Impact of Reduced Cannabis Use on Functional Outcomes

NCT03681353

Study Protocol and Statistical Analysis Plan

Document Date: 11/10/2020

SPECIFIC AIMS

More than 8 million Americans reported heavy cannabis use in 2013, representing a 59% increase since 2005 (Substance Abuse and Mental Health Services Administration, 2014). Heavy cannabis use (i.e., use on ≥ 40 of last 90 days) is associated with addiction, unemployment, neuropsychological deficits, lower educational attainment, and reduced physical activity (Substance Abuse and Mental Health Services Administration, 2014; Volkow et at., 2014; Hasin et al., 2015; Fergusson, Horwood & Beautrais, 2003; Compton et al., 2014; Jin et al., 2017; Pate et al., 1996; Hall & Degenhardt, 2009; McCaffrey et al., 2010; Zwerling, Ryan & Orav, 1990). Studies by our laboratory and others indicate that heavy cannabis use is associated with increased mental health problems as well as suicidal and nonsuicidal self-injury (Volkow et al., 2014; Hall & Degenhardt, 2009; Borges, Bagge, & Orozco, 2016); Kimbrel, Newins et al., 2017; Gentes et al., 2015; Kimbrel, Meyer et al., in press; Adkisson et al., manuscript submitted). Cannabis is also the illicit drug most strongly associated with drugged driving and traffic accidents, including fatal accidents (Volkow et al., 2014; Hall & Degenhardt, 2009; Kelly, Darke & Ross, 2004; National Institute on Drug Abuse, 2016). While there is evidence that sustained abstinence can lead to improvements in the functioning of former users (Bonnet et al., 2015; Schreider & Dunn, 2012; Bruins et al., 2016; Davis et al., 2014; Kimbrel, Calhoun et al., manuscript in preparation), the degree to which reductions in frequency and quantity of cannabis use alone (i.e., in the absence of sustained abstinence) are associated with positive changes in functional outcomes is largely unknown at the present time (Tiffany et al., 2011: Donovan et al., 2011). This is a critical gap in the literature, as many interventions for cannabis use disorder (CUD) are associated with decreases in frequency and quantity of use, but fail to reduce overall rates of sustained abstinence (Tiffany et al., 2011: Donovan et al., 2011; Copeland & Pokorski, 2016; Sherman & McRae-Clark, 2016).

The overall objective of the present research is to use ecological momentary assessment (EMA), a real-time, naturalistic data collection method, to prospectively study the impact of reduced cannabis use on functional outcomes in heavy cannabis users. EMA addresses several limitations of traditional assessment techniques by enhancing ecological validity, minimizing memory bias, and enabling examination of the impact of context on participants' behavior. Our central hypothesis is that reductions in frequency and quantity of cannabis use will lead to positive changes in cannabis users' functional outcomes. The rationale for this research is that it will provide real-time data concerning the impact of reductions in cannabis use on functioning and will support efforts to include reductions in illicit drug use as a valid outcome measure in pharmacotherapy studies (Tiffany et al., 2011: Donovan et al., 2011).

Contingency management (CM) will be used to promote reductions in frequency and quantity of 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 more portable and feasible. We have pilot-tested this approach with heavy cannabis users and found that it is an acceptable and feasible method to reduce cannabis use. 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 key functional outcomes.

We will pursue the following specific aims during the R21 phase:

R21 Aim 1: Refine the study procedures and the CM reinforcement schedule to ensure that a majority of participants will be adherent, find the study procedures acceptable, and substantially reduce their frequency and quantity of cannabis use.

Milestone 1: The majority (i.e., ≥ 65%) of participants will be adherent and rate procedures as acceptable.

Milestone 2: We will identify a CM reinforcement schedule that reliably produces ≥ 50% reductions in frequency and quantity of cannabis use among at least half of the heavy cannabis users enrolled.

R21 Aim 2: Examine the association between days of cannabis use and total amount of cannabis used.

Milestone 3: We will calculate the association between frequency of cannabis use (days) and total quantity of cannabis consumed per week based on participants' EMA data concerning quantity of cannabis use.

If the proposed R21 milestones are met, we will complete the following specific aims during the R33 phase:

R33 Aim 1: Assess the impact of reduced frequency and quantity of cannabis use on functioning.

Hypothesis 1a: Decreased cannabis use will be associated with significant improvements in mental health symptoms, self-efficacy, physical activity, and health-related quality of life.

Hypothesis 1b: Decreased cannabis use will be associated with significant improvements in working memory, impulsivity, and drugged driving.

R33 Supplementary Aim: Explore momentary (e.g., craving, sleep) and between-person factors (e.g., sex, baseline use) that might moderate the association between cannabis use and functioning.

Expected Outcomes: The proposed research will be the first study to systematically assess the impact of reduced frequency and quantity of cannabis use on functioning. As such, these findings will directly inform ongoing efforts to include reductions in illicit drug use as a valid, clinically-meaningful outcome measure in clinical trials of pharmacotherapies for the treatment of CUD and other substance use disorders (Tiffany et al., 2011: Donovan et al., 2011).

A. SIGNIFICANCE

Cannabis is the most widely used illicit drug in the U.S. (Substance Abuse and Mental Health Services Administration, 2014). While there are ongoing efforts to legalize cannabis for medicinal and recreational use throughout the U.S., many questions and concerns regarding the safety of this controversial drug exist, as prior research demonstrates that heavy cannabis use is associated with a host of negative outcomes (Volkow et al., 2014; Hasin et al., 2015; Fergusson, Horwood & Beautrais, 2003; Compton et al., 2014; Jin et al., 2017; Pate et al., 1996; Hall & Degenhardt, 2009; McCaffrey et al., 2010; Zwerling, Ryan & Orav, 1990; Borges, Bagge & Orozco, 2016; Kimbrel, Newins et al., 2017; Gentes et al., 2015; Kimbrel, Meyer et al., in press; Kelly, Darke & Ross, 2004; National Institute on Drug Abuse, 2016). While there is evidence that sustained abstinence may reduce some of the negative consequences associated with heavy cannabis use [e.g., neuropsychological deficits (Bonnet et al., 2015), psychiatric symptoms (Schreiner & Dunn, 2012; Bruins et al., 2016)], the degree to which reductions in cannabis use alone (i.e., reductions in frequency or quantity of use without sustained abstinence) might be associated with positive changes in functional outcomes, such as mental health and health-related quality of life, is unclear at the present time (Tiffany et al., 2011; Donovan et al., 2011; Copeland & Pokorski, 2016; Sherman & McRae-Clark, 2016). Our central hypothesis is that reductions in frequency and quantity of cannabis use will lead to positive changes in heavy cannabis users' functional outcomes. The rationale for the proposed research is that it will provide the first and only real-time, naturalistic data concerning the potential impact of reductions in cannabis use on a wide range of key functional outcomes. The objective of the current proposal is to prospectively study the impact of reduced cannabis use on functioning. Our central hypothesis is that reductions in cannabis use will lead to positive changes in heavy cannabis users' functioning. The rationale for this research is that it will provide the first and only real-time data on this important, but understudied topic. Thus, our findings will directly inform ongoing efforts to include reductions in illicit drug use as a valid, clinically-meaningful outcome measure for pharmacotherapy trials for the treatment of CUD and other SUDs (Tiffany et al., 2011: Donovan et al., 2011).

B. PRELIMINARY STUDIES

B.1. Development of Mobile CM for Smoking

Contingency management (CM) will be used to promote reductions in cannabis use in the present study so that the impact of these reductions on functioning can be systematically studied. CM is a behavioral therapy that provides positive reinforcers (e.g., vouchers, money) to individuals misusing substances contingent upon bioverification of abstinence from drug use. CM is a highly effective method for producing short-term abstinence among individuals who misuse substances, including cannabis (Schuster et al., 2016; Budney, Stanger et al., 2015; Kadden et al., 2007; Carroll et al., 2006). Further, CM has demonstrated effect sizes in excess of other behavioral treatments in several substance use trials (Dutra et al., 2008). We have previously developed and completed testing of a smartphone app that makes CM for smoking cessation portable (Carpenter et al., 2015; Hertzberg et al., 2013). Using the app, individuals generate video recordings of themselves blowing into a small CO monitoring device. The app uploads the video to a secure website using encrypted network

connections so that study staff can view the video *via* a web-interface and confirm abstinence based on the participant's CO reading. Upon confirmation, the program automatically calculates the compensation earned based on the current CO reading (as well as their previous readings). Abstinence rates across the studies were high (82-87%), and were substantially higher in the active mobile CM condition [82% vs. 45% in the yoked condition; (Carpenter et al., 2015; Hertzberg et al., 2013)]. These studies demonstrate our experience in the development of complex mobile CM protocols as well as the fact that participants are highly adherent to mobile CM protocols, uploading 96% of videos across studies.

