 total for completing all visits).

Pilot subjects:
The first 2 subjects will be pilot subjects to review standard procedures. Dosage of the medication, side effects, cue-induced cravings assessments, and safety protocol will be carefully evaluated to ensure that all risks are minimized for our participants. Data from pilot

subjects will be especially critical for fine-tuning the baseline cue-reactivity assessment, in that we want to ensure participants will be sufficiently reactive to cues at baseline. If the pilot subjects show insufficient baseline cue-reactivity, one potential modification would be the development of more appropriate evocative cues.

Timeline:

The proposed project's timeline is shown in Table 2. We have submitted the application for an FDA IND exemption (and have received the FDA IND exemption letter as of November 13, 2019), followed by the submission to the Partners IRB and registration of our trial with ClinicalTrials.gov. The PI will also obtain the Schedule V research license needed to conduct this trial. The first two months of the project will be devoted to hiring and training of research staff on the cue-induced craving protocol, and pilot testing of 2 subjects. Recruitment will continue for 8 months, or until target enrollment of 10 subjects is reached. The final month will be devoted to data analysis, manuscript preparation, and providing a final update to the BRI Research Oversight Committee and the BWH Health & Technology Sub-Committee/McGraw Family Foundation. If successful, we will utilize this preliminary data to submit a NIDA R01 or R21 application in Year 2 for a double-blind, placebo-controlled, randomized trial of CBD for OUD patients on buprenorphine.

	Pre-award	Year 1												Year 2
Activity		1	2	3	4	5	6	7	8	9	10	11	12	
Submit FDA IND														
Submit Partners IRB														
Clinicaltrials.gov registration														
Obtain Schedule IV research license														
Clear protocol with IDS Pharmacy														
Training of staff														
Pilot testing with 2 subjects														
Subject recruitment														
Progress reports to BRI														
Data analysis														
Manuscript preparation														
Final oral update to BRI														
Submit NIDA R01 or R21 application														

Table 2: Timeline of proposed project

Potential difficulties:

- *Insufficient recruitment*: The director of the BWH Bridge Clinic is a collaborator to help identify potential subjects. The PI directs the BWF Addiction Recovery Program that treats OUD with buprenorphine. Together there are over 200 active patients with OUD in those programs receiving buprenorphine. As such, we are confident in the ability to recruit a sufficient number of subjects to complete the study in the proposed timeline. Nevertheless, we will also recruit potential subjects using Rally (rally.partners.org), and internet advertisements such as Craigslist. In total, we expect to screen 25-30 patients per month with these strategies, enrolling at least 5% of those we screen, leading to the target enrollment of 10 subjects in 8 months.
- *Insufficient baseline cue-reactivity*: Cue-reactivity among OUD patients taking buprenorphine for at least one month is not known. Prior studies have demonstrated that OUD patients stabilized long-term on methadone remain cue-reactive, but at lower levels.[23,44] In the study by one of the consultants to this project (Dr McHugh), subjects taking buprenorphine for detoxification (i.e. for a few days) were sufficiently reactive to cues.[8] As such, in order to ensure enrollment of subjects who are cue-reactive, we will enroll subjects who have been stable for at least a month, but not more than one year of treatment. We believe this will ensure enrollment of the most homogenous population of subjects who are sufficiently reactive to cues. In addition, we will evaluate cue-induced anxiety (on a visual analog scale of 0 to 10) concurrently, which will provide valuable information about the impact of CBD even if subjects do not respond with cravings to cues.

- *Sex differences in cue-reactivity*: Prior research has indicated that females may be more reactive to cues.[20] Our pilot study will not be powered to detect sex differences. Nevertheless, based on the results of this study, future studies can be powered sufficiently to account for sex differences in cue-reactivity.

