Functional Outcomes of Cannabis Use (FOCUS) in Veterans with Posttraumatic Stress Disorder

NCT04565028

Protocol

Document Date:

4/9/2025

PROTOCOL TITLE: Functional Outcomes of Cannabis Use (FOCUS) in Veterans with Posttraumatic Stress Disorder
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SPONSOR/FUNDING SOURCE: Rehabilitation Research and Development Service (RR&D)

SPECIFIC AIMS

Posttraumatic stress disorder (PTSD) is a disabling psychiatric disorder that affects 20%-30% of U.S. Veterans (Fulton et al., 2015; Kulka et al., 1990). PTSD is strongly associated with increased risk for substance abuse comorbidity, including cannabis use disorder (CUD; Boden, Babson, Vujanovic, Short, & Bonn-Miller, 2013; Bonn-Miller, Harris, & Trafton, 2012; Cougle, Bonn-Miller, Vujanovic, Zvolensky, & Hawkins, 2011); however, multiple states now include PTSD as a condition for which patients can be legally prescribed medical marijuana, despite the fact that there has not been a single large-scale randomized clinical trial demonstrating the efficacy of cannabis to treat PTSD to date. Rates of heavy cannabis use among Veterans are rapidly increasing and are significantly higher in states allowing legalized medical marijuana use (Bonn-Miller, Harris, & Trafton, 2012), and a growing body of evidence suggests that heavy cannabis use may be associated with a wide range of problems in psychosocial functioning, including unemployment, lower educational attainment, psychosis, and neuropsychological deficits (Compton et al., 2014; Fergusson, Horwood, & Beatrais, 2003; Jin, et al., 2017; Hall & Degenhardt, 2009; McCaffrey et al., 2010; Pate et al., 1996; Volkow et al., 2014; Zwerling, Ryan & Orav, 1990). Cannabis is also the illicit drug most strongly associated with drugged driving and fatal traffic accidents (Kelly, Darke, & Ross, 2004; National Institute on Drug Abuse, 2016). Cannabis is also the illicit drug most strongly associated with drugged driving and fatal traffic accidents (Kelly, Darke, & Ross, 2004; National Institute on Drug Abuse, 2016). Moreover, multiple studies by our laboratory indicate that heavy cannabis use is associated with increased risk for a wide range of mental health problems among Veterans, including PTSD, depression, and suicidal and nonsuicidal self-injury (Adkisson et al., in press; Gentes et al., 2016; Kimbrel, Meyer, DeBeer, Gulliver, & Morissette, 2018; Kimbrel, Newins et al., 2017).

The *overall objective* of the current proposal is to prospectively study the impact of reduced cannabis use on psychosocial functioning among Veterans with PTSD. To do so, we will first use ecological momentary assessment (EMA) methods to evaluate the relationship between cannabis use and daily functioning among Veterans with PTSD. Next, we will use mobile contingency management (CM) and EMA to assess the impact of reduced cannabis use on daily functioning among Veterans with PTSD who are heavy cannabis users. Our *central hypothesis* is that reductions in cannabis use will lead to positive changes in the functional outcomes of Veterans. The *rationale* for this research is that it will provide the first and only real-time data concerning the impact of reduced cannabis use on daily functioning among Veterans with PTSD. We will test our central hypothesis and accomplish our overall objective by pursuing the following *specific aims*:

Aim 1: Evaluate the association between frequency of cannabis use and daily functioning among Veterans with PTSD. To achieve this aim, we will collect 2 weeks of ecological momentary assessment (EMA) data from 120 Veterans with PTSD, including 40 non-users, 40 light-to-moderate users, and 40 heavy users, to evaluate the impact of frequency of cannabis use on daily functioning.

H_{1A}: *More frequent cannabis use will be associated with worse functioning, lower quality of life, greater psychiatric distress, more frequent drugged driving, and increased likelihood of CUD.*

Aim 2: Assess the impact of reduced cannabis use on functioning among Veterans with PTSD who are heavy cannabis users. To achieve this aim, we will use mobile CM to reduce the frequency of cannabis use among all of the Veterans with PTSD from Aim 1 who report heavy cannabis use (*N*=40). EMA will be used to monitor Veterans' daily functioning before and after they have reduced their cannabis use.

H_{2A}: *Reductions in frequency of cannabis use will be associated with improvements in functioning, quality of life, psychiatric distress, drugged driving, and CUD symptomatology.*

Aim 3 (Exploratory): Additional analyses will be conducted on secondary outcomes of interest to explore: (1) the

association between frequency of cannabis use and working memory, executive functioning, community reintegration, and suicidal ideation among Veterans with PTSD; and (2) the impact of reductions in cannabis use on these same constructs among Veterans with PTSD who report heavy cannabis use.

H_{3A}: *More frequent cannabis use will be associated with deficits in working memory and executive functioning, less community reintegration, and increased suicidal ideation.*

H_{3B}: *Reductions in cannabis use will be associated with improvements in working memory, executive functioning, community reintegration, and suicidal ideation.*

Impact: The proposed research will provide the first and only real-time data on the effects of varying levels of cannabis use on daily functioning in Veterans with PTSD. It will also help to address the question of whether reduced cannabis use promotes or hinders Veterans' functional recovery. Thus, this innovative and timely project has the potential to significantly advance VHA healthcare and will directly inform the ongoing national debate concerning the impact of cannabis use on the long-term functional recovery of Veterans with PTSD.

BACKGROUND

PTSD and Cannabis Use among Veterans

PTSD is one of the most prevalent mental health conditions among Veterans (Fulton et al., 2015; Kulka et al., 1990), and there has been ongoing discussion regarding the possible medicinal use of cannabis for Veterans with PTSD (Steenkamp et al., 2017; Volkow et al., 2014). PTSD is associated with increased odds of cannabis use, even when adjusting for sociodemographic variables, alcohol use disorders, nicotine dependence, co-occurring anxiety and mood disorders, and exposure to traumatic events (Boden et al., 2013; Bonn-Miller, Harris, & Trafton, 2012; Cougle et al., 2011). Among Veterans, rates of PTSD are higher in those with CUD compared to those with other substance use disorders. In fact, among Veterans who have both PTSD and a substance use disorder (SUD), CUD has been the most frequently diagnosed SUD within this subset of the Veteran population since 2009. In fact, the percentage of Veterans diagnosed with PTSD and co-occurring CUD has increased by 174% since 2002, such that there were more than 40,000 Veterans with PTSD and CUD seeking care within VHA as of FY2014 (Bonn-Miller & Rousseau, 2018).

Cannabis Motives, Cravings, and Withdrawal among Veterans with PTSD

Consistent with self-medication theory, we hypothesize that Veterans with PTSD are at high-risk for CUD due to attempts to use cannabis to cope with their symptoms of PTSD (Boden et al., 2013). In support of this position, Veterans with PTSD and CUD have been found to be more likely than other cannabis users to use cannabis to cope with PTSD symptoms, anxiety, stress, insomnia, and depression (Boden et al., 2013; Bonn-Miller, Boden, Bucossi, & Babson, 2014; Gentes et al., 2016). Notably, the acute effects of cannabis use (e.g., a sense of relaxation, promotion of sleep, pleasant euphoria) are likely to provide short-term relief of key PTSD symptoms (e.g., hypervigilance, sleep disturbance, persistent negative emotional states) in some instances (Bonn-Miller, Boden et al., 2014); however, over time, many Veterans with PTSD who use cannabis are likely to become dependent and to experience a variety of negative consequences as a result (Adkisson et al., in press; Boden et al., 2013; Bonn-Miller, Harris & Trafton, 2012; Compton et al., 2014; Fergusson, Horwood, & Beautrais, 2003; Gentes et al., 2016; Hall & Degenhardt, 2009; Jin et al., 2017; Kelly, Darke, & Ross, 2004; Kimbrel et al., 2018; Kimbrel et al., 2017; McCaffrey et al., 2010; National Institute on Drug Abuse, 2016; Pate et al., 1996; Volkow et al., 2014; Zwerling, Ryan, & Orav, 1990). Even more problematic, discontinuation of cannabis use has the paradoxical effect of increasing cannabis users' PTSD symptoms while simultaneously increasing their cannabis cravings and withdrawal symptoms Boden et al., 2013). For example, Boden and colleagues (2013) found that Veterans with CUD + PTSD reported more severe cannabis withdrawal symptoms and cannabis cravings relative to other Veterans with CUD only. Moreover, PTSD symptom severity was directly related to severity of cannabis withdrawal symptoms, cannabis cravings, and cannabis use problems. Our research team has also recently examined the association between CUD and PTSD-related avoidance among more than 900 Veterans with PTSD (Kimbrel, Calhoun et al., manuscript in preparation). This analysis revealed that Veterans with PTSD + CUD reported significantly higher symptoms of PTSD-related avoidance. They were also more likely to endorse being unable to "handle unpleasant or painful feelings like sadness, fear and anger" (Kimbrel, Calhoun et al., manuscript in preparation).

Taken together, these findings suggest that many Veterans with PTSD are likely to begin using cannabis as a means of potentially coping with/avoiding their symptoms of PTSD. Unfortunately, over time, many may go on to develop problematic patterns of cannabis use and to experience a variety of negative consequences (Adkisson et al., in press; Boden et al., 2013; Bonn-Miller, Harris & Trafton, 2012; Compton et al., 2014; Fergusson, Horwood, & Beautrais, 2003; Gentes et al., 2016; Hall & Degenhardt, 2009; Jin et al., 2017; Kelly, Darke, & Ross, 2004; Kimbrel et al., 2018; Kimbrel et al., 2017; McCaffrey et al., 2010; National Institute on Drug Abuse, 2016; Pate et al., 1996; Volkow et al., 2014; Zwerling, Ryan, & Orav, 1990) due to increased avoidance and increasingly severe PTSD symptoms, cannabis cravings, and cannabis withdrawal symptoms (Boden et al., 2013) when they are not acutely intoxicated, resulting in a "pernicious feedback loop" (Boden et al., 2013).

