Title: Engaging the Endocannabinoid System with Cannabidiol to Reduce Anxiety Reactivity: A Randomized Controlled Trial in Social Anxiety Disorder (R61 Project)

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UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN

Instructions for completing the Research Plan are available on the HRPP website.
The headings on this set of instructions correspond to the headings of the Research Plan.
General Instructions: Enter a response for all topic headings.
Enter "Not Applicable" rather than leaving an item blank if the item does not apply to this project.

Version date: 9/30/2013

1. PROJECT TITLE

Engaging the Endocannabinoid System with Cannabidiol to Reduce Anxiety Reactivity: A Randomized Controlled Trial in Social Anxiety Disorder (R61 Project)

2. PRINCIPAL INVESTIGATOR

Charles T. Taylor, Ph.D. Associate Professor, Department of Psychiatry, UCSD (contact PI)
Murray Stein, MD, MPH FRCPC Distinguished Professor of Psychiatry and Public Health

3. FACILITIES

- Altman Clinical and Translational Research Institute (ACTRI) Building, 9452 Medical Center Drive, La Jolla, CA 92037. The following study procedures will occur at this facility: telephone pre-screening; informed consent; physical exams; clinical laboratory and safety assessments (blood and urine sample collection); ECGs; vital signs; data collection, management, and analysis; dispensing the study drug to participants; and manuscript preparation.
- Investigational Drug Service Pharmacy, ACTRI, 9452 Medical Center Drive, La Jolla, CA 92037. The ACTRI IDS will be responsible for obtaining, preparing, storing, and dispensing the study drug.
- UCSD Center for Medicinal Cannabis Research, 220 Dickinson Street, Suite B, MC8231, San Diego, CA, 92103-8231. The CMCR will be responsible for conducting blood plasma assays.

4. ESTIMATED DURATION OF THE STUDY

30 months

5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

This study seeks to understand how cannabidiol (CBD) – a non-intoxicating chemical compound obtained from the Cannabis sativa plant – affects biological and stress-related responses that are believed to underlie anxiety disorders. This study will evaluate the effects of different doses of CBD on blood plasma levels of anandamide (a molecule in the brain that has been shown to help regulate stress responses; primary biological signature) and anxiety reactivity to a social stress task (secondary target) in an acute (4-day) dosing study (i.e., when steady state CBD levels have been reached). Approximately 60 subjects with social anxiety disorder (SAD), ages 18-70, will participate in this study. They will be assigned by chance to receive one of two doses of CBD (300 or 900 mg/d) or placebo (which resembles the study drug but has no active ingredients), administered in two divided doses for 3 days and on the morning of day 4. Knowledge gained from this study will help determine the therapeutic potential of CBD for anxiety.

6. SPECIFIC AIMS

Aim 1 will test the hypothesis that CBD increases anandamide levels (primary biological target) and decreases anxiety reactivity (primary biobehavioral target) compared to placebo.

Aim 2 will determine which dose (300 or 900 mg/d) of CBD produces a greater effect on anandamide and anxiety reactivity.

To achieve these aims, 60 participants meeting diagnostic criteria for social anxiety disorder (SAD) will be randomized 1:1:1 to CBD 300 mg/d, CBD 900 mg/d, or placebo. They will complete standardized paradigms assessing anxiety reactivity (public speaking challenge) and blood draws for determination of CBD and anandamide levels at baseline and day 4 (when steady state CBD levels have been reached).

Exploratory Aim: To examine whether CBD in combination with a brief safety behavior reduction intervention produces larger reductions in social anxiety symptoms compared to placebo with safety behavior reduction.

Following the day 4 post-test procedures, participants will be invited to complete three weeks of a digitally assisted (text message) safety behavior reduction protocol (Cougle et al., 2020) along with their assigned CBD vs. placebo regimen. CBD/placebo dose will be adjusted to 300 mg per day for all subjects, which matches the dose regimen from a one-month clinical trial showing superiority of CBD vs. placebo in reducing social anxiety symptoms (Masataka, 2019).

7. BACKGROUND AND SIGNIFICANCE

Anxiety disorders are the most common mental health problem, affecting 1 in 5 adults each year and ~30% of adults during their lifetime. These conditions are a leading cause of disability worldwide and greatly diminish quality of life. First-line treatments are efficacious for only half of treated patients – contributing to protracted costs and personal suffering. Leading pharmacotherapies (e.g., antidepressants) are often associated with significant side effects that increase non-adherence and lead many individuals to search for alternative options. No new anxiolytics have been approved by the FDA in nearly 15 years. New treatment options are therefore sorely needed for this common and disabling class of disorders.

Several compounds derived from the *Cannabis sativa* plant show promise as natural therapeutics for anxiety and stress-related disorders. In a recent survey of over 2,000 registered medicinal cannabis users, over 40% reported authorization to use cannabis to treat anxiety symptoms and over 60% met probable diagnostic criteria for at least one anxiety and/or depressive disorder – most commonly social and generalized anxiety disorders (>40% each). Half of survey respondents endorsed *replacing* a physician-prescribed medication with cannabis, suggesting a strong desire by the public to use cannabinoid-based products to self-manage symptoms in lieu of medication**.** These individuals are making decisions about what type of cannabinoid product to use (e.g., CBD, THC), and in what doses, in the absence of rigorous empirical data. This study seeks to address this critical gap by establishing the dose-dependent effects of cannabidiol (CBD)—a non-intoxicating phytocannabinoid—on endocannabinoid system function (biological target) and anxiety responses to stress (biobehavioral target) in individuals with social anxiety disorder.

Exaggerated reactivity to perceived danger is a defining feature of anxiety and related disorders. Responses to acute threat originate from a defensive motivational system that operates to protect the organism from danger. This system is regulated by limbic (e.g., amygdala) and paralimbic (e.g., insula, anterior cingulate cortex) brain regions that help the individual identify and respond to salient events (e.g., potential threat). We and others have shown that this neurobiological salience system is hyperactive in anxious subjects – especially to threat-relevant cues. The perception of threat activates heightened expectancies about the likelihood and cost of feared outcomes. Inflated fear expectancies induce subjective distress (the feeling of anxiety or fear), defensive physiological states (e.g., vasoconstriction), and avoidance behaviors intended to mitigate perceived danger. Avoidance behaviors provide temporary relief from anxiety but maintain exaggerated threat responses over the long-term because the individual fails to learn that the situation poses less danger than predicted. Recovery from anxiety disorders is thought to occur when the individual repeatedly confronts fear provoking cues or contexts and learns that the feared stimulus is no longer associated with aversive outcomes. symptoms and associated impairment.

The endocannabinoid system, consisting of the cannabinoid receptors, endogenous cannabinoid ligands and their biosynthetic and degradative enzymes, seems to participate in the regulation of anxiety and fear responses. In particular, this system is considered an integral regulator of the stress response to anxiety-provoking stimuli. Stress downregulates cannabinoid type 1 (CB1) receptors, reduces anandamide, and increases 2-arachidonoyl glycerol (2-AG). Several investigators have proposed that endocannabinoid signaling determines the value of aversive (threat-relevant) stimuli and thereby helps to tune adaptive behavioral responses, which are essential for the organism's long-term viability, homeostasis and stress resilience. Preclinical and human data suggests that anandamide attenuates the anxiogenic effects of stress and facilitates fear extinction learning. In humans, pharmacological inhibition of the anandamide-degrading enzyme, fatty acid amide hydrolase (FAAH) results in increased anandamide levels alongside reduced anxiety reactivity under stress and diminished neural reactivity in limbic and paralimbic regions during emotion processing. Thus, targeting the endocannabinoid system represents an attractive and novel approach to the

treatment of anxiety-related disorders.

The hypothesized anxiolytic effects of CBD are believed to occur, in part, through its effects on enhancing endogenous anandamide signaling. CBD has been shown to inhibit anandamide degradation in animal models and to increase serum anandamide levels over one month of CBD treatment (800 mg/d) in patients with schizophrenia. Acute administration of CBD has been shown to facilitate fear extinction learning, dampen neural activity to unconditioned emotional stimuli (e.g., fearful faces), and produce anxiolytic effects in animals and healthy human subjects. Most relevant to the proposed project are acute dosing studies in patients with an anxiety disorder diagnosis. In a single session cross-over, double-blind, placebo-controlled study in 10 patients with social anxiety disorder (SAD), CBD (400mg) was found to significantly reduce subjective current anxiety and modulate regional cerebral blood flow at rest in limbic and paralimbic brain regions implicated in emotional processing. A randomized double-blind study of 24 patients diagnosed with SAD found that acute administration of CBD (600mg) compared to placebo resulted in significantly less anxiety and negative self-evaluations in anticipation of and during a social stressor (i.e., public-speaking task). Negative self-evaluations in the CBD group were diminished to levels comparable with a group of non-anxious (healthy) control subjects who completed the procedures without the study drug. Those findings support the acute anxiolytic effects of CBD in patient samples—consistent with observations that individuals in the community use cannabis to self-manage their anxiety symptoms.

Previously observed anxiolytic effects of CBD are hypothesized—based on strong preclinical evidence—to be mediated in part through elevation of the endogenous cannabinoid anandamide via inhibition of its main degradative enzyme, fatty acid amide hydrolase (FAAH). The dose-dependent effects of CBD on plasma anandamide levels in anxiety disorder samples, however, remain unknown. It is also unknown whether changes in anandamide track with changes in anxiety—both acutely and following chronic CBD administration. To realize the therapeutic potential of CBD for anxiety, there is therefore a critical need to determine (1) whether and at what doses CBD elevates anandamide and reduces anxiety reactivity in clinically anxious patients, and (2) if doing so leads to improvements in anxiety symptoms and associated impairment. We propose to address the first part of this gap by conducting a sub-acute (4-day) steady state dosing study to establish the dose-dependent effects of CBD on plasma anandamide levels (primary biological target) and anxiety reactivity to a standardized laboratory stressor (biobehavioral target).

8. PROGRESS REPORT

Not applicable.