B.2. Adaptation of Mobile CM App to Reduce Cannabis Use

Our programmer, Jeff Hertzberg, has already adapted our existing mobile CM application for cannabis. Though most of the procedures used in our previous mobile CM studies were easily applied to cannabis use, we have made several important changes, including adding a videotaped saliva assessment component that records participants self-administering the saliva test kit to themselves. In addition, because reinforcers are most effective when delivered immediately after a target behavior is performed (Lattal, 2010), the app now also provides daily feedback on amount of money earned to date as well as how the amount was calculated.

B.3. Bioverification of Cannabis Use via Saliva Test Kits

For many years, the standard for detection of cannabis use has been urinalysis examining excretion of the cannabis metabolite 11-nor-Δ9-tetrahydrocannabinolic acid (THC-COOH) *via* immunoassay completed in a clinic setting (Budney, Stanger, et al., 2015). There are several drawbacks to this approach for CM. While multiple factors affect detection times for cannabis use *via* urine screening (e.g., frequency of use, dosage, individual metabolism), THC-COOH levels are typically elevated in regular cannabis users (e.g., background levels ≥1,000 ng/ml). As a result, a washout period (1-2 weeks or longer) is needed between cessation of use and submission of negative urine samples to verify daily abstinence. As a result, implementation of CM for CUD has been discouraged in health care settings because the lag-time between cessation of use and submission of negative samples makes CM for CUD more complicated to administer (Petry, DePhilippis, Rash, Drapkin, & McKay et al., 2014). As a result, most previous CM approaches for CUD have required clinic-based monitoring at least twice a week to verify abstinence. Consequently, detection of cannabis use via traditional urinalysis methods makes it impossible to contingently reinforce reductions in ***daily*** cannabis use. In contrast, saliva [i.e., oral fluid (OF)] testing is non-invasive and has the benefits of directly observable sample collection methods (reducing potential for sample adulteration), lower biohazard risk during collection, ease of multiple sample collections, and stronger correlation with blood-based drug-testing results than urine concentrations (Lee & Huestis, 2014). Moreover, the reliability/validity of OF drug testing has improved significantly over the past decade (Lee & Huestis, 2014) and there is currently one FDA-approved saliva testing method (Oratect® Oral Fluid Drug Screen Device) that can be used to detect THC use (40 ng/mL) in the past 12-14 hours. In order to evaluate the accuracy of this saliva test kit compared to newer test kits that are more sensitive to THC use, at the baseline, post-ad lib, and follow-up visits, we will ask participants to use two additional saliva test kits. We will compare results from the three tests to urine cannabinoid analyses to determine the most accurate test.

B.4. Preliminary Data on Saliva Testing with Heavy Cannabis Users

We have now collected feasibility and acceptability data from 4 heavy cannabis users on the use of the saliva test as part of the mobile CM for cannabis protocol (PRO00072366; Beckham, Adkisson et al., manuscript submitted). Participants were trained to self-administer the test. They were then asked to videotape themselves twice daily (at least 8-hours apart) while taking the test during a 1-week *ad lib* period followed by 4-weeks of mobile CM. During each video recording, participants: 1) started a video recording session using the smartphone; 2) showed the unused test strip to the camera; 3) swabbed his/her cheek while on camera; 4) placed the strip on a flat surface for 5 minutes; and 5) recorded the final result with the camera. Saliva sticks were numbered to ensure they were not reused or substituted. Videos were uploaded and transmitted to our secure server using the app described above. Two raters independently reviewed each video and indicated if the saliva test was positive or negative. In 1% of videos, coordinators identified a problem (i.e., control strip was not legible) and the sample was rated as invalid (participants were given the benefit of the doubt and were paid in these rare instances). Agreement between raters was excellent (100%) as was agreement between participant self-report and saliva results (96%).

B.5. Preliminary Pilot Data on Mobile CM for Cannabis

As noted above, 4 participants have completed the mobile CM for cannabis protocol to date. All of the heavy cannabis users who completed the 4-week mobile CM for cannabis protocol reduced their cannabis use. On average, participants reduced the number of days they used cannabis from 17.5 days to 10.3 days per month, representing a 41% reduction in frequency of cannabis use on average. These preliminary findings demonstrate that: (1) we can recruit and retain heavy cannabis users in the proposed mobile CM protocol; (2) mobile CM for cannabis is feasible and accepted by heavy cannabis users; and (3) mobile CM produces a range of reductions in frequency of daily cannabis use (18-93%) that make it an ideal platform from which to study the impact of reduced frequency of cannabis use on functional outcomes.

C. R21 APPROACH

C.1. R21 Aims and Milestones

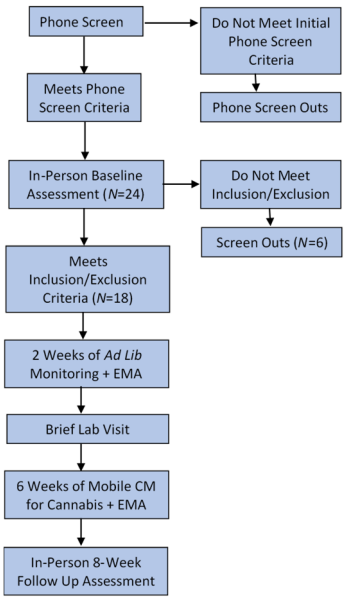
In Aim 1 of the R21 phase of the project, we will evaluate the acceptability of the study procedures and further refine the CM reinforcement schedule to ensure that a majority of participants will be adherent, find the study procedures acceptable, and substantially reduce their cannabis use. In Aim 2, we will examine the association between frequency of cannabis use and total amount of cannabis consumed per week.

C.2. Overview of the R21 Study Design and Participant Flow

Figure 1 depicts the R21 study design and participant flow. Interested participants that meet initial eligibility criteria during a phone screen will complete an in-person baseline assessment to determine final eligibility. We anticipate that we will need to complete 24 baseline assessments to enroll a final sample of 18 eligible participants. Eligible participants will complete 2 weeks of *ad lib* monitoring during which time they will use cannabis typically to establish baseline patterns of use. Following the 2-week *ad lib* period, participants will complete the 6-week mobile CM for cannabis protocol aimed at

reducing their cannabis use. Afterwards, participants will return to the laboratory to return equipment and to complete an in-person 8-week follow-up.

Figure 1. R21 Study Design & Participant Flow



C.3. R21 Inclusion/Exclusion Criteria

Inclusion criteria include: (a) cannabis use other than ingested cannabis (i.e., edibles) on ≥40 of past 90 days; (b) ability to speak and write fluent English; (c) 18-80 years of age; and (d) willingness to attempt to temporarily reduce cannabis use. Participants will be excluded if they: (a) expect to have an unstable medication regimen during the study; (b) are currently receiving non-study CUD treatment; (c) meet criteria for serious mental illness (e.g., bipolar disorder, schizophrenia); (d) become imprisoned; (e) become hospitalized for psychiatric reasons; (f) become pregnant; (g) report imminent risk for suicide or homicide; or (h) meet criteria for a substance use disorder other than CUD or tobacco.

C.4. Recruitment & Enrollment

We estimate that we will need to recruit 24 participants to meet our overall goal of enrolling 18 eligible participants. Participants will be recruited from the community and from outpatient clinics at Duke University Medical Center (DUMC). Several methods will be used to recruit potential participants at these sites. Recruitment materials such as IRB-approved study flyers will be placed in mental health clinic areas at DUMC. In addition, study flyers will be placed throughout these medical centers in centrally located posting areas.

We will identify potentially eligible participants using searches using Duke's Deduce and Maestro Care systems. We will identify potentially eligible participants, using diagnostic and contact information in those systems. Potentially eligible participants will be sent an introductory letter or email asking them to consider participation, and they will be provided contact information for the study coordinator. Potential participants may also be called about a week after they are sent the letter to determine interest. Potential participants will be contacted no more than three times, as indicated by DOCR guidelines. They will also be provided information about how to opt out of additional contact from the study team re: this study.

