Behavioral Pharmacology of THC and Alpha-pinene

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JHM IRB - eForm A – Protocol

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1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

1) Tetrahydrocannabinol (THC) has been the primary focus of cannabis research since its isolation and synthesis in 1964 (Gaoni and Mechoulam 1964). Currently there is a lot of debate regarding whether, and which, non-THC constituents of the cannabis plant contribute to the overall pharmacodynamic effects of cannabis. In recent publications, Ethan Russo has hypothesized that specific cannabis terpenoids, aromatic essential oil (EO) components, may selectively mitigate or exacerbate some acute effects of THC (McPartland and Russo 2001, Russo 2011, McPartland and Russo 2014). This purported "entourage effect" has been the driving force behind state legalization of cannabis for medicinal purposes despite THC (as dronabinol) being available as an FDA approved medication. However, there have been no empirical research studies conducted to evaluate the interactions of THC and terpenoids found in the cannabis plant. The proposed study will be a controlled human laboratory evaluation of the acute dose effects of THC and alpha-pinene (pinene) alone and in combination. Pinene is a flavor and fragrance component common to many plants (e.g., conifers), is one of the most abundant terpenoids in cannabis, is a fragrance ingredient in many household products, and is part of the typical human diet as it is a common food additive found in baked goods, beverages, candy, and ice cream. Oral ingestion of pinene is Generally Recognized as Safe (GRAS) by the US Food and Drug Administration and other regulatory agencies, and studies have been conducted evaluating its effects when inhaled in ambient air. Prior pre-clinical research has demonstrated that pinene administration can enhance memory (Buchbauer et al. 1993, Carvalho-Freitas and Costa 2002, Pultrini Ade, Galindo, and Costa 2006, Falk-Filipsson et al. 1993). Further evidence for pinene's potential as a memory enhancer, is the fact that it shares the same mechanism of pharmacological action (i.e., acetylcholinesterase inhibitor) as many medications prescribed to combat dementia (Perry et al., 2000). This study will evaluate whether pinene, compared with placebo, attenuates the memory impairing effects that often occur following acute THC administration. A controlled laboratory study will be

conducted with healthy adults who have experience inhaling cannabis. Participants will complete 6 acute drug administration sessions at the Behavioral Pharmacology Research Unit (BPRU). Sessions will involve double blind administration of: 1) Placebo, 2) 30mg THC, 3) 15mg pinene, 4) 30mg THC + 0.5mg pinene, 5) 30mg THC + 5mg pinene, 6) 30mg THC + 15mg pinene.

At baseline and following drug administration, a battery of subjective, physiological, and cognitive performance assessments will be completed and biological specimens obtained. The study will conclude when 20 participants complete all 6 experimental sessions. The outcomes of this study will be useful to inform clinical decision making and policy regarding the use of cannabis versus pure THC (dronabinol), and will provide needed empirical data to either support or refute claims made in the cannabis industry that pinene mitigates the anxiogenic effects of high doses of THC.

2. Objectives (include all primary and secondary objectives)

Objective 1: Examine the pharmacodynamics and pharmacokinetics of vaporized THC and pinene alone and in combination.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Delta-9-tetrahydrocannabinol (THC) is the primary psychoactive chemical constituent of the cannabis plant. The effects of THC have been well characterized in controlled research. Positive and/or therapeutic effects include feelings of euphoria, relaxed mood, enhanced enjoyment of music/art, as well as analgesic, anti-inflammatory, hypnotic, muscle relaxant, bronchodilatory, antiemetic, and appetite stimulant effects. Negative or unwanted side effects include dysphoria (panic, paranoia, acute psychosis), nausea/emesis dry mouth, irritated eyes, hallucinations, and cognitive impairment (working memory, divided attention, time estimation, complex cognition). These effects are produced through a combination of partial agonism at the CB_1 and CB_2 receptors, as well as non-receptor mechanisms (Russo 2011). For many, THC is synonymous with cannabis, and, over the past 30 years, illicit drug producers have selectively bred cannabis plants to contain ever-greater concentrations of THC, which now accounts for 15-25% of the dried flowers of the plant sold to consumers in the U.S. Also, with the advent of a legal medicinal and non-medicinal cannabis market in over half the U.S. states, a larger emerging product market of “concentrates” has developed. In production of these products, THC is extracted from the plant material resulting in a resin that contains 75-90% THC. Recently, a trend has emerged among manufacturers to “spike” these cannabis resins with select terpenoids or terpenoid combinations as a means of producing tailored pharmacodynamic effects.

