Official Title: **Sublingual Cannabidiol for Anxiety**

Principal Investigator: **Dr. Staci A. Gruber, Ph.D.**

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PARTNERS HUMAN RESEARCH COMMITTEE
PROTOCOL SUMMARY

Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR
Staci A. Gruber, Ph.D.

PROTOCOL TITLE
Sublingual Cannabidiol for Anxiety

FUNDING
Sundry Funds/Department

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1/21/2025

SPECIFIC AIMS

Concisely state the objectives of the study and the hypothesis being tested.

This investigation is designed to examine how the impact of the administration of sublingual high-cannabidiol (CBD) compounds on individuals with anxiety disorders.

Specific Aim 1: To assess pre- and post-CBD treatment clinical state ratings of anxiety and quality-of-life ratings in individuals with anxiety disorders.

Specific Aim 2: To assess pre- and post-CBD treatment performance on a range of neurocognitive measures designed to examine cognitive function.

Specific Aim 3: In a subset of individuals, to examine structural and functional changes that may occur in the brain following treatment with CBD using magnetic resonance imaging (MRI).

Exploratory Aim: In a subset of individuals, to examine the pharmacokinetics and pharmacodynamics (PK/PD) of this CBD tincture via continuous blood draw.

Exploratory Aim: In a subset of individuals, to assess potential changes in circulating endocannabinoids pre- and post-CBD treatment.

BACKGROUND AND SIGNIFICANCE

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

Cannabis has been used for medicinal purposes across many cultures for a range of disorders dating as far back as 4000 BC. The flowering plant has been used to treat a wide range of maladies due to its effects on both physical and psychological conditions. The plant is comprised of phytocannabinoids, terpenoids, flavonoids, steroids and enzymes, the concentrations of which vary depending on the strain; the phytocannabinoids are the most cannabis-specific of these components, and bind to receptors typically modulated by endogenous cannabinoids (Zhornitsky

& Potvin, 2012). These endocannabinoids act via G-protein-coupled cell membrane receptors in the central and peripheral nervous system, specifically CB1 and CB2 receptors. One phytocannabinoid in particular, delta-9 tetrahydrocannabinol (Δ9-THC), is the major psychoactive constituent of cannabis, and is a Schedule I substance in the United States. Δ9-THC exerts its effects acting as an agonist at CB1 receptors. Apart from Δ9-THC, there are many other phytocannabinoids present in cannabis, including cannabidiol (CBD), a non-psychoactive constituent of cannabis, which acts as a CB1 receptor antagonist; CBD does not have abuse potential, and thus does not appear on the DOJ's scheduled substance list (http://www.deadiversion.usdoj.gov/schedules/). CBD, as well as other phytocannabinoids present in cannabis, contribute to the medicinal effects of cannabis. There is increasing evidence that CBD in particular may have significant medicinal properties and benefits; experimental studies in both animals and humans have demonstrated the CBD can act as an anticonvulsant, antipsychotic, and muscle relaxant. CBD has also been shown to be responsible for anxiolytic effects in animals and humans, although no clinical trials of CBD have been conducted to date in patients with anxiety. Additionally, a recent Canadian study reported that anxiety was the third most common symptom for which patients reported using medicinal cannabis (Walsh et al. 2013). In contrast to THC, CBD is a CB1 receptor antagonist, and does not have abuse potential; thus, CBD is not a scheduled substance.

Studies in animals have revealed that acute treatment with CBD can exert anxiolytic effects in tests of experimentally-induced anxiety. Fogaca et al. (2014) infused CBD into the prelimbic medial prefrontal cortex in rats, resulting in anxiolysis during the contextual fear conditioning test and the elevated plus maze after rats submitted to a two-hour stressful event. Soares et al. (2010) and Campos et al. (2008) showed that both panic-like responses as well as anxiety induced by the elevated plus maze are reduced in male rats receiving CBD in the dorsal periaqueductal gray. Additionally, Resstel et al. (2009) concluded that CBD can attenuate acute autonomic responses to stress following restraint, as well as delayed emotional consequences. Chronic administration of CBD in animals is also associated with anxiolytic effects. Campos, de Paula Soares, et al. (2013) showed that repeated administration of CBD had a panicolytic effect in rats subjected to the elevated T-maze. Another study from Campos and Ortega (2013) determined that chronic CBD administration following daily unpredicatable stress reduced anxiety.

