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HUMAN SUBJECTS RESEARCH PROTOCOL

COVER PAGE

Official Study Title: Enhancing Prolonged Exposure with Cannabidiol to Treat PTSD

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1. PROTOCOL TITLE: Enhancing Prolonged Exposure with Cannabidiol to Treat PTSD

2. ABSTRACT

Posttraumatic stress disorder (PTSD) is considered a signature psychiatric disorder among military populations. When left untreated, the symptoms of PTSD can cause significant health and functional impairments. While established treatments for PTSD exist, there remains room for improvement in outcomes since almost half of military patients fail to benefit from treatment. Epidiolex (Cannabidiol [CBD]) is an FDA-approved, non-controlled prescription medication with promising potential for the treatment of PTSD.[1,2] To date, there are no published clinical trials investigating CBD in reducing PTSD, and existing literature in humans with PTSD only includes healthy individuals or case study data. Greater research is needed to fully understand the benefits of CBD for PTSD and to better understand biological mechanisms for its effect. The primary goal of this pilot project is to demonstrate the safety and feasibility of using CBD in combination with standard of care prolonged exposure (PE) psychotherapy to reduce PTSD symptoms (Aim 1). We will also assess possible biochemical and physiological outcomes associated with treatment (Aim 2) and evaluate the relationship between changes in biochemical/physiological measures with PTSD symptom reductions (Aim 3). To address study aims, we will enroll 24 individuals with PTSD to be randomized to CBD (n=12) or placebo (n=12) and all participants will receive 10 daily sessions of PE.

3. OBJECTIVES/SPECIFIC AIMS/RESEARCH QUESTIONS

This project will be a pilot, double-blind randomized controlled trial of CBD effects to pursue three goals: (1) to demonstrate the safety and feasibility of using CBD to reduce PTSD symptoms in conjunction with massed PE (mPE); (2) to assess biochemical and physiological outcomes associated with PTSD treatment; and (3) to evaluate the possible relationship between changes in biochemical/physiological measures with PTSD symptom reductions.

Aim 1: To examine the safety, feasibility, and PTSD symptom reductions associated with CBD (n=12) vs. placebo (n=12) in 24 individuals receiving 10 daily sessions of mPE as a standard of care for PTSD.
- Hypothesis 1: Combining CBD with mPE will be safe based on minimal (< 5%) adverse events and no serious adverse events related to treatment in the study.
- Hypothesis 2: A CBD vs. placebo trial design will be feasible defined as 75% or more of assessed individuals meeting all eligibility criteria and 80% or more of CBD participants completing all 10 mPE sessions.
- Hypothesis 3: Participants in the CBD condition will have greater treatment-related PTSD reductions than placebo as measured by the Clinician Administered PTSD Scale (CAPS-5)[3] and PTSD Checklist (PCL-5).[4]

Aim 2: To evaluate biochemical and physiological levels associated with the eCB system and stress response in CBD vs. placebo.
- Hypothesis 4: Participants in the CBD condition will have higher levels of AEA and 2-AG, and lower levels of cortisol than placebo following treatment.
- Hypothesis 5: Participants in the CBD condition will have lower average heart rate during exposure therapy sessions than placebo.

Aim 3: To determine the association between changes in biomarker levels (cortisol, AEA, 2-AG), physiology (heart rate), and PTSD symptom reduction following treatment.
- Hypothesis 6: Reductions in cortisol and increases in AEA and 2-AG will be associated with PTSD symptom reductions following treatment.
- Hypothesis 7: Lower average heart rate observed during exposure therapy sessions will be associated with PTSD symptom reductions following treatment.

4. MILITARY RELEVANCE

As compared to civilians, the rate of PTSD is particularly elevated among military populations, with approximately 23% of military vs. 6-8% of civilians meeting criteria for PTSD.[5] PTSD has been identified as the signature deployment-related psychiatric condition among service members. The functional impact of PTSD can cost service members their military careers and veterans with PTSD are at increased risk of unemployment and homelessness following military separation.[6] Notwithstanding evidence that PE is an effective treatment for PTSD, there remains room for improvement in outcomes given that a large proportion of patients (~50%) fail to significantly benefit from treatment.[7] This issue is especially problematic among military populations who generally demonstrate poorer treatment gains from first-line psychotherapies for PTSD including PE.[8,9] Given that almost three million U.S. military service members have deployed to Afghanistan, Iraq, and surrounding locations in support of military combat operations since September 11, 2001, the need for effective treatment for PTSD is critical. Research dedicated to target mechanisms associated with PTSD symptomatology has the

potential to promote greater PTSD treatment efficacy that will lead to greater symptom reductions, positive well-being, and improved functioning in civilians and military veterans.

5. BACKGROUND AND SIGNIFICANCE

PTSD Prevalence and Impact. PTSD is a chronic and debilitating condition triggered by exposure to a traumatic event. Symptoms of PTSD can include anxiety, negative mood, sleep disruption, nightmares, and negative, uncontrollable thoughts about the event. When left untreated, it can lead to detriments in mental health and psychosocial functioning.[10,11] The overall impact of PTSD is substantial and often leads to significant burdens on the individual, their family, and the community.[12] The sequalae of PTSD not only impacts an individual's immediate environment but also places significant burden on society due to increased work sick days and greater healthcare utilization.[6,11] The rate of PTSD is particularly elevated among military populations, with approximately 23% of military meeting criteria for PTSD annually.[5] PTSD has been identified as the signature deployment-related psychiatric condition among service members. The functional impact of PTSD can cost service members their military careers and veterans with PTSD are at increased risk of unemployment and homelessness following military separation. Given that almost three million U.S. military service members have deployed to Afghanistan, Iraq, and surrounding locations in support of military combat operations since September 11, 2001, the need for effective treatment for PTSD is critical.

Behavioral Therapy Approaches to PTSD Treatment. Evidence-based treatments for PTSD exist and are well-established.[13] PE is a type of Cognitive Behavioral Therapy (CBT) and one of the most widely used first-line interventions for PTSD. PE has been validated across various populations and trauma types.[e.g.,14–16] Preliminary evidence suggests that PE can even be effectively delivered in deployed settings, potentially helping service members return to duty without being aeromedically evacuated out of theater.[17] PE aims to reduce trauma-related distress and PTSD symptomatology through extinction learning interventions (i.e., repeated exposure) to internal (e.g., trauma memory) and external (e.g., environmental stimuli) trauma cues under objectively safe conditions. Notwithstanding evidence that PE is an effective treatment for PTSD, there remains room for improvement in outcomes given that a large proportion of patients (~50%) fail to significantly benefit from treatment.[7] This issue is especially problematic among military populations who generally demonstrate poorer treatment gains from first-line psychotherapies for PTSD including PE.[9] Based on the rising number of service members returning from combat deployments to Afghanistan, Iraq, and surrounding areas, there is a high priority need for the most effective treatments for PTSD. Research dedicated to target mechanisms associated with PTSD symptomatology has the potential to promote greater PTSD treatment efficacy that will lead to greater symptom reductions, positive well-being, and improved functioning in civilians and military veterans.

Medication Approaches to PTSD Treatment. Despite the benefits of first-line CBT interventions for PTSD treatment, pharmacotherapy remains the most commonly used approach to treat PTSD in civilians and military veterans.[18] The only pharmacological interventions for PTSD approved by the Food and Drug Administration (FDA) are the selective serotonin reuptake inhibitors (SSRIs) fluoxetine and sertraline. Although approved by the FDA for PTSD treatment, these drugs have relatively modest benefits to reduce PTSD and often fail to help patients reach PTSD remission.[19,20] Based upon expert panel psychological trauma recommendation guidelines[21], no medication treatments have been determined to be a first-line option for treatment of PTSD. Unfortunately, this state of pharmacotherapy for PTSD has prompted many providers to use polypharmacy in which patients are prescribed a combination of medications with little to no empirical guidance on either the benefits or adverse reactions.[22]

Endocannabinoid System and PTSD. One potential reason for the low efficacy of SSRIs and the use of polypharmacotherapy is that these medications do not directly target PTSD symptomatology. A rapidly growing body of evidence has highlighted the endocannabinoid (eCB) system as a critical regulator of the stress response.[23] Further, it has been suggested that psychological trauma can lead to long-term alterations in the eCB system.[24] The eCB system is a neuromodulatory system comprised of two primary receptors (CB1 and CB2), two main neurotransmitters (anandamide [AEA] and 2-arachidonylglycerol [2-AG]), and several enzymes that synthesize and degrade these neurotransmitters.[25] Most research has focused on CB1 receptors, which are primarily located in the central nervous system and have the highest densities in brain regions associated with anxiety and fear learning (e.g., cortex, amygdala, and hippocampus). Preclinical animal models have shown that CB1 antagonists increase anxiety, while agonists produce anxiolytic effects.[26] AEA and 2-AG are the two primary endogenous eCBs that act as agonists at CB1 receptors.[27,28] These eCBs are critical nerve signaling chemicals shown to regulate mood, memory, perception, and sleep.[29]. Overall, novel pharmacological approaches targeting the eCB system have promising potential to improve anxiety, mood, and sleep problems, while facilitating extinction learning, all of which characterize PTSD symptoms and seem particularly important to compliment first-line psychotherapy interventions.