Impact of Heavy Cannabis Use on Functioning

Heavy cannabis use is associated with a host of negative outcomes (Adkisson et al., in press; Boden et al., 2013; Bonn-Miller, Harris & Trafton, 2012; Compton et al., 2014; Fergusson, Horwood, & Beautrais, 2003; Gentes et al., 2016; Hall & Degenhardt, 2009; Jin et al., 2017; Kelly, Darke, & Ross, 2004; Kimbrel et al., 2018; Kimbrel et al., 2017; McCaffrey et al., 2010; National Institute on Drug Abuse, 2016; Pate et al., 1996; Volkow et al., 2014; Zwerling, Ryan, & Orav, 1990). For example, cannabis is the illicit drug most strongly associated with drugged driving and motor vehicle accidents, including fatal accidents (Hartman & Huestis, 2013; Kelly, Darke, & Ross, 2004; National Institute on Drug Abuse, 2016; Ramaekers et al., 2004; Volkow et al., 2014). In fact, overall risk for involvement in a motor vehicle accident is doubled when a person drives after cannabis use (Hartman & Huestis, 2013; Kelly, Darke, & Ross, 2004; National Institute on Drug Abuse, 2016; Ramaekers et al., 2004; Volkow et al., 2014), and accident culpability analyses indicate that individuals who test positive for Δ9-tetrahydrocannabinol (THC) are 3-7 times more likely to be responsible for accidents compared with those who were sober while driving (Hartman & Huestis, 2013; Kelly, Darke, & Ross, 2004; National Institute on Drug Abuse, 2016; Ramaekers et al., 2004; Volkow et al., 2014). Cannabis use is also associated with mental health problems and reduced quality of life (Adkisson et al., in press; Boden et al., 2013; Bonn-Miller, Harris, & Trafton, 2012; Borges, Bagge, & Orozco, 2016; Cougle et al., 2011; Gentes, et al., 2016; Goldenberg, IsHak, & DAnovitch, 2017; Kimbrel et al., 2018; Kimbrel et al, 2017; Volkow et al, 2014). For example, studies by our team indicate that heavy cannabis use is associated with depression, PTSD, suicidal ideation, and reduced quality of life (Adkisson et al., in press; Gentes, et al., 2016; Kimbrel et al., 2018; Kimbrel et al, 2017). Other published studies by our laboratory suggest that CUD is associated with both nonsuicidal and suicidal self-injury (i.e., suicide attempts ; Adkisson et al., in press; Gentes, et al., 2016; Kimbrel et al., 2018; Kimbrel et al, 2017). Research by others indicates that heavy cannabis use is associated with neuropsychological deficits (e.g., poor memory), low self-efficacy, poor grades, school dropout, unemployment, lower income, need for financial assistance, criminal behavior, work-related absences, injuries, and reduced quality of life (Boden et al., 2013; Bonn-Miller, Harris & Trafton, 2012; Compton et al., 2014; Bruins et al., 2016; Fergusson, Horwood, & Beautrais, 2003; Goldenberg, IsHak, & Danovitch, 2017; Hall & Degenhardt, 2009; Hartman & Huestis, 2013; Jin et al., 2017; Kelly, Darke, & Ross, 2004; McCaffrey et al., 2010; National Institute on Drug Abuse, 2016; Pate et al., 1996; Ramaekers et al., 2004; Schreiner & Dunn, 2012; Volkow et al., 2014; Zwerling, Ryan, & Orav, 1990). Cannabis use may also increase risk of dropping out of evidence-based PTSD treatment (*OR*=3.38; Bedard-Gilligan, Garcia, Zoellner, & Feeny, 2018). In addition, preliminary data gathered by our laboratory (Kimbrel et al., manuscript in preparation) indicate that Veterans with PTSD + current CUD report significantly higher levels of PTSD, anxiety, hostility, paranoia, and psychotic symptoms than Veterans with PTSD only (all p's < .05). In contrast, Veterans with PTSD + CUD in remission do not differ significantly from Veterans with PTSD only (Kimbrel et al., manuscript under preparation). Veterans with PTSD + current CUD were also more likely to have been incarcerated (68% vs 28%), to be unemployed (76% vs. 52%), and to have difficulty controlling violent behavior (32% vs. 18%) compared with Veterans with PTSD only (Kimbrel et al., manuscript in preparation). In contrast, the rate of unemployment among Veterans with PTSD only and PTSD + CUD in remission did not differ, suggesting that sustained abstinence from cannabis may help Veterans with PTSD + CUD return to work (Kimbrel et al., manuscript in preparation).

Impact of Sustained Abstinence on Functioning

Despite the numerous negative outcomes associated with heavy cannabis use, growing evidence suggests that sustained abstinence can lead to improvements in some areas of functioning (Bonnet, Borda, Scherbaum, & Specka, 2015; Bruins

et al., 2016; Kimbrel et al., manuscript in preparation; Schreiner & Dunn, 2012). Schreiner and Dunn's (2012) meta-analysis of the effects of cannabis use on neuropsychological outcomes found that cannabis use was associated with negative effects on neurocognitive functioning; however, when the meta-analysis was re-run and restricted to studies that only included former cannabis users who had abstained from cannabis for at least 25 days, the negative effects of cannabis use were no longer observed, suggesting that neuropsychological functioning may return to normal levels of functioning following a period of sustained abstinence from cannabis (Schreiner & Dunn, 2012). Similar findings have been observed for mental health outcomes (Bonnet et al., 2015; Bruins et al., 2016; Kimbrel et al., manuscript in preparation). For instance, Bonnet et al. (2015) recently studied the impact of sustained abstinence on a range of mental health symptoms among 35 patients seeking treatment for CUD. After 16 days of sustained abstinence, significant improvements were observed across a broad array of mental health outcomes, including large effects for depression (*d* = 0.90), anxiety (*d* = 1.4), and global symptomatology (*d* = 0.90).

Rationale for the Proposed Study

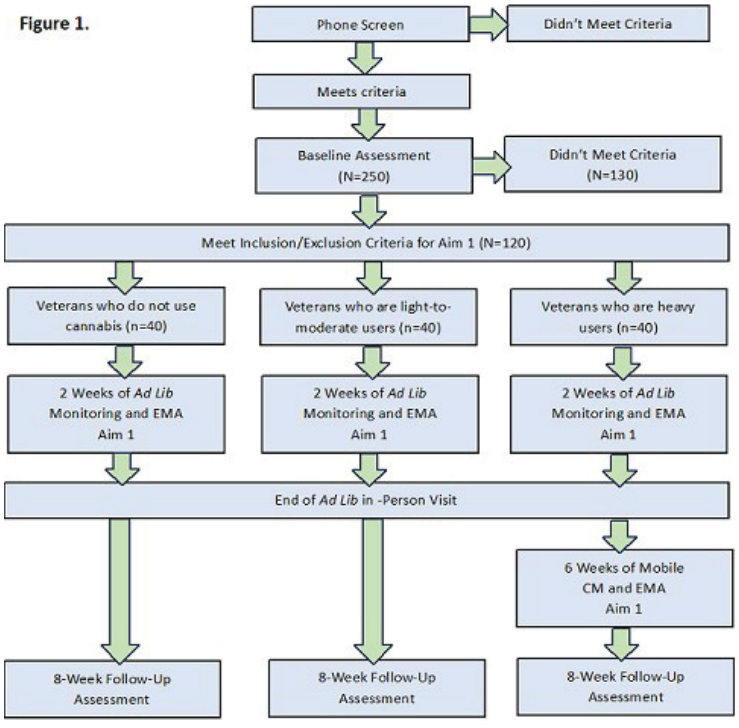
PTSD is one of the most prevalent and disabling psychiatric conditions affecting Veterans (Fulton et al., 2015; Kulka et al., 1990; Shalev, Liberzon, & Marmar, 2017). Cannabis use is rapidly increasing among Veterans with PTSD, despite the fact that numerous concerns regarding the safety of this drug exist. Given the significant increase in cannabis use observed among Veterans with PTSD in recent years (Bonn-Miller & Rousseau, 2018) as well as widespread efforts to legalize cannabis use throughout the U.S., we believe that **there is an urgent need to study the effects of cannabis use on functioning among Veterans with PTSD at the present time**. Our ***central hypothesis*** is that reductions in cannabis use will lead to positive changes in the functional outcomes of Veterans with PTSD. The ***rationale*** for this research is that it will provide the first and only real-time data on the effects of varying levels of cannabis use on daily functioning in Veterans with PTSD. This project will also provide data that can directly address the question of whether reduced cannabis use promotes or hinders Veterans' functional recovery. As such, this innovative and timely project has the potential to significantly advance VHA healthcare and will directly inform the ongoing national debate concerning the impact of cannabis use on the long-term functional recovery of Veterans with PTSD.

METHODS

Study Design and Participant Flow

Figure 1 depicts the overall study design and participant flow. Interested participants that meet initial eligibility criteria during a phone screen will complete an in-person assessment to determine final eligibility. We anticipate that we will need to recruit up to 250 participants to enroll a final sample of 120 eligible participants, all of whom will be Veterans with current PTSD. To ensure the final sample represents the full range of cannabis consumption among Veterans with PTSD, the sample will be stratified to include 40 Veterans with PTSD who don't use cannabis, 40 Veterans with PTSD who are light-to-moderate users; and 40 Veterans with PTSD who are heavy users. Non-users and light-to-moderate users will only participate in Aim 1, which will consist of completion of the baseline interview, 2 weeks of ad-lib EMA monitoring, an end-of-ad lib visit, and a 8-week follow-up assessment. Heavy cannabis users (n=40) will participate in both Aim 1 and Aim 2. Their participation will entail completion of the baseline interview, 2 weeks of ad-lib EMA monitoring, an end-of-ad lib visit, 6 additional weeks of CM + EMA monitoring, and a 8-week follow-up assessment.

Figure 1.



Inclusion/Exclusion Criteria

Inclusion criteria for the 40 non-users will include: (a) Veteran status; (b) Ability to speak and write fluent English; (c) Current PTSD diagnosis; (d) No cannabis use in the past year; (e) Has a smart phone; and (f) Minimal lifetime cannabis use (i.e., ≤ 5 times lifetime).

Inclusion criteria for the 40 light-to-moderate users will include: (a) Veteran status; (b) Ability to speak and write fluent English; (c) Current PTSD diagnosis; (d) Has a smart phone; and (e) Use of cannabis other than edibles solely on 1-12 days in the past month (i.e., cannabis use < 3 days per week).

Inclusion criteria for the 40 heavy users will include: (a) Veteran status; (b) Ability to speak and write fluent English; (c) Current PTSD diagnosis; (d) Has a smart phone; and (e) Use of cannabis other than edibles solely on 13+ days in the past month (i.e., use on 3+ days per week). Please note that there are presently no universal definitions for moderate vs heavy cannabis use. Accordingly, our definitions are based on: (1) Frequency of use observed in our prior work with Veterans with PTSD (Gentes et al., 2016); and (2) Latent classes of cannabis use observed in large samples of civilian users (Pearson, Bravo, Conner, & Marijuana Outcomes Study Team, 2017).

Participants will be excluded if they: (a) Have experienced a change in their psychiatric medication regimen during the past month (e.g., a new medication has been prescribed or the dose of an existing medication has been changed), or expect to experience a such a change during the course of the study; (b) Are receiving non-study CUD treatment; (c) Meet diagnostic criteria for bipolar disorder or a psychotic spectrum disorder (note that the SCID-5 (First et al., 2015) will be used to diagnoses these and other disorders); (d) Become imprisoned; (e) Become hospitalized for psychiatric reasons; (f) Report imminent risk for suicide or homicide; or (g) Meet current criteria for a SUD other than CUD or tobacco.

Recruitment & Enrollment

Potential participants will be recruited through established laboratory procedures. We will use VA Data Access Request Tracker (DART) requests to identify Veterans with PTSD and cannabis use to be mailed invitational letters and/or emails informing them of this study. In addition, the Traumatic Stress and Health Research Laboratory has a contact database (see IRB #1080), which contains the contact information of participants in previous studies who have indicated a desire to be contacted about other research projects in our lab.

Any potential participant who is identified in one of these two ways will be sent a recruitment letter and/or email that provides basic information about the study. The letter will a) provide Veterans with a QR code or url that links directly to a Qualtrics survey in which they can answer basic questions about eligibility and provide contact information for follow-up, and b) inform Veterans that they will be contacted by phone in the coming days regarding their interest in participating in the study. In the letter and email, potential participants will be given an "opt-out" number to call in order to decline participation and/or further contact regarding participation. Seven business days after the mailing, Veterans who have not called the toll-free number to decline participation will be called by the study coordinator to request their participation in the research study.

We will complement our proactive recruitment by displaying IRB-approved flyers in local hospitals and community settings, as well as inviting patients from among outpatients at the Durham VAHCS PTSD clinic, Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn (OEF/OIF/OND) clinic, Women's Health clinic, SUD clinic, and Mental Health clinic. If recruitment procedures are slower than expected, our coordinator and recruitment specialist will employ social media recruitment methods used in our previous trials, and will work with Veterans' Service Organizations to inform more potential participants about this trial. We will also post advertisements on Craigslist.com.

Clinicians in clinics throughout the medical center will be provided information about study eligibility and basic procedures, and will be asked to refer potentially eligible veterans. Clinicians have reported that Veterans often indicate that they prefer that their names and contact information be provided directly to study staff. We'd like to make it easy for interested Veterans to get involved in research, while protecting the privacy of those Veterans who are not interested in research. Towards that end, we would like to allow a clinician to refer a participant directly to our clinic by

adding the study PI or study coordinator as a co-signer to a note in CPRS in which the clinician has documented that the participant wishes to be contacted about participation.

