Administrative Information

1. TITLE: Cannabis's Impact on Alcohol Motivation and Consumption: Trial Protocol

2a. TRIAL REGISTRATION: ClinicalTrials.gov: NCT02983773; IND Number: 129490

3. PROTOCOL AMENDMENT NUMBER: 17; PROTOCOL VERSION DATE: July 9, 2020

4. FUNDING: National Institute of Health, National Institute on Alcohol Abuse and Alcoholism (R01 AA024091)

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5b. Trial Sponsor: National Institute of Health, National Institute on Alcohol Abuse and Alcoholism.

Introduction

6a. BACKGROUND AND RATIONALE:

Among individuals with alcohol use disorders (AUDs), cannabis use disorder (CUD) is the most prevalent comorbid drug use disorder (Agrawal et al., 2007; Regier et al., 1990; Stinson et al., 2006). Cannabis use has been associated with greater number of heavy drinking episodes (Midanik et al., 2007; Pape et al., 2009; Schulenberg et al., 2005; Stinson et al., 2006; Windle & Wiesner, 2004) and worse AUD treatment outcomes (Staiger et al., 2013). Among patients with alcohol dependence, cannabis use following alcohol treatment appears to reduce sustained remission from alcohol and increases risk of alcohol relapse (Aharonovich et al., 2005; Mojarrad et al., 2014). Cannabis enhances the subjective effects of alcohol (Lukas & Orozco, 2001) and

increases motivation for alcohol use (Colombo et al., 2005, 2007; Linsenbardt & Boehm, 2009; López-Moreno et al., 2012; McMillan & Snodgrass, 1991), which may explain why it hinders alcohol treatment and maintains heavy drinking. However, findings from the few human studies on cannabis's acute influence on alcohol motivation are limited (Ballard & de Wit, 2011; Lukas et al., 1992; Lukas & Orozco, 2001) and little is known about the mechanisms by which cannabis may lead to increased alcohol use.

The endogenous cannabinoid system (eCB) has been implicated in reward and motivational circuits and as a relevant contributor to alcohol use disorder (de Fonseca & Schneider, 2008). Animal studies have found that cannabis increases motivation for alcohol (Colombo et al., 2005, 2007; Linsenbardt & Boehm, 2009; López-Moreno et al., 2012; McMillan & Snodgrass, 1991), which ultimately may increase the probability of drinking to high levels of intoxication. Alcohol craving and demand may increase as a result of cannabis-induced positive subjective effects; higher cannabis doses may also induce aversive effects (e.g., anxiety) that may in turn lead to anticipation of relief from such negative affective states with alcohol; cannabis may affect executive functions including disinhibition and working memory (Metrik et al., 2012; Ramaekers et al., 2006, 2009), which could increase preference for alcohol, potentially at excessive levels. When smoking cannabis, individuals may value alcohol more highly because cannabis administration can potentiate subjective intoxication from alcohol, particularly at lower doses (Lukas & Orozco, 2001) and alcohol consumed shortly after cannabis smoking can enhance THC plasma levels (Hartman et al., 2015; Lukas & Orozco, 2001).

To date, no human studies have fully examined whether and how cannabis increases motivation for alcohol and alcohol consumption. This laboratory study will employ a repeated measures experimental design to examine the effect of 7.2% THC and 3.1% THC dose of cannabis, relative to placebo, on alcohol craving and on subsequent drinking in an alcohol choice task in which participants choose either to drink or receive monetary reinforcement for drinks not consumed (Drobes et al., 2003; O'Malley et al., 2002). The study will recruit up to 336 individuals who are non-treatment seeking, endorse heavy episodic alcohol use, and smoke cannabis at least twice weekly to account for attrition in order to obtain 150 participants as the total sample.

7. OBJECTIVES:

1. To test cannabis's acute effects on incentive salience of alcohol after exposure to alcohol cues and on alcohol consumption, as indexed by: 1) subjective craving for alcohol and 2) alcohol consumption (number of drinks consumed on an alcohol choice self-administration task). These domains are all components of "wanting" alcohol. We hypothesize that, relative to placebo, cannabis (with 3.1% THC, 7.2% THC) will dose-dependently increase alcohol craving and amount of alcohol consumed in the context of alternative monetary reinforcement.

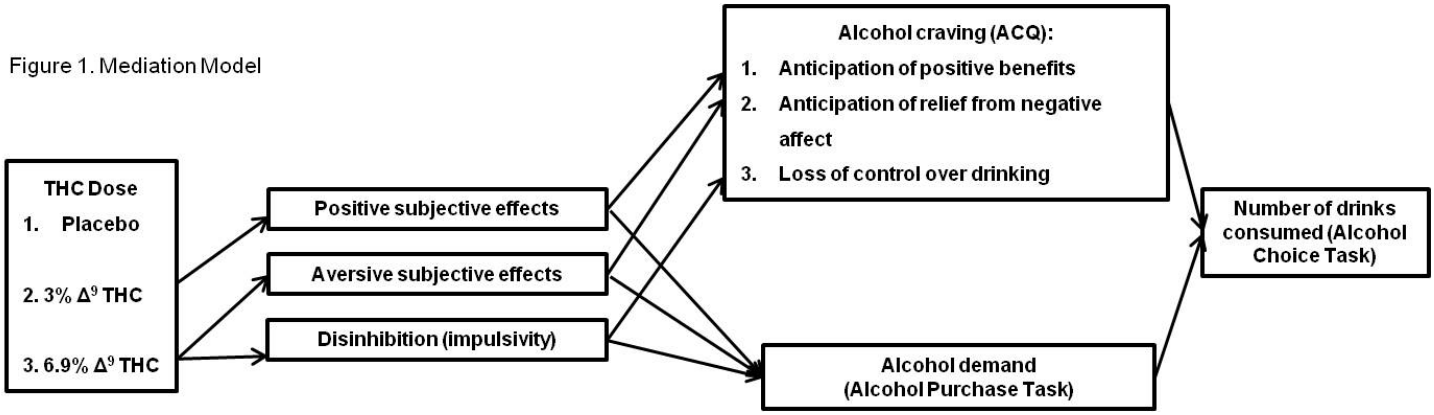
2. To identify mechanisms (mediators) whereby cannabis may acutely increase alcohol motivation.
2.a. The effect of cannabis dose on increases in alcohol demand (on the alcohol purchase task) will be mediated by increases in (a) positive subjective effects, (b) aversive subjective effects (7.2% THC dose only), and decreases in executive control (c) disinhibition of prepotent response on the Stop Signal Task.
2.b. The effect of cannabis dose on increases in specific dimensions of alcohol craving (as indexed by the 3 subscales on the alcohol craving questionnaire (ACQ) will be mediated by the following: (a) ACQ anticipation of positive benefits mediated by positive subjective effects; (b) ACQ anticipation of relief from negative affect craving subscale mediated by aversive subjective effects at the high THC dose (7.2%), (c) ACQ loss of control over drinking mediated by increases in disinhibition.

3. To identify potential moderators of cannabis's acute effect on alcohol dependent variables. The effects of cannabis dose on the dependent variables will be moderated by a) alcohol use disorder severity, b) affective vulnerability, and c) trait impulsivity such that dose-dependent effects will be greater among those with a) more severe DSM-5 alcohol use disorder, b) low tolerance for negative emotions and high sensitivity to anxiety (specific to the high THC dose), and c) greater trait impulsivity, d) greater deficits in working memory (Trail Making Test B, N-BACK, Complex Working Memory Span Tasks).