Cannabidiol for Augmentation of PE Treatment for PTSD. Based on growing evidence on the synergistic relationship between the eCB system and PTSD, increasing efforts have been devoted to pharmacotherapy options. The recently FDA-approved prescription medication, Epidiolex (Cannabidiol [CBD]) is a cannabis-derived, non-controlled drug that may

be beneficial for PTSD. Existing research has shown that CBD may facilitate extinction learning, decrease anxiety, and improve mood and sleep, all of which might enhance the effectiveness of mPE for PTSD.[30,31] Furthermore, CBD is well tolerated, even in large doses, and has not been shown to produce adverse side effects associated with other cannabis-derived medications (e.g., dependence, withdrawal, psychoactive effects, increased anxiety, memory and concentration difficulties, slowed reaction time, coordination problems, and elevated heart rate). Thus, CBD may be able to maximize the positive benefits associated with the eCB system, while mitigating adverse events that occur with other cannabis-derived drugs.

Most of the existing literature indicating the benefits of CBD for PTSD treatment has involved preclinical animal studies, case studies, and a few proof-of-concept trials with healthy humans. Preclinical animal models have used a fear-based conditioning paradigm[e.g.,32] designed to parallel the impact of trauma in humans with PTSD to investigate the effects of CBD. Animal models have shown that CBD can reduce cardiovascular and anxiogenic effects of stress.[30,31] CBD has been found to decrease retrieval and acquisition of fear memories[33,34] and even block reconsolidation of the trauma memory in animal models.[30] The most promising outcome of preclinical PTSD research is evidence that CBD can facilitate and enhance the extinction learning process, a key component of exposure-based psychotherapies for PTSD.[35,36] Consistent with preclinical animal research, Das et al.[37] found that CBD facilitated extinction learning and decreased cue-based fear response in a sample of healthy humans.

Only a few studies have been completed in humans. A case report found that daily use of CBD was associated with reduced anxiety and improved sleep in a child with treatment resistant PTSD despite the fact that standard pharmacotherapy for PTSD had produced only limited and acute symptom relief.[38] In a retrospective case series analysis of adults (N=11) with PTSD, participants received oral CBD in combination with routine psychiatric and psychotherapy care over 8 weeks.[2] Results suggested that CBD was associated with a 28% decrease in PTSD symptom and was well tolerated (with no discontinuation due to side effects) among participants. Though these findings suggest that CBD may be used for the treatment of PTSD, there is a paucity of research on the safety, feasibility, and efficacy of CBD as a treatment for PTSD in human trials.

Furthermore, although preliminary evidence suggests CBD may benefit PTSD symptom reduction, the specific mechanisms of action of CBD on the eCB remains unclear. One possible mechanism may include modulation of the eCB system since research has shown that CBD may have low affinity for CB receptors, but nonetheless is able to bind to CB1.[39] CBD may also act as an antagonist to other agonists due to effects at different prejunctional sites and indirect interactions with non-cannabinoid receptors.[40] In turn, this may explain possible effects on eCB metabolism including inhibition of the uptake and degradation of critical eCBs associated with stress response including AEA and 2-AG.

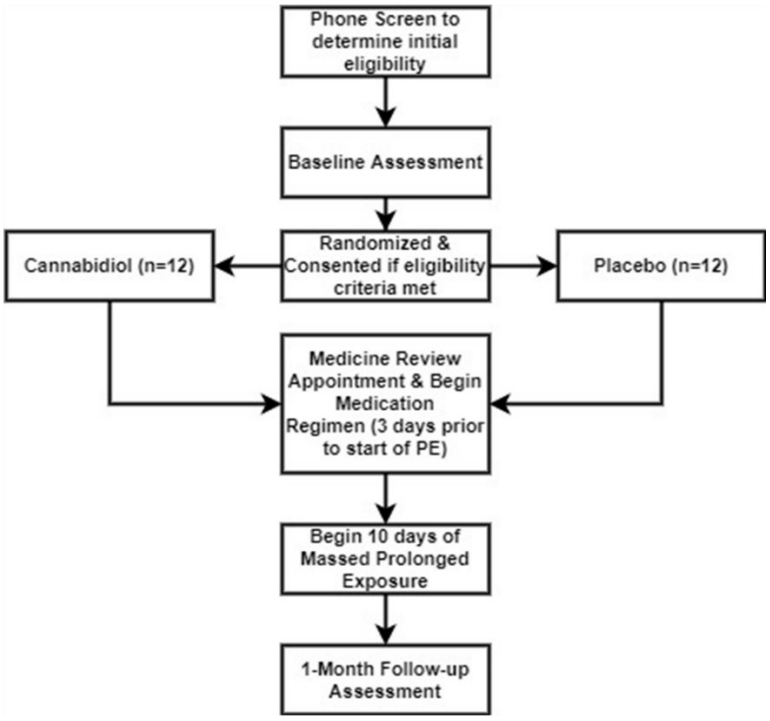
Innovation. Additional research is warranted to fully understand the benefits of CBD for PTSD. Currently, there are no published clinical trials investigating the efficacy of CBD in reducing PTSD and existing PTSD literature in humans only includes healthy individuals or case study data. Research on cannabinoids and PTSD remains in the early stages of development and more research is needed to understand how CBD modulates the eCB system. Based on existing research, the next logical step is to investigate CBD as an augmentation treatment for an established psychotherapy that targets extinction learning mechanisms for PTSD symptom reduction. This proposal will examine CBD as an adjunct for mPE and explore potential biological mechanisms for its effect, making it the first study of its kind. Findings from this study have the potential to improve outcomes among military and civilians with PTSD and mitigate the personal, social, and economic costs of this debilitating, chronic condition. This study will also expand understanding of the relationship between PTSD, CBD, and the eCB system.

6. RESEARCH DESIGN

This study is an early Phase II double-blind, pilot randomized controlled clinical trial. We will use a permuted block randomization design stratified by PTSD severity median score of 51 on the PCL-5 and population type (military or civilian). The median score stratification was derived from a recently completed STRONG STAR randomized clinical trial of military veterans seeking treatment for PTSD (manuscript in press). The decision to stratify by population was based on existing literature that has found differences in treatment response between military and civilian samples (e.g., Steenkamp et al., 2015; Straud et al., 2019). Participants will be 24 individuals with PTSD to investigate the safety, feasibility, and PTSD symptom change associated with CBD 250mg taken twice a day for 18days (n=12) vs. placebo (n=12) in combination with a standard of care, 10-sessions mPE psychotherapy administered over 2 weeks. Aims 2 and 3 will evaluate biochemical and physiological outcomes associated with eCB and PTSD that may be affected by CBD. Permuted block randomization is advantageous in small clinical trials to ensure equal allocation of participants in each condition. Participant randomization will be subdivided into randomized blocks of four, two patients in each block will be assigned to CBD and two will be assigned to placebo. Randomization will occur after the participant consents to the study and eligibility is determined. John Roache, PhD (Co-Mentor on this KL2) will determine randomization codes and coordinate with the compounding pharmacy (Oakdell Pharmacy) providing the medication and placebo for this trial to

ensure blocking procedures are appropriately carried out. All other study team members will be blinded to randomization. The study assessments and the timing for repeated assessments conducted are described in detail in section 7.3.

Figure 1. General Study Design Overview



***Notes.* See Section 7.3 for detailed study procedures.**

7. RESEARCH PLAN

7.1 Selection of Subjects

Number of subjects to be screened for eligibility: *40*
Target number randomized: *28*
Target enrollment number for completers: *24*

7.1.1. Subject Population.

Individuals between 18-65 years old recruited from the San Antonio community will be invited to participate in this research. Efforts will be tailored to equally recruit diverse individuals across sex, gender/sexual orientation, race, age, disability, socioeconomic status, national origin, and branch of military service.

7.1.2. Inclusion and Exclusion Criteria.

Inclusion Criteria

1. Individuals between the age of 18 to 65 years old at time of screening.
2. Able to write, read, and speak English
3. PTSD diagnosis as assessed by Clinician-Administered Posttraumatic Stress Scale (CAPS-5)
4. Stable medication regimen for at least four weeks prior to the onset of study participation.

Exclusion Criteria

1. History of opiate, cocaine, methamphetamine, benzodiazepine, or cannabis abuse as determined by the National Institute of Drug Abuse Quick Screen (NIDA-Q).
2. Currently using opiates, cocaine, methamphetamines, benzodiazepines, or cannabis as evidenced by a positive urine drug screen prior to enrollment.
3. Currently pregnant as determined by a positive urine pregnancy test prior to enrollment.
4. Current clinically significant alcohol abuse in the past two weeks on the Quick Drinking Screen (QDS).
5. Currently breastfeeding.