If any participant contacts or is contacted by the study coordinator regarding participation, a telephone script will be used to inform them about the study and do a preliminary determination of eligibility. If after the telephone screening a participant is considered potentially eligible for participation, he/she will be scheduled for a consent session and/or an initial screening session. The study staff member obtaining consent will explain the study in detail, provide the participant with an IRB-approved written consent form explaining the procedures and risks, and answer any questions. The initial consent process and documentation takes place in a quiet, private office in the Traumatic Stress and Health Research Laboratory (TSHRL) at DVAHCS, by mail, or via DocuSign where available, and participants will be given the chance to thoroughly read the consent prior to participation. Participants will also be given a copy of the signed informed consent form and phone numbers to call if they have additional questions about the consent form or the research, if they have any problems during the study, or if they have questions about participating in research studies in general. No study procedures will begin until informed consent has been obtained.

Screening Procedures

Prior to study entry, potential participants will complete screening procedures as part of the baseline assessment (**Figure 1**), including informed consent, diagnostic interviews, self-report measures, demographic data, and cannabis history. Urine and saliva samples will be collected to assess for cannabis use and other illicit drugs. During the screening visit, participants who are marijuana users will estimate the amount of marijuana they typically use in a joint, bowl, etc. by using catnip as a marijuana substitute. In this task, they will be asked to roll their joint, pack their bowl, etc. by using catnip. The study coordinator can then measure the amount of catnip used to provide participants with additional information to inform their estimates of daily use in later parts of the study.

Diagnostic Reliability and Training of Interviewers

The CAPS-5 (Weathers et al., 2013) will be used to diagnose PTSD and determine study eligibility. Interviewers will be trained to conduct the CAPS-5 and the other diagnostic interviews using our standardized lab procedures, including rating videotaped interviews and participation in ongoing weekly supervision. These procedures have produced consistently high interrater reliability, with Fleiss' kappa values ranging from .92-.94 in prior studies (Kimbrel et al., 2014) Kimbrel et al., 2017).

Table 1. Potential Participant Payments for Heavy Users Group

Procedure	Amount Earned in $	
	Aim 1	Aim 2
Baseline assessment	125	125
Saliva readings during *ad lib* period*	70	70
EMA during *ad lib* period*	150	150
CM with perfect abstinence*	n/a	1130.50
EMA during CM period*	n/a	450
8-week follow-up visit	150	150
TOTAL	**$495**	**$2075.50**

*payment contingent upon receipt of data from Duke

Participant Payment Procedures

Tables 1 and 2 summarize potential payments for participants. Participants will be paid for partial completion of study procedures. These procedures have worked well (i.e., with high adherence and equipment return rates) in our previously published (Carpenter et al., 2015; Hertzberg et al., 2013) and preliminary studies. Any potential participant who attends the baseline assessment but does not meet eligibility criteria will be paid $50 for that session.

Table 2. Potential Participant Payments for Non-Users and Light-to-Moderate Users Groups

Procedure	Amount Earned in $
Baseline assessment	125
EMA during *ad lib* period*	150
8-week follow-up visit	150
TOTAL	**425**

Careful consideration has been given to the amount participants can earn for full participation in this study. Aim 1 participants can earn $425 for full participation in the study. Participants in Aim 2 can earn more, up to $1925.50 for full participation because they are being provided contingency management as a treatment intervention. Nearly half of all payments for Aim 2 participants are directly related to remaining abstinent from cannabis use. A grant reviewer had concern that participants might use study payment to purchase other drugs. In a study designed to examine whether or not research payments facilitated drug use, Festinger et al. (2008) found that magnitude of payment did not impact drug use. Once per week, we will ask participants to complete a saliva test kit that evaluates for other substances (including cocaine, methamphetamines, heroin), too. This

will allow us to evaluate whether or not the research payments facilitate other substance use. The rate of payment for EMA is consistent with that of other studies run in our laboratory (see Kimbrel IRB #2015). With regards to concern about coercion, it is important to note that bioethicists have concluded that payments for research participation does not coerce, particularly because coercion involves the possibility of the research participant being made worse by participation (Millum & Garnett, 2019). Adhering to EMA or reducing drug use is NOT dangerous or risky. It is, however, time intensive and potentially burdensome, for which the payments are an appropriate compensation.

Description and Timing of In-Person Assessments

Table 2 describes the clinical measures that will be administered at the baseline and 8-week in-person assessments. Whenever possible, we have selected Common Data Elements from the PhenX Toolkit (Hamilton et al., 2011) to maximize the impact of the proposed research as well as brief measures to minimize participant burden.

Table 3. ***Measures to Be Administered During the In-Person Assessments.***

MEASURE	DESCRIPTION	BL	8-WK
Timeline Followback (Robinson, Sobell, Sobell, & Leo, 2014)	Used to determine eligibility and assess frequency and quantity of cannabis use, including use of novel methods (e.g., vaping, dab rigs) and products (e.g., edibles). Participants are provided with digital scales, catnip (which is similar in weight and consistency to cannabis), and paraphernalia to ensure that quantity of cannabis used is accurately assessed. Re-administered at 8-weeks.	X	X
SCID-5 (First et al., 2015)	Used to diagnose CUD and other disorders based on DSM-5 criteria to determine eligibility, to characterize CUD severity, and assess CUD symptom changes over time.	X	
Timeline Followback (Robinson, Sobell, Sobell, & Leo, 2014)	TLFB will also be used to assess drugged driving in relation to cannabis use at baseline and 8-week follow-up.	X	X
WHODAS 2.0 (Utsun, Kostanjesek, Chatterji, Rehm, & World Health Organization, 2010)	36-item self-report of functional disability; total score and 6 domains of functioning. Has excellent psychometric properties.	X	X
Brief Inventory of Psychosocial Functioning (B-IPF; Kleiman et al., 2018)	7-item self report measure of PTSD-related functional impairment.	X	X
WHOQOL-BREF (The WHOQOL Group, 1994)	26-item measure of health-related quality of life developed by WHO.	X	X
Quality of Life Scale (Burckhardt & Anderson, 2003)	16-item self-report measure of satisfaction in 16 areas. Good internal consistency and test-retest reliability.	X	X
CAPS-5 (Weathers et al., 2013)	Gold standard clinical interview for PTSD. Will be used to determine eligibility, to characterize PTSD symptom severity, and to assess PTSD symptom changes over time.	X	X
SCL-90 (Derogatis, 1983)	90-item measure of mental health symptoms that has previously been shown to be sensitive to sustained abstinence from cannabis (Kimbrel et al., 2018).	X	X
WM & EF Tasks (Tombaugh, 2004; Stroop, 1935; Wechsler, 2008a, Wechsler, 2008b)	Symbol Span (Wechsler, 2008b) and Spatial Addition (Wechsler, 2008a) will assess visual working memory (WM). Digit Span (Wechsler, 2008b) and Letter-Number Sequencing (Wechsler, 2008b) will assess auditory WM. Trail Making Test - Form B (Tombaugh, 2004) and the Stroop (Stroop, 1935) will be used to assess executive functioning (EF).	X	X
BRIEF (Roth, Isquith, Gioia, 2005)	75-item self-report of perception of WM and EF; contains nine subscales (e.g., WM, Inhibit, Shift, Plan/Organize).	X	X
CIM (McColl et al., 2001)	10-item self-report measure of community integration that has 4 domains: general assimilation, support, occupation, and independent living.	X	X
Dimensions of Anger Reactions (DAR; Novaco, Swanson et al., 2012)	7-item scale measuring the frequency, duration, and behavioral response to anger, and anger-related functional impairment on social relationships, health, and work	X	X
Conflict Tactics Scale, version 2 (CTS2; Straus, Hamby, Boney-McCoy, & Sugarman, 1996)	Scale measuring interpersonal aggression	X	X
Medical Problems List	Measure designed to evaluate presence of major medical problems ever	X	

	and in the past year.		
Medications List	Measure designed to record current prescriptions, with dose and frequency.	X	
Brief Perceived Ethnic Discrimination Questionnaire – Community Version (Brondolo et al., 2005; Keum et al., 2018)	Multidimensional measure of exposure to ethnic/racial discrimination.	X	
Experiences of Discrimination (Krieger et al., 2005)	Measures "self-reported experiences of discrimination."	X	
The Everyday Discrimination Scale (Williams, Yu, Jackson, & Anderson, 1997)	Measure used to assess the relative frequency of chronic, routine, and subtle experiences of unfair treatment that occur in day-to-day life.	X	
Marijuana Problems Scale (Stephens, Roffman & Curtin, 2000)	Self-report assessment of cannabis-related symptoms and problems.	X	X
Cannabis Withdrawal Scale (Allsop et al., 2011))	Self-report assessment of cannabis withdrawal symptoms.	X	X
Marijuana Motives Questionnaire (Lee et al., 2009)	Self-report assessment of motives for using cannabis.	X	X
Cannabis and PTSD Symptoms measure	Self-report assessment of cannabis use impact on PTSD symptoms (given to light and heavy users groups)	X	
Recreational and Medicinal Marijuana Use Questionnaire	Self-report assessment of cannabis use symptoms, based on Metrik et al., 2018.	X	X
Alcohol Use Disorders Identification Test (Babor et al., 1989)	Self-report of alcohol use and related consequences	X	X
Deliberate Self-Harm Inventory	17-item self-report of nonsuicidal self injurious behavior	X	X
PTSD Checklist 5 (PCL-5; Weathers, Litz et al., 2013	20-item self-report of PTSD symptoms	X	X
Traumatic Life Events Questionnaire (Kubany et al., 2000)	23-item self-report of history of traumatic events	X	
PEG (Krebs et al., 2009)	3-item self-report measuring pain	X	X
Insomnia Severity Index (Morin, et al., 2011)	7-item self-report of insomnia symptoms	X	X
STOP BANG (Chung et al., 2012)	Brief measure to screen participants for obstructive sleep apnea	X	
Marijuana Reduction Strategies Self-Efficacy Scale (Davis et al., 2014)	21-item assessment of self-efficacy related to strategies intended to reduce the amount and/or frequency of cannabis consumption.	X	X
Godin Leisure Time Exercise Questionnaire (Godin, 2011)	4-item measure of physical activity	X	X
UPPS-P (Lynam et al., 2006)	59-item self-report that assesses multiple facets of impulsivity, including: urgency, premeditation, perseverance, sensation seeking, positive urgency.	X	X
Cannabis Problems Questionnaire (Copeland, Gilmour, Gates, & Swift, 2005)	22-item measure to evaluate cannabis-related problems.	X	X
Fagerström Test of Nicotine Dependence (Heatherton, et al., 1991)	Measure designed to evaluate nicotine dependence	X	X
Marijuana Ladder (Slavet et al., 2006)	Measure of motivation to change marijuana use.	X	X
Cannabis Modes and Quantities	Self-report measure designed to capture information about participants' modes of cannabis use and estimates of amount used (modified from Hammond et al., 2020, International Cannabis Policy Survey).	X	
Impulsivity Tasks (Richards, Zhang, Mitchell, De Wit, 1999; Bechara et al., 1994; Lejuez et al., 2002)	The Delay Discounting Task, Iowa Gambling Task, and Balloon Analogue Risk Task will assess impulsivity, particularly impulsive choice. Administered via computer using software by Inquisit Lab.	X	X
Sheehan Disability Scale (Sheehan, 1983)	3-item assessment of work, social, and family impairment.	X	X
Int'l Physical Activity Questionnaire (Booth, 2000)	27-item physical activity scale that focuses on the past 7 days.	X	X
CSSR-S (Posner et al., 2011)	State-of-the-art interview to assess suicidal behavior. Will be used to	X	X

	determine study eligibility and to assess changes in suicidal ideation over time (Wilson, Alderman, Burgess, Emslie, & Evans, 1997).		
Beck Scale for Suicide (Beck & Steer, 1991)	21-item self-report of suicidal thoughts and behaviors (Simes, 1986).	X	X
Demographic Assessment (Hamilton et al., 2011)	PhenX (Hamilton et al., 2011) protocols will assess age (#010101), race (#010601), ethnicity (#010501), gender (#010700), and sexual orientation (#101401).	X	
Sound Sensitivity Measures (Hiller & Goebel, 1992; Khalfa et al., 2002; Wu et al., 2014)	Several measures, including the Mini Tinnitus Questionnaire, Misophonia Questionnaire, and Hyperacusis Questionnaire, will measure sound sensitivity.	X	X
Brief Experiential Avoidance Questionnaire (Gamez et al., 2014)	15-item measure of experiential avoidance.	X	X
OSU TBI Assessment (Corrigan & Bogner, 2007)	Structured clinical interview for lifetime history of TBI (Benjamini, 2010). Will be used to characterize sample and as a potential covariate in analyses.	X	
Brief Qualitative Interview and Post-Treatment Survey	At the final visit, participants in the heavy users group will complete a brief interview and self-report measure to describe their experiences in the study. This interview will be audio-recorded via Audacity, VA's WebEx, or Windows voice recorder.		X