Mediators (see Figure 1)	Moderators
Positive subjective effects Aversive subjective effects Disinhibition/impulsivity (Stop Signal Task)	Alcohol use disorder (AUD) severity Affective vulnerability (distress intolerance, anxiety sensitivity) Working memory

This human cannabis administration research will provide the most comprehensive controlled test of how cannabis affects alcohol motivation and consumption. It may yield substantial information about the mechanisms whereby cannabis may pose a risk for the development and maintenance of problem drinking; the relative roles of these different mechanisms could inform clinical treatment and prevention efforts. The outcomes of this investigation have direct implications for public health policy as they can inform efforts to reform cannabis legislation by bridging the gap between the public's considerable misconception about perceived low risks from cannabis and lesser-known risk of increased drinking from cannabis. Characterizing cannabis's putative effects on alcohol can potentially decrease consumption by framing public health messages and via regulation of advertising and retail marketing practices in states that have or will move towards cannabis legalization.

Figure 1. Mediation Model



8. TRIAL DESIGN: Repeated measures double-blind crossover design.

Methods: Participants, interventions, and outcomes

9. STUDY SETTING: Brown University, Providence, RI, United States of America.

10. ELIGIBILITY CRITERIA: English speaking, age 21 to 44, past month cannabis use ≥ twice weekly and ≥ weekly in the past six months, positive urine toxicology screen for THC at baseline, smoking as a familiar mode of cannabis administration, heavy episodic drinking (≥5 drinks for men, ≥4 drinks for women per occasion) ≥ once monthly over the past 12 months[1], not meeting criteria for current DSM-5 major depressive episode, manic or hypomanic episode, panic disorder, or psychotic symptoms as assessed by the SCID, ability to abstain from alcohol and cannabis for 24 hours without withdrawal (Clinical Institute Withdrawal Assessment for Alcohol, revised-CIWA-AR score < 8 at each experimental visit), no intent to quit or receive treatment for cannabis or alcohol use disorder, negative pregnancy test and not nursing, negative urine toxicology screen for drugs other than cannabis, no contraindicated medical issues and body mass index ≤ 30 and weighing < 250 lbs confirmed via physical exam, no history of seizures; ≤20 tobacco cigarettes daily for tobacco smokers; history of simultaneous alcohol and cannabis use on the same occasion.

10a. ELIGIBILITY CRITERIA selection:

[1] Eligibility criteria for heavy episodic drinking changed from twice per month to once per month on 10/27/2017 after 15% of the sample was recruited.

The lower limit of the 21-44 age range was selected due to the ethical and legal restrictions and risks of alcohol administration to younger individuals. Younger individuals (< 30 years of age) and middle-age individuals (between 31 and 50) have the highest rates of cannabis and alcohol use (SAMHSA, 2019). Cardiovascular risk (e.g., myocardial infarction/fatal coronary heart disease) (Vassale et al., 2009; Stramba-Badiale et al., 2006; Dhingra & Vasan, 2012; Barnett et al., 2006; Mozaffarian et al., 2015) significantly increases in middle age (i.e., after the age of 40), and cardiovascular risk is of particular concern due to the well-established acute effects of cannabis involving ventricular tachycardia and increased risk of myocardial infarction in individuals with underlying cardiovascular disease (Goyal et al, 2017). Further, there are notable differences in liver function (Cieslak et al., 2016; Meier et al., 2008), body composition (i.e., decreased lean muscle, mass, decreased volume of body water) (St-Onge & Gallagher, 2010), and resting metabolic rates (Krems et al., 2005) that alter the body's ability to process alcohol in later middle age. Thus, the cutoff age of 44 was conservatively selected to minimize health risks and to ensure findings on alcohol-related outcomes would not be confounded by age-related changes.

History of simultaneous alcohol and cannabis use is assessed at study screening with the following question, "*Have you ever used marijuana and drank alcohol on the same occasion?*" This criterion was included for ethical and for safety reasons to ensure participants have prior experience of using cannabis and alcohol on the same occasion. It also ensures findings are generalizable to all individuals who co-use cannabis and alcohol.

11a. INTERVENTIONS: Three experimental double-blind sessions in which participants smoke 1 cannabis cigarette with 7.2% THC, 1 cannabis cigarette with 3.1% THC, and 1 cannabis placebo cigarette, with the order of administration counterbalanced across subjects.

11b. Discontinuing the administration of cannabis and alcohol in an experimental session

1) Consistent with our prior alcohol and cannabis administration studies, if a participant experiences any behavioral or physiological adverse reaction to cannabis (e.g., an acute anxiety reaction to cannabis, dose-related tachycardia) or alcohol (e.g., nausea, vomiting), they can always stop smoking cannabis or drinking alcohol (which is self-administered) at any point during the study session. The nurse coordinator is a research nurse with specific experience in managing drug administration studies and along with the experimenters conducting sessions will be well-trained to handle the most likely adverse drug effects. To maximize detection of negative consequences, participants will be monitored continuously during cannabis administration, alcohol self-administration and absorption phases, and monitored afterwards so that medical attention can be rendered if required. Participants are kept under direct observation in a safe private environment and are not released until the acute drug effects have dissipated.

2) Self-administration of each drug will also be stopped in the event that the nurse coordinator or the physician determines further self-administration is not behaviorally or medically safe for them to continue.

3) In the event that a BrAC level exceeds .10 g/dl, alcohol self-administration task will be stopped.

<u>Discontinuing an individual participant from the study</u>

Participant enrolled in the study may be withdrawn/discontinued from the study under the following circumstances:

1) As stated in the informed consent, if a participant chooses not to finish smoking the designated dose of the cannabis cigarette, they will not be able to continue in the study (but will receive compensation for their participation up to that point).

2) If a participant's safety is at risk at any point in the study (e.g., new report of taking a medication for which alcohol or cannabis is contraindicated; positive pregnancy test for female participants at any study visit; report of any new medical condition that was not previously reported at the physical exam or exacerbation of a medical problem for which alcohol or cannabis use is contraindicated; adverse reaction to cannabis or alcohol for which the nurse coordinator and/or study physician determine further participation in the study is no longer safe).

3) If a participant is unavailable to complete the study sessions in the designated timeframe, as stated in the informed consent, at the discretion of the Principal Investigator.

4) New report of a participant receiving treatment for alcohol or cannabis use since the study screening

Discontinuing the study

All adverse events are reported to the Brown University IRB, the study sponsor (the NIH: NIAAA), and the FDA in accordance with Investigational New Drug (IND) regulations Sec. 312.32. If either cannabis, alcohol, or their interaction are deemed to cause serious adverse events and/or life-threatening events that are determined to be study-related, we will consider discontinuation of the study on the advice of the IRB, the study sponsor, and the FDA.