6. Ongoing illness or physical health problem(s) that may be exacerbated by CBD (e.g., history of liver problems)
7. History of significant allergic condition, significant drug-related hypersensitivity, or allergic reaction to cannabinoids.
8. Regular use of the following concomitant medications because of the possible interaction with CBD
   - The anti-convulsant/anti-epileptics Carbamazepine and Phenytoin
   - The atypical antipsychotics Olanzapine, Quetiapine, and Risperidone
   - The entire class of barbiturates (Sedative-Hypnotics)
   - Chronic, daily use of any class of benzodiazepines. Intermittent or as needed dose of a benzodiazepine will be allowed.
   - The miscellaneous hypnotics Zaleplon, Zolpidem, Eszopiclone, Ramelteon, and Suvorexant
   - The herbal supplement St. John's Wort.
   - The entire class of glucocorticoids
   - Use of platelet inhibitors Clopidogrel and Warfarin unless the participant is on a stable dose.
   - The antiretrovirals Ritonavir and Indinavir
   - The antifungals Itraconazole and Ketoconazole (topical not exclusionary)
   - The antibiotics Clarithromycin, Erythromycin, and Rifampin
   - Chronic, daily use of opioids.
   - Patients taking the antidepressants Trazodone and Mirtazapine can be enrolled with additional monitoring as outlined below under Section 8.0 Risk Benefit.
9. Alanine transaminase (ALT) or Aspartate transaminase (AST) enzyme levels 3x normal limits.
10. Concurrent engagement in trauma-related psychotherapy for PTSD.
11. Current or past DSM-5 diagnosis of psychotic disorder or bipolar disorder requiring immediate stabilization or hospialization (as determined by clinical judgement)
12. Suicide attempt in the last year and/or suicide risk requiring immediate intervention or requiring a higher level of care than can be provided by the study treatment (as determined by the SIT-BI).
13. Allergy to sesame seed oil

7.1.3. Description of the Recruitment and Prescreening Process.
Potential participants will be between 18-65 years old recruited from recruitment events, flyers and provider referrals from the community, Providers can give their patients contact information for the study staff so that interested individuals may contact STRONG STAR directly. Alternatively, providers can obtain consent to contact from their patients that allows the study staff to contact the potential participant directly. Individuals who are not eligible or interested in other IRB-approved STRONG STAR protocols will be told about this study. Study information will be posted on the STRONG STAR website and social media to gain self-referrals for treatment-seeking patients. Under an IRB approved HIPAA Waiver of Authorization, study personnel will initially conduct a brief telephone interview where the basic study inclusion/exclusion criteria will be reviewed to help determine if the individual likely meets study criteria. This will mitigate unnecessary travel and more in-depth screening. Participants who appear eligible after telephone pre-screening will be invited into the STRONG STAR clinic to provide written informed consent and undergo more rigorous assessment for study eligibility.

7.1.4. Consent Process.
During the consent appointment, potential participants will have the study explained to them in a private location in-person at the UT Health San Antonio (UTHSA) STRONG STAR offices located at 7550 IH10 West, Suite 1325, San Antonio, TX 78229. The potential participant will be given a copy of the informed consent document (ICD) to read. After the potential participant has read the ICD, and a member of the study team has reviewed the risks and benefits of the study to ensure the participant understands the research, the participant will be given the opportunity to discuss the research with family and friends. The research team will be available to answer any questions about the research. Once the potential participant has reached a decision, the participant will sign the consent form. A copy of the signed ICD will be given to the participant.

7.1.5. Subject Screening Procedures
Following consent, screening assessment will take place to determine participant eligibility. The entire screening process will take approximately 4 hours. This will include the completion of the questionnaires, interviews, and screening tests outlined in the Table of Assessments below (see section 7.3). The baseline assessment may occur in-person using paper forms, or the participant will be logged into the STRONG STAR eCAP online data capture system to complete self-report questionnaires. For individuals not meeting study inclusion criteria, the study staff will assist coordinating appropriate care outside of the study.

If the participant has been referred from another STRONG STAR study and already undergone baseline testing within the past 30 days, the participant will be asked as part of the consent process to use these assessments rather than repeating the assessment battery. If the participant is newly referred to this study, if it has been more than 30 days since baseline testing for another study, or the participant declines use of previously completed assessments, he or she will meet with an evaluator and complete the full baseline assessment per protocol.

7.1.6. Source of Research Material.

All measures will be administered for research purposes. For a complete list of measures see Section 7.3.

Source of Research Material	Conducted for Clinical Purposes(Y/N)	Conducted for Research Purposes (Y/N)
Clinician Rating Scales	No	Yes
Self-Report Questionnaires	No	Yes
Biological Samples	No	Yes
Heart Rate Monitoring	No	Yes

7.1.7. Compensation for participation

Participants will be paid for each blood draw as follows for a total of up to $100:

- $10 pre-treatment medication appointment
- $20 Interim Assessment 1
- $30 Interim Assessment 2
- $40 Interim Assessment 3

Payment will be provided via a rechargeable MasterCard® ClinCard. The MasterCard® ClinCard is a debit card issued to the study participant. Funds are loaded onto card through the ClinCard website at www.clincard.com. Only authorized users will be able to access the ClinCard website to add funds with a username and password. The ClinCard funds will be available to recipients within 1 business day and can be used as the participant chooses. The participant will be notified that their name, address, and date of birth will be shared with a third-party (ClinCard) solely for the purposes of payment processing. This information will only be used for the administration of the payment and will be kept strictly confidential.

7.2 Study Drug Overview

7.2.1 Epidiolex will be the active intervention used in this study. Epidiolex is an FDA approved non-controlled prescription medication indicated for the treatment of seizure disorders. Prior research has demonstrated the safety and early positive benefits of off-label use of Epidiolex for Anxiety and Trauma-Related symptoms in humans.

- Complete names and composition of drugs:
  - Epidiolex is a clear, colorless yellow oral solution containing cannabidiol at a concentration of 100 mg/mL. Cannabidiol is the active ingredient in Epidiolex and naturally occurs in the *Cannabis sativa* L. plant. Cannabidiol is a natural cannabinoid designated chemically as 2-[(1R,6R)-3-Methyl-6-(1-methylethenyl)-2cyclohexen-1-yl]-5-pentyl-1,3-benzenediol (IUPAC/CAS). Its empirical formula is $C_{21}H_{30}O_2$ and its molecular weight is 314.46. Inactive ingredients of Epidiolex include dehydrated alcohol, sesame seed oil, strawberry flavor, and sucralose.
  - The Placebo liquid solution will be compounded by Oakdell Pharmacy using the inactive ingredients of Epidiolex to match the composition and blind participants and team members to the medication.
- Source of the product(s): Oakdell Pharmacy (7220 Louis Pasteur Dr. San Antonio, TX 78229) will obtain Epidiolex from Manufacturer and prepare oral solution bottles of Epidiolex and matching placebo under the prescription authority of physician collaborator, Van King, MD.
- Location where study product(s) will be stored: The medication will be received from Oakdell Pharmacy by a trained study team member and transported to the STRONG STAR clinic where it will be stored in a locked cabinet until the participant arrives to receive the medication at the medication review appointment.
- Dose range, schedule, and administration route of study product(s): 2.5 mL (250mg) taken twice daily in the morning and evening after meals for (500mg per day) for 18 consecutive days beginning three days prior to the

start of mPE. Epidiolex and placebo will be prepared by Oakdell Pharmacy in a strawberry-flavored liquid solution administered using an oral syringe.

- Plan for disposition of unused study product(s): Any unused study products will be disposed of in accordance with the STRONG STAR Drug Accountability and Storage SOP.
- FDA status: The FDA has approved the use of Epidiolex for seizure disorders. Prior research has demonstrated the safety and early positive benefits of off-label use of Epidiolex for Anxiety and Trauma-Related symptoms in humans. We are not seeking a new indication with this research project.

7.3. Research Interventions/Study Procedures.

Interventions.

Participants will be randomized to either Epidiolex (CBD) or placebo. All participants will receive 10 sessions of mPE administered weekdays over 2 weeks.

Epidiolex (CBD) is an FDA approved, non-controlled prescription medication indicated for the treatment of seizure disorders. Prior research has demonstrated the safety and early positive benefits of off-label use of CBD for Anxiety and Trauma-Related symptoms in humans. CBD comes in a 100-mL bottle containing 100 mg of CBD per ml of strawberry-flavored liquid solution that is taken using an oral syringe. Strawberry-flavored liquid solution is also available for Oakdell pharmacy to create a comparable placebo to maintain the blind. Starting recommended dose is 2.5 mL (250mg) taken twice daily (total = 5 mL/500mg) in the morning and evening after meals.[1] We will employ this dosing recommendation for this study for 18 consecutive days. Steady state has been shown to occur in 2 days.[41] To ensure maintenance on an adequate steady state dose for all randomized participants, we will begin medication 3 days prior to the start of mPE. CBD and matching placebo for this study will be obtained through Oakdell Pharmacy which will obtain a sufficient supply of CBD for 12 participants from their supplying manufacturer. They will then prepare CBD (n = 12) and matching placebo (n =12) dosage for 24 participants in blinded containers that will be numbered per the randomization design. The medication and placebo will be dispensed to a trained study team member and transported in a locked container to the STRONG STAR Clinic where it will be stored in a locked cabinet until the participant arrives to receive the medication at the medication review appointment 3 days prior to beginning mPE.