The study will be registered at clinicaltrials.gov, which will allow for online recruitment during the course of the study. As needed, we will advertise the study in local area newspapers, on Duke University's clinical research website, and on online classified advertising websites such as Craigslist.com, DukeList, or JobFinder.com. In addition, we will post study recruitment materials at local community areas such as laundromats, Bull Connector bus lines, substance use treatment centers, restaurants, and grocery stores.

Our study team will use social media to reach potentially eligible participants. We have developed a Facebook page for posting IRB-approved study flyers and information for this and other studies in the Traumatic Stress and Health Research Laboratory, https://www.facebook.com/Duke-Traumatic-Stress-

and-Health-Research-Lab-379366159145563/. We plan to place pictures of our study flyers on the Facebook page, and use Facebook's post boost to draw attention to the post. The post itself will say "Enroll now!" or "Now enrolling!" We will also plan to use Facebook ads to target potential participants within a 50-mile radius of Duke. If any participant contacts the email associated with the Facebook page (TSHRLab@dm.duke.edu, he/she will be sent an automatic email response.

We will plan to use a recruitment method referred to as respondent-driven sampling, or "seed recruitment" (Christina Meade, Ph.D., personal communication). Seed recruitment is suitable for sampling "hidden populations" of participants who are best known by their own peers (Heckathorn, 1997). It includes providing incentives to participants for referral of other eligible participants. In our model, each participant, or seed, will receive a coupon to recruit another person in his/her social networks. The recruitment coupon will provide a brief description of the survey and a phone number for contacting the study coordinator. The coupon will be marked with a unique identification number (not the study identification number) so that when the coupons are returned to us, the ID number can be used to provide payment ($20) to the participant who made the referral. The key connecting the participant's study ID number with the seed ID number will be kept in a database separate from other PHI, creating two layers of separation between the seed ID and the already-participating person's identifying information. Any participant who does not wish to recruit in this manner will not be required to do so.

Any participant who contacts by telephone the study coordinator or other study staff regarding the study will be provided more information, and will be interviewed using an IRB-approved telephone screening. If a participant is deemed potentially eligible in the telephone screen, he/she will be scheduled to attend a formal screening visit. We will send, via Duke secured email, appointment reminders to any participant who wants to receive them. Once a participant reports to the laboratory to begin the study, 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 at Duke University Medical Center, and participants are given the chance to thoroughly read the consent prior to participation. Participants are given a copy of the signed informed consent form, and are given 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. With regards to determination of decision making capacity of potential participants, our laboratory has a standard procedure for determining understanding of the study procedures, risks, and benefits. We utilize this procedure if we have any reason to suspect that the participant may have difficulty in the consent process (e.g., traumatic brain injury impacting cognitive function, active psychotic symptoms). In this procedure, the study coordinator providing the informed consent information evaluates understanding of the procedures at several different time points during the process by asking questions like "Do you understand what we're asking you to do?" and "Do you have any questions about the risks of the study? Can you tell me what you understand the risks to be?" Prior to having a participant sign consent, the study coordinator may ask the potential participant to outline the study procedures, risks, and benefits so that he can make sure that the participant is aware of them. If the participant is unable to summarize these, he/she will not be allowed to sign the

informed consent form, and may be referred for other treatment. No study procedures will begin until informed consent has been obtained.

C.5. Screening Procedures

Prior to study entry, potential participants will complete screening procedures as part of the baseline assessment, including informed consent, diagnostic interview, self-report measures, demographic data, and cannabis history. Urine and saliva samples will be collected to assess for cannabis use and other illicit drugs. Women of childbearing potential will be given a pregnancy test. Urine samples will be assayed by a trained staff member using a Quidel QuickVue pregnancy test. We have developed a short interview for female participants; this interview will help us determine which female participants must have a urine pregnancy test, and when the test should be done. Female participants of childbearing potential who are not pregnant must agree to use appropriate contraception during the course of the study, and to notify study staff if they become pregnant during the study. During the screening visit, if there is any indication that a participant is at greater than minimal risk for suicide (using the Columbia Suicide Scale), he/she/they will work with a trained study staff member to complete a safety planning worksheet (Stanley & Brown, 2012). This will help mitigate suicide risk. If necessary, this safety plan will be reviewed during the post-treatment visit as well.

C.6. Refining the Study Procedures and the CM Reinforcement Schedule (R21 Aim 1)

In Aim 1 of the R21, we will use an iterative process to refine the study procedures and the CM reinforcement schedule in 3 cohorts of 6 participants each (total *N*=18) to ensure that a majority of participants will be adherent, find the study procedures acceptable, and substantially reduce their cannabis use. Note that while we will pilot test all of the EMA procedures during this phase, inclusion of these procedures is solely to determine feasibility, acceptability, and impact of the CM schedule on cannabis use, as we will not be powered to analyze the functional outcomes of interest during this phase. Note that we anticipate that the majority of adjustments to the protocol that will be made during the R21 phase of this project will be related to "fine tuning" the CM reinforcement schedule to ensure optimal reductions in use.

C.6.1. Determining the Initial CM Reinforcement Schedule. Building upon our pilot findings, we will use an escalating reinforcement schedule (see Table 1), such that each subsequent day of abstinence will be reinforced with a greater amount of money; however, to ensure that participants are not motivated to achieve sustained abstinence, we will program our CM schedule such that participants will be able to use cannabis one day each week without penalty. That is, there will be 1 "free" day per week when participants will not be penalized for using cannabis. This procedure will help to ensure there is an upper limit on reduced use, as our goal is to motivate participants to substantially reduce their use, but not to the point that they achieve sustained abstinence. Participants will earn $10.00 for their first day of abstinence. Each subsequent day of bioverified abstinence/free day will result in participants' compensation increasing by $1.00. We also considered use of 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. While we have used reset contingencies successfully in the past, we have elected to not use a reset contingency in this study because our goal is to promote reduced use, not sustained abstinence. We have also elected to

increase (relative to our pilot) the amount of money that participants can receive to increase the likelihood that a majority (i.e., ≥ 50%) of participants will decrease their use by 50% or more.

Table 1. R21 phase otential payment schedule with "free day" allowance								
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	$7.50 ($2.50 per video) payment for uploading saliva testing videos (regardless of cannabis use). $5 for providing a self-initiated reading.	$12.50 each day	175.00
		2	$2.50	As Usual				
		3	$2.50	As Usual				
		SI*	$5.00	As Usual				
Weeks 3 to 7 (CM Phase 1), one example week shown	**15**	1	$2.50	No	$10.00	Participants will earn $10 for their first day of verified abstinence. $1 bonus marijuana payment for verified marijuana-free day or if the once-a-week cheat day is used.	$17.50	$192.50
		2	$2.50	No				
		3	$2.50	No				
	16	1	$2.50	No	$11.00		$18.50	$211.00
		2	$2.50	No				
		3	$2.50	No				
	17	1	$2.50	No	$12.00		$19.50	$230.50
		2	$2.50	No				
		3	$2.50	No				
	18	1	$2.50	No	$13.00		$20.50	$251.00
		2	$2.50	No				
		3	$2.50	No				
	19	1	$2.50	Yes	$14.00		$21.50	$272.50
		2	$2.50	Yes				
		3	$2.50	Yes				
	20	1	$2.50	No	$15.00		$22.50	$295.00
		2	$2.50	No				
		3	$2.50	No				
	21	1	$2.50	No	$16.00		$23.50	$318.50
		2	$2.50	No				
		3	$2.50	No				
Week 8 (CM Phase 6)	**50**	1	$2.50	No	$45.00	1 dollar increase to bonus marijuana payment for verified marijuana-free day or if the once-a-week cheat day is used.	$52.50	$1435.00
		2	$2.50	No				
		3	$2.50	No				
	51	1	$2.50	No	$46.00		$53.50	$1488.50
		2	$2.50	No				
		3	$2.50	No				
	52	1	$2.50	No	$47.00		$54.50	$1543.00
		2	$2.50	No				
		3	$2.50	No				
	53	1	$2.50	No	$48.00		$55.50	$1598.50
		2	$2.50	No				
		3	$2.50	No				