12. OUTCOMES:

Primary Outcome Measure: Alcohol craving [Time Frame: prior to smoking (T_0) and at 12 minutes (T_1: post-smoking), 47 minutes (T_2: post neutral cues), 58 minutes (T_3: post alcohol cues), 116 minutes (T_4: end of Alcohol Choice block 1), and 178 minutes (T_5: end of Alcohol Choice block 2) on the Alcohol Craving Questionnaire-Short Form-Revised (ACQ-SF-R) and a single alcohol urge item. ACQ-SF-R is assessed on a 1="strongly disagree" to 7="strongly agree" scale, with higher scores indicating greater urge, and averaged to yield a total craving score. Alcohol urge is assessed with a single item "*I have an urge for alcohol*" on a 1="strongly disagree" to 7="strongly agree scale," with higher scores indicating greater urge, at T_0, T_1, and T_5.

Secondary Outcome Measure: Percent of total available alcohol consumed [Time Frame: post-smoking during the two-hour alcohol choice task during the experimental session].

13. PARICIPANT TIMELINE: Following remote screening procedures (see data collection methods below), participants complete a baseline session followed by 3 experimental sessions. All experimental sessions are conducted at least 5 days apart and within three weeks from the previous session. If participants are unable to complete the sessions within this time frame, they may be withdrawn from the study at the discretion of the Principal Investigator. The PI allows participants to complete sessions outside of the 5-21 day timeframe due to extenuating circumstances (e.g. winter break, inclement weather, sickness, shared lab space scheduling conflicts, etc.)

14. SAMPLE SIZE: A sample size of 120 is required to test Primary Aim 1: cannabis's acute effects on incentive salience of alcohol after exposure to alcohol cues and on alcohol consumption, as indexed by subjective craving for alcohol and alcohol consumption (percent of total available alcohol consumed on an alcohol choice self-administration task).

Power estimates and sample size calculations were conducted with a two-tailed $\alpha = .017$ and power of at least .80 (Cohen, 1988). Effect size estimate was informed by our preliminary results and the literature (Ballard & de

Wit, 2011; Lukas & Orozco, 2001; Metrik et al., 2011, 2012), which indicated a large effect of cannabis administration (3.0%THC) on positive subjective effects (d = 2.45), a moderate effect on negative emotional processing (d = .56), a small (sr^2 = .03) effect on disinhibition; a small effect (d = .12) of cannabis cue reactivity on alcohol craving. The effect size of low dose of THC combined with low dose of alcohol on self-report of "wanting more drug" was found to be large, r^2 = .48 (Ballard & de Wit, 2011). The effect size for a low dose of alcohol pretreatment combined with moderate dose cannabis on the number r^2 = .47 and duration r^2 = .63 of euphoric events was found to be large (Lukas & Orozco, 2001). The above referenced literature demonstrates highly relevant effect size estimates, although there is no one study that has tested directly the hypotheses in this application. Thus, we assumed conservatively that the effect of cannabis administration on alcohol craving and consumption will be at least of medium magnitude, accounting for at least 5% of the variance in a given alcohol DV. With power of .80 and alpha at .01, a sample size of 120 would be required to detect an effect of cannabis dose when tested in conjunction with the relevant covariates.

15. RECRUITMENT: Participants are recruited through advertisements in newspapers, on Craig's list, through community bulletin boards including digital university-specific newsletters, and community-based events. Responders to study advertisements are asked to complete an initial brief screen using online survey software. If eligible, they are then screened by phone), followed by more rigorous screening at baseline for inclusion criteria.

16. Methods: Assignment of interventions (for controlled trials)

16a. SEQUENCE GENERATION: Randomization to the cannabis dose order for the three available doses (i.e., 7.2%, 3.1%, and 0% THC) occurs before the first experimental session. The six predefined order permutations are: (1, 2, 3), (1, 3, 2), (2, 1, 3), (2, 3, 1), (3, 1, 2), and (3, 2, 1). For randomization to one of the six orders, each participant is assigned to the next available order in the sequence. Once all orders are filled, the assignment continues from the beginning of the list, ensuring all orders are used in a balanced manner.

16b. ALLOCATION CONCEALMENT MECHANISM: In order to maintain double-blind conditions (participants and research assistants), cannabis cigarettes are prepared by the PI or Co-I who randomizes participants to the cannabis dose conditions but who has no contact with study participants.

16c. IMPLEMENTATION: The PI or Co-I assigns participants sequentially to the next available drug dose order.

17a. BLINDING: Research assistants and participants remain blinded to the cannabis dose order assignment.

17b. Unblinding may be permissible if necessary in the event that an individual participant were to be discontinued from the study if their safety were at risk (e.g., adverse reaction to cannabis or alcohol for which further participation in the study is no longer safe).

18. Methods: Data collection, management, and analysis

18a. DATA COLLECTION METHODS:

The following sections describe protocol procedures from the start of study recruitment in February 2017 through March 16, 2020 when research operations were ceased due to the mandatory COVID-19 pandemic laboratory closure. The study was permitted to resume laboratory research operations in July 2020 under a modified protocol due to COVID-19 precautions and was completed in May 2021. As a result of the COVID-19 pandemic, some of the in-person research procedures were suspended. Specifically, the modified study protocol did not include blood collection or computer-based tasks during the experimental sessions. Study screening procedures were also designed to minimize in-person contact [see COVID-19 Modifications to Protocol below].

Design Overview. This project uses a within-subjects repeated measures experimental design to examine the effect of 7.2% THC and 3.1% THC dose of cannabis, relative to placebo, on alcohol craving, cue-induced incentive salience, and subsequent drinking in an alcohol choice task in which participants choose either to

drink or receive monetary reinforcement for drinks not consumed. Following remote screening procedures, participants complete an in-person screening visit with physical exam, a basement assessment, and three experimental double-blind sessions in which they smoke a 7.2% THC, 3.1% THC, and a cannabis placebo (0.0% THC) cigarette, with the order of administration counterbalanced across participants. At each session, participants complete alcohol cue reactivity procedures after the cannabis smoking followed by the alcohol choice task.

Procedures. Responders to study advertisement will be first asked to complete an initial brief online screen. If eligible, they will then be further screened on the phone by a research assistant to ensure that they meet the self-reported study inclusion criteria. If an individual qualifies for participation on the phone, we will provide information about the study procedures (e.g., medical screening, drug testing, smoking cannabis, and drinking alcohol), potential risks and benefits, and confidentiality. Participants will be told to refrain from all cannabis and tobacco smoking for 15 hrs, alcohol for 24 hrs for all laboratory sessions, and avoid eating or consuming any caffeinated beverages for 2 hrs prior to all experimental sessions.

COVID-19 Modifications to Protocol: Remote Screening Session. After phone screening, participants complete a videoconference (Zoom) session conducted by a research staff member. During this remote session, participants review and digitally sign a consent form in Qualtrics. It will be made clear that all information obtained during assessments is confidential. Participants are also informed in the consent of the voluntary nature of the study and their right to choose not to participate, and the PI's name and research office phone number will be provided should they have questions. The participant will be provided with a copy of the consent form via email. Then they complete online questionnaires in Qualtrics and interviews to confirm initial study eligibility. These assessments, including the SCID-5-RV (Research Version), to rule out major DSM-5 diagnoses, and a medical screening questionnaire, are administered by clinically-trained RAs. Those eligible schedule an in-person visit to the study center for further screening. Following the in-person screening and physical exam, eligible participants will complete online baseline questionnaires in Qualtrics prior to the first experimental session.