Mobile Health Procedures

All participants will complete mobile health procedures using VA Qualtrics. Participants will be prompted to respond to EMA inquiries and mCM recordings within Qualtrics. Participants will access VA Qualtrics using their own electronic devices (e.g., smart phones, computers, tablets). If any participant does not have such a device, we will complete a consult to have a tablet issued by the VA. Qualtrics will be used to collect EMA data in a typical online survey style. Participants in the heavy users group will use their devices to take a video-recording of their saliva readings and upload them to Qualtrics. Videos taken on participant personal devices do not become VA data until they are uploaded to VA Qualtrics. All data will be stored at VA Qualtrics, which is FedRAMP approved for collection and storage of VA PHI and VA sensitive information.

Ecological Momentary Assessment (EMA) Procedures. EMA addresses the limitations of traditional assessment techniques by (a) repeatedly assessing participants in their normal daily environment, which enhances ecological validity; (b) assessing experiences and behaviors at the time they occur, which minimizes memory biases associated with retrospective recall; and (c) allowing for examination of the context of participants' experiences. Non-users (n=40) and light-to-moderate users (n=40) will only participate in Aim 1, which will consist of two weeks of ad-lib EMA monitoring. Heavy cannabis users (n=40) will participate in both Aim 1 and Aim 2. Thus, their participation will entail completion of two weeks of ad-lib EMA monitoring (Aim 1) as well as six additional weeks of EMA monitoring during CM (Aim 2). EMA topics include cannabis use, drugged driving, cannabis-related impairment in the domains of work/school, social, and family life (Sheehan, Harnett-Sheehan, & Raj, 1996), health related quality of life (The WHOQOL Group, 1994), psychological symptoms [PCL-5 (Blevins, Weathers, Davis, Witte, & Domino, 2015) and Positive And Negative Affect Scale (PANAS, Watson, Clark, & Tellegen, 1988)], suicidal ideation, working memory, community integration (McColl et al., 2001) and social contact. In the nightly EMA diary, participants will be asked to estimate the total amount of cannabis they have used in the past 24 hours. Participants will also be given a small scale to use to measure their marijuana stash at the end of each day (to assist them in estimating daily use). Participants who miss no more than one alarm per day will be paid a bonus of $25 each week they do EMA. In our review of data from the first cohorts of our cannabis CM treatment development grant at Duke, we observed that participants who do not do at least 10 of the 14 nighttime diary readings during the ad lib period are much less likely to participate in the study fully, and are much more likely to be lost to contact during the treatment phase. Therefore, we would like to include in the treatment phase (Aim 2) only those heavy cannabis using participants who complete 10 of the 14 nightly diaries. Additionally, we will include in the treatment phase of the study only those participants who upload at least 22 of the 28 saliva reading video uploads. Any participant who does not meet these criteria will not participate in Aim 2 of the study.

Contingency Management (CM) Procedures. Mobile CM will be used to promote reductions in cannabis use among the 40 Veterans with PTSD who are heavy cannabis users in Aim 2. *Note that the 40 non-users and 40 light-to-moderate users will not participate in this part of the study*. Following a 2-week *ad lib* monitoring period during which time

participants will use cannabis typically to establish baseline patterns of use, heavy cannabis users will participate in 6 weeks of mobile CM to reduce their cannabis use. CM is an intensive behavioral therapy that is highly effective at producing short-term reductions in illicit drug use. Moreover, we have developed a novel approach that leverages mobile technology and recent developments in cannabis testing to make daily CM for cannabis feasible. The present research will use this technology in conjunction with state-of-the-art EMA methods to study the impact of reduced cannabis use on daily functioning among Veterans with PTSD who use cannabis.

Reinforcement Schedule. We will utilize an *escalating reinforcement schedule*, such that each subsequent day of abstinence will be reinforced with more money, see **Table 3**. Participants will earn $10.00 for their first day of abstinence, and each subsequent day of bioverified abstinence will result in compensation increasing by $.50. We will also utilize a *reset contingency*. Reset contingencies are designed to promote sustained abstinence because any post-abstinence substance use results in the level of reinforcement being reset to the initial (i.e., day 1) amount. We have pilot tested our proposed reinforcement schedule with 6 heavy cannabis users and have observed a 98% reduction in number of days cannabis was used. We are confident that the proposed CM schedule will produce similarly large reductions in cannabis use in the proposed project as well.

Saliva Testing Schedule. During the *ad lib* and CM procedures, participants in the heavy users group will receive an alarm twice daily, and will be asked to videotape themselves while taking the saliva test. If they test negative at both times, they will be reinforced with a bonus for that day. Note that they will be reinforced separately for both positive and negative saliva tests (i.e., will receive $2.50 per upload, regardless of use), enabling us to compare saliva test results with self-report. In the unlikely event that we find multiple discrepancies between self-report and saliva, we can easily add a random alarm prompting an additional saliva test; however, because this additional alert would create more burden, we have elected to not employ such a system unless necessary, as our pilot data indicate high concordance between self-report and saliva results (96%).

Additional Bioverification of Cannabis Use. At three time points (screening, end of the *ad lib* period, end of treatment), we will ask participants to provide urine and saliva samples. These samples will be sent to Lab Corp for analysis. Urine will undergo creatinine normalization analyses to determine cannabinoid concentrations. Measurement of cannabinoid concentration will allow analyses of reduced cannabis use. Saliva will undergo THC mass spectrometry analyses.

Optional Study Procedures

If any participant indicates that he/she/they has an email address and would prefer to receive communications about the study (e.g., appointment reminders, appointment rescheduling) via email, the study team will use Azure, an encrypted email program. Participants may opt out of receiving study emails at any time during the study. Similarly, we will provide appointment reminders to participants via text if they would like to receive such reminders.

Table 4. Potential payment schedule with "free day" allowance (heavy users group only)

Week	Day	Saliva videos	(Regardless of use) Daily Saliva Video Uploads	Smoking?	Daily Saliva Video Uploads	Explanation	Total	Running Total
Week 1 & 2 (*Ad Lib*)	1-14	1	$2.50	As Usual	No Bonus yet	$5.00 ($2.50 per video) payment for uploading saliva testing videos (regardless of cannabis use).	$5 each day	$70.00
		2	$2.50	As Usual				
Weeks 3 to 7	15	1	$2.50	No	$10.00	Participants will earn $10 for their first day of verified abstinence. Bonus payment increases after verified marijuana-free day or if the	$15.00	$85.00
		2	$2.50	No				
	16	1	$2.50	No	$10.50		$15.50	$100.50
		2	$2.50	No				
	17	1	$2.50	No	$11.00		$16.00	$116.50

Table 4. Potential payment schedule with "free day" allowance (heavy users group only)								
Week	Day	Saliva videos	(Regardless of use) Daily Saliva Video Uploads	Smoking?	Daily Saliva Video Uploads	Explanation	Total	Running Total
(CM Phase 1), one exam		2	$2.50	No		once-a-week cheat day is used.		
	18	1	$2.50	No	$12.50		$16.50	$133.00
		2	$2.50	No				
	19	1	$2.50	Yes	$13.00		$17.00	$150.00
		2	$2.50	Yes				
	20	1	$2.50	No	$13.50		$17.50	$167.50
		2	$2.50	No				
	21	1	$2.50	No	$14.00		$18.00	$185.500
		2	$2.50	No				
Week 8 (CM Phase 6)	50	1	$2.50	No	$27.50	$.50 increase to bonus marijuana payment for verified marijuana-free day or if the once-a-week cheat day is used.	$32.50	$925.00
		2	$2.50	No				
	51	1	$2.50	No	$28.00		$33.00	$958.00
		2	$2.50	No				
	52	1	$2.50	No	$28.50		$33.50	$991.50
		2	$2.50	No				
	53	1	$2.50	No	$29.00		$34.00	$1025.50
		2	$2.50	No				
	54	1	$2.50	Yes	$29.50		$34.50	$1060.00
		2	$2.50	Yes				
	55	1	$2.50	No	$30.00		$35.00	$1095.00
		2	$2.50	No				
	56	1	$2.50	No	$30.50		$35.50	$1130.50
		2	**$2.50**	**No**				

Data Sharing

We will share deidentified data sets via email with Sara Cratsenburg at University of North Carolina at Chapel Hill. Ms. Cratsenburg will assist with data analyses and manuscript preparation.

HUMAN SUBJECTS PROTECTIONS

Potential Risks

With regards to completing study measures, there is a risk of discomfort or distress in answering questions. However, distress and discomfort related to questionnaire completion and the psychiatric interview are usually temporary and well-tolerated. Participants are informed that they may refuse to answer any questions while completing the questionnaires. Risks also include discomfort related to reducing cannabis use. Reduction of marijuana use can cause withdrawal symptoms. Symptoms can last for a few days to several weeks. These may include: headache, trouble sleeping, sweating, night sweats, anxiety and/or depression, nightmares or vivid dreams, irritability, and cravings for use. Because of these risks, the data and safety monitoring plan (DSMP) for this trial focuses on monitoring by the principal

Protections Against Risk

The study is completely voluntary and participants are informed that they are free to refuse to answer any items on the questionnaires or questions from the interview that they do not wish to answer. They are also informed that they are free to decline participation in any procedure and can withdraw from the study at any time. We will obtain an NIH

Certificate of Confidentiality to further protect participants' confidentiality.

Potential risks will be minimized by carefully screening potential participants according to the inclusion/exclusion criteria, closely monitoring symptom levels, and following established laboratory procedures associated with psychiatric emergencies and substance use. Finally, all project staff will complete educational units required by DVAHCS's IRB.

With regards to data security, potential risks will be minimized in several ways. Subjects' identifying information will only be available to Drs. Beckham and Kimbrel and their research staff at DVAHCS. Data that links participants to information collected in the course of a given study will be kept separately from identifying information in a computerized logbook. All study data will be kept in a secured file to which only study investigators will have access. Hard copy paper records will be stored in a locked filing cabinet in the study coordinator's locked offices at DVAHCS. Information from the interview and/or questionnaires will be entered into a computerized database. This password-protected database will be stored on a DVAHCS networked computer on a server that is encrypted, password-protected, and only accessible by Dr. Beckham, Dr. Kimbrel, and study staff. The key linking code numbers and identifying information will be will be maintained in a separate database and stored in the same protected computer environment described above.