	54	1	$2.50	Yes	$49.00		$56.50	$1655.00
		2	$2.50	Yes				
		3	$2.50	Yes				
	55	1	$2.50	No	$50.00		$57.50	$1712.50
		2	$2.50	No				
		3	$2.50	No				
	56	1	$2.50	No	$51.00		$58.50	$1771.00
		2	$2.50	No				
		3	$2.50	No				

C.6.2. Saliva Testing Schedule. Saliva testing will occur contemporaneously with EMA alarms. Participants will be required to video record themselves taking a saliva test each time they are alarmed to complete EMA, i.e., three times per day. During the *ad lib* phase of the monitoring, we will ask participants to do a self-initiated EMA and saliva test if they use marijuana. Participants will be asked to begin a reading when beginning to use marijuana. An alarm will be set for 60 minutes later. At the alarm, participants will complete a saliva test. Participants will be paid $5 each day if they do a self-initiated reading. During the active CM phases of the study, if a participant tests negative at each time point, he/she will by reinforced for abstinence that day. In addition, participants will be granted one "free day" per week in which they can use cannabis and still be reinforced if they upload their saliva tests. Please note that participants are reinforced separately for uploading both positive and negative saliva tests (they receive $2.50 per upload, regardless of cannabis use), enabling us to compare participants' saliva test results with their self-report. Participants will be given half of the required saliva screening strips at their screening visits, and then will be mailed remaining strips about halfway into the treatment period.

C.6.3. Cohort 1: Protocol Refinement. After the first 6 participants have completed the mobile CM for cannabis protocol, we will ask each of them to rate the acceptability of the procedures. We will also conduct interviews with participants to identify and resolve any issues that may have contributed to poor adherence and/or poor response to the CM procedures. A summary of this feedback will then be evaluated by the study team (i.e., Co-PIs, Co-I's, Consultant, and computer programmer) and incorporated into the revised protocol. We will also evaluate compliance data and calculate the reduction in cannabis use that participants achieved during CM to determine if further adjustments to the reinforcement schedule are needed.

C.6.4. Cohort 2: Further Protocol Refinement. Once the protocol and/or reinforcement schedule have been modified based on information learned from the first cohort, we will administer the revised mobile CM for cannabis protocol to a second cohort of heavy cannabis users (n=6) and repeat the evaluative measures described above**.** Any additional modifications needed to improve adherence, acceptability, or efficacy of the mobile CM for cannabis protocol will be implemented at this time. We have found this second small cohort particularly helpful in previous treatment development studies, as it allows for careful evaluation of changes in procedures and reinforcement schedules.

C.6.5. Cohort 3: Milestone Assessment. Once the EMA protocol and CM reinforcement schedule have been finalized based on information learned from cohort 2, we will administer the final version of the

protocol to a third cohort (*n*=6) to determine if our first two milestones have been met. Our first milestone will be to demonstrate that a majority (i.e., 4/6) of cohort 3 participants will be adherent to the study protocol and rate the study procedures as acceptable. Protocol adherence will be defined as completing the baseline assessment, 8-week follow-up assessment, and 1 or more EMA assessments per day (total ≥56) for the duration of the 8-week EMA protocol. Acceptability will be assessed with a questionnaire specifically designed for this study. Our second milestone will be to demonstrate that we have identified a reinforcement schedule that reliably produces ≥ 50% reductions in frequency and quantity of cannabis use in at least half of the participants in cohort 3 (i.e., 3/6). By aiming to reliably produce clinically meaningful reductions in frequency and quantity of cannabis use in at least half of the participants, we will maximize our ability to study the impact of reduced cannabis use on key functional outcomes during the R33 phase of the project. To evaluate if this milestone has been met, we will calculate the percentage reduction in bioverified abstinent days and overall cannabis quantity by comparing the *ad lib* monitoring period to the mobile CM period.

C.7. Association between Frequency of Use and Total Amount of Cannabis Consumed (R21 Aim 2)

In Aim 2 of the R21, we will examine the association between number of bioverified abstinent days and self-report of total quantity of cannabis use per week. Quantity of cannabis consumed during EMA assessments will be calculated as the inverse of the self-reported average number of joints made from 1 gram of cannabis (joints/gram) consumed per EMA period, as this approach has been demonstrated to reliably assess cannabis quantity (van der Pol, Liebregts, Graff, Korf, van den Brink & van Laar, 2013). We will use van der Pol et al.'s (van der Pol, Liebregts, Graff, Korf, van den Brink & van Laar, 2013) methods to assess cannabis potency *via* self-report, and total THC load will be calculated as joints/gram x potency. Participants will also be prompted at the end of each day (~11 pm) to estimate the total amount of joints/gram they used that day. Our third milestone involves examining the association between frequency of cannabis use (i.e., days) and total amount of cannabis consumed per week based on participants' EMA data on quantity of cannabis use. By tracking the total amount of cannabis that participants use, we will be well-positioned to account for such an effect in the R33 analyses. To assess this milestone, we will calculate days since last use for each report of cannabis use. We will use count-adjusted (i.e., negative binomial or Poisson) MLM to model the equivalent number of joints/gram smoked on a given day as a function of days since last use. We anticipate the association of latency between days since last use and amount consumed will be small (i.e., Cohen's $d \leq 0.10$).

C.8. 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 a urine sample. These urine samples will be sent to Lab Corp for creatinine normalization analyses to determine cannabinoid concentrations. Measurement of cannabinoid concentration will allow analyses of reduced cannabis use.

D. R33 APPROACH

D.1. Overview of the R33 Study Procedures

If the proposed R21 milestones are met, the R33 phase of the project will be used to conduct a fully powered test of our central hypothesis that reductions in frequency and quantity of cannabis use will

lead to positive changes in cannabis users' functional outcomes. The R33 study will be directly modeled after the R21 study and will use the final reinforcement schedule developed through the R21 as well as the same recruitment, enrollment, and screening procedures described herein. Based on evaluation of the R21 data, we have modified the contingency management procedures such that participants are

Table 2. R33 Phase potential payment schedule with "free day" allowance

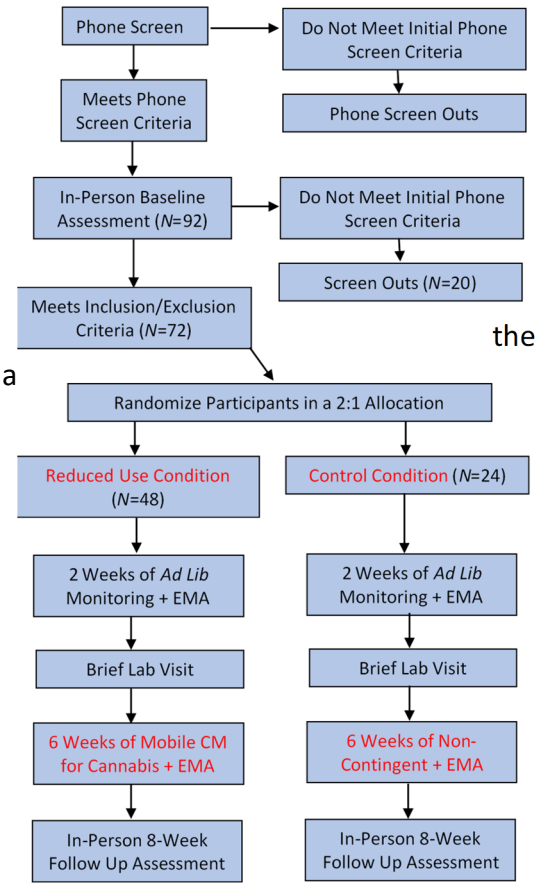
Week	Day	Saliva videos	(Regardless of use) Daily Saliva Video Uploads	Smoking?	Daily Saliva Video Uploads	Explanation	Total	Running Total
Week 1 & 2 (*Ad Lib*)	1-14	1	$2.50	As Usual	No Bonus yet	$5.00 ($2.50 per video) payment for uploading saliva testing videos (regardless of cannabis use). $5 for providing a self-initiated reading.	$10.00 each day	$140.00
		2	$2.50	As Usual				
		SI*	$5.00	As Usual				
Weeks 3 to 7 (CM Phase 1), one example week shown	15	1	$2.50	No	$10.00	Participants will earn $10 for their first day of verified abstinence. $1 bonus marijuana payment for verified marijuana-free day or if the once-a-week cheat day is used.	$15.00	$155.00
		2	$2.50	No				
	16	1	$2.50	No	$11.00		$16.00	$171.00
		2	$2.50	No				
	17	1	$2.50	No	$12.00		$17.00	$188.00
		2	$2.50	No				
	18	1	$2.50	No	$13.00		$18.00	$206.00
		2	$2.50	No				
	19	1	$2.50	Yes	$14.00		$19.00	$225.00
		2	$2.50	Yes				
	20	1	$2.50	No	$15.00		$20.00	$245.00
		2	$2.50	No				
	21	1	$2.50	No	$16.00		$21.00	$266.00
		2	$2.50	No				
Week 8 (CM Phase 6)	50	1	$2.50	No	$45.00	1 dollar increase to bonus marijuana payment for verified marijuana-free day or if the once-a-week cheat day is used.	$50.00	$1310.00
		2	$2.50	No				
	51	1	$2.50	No	$46.00		$51.00	$1361.00
		2	$2.50	No				
	52	1	$2.50	No	$47.00		$52.00	$1413.00
		2	$2.50	No				
	53	1	$2.50	No	$48.00		$53.00	$1466.00
		2	$2.50	No				
	54	1	$2.50	Yes	$49.00		$54.00	$1520.00
		2	$2.50	Yes				
	55	1	$2.50	No	$50.00		$55.00	$1575.00
		2	$2.50	No				
	56	1	$2.50	No	$51.00		$56.00	$1631.00
		2	$2.50	No				