In-person Baseline Screening Session: The study's informed consent will be signed at the beginning of the baseline session (in the pre-COVID protocol). The participant will be provided with a copy of the consent form and an original will be kept in a locked filing cabinet. After informed consent, participants will complete an alcohol breath analysis, a urine drug screen and pregnancy (women only), and a carbon-monoxide (CO) reading to confirm no recent smoking. Those with a positive breath alcohol concentration (BrAC) or a positive screen for drugs other than cannabis will reschedule baseline assessment. A positive THC screen will be required at this time to confirm cannabis use status. For those with a CO reading of more than 8 ppm, research staff will consult with the PI on a case-by-case basis, as it would be difficult to confirm overnight cannabis abstinence with higher CO levels (tobacco smokers will be allowed to smoke a cigarette following the CO test to prevent nicotine withdrawal) but rescheduling all such appointments may lead to participant attrition. We (Metrik et al., 2012) and other cannabis researchers (Cooper & Haney, 2009) have been using these CO-based procedures with the overnight window to avoid the onset of cannabis withdrawal, because negative urine THC screen to rule out residual effects of cannabis could require several weeks. The SCID-5-RV (Research Version), to rule out major DSM-5 diagnoses, and a medical screening questionnaire will be administered next by clinically-trained RAs. Participants will also have their height, weight, and vital signs measured to confirm study eligibility. Those eligible will continue on to complete a medical screening exam. This physical exam must be completed prior to the first experimental session. The exam will be conducted by the study physician or nurse practitioner. This individual will determine that recruits are physically healthy and have no medical conditions that would carry a risk from acute exposure to cannabis or alcohol. Participants' body mass index in the range of 18.5-30 kg/m^2 and under 250 lbs will also be confirmed during the medical exam (extreme BMIs can also influence drug blood levels, and BMIs in the obese range are considered cardiovascular risk factors). The physician or nurse

practitioner conducting the physical exam may determine, based on his or her medical expertise, that a participant needs to complete an electrocardiogram (EKG) to provide an additional safety measure. The EKG will also be administered to every individual over the age of 40. If medical history or exam precludes participation, the recruits will be informed about the reason they were ineligible to participate. We will provide referral information for psychiatric services and substance use treatment to all participants who meet criteria for exclusionary DSM-5 disorders or re-screen positive for other illicit drugs on the urine toxicology test and are thus ineligible to participate in the study. All assessment instruments will be administered by study research assistants who are specifically trained in these assessments. Following the in-person screening and physical exam, eligible participants will next complete baseline study assessments prior to the first experimental session.

Randomization: Prior to the first experimental session, eligible participants will be randomized to either the 7.2% THC, 3.1% THC, or 0% THC dose for the first experimental session and will receive the other dose(s) at the following sessions. In the study consent, participants will be informed that they will receive three different strength cannabis cigarettes ("Dose A" ,"Dose B", "Dose C") varying in their concentrations of delta-9-THC in the low to moderate potency range (Haney et al., 2008). Placebo cannabis is harder to disguise in longitudinal designs with repeated exposure to placebo cigarettes. Therefore, in the consent, the 0.003% THC dose is intentionally described as a "low" dose rather than placebo to avoid potential expectancy effects (Metrik et al., 2009). This is indeed a low dose, as a small proportion of THC is still contained in placebo cigarettes.

Experimental Cannabis/Placebo Administration Sessions:

Participants will complete the study in 4 in-person study visits (screening session/physical exam + 3 experimental sessions). For the three experimental smoking sessions, participants will be asked to refrain from all cannabis use and tobacco smoking for 15 hrs, refrain from alcohol use for 24 hrs, and avoid eating or consuming any caffeinated beverages for 2 hrs prior to the sessions. After checking alcohol breath level and CO levels, participants will complete a urine screening, and then consume a standardized lunch based on 400 kal. Participants will then complete pre-smoke measures (see Table 1 Schedule of Assessments), and a blood pressure (BP) cuff will be secured to record heart rate and BP during the entire experimental session. Participants will then smoke the assigned cannabis (or placebo) cigarette (see below) and complete questionnaires assessing subjective effects and a computer-based Stop Signal Task. Participants will then complete alcohol cue-reactivity (see below) with measures of state affect, alcohol urge, and Alcohol Purchase Task after both sets of cues. Then, they will complete the Alcohol Choice Task (see below). Alcohol self-administration is scheduled to begin at around 1:00 pm to allow for 2 hours of not eating before alcohol consumption and following consumption of the standardized meal at 11 am, in consideration of typical drinking time outside of the laboratory, and in consideration of wait time post drinking.

Cannabis Administration: Cannabis (7.2%, 3.1% THC) and placebo (0% THC) cigarettes are provided

by the NIDA Drug Supply Program. To conceal potential differences in color of placebo cannabis leaves, all cigarettes will be rolled at both ends. Following our standard protocol (Metrik et al., 2012) for paced-puffing procedures (Foltin et al., 1987), participants will be asked to smoke up to the 10 mm line at the end of the cigarette (a little over ¾ of the cigarette) to ensure participants smoke the same amount. We expect that most participants will smoke the entire cigarette in the allotted 10 minutes, as non-treatment-seeking cannabis users self-administer active cannabis virtually each time it is made available (Haney, 2009).

Alcohol Cue-Reactivity (CR) Procedure: This CR procedure includes direct sensory exposure to visual, tactile, olfactory, and proprioceptive stimuli associated with drinking alcohol and exposure to neutral control stimuli. The sensitivity of CR is further enhanced by use of personally-relevant alcoholic beverage cues (MacKillop et al., 2010). Once the reactivity procedures begin, all instructions are standardized and presented by an audio

recording. Participants will be first brought into a neutral room absent of any substance stimuli. They will sit at the table, and after the blood pressure/heart rate reading, will be instructed to remain in their seat and take a look around the room. Similar to procedures used in previous research (Stojek et al., 2015), neutral stimuli will be presented [these are always first to avoid carryover effects (Rohsenow et al., 2001)], which are an empty glass and a commercial bottle of water. Participants will then be instructed to pour a glass of water and asked to practice raising the glass up to their nose and inhaling the beverage before listening to the audio recording. Participants will then be asked to take one single sip of the beverage to increase reactivity to cues. The participant will begin the audio recording, and as instructed, will raise the glass up to their nose and mouth and inhale the smell of the water (4 olfactory exposures for ~5 s each). After the second blood pressure/heart rate reading, the post-neutral cues assessment measures are then taken. The participant will then be escorted to a separate room (i.e. bar lab) for the alcohol cue exposure. They will sit at the table, and after the blood pressure/heart rate reading, will be instructed to remain in their seat and take a look around the room. The active stimuli, an empty glass (a prototypical glassware for the type of alcohol provided) and participant's alcoholic beverage of choice, will be brought in. The participant is instructed to pour a glass of their preferred alcoholic beverage and asked to practice raising the glass up to their nose and inhaling the beverage before listening to the audio recording. Participants will then be asked to take one single sip of the beverage to increase reactivity to cues. The participant will begin the audio recording and as instructed, participants will raise it to their nose and mouth to inhale the smell of the beverage using the same procedures as the water trial. After the second blood pressure/heart rate reading, the post-alcohol cues assessment measures are then taken. The neutral cue exposure acts a controlled baseline against which to compare the effects of alcohol cues with matched standardized instructions (Rohsenow et al., 2001).