9. RESEARCH DESIGN AND METHODS

Design and Randomization: This Phase II, 3-arm, sub-acute (4-day) steady state dosing clinical trial will randomize 60 subjects diagnosed with SAD using a double-blinded, parallel group design, 1:1:1 to CBD 300 mg/d, CBD 900 mg/d, or placebo (administered in two daily divided doses). Randomization will be stratified by sex using randomly permuted blocks. Study personnel and subjects will be blinded throughout.

Participants:
We will enroll and randomize approximately 60 individuals age 18-70 recruited from the general community who meet diagnostic criteria for social anxiety disorder (SAD). For this study, an enrolled subject is defined as a subject that has been randomized to the study drug.

Recruitment and referral resources: Participants will be drawn from consecutive referrals to the Anxiety & Traumatic Stress Disorders Program at UCSD (directed by Drs. Stein and Taylor) or recruited through IRB-approved announcements posted online and in public community and healthcare settings. Our research clinic has established collaborative and productive relationships with UCSD Primary Care Clinics (with whom we have worked collaboratively and very productively on prior projects; e.g., HRPP protocols #140102 and 202047) that facilitate physician- and self-referrals. We will also leverage freely available online clinical research recruitment registries (e.g., ResearchMatch), and fee-for-service online registries (e.g., BuildClinical).

Procedures:

Pre-Screening:
We anticipate screening approximately 150 individuals to obtain the targeted 60 participants that meet criteria for the study.

Individuals presenting to UCSD primary care clinics will be screened as part of their routine visit using the Generalized Anxiety Disorder 7 (GAD-7). The GAD-7 is a brief (7-item) self-report questionnaire for screening and assessing severity of generalized anxiety disorder. Those who meet initial screening criteria (GAD-7 ≥ 8) will be sent a form IRB-approved letter describing the study and providing study contact information.

Upon expressing interest in the study, potential participants will first complete a brief telephone interview (< 30 minutes) with a trained research assistant as follows: receive explanation about the study procedures, provide verbal informed consent, and answer questions regarding basic demographic, medical information, and symptoms of social anxiety disorder. We will administer (1) the 3-item mini-Social Phobia Inventory (Connor, Kobak, Churchill, Katzelnick, & Davidson, 2001), a brief, reliable and valid social anxiety screening measure, to select participants who score 6 or higher, and (2) the 3-item Sheehan Disability Scale (Sheehan, 1983) to confirm at least moderate or greater (≥5) functional interference due to social anxiety symptoms. Eligible applicants will be scheduled to complete the full initial screening session.

Electronic pre-screen survey: To reduce participant and research staff burden, before completing the telephone interview, potential participants will have the option of completing a brief (< 5 mins), web-based survey administered via REDCap (a secure, HIPAA-compliant platform managed by the UCSD ACTRI – described more fully below) to determine whether the full telephone screening should be completed (Pre-Screen survey included with the HRPP submitted materials). Study applicants will be given the option to not complete this pre-screen survey and instead proceed to the full telephone screening survey.

Initial Screening / Intake:
After potential participants are pre-screened by phone using the screening protocol submitted with this research plan, they will be scheduled for an initial screening session to determine final eligibility and baseline symptom severity. They will complete self-report assessments of basic demographic and medical information, followed by a clinician-administered Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987) to determine social anxiety symptom severity. Participants scoring 60 or higher on the LSAS will then complete a brief diagnostic interview to determine DSM-5 diagnoses for anxiety, mood, and substance use disorders and eligibility criteria (Mini International Neuropsychiatric Interview – Version 7.0.0; Sheehan et al., 2006). Clinical interviews will be video recorded for purposes of reliability analysis. Video recording of the clinical interview will be optional. Participants will be informed verbally and in the consent form that they may stop the video recording of the interview at any time, and that portions and/or the entire tape may be erased at the subject's request. Participants will also be informed that they may decline to be videotaped for the clinical interview and still complete the study. Following confirmation of diagnostic eligibility, a thorough, standardized past and current medical history and review of symptoms (including allergies to cannabis or cannabinoids, or any other medications) will be obtained. The study physician will also conduct a screening medical examination to review vital signs (e.g., blood pressure). The patient will have blood drawn for liver function tests, urine for drug screen, and a baseline ECG. If the patient is a woman of childbearing potential we will also collect a urine sample to test for pregnancy . The study physician and PI will review these results to determine eligibility. All participants (whether or not they meet eligibility criteria following the baseline session) will be provided with community mental health referrals as needed. Screening assessments are estimated to take approximately 3-4 hours to complete in total; however, the screening assessments will end at the point of determining ineligibility.

We are prepared to conduct the initial portion of the screening intake (self- and clinical interview assessments) remotely given the COVID-19 pandemic, or for other reasons (e.g., participant unavailability to attend an in-person session). These assessments will be done via HIPAA compliant videoconference. Remote procedures will follow FDA guidance ("FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency" and "Use of Electronic Informed Consent Questions and Answers") for participant and staff safety. To do electronic consenting, research staff will 1) identify the participant via telehealth communication, 2) review the informed consent with the participant and response to any questions the patient may have; 3) confirm that the participant's questions have been answered; 4) confirm that the participant is willing to participate in the study and sign the informed consent document while the witness is listening via telehealth technology; and 5) obtain verbal confirmation by the patient that they would like to participate in the study. The IRB-approved consent form will be provided to participants via REDCap or DocuSign which will allow for capture of a handwritten signature on the pdf form using a stylus, computer mouse, or their finger, depending on what type of device they are using (e.g., desktop computer, mobile device) per FDA guidance (21 CFR part 11: Handwritten signature means the scripted name or legal mark of an individual handwritten by that individual and executed or adopted with the present intention to authenticate a writing in a permanent form. The act of signing with a writing or marking instrument such as a pen or stylus is preserved. The scripted name or legal mark, while conventionally applied to paper, may also be applied to other devices that capture the name or mark). All other elements of the consenting process will be the same as in-person. Subjects who appear eligible after the self- and clinician-assessments will be invited to complete the remaining portion of the screening intake in person (e.g., vital signs, blood draw).

If there are more than 21 days between the initial screening visit and the baseline visit, participants will re-complete (either all or a portion of) the screening measures to ensure they still meet eligibility criteria. If they no longer meet eligibility, they will be withdrawn from the study.

Intervention Phase:

Baseline Visit:
The baseline visit will include vital signs, blood draw (to assess plasma CBD and endocannabinoid metabolites), urine drug screen, urine pregnancy test (if the patient is a woman of childbearing potential), state mood assessments, emotional processing tasks, and anxiety reactivity social stressor (speech task). Following the baseline assessments, participants will be randomized 1:1:1 to receive CBD (300 or 900 mg/d) or placebo, stratified by sex (given sex differences in response to cannabinoids). The randomization list (using permuted blocks) will be generated by the UCSD Biostatistician using R (version 3.6.1). Study personnel and subjects will be blinded throughout. Only the study biostatistician and pharmacist will be unblinded.

Study drug: The CBD product to be used in this study is Epidiolex® (Greenwich Biosciences), a plant-derived, highly purified CBD oral solution that is FDA approved for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older. Epidiolex is no longer on the DEA controlled substance list. Drug administration: Participants will receive CBD or placebo oral solution twice daily (evenly split doses at morning and evening meals) for three days (to achieve steady state) following the baseline assessment (day 0), and in the morning of day 4 (before the post-test). Epidiolex is a strawberry flavored clear, colorless to yellow solution supplied in a 105 mL amber glass bottle with a child-resistant closure containing 100 mL of oral solution (NDC 70127-100-01). Eligible participants will be randomized to receive either Epidiolex or an equivalent volume of placebo solution (excipients only, also to be provided by Greenwich Biosciences). The UCSD Investigational Drug Service Pharmacy will dispense the allotted 4-day dose to participants in two bottles as follows:

Intervention Arm	Study Product Bottle 1 Dose: Take 1.5 ml BID	Study Product Bottle 2 Dose: Take 4.5 ml BID
CBD 300 mg/d	CBD	Placebo

CBD 900 mg/d	Placebo	CBD
Placebo	Placebo	Placebo

This dispensation schedule ensures that participants and study personnel will remain blind to both study drug (CBD vs. placebo) and dose (300 mg/d vs. 900 mg/d). The pharmacy will remain unblinded.

Dose rationale: The selected doses were chosen because they represent the lower and upper ends of dose ranges established in prior human studies (healthy or clinical samples) to demonstrate effects on anandamide (800 mg/d chronic dosing in schizophrenia patients) or anxiety reactivity (300-600 mg/d single dose effects). Doses < 200 mg/d have consistently failed to separate from placebo on anxiety-relevant measures in healthy samples. Evidence is mixed for anxiety-relevant effects at doses ≥ 600 mg/d, with both positive and null effects vs. placebo. Note that anandamide and anxiety reactivity measures have not been collected together in prior dose effect studies. The chosen doses are therefore expected to cover the possible anxiolytic effect range, while allowing for a determination of whether dose-dependent effects occur for anandamide, anxiety reactivity, or both outcomes. These doses (and higher; e.g., 1500mg twice daily) have been safely administered chronically to human subjects, and so we do not anticipate tolerability or safety issues at the proposed doses. Thus, this study will not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product.

Post-Test Session / Day 4:
The post-test session will occur on the morning of day 4 (time of day standardized ±1h across participants and matched to baseline). Participants will be instructed to take their morning dose with a meal as done in previous days. Post-test assessments will be the same as those taken at baseline, including blood draw, urine pregnancy test (if the patient is a woman of childbearing potential), state mood assessments, computerized emotional processing tasks, and anxiety reactivity social stressor (speech task). Frequency of adverse and serious adverse events (AE/SAEs) and medication adherence will be assessed by the study physician and by measuring the amount of medication received when it is returned. At the end of this session, subjects who decide not to take part in the three-week safety behavior reduction intervention (described below) will be debriefed and referred for additional care as appropriate.

Assessment Schedule – CBD/Placebo (Aims 1 and 2).