only asked to respond to two daily alarms (instead of three). Note, this decreases the potential amount of money earned.

Seventy-two participants will be randomized using a 2:1 allocation ratio to either the Reduced Use

Condition (n = 48) or a Control Condition (n = 24). Inclusion of a control group will allow clear inferences to be drawn regarding the effects of reduced cannabis use on functional outcomes. Study participation will entail completion of the baseline assessment, completion of the 8-week EMA study, and completion of the 8-week follow-up assessment.

Figure 2. R33 Study Design & Participant Flow



D.2. R33 Inclusion/Exclusion Criteria and Recruitment Timeline

The final inclusion/exclusion criteria for the R33 phase of the project will be identical to the R21 inclusion/exclusion criteria with one exception: Participants who are found to meet criteria for bio-verified sustained abstinence (i.e., all of their saliva tests are negative during the 6-week experimental phase of the study) will be excluded from the statistical analyses to ensure that there is an upper limit on reduced use. Thus, we will exclude any participants who achieve sustained abstinence to ensure that any improvements in functioning observed among participants in the experimental condition are not being driven by inclusion of a subset of participants who achieve sustained abstinence. Please also note that we can exclude up to 12 of the 72 enrolled participants from the statistical analyses (remaining *N* = 60) and still be adequately powered to conduct all of the proposed analyses.

D.3. Diagnostic Reliability and Training of Clinical Interviewers

Interviewers will be trained to conduct the interviews using our standardized laboratory 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 previous studies (Kimbrel, Newins et al., 2017; Kimbrel, Calhoun et al., 2014).

D.4. Participant Reimbursement

In addition to the compensation that participants will receive from the CM procedures, participants will also receive $75 for completion of the baseline assessment, $25 for the post *ad lib* period urine testing, $150 for the 8-week follow-up, and $400 for the EMA study ($50 per week). They will also be eligible to receive a $25 bonus per week for not missing more than 1 EMA alarm per day, and a $50 bonus for returning their equipment on time. These procedures have worked well (high compliance and equipment return rates) in previous studies (Carpenter et al., 2015; Hertzberg et al., 2013; Beckham, Calhoun et al., 2013; Dennis et al., 2016; Volz et al., 2014). Participants may also receive $20 for successfully recruiting another participant in his/her/their social network.

D.5. Description and Timing of In-Person Assessments

Table 2 describes the laboratory and self-report assessments that will be collected at the baseline and 8-week follow-up assessments as well as their administration schedule. Whenever possible, we have selected Common Data Elements from the PhenX Toolkit (Hamilton et al., 2011) to maximize the impact of the proposed research. We have also elected to use brief measures when possible to reduce burden. Whenever possible, participants will complete questionnaires remotely using Duke's instance of RedCap.

D.6. EMA and CM 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. Eligible participants will be trained in the EMA procedures following established procedures at the end of the baseline assessment (Beckham, Calhoun 2013). Participants will then practice with the electronic diary at home for 24 hours. Once the training period is complete, participants will complete an 8-week EMA study in which they will carry the diaries with them on a daily basis. The first 2 weeks of the EMA study will involve daily assessments of cannabis use and participants' functional outcomes during the *ad lib* period to establish baseline patterns of use. During the *ad lib* period,participants will also be asked to perform self-initiated diary readings when they begin cannabis use. When participants begin the diary reading, the phone will set an alarm for 60 minutes later. When the alarm sounds, the participant will use a saliva test kit and upload the readings. Participants will be paid $5 once per day if they begin a self-initiated reading on that day. On day 15, participants in the Reduced Use Condition (*n* = 48) will begin reducing their cannabis use through participation in the mobile CM for cannabis protocol, whereas participants in the Control Condition (*n* = 24) will receive non-contingent payments based on the mean of two yoked participants' earnings. All participants will continue to provide EMA assessments of their functional outcomes during the 6-week experimental period so that we can study the impact of reduced cannabis use on functioning. Electronic diary data stored on the smart phone are encrypted at rest. Data will be downloaded from the smart phones to duhsnas-pri\dusom_psych\private\irb\kimbrel\Marijuana.

Table 3. ***Description and Timing of In-Person Assessments***

MEASURE	DESCRIPTION	BL	End of *ad lib*	8-wk
Demographic Assessment	PhenX (Hamilton et al., 2011) protocols will assess age (#010101), race (#010601), ethnicity (#010501), gender (#010700), and sexual orientation (#101401).	X		
Structured Clinical Interview for DSM-5 (First et al., 2015)	Will be used to diagnose CUD and other psychiatric disorders based on DSM-5 criteria in order to determine study eligibility and characterize sample.	X		
Columbia Suicide Severity Rating Scale (Posner et al., 2011)	State-of-the-art interview that assesses the full continuum of suicidal behavior. Will be used to determine study eligibility and assess suicidal behavior.	X		X
Medication List	Patients will be asked to bring their medications to the baseline visit and record their current prescription medication use.	X		

Timeline Followback for Cannabis (Robinson, Sobell, Sobell & Leo, 2014)	TFLB will be used to establish participants' cannabis use in the past 90 days to determine eligibility; will be re-administered at follow-up.	X		X
Marijuana Problems Scale (Stephens, Roffman & Curtin, 2000)	Self-report of cannabis-related symptoms and problems.	X		X
Marijuana Motives Questionnaire (Lee et al., 2009)	Self-report assessment of motives for using cannabis.	X		X
Marijuana Withdrawal Checklist (Budney, Novy & Hughes, 1999)	Self-report assessment of cannabis withdrawal symptoms	X		X
Recreational and Medicinal Marijuana Use Questionnaire	Self-report assessment of cannabis use symptoms (based on Metrik et al., 2018)	X		X
Alc. Use Dis. Identification Test (Babor et al., 1989)	Self-report of alcohol use and related consequences.	X		X
Symptom Checklist-90 (Derogatis, 1983)	90-item measure of mental health symptoms that has previously been shown to be sensitive to sustained abstinence from cannabis.	X		X
Beck Scale for Suicidal Ideation (Beck & Steer, 1991)	21-item self-report of suicidal thoughts and behaviors.	X		X
Deliberate Self-Harm Inventory (Gratz, 2001)	17-item self-report of frequency of nonsuicidal self-injurious behaviors.	X		X
PTSD Checklist – (PCL-5; Weathers, Litz et al., 2013)	20-item self report of posttraumatic stress disorder (PTSD) symptoms.	X		X
Traumatic Life Events Questionnaire (TLEQ; Kubany et al., 2000)	23-item self report of history of traumatic events	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
PEG (Krebs et al., 2009)	3-item self report measure of pain (brief version of the Brief Pain Inventory).	X		X
Insomnia Severity Index (ISI; 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		
WHOQOL-BREF (The WHOQOL Group, 1994)	26-item measure of health-related quality of life developed by WHO.	X		X
Sheehan Disability Scale (Sheehan, 1983)	3-item assessment of work, social, and family impairment.	X		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
Int'l Physical Activity Questionnaire (Booth, 2000)	27-item physical activity scale that focuses on the past 7 days.	X		X
Working Memory Tasks from Wechsler Adult Intelligence Scale (WAIS) and Wechsler Memory Scale (WMS) (Wechsler, 2008; Wechsler, 2008)	Symbol Span and Spatial Addition will assess visual working memory (WM). Digit Span and Letter-Number Sequencing will assess auditory WM. Arithmetic will measure concentration, quantitative reasoning, and mental manipulation.	X		X