VI. Biostatistical analysis:

Our primary interest in this pilot study is in estimating the effect sizes and variance in the outcomes to inform the design of a larger randomized trial. We will calculate the effect size representing the magnitude of change over time in the cue-reactivity score, defined as the difference in scores between heroin-related and neutral cues. The primary outcome is the change in cue-induced craving from pre-exposure to post-exposure. If the change in cravings is normally distributed, then a paired-samples t-test will be used to examine the statistical significance of the change in cue-induced craving. Accounting for the possibility of reduced cue-reactivity for participants taking buprenorphine compared to those not taking any medications, the estimated mean change in cue-induced cravings scores from prior studies is -1.5 (SD 1.5). Based on this estimate, and a conservative estimate of a correlation of r=0.60 between the two time points, a sample size of 10 is needed for 88% power and two-tailed alpha set at 0.05 for a paired-samples t-test. A point estimate of the difference in the change and the 95% confidence interval will be reported. Conversely, if the change in cravings is not normally distributed, then a sum rank test will be used.

VII. Risks and discomforts

The well-being of the study participants is of utmost importance. The in-depth screening procedure has been designed to ensure that individuals with any underlying medical or psychiatric illness are identified that may place them at greater risk for experiencing adverse effects during the study. The protocol raises several areas of concerns: confidentiality, emotional distress, adverse reactions to cue-exposure, suicidal ideation, cannabidiol medication, buprenorphine medication, and cue-reactivity safety.

Confidentiality: Confidentiality is of utmost importance given the sensitive nature of the illness and data collected. During research there is always a possibility for a breach of confidentiality, which may potentially cause personal, social, occupational, legal, and other harm. Our research team is very aware of the importance of maintaining strict confidentiality and has prior experience dealing with sensitive information. The following precautions will be used to protect the privacy of participants and maintain confidentiality of research data: all staff will be trained in confidentiality and data security procedures; privacy will be maintained by conducting all study procedures in private hospital rooms or in close, sound-proof rooms; data will be de-identified and coded with unique ID numbers; data will be securely stored in locked filing cabinets in locked rooms; electronic data will be stored in password protected documents located on password protected computers and secure servers; the key linking participants names and ID numbers will be stored in a separate password protected document in a password protected computer; access to data storage areas will be restricted to authorized study personnel; and all analysis will be conducted on de-identified data. While breach of confidentiality is possible, these safeguards will ensure that such a breach will be highly unlikely.

Emotional distress: Some patients may experience discomfort or embarrassment related to providing urine samples or answering questions about substance use and other personal behaviors. They could also experience unexpected encounters with friends or associates while in the study. However, based on prior studies with this population, we expect

the degree of distress to be very limited. All research personnel will be extensively trained on study procedures, including the conduct of the interviews that elicit personal information, and the importance of being sensitive to and respectful of all participants. In cases where emotional distress does occur, research personnel will be trained on how to identify and address it, and when to terminate an interview. Multiple levels of back-up support for research personnel will be developed. The candidate is a board certified psychiatrist, and will be able to ensure that appropriate services are received.

Adverse reactions to cue-exposure: The cue exposure procedure will end with a standardized relaxation and debriefing exercise. Before participants are discharged from each study session, their well-being will be assessed by the study staff and a standardized safety and adverse events questionnaire will be used to assess any adverse events. If needed, participants will be referred for further clinical evaluation and assistance. It is important to note that cue-exposure is a safe paradigm for studying craving in this population when employing debriefing procedures.[39]

Suicidal ideation: Patients with OUD frequently have psychiatric co-morbidities, namely depression. Participants who disclose any suicidal ideation during the study (either through spontaneous expression of suicidal ideation, or self-reported on the M.I.N.I. screen or the PHQ-9) will result in emergent evaluation by a licensed clinician member of the study staff for appropriate assessment and triage. Any disclosures will be handled within existing legal mandates, clinical practice, and social norms. Consistent with standard clinical practice, when possible, disclosures will be discussed with the participant to determine the best management options. This may include notifying the outpatient providers or family members, referring to medical treatment, calling emergency services, or escorting the participant to the Emergency Room at Brigham and Women's Hospital. When required by law, the police department will be notified. The candidate is a board certified psychiatrist and has extensive experience managing acutely distressed patients with mental or substance use disorders.