Measures	Intake	Baseline	Day 4
Sample Characterization			
Demographics	x		
MINI	x		
LSAS	x	x	
SDS		x	
PHQ-9		x	
GAD-7		x	
ATQ		x	
F-MPS		x	
Expectancies		x	
PSAS		x	
Target Engagement Outcomes			
Anandamide (+ secondary biological signatures)		x	x
Social stressor (speech)		x	x
PANAS - State		x	x
STAI - State		x	x
Emotion recognition task		x	x
Attentional bias task		x	x

Driving Task		x	x
Social Approach-Avoidance Paradigm		x	x
Clinical and Side Effect Monitoring			
Global Rating of Change			x
C-SSRS	x	x	x
FIBSER			x
Adherence			x
Adverse events			x
Medications	x	x	x
Medical exam	x		
Medical history	x		
Blood draw for safety	x		
Urine drug screen	x	x	

Note. MINI = Mini-International Neuropsychiatric Interview for DSM-5. LSAS = Liebowitz Social Anxiety Scale. SDS = Sheehan Disability Scale. PHQ-9 = Patient Health Questionnaire-9. GAD-7 = Generalized Anxiety Disorder-7. C-SSRS = Columbia-Suicide Severity Rating Scale. FIBSER = Frequency, Intensity, and Burden of Side Effects Rating. Secondary biological signatures include 2-arachidonoylglycerol (2-AG), N palmitoylethanolamide (PEA), N oleoylethanolamide (OEA), 6-OH-CBD (6-hydroxy-cannabidiol), 7-OH-CBD (7-hydroxycannabidiol), 7-COOH-CBD (7-carboxy-cannabidiol,) and CBD (cannabidiol). PSAS = Public Speaking Anxiety Scale.

Safety Behavior Reduction Plus CBD/Placebo Intervention (3 weeks; Exploratory Aim):
At the end of the post-test (day 4) session, participants will be invited to complete a three-week safety behavior reduction intervention in combination with their assigned study drug. An informed consent form separate from the main study aims 1 and 2 will be used for this purpose. Participants who consent to taking part in this component will complete surveys measuring symptoms and associated outcomes (see Assessment Schedule – Safety Behavior Reduction Plus CBD/Placebo [Exploratory Aim]). The safety behavior reduction protocol (Cougle et al., 2020) begins by defining safety behaviors (i.e., behaviors intended to make us feel less anxious and prevent bad things from happening), describing how safety behaviors can maintain or exacerbate anxiety and therefore why it can be helpful to reduce or eliminate them, and instructions encouraging participants to do so. Participants will be sent a text message every other day containing a message reminding them to attempt to avoid using their safety behaviors, as well as a listing of the three most frequently used safety behaviors they selected when completing the Subtle Avoidance Frequency Examination (SAFE; Cuming et al., 2009) on day 4 (measure described below). Example text message: “Please remember to avoid using the safety behaviors listed below. As you drop them, you’ll be able to go into social situations with greater confidence. 1) Before you arrive, excessively rehearse what you might say or how you might behave. 2) Avoiding eye contact. 3) Positioning yourself so as not to be noticed.” This protocol produced large reductions in social anxiety symptoms in prior work (Cougle et al., 2020). A single-item, weekly measure of adherence will be sent to participants: How many days during the past week did you attempt to reduce your safety behaviors in social situations? (response options = 0-7 days). Weekly assessments of symptoms will also be sent to participants to monitor response to the intervention (see Assessment Schedule – Safety Behavior Reduction Plus CBD/Placebo [Exploratory Aim]).

In addition to the safety behavior reduction protocol, participants will be instructed to take 1.5 ml BID (300 mg/d) from each bottle of their study drug/placebo. For the exploratory arm, the dose is 300 mg per day. This dosing regimen matches dosing from a one-month clinical trial in social anxiety disorder showing superiority of CBD vs. placebo in reducing social anxiety symptoms (Masataka, 2019). The “Placebo” bottle will have no CBD. It will have an oral solution without any active ingredients (excipients only, also to be provided by vendor). Following three weeks (i.e., follow-up), participants will be asked to complete surveys measuring symptoms and related outcomes. Frequency of adverse and serious adverse events (AE/SAEs) and medication adherence

will be assessed by the study physician and by measuring the amount of medication received when it is returned. A blood sample (approximately 6 ml or 1 teaspoon) for safety monitoring (i.e., liver function tests) will be collected during the follow-up visit, which will occur on the 21st day of the 3 week intervention, or within +/- 2 to 3 days of the 21st day. At the end of this session, subjects will be debriefed and referred for additional care as appropriate.

Assessment Schedule – Safety Behavior Reduction Plus CBD/Placebo (Exploratory Aim).

Measures	Day 4 (Baseline for Exploratory Aim; Week 0)	Weekly (For 3 weeks)	Follow-up (Week 3)
Symptom and Functioning Outcomes			
LSAS	x	x	x
SDS	x	x	x
PHQ-9	x		x
PHQ-8		x	
GAD-7	x	x	x
SCSR	x	x	x
PANAS	x	x	x
PROMIS Sleep Disturbance	x	x	x
SAFE	x	x	x
Q-LES-Q-SF	x	x	x
Treatment Expectancies	x		
Adherence		x	x
Global Rating of Change			x
CGI-I			x
Clinical and Side Effect Monitoring			
C-SSRS	x		x
FIBSER	x		x
Adherence	x		x
Adverse events	x		x
Medications	x		x
Blood draw for safety			x

Note. LSAS = Liebowitz Social Anxiety Scale. SDS = Sheehan Disability Scale. PHQ-9 = Patient Health Questionnaire-9. PHQ-8= Patient Health Questionnaire-8. GAD-7 = Generalized Anxiety Disorder-7. SCSR = Social Connectedness Scale Revised. PANAS = Positive and Negative Affect Schedule. SAFE = Subtle Avoidance Frequency Examination. Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form. PROMIS = Patient Reported Outcomes Measurement Information System. C-SSRS = Columbia-Suicide Severity Rating Scale. FIBSER = Frequency, Intensity, and Burden of Side Effects Rating. CGI-I= Clinical Global Impressions Improvement Scale

Clinical Interviews:

The following will be administered by a clinically experienced and trained research team member.

Mini International Neuropsychiatric Interview (MINI Version 7.0.2) (Sheehan, 2016). The MINI will be administered at baseline to assess current DSM-5 diagnoses, including social anxiety disorder (SAD) and comorbid disorders. The MINI is relatively brief (< 60 minutes) and possesses good inter-rater reliability. It will be used to determine participant inclusion and exclusion criteria, and to characterize the sample.

The Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987) is the gold standard clinician-administered assessment for SAD. It consists of 24 social situations, and individuals are asked to rate both their level of Fear and Avoidance for each situation on a 4-point scale ranging from 'none/never' to 'severe/usually'. Items are summed to create a total score reflecting social anxiety severity. The LSAS has excellent psychometrics, including high inter-rater reliability and test-retest reliability.

Columbia-Suicide Severity Rating Scale (C-SSRS; (Posner et al., 2011)) is a standardized 8 point clinician-administered suicidal rating system designed to track suicidal adverse events covering the wide spectrum of suicidality. It is principally being used as a safety measure for use in this trial. Following intake, the C-SSRS self-assessment version will be administered at each study visit with follow-up by the clinician for any positive endorsement of suicidal ideation or behavior.

Clinical Global Impressions Improvement Scale (CGI-I; Guy 1976): The CGI-I allows for the clinician to assess how much the subject's illness has improved or worsened relative to the baseline state at the beginning of the intervention. The assessment uses a 7-point scale. The CGI-I will be administered at the last follow up visit of the exploratory aim study.

Adherence Questionnaire (AQ): a 2-item questionnaire will be used to determine what proportion of the time between visits the participant took their study drug as recommended, and to establish the reason(s) for deviating from the recommended dose (e.g., forgot, side effects, thought not needed, etc.).

Adverse Events (AE): This checklist will be used for clinicians to assess any adverse events that patients experienced since their last visit. It will be reviewed and filled out at all study visits.

Concomitant Medications: This form will be used for clinicians to review and update any concomitant medications the patient took or is taking. It will be reviewed at all study visits.

Self- Report Questionnaires:
The following reliable and valid questionnaires will be used to characterize the sample, monitor response to CBD, and examine potential moderators of CBD effects:

Sheehan Disability Scale (SDS; Leon, Olfson, Portera, Faber, & Sheehan, 1997). The SDS is a three-item instrument for assessing functional interference in social, work, and family/home responsibilities. The SDS will be used to assess current level of interference due to psychiatric symptoms. The SDS demonstrates satisfactory reliability and correlates highly with other commonly used disability measures in social anxiety (e.g., Hambrick, Turk, Heimberg, Schneier, & Liebowitz, 2004; Leon et al., 1997).

The Patient Health Questionnaire-9 (PHQ-9; (Kroenke et al., 2010)) is a 9-item self-report measure of depression severity that is widely used in clinical trials and has excellent psychometric properties.

The Patient Health Questionnaire-8 (PHQ-8; (Kroenke et al., 2009)) is a 8-item self-report measure of depression that is widely used in clinical trials. We will use the PHQ-8, which does not explicitly ask about suicide, for remote administration. This version of the PHQ-8 is widely used for remote administration.

The Generalized Anxiety Disorder-7 (GAD-7; Spitzer et al., 2006) is a 7-item self-report measure that assesses worry and general somatic tension—common secondary symptoms of SAD. The GAD-7 has strong psychometric properties and is commonly used in clinical trials for anxiety.

Treatment expectancies will be assessed at baseline by asking participants to rate their perceptions about the therapeutic potential of CBD (Spinella et al., 2021, 2023).. Following the post-test, participants will be asked which treatment group they thought they were assigned to in order to verify that the blind was maintained.

Spielberger State-Trait Anxiety Inventory (STAI; Spielberger et al., 1983). The STAI is a 40-item self-report measure of anxiety with items scored on a one to four scale; 20 items reflect current state anxiety and 20

items reflect more general feelings of trait anxiety. State anxiety will be assessed before and after the Behavioral Approach Tests (see below) to measure anxiety reactivity. The STAI possesses adequate psychometric characteristics (Spielberger, Gorusch, & Lushene, 1970).