A key controversy in understanding the pharmacology of cannabis is whether its behavioral and psychoactive effects are wholly accounted for by THC, or whether, in contrast, other cannabis components including “minor” cannabinoids (e.g. cannabidiol, cannabinol, cannabigerol) and terpenoids substantively influence its effects. Part of the problem has been compounded by the fact that cannabis supplied for experimentation in the USA is notably deficient in minor cannabinoid and terpenoid content as compared to that available via the black market, where plants are selectively bred to have specific cannabinoid and terpenoid profiles based on the belief that certain ratios confer different effects on the user (Bloor et al.

2008). These beliefs, however, are based largely on anecdote, with little controlled research to inform the interaction of THC and minor cannabinoids and no published human research on the interaction between THC and terpenoids.

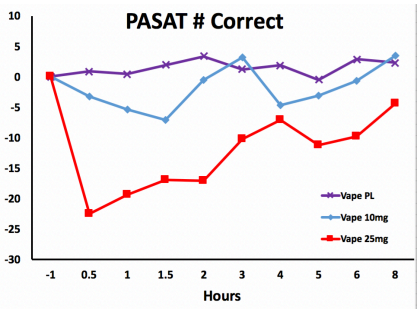
Terpenoids are produced in glandular trichomes of cannabis along with phytocannabinoids, and are pharmacologically versatile: interacting with cell membranes, neuronal and muscle ion channels, neurotransmitter receptors, G-protein coupled (odorant) receptors, second messenger systems and enzymes (Bowles 2003, Buchbauer 2010). Alpha-pinene is common to conifers such as pine trees and the is most widely distributed terpenoid in nature (Noma and Asakawa 2010). Pinene is Generally Recognized As Safe (GRAS), by the US Food and Drug Administration (FDA) and the Food Extract Manufacturers Association (FEMA) as a food additive and found commonly in food items such as beverages, candy, baked goods, and ice cream (Joint FAO/WHO Expert Committee on Food Additives, 2006). Pinene is a principal component of many essential oils (EOs), including turpentine, and is found in many perfumes and deodorants due to its potent fragrance. Pinene is also one of the most abundant terpenoids found in the cannabis plant. Beyond commercial products, humans are also exposed regularly to pinene in the ambient air, particularly in forested areas, where they form one component of ambient volatile organic compounds (VOCs; Guenther et al., 1994). In a similar vein, the indoor ambient environment is also rich in pinene and other terpenoids (Krol, Namiesnik, and Zabiegala 2014) due to emissions from wood building materials, furniture, and their use in air fresheners and other products. Thus, humans are exposed to pinene via several sources daily and certain occupational settings (e.g., sawmills) may expose individuals to abnormally high levels (Namieśnik et al., 1992). While ingesting excessive quantities of pinene or other EOs (e.g., turpentine) of which pinene is the principal component can be toxic. However, clinical studies have revealed minimal irritative symptoms and no CNS events or acute changes in lung functioning following acute inhalation of large concentrations (e.g., 450 mg/m^3) of pinene in an enclosed chamber, despite pulmonary uptake of over 60% of the pinene supplied (Falk et al. 1990). Pinene is also pharmacologically active, acting as a competitive acetylcholinesterase inhibitor. This mechanism is known to enhance memory, and indeed is a target for medications to combat dementia (Perry et al., 2000). Confirmatory evidence for pinene's memory-enhancing effects was provided in a pre-clinical study in which administration of an EO containing pinene resulted in a 72% increase in memory performance compared with placebo (Kim et al., 2006). However, there have been no in-vitro or human studies of pinene alone as a memory enhancer.

Currently, there is rapidly growing interest in the development of cannabis and cannabinoid-based medicines for the treatment of myriad health conditions. THC (dronabinol) has been approved by the FDA for over 30 years, yet is rarely used in medicine. Part of the reason for that is because the therapeutic index of pure THC, when given intravenously (D'Souza et al. 2004) or orally (Favrat et al. 2005) is narrow, especially among individuals previously naïve to its effects. Acute overdose incidents involving THC or THC-predominant cannabis commonly include anxiety, panic reactions or toxic psychoses, for which no pharmacological intervention is generally necessary, but which can result in significant and sustained discomfort to the individual. In recent years, advocates for cannabis legalization have argued that the use of cannabis (versus pure THC) reduces the rate and severity of adverse effects in the treatment of medical conditions, and this argument has been the basis for establishing medicinal cannabis laws in 34 of the 50 U.S. states and the District of Columbia.