Behavior Rating Inventory of Executive Function (Gioia, Isquith, Guy & Kenworthy, 2000)	75-item self-report of perception of working memory and executive functioning; contains nine subscales (e.g., Working Memory, Inhibit, Shift, Plan/Organize).	X		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.	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
Brief Interpersonal Psychosocial Functioning Measure (Bovin et al., 2018)	7-item measure of PTSD-related psychosocial functional impairment.	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
World Health Organization Disability Assessment Schedule (Üstün, 2010)	36-item interview version of functional disability.	X		X
Marijuana Ladder (Slavet et al., 2006)	Measure of motivation to change marijuana use	X		X
Timeline Followback of Drugged Driving (Robinson, Sobell, Sobell, & Leo, 2014)	Participants will be asked to report days they have driven within 2 hours of using cannabis use in the past 28 days using Timeline Followback method.	X		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		

D.6.1. Electronic Diary System Hardware and Data Security. We have established methods to limit risk of breach of confidentiality in EMA studies (Carpenter et al., 2015; Hertzberg et al., 2013; Beckham, Calhoun et al., 2013; Dennis et al., 2016; Volz, et al., 2014). The smart phone used will be any one of four models of Droid phones: 1) Droid Turbo 2 (Motorola Mobility Inc, Libertyville, IL) with a Qualcomm Snapdragon 810 processor, 5.4" Quad HD display; 2)Droid Turbo, with 5.2" Quad HD Super AMOLED™ Corning® Gorilla® Glass 3 Display; 3) Droid MAXX, with a dual-core 1.2 Ghz processor, I GB DDR2 RAM, and 4.3" gHD display; or 4) Droid MAXX 2 DROID MAXX 2 with an octa-core 1.7 Ghz processor, 2 GB RAM, and 5.5" full HD display. Each will be equipped with an Android operating system that is compliant with Federal Information Processing Standard (FIPS) 140-2 standards. Features other than the electronic diary, calling, and texting features will be locked out. The phone will be programmed so that staff can set up the phone by simply entering a participant's code. Encrypted TLS connections will be used to upload data to the server. The study's website will use a Virtual Private Server provided by InMotion Hosting, Inc. The data at InMotion Hosting are Advanced Encryption Standard (AES)-256 encrypted at rest, and the data being transferred are encrypted at transfer AES-256 & Transport Layer Security (TLS). Website properties include TLS 1.0, AES w/ 128 bit encryption (High); Rivest-Shamir-Adleman (RSA) with 2048 bit exchange. The web application written for this study has been checked for SQL injection, Code Injection, XSS, and RFI vulnerabilities and has passed. The site will only be

accessible to staff via 512-bit SHA-2 hashed passwords.

The software used in this study will be developed by our IT specialist, Mr. Jeffrey Hertzberg, who has developed and implemented similar programs for other EMA and mobile health studies conducted by our laboratory (see PRO00072366 and PRO00067912) (Carpenter et al., 2015; Hertzberg et al., 2013; Beckham, Calhoun et al., 2013; Dennis et al., 2016; Volz, et al., 2014). Participants will be prompted to complete a morning diary entry at the beginning of each day. Throughout the day, EMA data entries will be initiated by an audible alarm 3 times per day. Electronic diaries will be programmed to prompt responses at random times during waking hours, ~4 hours apart (Beckham, Calhoun et al., 2013; Dennis et al., 2016; Volz, et al., 2014). Participants will also be prompted to complete a full EMA assessment at the end of each day (~11 pm), resulting in 5 entries per day. After the alarm sounds, participants will have 5 minutes to respond. If participants do not respond in 5 minutes, a missed alarm will be recorded, and a subsequent alarm will be prompted 30-40 minutes later. If participants respond in 5 minutes, they can choose to "snooze" the alarm for 5 minutes, "skip" the alarm until 30-40 minutes later, or "answer" the alarm. Participants will be instructed on how to turn off the alarm while they sleep or during short periods of time when it might be dangerous (e.g., driving) or disturbing (e.g., during a work meeting) to respond. To reduce burden, EMA entries will be programmed to present full assessments ~1x daily, whereas the remaining assessments will be abbreviated. Specifically, we will abbreviate EMA assessments of mental health, health-related quality of life, and cannabis withdrawal symptoms at these times to reduce participant burden, as these are the most time-intensive sections. Full entries are estimated to take ~3-5 minutes, whereas abbreviated entries are expected to take ≤ 2 minutes. If any participant would like to have text messages sent to his/her/their personal phones when the study phone alarms, we will provide this service to them. Participants who opt in for text messaging may receive other study-related communications, such as "You missed an alarm. Remember to respond to the next one!" and "Contact [name of study coordinator] if you're having problems with your equipment." Participants can opt out of text messages during the initial informed consent process, or at any time during the study. Text messages sent will not contain PHI or PII.

EMA of mental health symptoms will include administration of the K-10 (Kessler et al., 2002) and PANAS (Watson, Clark & Tellegen, 1988), well-validated measures of psychological distress and positive and negative affect, respectively. Given our prior work demonstrating associations between cannabis use and self-injury (Kimbrel, Newins et al., 2017; Kimbrel, Meyer et al., in press), we will also assess self-injurious thoughts and behaviors using a state-of-the-art protocol developed and implemented by Dr. Kimbrel (Co-PI) as part of his ongoing EMA study of NSSI (I01CX001486). The WHOQOL-BREF and the Sheehan Disability Scale (SDS; Sheehan, 1983) will be used to assess health-related quality of life. We will evaluate impulsivity with the Momentary Impulsivity Scale (MIS; Tomko et al., 2014) is a brief 4-item EMA of momentary impulsivity that correlates with gold standard measures of impulsivity and has good psychometric properties.

Cannabis reduction self-efficacy will be assessed at each time point. EMA of self-efficacy will be modeled after prior EMA self-efficacy work (Gwaltney et al., 2005) and will ask participants how confident they are in their ability to reduce their cannabis use on an 11-point scale where 0 = "not confident at all" and 10 = "extremely confident."

Participants will be asked at each EMA assessment if they have used cannabis, alcohol, or any other illicit drugs, and, if so, how much of each substance they used. Participants will also be prompted each night (~11pm) to estimate the total amount of cannabis, alcohol, and illicit drugs they used in the past 24 hours. Quantity and potency of cannabis consumed during each EMA assessment will be calculated using van der Pol's methods (van der Pol et al., 2014). 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). If participants report use, they will also be asked if they drove a vehicle within two hours of use. We will also ask participants to report the total number of times they engaged in any form of drugged driving during the past 24 hours at the end of each night. EMA-based assessment of cannabis craving will use an 11-point Likert scale that ranges from 0 = "*No urge*" to 10 = "*Extreme urge* (Buckner et al., 2012). EMA of cannabis withdrawal will be completed with the Marijuana Withdrawal Checklist (Budney, Novy & Hughes, 1999; Budney et al., 2003). In our review of data from the first cohorts, we noticed 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 only those participants who complete 10 of the 14 nightly diaries. Any participant who does not meet this criterion will be withdrawn from the study.

EMA of physical activity will be conducted with the Fitbit Charge 2, a light-weight wristband capable of tracking steps, calorie consumption, and sleep. The Vivofit has been validated previously (Simunek et al., in press) and features a 1-year battery life, making it an attractive alternative to more expensive devices. Our programmer, Mr. Jeffrey Hertzberg, has already written a program that enables us to capture participants' daily step data *via* Fitbit's Bluetooth syncing technology.