While few human studies have been conducted to investigate CBD's effects on anxiety, those that have been published confirmed the previous findings in animals that CBD can be anxiolytic. Fusar-Poli et al. (2009) demonstrated that 600 mg of CBD reduced anxiety in healthy subjects viewing fearful faces while undergoing functional magnetic resonance imaging (fMRI); the authors concluded that this effect was likely due to modulating the activation of limbic and paralimbic regions. This same group later reported that CBD alters subcortical prefrontal connectivity via the amygdala and anterior cingulate (Fusar-Poli et al. 2010). Additionally, in a model of experimentally induced anxiety in healthy subjects, Zuardi et al. (1993) found that 300mg of CBD attenuated anxiety, as did the anxiolytic drugs diazepam and ipsapirone. To induce anxiety, the authors used the simulated public speaking test (SPST), which involves a subject speaking in front of a video camera for several minutes while physiological correlates of anxiety are measured (including heart rate and blood pressure), and self-report scales are administered to measure subjective anxiety. This model has also been used to induce anxiety in patients with social anxiety disorder (SAD); Bergamaschi et al. (2011) demonstrated that pretreatment with a single dose of CBD results in an anxiolytic effect for SAD patients. This single dose (600mg) was sufficient to reduce subjective anxiety, cognitive impairment, and

discomfort in SAD patients completing the SPST, compared to placebo, and reduced anxiety in the CBD-treated patients to a level similar to that of healthy controls. Crippa et al. (2011) confirmed CBD's effects in SAD and further investigated the basis of CBD's anxiolytic effect in SAD patients using neuroimaging. Relative to placebo, a single dose of CBD (400mg) was associated with significantly decreased subjective anxiety scores in SAD patients.

Despite the recent interest in cannabinoid-based products, no published studies to date have conducted a clinical trial of products high in CBD in individuals who suffer from anxiety. Further, none have systematically evaluated baseline and follow-up clinical state and related quality of life measures in individuals taking CBD, or assessed measures of brain structure and function before and after treatment with CBD using neuropsychological measures or neuroimaging. As a growing number of states are legalizing medical marijuana and increasing evidence suggests that CBD may exert anxiolytic effects, there is a gap in the literature regarding the effects of CBD, often found in higher levels in medical marijuana than recreational marijuana, on anxiety. This investigation will be the first of its kind to conduct a double-blind clinical trial of high-CBD compounds (both full-spectrum and single-compound) in individuals with anxiety. The main outcome measures of the project will include a comprehensive assessment of anxiety using both self-report and administered scales pre- and post-treatment, as well as range of quality of life measures. In addition, this project will examine the impact of high CBD products relative to placebo on several cognitive domains using neuropsychological testing. Furthermore, a subset of eligible participants will complete a structural and functional MRI scanning to assess brain function and connectivity using a multimodal neuroimaging protocol prior to and following four weeks of treatment with high CBD compounds vs placebo.

RESEARCH DESIGN AND METHODS

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, "Enrollment at Partners will be limited to adults although the sponsor's protocol is open to both children and adults."

This study is an investigation of 97 subjects who have expressed interest in using CBD for anxiety. Subjects will complete study visits at McLean Hospital. Following a preliminary phone screen and prior to any evaluation, all study subjects will be required to sign a McLean Hospital approved informed consent form that describes all study procedures. The phone screen includes questions related to medical history, substance use history, demographics, and screening questions from the OASIS (see below) to determine whether the subject has anxiety.

Individuals will be assessed at baseline and weekly for four weeks of treatment with compounds administered as sublingual tinctures in a double-blind, randomized procedure: subjects will receive either a full-spectrum high CBD product, a single-compound CBD product, or matched placebo in a 3:1:1 randomization schedule. Each product will be analyzed and verified at an outside lab for safety and potency. Subjects will self-administer 1 ml (10mg/ml) of CBD or placebo sublingually three times daily. At each weekly visit, individuals will complete clinical scales and have a check-in with study staff. Neuropsychological testing will be performed at baseline and the final visit in order to assess cognitive performance. Buccal swabs will be collected for DNA analysis from all participants in the double-blind phase, and a subset of

individuals will complete blood draws at baseline and week 4 in order to assess levels of circulating endocannabinoids. Finally, a subset of individuals will receive an hour-long MRI scan at baseline and the final visit, with both resting state and task-related functional magnetic resonance imaging (fMRI) in each MRI session. In addition, a brief diffusion tensor imaging (DTI) sequence will also be acquired to examine white matter fiber tract integrity, and magnetic resonance spectroscopy (MRS) will be conducted to examine levels of certain metabolites in the brain.