Massed Prolonged Exposure (mPE)**.** Prolonged Exposure (PE) is a first-line, empirically supported cognitive behavioral treatment for PTSD and serves as the foundation for mPE.[16] mPE, delivered daily Monday through Friday over two weeks, utilizes exposure-based interventions to target psychological mechanisms (i.e., experiential and behavioral avoidance; maladaptive cognitive changes) that are thought to maintain trauma-related symptoms. Ten 90-minute sessions of mPE, which has been found to be non-inferior to ten 90-minute spaced PE delivered once or twice a week over eight weeks, helps minimize military-specific treatment barriers, and decreases treatment dropout rates.[14] For this study, each participant will receive ten 90-minute mPE daily over two weeks. Up to 19 days following initiation of the medication regimen will be allowed to complete the ten sessions of mPE to accommodate scheduling constraints. Consistent with the standard spaced PE therapy manual, mPE includes four primary treatment components: (1) psychoeducation on common reactions to trauma; (2) relaxation training; (3) in vivo exposure; and (4) imaginal exposures. In vivo exposure involves approaching avoided situations, people, places, and/or objects that are realistically safe. With imaginal exposure, participants repeatedly and systematically revisit their trauma memory and related thoughts and feelings. Participants also will be asked to complete homework, including reviewing treatment materials, listening to recordings of their imaginal exposure, and completing in vivo exposures. Since mPE requires considerable time and effort, the study team will work with the participant to receive a release from work while participating in the treatment.

Study Procedures.

	Visit / Follow Up (F/U) Interval										
Study Procedure	**Base-line**	**Medi-cation Review* (Day 1)**	**PE 1**	**PE 2**	**PE 3-4**	**Interim Assess (PE 5)**	**PE 5-9**	**Interim Assess (PE 10)**	**PE 10**	**18 days following medication review**	**1 Month from completion of treatment Follow-up**
Study Days		**1**	**4**	**5**	**6-7**	**8**	**8, 11-14**	**15**	**15**	**18**	**45**
Informed Consent	R										
1. Demographics and Military Service Characteristics Form	S,R										
2. Life Events Checklist-5	S,R										
3. Deployment Risk and Resilience Inventory-2	S,R										
4. STRONG STAR Health Questionnaire	S,R										R

5.	Prior and Concomitant Medications Interview	S,R									
6.	Self-Injurious Thoughts and Behaviors Interview short form	S,R									R
7.	Depressive Symptom Index – Suicidality Subscale	S,R		R			R		R		R
8.	Clinician-Administered PTSD Scale for the DSM-5(CAPS-5)	S,R									R
9.	PTSD Checklist for the DSM-5 (PCL-5)	R		R			R		R		R
10.	Patient Health Questionnaire-9	S,R		R			R		R		R
11.	Generalized Anxiety Disorder-7	R		R			R		R		R
12.	Brief Inventory of Psychosocial Functioning	R									R
13.	Veterans RAND 12 Item Short Form Health Survey	R									R
14.	Quick Drinking Screen	S,R									R
15.	National Institute of Drug Abuse-Quick Screen	S,R									R
16.	Insomnia Severity Index	R									R
17.	Posttraumatic Cognitions Inventory	R		R			R		R		R
18.	Credibility and Expectancy Questionnaire for PE				R						
19.	Credibility and Expectancy Questionnaire for CBD				R						
20.	AEA, 2-AG (Blood Draw Collection)		R	R			R		R		
21.	Cortisol (Saliva Collection)		R	R			R		R		
22.	HR Monitoring During Exposure (PE 3, 5, 10)					R		R		R		
23.	Adverse Event Monitoring		R**	R	R**	R**	R	R**	R	R**	R**	R
24.	Urine Pregnancy/Drug Screen	S										
25.	Liver Function Tests Labs*(LFTs)	S										
26.	Massed Prolonged Exposure			R	R	R		R		R		
27.	CBD 500mg/daily or placebo daily+		R^{start}	R	R	R		R		R	R^{end}	

Table Notes. S=screening purposes; R= Research purposes; *Medication Review Appointment will occur three days prior to beginning Massed Prolonged Exposure. Start and End superscripts represent beginning and end of medication/placebo use. CBD=Cannabidiol; AEA=Anandamide; 2-AG=Arachidonoylglycerol; HR= Heart Rate; *All potential study candidates will be required to complete LFTs or provide a copy of recent LFT labs (completed within 90 days of baseline) and bring their lab results prior to randomization.
+CBD or placebo to be administered daily days 1-18.
** Daily Adverse Event monitoring to occur if participant taking one of the identified medications warranting additional monitoring. See Section

7.3.1 Collection and Storage of Human Biological Specimens.
Urine drug and pregnancy screen tests will be conducted at baseline for screening eligibility purposes.

Blood will be collected at four time points for a study total of about 28mLs. Approximately, 7mL of blood will be collected by venous puncture using a 7 mL EDTA blood collection tube immediately prior to the pretreatment medication review, and at interim assessments 1 (prior to PE session 1), 2 (prior to PE session 5), and 3 (prior to PE session 10). Blood will be immediately chilled in a cooler filled with ice.

Saliva will also be collected at four time points via passive drool. At the medication review appointment participants will be given a kit with salivette test tubes and instructions on how to collect early waking saliva samples (cortisol) upon waking. Saliva collections will be completed upon waking the day after the medication review appointment, and the day of sessions 1, 6, and 10. Participants will be instructed to immediately refrigerate the sample and bring it to the next scheduled appointment. Saliva samples will be collected from the participant by study staff when the participant arrives for their appointment and immediately chilled in a cooler filled with ice. Samples will be frozen at or below -20^{o}C upon arrival at the Biological Psychiatry Analytic Laboratory (BPAL).

Biological specimens will be coded when collected from the participant by the study staff with a digital bar code that can be linked to the study and subject only by key-codes maintained by the STRONG STAR Data and Statistics Services.

Heart rate will be monitored using a wearable device placed on the right wrist, and elevations will be recorded continuously during sessions 3, 6, and 10 to obtain an objective measure of arousal to assess possible within- and between- session extinction learning in response to rehearsal of the individual's primary traumatic event. This data can be beneficial for individuals who report subjectively being more aroused during the exposure or behaviorally appear to be more activated.

All biospecimen samples will be transported to the BPAL in the UTHSA Department of Psychiatry and Behavioral Sciences at the UT Health-Long School of Medicine in room 727F for processing and storage. This location is monitored 24-7 by a wireless monitoring system on the Isensix system.

7.3.1.1 Laboratory evaluations and special precautions:
All biospecimen collection procedures will be carried out by trained team members and appropriately transported, stored, and disposed of in accordance with STRONG STAR Biomarkers and Genomics Services SOP, International Air Transport Association (IATA), and UTHSA IRB guidelines. All samples will be labeled with coded subject numbers and dates to protect the identities of participants.

At the times designated in Section 7.3 Table, 7mL of venous blood will be drawn into one purple top tube for measurement of AEA, 2-AG, and CBD levels. Immediately upon collection, blood will be labeled, mixed, and chilled on ice. This blood will be transported to the BPAL as soon as possible, where it will be processed to separate out the plasma. Plasma will be aliquotted into two cryovials, labeled, and placed in the STRONG STAR-CAP biorepository for long-term storage at -80^0 C. Samples will be later analyzed in batches using HPLC/Tandem Mass Spectrometry.

On the days designated in Section 7.3 Table, saliva samples will be collected by participants immediately upon awakening in the morning. Samples are collected by passive drool saliva collection into saliva sample tubes labeled only by coded subject number and Day number. Participants will be instructed to refrigerate the sample upon collection and to bring the salivette to their next scheduled appointment. Saliva samples will be collected from the participant by study staff when the participant arrives for their appointment and immediately chilled in a cooler filled with ice and then brought to the BPAL for storage at -20^0 C as soon as possible. Subjects will bring these samples to their visit appointment and staff will receive them and transport them to the BPAL for long-term storage until later analysis for cortisol levels.

7.3.2 Data Collection.
See Table in Section 7.3 for a summary of the assessments and timing of administration. The data collected in the study will be coded using an assigned number. Hard copies of data collected during the study will be securely stored in locked cabinets at the STRONG STAR offices. Data will be entered into the STRONG STAR database by a member of the research team.

7.3.2.1. Instrumentation.
See the table in Section 7.3 for a summary of the assessments and timing of administration. A description of each of the assessments can be found at the end of this protocol. Assessments will be administered in person whenever possible. However, to accommodate participant schedules and/or instances in which a participant does not reside in the local area at the time of a follow-up assessment, we may collect full or partial assessments in person or via phone, video conferencing, and/or electronic data capture using a secure link to the encrypted STRONG STAR database. Reasonable efforts will be made to collect all data as described in this protocol, but we expect some participants may not be able to complete part or all of any given follow up assessment.

7.3.2.2 Data Storage, Access, and Protection.
Study files containing hard copies of data collected during study participation will be kept securely at the STRONG STAR offices in San Antonio. Files will be placed into locked cabinets and stored securely in a locked room by a STRONG STAR staff member.