EMA of working memory will be assessed with the visual working memory (VWM) EMA task developed by Schuster et al. (Schuster, Mermelstein & Hedeker, 2015). This task is quite brief (average assessment time of 7 sec following stimulus presentation), and participant compliance was high (87%) over a 1 week period across 38 prompts (Schuster, Mermelstein & Hedeker, 2015). Most important, performance on this task was associated with gold standard neuropsychological measures of visual working memory (Symbol Span, r = .60, p<.001; Spatial Addition, r = .53, p<.001) and auditory working memory (Digit Span, r = .42, p<.01; Letter-Number Sequencing, r = .44, p<.001).

Sleep will be carefully monitored as disturbed sleep is a common symptom of cannabis withdrawal (Budney, NOvy & Hughes, 1999; Budney et al., 2003) that could moderate the association between cannabis use and functioning**.** EMA of sleep will consist of daily sleep diaries and objective actigraphy data captured by the Fitbit Charge 2. Sleep estimates will be obtained each morning using the Consensus Sleep Diary (Carney et al., 2012), whereas the Fitbit will track total hours of sleep (including naps) and sleep movement. We have used these methods previously (5R01MH062482) and have experience analyzing this type of data (Ulmer et al., 2009; Ulmer et al., 2013; Calhoun et al., 2007).

D.6.2. Temporary Measures During COVID-19 Pandemic. Given that exposure to COVID-19 stressors could have an impact on cannabis use, we would like to ask participants to complete measures related

to stress, trauma, and coping strategies. Participants will be informed about these new study procedures verbally, and the study team member who informs them will provide a note-to-fil indicating so. Participants can refuse to complete these measures. We will ask ongoing participants to complete these measures at their next study visit or follow-up session. When study enrollment begins again, participants will complete these measures at the screening session. We are adding the CAIR Pandemic Impact Questionnaire (Lang, 2020; https://www.nlm.nih.gov/dr2/CAIR-PIQ_scoring.pdf), and another measure, COVID Core Questions, with variables of interest. If a participant endorses any item marked with an asterisk on the COVID Core Questions measure, we will ask them to complete a PTSD Checklist 5 related to that specific event. Finally, we have added a measure designed to evaluate participants' satisfaction with remote study procedures.

E. DATA ANALYSIS PLAN

Multilevel modeling (MLM) will be used to analyze the EMA data. MLM is a technique for analyzing repeated observations of data across multiple individuals. Unlike repeated-measures ANOVA, MLM can incorporate time-varying (Level-1) and time-invariant (Level-2) predictors. MLM can also accommodate imbalanced data and unequal variances. 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).

E.1. 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 H_{1A}, H_{1B}, and the supplementary aim, are based on maximum likelihood estimation and use all available data. As such, MLM can accommodate data missing at random. Missing data will be examined to determine whether missingness is random or systematically associated with baseline variables. Those baseline parameters associated with missingness will be covaried. If data are suspected to be missing not at random (i.e., only certain values are likely to be missing), multiple imputation will be used to analyze non-random patterns of missing EMA data (Schafer & Graham, 2002).

E.2. Electronic Diary Compliance and EMA Data Reduction.

During the 8-week 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. Data will be aggravated at the day-to-day level to indicate the following: whether cannabis was used; the total number of joints/grams consumed; mean daily potency; mean daily levels of mental health symptoms, self-efficacy, health-related quality of life, working memory, and impulsivity; whether participants drove while intoxicated; and total amount of physical activity. By using multi-daily records to examine day-level phenomena, we will minimize measurement error related to poor recall and random variability. For the 2-week baseline period and each week of the 6-week experimental period, we will calculate frequency of cannabis use as the number of days used per week. To quantify change in frequency of cannabis use from baseline, change scores will be calculated by subtracting number of days per week of cannabis use during the 2-week baseline from those levels

recorded during each week of the mCM treatment period. A dichotomous variable will also be calculated reflecting whether a given participant achieved at least a 50% reduction in cannabis use during a given week. Thus, the data will be structured such that each participant will have up to 56 rows of data corresponding to each day of the 2-week baseline period and 6-week mCM/non-contingent control. Each row will contain a dichotomous indicator of whether or not cannabis was consumed that day, total quantity of cannabis consumed that day, total THC load of the cannabis used that day, daily estimates of functioning, a baseline estimate of cannabis use, and three variables capturing weekly varying frequency, quantity, and total THC load of cannabis use: the aforementioned dichotomous variable measuring whether a 50% reduction from baseline use was achieved and a change score, with a *0* change-score value for days falling during the 2-week baseline.

E.3. Hypotheses 1a and 1b.

To examine the effect of reduced cannabis use on functioning assessed with EMA, day-by-day outcome variables will be modeled *via* MLM as a function of treatment group (Level 2), week (Level 1; with the two baseline weeks treated as a single week), and treatment-by-week interactions. Daily consumption (total equivalent number of joints/gram consumed and total potency; Level 1) will be examined as potential covariates. Linear and quadratic time effects will be explored. Week-by-week effects of cannabis reduction will be examined in separate models. We will also examine the effects of reduced use by modeling day-by-day and week-by-week outcomes as a function of week-by-week reductions in cannabis, independent of treatment group. Linear MLM will be used to model normally distributed outcome variables *via* PROC MIXED. Generalized linear MLM will be used to model dichotomous and otherwise non-normally distributed outcome variables *via* PROC GLIMMIX.

E.4. Supplementary Aim.

To examine whether reduced cannabis use moderates or is moderated by other factors (e.g., sex differences), the models examined in Hypotheses 1a and 1b will be modified to include potential Level-1 (e.g., day-to-day craving, sleep) and Level-2 (e.g., sex, baseline cannabis use, self-efficacy) predictors as well as their interactions with week-by-week change in cannabis use. For instance, to determine whether a week-by-week reduction in cannabis use moderates the association of day-by-day cannabis use (or abstinence) with daily working memory, whether or not participants used cannabis that day (Level 1) will be added as a predictor of working memory as will its interaction with week-by-week change in frequency or quantity of cannabis use. This particular model could thus determine whether cannabis users demonstrate greater cognitive functioning on abstinent days when they reduce their cannabis use.

E.5. Power Calculations.

Power calculations are based on Hypotheses 1a and 1b and were performed with Power Analysis and Sample Size software (PASS, Version 12: NCSS LLC, Kaysville, Utah). We conservatively estimate that as many as 12 participants could potentially need to be excluded due to sustained abstinence, leaving a minimum of 60 participants available for analysis. The corresponding analyses make use of multilevel data with a total sample of up to 3,360 records (60 participants X 56 daily observations). Because there will only be 7 unique estimates per participant of week-to week change in frequency of cannabis use, a conservative minimum estimate of the effective sample size is 420 (60 participants X 7 weekly

observations). Although these observations are non-independent given clustering within participants, hence the use of MLM, accounting for variation between participants will reduce the error variance in the dependent variables. Thus, the effective sample size will very likely exceed 420. An effective sample size of 420 has 90% power to detect small-to-medium treatment effects equivalent to Cohen's d = 0.30 or associations equivalent to r = .16.

References

Adkisson, K., Cunningham, K.C., Dedert, E.A., Dennis, M.F., Calhoun, P.S., Elbogen, E.B., Beckham, J.C., & Kimbrel, N.A. (manuscript under review). Cannabis use disorder and post-deployment suicide attempts in Iraq/Afghanistan-era veterans.

Babor TF, de la Fuente JR, 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.

Beckham, J.C., Adkisson, K.A., Hertzberg, J., Kimbrel, N.A., Budney, A.J., Stephens, R.S., Moore, S.D., & Calhoun, P.S. (manuscript under review). Mobile contingency management as an adjunctive treatment for co-morbid cannabis use disorder and cigarette smoking.

Beckham, J.C., Calhoun, P.S. et al., 2013. Predictors of lapse in first week of smoking abstinence in PTSD and non-PTSD smokers. *Nicotine & Tobacco Research, 15,* 1122-9. PMCID: PMC3646653.

Bonnet, U., Borda, T…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-tetrahydrocannibinol and its metabolites in serum. *Drug and Alcohol Dependence, 155,* 302-306.

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

Borges, G., Bagge, C.L., Orozco, R., 2016. A literature review and meta-analyses of cannabis use and suicidality. *J Affect Disord., 195,* 63-74.

Bovin, M.J., Black, S.K., Rodriguez, P., Lunney, C.A., Kleiman, S.E., Weathers, F.W., Schnurr, P.P., Spira, J., Keane, T.M., & Marx, B. (2018). Development and validation of a measure of PTSD-related psychosocial functional impairment: The Inventory of Psychosocial Functioning. Psychological Services, 15, 216-229.