Alcohol Choice Task. Alcohol self-administration period will begin ~50 mins from the end of cannabis smoking. Consistent with the established procedures (Anton et al., 2004; Drobes et al., 2003; O'Malley et al., 2002), participants will complete two 60-min choice blocks, in which a tray containing 4 drinks (each designed to raise BALs 0.0125 g/dl based on age, sex, weight, and height, calculated via standard calculations (Brick, 2006) and a $12 "tab" in which each drink is worth $3 are presented during each block. They will be told they can choose to drink as many of the drinks as they desire over 45 mins or to receive the corresponding dollar amount for drinks not consumed. Any money earned during the self-administration will be paid at the end of each experimental session. Breath alcohol readings (BrACs), a reliable estimate of blood ethanol concentrations (Swift, 2003), will be obtained at 60 mins at the end of each block (at least 10 mins from last consumption), and the BAES-B (to measure subjective stimulation), ACQ (to measure alcohol craving), and SAM/VAS (to measure affect) will be administered at the end of each drinking block. Milliliters of alcohol consumed per each drink, time to first drink, and inter-drink time interval will be recorded. Furthermore, milliliters of alcohol consumed will be converted to standard drinks based on 17.7 ml (or 14 grams/0.789 per mL density) of alcohol in a standard drink in the U.S. (*What Is A Standard Drink?*, 2024).

Blood Sampling Procedures. We will collect a blood sample (15.5 ml at the first draw and 16.5 ml at the subsequent four draws at each study visit) for analysis of cannabinoid plasma levels and for cannabis-induced changes in hormones and other biomarkers potentially related to appetite, inflammation and stress pre-smoking and near expected peak blood levels at termination of the smoking procedure (10 minutes post-smoking onset). Blood samples will also be obtained before cue reactivity at 37 mins post-smoking onset prior to the alcohol choice task, at the end of the first 60-min alcohol choice block (110 minutes post-smoking onset) and at the end of the second 60-min alcohol choice block (170 minutes post-smoking onset). Similar collection time points have been used successfully in prior research (Hartman et al., 2015). Blood cannabinoid levels will decline following cessation of smoking but will still be detectable and significantly different from placebo at 90 minutes post-smoking onset (Hartman et al., 2015). Collection of blood samples at pre-smoking baseline and at two time points prior to the alcohol choice task will allow for examination of the dose-dependent effects of cannabis on alcohol cue-induced craving and alcohol demand. Collection of a blood sample 60 minutes post initiation of the alcohol

choice task will allow for exploratory analysis of the effect of cannabinoids combined with alcohol (BrAC levels) on subsequent alcohol drinking, subjective effects, biphasic effects, and alcohol craving. Because the timing, number of drinks, and subsequent BrACs will vary across the participants, we will examine the effect of cannabis dose combined with number of drinks consumed in the first 60-min block on subsequent alcohol consumption. We do not expect cannabis to have an effect on plasma ethanol levels at the lower alcohol doses, only after higher alcohol dose is consumed (Lukas et al., 1992) in the self-administration task. However, we do expect a greater increase in cannabinoid plasma levels and a significant increase in positive subjective effects of cannabis (Lukas & Orozco, 2001) after the initial amount of alcohol (up to BAL of 0.06 g/dl) for those participants who elect to consume. Therefore, following alcohol consumption in the first 60-mins, we will collect a blood sample for cannabinoid analysis. Breath alcohol readings (BrACs), a reliable estimate of blood ethanol concentrations (Swift, 2003), will be obtained during the two-hour self-administration period (see session timeline table). An I.V. cannula will be inserted in an antecubital vein for blood withdrawal before cannabis administration. Blood samples for cannabinoid assays are collected using 6ml lavender-top vacutainer tubes for each timepoint. Samples are put on ice immediately after collection, centrifuged, and extracted plasma is aliquoted into vials for storage at -80°C until they are shipped for analysis at the Analytical Psychopharmacology Laboratory of the Nathan Kline Institute for levels of delta-9-THC and its primary inactive metabolite 11-nor-delta-9-tetrahydrocannabinol-9-COOH by a validated method using liquid/liquid extraction, derivatization, and gas chromatography-tandem mass spectrometry (Shaw et al., 1991). Blood draws may not always be performed for all participants or for all time points for a given participant. The study nurse may deem it necessary to cease blood draws at any experimental session, at any time point, based on clinical judgment, and will notify the PI.

Sobriety Assessment: Three hours after the smoking (psychotropic effects of smoked cannabis taper off within 2-3 hours (Grotenhermen, 2003)), during which participants receive a meal and rest and only after their BrAC has descended to the target range of .04 g/dl, they will be evaluated for motor signs of intoxication, required to pass a field sobriety test (Hart et al., 2001; Metrik et al., 2012), and be able to leave via a taxi service (paid by the project) to avoid driving. Participants will be able to leave on their own if their breath alcohol level is at or below .02 g/dl as long as they avoid driving. During the rest period, participants will be allowed to read magazines or watch TV at their leisure.

Compensation: To receive the initial payment, participants must be found eligible based on the remote screening procedures and attend the first in-person baseline screening visit. At this baseline screening visit, participants will be paid $10 if found ineligible prior to the medical exam due to the urine screen, pregnancy test, or vital signs measurements. Participants will receive $25 for completing the medical exam and $25 for completing baseline assessments. Participants will receive $60 for completing each experimental session (Sessions 1-3). Participants can earn up to an additional $24 per experimental session during the alcohol choice task. This amount will be paid out at the end of each experimental session in addition to the $60. To incentivize participants to keep appointments as scheduled, participants will receive a $10 bonus at Session 1 and a $15 bonus at Session 2, if participants show up for the scheduled appointments or reschedule a study visit at least two business days in advance. We will minimize attrition between sessions by paying participants an additional $80 at the final session for completing all 4 in-person sessions (total of up to $407).

Table 1: Any non-eligibility questionnaire listed in this table under “Baseline Measures” or the “Pre-smoking” time points at an experimental session may be completed at a later session during the “pre-smoking” period due to extenuating circumstances, such as a participant arriving late to a session and the timing of the cannabis administration being fixed.

Screening & Baseline Measures were completed in-person prior to the COVID-19 protocol changes. Post-COVID-19 modifications to the protocol, measures marked with Z = completed in Zoom videoconference

session, Q = Qualtrics survey, and Q/Z=completed in Qualtrics and reviewed during Zoom session; PE = In-person screening/physical exam visit; X = in-person experimental visits.