Data will be coded using an assigned number. Local study sites will maintain a list of assignment numbers for the purpose of linking subsequent research materials.

Data will be entered into the STRONG STAR password protected database housed on a secure UTHSA server by member of the research team. Electronic data will be stored, managed, and analyzed by the STRONG STAR Data and Statistics Services staff of the STRONG STAR consortium. The overall PI and named collaborators will have access to identifiable data through the STRONG STAR website and UTHSA server via direct request to STRONG STAR Data and Statistics Services.

All UTHSA STRONG STAR network connectivity is segmented with Access Control Lists and is not accessible to any other UTHSA network segments. The STRONG STAR data server is physically located at the Advanced Data Center (ADC), which has 24x7 onsite security, card key, biometric access controls and video surveillance. UTHSA ADC facility also maintains Gen 2 firewall devices to protect and prohibit any unauthorized access to UTHSA data. All UTHSA network devices are monitored by state-of-the-art monitoring applications that include configuration audit, management, and availability 24x7.

The UTHSA STRONG STAR data server is currently a VMware Instance running Windows Server 2016 Enterprise Standard with daily backup services and vSphere Business Continuity Advanced Failover.

Only select STRONG STAR Data and Statistics Services personnel have direct access to the data on a "need to access basis"; for example (but not limited to) detecting and repairing data corruption and producing reports not currently within the STRONG STAR system. STRONG STAR Data and Statistics Services also follows the Principals Of Least Privilege (POLP). All user activity is tracked and recorded within the system so if any records are added, altered, or viewed the action is recorded and can be recalled for auditing purposes. Access to this information will require a password-protected login available only to authorized STRONG STAR Data and Statistics Services staff.

Every member of the Research Team will be trained and monitored about how to handle and protect both medical and research records. Furthermore, the Research Team strictly controls access to study data.

The STRONG STAR Data Safety and Monitoring Plan (DSMP) that has been developed in accordance with the National Institutes of Health Office of Human Research Protection to assure the appropriate clinical safety monitoring of study subjects participating in research will be used to monitor this study.

7.4. Statistical Consideration

7.4.1. Sample Size Estimation.

Estimate Required Sample Size (Completed / Evaluable)	24
Estimate Participant Drop Out / Withdrawal after Randomization/Inclusion	4 (17%)
Total Required to Randomize / Include	28
Estimate Participant Screen Fail / Exclusion	12 (30%)
Total Required to Consent	40

7.4.2. Primary (i.e., primary outcome variables) and secondary endpoints

Health Questionnaire and Self-Report Measures: The primary aim of this pilot is to explore the potential feasibility, safety, and effect of CBD in reducing PTSD symptoms compared to placebo in retired service members receiving mPE. Therefore, the primary outcome variables will be the CAPS-5 total score, the PCL-5 total score, and adverse event monitoring. Secondary endpoints are listed in the table in Section 7.3 and include associated psychopathology, such as severity scores on measures of depression, general anxiety, disability, and PTSD-related cognitions.

Biospecimens & Heart Rate Monitoring Measures: We will also assess possible biochemical and physiological outcomes associated with treatment (Aim 2) and evaluate the relationship between changes in biochemical/physiological measures with PTSD symptom reductions (Aim 3). To address these aims we will collect blood and saliva samples and heart monitoring data via a wearable device as described in 7.3.1

7.4.3. Data analysis.

This pilot study was not powered for formal efficacy or mechanistic hypotheses testing.[42] Our primary interests are to evaluate the safety and feasibility of the proposed recruitment, assessment, and treatment protocols; and to detect a signal of possible PTSD symptom reductions associated with CBD in preparation for a larger trial. To inform future studies, we will calculate conventional effect sizes with 95% confidence interval limits. Hedges' g will be used to calculate continuous outcome effect sizes (e.g., CAPS-5, PCL-5). Hedges' g has been recommended over Cohen's d for small samples based on sample size adjustments yet can be interpreted using the same conventional recommendations as Cohen's d.[43]

Although the statistical power of this study is limited, we will perform statistical analyses appropriate for an adequately powered study to identify data analysis issues germane to future planning (e.g., data management and scoring, missing data, data distributions, outliers, trends over time, covariance structures). Statistical analyses will be intent to treat. We will complete descriptive statistics to describe the study sample and address the feasibility and safety hypotheses. Continuous outcome measures related to symptom changes and comparison of baseline and posttreatment means will be done with general or generalized linear mixed effects regression models with repeated measures, with fixed effects of time, group, and the group by time interaction. Measures with data collected during treatment will also be included in models. Little's[44] missing completely at random analysis will be completed to confirm likelihood-based model assumptions. Pearson correlation analyses will be used to examine associations between change in PTSD symptoms, biochemical markers, and

physiology. To address attrition and missing data, participants will have frequent follow-up to maintain contact with the study team. Participants who discontinue treatment will be asked their reasons at the point of drop-out.

7.5. Confidentiality.

PE sessions, interview assessments, and blood draws will be delivered in private offices at the STRONG STAR Clinic at the UTHSA. When travel to the STRONG STAR clinic is not feasible, Interview Assessments and PE sessions via video teleconferencing will be made available to mitigate missed appointments. Data will be stored by an assigned participant code number so that data records can be viewed by password-authenticated, authorized investigators and Consortium personnel. Every member of the research study team will be trained and monitored on how to handle and protect both medical and research records. Only authorized study staff, and members of the STRONG STAR Data and Statistics Services staff will have access to either the raw data or electronic study data.

7.6. Long Term Data Storage.

A *STRONG STAR Repository* has been approved by the UTHSA (HSC20100475H) IRB to enable the STRONG STAR Consortium to store specimens and data for future use. The *STRONG STAR Repository* is a large comprehensive database of information, biological specimens and neuroimages related to the identification, assessment, and treatment of posttraumatic stress disorder (PTSD), insomnia, pain, and related behavioral health conditions. All information entered into the *STRONG STAR Repository* will be extracted from primary datasets collected as part of IRB-approved studies, including this study, being conducted and /or supported in collaboration with the UTHSA STRONG STAR Consortium. Study databases are established and maintained by the STRONG STAR Data and Statistics Services. A unique, sequential alpha-numeric STRONG STAR ID will be assigned to each participant at the time of recruitment into this study. However, all Repository data will be identified with a different code number that can be cross linked to the original study code only through records maintained by the STRONG STAR Data and Statistics Services. At the conclusion of this study, participants who signed the consent to have their data placed in the *STRONG STAR Repository* will be maintained under the UTHSA IRB-approved Repository protocol. For participants who decline participation in the *STRONG STAR Repository*, their data will be de-identified, and the data maintained in the Repository without identifiers at the conclusion of the study.

8.0. RISKS/BENEFITS ASSESSMENT

8.1. Risks.

Likely, but Not Serious Risks:

Epidiolex (CBD): CBD is well tolerated in human subjects and is considered a safe drug, with minimal adverse events (AEs) and low abuse potential.[1,41,45–47] However, like almost all medications, toxicity and AEs are possible with CBD. The most common side effects of CBD can include fatigue, drowsiness, feeling weak, malaise, loss of appetite, diarrhea, skin rash, insomnia, and viral/fungal infections.

PTSD & Prolonged Exposure (PE): Potential risks associated with PTSD assessment and PE therapy can include temporary increase in distress, becoming emotionally upset or experiencing an initial increase of PTSD symptoms due to the consideration of traumatic events. Studies with PE suggest that a small minority experience an increase in symptoms of PTSD after the initiation of imaginal exposure and for this minority, the distress and increased symptoms are temporary, are not predictive of poor outcome, and are not associated with increased likelihood of dropout.[46]

Biospecimen Collection: Potential risks associated with blood draw may include pain, bruising, infection, lightheadedness, fainting, blood clots, and bleeding or other discomforts at the blood draw site.

Rare, but Serious Risks:

CBD: Serious side effects of CBD are very rare but can occur. Serious side effects include liver problems, sedation (e.g., sleepiness, loss of coordination, and difficulty with concentration), severe allergic reaction (skin rash, itchiness, flushed skin, angioedema, difficulty breathing), and in very rare circumstances (< 1%) suicidal thoughts or behavior.[1]

Biospecimen Collection: More rare risks of blood draw may include swelling and/or infection at the needle site, and thrombosis of the vein due to trauma. Proper training of study team members on biospecimen collection safety procedures can reduce the risk of contamination, clerical error, infection, injury, misuse of appropriate blood-sampling devices, and risk when transporting laboratory samples.

Risks to Confidentiality
With the handling of medical and research records there is always the possibility of a breach of confidentiality. We will maintain patients' names, contact information (i.e. Identifiers), and all PHI (protected health information) in an encrypted computer database and all PHI identifiers will be removed in the database during data analysis. Every member of the Research Team is carefully trained and monitored about how to store, handle, and protect participant records.

Risks of PTSD Diagnosis regardless of Treatment:
Possibility of increased suicidal risk. One of the risks of PTSD both in and out of treatment is attempted suicide, which can result in death.