Positive and Negative Affective Schedule - State/Trait (PANAS; (Watson, Clark, & Tellegen, 1988)): The PANAS is a widely used measure comprising 20-items assessing activated forms of positive affect (PA) and negative affect (NA) using 5-point scales (1 = very slightly/not at all, 5 = extremely). To assess trait PA and NA, participants will be asked to respond according to how they have felt "during the past week". State PA and NA will be assessed by asking participants to rate how they feel “right now (that is, at the present moment)” throughout the laboratory assessments (i.e., before and after the Behavioral Approach Tests; see below).

Frequency, Intensity, and Burden of Side Effects Rating (FIBSER; Wisniewski et al., 2006) is a self-report scale that provides 3 global ratings regarding the frequency, intensity, and degree of functional interference due to side effects attributable to the study drug. The FIBSER will be used to evaluate side effects.

Approach-Avoidance Temperament Questionnaire (ATQ; Elliot & Thrash, 2010) is a 12-item measure designed to measure sensitivity to positive (i.e., reward; 6 items) and negative (i.e., punishment; 6 items) stimuli or contexts. Items within each of these domains measure temperament dimensions of affective reactivity, perceptual vigilance, and behavioral inclination.

The full Frost Multidimensional Perfectionism Scale (F-MPS; Frost et al., 1990) is a 35-item scale containing six subscales. Each item is answered using a 5-point Likert-type scale ranging from 1 (strongly disagree) to 5 (strongly agree). Good internal consistency and convergent validity with other measures of perfectionism have been demonstrated for the F-MPS within community and clinical samples of adults (Frost et al., 1990; Purdon et al., 1999).

Public Speaking Anxiety Scale (PSAS; Bartholomay & Houlihan, 2016) is a 17-item self-report measure with responses measured in a Likert-format with score ranging from 1 “not at all” to 5 “extremely.” Scores on this scale can range from 17 to 85 (Bartholomay & Houlihan, 2016).

Subtle Avoidance Frequency Examination (SAFE; Cuming et al., 2009). The SAFE is a 32-item self-report measure designed to assess the frequency of safety behavior use on a scale from 1 (never) to 5 (always) Sample items: Rehearse sentences in your mind; Avoid eye contact. The SAFE has good internal consistency and is sensitive to change as a result of treatment (Cuming et al., 2009). It will be used to measure changes in response to the safety behavior reduction intervention.

Social Connectedness Scale – Revised (SCS-R; Lee, Dean, & Jung, 2008). The SCS-R is a 20-item self-report measure of the degree of connectedness to others and belongingness in one’s social environment. Items are scored on a one to six scale. The SCS-R has adequate psychometric properties and is associated with indices of subjective well-being (Lee et al., 2008).

PROMIS Sleep Disturbance – Short Form (Yu et al., 2011). The 8-item PROMIS Sleep Disturbance scale assesses self-reported perceptions of sleep quality, sleep depth, and restoration associated with sleep. This includes perceived difficulties and concerns with getting to sleep or staying asleep, as well as perceptions of the adequacy of and satisfaction with sleep. Items are rated based on the past 7 days.

Quality of Life, Enjoyment, and Satisfaction Questionnaire (QLES-Q short form; Endicott et al., 1993). The QLES-Q Short Form is a 16-item self-administered questionnaire designed to measure degree of enjoyment and satisfaction in general activities. The QLES-Q measured each of the items using a 5-point Likert-type scale. The QLES-Q is first scored as the sum of the first 14 items so that total scores ranged from 14 to 70 and then the sum is converted into a percentage of the maximum possible score. Higher QLES-Q scores reflected greater

enjoyment and satisfaction with activities. The QLES-Q has previously been found to have acceptable reliability and validity (Endicott, 1993) and will be used to assess changes in functioning following the intervention.

Global Rating of Change (GRC): The GRC is a single-item scale asking participants to rate, "How do you feel compared to before you started the intervention?" Change is rated on a 7-point scale with the following response options: "I feel …" − 3 (much worse), − 2 (moderately worse), − 1 (a little worse), 0 (about the same), + 1 (a little better), + 2 (moderately better), or + 3 (much better). The GRC has been widely used to assess responsiveness of patient-reported outcome measures in terms of minimally important clinically difference from the patient's perspective (Mouelhi et al., 2020).

Clinical Laboratory Tests: Collected for inclusion criteria and safety.

Blood samples for serum chemistry and hematology (~ 4 teaspoons), and a urine sample for a drug screen and pregnancy test will be collected at intake. A pregnancy test will also be performed at day 4 for any participants who could become pregnant. The following tests will be performed by the central laboratory:

- Hematology Panel: hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential, platelet count.
- Serum Chemistry Panel: sodium, alkaline phosphatase, potassium, chloride, calcium, blood urea nitrogen (BUN), creatinine, albumin, glucose, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT). A liver function panel (AST, ALT, total bilirubin) will also be obtained at follow-up (one month after starting CBD/placebo – per FDA package insert).
- Urine Drug Screen (cocaine, marijuana, opiates, amphetamines, methamphetamines, phencyclidine, benzodiazepines, barbiturates, methadone, and oxycodone).

Electrocardiogram (ECG)
A twelve-lead ECG will be collected so that the different ECG intervals (RR, PR, QRS, QT) can be derived. The ECG will be recorded until 4 regular consecutive complexes are available.

Vital Signs
Blood pressure and heart rate measurements will be assessed in a seated position with a completely automated device. Manual techniques will be used only if an automated device is not available.
Blood pressure and heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (e.g., television, cell phones). Vital signs will be taken at every study visit.

Physical Examination
A physical examination will be performed by a physician at screening (or at baseline before randomization), including height and weight.

Blood samples for targeted biomarkers (e.g., anandamide, CBD metabolites) will be collected at baseline and post-test (~ 4 teaspoons per visit). Measurement and pharmacokinetic interpretation of the proposed biological signatures will be led by Dr. Robert Fitzgerald, Director of the Chemistry and Toxicology Laboratory at the UCSD Center for Medicinal Cannabis Research.

Dependent Outcomes:

Biological Signatures: A blood sample will be collected at baseline and post-test for measurement of plasma concentrations of anandamide (AEA; primary biological signature/target). To more fully characterize the biological signature of CBD to inform explanatory models and future studies, secondary measures will include 2-arachidonoylglycerol (2-AG), N palmitoylethanolamide (PEA), N oleoylethanolamide (OEA), 6-OH-CBD (6-hydroxy-cannabidiol), 7-OH-CBD (7-hydroxycannabidiol), 7-COOH-CBD (7-carboxy-cannabidiol,) and CBD (cannabidiol). These secondary outcomes were chosen because they are believed to contribute to endocannabinoid-mediated stress regulation and because the CBD metabolites have been well-characterized

in prior pharmacokinetic work of the study drug, permitting an examination of the association between CBD plasma concentrations and both endocannabinoid and anxiety reactivity outcomes. Assays and pharmacokinetic interpretation will be conducted in batch, blind to treatment assignment, under the direction of Dr. Robert Fitzgerald, Director of the Chemistry and Toxicology Laboratory at the UCSD Center for Medicinal Cannabis Research.

Primary Biobehavioral Signature – Anxiety Reactivity: Participants will complete a standardized assessment of anxiety reactivity by delivering a 5-minute videorecorded speech. Measures will be collected during a resting baseline, anticipation, during, and post-speech.

Speech task: Participants will be asked to complete a five-minute impromptu speech, which is a well-established and commonly used way to assess anxiety and avoidance responses (Amir et al., 2008; Hofmann et al., 1995) as well as response to pharmacologic (Bergamaschi et al., 2011) and non-pharmacologic (Taylor et al., 2014) interventions. The experimenter will inform participants that their speech will be video recorded so that it can later be rated by a graduate student for its quality. Video recording for the speech task is not optional, given that this is a main study outcome. Participants will choose one topic for their speech selected from a list of 5 topics (e.g., abortion, the American health system). Following a two-minute preparation period, participants will be instructed to stand in a designated area in front of a video camera to deliver the speech. The behavioral assessment will end after 5 minutes. Different speech topics will be selected for baseline and post-test to reduce practice effects.

Our primary measure of anxiety reactivity is change in state anxiety from baseline to (1) anticipation of or (2) during the speech measured using a 0-100 Subjective Units of Distress Scale (Wolpe & Lazarus, 1966) ranging from 0 (no fear) to 100 (extreme fear). Both anticipatory and during the stressor measures are relevant to anxiety pathophysiology and were found to be differentiate CBD from placebo in single dose studies.

Secondary outcomes will include: the Spielberger State-Trait Anxiety Inventory-State (STAI-S; Spielberger et al., 1983); *threat-related predictions* (probability and cost of feared outcomes, including whether the predicted outcomes occurred, i.e., expectancy violation; Taylor & Alden, 2010); *observer-rated anxious behavior* (Taylor & Alden, 2010); *negative cognitions* (Self-Statements during Public Speaking Scale; Hofmann & Dibartolo, 2000), and *heart rate variability* (a physiological index of parasympathetic activation obtained using the MP150 BIOPAC Systems platform and computed from the R-wave to R-wave interbeat interval series in the frequency range of spontaneous breathing, .12 Hz - .40 Hz).

Safety Behaviors Questionnaire (SBQ; Clark et al., 1994; Taylor & Alden, 2010) The SBQ is a 20-item list of in-situation safety behaviors commonly reported by individuals with social anxiety disorder (SAD; Taylor & Alden, 2010). This scale will be used to measure participant's safety behavior use during the speech. Sample items include "Try to conceal your anxiety," "Rehearse sentences in your mind," "Try to keep tight control of your behavior," and "Censor what you are going to say." Participants will rate the extent to which they use each safety behavior during the speech using a 9-point scale ranging from 0 (not at all) to 8 (all the time).