Table 1. Assessment Instruments Schedule of Administration

	Screening & Baseline Measures	Experimental Cannabis+Alcohol Sessions 1, 2, & 3				
		Pre-Smoking	Post-smoking	Cue exposure	Post-Drinking (Block	Post-Drinking (Block
		Neu Alc				
Qualtrics Online Screen						
Telephone Screen						
Baseline Questionnaire + sex, race, ethnicity	Q/Z					
Demographics (sans sex, race, ethnicity)	Q					
Health Questionnaire (medical screen)	Q/Z					
Physical exam	PE					
Family History		X				
Trails A & B		X				
Stop Signal Task	X		X			
N-Back (computer)	X					
Structured Clinical Interview for DSM Disorders (SCID-5-RV)	Z					
Time estimation tasks-(computer)		X				
Attention set shifting-(computer)		X				
Complex Working Memory Span Tasks (computer)	X					
Psychomotor Vigilance Test (PVT)-computer		X				
NAB Numbers & Letters Test		X				
Timeline Follow Back	Z	X				
Breath Holding Task	X					
Tobacco Smoking Questionnaire	Q					
Alcohol Use Disorders Identification Task (AUDIT)	Q					
Short Inventory of Problems (SIP)	Q					
Alcohol Expectancy Questionnaire (AEQ)	Q					
Alcohol Purchase Task (APT-State)		X		X X	X	X

Alcohol Purchase Task (APT-Trait)	Q					
Marijuana History Questionnaire	Q					
Marijuana Problems Scale (MPS)	Q					
Reasons for Using Marijuana	Q					
Reasons for Using Medical Marijuana	Q					
Marijuana Effect Expectancy Questionnaire (MEEQ)	Q					
Marijuana Cessation Expectancies (MCE)	Q					
Marijuana Purchase Task- Trait (MPT-T-R3)	Q					
Marijuana Purchase Task – State (MPT)		X				X
Anxiety Sensitivity Index-3 (ASI-3)	Q					
Inventory of Anxiety and Depression Scale (IDAS)		X [1]				
Brief Positive and Negative Urgency Measure (UPPS)	Q					
Distress Tolerance Scale (DTS)	Q					
Tridimensional Personality Questionnaire (TPQ)	Q					
Readiness to Change Questionnaire/Rulers-Alcohol	Q					
Readiness to Change Questionnaire/Rulers- Marijuana	Q					
Clinical Institute Withdrawal Assessment of Alcohol (CIWA)		X				
Behavior Checklist Diary		X				
Alcohol Craving Questionnaire (ACQ)	Q	X	X	X X	X	X
Marijuana Craving Questionnaire (MCQ)	Q	X	X			X
Addiction Research Center Inventory (ARCI)		X	X		X	X
Marijuana Rating Form			X			X
Self-Assessment Manikin/Visual Analogue Scale		X	X	X X	X	X
Biphasic Alcohol Effects Scale (BAES-B)		X		X	X	X
Subjective Intoxication (SIE)		X			X	X
Blood Draw		X	X	X	X	X

18b. In order to enhance study retention procedures, eligible participants will be asked to provide contact information for two locators. Participants will be asked to provide the names of two friends or relatives who can act as locators in the event that the participant moves or does not respond to our outreach attempts. This information will be collected at the first experimental session. No information regarding the participant will be provided to the locators. If we are unable to track a participant, we will attempt to contact these locators via telephone and email. If a participant declines providing this information on locators, they can still participate in the study without any restrictions.

19. DATA MANAGEMENT:

Research material obtained from living human subjects.
Data will be collected directly from participants using (a) questionnaires and interviews; (b) physiological measures (i.e., heart rate and blood pressure); (c) assessment of smoking and drinking behaviors through observation; and (d) biochemical measures to verify abstinence from smoking, alcohol, and other drugs and to assess BrAC levels. Data will be obtained specifically for research purposes. As part of the screening process, participants will provide urine samples for pregnancy (female only) and toxicology screens for illicit drugs.

Linkages to subjects and access to subject identities.
For each stage of the research, participant names and contact information will be maintained in a recruitment/enrollment database during the course of the study. Once individuals enroll in the study, names will be linked to participant ID number in this database, which will be kept in a restricted access folder on a secure server. This file will be assigned a code name unrelated to the name of the study. Signed consent forms will be kept in a locked file cabinet, separate from any other project data. Consent forms signed in Qualtrics are digitally stored separate from any other project data. Once data collection is completed, the corresponding recruitment/enrollment database will be deleted as it is unnecessary to maintain the link between participant identity and study data. All information collected as part of this study will be accessible only to research staff who have completed mandatory training in the protection of human subjects.

20a. STATISTICAL METHODS: The dose-dependent effect of THC on alcohol DVs: (1) post-smoking urge to drink alcohol and cue-induced alcohol craving on the ACQ, and (2) amount of alcohol consumed on the Alcohol Choice Task will be tested using repeated measures mixed model analyses. The first step in the model tests Aim 1 (the primary outcome of the grant) and includes 1) static covariates (session order number), 2) session-varying (cannabis vs placebo dose) value of the respective DV assessed before smoking or after neutral cue (craving); 3) and dummy-coded cannabis condition with placebo as the reference group. Analysis of the percent alcohol consumed will mirror the above analytic approach.

20b. Methods for Plasma THC Concentrations Analysis

All participants included in the blood data analysis had data from the pre-smoking and immediate post-smoking timepoints, with some blood draws not done for 2 to 6 participants across the other three post-smoking timepoints. Blood samples collected post-smoking in the placebo condition were assayed for the first 25 participants because THC levels remain stable in this condition over several hours. To analyze cases where the post-smoking placebo values were not available, post-smoking cannabinoid levels in the two active THC conditions were compared to the pre-smoking placebo levels, covarying for the pre-smoking value of the respective active THC dose.

Methods: Monitoring

21a. DATA MONITORING: The following data and safety monitoring plan will be implemented for the protection of research participants and data. The study coordinator will monitor protocol adherence and will report to the PI. This individual will assess adherence via direct observation of the study visits, visual inspection of the completeness of data collection, verification procedures for the scanned scantrons of the case report forms, and all participant communication outside of study visits. Weekly reporting procedures are in place for routine operations and immediate/daily communication will take place depending on the time sensitive nature of communication. The PI will be informed immediately of any adverse event.

21b. N/A

22. HARMS:

Potential Risks to Subjects.

Potential risks in the study are considered minimal to moderate. Risks include: 1) intoxication and possible adverse reactions from cannabis, 2) adverse reactions to alcohol including dizziness, nausea and/or vomiting (and aspiration of vomit if asleep or unconscious); 3) injury due to slips and falls, physical constraint in response to aggressive behavior; fetal damage from alcohol consumption; 4) adverse interactions between alcohol and medications for which alcohol use is contraindicated (e.g., psychotropic drugs, antihistamines) or between alcohol and cannabis; 5) exacerbation of medical problems for which alcohol use is contraindicated; 6) aggravation of pre-existing alcohol problems or promotion of alcohol consumption for alcohol-dependent individuals; 7) breach of confidentiality and emotional discomfort from answering questions about personal behavior in the assessment including illicit substance use; and 8) risk of coercion.

Adequacy of Protection against Risks

We will make every attempt to minimize risks to participants throughout the study protocol, including loss of privacy or confidentiality and psychological and physical discomfort. Based on the prior experience of the PI (Dr. Metrik) co-investigators, we believe that our planned procedures (described below) will be highly effective for minimizing risk.