With regards to other potential risks, they will be minimized by carefully screening potential participants according to the inclusion/exclusion criteria, closely monitoring symptom levels, and following established laboratory procedures associated with substance use. The study's safety monitoring plan is based on long-term clinical and research experience with patients with psychiatric illness. It is not unexpected that participants experience increased distress associated with the assessment procedures and diagnostic clinical interview. Our extensive clinical and research experience suggest that there is no serious risk in these patients associated with assessment and interview procedures as proposed. In addition, it is not unanticipated that participants may endorse suicidal or homicidal ideation. In determining risk of suicide or homicide, we will review all sources of data, including EMA data. EMA data are reviewed within 24 hours of data being returned. If EMA data reveal suicidal ideation, we will review this with the participant to determine risk of suicide. We have developed a homicidal (HI) and suicidal (SI) risk assessment checklist based on the currently available research evidence base. All staff members are trained in the use of the instrument, and attend monthly supervision meetings in which HI/SI assessments are regularly reviewed. Our laboratory has a Standards of Practice (SOP) regarding SI and HI risk assessment and follow-up, and this policy has been reviewed and approved by both the DVAHCS and DUMC IRB. According to the policy, if a participant is deemed at "high" risk of suicide or homicide, the study staff providing the assessment will contact a senior staff member with clinical training who will provide a second opinion. If the senior staff member feels that the participant is in imminent risk of suicide or homicide, that participant will be escorted to the DVAHCS emergency room for evaluation for psychiatric hospitalization. If at any time a participant is deemed by our staff to be at imminent risk of harm to self or others, he/she will be immediately withdrawn from the study upon being escorted to the emergency room. If a participant is deemed to be at "low" risk, the study staff member performing the assessment will discuss treatment options with the participant and discuss psychiatric emergency resources that may be available to him or her. Finally, in the case of moderate SI or HI, study staff will review the assessment with a senior staff member in order to ensure that follow-up has been adequate. The senior staff member will complete a safety plan for suicide risk. Finally, the study PI will be on call at all times to receive calls from participants regarding any adverse events; participants will be provided with 24-hour emergency phone numbers.

Potential Benefits of the Proposed Research to the Subject and Others

While participants may benefit from reducing cannabis use, there are no guaranteed benefits to the individual participant and no immediate benefits of the proposed research to others. There are potential benefits to others from the information generated that potentially will be helpful in understanding the impact of reduced cannabis use on the psychosocial functioning among Veterans with posttraumatic stress disorder.

Data and Safety Monitoring Plan

Reducing cannabis use should enhance, rather than jeopardize, health status, and study-related serious adverse events (SAE) for participants in this project are not expected. The individuals responsible for data and safety monitoring will be Dr. Beckham, Dr. Kimbrel, and the clinical research coordinator. There will be several ongoing mechanisms for monitoring and reporting of adverse events (AEs): 1) ongoing participant contact via study personnel; 2) a telephone

number provided to participants to report concerns related to study participation; 3) weekly meetings between the PIs and study personnel. The PIs will meet at least weekly with study personnel to discuss participants' reactions to the intervention, delivery of the intervention, and any adverse events or unanticipated problems. Safety monitoring for adverse events will be conducted in real time by the PIs and/or research coordinator. The following information about adverse events will be collected: 1) the onset and resolution of the AE, 2) an assessment of the severity or intensity (use existing grading scales whenever possible), 3) an assessment of the relationship of the event to the study (definitely, probably, possibly or not related), and 4) action taken (e.g., none, referral to physician, start or increase concomitant medication). The PIs will determine the severity of the event, will assign attribution to the event, and will monitor the event until its resolution. Any adverse events will be reported to the DVAHCS IRB (or DUMC IRB where relevant) in accordance with their Human Research Protection Program's Standards of Practice.

ClinicalTrials.gov Requirements

The proposed clinical trial will be registered with clinicaltrials.gov as recommended by NIH.

STATISTICAL ANALYSES

General Considerations

Multilevel modeling (MLM) will be used to analyze the EMA data. Unlike repeated-measures ANOVA, MLM can also incorporate time-varying (Level-1) and time-invariant (Level-2) predictors. MLM can also accommodate imbalanced data and unequal variances. In the case of drugged driving, generalized linear MLM will be used. As proposed, drugged driving will be examined as a count distribution; however, if the variance is minimal, it will be explored as a binary outcome using logistic MLM. If count modeling is used, the appropriateness of Poisson vs. negative binomial modeling will be examined via log-likelihood testing, and the potential for zero-inflation modeling will be examined via comparison of Aikake Information Criteria (AIC) values. In-person baseline and 8-week data will also be used to test study hypotheses using validated clinical measures. For Aims 1, 2, and 3, this will entail ordinary least squares regression. Distributional assumptions will be examined using residuals, and comparison of AIC. The main conclusions drawn from this study will be based on the pre-specified hypotheses, which will be tested with two-sided statistical tests at an alpha of .05. Analyses will be performed with SAS for Windows (Version 9: SAS Institute, Cary, NC). To manage the problem of random positive findings when making multiple comparisons within each aim (i.e., random significant findings occurring due to multiple analyses), we will correct alpha using Glickman's (Glickman, Rao, & Schultz, 2014) false discovery rate approach. This methodology differentiates random findings from hypothesis-driven outcomes and is more powerful than Bonferroni-type alpha adjustments that control the false-positive rate (Glickman, Rao, & Schultz, 2014). Alpha correction will be applied to Aims 1 and 2, but not to Aim 3, which is exploratory, given that any exploratory hypotheses supported by project findings will necessarily require validation with further research.

Electronic Diary Adherence and EMA Data Reduction

During EMA data collection, we will calculate the percentage of responses recorded within 5 minutes of the random prompts. We will exclude responses delayed by longer than 5 minutes from the analyses. We will also test for cyclicity in psychiatric symptoms and cannabis use to determine if temporal patterns in these variables are evident and should be controlled in the analyses. Daily data corresponding to the total number of days cannabis was used, the total amount of grams consumed, and total THC load will be derived from random prompts and self-initiated entries collected multiple times per day as well as evening entries collected once a day. Otherwise, diary data corresponding to levels of functioning, quality of life, psychiatric distress, etc. will not be aggregated. We will calculate week-by-week cannabis consumption (total number of days used, total number of grams consumed, total THC load), aggregating baseline weeks together, to examine the weekly effects of reduced cannabis use. We will also calculate the percentage reduction (or increase) in cannabis use from the baseline weeks as an alternative means to examine how reductions in cannabis use may be associated with functional improvements.

Missing Data

Although we do not anticipate much missing baseline data, we do anticipate missing values in the EMA data. MLM procedures, which will be used to analyze each of the hypotheses, are based on maximum likelihood estimation and use all available data. As such, MLM can accommodate data missing at random. Given this, we expect to retain all enrolled

participants for the analysis of EMA data; however, we have derived power estimates that account for attrition using the conservative estimate that we will have available, on average, just two of the four potential daily observations. For non-EMA data, missing 8-week data will be examined to determine whether missingness is random or systematically associated with baseline variables. Multiple imputation will be used to impute missing 8-week data, and sensitivity analyses will be conducted comparing analysis of complete data only with those conducted on imputed data.

Hypothesis Testing

To examine the association between frequency of cannabis use and the continuous functional outcomes of interest among Veterans with PTSD (H_{1A}), four models will be analyzed in which each of the continuous outcome variables recorded during EMA (i.e., functioning, quality of life, psychiatric distress, and drugged driving) will be modeled *via* MLM during the 2-week ad lib period as a function of frequency of cannabis use (CUD will not be included in these analyses because it will not be assessed via EMA). In each model, cannabis use will be operationalized as a continuous Level-2 variable capturing the proportion of days in which cannabis was used. Daily consumption (total equivalent number of grams consumed and total THC load; Level 1) will be examined as a potential covariate in both models to disentangle the immediate effects of cannabis use from longer terms effects. Potential non-linear associations of cannabis use with outcomes will be examined via quadratic and exponential effects, using AIC to select the best-fitting function. To examine the association of cannabis use with functional outcomes and quality of life using validated clinical outcomes, TLFB data will be used to generate an index of cannabis use frequency equivalent to the proportion of days in which cannabis was used. These in turn will be used to model clinical assessments of functional outcomes via regression. Potential quadratic or exponential effects of cannabis use on these outcomes will be examined. To examine the effect of reduced cannabis use on functioning (H_{2A}), day-by-day outcome variables assessed using EMA will be modeled in four independent analyses, one for each outcome evaluated via EMA (functioning, quality of life, psychiatric distress, drugged driving), via MLM as a function of the 8 weekly assessments of cannabis consumption (Level 1). As in the Aim 1 model, daily consumption (Level 1) will be examined as a potential covariate. Non-linear (i.e., quadratic or exponential) effects of cannabis use will also be examined. Random effects will be considered given the potential for significant between-person variance in the effect of reduced cannabis use on outcomes. We hypothesize that reductions in cannabis use will be associated with improved functioning, better quality of life, decreased psychiatric distress, and less drugged driving. We will also conduct a complementary analysis using TLFB data and clinical assessments collected at baseline and 8-weeks for all five outcomes. Specifically, using the proportion of days of cannabis used tabulated at each time point, we will calculate the proportion reduction (or increase) in cannabis consumption by dividing the difference between baseline and 8-week follow-up cannabis use by baseline cannabis use. We will also calculate difference scores for each of the five outcome variables by subtracting baseline levels from 8-week follow-up levels. These difference scores will then be regressed in five separate models on the proportion change in cannabis use, covarying for baseline cannabis use and baseline outcome level. Potential non-linear effects of proportion change in cannabis use will be examined, as described above. Exploratory hypotheses H_{3A} and H_{3B} will be tested using identical methods, but will instead focus on the following secondary outcomes: working memory, executive functioning, community reintegration, and suicidal ideation.

Power Calculations

Given that the EMA data will feature multiple observations per person, statistical power will be greater, depending on the total effective sample size (ESS), or the number of statistically independent observations available. ESS is the total number of observations (# of participants x # of data collections), adjusted for the intra-class correlation (ICC). Using data from two prior trials (Dedert, Dennis, Calhoun, Dennis & Beckham, in press; Dennis et al., 2016) in which 126 smokers with PTSD (44% with lifetime drug dependence) provided EMA readings for a mean of 8.14 days while *ad lib* smoking, we calculated an ICC of .61 for PTSD symptom severity recorded during those readings, meaning that 61% of the variance in PTSD symptom severity was attributable to between-person differences and 39% to intraindividual variability. Applying this estimate of ICC, given 120 participants completing 14 days of diary entries twice per day, we will have an ESS of 192, which will have 80% power to detect βs of .20 and .22 in two separate regression analyses with two covariates each using the alpha-correction procedure. For reference, in a sample of over 900 Veterans with PTSD, we found that CUD was associated with more severe PTSD symptoms (Cohen's d=0.43), anxiety (Cohen's d=0.45), and hostility (Cohen's d=0.63; all ps<.05). For the Aim 1 analyses that will utilize the clinical data, the statistical power to detect an association of cannabis use with the clinical outcomes will be 80% for a medium-sized effect (β=.25). Using the aforementioned alpha-correction procedure, which is applied only to subsequent outcomes, the second analysis will

have 80% power to detect an effect equivalent to β=.28, and so on. For Aim 2, which will examine the within-person relationship of cannabis use reduction with changes in functioning, symptoms, and behaviors, if we assume 15% attrition for the 8-week clinical assessments, we will have 80% power to detect a β of .28 for the first outcome using multiple regression with two covariates. Using the alpha-correction procedure for the remaining outcomes, there will be 80% power to detect βs of .29, .30, and so on. By contrast, because Aim 2 EMA data will be analyzed using MLM to detect Level-1 effects, the ESS will be roughly equivalent to the total number of observations: 3,360 (40 Veterans x 42 days x 2 EMA entries per day). Thus, these analyses will have 80% power to detect βs ranging from .04 to .05 across the five models. Aim 3 analyses, which will be identical to Aim 2 analyses, will have the same power for each outcome, without adjustments for multiple comparisons.