Global Rating of Change (GRC): The GRC is a single-item scale asking participants to rate, "How do you feel compared to when you completed the speech assessment last session?" Change is rated on a 7-point scale with the following response options: "I feel …" − 3 (much worse), − 2 (moderately worse), − 1 (a little worse), 0 (about the same), + 1 (a little better), + 2 (moderately better), or + 3 (much better). The GRC has been widely used to assess responsiveness of patient-reported outcome measures in terms of minimally important clinically difference from the patient's perspective (Mouelhi et al., 2020). Participants will also rate a single-item scale asking, "How satisfied would you be if you experienced this amount of change in your daily life?" Satisfaction is rated on a 7-point scale with the following anchors: "I would feel …" − 3 (very dissatisfied), − 2 (moderately dissatisfied), − 1 (a little dissatisfied), 0 (neutral; neither satisfied nor dissatisfied), + 1 (a little satisfied), + 2 (moderately satisfied), or + 3 (very satisfied).

Exploratory Biobehavioral Signature – Emotional Processing Bias: Participants will complete reliable and valid computer assessments measuring emotional biases shown to characterize anxiety and that are sensitive to detecting early response to established pharmacotherapies.

Emotion Recognition Task (ERT; Browning et al., 2007). This task features six basic emotions (happiness, surprise, sadness, fear, anger and disgust), which are morphed between each prototype and a neutral face stimulus at varying intensity levels. A discriminability (d') index based on signal detection theory will be computed to measure subjects' ability to detect subtle emotion displays.

Modified Probe Detection Task (MPDT; MacLeod et al., 1986). Attentional bias (AB) for positive (happy) and negative (disapproving) faces will be measured by instructing subjects to identify a visual probe that replaces one of two simultaneously presented face stimuli (an emotionally valenced stimulus paired with a neutral stimulus). Faster response latencies to probes replacing emotional compared to neutral stimuli reflect emotional AB. Our dependent outcome will be derived using a response-based AB computation that demonstrates high test-retest reliability (Evans & Britton, 2018). We will also explore drift-diffusion modeling approaches (Price et al. 2019).

Driving Task (Howlett et al., 2020). A simulated 1-dimensional driving task. The position of a virtual car is controlled with a gaming joystick. Each subject completes 30 trials. In each trial, subjects are instructed to drive the car as quickly as possible and stop as close as possible to a stop sign without crossing the stop-line. Each trial has a fixed duration of 10 seconds. The car is controlled according to a linear dynamical system, in which car velocity is proportional to joystick displacement. Throughout each trial, continuous joystick displacement is recorded with a sampling window of 1/60 second. Behavior on this task can be modelled according to continuous adjustments in response to both current error (i.e., distance from goal state) and predicted future error, and has been shown to be predictive of self-reported fear (i.e., fear is associated with reduced weighting of current error and overestimation of future error).

Social Approach-Avoidance Paradigm (SAAP; Evans & Britton, 2020; Evans, Esterman, & Britton 2022). The SAAP measures the degree to which morphed facial expressions elicit motivation to approach and avoid another individual. On each trial in the SAAP, participants are presented with a single facial expression and asked to self-report the degree to which they would like to approach and avoid (Approach: "How much would you want to approach this person?"; Avoid: "How much would you want to avoid this person?"). Using Morpheus software (Broad Institute), facial expressions are visually blended to parametrically vary in social reward (i.e., happiness), social threat (i.e., anger), or social reward-threat conflict (i.e., simultaneous happiness and anger; see attached figures). To parametrically modulate social signals, morphed facial expressions vary in 25% increments of social reward (e.g., 25%Happy, 50%Happy, etc.), social threat (e.g., 25%Angry, 50%Angry, etc.), or social reward-threat conflict (25%Angry/25%Happy, 50%Angry/50%Happy, etc.). To reduce habituation of emotion-related effects across the task, morphed facial expressions were created using 6 Male and 6 Female actors selected from the publicly available NimStim stimulus set (Tottenham et al., 2009). The entire experiment requires approximately 15 minutes to complete.

Data Analysis:

General Approach:
Analyses will incorporate the modified intention-to-treat (mITT) principle, including subjects who are randomized and dispensed the study drug/placebo. We expect that missing data will be minimal (<10%) for our primary outcomes. Missing data will be evaluated. If the missingness is not random (non-ignorable), multiple imputation and/or propensity weighting will be considered, but this will not be applied without extensive sensitivity analysis. All results will be reported as point estimates (means and standard deviations) and interval estimates (95% confidence intervals). All tests of significance will be 2-sided. A *p*-value of 0.05 will be considered statistically significant. Analysis will be conducted using R v.3.6.1. Demographic and baseline

characteristics will be compared between study arms using Fisher's exact test for categorical variables, and a 2-sample t-test for continuous variables. Non-parametric alternatives will be considered, if parametric assumptions fail. There will be no planned interim analyses for efficacy or futility conducted in this study.

Given the limited scope and sample size afforded by this early phase R61 trial, our primary approach will involve determining whether the effect size difference between treatment arms meets the effect size benchmarks established for the go/no-go criteria to proceed to the R33 phase trial (effect size justification below). We will also consider a per protocol sensitivity analysis within subjects who complete all procedures and for those in the CBD arms who have a detectable level of whole blood plasma CBD (i.e., LLOQ ≥ .5 ug/L). We will also consider a sensitivity analysis in those subjects who displayed a score of 75 or higher on the Subjective Units of Distress Scale during the baseline (pre-randomization) speech assessment performance period, consistent with similar prior studies (Liebowitz et al., 2014).

Aim 1: To test the hypothesis that CBD increases plasma anandamide levels (biological signature) and decreases anxiety reactivity (biobehavioral signature) compared to placebo.

Primary Outcomes and Go/No-Go Criteria. Our first criterion is that CBD (either 300 mg/d, 900 mg/d, or both) is superior to placebo on increases in plasma anandamide levels (primary biological signature) from baseline to day 4 (sub-acute steady state dosing) – demonstrating at least a medium effect size mean change difference (Cohen's d≥0.5). The second criterion is that participants assigned to CBD (either 300 mg/d, 900 mg/d, or both) will display a larger reduction in anxiety reactivity (SUDS) from baseline to day 4 compared to placebo – demonstrating at least a small-to-medium effect size difference (Cohen's d≥0.30). The effect size benchmark for our primary biological target (anandamide) is higher than that for our biobehavioral target (anxiety reactivity) because anxiety reactivity is a more distal treatment target and small-to-medium effects of clinical targets are deemed clinically relevant (Cuijpers et al., 2014). Criterion 1 and 2 must be met to support proceeding to the R33 trial.

Analysis of Secondary Biological Outcomes. Methods analogous to the effect size comparison of the primary outcome will be applied to plasma levels of 2-AG, PEA, OEA, 7-OH-CBD, 7-COOH-CBD, and CBD.

Analysis of Secondary and Exploratory Biobehavioral Outcomes. Methods analogous to the effect size comparison of the primary biobehavioral outcome will be applied to secondary measures of anxiety reactivity (i.e., threat-related predictions, anxiety-related behavior, negative self-statements, and heart rate variability) and exploratory emotional processing bias measures (i.e., emotion detection accuracy, attentional bias for threat and positive faces). As above, effect size differences on change in the secondary and exploratory outcomes from baseline to day 4 will be compared in the CBD vs. placebo arms, using Cohen's d≥0.30 as a clinically relevant benchmark to compare groups.

Subgroups: To determine heterogeneity of treatment effects, we will consider *a priori* subgroup analysis, including sex as a biological variable. Given the limitations in sample size, we will consider effect sizes and mean estimates that are expressed in terms of their 95% confidence intervals.

Aim 2: To determine which dose (300 or 900 mg/d) of CBD maximizes target engagement.

Effect size estimates will be compared by CBD dose for differences in mean change on plasma anandamide levels and anxiety reactivity from baseline to day 4. A Cohen's d≥0.20 (for the 900 vs. 300 mg dose difference) in favor of the 900 mg/d dose on either increases in anandamide levels or reductions in anxiety reactivity will support its testing in the R33 phase. Both targets are potentially relevant to clinical response in SAD, and therefore achieving a greater effect on one or both targets with the higher dose would justify its further testing. Cohen's d<0.20 distinguishing the doses on both outcomes will favor the 300 mg/d dose being carried forward to the R33 project.

Exploratory Aim: To examine whether CBD in combination with a brief safety behavior reduction intervention produces larger reductions in social anxiety symptoms and associated outcomes compared to placebo with safety behavior reduction.

Primary outcome: Change in social anxiety symptoms (LSAS) from day 4 to one-month follow-up will be analyzed using a linear mixed effects model. Independent variables will include treatment arm (CBD vs.

placebo), visit (baseline, weekly, follow-up), and treatment-by-visit interaction. Hypothesis: Participants assigned to the CBD plus safety behavior reduction group will experience a larger reduction in social anxiety symptoms from day 4 to follow-up compared to the placebo group. Secondary outcomes (safety behaviors [SAFE], functional interference [SDS] and depression [PHQ-9]) and exploratory outcomes (social connectedness [SCSR], general anxiety [GAD-7], positive affect [PANAS], sleep disturbance (PROMIS), and quality of life (QLES-Q-SF) will be analyzed using methods analogous to the primary outcome. The global rating of change index will be compared using an independent samples t-test.

10. HUMAN SUBJECTS

The proposed project plans to enroll and randomize approximately 60 individuals recruited from the general community who meet diagnostic criteria for social anxiety disorder (SAD). Participants will be between the ages of 18 to 70.