Protection against Risks

Medication and Alcohol-Cannabis Interactions: (1) Candidate subjects may be using medications for which alcohol or cannabis are contraindicated (e.g., psychotropic drugs, antihistamines). To safeguard against such reactions, enrollment procedures will involve questions regarding current medication or illicit drug use. The study physician or nurse practitioner will review all medications and determine the individual's eligibility. (2) Acute effects of combined cannabis and alcohol administrations on performance are additive with respect to performance impairment on tests of reaction time and psychomotor speed [e.g., (Perez-Reyes et al., 1988), and on driving performance (Bramness et al., 2010; Ramaekers et al., 2000). Furthermore, several studies demonstrated cross-potentiation of alcohol/cannabis effects with respect to increased duration of positive subjective effects of cannabis, higher THC plasma levels, and reduced blood alcohol levels along with positive subjective effects from both drugs at higher alcohol doses (Lukas et al., 1992; Lukas & Orozco, 2001). Therefore, it will be clearly stated in the consent form and to the participants verbally, that cannabis and alcohol can cause increased impairment and that a combination of these drugs may enhance the intoxicating effects. Our rigorous screening procedures help to ensure that only individuals who have experienced drinking alcohol and using cannabis concurrently and who are physically and psychologically healthy will be accepted for participation. We take multiple precautions and a very conservative approach to safeguard against any adverse reactions to cannabis and to alcohol administrations, as detailed below.

Intoxication and Adverse Reactions: Cannabis has been extensively studied in humans, and the dose selected is in the moderate range. The likelihood of an adverse physiological or psychological response to administration of cannabis is small since only participants experienced in the use of cannabis are included in the study and individuals with a history of adverse responses to cannabis will be excluded. The adverse effects caused by acute administration of a moderate dose of THC are minor and transient in nature (e.g., impaired ability to operate vehicles or heavy equipment). The most likely adverse drug effects are 1) an acute anxiety reaction to cannabis, and 2) dose-related tachycardia (Grotenhermen, 2003). Participants' heart rate and psychological state will be continuously monitored in the smoking sessions. The risk of a serious adverse drug reaction in experienced users is rare. Participants will be informed that, cannabis is classified as controlled substance; that it contains tar and smoking of these cigarettes results in carbon monoxide increases. Smoking a cannabis cigarette results in greater amount of tar inhaled and retained, as compared to tobacco due to differences in smoking behavior (e.g., inhalation) and a higher combustion temperature of cannabis (Grotenhermen, 2003). As

a psychoactive agent, delta-9-THC may impair judgment and/or decrease motor coordination, but these effects dissipate within 3 hours of smoking (Grotenhermen, 2003).

Alcohol has been extensively studied in humans, and the maximum dose that participants can consume is in the moderate range. Research with the same alcohol self-administration paradigms shows that participants drink 4 to 5 drinks on average (of the available 8) and that their blood alcohol levels average about .06 g/dl (Anton, 2008; Drobes et al., 2003; O'Malley et al., 2002). Furthermore, the likelihood of an adverse physiological or psychological response to administration of alcohol is small since only participants experienced in drinking the doses of alcohol administered in the study will be eligible. Even with the moderate level of drinking, participants could experience unpleasant side effects from acute alcohol exposure, including dizziness, nausea and/or vomiting (and aspiration of vomit if asleep or unconscious). To reduce the likelihood of these side effects only subjects who have previously had five or more drinks (four or more for females) on at least some drinking occasions in the prior month and only those who have experience with concurrent drinking and cannabis using will be permitted to participate. Participants who drink to a level of intoxication are at increased risk for injury due to slips and falls, or physical constraint in response to aggressive behavior. All participants will be kept under supervision until their BrAC has descended to a target, and will be provided a meal and TV to watch to ensure a positive environment.

Cannabis and/or alcohol will be administered in a central location, where daily alcohol and cannabis administration experiments are performed and where medical assistance is readily available in case of a serious medical emergency. A research nurse with specific experience in managing drug administration studies and along with the experimenters conducting sessions will be well-trained to handle the most likely adverse drug effects. To maximize detection of negative consequences, participants will be monitored continuously during cannabis administration, alcohol self-administration and absorption phases, and monitored afterwards so that medical attention can be rendered if required. If any significant adverse reactions are observed, the study physician, or nurse practitioner, will be available. This individual will review the participant's current status with the study staff and will advise whether emergency medical services should be called. Dr. Swift (Co-I) is a licensed medical physician and will be available to consult in the event of any significant adverse reactions. The PI (Dr. Metrik) and Co-I (Dr. Kahler) are licensed clinical psychologists readily available in case of any psychological adverse reaction. Participants are free to stop both cannabis and alcohol administration at any point during the experiment. Participants' heart rate and blood pressure will be regularly monitored during the whole experiment. Participants are kept under direct observation in a safe private environment and are not released until the acute drug effects have dissipated. To reduce the likelihood of injury following drinking or cannabis smoking, all participants will be monitored at all times and escorted to restrooms as needed by study staff. Participants who appear unsteady or otherwise exhibit difficulty walking, will be supported by their escort or placed in a wheelchair kept on site. Prior to departure from the laboratory, all participants will be evaluated for BrAC levels, motor signs of intoxication and will be required to pass a field sobriety test of walking a straight line heel to toe and a one-leg stand. After a minimum of 4 hours after completing smoking and once BrAC reaches .04 g/dl, we will provide a taxi service (paid by the project) to avoid driving only after satisfying the sobriety requirements. Participants will be able to leave on their own if their breath alcohol level is at or below .02 g/dl as long as they avoid driving.

Fetal Damage: Because of the potential effects of alcohol and drugs on fetal development, all participating women will be required to undergo a pregnancy test prior to all study sessions and will be asked to agree to use reliable birth control throughout the course of study participation if they engage in sexual intercourse with a man. Subjects who test positive for pregnancy will be informed that they have had a positive test result and are not eligible to participate in the study. They will be informed that it is possible to have a false positive and will be given information encouraging them to follow up with a medical provider of their choosing. Subjects who are positive for pregnancy or are nursing will be excluded from the study.

Contraindicated Health Conditions: Some subjects may have medical histories incompatible with safe participation in this study. Subjects with heart conditions, liver disease, diabetes, neurological disorders and any other medical conditions determined by the study physician to carry a risk from cannabis and alcohol administration would be excluded.

Aggravation of Drinking Problems: Some individuals volunteering to participate in the study may have a history of alcohol problems or meet criteria for alcohol dependence. Alcohol administration could result in an aggravation of these problems. To reduce the likelihood of this occurring, we will inquire as to participant's interest in receiving treatment for alcohol problems, and provide referrals to anyone who provides a positive response. To minimize the possibility of alcohol withdrawal, all participants reporting they are unable to abstain from alcohol for 24 hours without withdrawal are excluded at screening, and all eligible individuals are further screened before experimental sessions for alcohol withdrawal symptoms in person with the Clinical Institute Withdrawal Assessment for Alcohol revised (CIWA-Ar). Any participant with a CIWA score $\geq$ 8 at any time will be excluded and immediately referred for medical follow-up. In addition, participants with a history of seizures are excluded. During the course of the study, participants are monitored for withdrawal symptoms at each visit. Any participant who experiences significant withdrawal (CIWA score $\geq$8) will be referred for medical evaluation and possible treatment. Furthermore, this study is conducted in accordance with the NIAAA National Advisory Council recommended guidelines for the administration of ethyl alcohol and will minimize the chance of increased drinking due to the administration of alcohol.