At the investigators' discretion, in order to assess clinical state, participants may complete daily mood ratings either on paper or electronically via REDCap or StudyTrax. Additionally, subjects will be given the option to complete study drug diaries manually (pencil and paper) or via a secure web portal.

In order to assess the efficacy of the dose chosen for the double-blind study, we will also conduct a small open-label phase I trial of the full-spectrum CBD tincture prior to initiating the double-blind study. This open-label trial will enroll up to 22 participants who are interested in using CBD, and who have anxiety. This trial will determine whether patients derive clinical benefits at the current dosage proposed for the active treatment arm of the double-blind trial. This trial will examine all components of the originally proposed study. During the open-label phase, a subset of participants (up to n=16) will complete an extra visit that includes clinical rating scales and a 2-hour continuous blood draw directly following administration of the tincture in order to assess plasma concentration of CBD over time and correlation with anxiety.

Subjects will be recruited through IRB-approved advertisements and flyers in regions that have approved medical marijuana. Additionally, medical marijuana healthcare facilities throughout New England, including CannaCare, Integr8, MMJ Physician Practice, and others, may also refer interested patients to contact the study recruitment line for further screening. These healthcare groups provide their interested patients who meet for general inclusion criteria with study recruitment materials. The total sample size for the double-blind study is 75 (45 full-spectrum CBD, 15 single-compound CBD, and 15 placebo); up to 15 of each group (45 total) will also complete the MRI scanning protocol. For the open-label trial, the total sample size is 16 (we will enroll up to 22 to ensure 16 completers); up to 16 subjects will complete the MRI scanning protocol.

Inclusion Criteria

1) Subject has provided informed consent
2) Subject is 18 or older
3) Subject is a native English speaker or acquired English prior to age 5
4) Subject scores a minimum of 16 on the Beck Anxiety Inventory (BAI) OR a minimum of 11 on the Overall Anxiety Severity and Impairment Scale (OASIS) at the screening/baseline visit or at phone screening if within 2 weeks of the baseline visit

Exclusion Criteria

Subjects will be excluded if they report any of the following:

1) Non-native English speakers
2) Estimated IQ < 75
3) Meets criteria for DSM-V classification of current substance abuse/dependence, a psychotic disorder, bipolar disorder, or an eating disorder

4) A history of head injury or loss of consciousness greater than 5 minutes
5) Currently uses recreational marijuana more frequently than 1x/month
6) Female subjects will be excluded if they have a positive urine pregnancy test
7) Presence of a serious medical illness, including liver or kidney disease, or neurological disorder
8) Allergy to coconut, as product is formulated in MCT (coconut) oil

Additional Exclusions for Driving Simulator:

1) Does not drive
2) Endorses experiencing motion sickness

Additional Exclusions for MR Component:

1) Claustrophobia or metal implanted within the body, body piercings which are not removable
2) Cardiac pacemakers, metal clips on blood vessels (also called stents), artificial heart valve, artificial arms, hands, legs, etc., brain stimulator devices, implanted drug pumps, ear implants, eye implants or known metal fragments in eyes, exposure to shrapnel or metal filings (wounded in military combat, sheetmetal workers, welders, and others), other metallic surgical hardware in vital area, certain tattoos with metallic ink, certain transdermal (skin) patches such as NicoDerm (nicotine for tobacco dependence), Transderm Scop (scopolamine for motion sickness), or Ortho Evra (birth control), certain intrauterine devices (IUDs) containing metal.
3) Poor vision, as subjects must have normal or corrected-to normal vision for viewing of cognitive challenge paradigms during fMRI protocols

Subjects who participate in the open-label phase of the study will not be eligible to also enroll in the double-blind study.

Briefly describe study procedures. Include any local site restrictions, for example, "Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study." Describe study endpoints.

Subjects will meet with the Principal Investigator, a Clinical Neuropsychologist, or a trained Research Assistant at McLean Hospital for five visits (baseline, and four weekly visits throughout the four-week treatment period). A subset of subjects in the open-label phase will also complete an optional 6th visit; this visit will occur after a >1 week washout period after the final (week 4) visit, where they will return to the lab to complete a 2-hour continuous blood draw after administration of the tincture. Subjects will review and sign the approved informed consent form prior to engaging in any study procedures. A structured clinical screening interview (SCID-P or QuickSCID) will be administered, and demographic information, substance abuse/use, and medical histories will also be obtained. Study inclusion/exclusion criteria will be applied, and appropriate subjects will be enrolled and complete the rest of the study visit, which will consist of clinical ratings and quality of life scales, a neuropsychological assessment, a driving simulation task, and an hour-long MRI scan for a subset of eligible individuals. The imaging protocol will include structural and functional imaging techniques, as well as diffusion tensor imaging/diffusion kurtosis imaging and magnetic resonance spectroscopy.