Inclusion criteria are:

(1) Principal diagnosis of SAD according to the Mini-International Neuropsychiatric Interview for DSM-5 (MINI Version 7.0.2)
(2) Clinician-administered Liebowitz Social Anxiety Scale (LSAS) score ≥ 60 and score ≥2 on Question 6 (public speaking fear/anxiety sub-scale) to ensure significant associated severity and impairment
(3) Ages 18-70
(4) Able to provide informed, written consent
(5) English proficiency

Exclusion criteria are:

(1) Current or imminent risk of suicide assessed using the Columbia Suicide Severity Rating Scale (C-SSRS)
(2) Bipolar or psychotic disorders
(3) History of major neurological disorder or moderate to severe traumatic brain injury or severe or unstable medical conditions that might be compromised by participation in the study.
(4) Past 6-month substance use disorder (any severity, with the exception of mild alcohol use disorder)
(5) Prior history of cannabis use disorder, or allergy or intolerance to cannabinoids
(6) Current (within past 7 days) cannabinoid use (medicinal or recreational; assessed using patient report and a urine sample). Concurrent cannabinoid use is prohibited during the study.
(7) Positive urinalysis screen for psychoactive drug use (that is not physician prescribed)
(8) Abnormal and clinically relevant blood count, liver, renal or EKG findings as determined by physician
(9) Currently prescribed medications with known CBD-interactions (e.g., amiodarone, fluconazole, metronidazole, miconazole, sulfamethoxazole, clarithromycin, erythromycin, cyclosporine, verapamil, itraconazole, voriconazole, boceprevir, St. John's Wart, and carbamazepine)
(10) Women who are pregnant, breastfeeding, or planning to become pregnant within the next 6 months. Women of childbearing potential who do not meet those exclusions must agree to use an acceptable method of contraception from at least 21 days prior to the first dose of study drug and for 3 months after the last dose of study drug for study entry.
(11) Concurrent empirically supported psychosocial treatments for anxiety or mood disorders (e.g., cognitive behavioral therapy)
(12) Use of any psychotropic medication (e.g. SSRIs, benzodiazepines) within 14 days before study entry [except for fluoxetine within 30 days]. Concurrent use is prohibited during the study.
(13) Use of beta-adrenergic blocking agents ("beta blockers") within 14 days before study entry. Concurrent use is prohibited during the study.
(14) Use of any over-the-counter, prescription, or herbal product for treating symptoms of anxiety or social anxiety within 14 days before study entry. Concurrent use is prohibited during the study.
(15) Inability to complete the assessments or test sessions.
(16) Clinical conditions assessed by the interviewer that necessitate more imminent clinical care. These criteria are in place so participants with these other, more several symptoms can be referred for appropriate services.
(17) Prior participation in a clinical trial involving cannabinoids.

(18) Non-correctable vision or hearing problems, as some tests require intact sensory functioning.
(19) No telephone or easy access to telephone.
(20) Severe depression symptoms (PHQ-9 >= 20)

Exclusion criteria will be assessed using the MINI for DSM-5, medical history, and urine and blood test. Patients excluded from the study will be referred for additional care as appropriate.

Gender/Minority/Pediatric Inclusion for Research: Women and minorities will be included in the study without prejudice according to their representation in the study population. All efforts will be made to ensure that our subject population closely resembles the gender, ethnic and racial composition of the communities from which we are recruiting. Children are not included in this protocol due to its focus on identifying the feasibility of this intervention for adults with SAD.

11. RECRUITMENT AND PROCEDURES PREPARATORY TO RESEARCH

Individuals will be recruited from the community through strategies successfully employed in the context of the PI's previous studies, including through consecutive referrals to the Anxiety & Traumatic Stress Disorders Program at UCSD (directed by Drs. Stein and Taylor) and through IRB-approved advertisements and announcements posted throughout community settings, online media (e.g., Craigslist), social media (e.g., Facebook), and ResearchMatch.

We will also recruit participants from UCSD primary care clinics using methods identical to those being implemented under HRPP protocol #202047. Specifically, primary care patients that screen positive for anxiety and/or depression as part of their routine clinic visit will be sent an HRPP-approved recruitment letter electronically for UCSD patients registered for 'MyUCSDChart' which provides private and secure online access to health information, or hardcopy mailed to addressee only from their Primary Care Physician/Clinic with information about the research and study contact information.

Individuals will also be recruited from other IRB-approved studies in the laboratory and only individuals who previously agreed to be contacted for other research will be recruited. The investigator will make clear that this is a separate study and is completely voluntary and up to the discretion of the participant whether or not to participate.

We will also utilize BuildClinical to post ads online. BuildClinical is a data-driven, clinical trial recruiting system that helps investigators recruit patients/participants for clinical trials more efficiently using social media, software, and machine learning. They have provided PDF previews of all ads (uploaded to the IRB website) and will target adults between 18 and 70 in the San Diego area. Once an individual clicks on an ad, they are directed to the study's IRB approved landing page. From there, they can click to sign up via the IRB approved pre-screening form. Once someone responds to an ad, they will submit their name and email to register interest. This information is made available only to our study trial staff, who sign in to a secure web system to retrieve the registered information. The data is used only for the research recruitment purposes. BuildClinical does not use the data in other ways and the data is deleted upon completion of the contract. BuildClinical never communicates with study participants.

BuildClinical's Foundation Platform is HIPAA-compliant, and maintains ongoing compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA), powered by Amazon Web Services (AWS). All data is encrypted and is transmitted via HTTPS to a dedicated network which is secured with firewalls and intrusion detection technology.

12. INFORMED CONSENT

Informed Consent will be obtained by members of the research team that have received training from the PI to obtain consent for this study. All participant interactions including consenting will be conducted in private

interview/exam rooms. Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant and written documentation of informed consent will be completed prior to starting the study procedures. The consent materials are submitted with this protocol.

Verbal Consent: Individuals will be contacted via phone and will be informed about the purpose of this study and asked to provide verbal consent for screening procedures using the IRB-approved Verbal Consent and Telephone Screening Form. A Waiver of Documented Consent for recruitment screening purposes is justified since the only record linking the subject and the research would be the consent document and the principal risks would be the potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern. At the same time, we provide our contact information so that the individual is able to contact us at any time.

Documented Consent: If the individual appears eligible, we schedule the documented informed consent process in order to conduct the full Screening Intake. Documented informed consent will be obtained once the consent has been reviewed and the individual agrees to participate using the appropriate approved informed consent document. Participants are provided a copy of the consent. All volunteers are of legal age and will be asked to give fully informed documented consent following consent procedures already approved. Care is taken to appropriately describe IRB-approved consent forms as documented by signature of the person giving permission and person obtaining informed consent. We review consents for completeness and file them in a locked file cabinet in a locked office. Consent may be obtained electronically using tablet computers, in which case a full copy of the informed consent will still be provided to the participant. For documented consent completed remotely (described fully in Section 9 under Remote Study Procedure), consent forms will be uploaded to REDCap or DocuSign. If participants agree to participate, they will electronically sign the consent form through the REDCap or DocuSign system. They will be able to download a copy of the consent and Experimental Subject Bill of Rights to keep.

13. ALTERNATIVES TO STUDY PARTICIPATION

Participants may opt not to enroll in the study.

14. POTENTIAL RISKS

Loss of confidentiality: The provision of personal information carries with it a small risk that this information could become known outside the research context. Since loss of confidentiality is a potential hazard of any protocol involving mental health measures, we are taking precautions to guard against data being released to unauthorized persons. Policies and procedures to minimize this risk are discussed below.

Risks associated with the study drug: The most common side effects associated with cannabidiol are generally mild and may include somnolence, diarrhea, psychomotor slowing, light-headedness, appetite loss, and/or insomnia (Iffland & Grotenhermen, 2017). The research design formalizes assessment and monitoring of symptoms and possible side effects throughout the treatment process (described below).

The CBD product being used for this study (Epidiolex) may result in a positive drug test. Participants will be asked to inform the study physician if they think they may have a cannabis drug screen at work or elsewhere during the duration of the study and for one to two months afterward. If yes, they have the option of not participating in this study. If they do wish to participate, we can provide a letter to their employer (or other drug test administrator) indicating that they are participating in a federally funded research study, and they may test positive for CBD while in the study and for up to two months afterward.

Risks associated with screening, interviewing, and assessments: Mild fatigue or mild to moderate demands on attention may occur when completing the assessments. These are not seen as significant risks. During the clinical interview and self-report symptom assessments, participants will be asked questions about their anxiety, mood, and other psychological symptoms that may cause discomfort. Delivering a speech in front of a video camera and research personnel may also cause discomfort. Participants will be informed about

the possibility of experiencing distress during the procedures in the consent form and notified that they can stop the assessment procedures, or refuse to answer any questions at any point. Study staff members are trained to handle any distress that arises. The PI will be available to meet with any participants who express distress during the procedures and make referrals to outside clinical care as deemed appropriate.

Blood draw: As any blood draw carries some risk, the subject will be informed that the blood draw may be associated with mild pain, bruising and infection at the puncture site, as well as a possible risk of fainting or dizziness.

Drug Testing: Participation in this study will require that urine be tested for drugs, including cocaine, marijuana, opiates, amphetamines, methamphetamines, phencyclidine, benzodiazepines, barbiturates, methadone, and oxycodone. These drug tests are necessary to make sure that study procedures are appropriate for the participants. Copies of the drug test results will not be provided to study participants. The drug tests are conducted in instant read cups with immediate results. Efforts will be made to keep personal information confidential. The cups are not labeled with any participant information, results are read immediately after the subject provides urine sample, and the urine and cup are promptly and properly discarded. Awareness of a positive drug test may have serious personal or social consequences which may include difficulty obtaining insurance (e.g., health, life, and disability insurance) or employment, and difficulty traveling to some foreign countries.

ECG: The procedures for electrocardiogram recording are quite safe, completely noninvasive, and involve no physical or psychological harm. The sticky patches may pull on the skin or cause redness or itching.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

Risks associated with participation: We have instituted the following measures to protect the privacy of participants and confidentiality of research data:

- Data will be collected by study staff who completed training in human subjects' research, HIPAA, and research integrity, on research data management, confidentiality and mandatory reporting, and project specific training on the protocol.
- To protect confidentiality, no personally identifying information will be coded on questionnaires, interviews, or other study records. Further, subjects will not be identified in any reports or publications.
- All de-identified hard-copy data will be stored in locked file cabinets in a locked office. A unique subject identification number is assigned to each participant and linked to the study participant name in an established, password-protected, database in use by our research group with access limited by the PI, Study Psychiatrist or Physician, and designated Study Coordinator. This database uses the secure web application Research Electronic Data Capture (REDCap) (Harris et al., 2009) and is supported and maintained by the UCSD Clinical and Translational Research Institute (CTRI).
- The data key needs to be maintained in order to inform participants of new information that may be derived from the results of the study. The data key that relates the de-identified subject identification numbers to participants will be kept in a locked cabinet (separate from any study records) in the principal investigator's locked office. Destruction and responsibility of hard copy data will be destroyed in accordance with UCSD policy and electronic study records will be destroyed in coordination with UCSD HRPP policy.
- A study drug prescription form that includes the subject ID and name of the subject will be stored in a locked filing cabinet behind locked doors in the Investigational Drug Service (IDS) located within the UCSD Altman Clinical and Translational Research Institute. This record is needed in the event that unblinding is required.
- The original signed consents, screening form, locator form with contact information, the Research Privacy Form, and any other forms or papers containing personally identifiable information (PII) will be stored in a secured medical records room with access granted only to authorized study personnel.
- Electronic data will be stored securely on servers and databases accessible only to study personnel.