Cannabidiol medication safety: All subjects in this pilot trial will receive 600mg of cannabidiol for 3 consecutive days. Cannabidiol (Epidiolex) is approved by the U.S. Food and Drug Administration (FDA) for the treatment of seizures associated with two rare and severe forms of epilepsy. However, cannabidiol is not approved by the FDA for treatment of opioid use disorder. This protocol has been reviewed by the Center for Drug Evaluation and Research at the Food and Drug Administration to determine whether it meets the regulatory criteria for an exemption from the requirement for the submission, and we received the FDA IND exemption letter November 13, 2019. Although this proposed clinical evaluation is for an "off-label" indication of cannabidiol, it does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the Epidiolex (cannabidiol). The proposed dose is within FDA-approved mg/kg maximum daily dose limits. There are now two randomized placebo-controlled studies of administering 400mg or 800mg of cannabidiol to participants with opioid use disorder with no adverse effects.[20,22] Nonetheless, cannabidiol may cause participants to experience side effects such as: somnolence; decreased appetite; diarrhea; transaminase elevations; fatigue, malaise, and asthenia; rash; insomnia, sleep disorder, and poor quality sleep; infections; and suicidal thoughts or actions. All participants will be told of these potential side effects, and the screening procedures, including liver function tests, are in place to minimize these potential risks. The principal investigator will continually assess and monitor adverse effects both during and after cannabidiol administration, as noted in the Schedule of Measures.

Buprenorphine medication safety: All subjects in this pilot trial will be stable on buprenorphine prior to enrolling, and were thus previously deemed appropriate for the medication by their buprenorphine-waived physician. Buprenorphine has been tested extensively and is FDA-approved for the treatment of OUD. Indeed, medication-assisted

treatment (with buprenorphine, methadone or naltrexone) is the standard of care for the treatment of OUD. Because buprenorphine is a partial mu-opioid agonist, the medication can in some individuals cause intoxication, especially if used intravenously. As such, only the combination tablet that contains naloxone will be used, unless the participant has a documented allergy to naloxone. The combination tablet will produce a clinically significant opioid withdrawal if injected. All participants will be told of this reaction, and will also be asked to refrain from injecting the medication. Buprenorphine can also cause a mild euphoria and respiratory depression, but much less than compared to full agonists. The candidate has extensive experience managing OUD patients with buprenorphine, and is well versed in the appropriate clinical management of any emergent side effects from buprenorphine. Subjects will also be advised that ingesting buprenorphine with other sedative drugs, such as benzodiazepines, dramatically raises the possibility for a synergistic reaction that can cause an overdose or even death. Individuals with any underlying liver disease or have a history of hepatitis C will be informed that buprenorphine use has been rarely associated with liver failure, and that liver function test will be obtained. Subjects will be informed that buprenorphine medication should be stored in a secure location, ideally with a lock-box, to ensure no one else can access the medication including children.

Cue-reactivity testing safety: The risks associated with the proposed study are minimal. It is hypothesized that participants may experience mild to moderate and transient opioid craving in response to images. All participants will be currently in stable treatment with sublingual buprenorphine. Nonetheless, if a participant experiences more than mild to moderate distress at any time during the study, he or she will be given the option to discontinue participation and to meet with a research staff member. Study staff will conduct informal assessment of craving following completion of the study and if the distress persists, the principal investigator will be notified to determine whether further assessment is indicated. Dr. Suzuki is extensively trained in managing patient in acute distress.

Pressure pain and temporal summation of pain testing: All procedures will be performed only with the approval of Partners Human Research Committee. Written informed consent will be obtained from every subject by one of the study team members. We will demonstrate the nociceptive testing during the consent process, performing the procedure in front of potential subjects, and offering participants the option to discontinue quantitative sensory testing at any time. There is a slight chance of mild transient bruising associated with use of the algometer. In our experience with previous studies, this is quite rare (< 5 % of cases). No skin breakage has been observed by investigators in previous studies or reported in literature with the specially machined pinprick probes. Despite not breaking the skin, all pinprick probes will be disinfected in a 10% bleach solution between participants. Both QST measures (pressure algometer and pinprick probes) will be demonstrated to the patient on study staff as part of the informed consent process.