The baseline visit is estimated to take approximately 6-7 hours, and the final study visit is estimated to take approximately 3-4 hours, with the weekly visits in the interim estimated to take approximately 1 hour, for a total of approximately 12-14 hours required to complete all possible visits. The optional 6th visit will take approximately 3 hours to complete. [redacted] rine samples will be collected at each visit to measure THC and other substance levels throughout the study. Female subjects who enroll in the study will be informed that their sample will also be used to confirm negative pregnancy (HCG) status (QuPID One-Step Pregnancy). A buccal swab sample will also be collected for DNA analysis in the double-blind phase.

A subset of patients in the open-label phase (up to n=16) will complete an optional 6th visit at least one week after completing the open-label phase of the clinical trial. At this visit, an intravenous catheter will be inserted in an antecubital vein for withdrawal of blood samples for subsequent measure of blood CBD and THC levels. The catheter will be inserted 5 to 10 minutes before the sublingual administration of the standard dose of full-spectrum CBD tincture (1mL of 10mg/ml CBD). Blood will be drawn at a maximum rate of 1 mL/min, and five (5) minute samples will be drawn from 5 to 90 minutes after tincture administration and every 10 minutes from 90 to 120 minutes. Quantitative analyses of CBD and THC levels will be performed by gas chromatography. A total of less than 120 mL of whole blood will be drawn on the study day. This method of continuous sampling has been in place and used successfully in Dr. Scott Lukas's laboratory since 1986 (including current approved protocol [redacted]).

A subset of patients in the double-blind phase (up to n=75) will complete a blood draw at baseline and week 4. Plasma will be analyzed for circulating levels of endocannabinoids, including: AEA, 2-AG, 2-OG, PEA, and OEA. Levels of cortisol will also be analyzed. Approximately 10ml of whole blood will be drawn into a non-heparinized tube, centrifuged to separate the plasma, flash frozen and transported to [redacted]. The samples will be analyzed via mass spectrometry and levels of each endocannabinoid will be assessed pre- and post-CBD treatment.

For the double-blind study, at the end of the baseline visit, eligible subjects will be randomized to either full-spectrum CBD, single-compound CBD, or placebo using a standard 3:1:1 randomization procedure. In the open-label trial, all subjects will be provided with the full-spectrum CBD tincture at the conclusion of the baseline visit. Subjects will be instructed on how to administer the compound in the morning, midday, and evening; they will be instructed how to draw one full dropper of compound, deposit the amount in the dropper under the tongue, hold for 45-60 seconds, then swallow.

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

Standard of care for anxiety treatment includes medications, such as antidepressants, buspirone, and benzodiazepines, as well as psychotherapy. This study is an investigation of a plant-derived compound that has promise in the treatment of anxiety. Subjects will not be asked to change their current treatment regimen to participate in this study (i.e. discontinue other medications); this study will add CBD to their current regimen.

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

Risks to subjects will be minimal throughout this study; please see below for detailed explanation of foreseeable risks and discomforts. The components of this study, including the clinical rating scales, neurocognitive tasks, and MR scanning have previously been used by the investigator in multiple studies. The administration of CBD will be low risk due to the add-on design of the study; patients will proceed with their treatment as usual, with CBD or placebo added to their medication regimen. See below for a detailed explanation of the risks of CBD administration in this population.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

The side-effect profile of CBD is extremely low, and adverse events are not anticipated. Subjects may withdraw from the study at any time and for any reason. A subject's participation in the trial will end if they report adverse effects of CBD or placebo administration and wish to leave the study, or if study staff determine that study termination is appropriate due to adverse events.

FORESEEABLE RISKS AND DISCOMFORTS

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

Risks Associated with Neuropsychological and Clinical Assessment/Rating Scales
Although unlikely, it is possible that during the structured assessment or rating scales, subjects may become distressed when recalling periods of their lives or their current mood state. Subjects may also become frustrated during the neuropsychological testing. Subjects are informed that they can take a break and/or can choose to stop answering questions at any time. To mitigate any risks associated with the neurocognitive assessment or clinical ratings, clinical staff will be available to evaluate and advise the subject during study visits.