Safeguards for Protecting Participants:
CBD: Participants will be required to complete a liver function test (LFT) or provide a copy of recent LFT lab results (completed within the last 90 days) to the study team prior to randomization to be considered for study eligibility. To mitigate unnecessary LFTs, candidates will complete the full assessment to determine eligibility. If the candidate is deemed eligible, the final step of the assessment process will be to complete an LFT or provide a copy of a recent (LFT). The study team will work with the candidate to obtain LFTs and pay for them if necessary. All LFT labs will be reviewed by Dr. King to determine study eligibility. Participants with enzyme levels 3x the normal limit will be excluded from the study.

CBD, like most drugs, can lead to AEs and has drug-drug interactions. To safeguard against potential risk, we have developed exclusionary criteria related to the individual's medical history and concomitant medication regimen. Participants prescribed medications listed in the exclusion criteria will be excluded . Exceptions will be made for participants taking the antidepressants Trazodone and Mirtazapine, a benzodiazepine just as needed, and/or stable doses of the platelet inhibitors Clopidogrel or Warfarin. These participants will be monitored for AEs on a more frequent basis (daily at each session). Additionally, consultation between the study team and Dr. King may occur on a more regular basis regarding potential medication/health risk and additional risk management procedures. Individuals on medications with known drug-drug interactions may also complete an additional LFT during study participation.

All participants will complete the STRONG STAR Health Questionnaire and the Prior and Concomitant Medications Interview at the baseline assessment. These measures assess medical and psychiatric diagnoses, current prescription and over the counter medication use, and caffeine use. Prior to enrollment in the study, Van King, MD (physician collaborator) and Casey Straud, PsyD (principal investigator) will review participants' Health Questionnaire and Medication Interview to determine potential for risk and confirm eligibility based on self-reported health history, current prescribed medications, and current substance use.

For participants identified as having low to moderate risk of AE or drug-drug interaction, the patient will be maintained on protocol and additional risk management procedures will be implemented within the context of the study treatment. All enrolled participants will be monitored for AEs by the study therapist on Day 1 (beginning of mPE), Day 5-Interim Assessment, Day 10-Interim Assessment, and at the 1-month follow-up. For participants identified as being at high risk for a health/medication-related AE or drug-drug interaction, ineligibility will be considered if it is unlikely that standard treatment plus additional risk management procedures (i. e., adverse event monitoring at every visit) will maintain safety. Dr. King, Casey Straud, PsyD (PI), and study team members will meet each week to review reported AEs. AE meetings will involve consultation with Dr. King on potential medication/health risk and additional risk management procedures as described above. For urgent issues, whether potentially related to CBD or mPE, participants will be instructed to get help immediately by going to the nearest emergency room.

All participants will also be given a medication emergency department wallet card at the beginning of the study. Participants will be instructed to keep this card on their person throughout the study. The wallet card briefly describes the study intervention (Epidiolex vs. Placebo) and drug dose (250mg b.i.d), and provides a study team contact number.

PTSD & PE: Psychological distress experienced by participants is expected to be temporary and participants will be provided immediate coping tools and techniques to manage distressing emotions by the study therapist. Any indication that the participant is considering suicide, endorses active psychosis/mania, or other harm to self/others will be handled using evidence-based procedures and policies developed by the STRONG STAR Consortium. Participants who endorse mania/psychotic symptoms will prompt a clinical interview with a licensed clinical provider to assess current risk and risk of active mania/psychosis during study participation. Individuals with active mania/psychosis will be excluded from study participation. Trained clinicians and evaluators will assess history of suicide and current suicidal ideation using the

Suicidal Ideation Thoughts and Behaviors Interview at the baseline assessment. For participants identified as having low to moderate risk for suicide based on the assessment results, the patient will be maintained on protocol and additional risk management procedures will be implemented within the context of the study treatment. For participants identified as being at high risk for suicide based on the assessment results, disenrollment will be considered if it is unlikely that standard treatment plus additional risk management procedures will maintain safety. High risk participants who are disenrolled from the study will be referred for more intensive treatment (outpatient or inpatient).

If the research team feels that hospitalization should be considered, the participant's primary care provider or unit will be contacted to escort the individual to the ED. If a participant reports experiencing psychotic or mania symptoms, or reports dangerous amounts of alcohol and/or substance use, additional assessment by a licensed provider for consideration of referral for clinical care and for disenrolling participants from the study will be conducted.

Enrolled participants will be monitored for AEs by the study therapist at Interim Assessment 1 (PE Session 1), Interim Assessment 2 (PE Session 5), Interim Assessment 3 (PE Session 10), and at the 1-month follow-up. Dr. Straud and study team members will meet each week to review reported AEs and to consult on potential behavior health risks. For urgent issues, whether potentially related to psychotherapy or CBD, participants will be instructed to get help immediately by going to the nearest emergency room.

Biospecimen Collection: To reduce the risk of AEs for study participants, all staff members collecting biospecimens will be trained in procedures to reduce the risk of contamination, clerical error, infection, injury, use of appropriate blood-sampling devices, and safe transportation of laboratory samples via IATA guidelines. When collecting or handling biospecimens, staff members will wear well-fitting, non-sterile gloves, and carry out hand hygiene before and after each patient procedure, before putting on gloves and after removing them. To reduce the risk of environmental contamination with pathogens, the blood draw room will be appropriately sanitized before and after each blood draw and saliva collection. To prevent infections and other AEs, health workers should follow the guidelines on patient identification, hand hygiene, use of gloves, skin disinfection, use of appropriate blood-sampling devices and safe transportation of laboratory samples.

8.2 Potential Benefits.

Potential benefits of participation in this study may include a reduction in, or amelioration of, PTSD symptoms over the course of therapy. Collectively, the possible risks (i.e., temporary increase in distress and severity) associated with participation are low and reasonable within this context given the level of participant monitoring and access to research and clinical staff. We believe that the possible benefits from participating in this study significantly outweigh the possible risks. The knowledge gained from this study will serve to inform the most effective early interventions for the prevention and treatment of PTSD.

8.3 Alternatives.

Other choices to participating in this study include: not participating in this study; receiving psychotherapy or medications in the community; or participation in other research studies involving experimental treatments.

9.0 ADVERSE EVENTS, UNANTICIPATED PROBLEMS, AND DEVIATIONS

9.1. Adverse Events will be assessed and monitored according to the established STRONG STAR SOP and the IRB of record's policies and procedures.

9.2. Reporting Unanticipated Problems Involving Risks to Subjects or Others, Serious Adverse Events and Deaths to the IRB Office. All adverse events, unanticipated problems involving risk to subjects or others, and deviations will be reported to the Institutional Review Board (IRB) in accordance with current IRB policy. UPIRSOs and recurrent non-compliance with study procedures will be reported promptly to the IRB. All adverse events that do not meet the UPIRSO criteria and deviations that are not non-compliance will be summarized at Continuing Review per the IRB of record's policy.

10.0. WITHDRAWAL FROM STUDY PARTICIPATION.

Participation in the study may be discontinued by the principal investigator if continued participation is considered a danger to a participant's welfare. Reasons for discontinuation include: 1) a serious AE such that continued participation would be a danger to the participant; 2) clinical worsening for any reason that is deemed to necessitate non-study psychological or medical treatment; 3) exacerbation of PTSD, anxiety, or depressive symptoms that the participant cannot tolerate; or 4) drug interactions from concomitant medications that the participant cannot tolerate or would be a danger to the participant; or 5) discontinuation would be in the participant's best interest. Participants deemed candidates for discontinuation will be discussed in conference calls with relevant study team members and will be brought to the attention of the PI and mentor committee for final decision. Participants who are discontinued from the study for any

reason will be scheduled for a final evaluation within one week and given appropriate treatment referrals. If participants are discontinued due to a serious AE, they will continue to be followed clinically by the therapist and/or member of the research staff until the AE is resolved or becomes stable. The reason the participants are discontinued from the study will be documented for future study planning.

11.0. TIME REQUIRED TO COMPLETE THE RESEARCH (including data analysis).

The following table provides an overview of activities that the research team plans to accomplish. We anticipate recruiting and treating two eligible service members per month to meet study goals. We anticipate that the study will be completed by July 1, 2023.

	Year 1				Year 2			
Study Activities (Months)	0-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24
IRB Approvals, Prepare Materials, Train Staff	X							
Recruit, Screen, and Treat 24 Participants		X	X	X	X			
Follow-up Assessments			X	X	X	X		
Data Cleaning					X	X		
Data Analysis						X	X	X

12.0. STUDY CLOSURE PROCEDURES.

At the conclusion of the study all data will be stripped of identifiers. De-identified (anonymized) data will be maintained indefinitely in the STRONG STAR Repository. Informed consent documents will be stored securely for a minimum of three years following completion of the research in accordance with 45 CFR 46. HIPAA authorizations will be stored for a minimum of six years in accordance with HIPAA regulations. A Final Report will be submitted to the IRB to request inactivation of the study.

13. FUNDING.

This project is funded through the Institute for Integration of Medicine and Science Clinical and Translational Research Scholars Mentored Research Career Development Program at UTHSA (KL2 TR002646; PI: Casey Straud, PsyD).