VIII. Potential benefits:

No benefits can be guaranteed from participation in the study. However, all enrolled participants will be receiving an adjunctive agent that is hypothesized to help reduce cue-induced cravings associated with their opioid use disorder, and it is possible that at least some subjects will experience a decrease in the severity of their cravings. An extensive screening procedure will ensure that individuals entering the trial will have no contraindications. Trained research personnel will perform all study procedures to minimize risks, discomforts, and adverse effects. Buprenorphine treatment is an FDA-approved treatment for the treatment of OUD, and reduces illicit opioid use and related morbidities associated with opioid use disorders. This study will generate valuable information about the effect of combining cannabidiol with stable doses of buprenorphine for patients with OUD. The results will help inform the direction

needed to take in developing effective strategies to improve the care of OUD patients taking medications. If successful, this line of research has the potential to significantly impact clinical practice of treating OUD by providing a viable medication adjunct to existing evidenced-based therapies.

IX. Monitoring and quality assurance:

The Principal Investigator, Dr. Joji Suzuki, will be responsible for monitoring the safety of all subjects. The PI or study staff will review all data collection forms on an ongoing basis for data completeness and accuracy as well as protocol. All study staff are primarily located at Brigham and Women's Hospital. Study safety meetings, including the principal investigator, study coordinators, and study physicians will occur regularly to review the progress of currently-enrolled subjects and any reported side effects.

The Principal Investigator will assess all patients with regard to stopping criteria. This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial.

Confidentiality is of utmost importance given the sensitive nature of the illness and data collected. During research there is always a possibility for a breach of confidentiality, which may potentially cause personal, social, occupational, legal, and other harm. Our research team is very aware of the importance of maintaining strict confidentiality and has prior experience dealing with sensitive information. The following precautions will be used to protect the privacy of participants and maintain confidentiality of research data: all staff will be trained in confidentiality and data security procedures; privacy will be maintained by conducting all study procedures in private hospital rooms or in close, sound-proof rooms; data will be de-identified and coded with unique ID numbers; data will be securely stored in locked filing cabinets in locked rooms; electronic data will be stored in password protected documents located on password protected computers and secure servers; the key linking participants names and ID numbers will be stored in a separate password protected document in a password protected computer; access to data storage areas will be restricted to authorized study personnel; and all analysis will be conducted on de-identified data. While breach of confidentiality is possible, these safeguards will ensure that such a breach will be highly unlikely.

X. References

1. Sordo, L. *et al.* Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *BMJ* **357**, j1550 (2017).
2. Larochelle, M. R. *et al.* Medication for Opioid Use Disorder After Nonfatal Opioid Overdose and Association With Mortality: A Cohort Study. *Ann. Intern. Med.* (2018) doi:10.7326/M17-3107.
3. Volkow, N. D., Jones, E. B., Einstein, E. B. & Wargo, E. M. Prevention and Treatment of Opioid Misuse and Addiction: A Review. *JAMA Psychiatry* **76**, 208–216 (2019).
4. Suzuki, J. *et al.* Feasibility of implementing share medical appointments (SMAs) for office-based opioid treatment with buprenorphine: A pilot study. *Subst. Abuse Off. Publ. Assoc. Med. Educ. Res. Subst. Abuse* 0 (2015) doi:10.1080/08897077.2014.998400.