PRIVACY, CONFIDENTIALITY, AND INFORMATION SECURITY

1. Lists of Data Reviewed and/or Collected for Screening/Recruitment and Conduction of Study:

The Personal Health Information that will be obtained, used, and/or shared for this study includes:

Identifier(s)	Source(s) of Health Information
☒ Names	☐ Medical history & physical exam information
☒ All geographic subdivisions smaller than a State, including street address, city, county, precinct, and zip code. Describe: Participants' addresses will be collected 1) to allow for study correspondence to be mailed if necessary, and 2) so that payment can be mailed to them, if necessary.	☒ Photographs, videotapes, audiotapes, or digital or other images
☒ All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, visit or treatment dates, etc.; and all ages over 89 Describe: Dates of participation and study procedures will be collected.	☒ Biologic specimens (e.g., blood, tissue, urine, saliva). Describe: We will use salivary test kits to test for evidence of marijuana use. Urine and saliva samples will be sent to MCI Diagnostic Center, LLCfor additional analyses.
☒ Telephone numbers	☒ Progress notes
☐ Fax numbers	☒ Diagnostic / Laboratory test results
☒ Electronic mail addresses	☐ Operative reports
☒ Social Security Numbers	☐ Imaging (x-ray, CT, MRI, etc.)
☒ Medical record numbers	☐ Discharge summaries
☐ Health plan beneficiary numbers	☒ Survey / Questionnaire responses
☒ Account numbers	☒ Billing records
☐ Certificate and/or license numbers	☐ HIV testing or infection records
☐ Vehicle identifiers and serial numbers, including license plate numbers	☐ Sickle cell anemia information
☐ Device identifiers and serial numbers	☒ Alcoholism or alcohol use information
☐ Web Universal Resource Locators (URLs)	☒ Drug abuse information
☐ Internet Protocol (IP) address numbers	☒ Mental health (not psychotherapy) notes
☐ Biometric identifiers, including finger & voice prints	☐ Psychological test results
☐ Full-face photographic images and any comparable images	☐ Genetic testing
☐ Any other unique identifying number, linked study ID, characteristic, or code, describe:	☐ Other, describe:

2. Data and/or Specimen Acquisition:

Data for this study will be collected through (*check all that apply*):

☒ Prospective data and/or specimen collection obtained from participants. Provide description of processes: Data will be obtained through self-report questionnaires, semi-structured interviews, and app utilization.

☒ Retrospective data collection and/or specimens obtained from medical chart review/data access. Describe how data will be obtained (e.g., fileman, CDW, etc.): In accordance with a Waiver or Alteration of HIPAA Authorization, names, addresses, telephone numbers, social security numbers, and diagnostic information of potential participants will be obtained from the VA's Regional Data Warehouse.

☐ Retrospective data collection and/or specimens obtained from an IRB-approved data and/or specimen repository. Indicate the repository source including name, VA location, and IRB number: .

Note: for data and/or specimens obtained from a VA approved data repository, a Data Use Agreement (DUA) must be executed prior to obtaining data and/or specimens. See VHA Handbook 1200.12 for further information.

3. Level of Data:

The following level(s) of data will be acquired/maintained for this study (*check all that apply*):

☒ Identified (e.g., names, addresses or other identifiers included)

☒ Coded (direct and/or all identifiers removed, but study code/ID included)

☒ De-Identified (all HIPAA 18 and study ID/code removed):

- ☐ Verified Statistically

  OR

- ☒ Verified by Absence or Removal of HIPAA 18 and study ID

☐ Limited Data Set

☐ Other: Describe:

4. Location of Data and/or Specimens, and Data Retention Plan:

A. Data and/or Specimen Location: Data will be stored electronically in \\VHADURFPC02B\groups1\Nicotine Research\Study Information\Study Logbooks\FOCUS Merit Review and \\VHADURFPC02B\groups1\Nicotine Research\Study Information\Study Databases\FOCUS Merit Review. Data that will be stored electronically include name, address, phone number, social security number, amount of study payment earned, and date of visits (in Study Logbooks location). The study logbook will contain the key connecting PHI and the study identification number. Paper records of data include study consent form and HIPAA authorization (identified), questionnaire responses, and interview notes (coded). Data will be transferred via a VA-owned FIPS-encrypted thumbdrive or via VA's S.A.F.E. Data will also be stored within VA Qualtrics, which is FedRAMP approved for collection and storage of PHI and sensitive information, and has an Authority to Operate (ATO) within VA. Data will be moved from Qualtrics \\VHADURFPC02B\groups1\Nicotine Research\Study Information\Study Databases\FOCUS Merit Review for permanent storage. Urine and saliva specimens will be collected and stored temporarily in a specimen refrigerator at the MIRECC space at 3022 Croasdaile Drive, Durham, NC. Specimens will be picked up by MCI Diagnostic Center, LLC. for urinary creatinine normalization analyses and salivary mass spectrometry analyses. Specimen cups and vials will be coded, and no staff at MCI Diagnostic Center, LLC will have access to the key connecting the coded ID with other identifying information. Audio-recordings of the qualitative interview made using Audacity, VA's WebEx, or voice recorder will be transferred to \\VHADURFPC02B\groups1\Nicotine Research\Study Information\Study Logbooks\FOCUS Merit Review for storage.

☒ Data will be also be placed at the VA Informatics and Computing Interface (VINCI; http://vaww.vinci.med.va.gov/vincicentral/VINCIWorkspace.aspx). The VA Informatics and Computing Infrastructure is a partnership between the VA Office of Information Technology and the Veterans' Health Administration Office of Research and Development. Researchers and operations staff can use VINCI to access data and statistical analysis tools in a virtual working environment through a certified VHA network computer using the VA Intranet or Virtual Private Network (VPN).

B. Data Retention Plan

☒ Research records will be maintained and destroyed according to the National Archives and Records Administration, Records Schedule Number: DAA-0015-2015-0004. Records destruction, when authorized, will be accomplished using the then current requirements for the secure disposal of paper and electronic records. Currently, destruction of research records (see DAA-0015-2015-0004, section 7.6 "Research Investigator Files" for materials included in research records) is scheduled for 6 years after the cut-off (the cut-off is the completion of the research project) and may be retained longer if required by other federal agencies. Records will not be destroyed without pre-notification to the facility records manager.

☐ Other data retention plan, describe:

5. Data Access and Data Recipients: Only members of our DVAMC research team will have access to identifiers and coded data. A dataset will be uploaded to VINCI for analysis using VA-owned data analysis software. In the event that the SAS modules necessary for data analyses are not available via VINCI, the team may move a deidentified dataset to Duke for further analyses. Data will be stored at Duke on a protected server to which only Dr. Beckham and her study staff have access; data are encrypted at rest. In addition, deidentified data shared with Duke may be combined with data from another cannabis reduction research project being run there. VA participants will provide express consent for data to be combined with data at Duke with a checkbox embedded in the informed consent form.

A deidentified dataset may be sent to any collaborators listed herein (see "Data Sharing" above). The deidentified dataset will be emailed to them.

All VA research personnel who have access to VHA records are instructed, in accordance with VA policy, on the requirements of Federal privacy and information laws and regulations, VA regulations and policies, and VHA policy. All study personnel who are VA employees working within the VA system have fulfilled all required HIPAA and other VA security and privacy policy training requirements and have agreed to follow guidelines pertaining to the protection of patient data. All research staff sign VA Rules of Behavior, and all study staff are up-to-date with VHA Privacy Policy Training and the VA Office of Cyber and Information Security Awareness Training Course. The data security and privacy procedures summarized in that course include logging off or locking the computer when walking away from it; no sharing of access codes, verify codes or passwords; not allowing anyone else to use the computer under one's password; and disposing of sensitive information using VA-approved methods (e.g., shredder bins). Access to study data will be removed for all study personnel when they are no longer part of the research team.

Study visits will either be conducted at the main VA Hospital or at the MIRECC at Croasdaile, based on participant preference and space availability. Data that is transported between the main hospital and Croasdaile offices will be secured in a lockable briefcase.

Access to study data will be removed for all study personnel when they are no longer part of the research team.

6. Data and/or Specimen Transportation and/or Transmission for all data and/or specimens involved in the study:

I. ☐ Data and/or specimens will <u>not</u> be transported or transmitted outside of Durham VAMC environment.

II. ☒ Data and/or specimens will be transported BETWEEN sites that are under the auspices of the Durham VA Medical Center.

III. ☐ Data and/or specimens will be transmitted to <u>other VA sites</u> using the following method(s):

A. Data

☐ Data are de-identified and thus will be sent via unencrypted e-mail or unencrypted disk (encryption is optional).

☐ Data are coded or contain identifiers and thus will be sent

☐ Other, describe:

B. Specimens

☐ Specimens are de-identified and thus will be sent via standard carrier (tracking is optional).

☐ Specimens are coded or contain identifiers and thus will be sent via VA-authorized carrier with tracking.

☐ Other, describe:

IV. ☒ Data and/or specimens will be transported to <u>non-VA/VHA sites (e.g., academic affiliates, laboratories, etc.)</u> using the following method(s):

A. Data

☒ Data are de-identified and thus will be sent via unencrypted e-mail or unencrypted CD.

☐ Data are coded or contain identifiers and thus will be sent via <chose method of transfer such as FIPS 140-2 encrypted CD or FIPS 140-2 encrypted hard drive/flash drive> using VA—approved carrier with tracking.

☐ Data are coded or identified and will be uploaded to sponsor website using electronic case report form (eCRF) <insert information including sponsor name and URL and the encryption the site uses.>

☐ Other, describe:

B. Specimens

☐ Specimens are de-identified and thus will be sent via standard carrier (tracking is optional) or will be hand-delivered by research study personnel. Specify method of delivery:

☒ Specimens are coded and thus will be sent via VA-approved carrier with tracking or will be hand-delivered by research study personnel. Specify method of delivery: MCI Diagnostic Center, LLCwill pick up the specimens directly from our lab location, and coded specimens will be sent to the Texas lab for analyses

In accordance with the HIPAA and the Privacy Act, for any coded or identifiable data or specimens released from the Durham VAMC (with the exception of Limited Data Sets), an Accounting of Disclosure (AOD) will be maintained (e.g., in a database or spreadsheet) that includes the participant's name, date of the disclosure, description of the nature of the Individually Identifiable Information (III) disclosed, purpose of each disclosure, and the name and address of the person/agency to whom the disclosure was made.

C. ☒ Local DVAMC memorandum "Authorization to Use, Process, Store, or Transmit VA Sensitive Information Outside VA Owned or Managed Facilities" has been pre-filled out for each study team member who may transport the data and/or specimens off-site. This (these) forms are included with the IRB materials.

D. ☒ Containers (e.g., briefcase, bin) are labeled with the following notice (label placed on the outside of container) in accordance with VHA Directive 6609:

NOTICE!!!
Access to these records is limited to: AUTHORIZED PERSONS ONLY.
Information may not be disclosed from this file unless permitted by all applicable legal authorities, which may include the Privacy Act; 38 U.S.C. §§ 5701, 5705, 7332; the Health Insurance Portability and Accountability Act; and regulations implementing those provisions, at 38 C.F.R. §§ 1.460 – 1.599 and 45 C.F.R. Parts 160 and 164. Anyone who discloses information in violation of the above provisions may subject to civil and criminal penalties.

7. Risk Mitigation Strategies:

☒ Data are fully de-identified (stripped of HIPAA 18 and study ID/code) before being shared outside of Durham VAMC.

☐ Specimens are fully de-identified (stripped of HIPAA 18 and study ID/code before being shared outside of Durham VAMC.

☒ Direct identifiers will be maintained separately from data and or specimens by using a code to "identify" subjects. In a separate database (i.e., a "linking" or "cross-walk" database) this code will be linked to identifying subject information.