14.0 DESCRIPTION OF ASSESSMENTS.

The majority of the measures listed below is commonly used, have adequate to good psychometrics, and are part of the Consortium common data elements (CDE). As outlined in the National Research Action Plan, evidence-based CDEs and measures for STRONG STAR studies will ensure comparability of results across the consortium as well as other clinical trials and epidemiological studies of PTSD.

1. Demographics and Military Service Characteristics Form: The Demographics Form measures standard demographics (race, gender, age) and military service information (e.g., rank). This measure will be administered at the baseline assessment.

2. Life Events Checklist-5 (LEC-5).[48] The LEC includes a list of 24 potentially traumatic life events commonly associated with PTSD symptoms. The instrument was designed to facilitate the diagnosis of PTSD. In this study, the LEC-5 will also be used to identify the index event and focus of the PTSD treatment. For each potentially traumatic life event, respondents rate their experience of that event on a 5-point nominal scale (1 = happened to me, 2 = witnessed it, 3 = learned about it, 4 =part of my job, 5= not sure, and 6 = does not apply). Each nominal point will be scored separately, as either 0 (=not endorsed by participant) or 1 (=endorsed by participant). This measure will be administered at the baseline assessment.

3. Deployment Risk and Resilience Inventory-2 (DRRI-2) Combat Experience and Post-battle -Scales.[49,50] High- and low-intensity deployment stress exposure will be assessed using scales from the DRRI-2. The DRRI-2 is an update of the original DRRI, which was developed and tested in three separate national samples of veterans of the first Gulf War. It has been revised and tested with OEF/OIF/OND returnees. The DRRI-2 provides an update of the DRRI's assessment of deployment-related factors to ensure the instrument's applicability across a variety of deployment circumstances (e.g., different eras of service) and military subgroups (e.g., men and women), as well as to validate updated measures in a contemporary Veteran cohort. High intensity stressor exposures will be assessed using the DRRI Combat Experiences and Aftermath of Battle subscales. Responses to these scales are on a 6-point Likert scale. The total score is the sum of the item scores, where higher scores signify greater exposure to combat or exposure to the consequences of combat, respectively. Both subscales have very good internal consistency (α = .90 to .92) and construct validity. This measure will be administered at the baseline assessment and only among participants who identify as a military veteran.

4. Health Questionnaire. The Health Questionnaire includes items regarding physical and mental health history, diagnoses, utilization of services, and military medical board evaluation/VA disability. Participants are also asked about current medications being used and provide information on how long they have been taking the medication. The Health Questionnaire also asks about caffeine use and frequency of use in the past month. Overall, this measure provides a brief, yet comprehensive overview of the patient's medical and psychiatric history as well as relevant information regarding caffeine use and medications. This measure will be administered at the baseline assessment and 1-month follow-up.

5. Prior and Concomitant Medications Interview. The Prior and Concomitant Medication Interview is a brief, semi-structured interview to assess medication use, dose, frequency, route of administration, and course of medication use in the past 30 days prior to the assessment. The interview also assesses if medication use is ongoing and the indication for the medication use. This measure will be administered at the baseline assessment.

6. Self-Injurious Thoughts and Behaviors Interview (SITBI).[51] The SITBI is a structured interview assessing the presence, frequency, and characteristics of self-injurious and suicidal thoughts and behaviors. The SITBI will be administered by an Independent Evaluator, who will instruct the participants to answer the questions based on their entire lifetime of experience. The SITBI has shown high interrater reliability, test-retest reliability, and concurrent validity. This measure will be administered at the baseline assessment and the one-month follow-up assessment.

7. Depressive Symptoms Index-Suicidality Subscale (DSI-SS).[52] The DSI-SS will be used to assess current suicidal ideation. The DSI-SS is a 4-item self-report measure of suicidal ideation that focuses on ideation, plans, perceived control over ideation, and impulses for suicide. It is being used as a core measure in the Military Suicide Research Consortium. Scores on each item range from 0 to 3, with higher scores reflecting greater severity of suicidal ideation. Instructions will instruct the participants to respond based on the past two weeks. A systematic review of measures of suicidal ideation and behaviors found that the DSI-SS had evidence of excellent internal consistency and concurrent validity. This measure will be administered at the baseline assessment, interim assessments, and the one-month follow-up assessment.

8. The Clinician Administered PTSD Scale for DSM-5 (CAPS-5).[3] The CAPS-5 is structured interview that assesses the DSM-5 criteria for PTSD. Each item is rated on a severity scale ranging from 0 (Absent) to 4 (Extreme/incapacitating) and combines information about frequency and intensity for each of the 20 symptoms. Additional items that are not included in the total score evaluate overall symptom duration, distress, impairment, dissociative symptoms, and global ratings by the interviewer. Validation studies are nearly complete to establish the psychometric properties of the CAPS-5 and findings will be reported in peer-reviewed publications. This interview is very similar to its predecessor, the CAPS for DSM-IV, which has been considered the gold standard for evaluating PTSD and demonstrated good reliability and validity. In addition to reflecting diagnostic changes for PTSD in DSM-5, the CAPS-5 differs from the CAPS in that frequency and intensity ratings for each symptom are no longer scored separately, so the severity rating for each item determines whether a symptom is present or not. Subscale scores are calculated by summing severity scores for items in the following PTSD symptom clusters: re-experiencing, avoidance, negative alterations in cognitions and mood, and hyperarousal. Scores ≥ 25 indicate a probable diagnosis of PTSD. This measure will be administered at the baseline assessment and the one-month follow-up assessment.

9. PTSD CheckList-5 (PCL-5).[4] The PCL-5 is a 20-item self-report measure update of the PCL designed to assess PSTSD symptoms as defined by the DSM-5. The PCL-5 is currently available and has been shown to have good psychometric properties. The PCL-5 evaluates how much participants have been bothered by PTSD symptoms in the past week (for all assessments during treatment) or the past two weeks (all other assessment time points) as a result of a specific life event. Each item of the PCL-5 is scored on a five-point scale ranging from 0 "not at all") to 4 ("extremely). This measure will be administered at the baseline assessment, the interim assessments, and the one-month follow-up assessment.

10. Patient Health Questionnaire-9 (PHQ-9).[53] The PHQ-9 is a widely used and well-validated instrument for measuring the severity of depressive symptoms. It consists of 9 items that assess both affective and somatic symptoms related to depression and depressive disorders; these 9 items correspond to the diagnostic criteria for DSM MDD. Respondents rate the frequency with which they have been bothered by depressive symptoms within the past two weeks on a scale ranging from 0 ("not at all") to 3 ("nearly every day"). Scores on all items are summed to obtain a total severity score. Scores reflect no significant depressive symptoms (0-4), mild depressive symptoms (5-9), moderate depressive symptoms (10-14), moderately severe depressive symptoms (15-19), and severe depressive symptoms (>19). Respondents also indicate the degree to which their depressive symptoms have made it difficult for them to do their work, take care of things at home, or get along with other people, from "not difficult at all" to "extremely difficult." The PHQ-9 has high internal

consistency (e.g., alpha ranging from .83 to .92) and correlates strongly with other measures of depression. This measure will be administered at the baseline assessment, the interim assessments, and the one-month follow-up assessment.

11. Generalized Anxiety Disorder Screener (GAD-7).[54] The GAD-7 will be used to assess generalized anxiety symptomology. This is a 7-item measure that asks participants to rate the frequency with which they have been bothered by anxiety symptoms within the past two weeks on a scale ranging from 0 ("not at all") to 3 ("nearly every day"). Scores on all items are summed to obtain a total severity score. Scores reflect no significant anxiety symptoms (0-4), mild anxiety symptoms (5-9), moderate anxiety symptoms (10-14), and severe anxiety symptoms (>15). Respondents also indicate the degree to which their anxious symptoms have made it difficult for them to do their work, take care of things at home, or get along with other people, from "not difficult at all" to "extremely difficult." The GAD-7 has been shown to have high internal consistency (e.g., α = .89) and has been shown to reliably discriminate between anxious and non-anxious diagnostic groups. This measure will be administered at the baseline assessment, interim assessments, and the one-month follow-up assessment.

12. Brief Inventory of Psychosocial Functioning (BIPF).[55] The BIPF is a 7-item self-report instrument measuring respondents' level of functioning in seven life domains: romantic relationship, relationship with children, family relationships, friendships and socializing, work, training and education, and activities of daily living. Respondents indicate the degree to which they had trouble in the last 30 days in each area on a 7-point scale ranging from "0 = Not at all" to "6 = Very much." This measure will be administered at the baseline assessment, and the one-month follow-up assessment.