5. Koob, G. F. & Volkow, N. D. Neurobiology of addiction: a neurocircuitry analysis. *Lancet Psychiatry* **3**, 760–773 (2016).
6. Kakko, J. *et al.* Craving in opioid use disorder: From neurobiology to clinical practice. *Front. Psychiatry* (2019).
7. Fischer, G., Nava, F. & Stover, H. Outcomes of opioid-dependence treatment across Europe: Identifying opportunities for improvement. *Heroin Addict Relat Clin Probl* **14**, 39–50 (2012).
8. McHugh, R. K. *et al.* Assessing craving and its relationship to subsequent prescription opioid use among treatment-seeking prescription opioid dependent patients. *Drug Alcohol Depend.* **145**, 121–126 (2014).
9. Serre, F., Fatseas, M., Swendsen, J. & Auriacombe, M. Ecological momentary assessment in the investigation of craving and substance use in daily life: a systematic review. *Drug Alcohol Depend.* **148**, 1–20 (2015).
10. Fatseas, M., Serre, F., Swendsen, J. & Auriacombe, M. Effects of anxiety and mood disorders on craving and substance use among patients with substance use disorder: An ecological momentary assessment study. *Drug Alcohol Depend.* **187**, 242–248 (2018).
11. Wang, G.-B. *et al.* Drug-related cues exacerbate decision making and increase craving in heroin addicts at different abstinence times. *Psychopharmacology (Berl.)* **221**, 701–708 (2012).
12. Fiellin, D. A. *et al.* A randomized trial of cognitive behavioral therapy in primary care-based buprenorphine. *Am. J. Med.* **126**, 74.e11–17 (2013).
13. Weiss, R. D. *et al.* Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. *Arch. Gen. Psychiatry* **68**, 1238–1246 (2011).
14. Ling, W., Hillhouse, M., Ang, A., Jenkins, J. & Fahey, J. Comparison of Behavioral Treatment Conditions in Buprenorphine Maintenance. *Addict. Abingdon Engl.* (2013) doi:10.1111/add.12266.
15. Amato, L., Minozzi, S., Davoli, M. & Vecchi, S. Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence. *Cochrane Database Syst. Rev.* CD004147 (2011) doi:10.1002/14651858.CD004147.pub4.
16. Carroll, K. M. & Weiss, R. D. The Role of Behavioral Interventions in Buprenorphine Maintenance Treatment: A Review. *Am. J. Psychiatry* appiajp201616070792 (2016) doi:10.1176/appi.ajp.2016.16070792.
17. Crippa, J. A., Guimarães, F. S., Campos, A. C. & Zuardi, A. W. Translational Investigation of the Therapeutic Potential of Cannabidiol (CBD): Toward a New Age. *Front. Immunol.* **9**, 2009 (2018).
18. Premoli, M. *et al.* Cannabidiol: Recent advances and new insights for neuropsychiatric disorders treatment. *Life Sci.* **224**, 120–127 (2019).
19. Chye, Y., Christensen, E., Solowij, N. & Yücel, M. The Endocannabinoid System and Cannabidiol's Promise for the Treatment of Substance Use Disorder. *Front. Psychiatry* **10**, 63 (2019).
20. Hurd, Y. L. *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. *Am. J. Psychiatry* appiajp201918101191 (2019) doi:10.1176/appi.ajp.2019.18101191.
21. Manzanares, J., Julian, M. & Carrascosa, A. Role of the Cannabinoid System in Pain Control and Therapeutic Implications for the Management of Acute and Chronic Pain Episodes. *Curr. Neuropharmacol.* **4**, 239–257 (2006).
22. Hurd, Y. L. *et al.* Early Phase in the Development of Cannabidiol as a Treatment for Addiction: Opioid Relapse Takes Initial Center Stage. *Neurother. J. Am. Soc. Exp. Neurother.* **12**, 807–815 (2015).