- In cases when the participant contact information is no longer valid and we contact family or friends who were provided by the subject, no information will be provided about the nature of the study or the participant (i.e. study staff will state that the individual had participated in a research study at UCSD and that the project requires a follow up interview).

All clinical interview assessments will be conducted by trained research staff who are experienced in structured diagnostic assessment. Project staff will review each completed clinical interview with the PI, Co-Is or study physician. If a participant expresses significant distress or discomfort during the diagnostic or any other assessment procedures (e.g., social stress test), the PI will be notified. The PI will also provide appropriate referrals if the participant elects not to complete the assessment. Thorough assessment of suicidal, homicidal, or self-injurious ideation or behaviors will be conducted using the MINI for DSM-5 suicide assessment protocol (baseline screening) and Columbia-Suicide Severity Rating Scale (C-SSRS; Posner et al., 2011) administered during each study visit. Any such incidences will be reported to the PI and handled in accordance with ethical and legal guidelines (e.g., Tarasoff reporting). Any participants reporting imminent risk of suicidal behavior will be escorted to the local Emergency Department at UCSD.

Side Effects Management: The most common side effects associated with CBD are noted above. Subjects will be informed of the possible side effects. Side effects will be tracked with the Frequency, Intensity, and Burden of Side Effects Ratings scale (FIBSER; Wisniewski et al., 2006) with follow-up by the pharmacotherapist. Participants will be carefully evaluated for adverse events after study drug administration. Mild side effects can be managed by empathic concern, reassurance, and an explanation that severity of side effects may decrease over time. The physician will do everything possible to keep the participant comfortable and to address common side effects as medically appropriate.

Laboratory Results: Analysis of fluids done for this study may indicate clinically significant lab values. If a subject has not reported being aware of such clinical findings, they will be notified in a face-to-face meeting with the study physician as soon as possible and this information will be documented in the research record. If needed, the subject will be provided with a referral to a medical professional for further assessment and/or treatment. Individuals will be able to decide if they wish to take this risk prior to any study procedures, including lab tests and physical examinations that might reveal a reportable condition.

Suicidality. There is no expectation that CBD will have a deleterious impact on suicidality. Nevertheless, it is prudent to carefully monitor suicidality in the target population, and so this will be routinely and rigorously assessed throughout this study using the Columbia Suicide Severity Rating Scale (C-SSRS; Posner et al., 2011) administered during each study visit. The clinician will strongly encourage the participant to call and let the study staff know immediately if they are experiencing thoughts or impulses that might lead them to hurt themselves. The clinician will also remind the patient that they should utilize emergency services if needed. Participants will be informed of the National Suicide Prevention Lifeline (1-800-273-8255) as an additional resource should they experience suicidal thoughts or impulses.

Medication Discontinuation: Participants will be asked to contact the study physician before discontinuing the study medication.

Upon study completion, patients who are currently under treatment by an external provider will be referred to their own clinician. Subjects who are dropped from study participation, or patients who complete the study and are not under the care of a clinician, will be provided a referral to a psychiatrist or other mental health professional within their community (regardless of the reported level of post-treatment symptoms).

Adverse Events:

Definition of Adverse Events: This protocol uses the definition of adverse event from 21 CFR 312.32 (a): any untoward medical occurrence associated with the use of an intervention in humans, *whether or not considered intervention-related*.

Definition of Serious Adverse Events: A serious adverse event will be considered any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

1. results in death;
2. is life-threatening (places the subject at immediate risk of death from the event as it occurred);
3. requires inpatient hospitalization or prolongation of existing hospitalization;
4. results in a persistent or significant disability/incapacity;
5. results in a congenital anomaly/birth defect; or
6. any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Classification of an Adverse Event:

Severity of Event: For adverse events (AEs) not included in the protocol-defined grading system, the following guidelines will be used to describe severity.

- Mild – Events require minimal or no additional treatment and do not interfere with the participant's daily activities to a greater degree than when enrolled in the study.
- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning that is somewhat greater in degree than when enrolled in the study.
- Severe – Events interrupt a participant's usual daily activity and may require a modification in their current treatment plan external to the study. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

Relationship to Study Intervention/Experimental Manipulation: All adverse events (AEs) will have their relationship to study procedures, including the intervention, assessed by the PIs based on temporal relationship and his clinical judgment. The degree of certainty about causality will be graded using the categories below.

- *Definitely Related* – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study procedures administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study procedures should be clinically plausible. The event must be pharmacologically or phenomenologically definitive.
- *Probably Related* – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study procedures, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.
- *Potentially Related* – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of study procedures). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- *Unlikely to be related* – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study procedures administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study procedures) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- *Not Related* – The AE is completely independent of study procedures administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Expectedness: Expected adverse reactions are AEs that are known to occur for the study procedures being studied. The PIs will be responsible for determining whether an adverse event (AE) is expected or unexpected.

An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures.

Time Period and Frequency for Event Assessment and Follow-Up:
The occurrence of an adverse event (AE) or serious adverse event may come to the attention of study personnel during study visits and interviews or electronic surveys. All AEs, not otherwise precluded per the protocol, will be captured on an adverse event form. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical or psychiatric condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates significantly at any time during the study, it will be recorded as an AE (see above sections concerning monitoring of suicidal ideation and mental health symptoms).

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.

The PI will record events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

Adverse Event Reporting:
Unanticipated, serious adverse events will be reported to the IRB within 24 hours of the time project staff become aware of the incident. In addition, at yearly intervals throughout the course of the study, the IRB will receive a summary of all other safety-related reports including safety-related protocol deviations, treatment retention, and reasons for dropout. Should the protocol or data collection plans be amended as a result of adverse events or subsequent data review, the IRB will be notified, and the amendment approved prior to study amendment implementation. In addition, the participants will be notified of any significant new findings that develop during the course of research (e.g., other potential risks) that may affect their wish to continue participation in the study.

Events of Special Interest:
Participants will be informed that study personnel are mandated reporters of child, dependent, or elder abuse and that confidentiality may be broken in these instances, or in the instance in which the participant is considered to be of danger to themselves or others.

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

We have instituted the following measures to protect the privacy of participants and confidentiality of research data:

- Screening and consent will be conducted in private conference rooms.
- Data will be collected by study staff who completed training in human subjects' research, HIPAA, and research integrity, on research data management, confidentiality and mandatory reporting, and project specific training on the protocol.
- To protect confidentiality, no personally identifying information will be coded on questionnaires, interviews, or other study records. Further, subjects will not be identified in any reports or publications. All de-identified hard-copy data will be stored in locked file cabinets in a locked office. A unique subject identification number is assigned to each participant and linked to the study participant name in an established, password-protected, database in use by our research group with access limited by the PI,

Study Psychiatrist or Physician, and designated Study Coordinator. This database uses the secure web application Research Electronic Data Capture (REDCap) (Harris et al., 2009) and is supported and maintained by the UCSD Clinical and Translational Research Institute (CTRI).

- The original signed consents, screening form, locator form with contact information, the Research Privacy Form, and any other forms or papers containing personally identifiable information (PII) will be stored in a locked cabinet in a locked office with access granted only to authorized study personnel.
- Video recordings will be stored digitally on secure, password-protected computers and hard drives stored in a locked filing cabinet drawer within a locked office. Video records will be numerically coded so that the participant's name and other personally identifying information will not be used. Only the Investigator and research assistants will have access to video recordings, and video recordings will be viewed only to rate participant behavior and ensure that research protocols have been adhered to. In any use of the video recording, the participant's name will not be identified. Upon the participant's request or seven years after termination of the study, video recordings will be destroyed.
- Electronic data will be stored behind secure firewalls on password-protected servers and databases accessible only to study personnel.
- In cases when the participant contact information is no longer valid and we contact family or friends who were provided by the subject, no information will be provided about the nature of the participant, (i.e. study staff will state that the individual had participated in a research study at UCSD and that the project requires a follow up interview).
- Information reported will be kept in confidence with the exception that disclosure of suicidality, homicidality, or child or elder abuse warrant reporting to appropriate authorities to appropriate external authorities and University officials including the use of the University Compliance Hotline (by phone 1-800-403-4744).
- Text (SMS) messages for the safety behavior reduction protocol will be sent using a third-party web service, Twilio. Only phone numbers are temporarily logged on the Twilio site and Twilio does not have access to participant study responses (i.e., weekly ratings) that are directly entered into the REDCap database, therefore ensuring confidentiality of participant data. No personal health information will be obtained as part of the text message prompts or surveys.

17. POTENTIAL BENEFITS

Subjects will receive best-practices psychiatric evaluation and medical clearance assessments. Knowledge gained from the study may lead to improvement in the care of future patients.

18. RISK/BENEFIT RATIO

Subjects will receive best-practices psychiatric evaluation and medical clearance assessments. Knowledge gained from the study may lead to improvement in the care of future patients by informing the therapeutic potential of CBD for anxiety. Risk to participants is minimal. Primary risks include discomfort associated with the assessments and side effects due to the study drug. Side effects are generally mild and will be monitored throughout the study, with follow up by the pharmacotherapist. Reporting side effects documented in this trial will contribute to the extant literature and clinical practice guidelines, which will benefit others. Participants will be closely and frequently monitored for emerging suicidality, or worsening of symptoms, that are beyond standard of care for individuals in the community without treatments. Thus, we believe the risk/benefit ratio is acceptable.