MR/fMRI/DTI/DKI/MRS
Currently, there are no known risks associated with fMRI, MRI, DTI/DKI, or MRS scanning in the 3T scanner, however, there are some areas of concern that must be addressed. First, participation in an MRI study requires subjects to be exposed to strong magnetic fields, the long-term effects of which are unknown. The magnetic fields also require caution given the risk of attraction of ferromagnetic metal objects by the high strength magnetic field. Second, some subjects express discomfort by the relatively confined space within the bore of the MR scanner. Finally, some subjects find the scanning experience unpleasant because of the noise of the gradients during MRI image acquisition. Each of these risks is present for a clinical MR scan, which are not increased by the research project proposed in this application.

CBD Administration
The administration of CBD is considered low-risk because of the add-on design of the study; in addition, previous studies of CBD administration have reported no signs of toxicity or serious side effects (Cunha et al. 1980; Consroe et al. 1991; Leweke et al. 2012; Zuardi et al. 2006 and 2009). The safety of CBD administration in pregnant women and fetuses is currently unknown; thus, female participants capable of child-bearing will be screened for pregnancy prior to the study and at each study visit. Participants will be immediately disqualified and excluded from further participation in the study if they have a positive pregnancy test at any point during the study.

Additionally, CBD is not a scheduled substance, and there is no risk of intoxication or addiction. The amount of THC included in the high CBD tincture is minimal, and will not exceed 0.3% by weight; therefore, the risk of significant side effects or psychoactive effects is extremely low. Sublingual tinctures are unlikely to be viewed by the public as analogous to recreational smoked marijuana, thus decreasing the risk that the subject will experience any potential negative appraisal arising from perceived notions associated with marijuana use.

Blood Draw
Subjects may have a bruise or pain from the site where the blood sample is acquired. There is also a small risk of feeling lightheaded, fainting, or infection. Clinical staff will be available to evaluate the subject if they experience any of these symptoms.

DNA Collection
The primary risk of collecting and examining genetic information is the remote possibility of future genetic discrimination. It is possible that these data or the buccal swab samples from which they were derived could be stolen, analyzed, and used to reveal sensitive information that may in turn lead to insurance coverage or employment denial. There is a very remote possibility that enough information could be stolen to help identify a person, exposing individuals to any risks that result as that identification. Procedures described below minimize the possible breach of confidentiality.

Protection of risks: To reduce the possible risk of a breach of confidentiality regarding genetic material, the informed consent will include a specific section addressing risks associated with collecting genetic material. The consent form will have choices regarding the permissible uses of his/her DNA. These range from “restriction to this study only” to “any future research use by the study investigators” (provided that any future study is approved by an IRB). One of the choices must be initialed by the participant. Participants will also be informed that they may have their DNA samples destroyed at any time, and will provide the necessary information on how to inform investigators to do this.

EXPECTED BENEFITS

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, "It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects." Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

There may be no direct benefits to the subjects; however, based on previous research, it is reasonable to expect that some subjects may experience an improvement in clinical state or quality of life related to a reduction in anxiety.

It is reasonable to expect that this study will contribute to overall knowledge in this field and potentially provide benefits to society in general through improvements in treatment and management as a result of this increased level of understanding.

Subjects are informed that there may be no direct benefit to them from participating in this study. Subjects may benefit from knowing that the results of this study may improve the future care of people prescribed medicinal marijuana, particularly those with anxiety.

EQUITABLE SELECTION OF SUBJECTS

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children, and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

No subjects will be excluded on the basis of race, sex, ethnicity or sexual orientation.

When people who do not speak English are excluded from participation in the research, provide the scientific rationale for doing so. Individuals who do not speak English should not be denied participation in research simply because it is inconvenient to translate the consent form in different languages and to have an interpreter present.

All subjects must be native English speakers because several of the cognitive tasks require English as the native language in order to accurately assess cognitive state.

For guidance, refer to the following Partners policy:
Obtaining and Documenting Informed Consent of Subjects who do not Speak English
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Non-English_Speaking_Subjects.1.10.pdf

RECRUITMENT PROCEDURES

Explain in detail the specific methodology that will be used to recruit subjects. Specifically address how, when, where and by whom subjects will be identified and approached about participation. Include any specific recruitment methods used to enhance recruitment of women and minorities.