☐ Other, specify:

8. Suspected Loss of VA Information:

Should any incident such as theft or loss of data, unauthorized access of sensitive data or non-compliance with security controls occur it will be immediately reported according to VA policy. All incidents regarding information security/privacy incidents will be reported to the ISO and PO within 1 hour of acknowledgement of issue and done so using the VHADUR Research Events Report e-mail group (VHADURResearchEventReport@va.gov).

9. Reporting of Results:

☒ Reporting of results, such as in scientific papers and presentations, will never identify individual subjects. Data will be presented in aggregate and individual-level data will not be published.

☐ Other results reporting plan, describe:

10. Future Use of Data:

☒ Data will be retained for future use. This is described elsewhere in the protocol and is noted in the HIPAA authorization.

☒ Future Use of data is optional (i.e., not required by the research subject).

☐ Future Use of data is required for participation in the study.

☐ No future use of data is currently planned.

11. Use of Mail Merge Technology

☒ Mail merge programs will be used to generate letters and/or address labels for mailings to potential or already enrolled research subjects. The study team is aware that to reduce risk of mail merge related privacy incidents, use of mail merge programs requires a 25% accuracy check to verify that (potential) research subject name and mailing address are properly "matched". If discrepancies are found, a 100% accuracy check is required before letters may be mailed.

12. Use of Non-Standard Software13-16

☐ I do NOT intend to use any new specialized software (i.e. Software that's not already approved OR installed) in this study.

☒ I intend to use specialized software that has not already been installed and it has been approved for use by the VA Technical Reference Model (TRM) Group.
(Note: All new software must be approved by TRM before it can be installed on VA systems.) Note: We will be using Inquisit Lab software to administer impulsivity tasks. Inquisit Lab is approved by TRM. Software will be loaded onto a VA computer. The participant will complete the impulsivity tasks on the VA computer while the study coordinator is in the room with them. The study coordinator will not leave the participant alone at the computer at any time during the session.

☐ I intend to use previously installed software on my VA computer.

13. Use of Cloud Computing Services

☐ Cloud computing services will NOT be used in this study.

☒ Cloud computing services WILL be used in this study as described below and have been approved nationally by the VA Chief Information Officer (CIO). (Note: ONLY cloud computing services that have been approved nationally may be used.)

REFERENCES

Adkisson, K., Cunningham, K.C., **Dedert, E.A.,** Dennis, M.F., **Calhoun, P.S**., Elbogen, E.B., **Beckham, J.C.,** & **Kimbrel, N.A.** (in press). Cannabis use and post-deployment suicide attempts in Iraq/Afghanistan-era veterans. *Archives of Suicide Research.* PMID: 29952737

Allsop, D.J., Norberg, M.M., Copeland, J., Fu, S., & Budney, A.J. (2011). The Cannabis Withdrawal Scale development: Patterns and predictors of cannabis withdrawal and distress. *Drug and Alcohol Dependence*, *119*, 123-9.

Babor, T.F., de la Fuente, J.R., et al. (1989). *AUDIT The Alcohol Use Disorders Identification Test: Guidelines for use in primary health care* (WHO/MNH/DAT 89.4). Geneva, Switzerland.

Bechara, A., Damasio, A.R... Anderson, S.W., 1994. Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition*, 50, 7-15.

Beck AT, Steer RA. (1991). Manual for Beck Scale for Suicide Ideation. Psychological Corp: San Antonio.

Bedard-Gilligan, M., Garcia, N., Zoellner, L.A. & Feeny, N.C. (2018). Alcohol, cannabis, and other drug use: Engagement and outcome in PTSD treatment. *Psychology of Addictive Behaviors*, 32, 277-88.

Benjamini, Y. (2010). Discovering the false discovery rate. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 72, 405-16.

Blevins, C. A., Weathers, F. W., Davis, M. T., Witte, T. K., & Domino, J. L. (2015). The Posttraumatic Stress Disorder Checklist for *DSM-5* (PCL-5): Development and initial psychometric evaluation. *Journal of Traumatic Stress*, *28*, 489-498. doi: 10.1002/jts.22059

Boden, M.T., Babson, K.A., Vujanovic, A.A., Short, N.A. & Bonn-Miller, M.O. (2013). Posttraumatic stress disorder and cannabis use characteristics among military veterans with cannabis dependence. *The American Journal on Addictions*, 22, 277-84.

Bonn-Miller, M.O., Boden, M.T., Bucossi, M.M. & Babson, K.A. (2014). Self-reported cannabis use characteristics, patterns and helpfulness among medical cannabis users. *American Journal of Drug & Alcohol Abuse*, 40, 23-30.

Bonn-Miller, M.O., Harris, A.H.S. & Trafton, J.A. (2012). Prevalence of cannabis use disorder diagnoses among veterans in 2002, 2008, and 2009. *Psychological Services*, *9*, 404-16.

Bonn-Miller, M.O., & Rousseau, G.S. (2018). Marijuana use and PTSD among Veterans. https://www.ptsd.va.gov/professional/treat/cooccurring/marijuana_ptsd_vets.asp.

Bonnet, U., Borda, T., Scherbaum, N. & Specka, M. (2015). Abstinence phenomena of chronic cannabis-addicts prospectively monitored during controlled inpatient detoxification (Part II): Psychiatric complaints and their relation to delta-9-tetrahydrocannabinol and its metabolites in serum. *Drug and Alcohol Dependence*, 155, 302-6.

Booth, M.L., 2000. Assessment of Physical Activity: An International Perspective. *Research Quarterly for Exercise and Sport*, *71*, s114-20.

Brondolo, E., Kelly, K.P., Coakley, V., Gordon, T., Thompson, S., Levy, E. & Contrada, R.J. (2005). The Perceived Ethnic Discrimination Questionnaire: Development and preliminary validation of a community version 1. *Journal of Applied Social Psychology*, 35, 335-65.

Bruins, J., Pijnenborg, M.G., Bartels-Velthuis, A.A., Visser, E., van den Heuvel, E.R., Bruggeman, R. & Jorg, F. (2016). Cannabis use in people with severe mental illness: The association with physical and mental health--a cohort study. A Pharmacotherapy Monitoring and Outcome Survey study. *Journal of Psychopharmacology*, 30, 354-62.

Burckhardt, C.S., & Anderson, K.L. (2003). The Quality of Life Scale: Reliability, validity, and utilization. *Health Qual Life Outcomes*, *1*, 60.

Carpenter VL, **Hertzberg JS**… **Beckham, J.C.** (2015). Multicomponent smoking cessation treatment including mobile contingency management for smoking cessation in homeless veteran smokers. *Journal of Clinical Psychiatry*, 76, 959-964. PMCID: PMC4522209.

Chung, F., Subramanyam, R., Liao, P., Sasaki, E., Shapiro, C., & Sun, Y. (2012). High STOP-Bang score indicates a high probability of obstructive sleep apnoea. *British Journal of Anaesthesia*, *108*, 768-775.

Compton, W.M., Gfroerer, J…Finger, M.S. (2014). Unemployment and substance abuse outcomes in the United States 2002-2010. *Drug and Alcohol Dependence*, *142*, 350-353.

Copeland, J., Gilmour, S., Gates, P., & Swift, W. (2005). The Cannabis Problems Questionnaire: Factor structure, reliability, and validity. *Drug and Alcohol Dependence*, *80*, 313-319.

Corrigan, J.D., Bogner, J.A. (2007). Initial reliability and validity of the OSU TBI Identification Method. J Head Trauma Rehabil, 22(6):318-329.

Cougle, J.R., Bonn-Miller, M.O., Vujanovic, A.A., Zvolensky, M.J. & Hawkins, K.A. (2011). Posttraumatic stress disorder and cannabis use in a nationally representative sample. *Psychology of Addictive Behaviors*, 25, 554-8.

Davis, A.K., Osborn, L.A…Baik, K.D., 2014. Development and evaluation of the Marijuana Reduction Strategies Self-Efficacy Scale. *Psychology of Addictive Behaviors*, *28*, 575-579.

Dedert, E.A., Dennis, P.A., Calhoun, P.S., Dennis, M.F. & **Beckham, J.C.** (in press). A randomized clinical trial of nicotine preloading for smoking cessation in people with posttraumatic stress disorder. *Journal of Dual Diagnosis*.

Dennis, P.A., Kimbrel, N.A., Dedert, E.A., Beckham, J.C., Dennis, M.F. & **Calhoun, P.S.** (2016). Supplemental nicotine preloading for smoking cessation in posttraumatic stress disorder: Results from a randomized controlled trial. *Addictive behaviors*, 59, 24-9.

Derogatis, L.R. (1983). SCL-90: *Administration, Scoring and Procedures Manual-I for the Revised Version and other Instruments of the Psychopathology Rating Scale Series*. Baltimore, MD: Johns Hopkins University School of Medicine, Clinical Psychometrics Research Unit.

Fergusson, D.M., Horwood, L.J., Beautrais, A.L. (2003). Cannabis and educational achievement. *Addiction*, *98*, 1681-1692.

Festinger, D.S., Marlowe, D.B., Dugosh, K.L, Croft, J.R., & Arabia, P.L. (2008). Higher magnitude cash payments improve research follow-up rates without increasing drug use or perceived coercion. Drug and Alcohol Dependence, 96, 128-135.

First et al. (2015). Structured Clinical Interview for DSM-5—Research Version. Arlington, VA: APA.

Fulton, J.J., **Calhoun, P.S.,** Wagner, H.R., Schry, A.R., Hair, L.P., Feeling, N., Elbogen, E. & **Beckham, J.C.** (2015). The prevalence of posttraumatic stress disorder in Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) veterans: A meta-analysis. *Journal of Anxiety Disorders*, 31, 98-107.

Gamez, W., Chmielewski, M., Kotov, R., Ruggero, C., Suzuki, N., & Watson, D. (2014). The Brief Experiential Avoidance Questionnaire: Development and initial validation. *Psychological Assessment*, *26(1)*, 35-45.

Gentes, E.L., Schry, A.R., Hicks, T.A., Clancy, C.P., Collie, C.F., Kirby, A.C., Dennis, M.F., **Hertzberg, M.A., Beckham, J.C.** & **Calhoun, P.S.** (2016). Prevalence and correlates of cannabis use in an outpatient VA posttraumatic stress disorder clinic. *Psychology of Addictive Behaviors*, 30, 415-21. PMCID: PMC5029083.

Glickman, M.E., Rao, S.R. & Schultz, M.R. (2014). False discovery rate control is a recommended alternative to Bonferroni-type adjustments in health studies. *Journal of Clinical Epidemiology*, 67, 850-57.

Godin, G. (2011). The Godin-Shephard leisure-time physical activity questionnaire. Health & Fitness *Journal of Canada*, *4*(1), 18-22.

Goldenberg, M., IsHak, W.W., Danovitch, I. (2017). Quality of life and recreational cannabis use. *American Journal on Addictions*, *26*, 8-25.

Gratz, K L., 2001. Measurement of deliberate self-harm: Preliminary data on the Deliberate Self-Harm Inventory. *Journal of Psychopathology & Behavioral Assessment*, *23*(4), 253-263.

Hall, W., Degenhardt, L. (2009). Adverse health effects of non-medical cannabis use. *Lancet*, *374*, 1383-1391.

Hamilton et al., 2011. The PhenX toolkit: Get the most from your measures. *Am J Epidem*, *174*, 253-260.

Hartman, R.L., Huestis, M.A. (2013). Cannabis effects on driving skills. *Clin Chem*, *59*, 478-492.

Heatherton, T.F., Kozlowski, L.T., Frecker, R.C. & Fagerström, K.O. (1991). The Fagerström Test for Nicotine Dependence: A revision of the Fagerström Tolerance Questionnaire. *British Journal of Addiction*, *86*, 1119-27.