To date, scientific evaluation of the "entourage" effects of cannabis versus THC alone have been largely limited to the study of cannabidiol (CBD) as a compound purported to attenuate

some of the untoward psychoactive effects of THC and generally reduce its adverse event profile. Clinical research by a UK pharmaceutical company suggests that producing cannabinoid medicine with a 1:1 ratio of THC:CBD produces better clinical results with fewer side effects relative to higher THC:CBD ratios (Russo and Guy 2006). However, laboratory studies have failed to detect a modulatory effect of CBD on the subjective effects of THC (Ilan et al. 2005, Haney et al. 2016). Though there is a lack of controlled research, numerous reports in published literature dating back to the 10th century indicate that the consumption of acetylcholinesterase inhibitors (e.g., Calamus root) have been utilized as an antidote to THC intoxication via inhalation of cannabis or hashish (Russo, 2011). In addition, cannabis retailers often advertise that cannabis containing high concentrations of pinene can serve as a memory enhancer. Thus, pinene could conceivably help counteract the well-documented acute working and episodic memory impairments induced by THC and/or cannabis, though this has never been examined empirically.

The aim of the proposed study is to evaluate, in a controlled laboratory experiment, whether and to what degree, pinene modulates the acute effects of inhaled THC. The procedures being used have been established in our lab during recent studies evaluating the dose effects of cannabis administered via oral ingestion, smoke, or vaporization. Results of those studies demonstrate that we can reliably produce and validly measure acute cannabis effects and were used to inform the THC doses selected for this study. We safely administered vaporized cannabis containing THC doses up to 25mg to healthy adult volunteers in a recent study (IRB00035394) without occurrence of unanticipated or serious adverse events. These doses produced dose-orderly drug effects. The 25mg THC produced moderate to high memory impairment as assessed using a working memory task (the Paced Serial Addition Task; PASAT) in these participants (see Figure below). In pilot testing of this protocol in 3 participants, however, we found that the 25mg doses of pure THC did not produce impairment of cognitive functioning. However, data from a concurrently run protocol (IRB00085652) vaporization of 30mg of THC reliably produced memory performance impairment, but was well tolerated by study volunteers. Thus, we have selected the THC dose of 30mg in order to test the ability of pinene to attenuate mild and moderate impairment of cognitive functioning induced by acute THC administration. Therefore, the study will address the cognitive and psychomotor impairment of placebo, pinene alone, and 30mg THC alone or combined with 0.5, 5, and 15mg of pinene.



The doses of pinene to be used in this study (0.5mg 5mg, and 15mg) were chosen based on comprehensive analyses performed on 107 samples of cannabis, representing 29 unique cannabis “strains”, being sold by a licensed medical cannabis producer, Tilray, in Canada. Specifically, these analyses revealed that the mean (range) concentration of pinene in the cannabis samples was 0.05% (0 – 0.5%), meaning 1 gram of cannabis would, on average,

contain 0.5mg of pinene and as high as 5mg of pinene. Importantly, 1 gram is the amount of plant material commonly used to make a single cannabis cigarette ("joint" or "blunt"). Thus, these doses are ecologically relevant and have demonstrated safety with respect to acute dosing via direct inhalation. The additional 15mg dose of pinene is higher than what would typically be consumed in 1 g of natural cannabis, but reflects the current practice in the cannabis industry in which terpenes are extracted from cannabis separately from cannabinoids and then reconstituted at unnatural ratios. The addition of the 15mg pinene dose is an amendment to the original protocol, at which time no adverse effects had been reported following either 0.5mg or 5mg pinene doses for the first 13 randomized participants and exposure to both doses of pinene did not differ from placebo on any pharmacodynamic outcomes assessed.

The results of this study will represent a significant initial advancement in understanding the behavioral pharmacology of cannabis. This is the second study in a series of similar experiments funded by NIH in which we will begin to systematically evaluate the interactions of multiple components of the cannabis plant. The first study (IRB00085652) showed that the terpene limonene exhibited a dose-orderly reduction in the acute anxiogenic effects of high doses of THC. In that study, as in this one, small effects were observed at low and medium doses (1mg and 5mg limonene), but 15mg limonene significantly reduced anxiety, paranoia and similar subjective effects compared with 30mg THC in the absence of limonene. Notably, the 15mg limonene dose also exceeded the amount typically found in a 1g cigarette of natural cannabis, so there is precedent from this prior study in needing to increase the maximum dose of terpenes in order to observe robust effects on target endpoints. Characterization of the interaction between THC and pinene will provide an initial scientific basis for whether or not there is benefit for including terpenoids in the development of cannabinoid-based pharmaceutical products as one means of reducing the incidence and/or severity of side effects.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