Recruiting and enrollment will be the responsibility of the McLean study coordinators. Subjects will be recruited from a number of sources, including IRB-approved flyers and post cards, as well as online postings (including the Partners Clinical Trials website), and through RPDR/RODY-Yes messaging.. Medical marijuana certification facilities may also refer interested patients to contact the study recruitment line for further screening. Potential subjects for this study must be capable of understanding the nature of this study as well as the discomforts and potential benefits. All subjects will be given as much time as they want to consider their participation in the study and ask any questions they may have before being asked to sign the consent form.

Provide details of remuneration, when applicable. Even when subjects may derive medical benefit from participation, it is often the case that extra hospital visits, meals at the hospital, parking fees or other inconveniences will result in additional out-of-pocket expenses related to study participation. Investigators may wish to consider providing reimbursement for such expenses when funding is available

Subjects will be compensated for their time using a tiered payment system, with a payment of $75 for visits 1 (baseline visit) and 5 (final visit), and $50 for three weekly visits for a total of $300; if termination occurs during any point of the visit, subjects are compensated at a rate of $25 per hour. Subjects who participate in the scanning component of study will receive an additional $75 at visit 1 and visit 5 for a potential total of $450. Subjects will receive a completion bonus of $50 if they complete the study, for a total of $350 or $500, dependent on whether they receive MR scanning. Subjects in the open-label phase who complete the optional 6th visit, which includes a blood draw, will receive an additional $150, for a total of $500 (if no MR scans are completed) or $650 (if MR scans are completed at Visits 1 and 5). Subjects in the double-blind phase who complete the optional blood-draws at Visits 1 and 5 will receive an additional $25/blood draw, for a total of $400 or $550 (if MR scans are completed).

For guidance, refer to the following Partners policies:

Recruitment of Research Subjects
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Recruitment_Of_Research_Subjects.pdf

Guidelines for Advertisements for Recruiting Subjects
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Guidelines_For_Advertisements.1.11.pdf

Remuneration for Research Subjects
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Remuneration_for_Research_Subjects.pdf

CONSENT PROCEDURES

Explain in detail how, when, where, and by whom consent is obtained, and the timing of consent (i.e., how long subjects will be given to consider participation). For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician investigator must obtain informed consent. When subjects are to be enrolled from among the investigators' own patients, describe how the potential for coercion will be avoided.

Written, informed consent will be obtained from all participants following a screening interview to determine eligibility. All subjects will be required to give informed consent and must understand all procedures prior to their participation in the study. Consent will be obtained by the principal investigator, Dr. Staci Gruber, or a licensed physician investigator on the protocol, either Dr. David Olson, Dr. Franca Centorrino, or Dr. Gordana Vitaliano. If consent is obtained by Dr. Gruber, a licensed physician investigator will review and sign off on patient enrollment. A physician will also be available if the patient has any additional questions during the consent process. The consent form will include a description of the study, information about procedures, and assurances of confidentiality. A member of the research staff will explain the consenting procedure and be available for any questions that arise from the consent form. Prior to signing the informed consent, subjects will be asked if they have any questions regarding the conduct or design of the study. A copy of the signed consent form will be given to the study subject, and a copy placed in their research record. All subjects will be reminded that their participation is completely voluntary, and may withdraw or discontinue the neuropsychological evaluation at any time. The informed consent will be approved by the McLean Hospital Institutional Review Board, which monitors study progress, safety and outcome on a regular basis. All signed consent forms will be kept in the subject's case report form in [redacted] under lock and key.

Remote Consenting Process

We will remotely consent patients by one of the two following options. The first option will consist of consenting via REDCap. The second option is to send the participant the consent form ahead of time for their review, consent them over the phone, and have the participant physically sign or e-sign the consent form and either scan or take a photo of all pages, and send to us; this will be signed by the investigator. In-person written consent may also occur in rare circumstances. Each subject's file will contain a note to file describing the procedure followed.

NOTE: When subjects are unable to give consent due to age (minors) or impaired decision-making capacity, complete the forms for Research Involving Children as Subjects of Research and/or Research Involving Individuals with Impaired Decision-making Capacity, available on the New Submissions page on the PHRC website:

https://partnershealthcare.sharepoint.com/sites/phrmApply/aieipa/irb

For guidance, refer to the following Partners policy:

Informed Consent of Research Subjects:

https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Informed_Consent_of_Research_Subjects.pdf

DATA AND SAFETY MONITORING

Describe the plan for monitoring the data to ensure the safety of subjects. The plan should include a brief description of (1) the safety and/or efficacy data that will be reviewed; (2) the planned frequency of review; and (3) who will be responsible for this review and for determining whether the research should be altered or stopped. Include a brief description of any stopping rules for the study, when appropriate. Depending upon the risk, size and complexity of the study, the investigator, an expert group, an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

NOTE: Regardless of data and safety monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care.