Breach of Confidence: (see below 27. CONFIDENTIALITY)

Coercion: The risk of coercion is low, as the total amount of compensation during the study is modest and commensurate with the time and effort on behalf of participants: $25 for completing the entire in-person screening/physical exam visit, $25 for completing online questionnaires, $60 for each experimental session (up to $84 if the participant elects not to drink at any of the experimental sessions), bonuses of $10-$15 for keeping appointments as scheduled or rescheduling at least 2 days in advance for Sessions 1 and 2, respectively, and an additional bonus of $80 for completing all sessions (total of up to $407). All research staff will be specifically instructed in the need to avoid coercion. Additionally, participants will be assured that they are free to refrain from answering any questions or completing any tasks they find objectionable. Participants will be reminded that the information is confidential, and they do not need to share this information with anyone. Participants will be assured that participation in this study is strictly voluntary, that they can refuse to answer any questions, and that they may withdraw from the study at any time without penalty. This will be made clear to the participants during all phases of the study. Participants will be provided with the opportunity to ask any questions and discuss their reactions to the study in the brief counseling (see Potential Benefits section).

23. AUDITING:

Entities Conducting Monitoring:

Institutional Review Board (IRB) at Brown University, the Drug Enforcement Administration (DEA), and the Food and Drug Administration (FDA) will review this protocol and all procedures and will provide oversight. Monitoring will be done by the Principal Investigator, the IRB, the DEA, and the FDA.

What is Monitored?

Monitoring is done of all procedures to ensure that they conform to approved protocol; of unforeseen circumstances that might arise and affect safety; of all reports of serious adverse events as defined in 38 CFR 46 and the FDA 312.32 (death, life-threatening experience, new or prolonged hospitalization, persistent or significant disability/incapacity, or congenital anomaly/birth defect); of other significant adverse events (adverse events that lead to drop out by participant or termination by the investigator); of unexpected adverse

events (i.e., an adverse drug experience that has not been previously observed) resulting from the study; and of expected adverse events. Any participants found to be experiencing adverse events will be immediately evaluated by a physician (for physical AEs) or a licensed clinical psychologist (for psychiatric AEs). All AEs will be reviewed by the PI (Dr. Metrik) and Co-Is (Drs. Kahler and Swift) at their weekly meetings. Serious AEs will be reviewed immediately upon discovery.

Frequency of Monitoring:

All adverse events will be continuously monitored by the PI (Metrik) on the experimental days and as reported to the investigator in between those dates or thereafter. Participants will be given contact information so that they can inform us of events that occur in between study visits.

Monitoring by the IRB is conducted at the continuing reviews as scheduled, whenever modification requests are considered, and upon receiving reports of adverse events from the PI or anyone else. Monitoring by the FDA is conducted at the review of annual reports on the progress of the investigation from the PI, upon receiving reports of serious or unexpected adverse events as caused by the drug, and in the final report at the conclusion of the investigation. Additionally, the DEA monitors the adequacy of the drug inventory systems and storage safety in scheduled site inspection visits and reserves the right to carry out unannounced record inspections. NIH monitors the study upon receipt of annual progress reports and whenever other information is received.

Reporting Plan:

Adverse events are reported to the Brown University IRB, the NIH, and the FDA in accordance with Investigational New Drug (IND) regulations Sec. 312.32. Brown's IRB requires fatalities related to the study be reported within 24 hours, all other serious adverse events related to the study be reported within 5 business days, and other adverse events related to the study be reported at the continuing review. NIH requires reports of adverse events annually in the Progress Report. Any actions taken by the IRB other than acceptance will be reported to NIH along with any changes or amendments to the protocol requested by the IRB in response to these reports. Proposed changes or amendments to the protocol in general must be requested first in writing to the IRB, which will then grant or deny permission to make the requested change or amendment in protocol. NIH will subsequently be informed of any and all changes or amendments in approved protocol. FDA requires a written IND safety report of any adverse experience associated with the use of the drug that is both serious and unexpected within 15 calendar days after the PI's initial receipt of the information. The FDA also requires a telephone or a facsimile report of any unexpected fatal or life-threatening experience associated with the use of the drug within 7 calendar days after the PI's initial receipt of the information. They require a summary of all adverse events (including non-serious and/or expected ones) in an annual report.

Ethics and Dissemination

24. RESEARCH ETHICS APPROVAL: The study was approved by the Brown University Institutional Review Board (IRB).

25. PROTOCOL AMENDMENTS: All protocol amendments were approved by the primary investigator and Brown IRB before being implemented. Details of all amendments were saved in the primary study folder.

26a. CONSENT: Written consent will be obtained by trained study staff.

26b. ADDITONAL CONSENT PROVISIONS: An additional written consent will be collected for use of participant blood sample data for additional analyses in future ancillary studies.

27. CONFIDENTIALITY: Given the sensitive nature of this research, we will implement multiple procedures to protect the identity of subjects who volunteer for this study. Study staff will maintain strict confidentiality regarding all aspects of a subject's participation in this study. Any individual information gathered in the course

of the study will not be discussed with anyone who is not directly involved with this study. Breach of confidentiality is highly unlikely because all information will be identified with a numeric code only and stored in a locked file cabinet. An enrollment database linking names and study identification numbers will be kept in a secure folder separate from other subject data sources. Only grant staff will have access to this database. All staff are or will be fully trained in relevant ethical principles and procedures, including confidentiality. All assessment procedures will be closely supervised by PI Metrik. Participants will be tested individually in a secure online setting and laboratory on the Brown Campus. In addition, we have a Certificate of Confidentiality to protect the confidentiality of the consent forms and data.

28. DECLARATION OF INTERESTS: None

29. ACCESS TO DATA: Brown University is committed to the sharing of research data, consistent with the regulations and policies of the NIH. The investigators involved in this project intend to share findings from its research through publications and presentations. After all data have been collected and the primary results of the study have been published, de-identified data will be made available to other qualified investigators upon request. Institutions and/or individuals wishing to access any resources or data must contact PI Metrik. Data will be made available to be shared in two formats. One will be a summary of the data, with graphs and tables, collected as pdf files. These data will be made available upon request of the PI prior to publication. Also, data will be available as raw individual-level data for analysis. However, this will not be available until paper(s) are accepted for publication.

30. ANCILLARY AND POST-TRIAL CARE: N/A

31a. DISSEMINATION POLICY: Primary study results will be submitted for peer-reviewed publication and posted on clinical trials.gov.

31b. Authorship of publications will be determined according to APA guidelines, by attributing credit only to individuals who made substantial contributions to this research project, including conceptualizing the study design, collecting and analyzing data, interpreting results, and drafting the manuscripts, and who accept responsibility for the published work.

31c. Persons requesting access to the protocol or the data must do so in writing, identifying their affiliation and how and by whom the data will be used. The request will be evaluated by the PI Metrik and Co-Investigators to ensure that it meets reasonable demands of scientific integrity. When data are shared, there will be no limits placed on how the data will be used; however, a data sharing agreement will be required before the data sharing occurs. The data sharing agreement will require that (1) the recipient must not transfer the data to other users without prior permission of the PI, (2) that the data are only to be used for research purposes, (3) the recipient will not identify any individual or personal information, (4) that proper data security using appropriate technology and restricted access privileges will be in place at each level of data transmission and storage, and (5) proper citation of the data will be made in publications or other written materials. A record of the transfer of data, a record of the signed and dated data sharing agreement, and a copy of the dataset that was distributed will be kept by Brown University.

Appendices

32. INFORMED CONSENT. Two recent versions of the informed consent are included in the Appendix. Version 9 (Pre-COVID protocol) and Version 10 (Post-COVID protocol).

33. BIOLOGICAL SPECIMENS. N/A

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