Hertzberg, J.S., Carpenter, V.L...**Beckham, J.C.** (2013). Mobile contingency management as an adjunctive smoking cessation treatment for smokers with posttraumatic stress disorder. *Nicotine & Tobacco Research*, 15, 1934-1938. PMCID: PMC3790624.

Hiller, W., & Goebel, G. (1992). Rapid assessment of tinnitus-related psychological distress using the Mini-TQ. *International Journal of Audiology*, *43*, 600-604.

Jin, L.Z., Rangan, A...Heitmann, B.L. (2017). Association between use of cannabis in adolescence and weight change into midlife. *PLoS One*, *12*, e0168897.

Kelly, E., Darke, S., Ross, J. (2004). A review of drug use and driving: epidemiology, impairment, risk factors and risk perceptions. *Drug and Alcohol Review*, *23*, 319-344.

Khalfa, S., Dubal, S., Veuillet, E., Perez-Diaz, F., Jouvent, R., & Collet, L. (2002). Psychometric normalization of a hyperacusis questionnaire. *ORL*, *64*, 436-442.

Kimbrel, N.A., Calhoun, P.S...& **Beckham, J.C.,** manuscript in preparation. *Impact of cannabis use disorder remission status on mental health outcomes among Veterans with and without PTSD.*

Kimbrel, N.A., Calhoun, P. S... Beckham, J. C. (2014). The factor structure of psychiatric comorbidity among Iraq/Afghanistan veterans and its relationship to violence, incarceration, suicide attempts, and suicidality. *Psychiatry Research*, *220*, 397-403. PMCID: PMC4697758.

Kimbrel, N.A., Meyer, E.C., DeBeer, B.B., Gulliver, S.B., & Morissette, S.B. (2018). The impact of cannabis use disorder on suicidal and nonsuicidal self-injury in Iraq/Afghanistan-era veterans with and without mental health disorders. *Suicide and Life-Threatening Behavior*, *48*, 140-148. PMID: 28295524.

Kimbrel, N.A., Newins, A.R., **Dedert, E.A.,** van Voorhees, E.E., Elbogen, E.B., Naylor, J.C., Wagner, H.R., Brancu, M., Wokgroup, V.M.-A.M., **Beckham, J.C. & Calhoun, P.S.** (2017). Cannabis use disorder and suicide attempts in Iraq/Afghanistan-era veterans. *Journal of Psychiatric Research*, 89, 1-5. PMCID: PMC5374045.

Kleiman, S.E., Bovin, M.J., ... Marx, B.P. (2018). Psychometric properties of a brief measure of posttraumatic stress disorder-related impairment: The Brief Inventory of Psychosocial Functioning. *Psychological Services*. Doi:10.037/ser0000306.

Krebs, E., Lorenz, K., Bair, M., Damush, T,M., Wu, J., Sutherland, J.M., Asch, S.M., & Kroenke, K. (2009). Development and initial validation of the PEG, a three-item scale assessing pain intensity and interference. *Journal of General Internal Medicine*, *24*, 733–8.

Krieger, N., Smith, K., Naishadham, D., Harman, C., & Barbeau, E.M. (2005). Experiences of discrimination: Validity and reliability of a self-report measure for populational health research on racism and health. *Social Science and Medicine*, *61*, 1576-1596.

Kubany, E.S., Haynes, S.N., Leisen, M.B. et al. (2000). Development and preliminary validation of a brief broad-spectrum measure of trauma exposure: The traumatic life events questionnaire. *Psychological Assessment*, *12*, 210-24.

Kulka, R.A., Schlenger, W.E., Fairbank, J.A., Hough, R.L., Jordan, B.K., Marmar, C.R. & Weiss, D.S. (1990). *Trauma and the Vietnam War Generation: Report of Findings from the National Vietnam Veterans Readjustment Study*. New York: Brunner/Mazel.

Lee, C.M., Neighbors, C... Grossbard, J.R., 2009. Development and preliminary validation of a comprehensive marijuana motives questionnaire. *Journal of Studies on Alcohol and Drugs*, 70, 279-287.

Lejuez, C.W., Read, J.P...Brown, R.A., 2002. Evaluation of a behavioral measure of risk taking: The Balloon Analogue Risk Task (BART). *Journal of Experimental Psychology: Applied*, 8, 75-84.

Lynam, D.R, Smith, G.T., et al., 2006. *The UPPS-P: Assessing five personality pathways to impulsive behavior.* West Lafayette, IN: Purdue University.

McCaffrey, D.F., Pacula, R.L...Ellickson, P. (2010). Marijuana use and high school dropout: The influence of the unobservables. *Health Economics*, *19*, 1281-1299.

McColl, M.A et al. (2001). The Community Integration Measure: Development and preliminary validation. *Archives of Physical Medicine and Rehabilitation*, *82*, 429-434.

Metrik, J., Bassett, s., Aston, E.R., Jackson, K.M., & Borsari, B. (2018). Medicinal versus recreational cannabis use among returning veterans. *Translational Issues in Psychological Science*, *4*, 6-20.

Millum, J. & Garnett, M., (2019). How payment for research participation can be coercive. The American Journal of Bioethics, 19, 21-31, DOI: 10.1080/15265161.2019.1630497

Morin, C.M., Belleville, G., Belanger, L., & Ivers, H. (2011). The Insomnia Severity Index: Psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep*, *34*, 601-608.

National Institute on Drug Abuse. (2016). Drug facts: Drugged driving. [Internet]. Retrieved 2/11/17. https://www.drugabuse.gov/publications/drugfacts/drugged-driving

Novaco, R. W., Swanson, R. D., Gonzalez, O. I., Gahm, G. A., & Reger, M. D. (2012). Anger and postcombat mental health: validation of a brief anger measure with U.S. soldiers postdeployed from Iraq and Afghanistan. *Psychological Assessment*, *24*(3), 661-675. doi:10.1037/a0026636

Pate, R.R., Heath, G.W...Trost, S.G. (1996). Associations between physical activity and other health behaviors in a representative sample of U.S. adolescents. *American Journal of Public Health*, *86*, 1577-1581.

Pearson, M.R., Bravo, A.J., Conner, B.T., & Marijuana Outcomes Study Team. (2017). Distinguishing subpopulations of marijuana users with latent profile analysis. *Drug Alcohol Depend*, *172*, 1-8.

Posner, K., Brown, G.K., Stanley, B., et al. (2011). The Columbia-Suicide Severity Rating Scale: Initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry*, *168*, 1266-1277.

Ramaekers, J.G., Berghaus, G...Drummer, O.H., 2004. Dose related risk of motor vehicle crashes after cannabis use. *Drug Alcohol Depend*, *73*, 109-119.

Richards, J.B., Zhang, L., Mitchell, S.H., De Wit, H., 1999. Delay or probability discounting in a model of impulsive behavior: Effect of alcohol. *Journal of the Experimental Analysis of Behavior*, 71, 121-143.

Robinson, S.M., Sobell, L.C., Sobell, M.B., Leo, G.I. (2014). Reliability of the Timeline Followback for Cocaine, Cannabis, and Cigarette Use. *Psychol Addict Behav*, *28*, 154-162.

Roth, R.M., Isquith, P.K., & Gioia, G.A. (2005). *Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A)*. Lutz, FL: Psychological Assessment Resources.

Schreiner, A.M. & Dunn, M.E. (2012). Residual effects of cannabis on neurocognitive performance after prolonged abstinence: a meta-analysis. *Experimental and Clinical Psychopharmacology*, 20, 420-29.

Shalev, A., Liberzon, I. & Marmar, C. (2017). Post-traumatic stress disorder. *New England Journal of Medicine*, 376, 2459-69.

Searle, S.R. & McCulloch, C.E. (1992). *Variance Components. Wiley Series in Probability and Statistics.* . New York: John Wiley & Sons Inc.

Sheehan, D.V., 1983. *The anxiety disease*. Charles Scribner and Sons.

Sheehan, D.V., Harnett-Sheehan, K, & Raj, B.A. (1996). The measurement of disability. *International Clinical Psychopharmacology*, *Suppl 3*, 89-95.

Simes, R.J. (1986). An improved Bonferroni procedure for multiple tests of significance. *Biometrika*, 73, 751-54.

Slavet, J.D., Stein, L.A.R., Colby, S.M., Barnett, N.P., Monti, P.M., Golembeske, C., & Lebeau-Craven, R. (2006). The Marijuana Ladder: Measuring motivation to change marijuana use in incarcerated adolescents. *Drug and Alcohol Dependence*, *83*, 42-48.

Steenkamp, M.M., Blessing, E.M., Galatzer-Levy, I.R... Anderson, W.T. (2017). Marijuana and other cannabinoids as a treatment for posttraumatic stress disorder: A literature review. *Depression and Anxiety*, *34*, 207-221.

Stephens, R.S., Roffman, R.A., Curtin, L., 2000. Comparison of extended versus brief treatments for marijuana use. *Journal of Consulting & Clinical Psychology*, 68, 898-908.

Straus, M., Hamby, S.L., Boney-McCoy, S., & Sugarman, D. (1996). The Revised Conflict Tactics Scales (CTS2): Development and preliminary psychometric data. *Journal of Family Issues*, *17*, 286-316.

Stroop, J.R. (1935). Studies of interference in serial verbal reactions. *J Exp. Psychology*, *18*, 643-662.

The WHOQOL Group. (1994).The development of the World Health Organization quality of Life Assessment instrument (the WHOQOL),"in *Quality of Life Assessment: International Perspectives*, eds J. Orley and W. Kuyken (Heidelberg: Springer).

Tombaugh, T.N. (2004). Trail Making Test A and B: Normative data stratified by age and education. *Archives of Clinical Neuropsychology*, *19*, 203-214.

Ustun, T.B., Kostanjesek, N, Chatterji, S, Rehm, J & World Health Organization. (2010). Measuring health and disability : Manual for WHO Disability Assessment Schedule (WHODAS 2.0)

Volkow, N.D., Baler, R.D... Weiss, S.R.B. (2014). Adverse health effects of marijuana use. *New England Journal of Medicine*, *370*, 2219-2227.

Watson, D., Clark, L.A., & Tellegen, A. (1988). Development of brief measures of positive and negative affect: The PANAS scales. *J Pers Soc Psychol*, *54*, 1063-1070.

Weathers, F.W., Blake, D.D., Schnurr, P.P., Kaloupek, D.G., Marx, B.P., & Keane, T.M. (2013). *The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)*. Interview available from the National Center for PTSD at www.ptsd.va.gov

Weathers, F.W., Litz, B.T., Keane, T.M., Palmieri, P. A., Marx, B. P., & Schnurr, P.P. (2013). *The PTSD Checklist for DSM-5 (PCL-5)*. Scale available from the National Center for PTSD at www.ptsd.va.gov.

Wechsler, D. (2008a). *Wechsler Memory Scale* (4th ed.). San Antonio, TX: Pearson.

Wechsler, D. (2008b). *Wechsler Adult Intelligence Scale* (4th ed.). San Antonio, TX: Pearson.

Williams, D.R., Yu. Y., Jackson, J.S., & Anderson, N.B. (1997). Racial differences in physical and mental health: Socioeconomic status, stress, and discrimination. *Journal of Health Psychology*, *2*, 335-351.

Wilson, B.A., Alderman, N., Burgess, P.W., Emslie, H., & Evans, J.J. (1997). Behavioural Assessment of the Dysexecutive Syndrome (BADS). Thames Valley Test Company, Bury St, Edmunds, England.

Wu, M.S., Lewin, A.B., Murphy, T.K., & Storch, E.A. (2014). Misophonia: Incidence, phenomenology, and clinical correlates in an undergraduate student sample. *Journal of Clinical Psychology*, *70*, 994-1007.

Zwerling, C., Ryan, J., Orav, E.J. (1990). The efficacy of preemployment drug screening for marijuana and cocaine in predicting unemployment outcome. *JAMA*, *264*, 2639-2643.