13. Veterans Rand 12-Item Health Survey (VR-12).[56] Because a certain level of PTSD symptoms is an occupational hazard among service members redeployed for combat, it is critical to pay close attention to functional capacities as an important index of intervention efficacy. The Veterans SF-36 (VR-36) was adapted from the RAND SF-36 Version 1.0 questionnaire, and spans the range of health domains from physical to psychological health status. It includes two modifications. The first modification is an increase in the number of response choices for the role physical (RP) and role emotional (RE) items from a two point yes/no choice to a five-point likert scale (no, none of the time, yes, a little of the time, yes, some of the time, yes, most of the time, yes, all of the time). The second modification is the use of two items to assess health change, one focusing on physical health and one on emotional problems, in contrast to the one general change item in the RAND SF-36.[56] The VR-36 has been widely used, distributed and documented in the Veterans Health Administration (VHA) with close to 2 million questionnaires administered nationally in six national surveys since 1996. The changes to the survey have increased the overall precision of the instrument and the discriminant validity of the physical and mental component summary scales.[57] The VR-36 is comprised of 37 items and eight scales: physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, energy/ vitality, social functioning, role limitations due to emotional problems, and mental health. Also, there are two summary scales: a physical component summary (PCS) and mental component summary (MCS). Higher scores indicate better health. Each summary is expressed as a T score, which facilitates comparisons between the VA patients and the general U.S. population. The PCS and MCS scores provide at least 90% of the reliable variance in the eight SF-36 concepts. The Veterans SF-12 was developed from the Veterans SF-36 and adapted from the MOS SF-36. It includes fewer items for seven of the eight scales and provides 90% of the reliable variance in the two component summary measures using the Veterans SF-36. Using independent results from the Veterans Health Study and the 1996 National Survey of Ambulatory Care Patients, the results for the Veterans SF-12 corresponded very closely with the results for the Veterans SF-36 (average differences of 0.06 points between them for PCS and 0.31 points for MCS). This measure will be administered at the baseline assessment and the one-month follow-up assessment and only among participants who identify as a military veteran.

14. Quick Drinking Screen (QDS).[58] The QDS will be used to assess hazardous or harmful patterns of alcohol consumption in the past two weeks. The QDS is a four-item screener that assesses average number of drinking days, average number of drinks on drinking days, number of heavy drinking days, and greatest number of drinks in a day over the past two weeks. The average total drinks consumed per week can also be calculated by multiplying items 1 (average number of drinking days per week) and 2 (average drinks per day). This measure will be administered at the baseline assessment and the one-month follow-up assessment. At the baseline assessment, the PI (Casey Straud, PsyD) and physician collaborator (Van King, MD) will review QDS scores to determine if the screened individual demonstrates clinically significant alcohol abuse that warrants exclusion from the study. This measure will be administered at the baseline assessment and the one-month follow-up assessment.

15. National Institute of Drug Abuse Quick Screen (NIDA-Q).[59] The NIDA-Q will be used to identify individuals with a history of or current substance abuse. The NIDA-Q is a brief interview to assess history and current alcohol, tobacco, and other substances. Each substance involves seven questions to determine a substance involvement score with scores ranging from 0-27 per substance. Scores greater than or equal to 27 indicate high risk and scores between 4-26 suggest

moderate risk. Participants are first asked about the frequency of substance use in the past year. If the patient reports none, then screening in this section for the past year is complete. If the participant endorses use in the past year, additional follow-up questions are asked to determine the frequency and severity of use for each substance. Part two of the NIDA-Q assesses lifetime substance use. If the participant responds "no" then screening for part two is complete. If the participant endorses a history of substance use, additional questions are asked to assess frequency and severity in the past three months. For the purposes of this study, participants who endorse current use (or a history of abuse) of the five listed substances described in the exclusion criteria section will be excluded from the study. This measure will be administered at the baseline assessment and 1-month follow-up.

16. Insomnia Severity Index (ISI).[60] The ISI is a 7-item self-report measure that assesses perceived severity of insomnia. Each item uses a 4-point Likert type scale from 0 (not at all satisfied) to 4 (very much satisfied). The items sum to produce a total score (range 0 – 28). The ISI has an internal consistency alpha coefficient of 0.74, and has shown convergent validity with other measures such as the Pittsburgh Sleep Quality Index (r = 0.67), the Dysfunctional Beliefs and Attitudes about Sleep (r = 0.55), and sleep diaries (r ranges from 0.32-0.91). This measure will be administered at the baseline assessment and the one-month follow-up assessment.

17. Posttraumatic Cognitions Inventory (PTCI).[61] The PTCI is a 36-item questionnaire that was developed to determine how an individual views the trauma and its sequelae in an attempt to understand both how PTSD develops and is maintained. Using an emotional processing theory, Foa and her colleagues have suggested that PTSD is a consequence of disruptions in the normal processes of recovery when an individual has excessively rigid concepts about self and world rendering the person vulnerable if a traumatic event occurs. Thus, the PTCI was developed as a measure of trauma-related thoughts and beliefs. It is comprised of three subscales (Negative Cognitions about the Self, Negative Cognitions about the World, and Self-Blame). The measure was tested in almost 600 adult volunteers recruited from two university PTSD treatment clinics as well as a university community. Approximately 65% (n=392) of individuals reported having experienced a trauma in which their own life or that of another person was perceived to be in danger and their response at the time included intense terror, horror, or helplessness (Criterion A event). The remaining 35% (n=162) denied such a traumatic experience. Of those who had experienced a trauma, 170 had PTSD symptoms of at least moderate severity while the remaining 185 reported a low symptom severity. The three subscales of the PTCI demonstrated internal consistency with alpha coefficients ranging from 0.86 to 0.97. Convergent validity was demonstrated comparing the PTCI to appropriate subscales of the World Assumptions Scale and Personal Beliefs and Reactions Scale. Significant correlations between the appropriate subscales ranged from 0.20 to 0.85. The PTCI was able to differentiate individuals with and without PTSD demonstrating discriminate validity (sensitivity = 0.78, specificity = 0.93). Test–retest reliability for each of the three subscales at a 1-week interval ranged from 0.75 to 0.89 and for a 3-week interval ranged from 0.80 to 0.86. This measure will be administered at the baseline assessment, the interim assessments, and the one-month follow-up assessment.

18. Credibility/ Expectancy Questionnaire (CEQ) for PE.[62] The CEQ is a 6-item measure that was designed to assess treatment expectancy and rationale credibility for use in clinical outcomes studies. This measure has been utilized across a number of STRONG STAR treatment trials and can be easily adapted to assess the target intervention(s). For the current proposed study, the CEQ will be adapted to assess the credibility and expectancy for PE and CBD separately will be assessed separately from the credibility and expectancy for Cannabidiol. The 6-item CEQ assesses both whether the person cognitively understands how the therapy works (credibility) as well as whether the person affectively believes that the therapy will work for them personally (expectancy). The 6-item CEQ has been tested in 217 individuals including 68 male Vietnam veterans and 58 female spouses, 69 individuals diagnosed with general anxiety disorder who had received treatment, and 22 individuals who had received either Cognitive Based Therapy (CBT) or Eye Movement Desensitization and Reprocessing (EMDR) for the treatment of PTSD. The scale demonstrated high internal consistency (alpha coefficients ranged from 0.84 to 0.85). Test-retest reliability over a one-week period was found to be 0.82 for expectancy and 0.75 for credibility. The CEQ was able to differentiate between two treatment rationales in one study, one with and one without an encompassing theory while maintaining equivalence between three rationales in another study. Responses to four questions are scored using a 9-point Likert scale (1= not at all, 9= extremely). Responses to two of the questions are scored using an 11-point Likert Scale (0% to 100%). The combined responses are used to generate a score for credibility and another score for expectancy. This measure will be administered prior to the second PE session following Session 1 which will review the PE rationale for the treatment of PTSD.

19. Credibility/ Expectancy Questionnaire (CEQ) for CBD. The CEQ is a 6-item measure that was designed to assess treatment expectancy and rationale credibility for use in clinical outcomes studies. The CEQ has been utilized across a number of STRONG STAR treatment trials and can be easily adapted to assess the target intervention(s). For the current proposed study, the CEQ will be adapted to assess the credibility and expectancy for PE and CBD separately will be

assessed separately from the credibility and expectancy for Cannabidiol. The 6-item CEQ assesses both whether the person cognitively understands how the therapy works (credibility) as well as whether the person affectively believes that the therapy will work for them personally (expectancy). The 6-item CEQ has been tested in 217 individuals including 68 male Vietnam veterans and 58 female spouses, 69 individuals diagnosed with general anxiety disorder who had received treatment, and 22 individuals who had received either Cognitive Based Therapy (CBT) or Eye Movement Desensitization and Reprocessing (EMDR) for the treatment of PTSD. The scale demonstrated high internal consistency (alpha coefficients ranged from 0.84 to 0.85). Test-retest reliability over a one-week period was found to be 0.82 for expectancy and 0.75 for credibility. The CEQ was able to differentiate between two treatment rationales in one study, one with and one without an encompassing theory while maintaining equivalence between three rationales in another study. Responses to four questions are scored using a 9-point Likert scale (1= not at all, 9= extremely). Responses to two of the questions are scored using an 11-point Likert Scale (0% to 100%). The combined responses are used to generate a score for credibility and another score for expectancy. This measure will be administered prior to the second PE session following Session 1 which will review the CBD rationale as an augmentation to PE for the treatment of PTSD.

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