23. Shi, J., Zhao, L.-Y., Epstein, D. H., Zhang, X.-L. & Lu, L. Long-term methadone maintenance reduces protracted symptoms of heroin abstinence and cue-induced craving in Chinese heroin abusers. *Pharmacol. Biochem. Behav.* **87**, 141–145 (2007).
24. Dengler-Crish, C. M., Bruehl, S. & Walker, L. S. Increased wind-up to heat pain in women with a childhood history of functional abdominal pain. *Pain* **152**, 802–8 (2011).
25. Maixner, W. Sensitivity of patients with painful temporomandibular disorders to experimentally evoked pain: evidence for altered temporal summation of pain. *Pain* **76**, 71–81 (1998).
26. Schreiber, K. L. Persistent pain in postmastectomy patients: comparison of psychophysical, medical, surgical, and psychosocial characteristics between patients with and without pain. *Pain* **154**, 660–8 (2013).
27. Staud, R. Temporal summation of pain from mechanical stimulation of muscle tissue in normal controls and subjects with fibromyalgia syndrome. *Pain* **102**, 87–95 (2003).
28. Staud, R. Brain activity related to temporal summation of C-fiber evoked pain. *Pain* **129**, 130–42 (2007).
29. Price, D. D., Hull, C. D. & Buckwald, N. A. Intracellular responses of dorsal horn cells to cutaneous and sural nerve A and C fiber stimuli. *Exp Neurol* **33**, 291–309 (1971).
30. Cook, A. J., Woolf, C. J., Wall, P. D. & McMahon, S. B. Dynamic receptive field plasticity in rat spinal dorsal horn following C-primary afferent input. *Nature* **325**, 151–153 (1987).
31. Simone, D. A. *et al.* Neurogenic hyperalgesia: central neural correlates in responses of spinothalamic tract neuronsJ. *Neurophysiol* **66**, 228–246 (1991).
32. Dickenson, A. H. & Sullivan, A. F. Evidence for a role of the NMDA receptor in the frequency dependent potentiation of the deep rat dorsal horn nociceptive neurons following C fiber stimulation. *Neuropharmacology* **26**, 1235–1238 (1987).
33. Dubner, R. Ruda MA.Activity-dependent neuronal plasticity following tissue injury and inflammation. *Trends Neurosci* **15**, 96–103 (1992).
34. Li, J., Simone, D. A. & Larson, A. A. Windup leads to characteristics of central sensitization. *Pain* **79**, 75–82 (1999).
35. Stubhaug, A., Breivik, H., Eide, P. K., Kreunen, M. & Foss, A. Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. *Acta Anaesthesiol Scand* **41**, 1124–1132 (1997).
36. Eisenberg, E., Midbari, A. & Haddad, M. Pud D.Predicting the analgesic effect to oxycodone by 'static' and 'dynamic' quantitative sensory testing in healthy subjects. *Pain* **151**, (2010).
37. Ram, K. C., Eisenberg, E. & Haddad, M. Pud D.Oral opioid use alters DNIC but not cold pain perception in patients with chronic pain - new perspective of opioid-induced hyperalgesia. *Pain* **139**, (2008).
38. Edwards, R. R., Wasan, A. D., Michna, E., Greenbaum, S. & Ross, E. *Jamison RN.Elevated pain sensitivity in chronic pain patients at risk for opioid misuse.J Pain*. vol. 12 (2011).
39. DeSantis, S. M., Bandyopadhyay, D., Back, S. E. & Brady, K. T. Non-treatment laboratory stress- and cue-reactivity studies are associated with decreased substance use among drug-dependent individuals. *Drug Alcohol Depend.* **105**, 227–233 (2009).
40. Brennum, J. Measurements of human pressure-pain thresholds on fingers and toes. *Pain* **38**, 211–7 (1989).
41. Edwards, R. R. Alteration in pain modulation in women with persistent pain after lumpectomy: influence of catastrophizing. *J Pain Symptom Manage* **46**, 30–42 (2013).
42. Rolke, R. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. *Pain* **123**, 231–43 (2006).
43. Greenspan, J. D. Pain sensitivity risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case control study. *J Pain* **12**, 61–74 (2011).

44. Wang, Y. *et al.* Reduced responses to heroin-cue-induced craving in the dorsal striatum: effects of long-term methadone maintenance treatment. *Neurosci. Lett.* **581**, 120–124 (2014).