Bruins, J., Pijnenborg, M.G…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,* 354-362.

Buckner, J.D., Crosby, R.D…Schmidt, N.B., 2012. Immediate antecedents of marijuana use: An analysis from ecological momentary assessment. *Journal of Behavior Therapy and Experimental Psychiatry, 43,* 647-655.

Budney, A.J., Moore, B A…Hughes, J.R., 2003. The time course and significance of cannabis withdrawal. *Journal of Abnormal Psychology, 112(3),* 393-402.

Budney, A.J., Novy, P.L., Hughes, J.R., 1999. Marijuana withdrawal among adults seeking treatment for marijuana dependence. *Addiction, 94(9),* 1311-1322.

Budney, A.J., Stanger, C…Walker, D.D., 2015. Computer-assisted behavioral therapy and contingency management for cannabis use disorder. *Psychology of Addictive Behaviors, 29,* 501-511.

Calhoun, P.S., Wiley, M…Beckham, J.C., 2007. Objective evidence of sleep disturbance in women with posttraumatic stress disorder. *Journal of Traumatic Stress,* 20, 1009-1018.

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.
Carney, C.E., Buysse, D.J…Morin, C.M., 2012. The consensus sleep diary: Standardizing prospective sleep self-monitoring. *Sleep,* 35, 287-302.
Carroll, K.M., Easton, C.J…Rounsaville, B.J., 2006. The use of contingency management and motivational/skills-building therapy to treat young adults with marijuana dependence. *Journal of Consulting & Clinical Psychology,* 74, 955-966.
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.
Copeland, J., Pokorski, I., 2016. Progress toward pharmacotherapies for cannabis-use disorder: An evidence-based review. *Substance Abuse and Rehabilitation, 7,* 41-53.
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.
Dennis, P.A., Kimbrel, N.A…Beckham, J.C., 2016. Trauma and autonomic dysregulation: Episodic – versus systemic – negative affect underlying cardiovascular risk in posttraumatic stress disorder. *Psychosomatic Medicine,* E-pub ahead of print.
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.
Donovan, D.M., Bigelow, G.E…Wells, E.A., 2011. Primary outcome indices in illicit drug dependence treatment research: Systematic approach to selection and measurement of drug use end-points in clinical trials. *Addiction, 107,* 694-708.
Dutra, L., Stathopoulou, G… Otto, M.W., 2008. A meta-analytic review of psychosocial interventions for substance use disorders. *The American Journal of Psychiatry,* 165, 179-87.
Godin, G. (2011). The Godin-Shephard leisure-time physical activity questionnaire. Health & Fitness *Journal of Canada, 4*(1), 18-22.
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.
Gwaltney, C.J., Shiffman, S…Paty, J.A., 2005. Dynamic self-efficacy and outcome expectancies: Prediction of smoking lapse and relapse. *J of Abnormal Psychology, 114,* 661-675.
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.
Hasin, D.S., Saha, T.D…Grant, B.F., 2015. Prevalence of marijuana use disorders in the United States between 2001-2002 and 2012-2013. *JAMA Psychiatry, 72,* 1235-1242.
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.

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

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

First MB, Williams JBW, Karg RS, et al., 2015. *Structured Clinical Interview for DSM-5*. American Psychiatric Association: Arlington, VA.

Gentes, E.L., Schry, A.R…Calhoun, P.S., 2015. Prevalence and correlates of cannabis use in an outpatient VA posttraumatic stress disorder clinic. *Psychology of Addictive Behaviors, 30,* 415-421.

Gioia G.A., Isquith P. K., Guy S. C., Kenworthy L., 2000. *Behavior Rating Inventory of Executive Function*. Odessa, FL: Psychological Assessment Resources.

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.

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.

Kadden, R.M., Litt, M.D… Petry, N.M., 2007. Abstinence rates following behavioral treatments for marijuana dependence. *Addictive Behaviors,* 32, 1220-36.

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., 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., Calhoun, P.S…Beckham, J.C., manuscript in preparation. *Mental health outcomes as a function of cannabis use disorder remission status.*

Kimbrel, N.A., Meyer, E.C…Morissette, S.B., in press. 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.*

Kimbrel, N.A., Newins, A.R... Calhoun, P.S., 2017. Cannabis use disorder and suicide attempts in Iraq/Afganistan-era veterans. *Journal of Psychiatric Research, 89,* 1-5.

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.

Kessler, R.C., Andrews, G., et al., 2002. Short screening scales to monitor population prevalence and trends in nonspecific psychological distress. *Psychological Medicine. 32(6),* 959-976.

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.

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.

Lattal, K.A., 2010. Delayed reinforcement of operant behavior. *Journal of the Experimental Analysis of Behavior,* 93, 129-39.

Lee, D., Huestis, M.A., 2014. Current knowledge on cannabinoids in oral fluid. *Drug Testing and Analysis,* 6, 88-111.

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.

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.

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.

Petry, N.M., DePhilippis, D., Rash, C.J., Drapkin, M., McKay, J.R., 2014. Nationwide dissemination of contingency management: The Veterans Administration initiative. *The American Journal on Addictions,* 23, 205-210.

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.

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.

Schafer, J.L., Graham, J.W., 2002. Missing data: Our view of the state of the art. *Psychological methods*, *7*, 147-177.

Schreiner, A.M., Dunn, M.E., 2012. Residual effects of cannabis use on neurocognitive performance after prolonged abstinence: A meta-analysis. *Experimental and Clinical Psychopharmacology, 20,* 420-429.

Schuster, R.M., Hanly, A., Gilman, J., Budney, A.J., Vandrey, R., Evins, A.E., 2016. A contingency management method for 30-days abstinence in non-treatment seeking young adult cannabis users. *Drug Alcohol Depend, 167,* 199-206.

Schuster, R.M., Mermelstein, R.J., Hedeker, D., 2015. Acceptability and feasibility of a visual working memory task in an ecological momentary assessment paradigm. *Psychological Assessment, 27,* 1463-1470.

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

Sherman, B.J., McRae-Clark, A.L., 2016. Treatment of cannabis use disorder: Current science and future outlook. *Pharmacotherapy, 36,* 511-535.

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.

Stanley, B., & Brown, G.K. (2012). Safety planning intervention: A brief intervention to mitigate suicide risk. *Cognitive and Behavioral Practice, 19*, 256-264.

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.

Substance Abuse and Mental Health Services Administration, 2014. *Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings (*HHS Publication No. (SMA) 14-4887. NSDUH Series H-49). Rockville, MD: Substance Abuse and Mental Health Services Administration.

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).

Tiffany, S.T., Friedman, L… Jackson, R., 2011. Beyond drug use: A systematic consideration of other outcomes in evaluation of treatments for substance use disorders. *Addiction, 107,* 709-718.

Tomko, R.L., Carpenter, R.W…Trull, T.J., 2014. Measuring impulsivity in daily life: The Momentary Impulsivity Scale. *Psychological Assessment, 26,* 339-349.

Ulmer, C.S., Calhoun, P.S…Beckham, J.C., 2009. Sleep disturbance and baroreceptor sensitivity in women with posttraumatic stress disorder. *Journal of Traumatic Stress,* 22. PMCID: PMC2798909.

Ulmer, C.S., Calhoun, P.S…Beckham, J.C., 2013. Nocturnal blood pressure non-dipping, posttraumatic stress disorder, and sleep quality in woman. *Behavioral Medicine,* 39, 111-121. PMCID: PMC3964784.

Üstün TB. (2010). Measuring health and disability: Manual for WHO disability assessment schedule WHODAS 2.0. WHO.

van der Pol, P., Liebregts, N., Graaf, R.D., Korf, D.J., van den Brink, W., & van Laar, M. (2013). Validation of self-reported cannabis dose and potency: An ecological study. *Addiction,* 108, 1801–1808.

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.

Volz, A.R., Dennis, P.A…Beckham, J.C., 2014. The role of daily hassles and distress tolerance in predicting abstinence among smokers. Nicotine and Tobacco Research, 16, 872-5.

Watson, D., Clark, L.A., Tellegen, A., 1988. Development and validation of brief measures of positive and negative affect: The PANAS scales. Journal of Personality and Social Psychology, 54(6), 1063–1070.

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

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

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.