19. EXPENSE TO PARTICIPANT

There is no expected expense to study participants other than travel to UCSD and the time to complete study procedures. For all participants, the study will take approximately 9-12 hours to complete, including the informed consent process, initial screening / intake, baseline visit, and post-test session (day 4). Appointments will be flexible to accommodate participant schedules, including evening times as needed. Parking will be provided at no cost to the participant (either free parking or we will reimburse for their parking fees).

20. COMPENSATION FOR PARTICIPATION

Participants who complete the entire protocol (Aims 1 and 2) will receive $225.

Intaking / screening: $20 for the clinical interview and $20 for the medical examination and tests
Baseline session: $80
Post-test session: $80

Participation in baseline and post-test sessions will be prorated at $20 per hour if participants discontinue before the end of a session. Participants who complete all study procedures from baseline to post-test (day 4) will receive an additional $25 gift card.

Participants who complete the exploratory aim protocol will receive $75:

Baseline surveys and orientation to the intervention: $20
Weekly surveys: $10 per week ($20 total)
Follow-up surveys (week 3) and visit: $30
Completing all exploratory aim procedures: $5

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

Principal Investigators

Charles Taylor, PhD is an Associate Professor in the Department of Psychiatry at the University of California, San Diego (UCSD).
Murray B. Stein, MD, MPH is a Distinguished Professor of Psychiatry and Public Health at UCSD, where he directs the Anxiety & Traumatic Stress Disorders Program.

Co-Investigators

Thomas Marcotte, PhD is a Professor of Psychiatry at UCSD and Co-Director of the UCSD Center for Medicinal Cannabis Research.

Sonia Jain, PhD, is a Professor in the Division of Biostatistics and Bioinformatics, School of Public Health at UCSD.

Robert Fitzgerald, PhD, is a Professor of Clinical Pathology and Director of the Chemistry and Toxicology Laboratory at the UCSD Center for Medicinal Cannabis Research. He is board certified in both clinical toxicology and clinical chemistry (Diplomate American Board of Clinical Chemistry).

Jonathan Howlett, MD is an Associate Physician in the Department of Psychiatry at the University of California, San Diego (UCSD).

I-Wei Shu, MD, PhD is an Associate Clinical Professor in the Department of Psychiatry at the University of California, San Diego (UCSD).

Consultants

Jessica Bomyea, PhD is an Assistant Professor in the Department of Psychiatry at the University of California, San Diego (UCSD).

Susan Murray, PhD, is a Post-doctoral Fellow at the Eating Disorders Center for Treatment and Research at the University of California, San Diego (UCSD).

All personnel associated with this project will complete the online HRPP Human Subjects training and certificates will be kept on file in the study office.

Research Staff

Taylor Smith, B.S., *Study Coordinator,* Clinical Research Coordinator, UCSD, will assist with behavioral experiments and score and enter study data. She will provide information and obtain documented informed consent/HIPAA and liaise with the CTRI. She will meet regularly with Dr. Taylor (once weekly or more as needed) to review new participants and to discuss any concerns with data collection. She will maintain all information in a locked file cabinet and password protected data bases.

Nuzhat Beg, MBBS, M.A.S, *Study Coordinator,* Clinical Research Coordinator, UCSD, will assist with behavioral experiments and score and enter study data. She will provide information and obtain documented informed consent/HIPAA and liaise with the CTRI. She will meet regularly with Dr. Taylor (once weekly or more as needed) to review new participants and to discuss any concerns with data collection. She will maintain all information in a locked file cabinet and password protected data bases.

Kush Bhatt, MD, is a *resident physician* in the Department of Psychiatry at the University of California, San Diego (UCSD). He will perform medical examinations at screening, review clinical lab results, determine eligibility, assess adverse and serious adverse events (AE/SAEs), and assess medication adherence.

Samantha Hoffman, B.A., *Study Coordinator,* Graduate Student Research Associate, SDSU/UCSD Joint Doctoral Program in Clinical Psychology, will assist behavioral experiments. She will meet regularly (once weekly or more as needed) with Dr. Taylor to review participants and to discuss any concerns with data collection, and with other project staff to review study operations.

Marissa Larkin, B.S., *Study Coordinator,* Staff Research Associate, UCSD, will assist with behavioral experiments and score and enter study data. She will provide information and obtain documented informed consent/HIPAA and liaise with the CTRI. She will meet regularly with Dr. Taylor (once weekly or more as needed) to review new participants and to discuss any concerns with data collection. She will maintain all information in a locked file cabinet and password protected data bases.

Margaret Satchwell, B.S., *Study Coordinator,* Staff Research Associate, UCSD, will assist with behavioral experiments and score and enter study data. She will provide information and obtain documented informed consent/HIPAA and liaise with the CTRI. She will meet regularly with Dr. Taylor (once weekly or more as needed) to review new participants and to discuss any concerns with data collection. She will maintain all information in a locked file cabinet and password protected data bases.

Madeleine Rassaby, B.A., *Study Coordinator,* Graduate Student Research Associate, SDSU/UCSD Joint Doctoral Program in Clinical Psychology, will assist with behavioral experiments. She will meet regularly (once weekly or more as needed) with Dr. Taylor to review participants and to discuss any concerns with data collection, and with other project staff to review study operations.

Isabella Spaulding, B.A., *Study Coordinator,* Graduate Student Research Associate, SDSU/UCSD Joint Doctoral Program in Clinical Psychology, will assist with behavioral experiments. She will meet regularly (once weekly or more as needed) with Dr. Taylor to review participants and to discuss any concerns with data collection, and with other project staff to review study operations.

Kaye Han, *Research Assistant*, will assist with fMRI and behavioral experiments and score and enter study data. She will meet regularly (once weekly or more as needed) with the project team (PI and study coordinators).

Juliana Himawan, *Research Assistant*, will assist with fMRI and behavioral experiments and score and enter study data. She will meet regularly (once weekly or more as needed) with the project team (PI and study coordinators).

Ivan Lagunas, *Research Assistant*, will assist with fMRI and behavioral experiments and score and enter study data. He will meet regularly (once weekly or more as needed) with the project team (PI and study coordinators).

Siyi He, *Research Assistant*, will assist with fMRI and behavioral experiments and score and enter study data. She will meet regularly (once weekly or more as needed) with the project team (PI and study coordinators).

Tess Oswalt, *Research Assistant*, will assist with fMRI and behavioral experiments and score and enter study data. She will meet regularly (once weekly or more as needed) with the project team (PI and study coordinators).

Michael Mansour, *Research Assistant*, will assist with fMRI and behavioral experiments and score and enter study data. He will meet regularly (once weekly or more as needed) with the project team (PI and study coordinators).

Alexa Duran, *Research Assistant*, will assist with fMRI and behavioral experiments and score and enter study data. She will meet regularly (once weekly or more as needed) with the project team (PI and study coordinators).

Jessica Sauceda, *Research Assistant*, will assist with fMRI and behavioral experiments and score and enter study data. She will meet regularly (once weekly or more as needed) with the project team (PI and study coordinators).

Amy Nguyen, *Research Assistant*, will assist with fMRI and behavioral experiments and score and enter study data. She will meet regularly (once weekly or more as needed) with the project team (PI and study coordinators).

Brentney Reynolds, *Research Assistant*, will assist with fMRI and behavioral experiments and score and enter study data. She will meet regularly (once weekly or more as needed) with the project team (PI and study coordinators).

Mehar Zaman, *Research Assistant*, will assist with fMRI and behavioral experiments and score and enter study data. She will meet regularly (once weekly or more as needed) with the project team (PI and study coordinators).

Ahladita Lotti, *Research Assistant*, will assist with fMRI and behavioral experiments and score and enter study data. She will meet regularly (once weekly or more as needed) with the project team (PI and study coordinators).

Zachary Yoo, *Research Assistant*, will assist with fMRI and behavioral experiments and score and enter study data. He will meet regularly (once weekly or more as needed) with the project team (PI and study coordinators).

Layla Farhan, *Research Assistant*, will assist with fMRI and behavioral experiments and score and enter study data. She will meet regularly (once weekly or more as needed) with the project team (PI and study coordinators).

Tina Dang, *Research Assistant*, will assist with fMRI and behavioral experiments and score and enter study data. She will meet regularly (once weekly or more as needed) with the project team (PI and study coordinators).

Ana Flores, *Research Assistant*, will assist with fMRI and behavioral experiments and score and enter study data. She will meet regularly (once weekly or more as needed) with the project team (PI and study coordinators).

Katherine Jamison, *Research Assistant*, will assist with fMRI and behavioral experiments and score and enter study data. She will meet regularly (once weekly or more as needed) with the project team (PI and study coordinators).

Sanjana Paul, *Research Assistant*, will assist with fMRI and behavioral experiments and score and enter study data. She will meet regularly (once weekly or more as needed) with the project team (PI and study coordinators).

Anthea Roshan, *Research Assistant*, will assist with fMRI and behavioral experiments and score and enter study data. She will meet regularly (once weekly or more as needed) with the project team (PI and study coordinators).

Isabella Agajanian, *Research Assistant*, will assist with fMRI and behavioral experiments and score and enter study data. She will meet regularly (once weekly or more as needed) with the project team (PI and study coordinators).

Maanith Shriyan, *Research Assistant*, will assist with fMRI and behavioral experiments and score and enter study data. He will meet regularly (once weekly or more as needed) with the project team (PI and study coordinators).

Ana Zamudio Aispuro, *Research Assistant*, will assist with fMRI and behavioral experiments and score and enter study data. She will meet regularly (once weekly or more as needed) with the project team (PI and study coordinators).

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23. FUNDING SUPPORT FOR THIS STUDY

This study was is funded by NIH/NCCIH as an R61/R33 application. The current phase is 1R61AT011735-01.

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

Not applicable.

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

This study is deemed IND exempt. A formal response from the FDA confirming IND exemption status was provided on 11/12/2021.

26. IMPACT ON STAFF

There will not be an impact on clinical staff.

27. CONFLICT OF INTEREST

There are no conflicts of interest to report.

28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES

Not applicable.

29. OTHER APPROVALS/REGULATED MATERIALS

Not applicable.

30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT

Surrogate consent will not be utilized for this study. We will not enroll those with impaired decisional capacity.