Data analyses will be conducted on the open-label phase of the study prior to initiating the double-blind phase in order to ensure that patients derive clinical benefit from the dose selected. Specifically, in conjunction with Dr. Olson, we will assess clinical response after the first 5 patients have completed their 4 week trial. [redacted] Findings will be used to inform the double blind phase of the study, which would not begin until adequate dose/response is achieved. An amendment would be submitted to the IRB for approval prior to adjusting the dose of CBD.

In the unlikely event that an adverse event occurs, it will be reported to the primary investigator and the Institutional Review Board's guidelines will be followed to ensure adequate reporting and response. All adverse events will be reported to the Partners Healthcare Internal Review Board for their records. There are currently no plans to utilize a Data Safety Monitoring Board (DSMB) due to the extremely low side-effect profile of CBD, but if the IRB deems that an independent DSMB is necessary, the investigators would be happy to suggest individuals who are appropriate or to consider outside suggestions from IRB members.

Subjects are required to have a structural MRI scan of clinical quality at least once per year at McLean Hospital that is reviewed by a board-certified radiologist or neurologist and a clinical report is generated usually within 2-4 days. If the subject has not received a structural clinical scan in the past year, one will be obtained for the present study. Subjects will not receive more than one structural clinical MRI within a given 12-month period unless a follow-up scan is recommended by the radiologist who reads the scan. Abnormal reports are reviewed by the Clinical Director of the McLean Imaging Center (MIC), Dr. David Olson and forwarded to the Principal Investigator, in this case, Dr. Gruber, and the designated study physician. If an abnormality is present, the study physician and PI will coordinate the process of contacting the subject so that an appointment can be made to discuss the findings. The MIC Clinical Director may also assist with this process when requested and appropriate. If a follow-up scan is recommended by the radiologist, we will offer the subject a cost-free repeat scan (with contrast if indicated). In all cases we offer a copy both of the clinical report and the MRI scan (on film or cd) to subjects to take to their primary care or other consulting physicians, at no cost.

FMRI, DTI/DKI, and MRS data collected will be processed with software available in the Neuroimaging Center. Echo planar images will be analyzed off line using a semi-automated fMRI data analysis tool and a motion correction algorithm developed on-site at McLean. Measures of signal intensity will be derived by averaging the signal measured in all pixels in each region of interest (ROI) for each time point during the task activation period.

Describe the plan to be followed by the Principal Investigator/study staff for review of adverse events experienced by subjects under his/her care, and when applicable, for review of sponsor safety reports and DSMB reports. Describe the plan for reporting adverse events to the sponsor and the Partners' IRB and, when applicable, for submitting sponsor safety reports and DSMB reports to the Partners' IRBs. When the investigator is also the sponsor of the IND/IDE, include the plan for reporting of adverse events to the FDA and, when applicable, to investigators at other sites.

NOTE: In addition to the adverse event reporting requirements of the sponsor, the principal investigator must follow the Partners Human Research Committee guidelines for Adverse Event Reporting

In the unlikely event that an adverse event occurs, it will be reported by the primary investigator to the Institutional Review Board, and the IRB's guidelines will be followed to ensure adequate reporting and response. All adverse events will be reported to the Partners Healthcare Internal Review Board for their records.

MONITORING AND QUALITY ASSURANCE

Describe the plan to be followed by the principal investigator/study staff to monitor and assure the validity and integrity of the data and adherence to the IRB-approved protocol. Specify who will be responsible for monitoring, and the planned frequency of monitoring. For example, specify who will review the accuracy and completeness of case report form entries, source documents, and informed consent.

NOTE: Regardless of monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for ensuring that the study is conducted at his/her investigative site in accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.

Regulatory binders are kept for all studies at McLean Hospital in order to constantly monitor investigations and ensure that all data is collected safely.

The principal investigator will be responsible for monitoring and ensuring the integrity of the data and adherence to the IRB-approved protocol. They will review any questions or concerns regarding data, and will review each signed consent form for the study.

For guidance, refer to the following Partners policies:
Data and Safety Monitoring Plans and Quality Assurance
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/DSMP_in_Human_Subjects_Research.pdf

Reporting Unanticipated Problems (including Adverse Events)
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Reporting_Unanticipated_Problems_including_Adverse_Events.pdf

PRIVACY AND CONFIDENTIALITY

Describe methods used to protect the privacy of subjects and maintain confidentiality of data collected. This typically includes such practices as substituting codes for names and/or medical record numbers; removing face sheets or other identifiers from completed surveys/questionnaires; proper disposal of printed computer data; limited access to study data; use of password-protected computer databases; training for research staff on the importance of confidentiality of data, and storing research records in a secure location.

NOTE: Additional measures, such as obtaining a Certificate of Confidentiality, should be considered and are strongly encouraged when the research involves the collection of sensitive data, such as sexual, criminal or illegal behaviors.

Confidentiality of information collected will be maintained with the assignment of an identification number or code, which will be used in place of subject names in all data analyses and reports. Computer systems are located in the Cognitive and Clinical Neuroimaging Core. Keys showing the assignment of identification numbers to subject names will be stored with subject files in room 204 of the Neuroimaging Building under lock and key. All of the data that is collected will be kept for a minimum of seven years once the study has been completed. Only the Principal Investigator, Dr. Staci Gruber, her research staff, and the study collaborators will have access to the data that is collected.

All subjects will be required to give informed consent and must understand all procedures prior to their participation in the study. Subjects are informed of their confidentiality and privacy rights in the informed consent form. To ensure that subjects' rights and safety are protected during the conduct of this research study, subjects consent to the inspection of their medical records by specifically authorized monitors. Such monitoring may be performed by the Human Research Protection Program of McLean Hospital, or by the FDA or other involved federal agency.

Subjects are informed that all the information obtained in this study will be used for research investigational purposes only. Name of subjects will never be publicly disclosed at any time. Subjects will not be identifiable in any publication that may arise from this research.

Subjects will receive a copy of the consent document to keep as well as a copy of the "Partners Healthcare Notice for Use and Sharing of Protected Health Information." Subjects will be informed that this research will be conducted and administered in compliance with all state and federal laws.

SENDING SPECIMENS/DATA TO RESEARCH COLLABORATORS OUTSIDE PARTNERS

Specimens or data collected by Partners investigators will be sent to research collaborators outside Partners, indicate to whom specimens/data will be sent, what information will be sent, and whether the specimens/data will contain identifiers that could be used by the outside collaborators to link the specimens/data to individual subjects.

In some cases, urine samples may be sent to Quest Diagnostics to assess recent illicit substance use. The samples will be labeled with the subject's initials, date of birth, and study ID.

Plasma samples will be sent to [redacted] for quantification of endocannabinoid levels pre- and post-treatment. The samples will be labeled with the ID number and visit number (e.g. CBD001-V1).

[redacted]

Specifically address whether specimens/data will be stored at collaborating sites outside Partners for future use not described in the protocol. Include whether subjects can withdraw their specimens/data, and how they would do so. When appropriate, submit documentation of IRB approval from the recipient institution.

Specimens will not be stored off-site for future use not described in the protocol.

RECEIVING SPECIMENS/DATA FROM RESEARCH COLLABORATORS OUTSIDE PARTNERS

When specimens or data collected by research collaborators outside Partners will be sent to Partners investigators, indicate from where the specimens/data will be obtained and whether the specimens/data will contain identifiers that could be used by Partners investigators to link the specimens/data to individual subjects. When appropriate, submit documentation of IRB approval and a copy of the IRB-approved consent form from the institution where the specimens/data were collected.

N/A

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Statistical Approaches

All statistical analyses will be conducted using IBM SPSS Statistics (version 25). Data will be screened for outliers (defined as outside 1.5x the interquartile range), skew, kurtosis, non-normality, and homogeneity of variance. If the assumptions of parametric inferential analyses are not met, the appropriate non-parametric analyses will be performed. Baseline demographic, clinical, and neuropsychological data will be assessed using 2-tailed analyses of variance (ANOVAs). Treatment effects over the course of the study will be assessed using mixed model ANOVAs with Scheffe post hoc tests utilized to assess between-group differences and Least Significant Difference (LSD) post hoc tests utilized to assess change over time (repeated-measures). Independent *t*-tests will be conducting for each individual treatment arm to assess post hoc differences between baseline data relative to post-treatment data. In order to observe small-to-medium effect interaction effect sizes (f=.20) with 85% statistical power with alpha set at .05, it is estimated that the sample size should be at least 45 participants.