Protocol Overview. The proposed study will be conducted at the Johns Hopkins Behavioral Pharmacology Research Unit (BPRU). The purpose of the study is to examine the behavioral pharmacology of THC, pinene, and their combination versus placebo. All procedures will be performed in double-blind manner using a within-subject crossover design. Participants will be healthy adults between the ages of 18 to 55. A total of 6 outpatient drug administration sessions will be conducted for each evaluable participant.

1) Placebo (ambient air)
2) THC (30 mg)
3) Pinene (15 mg)
4) THC (30 mg) + Pinene (0.5 mg)
5) THC (30 mg) + Pinene (5 mg)
6) THC (30 mg) + Pinene (15 mg)

We will obtain a battery of pharmacodynamic outcome measures at baseline and for 6 hours after each dose. Sessions will be conducted at a target rate of 1-2 times per week, with a minimum of 2 days between experimental sessions. We will recruit study volunteers until 20 participants complete the protocol. Participants who drop out of the study prior to completion of

all scheduled sessions will be considered “incomplete” and will be replaced. Drug administration sessions will be completed in a randomized order.

Participants. We will recruit and consent up to 75 research volunteers in order to obtain 20 study completers. This will exclude 3 pilot participants who completed the study using lower THC doses (10 and 25mg). Participants who completed the study prior to the addition of the 15mg pinene doses will be invited to return to the lab to complete the two new dose conditions (15mg pinene and 30mg THC + 15mg pinene). We anticipate that about 50% of those screened will not be eligible or interested in the study, and that post-randomization some participants may drop out of the study before completion. It is estimated that we will need to randomize 40 participants to achieve 20 completers given the length of the protocol.

The target demographic for study participation are healthy adults who: have a history of intentionally consuming cannabis, have not used cannabis more than an average of twice per week in the 3 months prior to study participation, and who are not currently dependent on or seeking treatment for use of cannabis or other drugs, including alcohol.

The selection of participants who have used cannabis, but are not current frequent users allows us to recruit individuals familiar with the effects of THC without issues of high levels of THC tolerance that might be present in daily users that could impact study outcomes. Any participant that reports having had an adverse reaction to cannabis that resulted in seeking medical treatment will be excluded.

Participant recruitment. Participants will be recruited into the study via media advertising (e.g. newspaper, internet) and word-of-mouth communication. Advertisements will seek healthy adults who occasionally use cannabis and are not currently trying to quit. Interested participants will receive an initial screening over the telephone, that includes interviews and self-report questionnaires that provide participant information regarding health status including physical, mental health, recreational drug use history, and experience of adverse effects following cannabis use, to determine eligibility for all criteria except those which require physical evaluation. Individuals who meet initial eligibility criteria will then be scheduled for an in-person physical evaluation.

Prior to the in-person assessment, written informed consent to participate in the study will be obtained. Urine specimens will be obtained and tested for evidence of recent use of commonly abused drugs. Participants must provide a government-issued photo ID confirming they are 18-55 years old, report prior use of cannabis, including at least 5 times in the past year, and report no allergies to cannabis or any of the test materials (e.g., products containing pinene or related substances such as turpentine). The physical exam will include clinical chemistry, hematology, serology, and serum pregnancy (females only) testing. Those who appear eligible for participation will receive training on study assessment measures (e.g. exposure to subjective questionnaires and cognitive performance tasks), as well as instruction on using the Mighty Medic vaporizer. Participants who successfully complete training and demonstrate competency on all performance measures will be invited to participate in the study.

Experimental Session Procedures. For all study sessions, participants will be scheduled to arrive at approximately 8:00 in the morning on the day of cannabis exposure. Until such time as Covid-19-related restrictions on day-to-day operations are no longer required, social distancing will be maintained to the extent possible and all staff and study participants will be required to wear PPE throughout all face-to-face interactions. This will include mandatory use of face

masks and, when closer than 6ft, use of face shields and disposable gloves. Participants will be provided PPE by study staff as necessary.

All participants will complete a breath alcohol test on arrival. Urine drug and pregnancy testing will then be conducted for all participants to test for evidence of recent illicit drug use (e.g. cannabis, cocaine, opioids) and pregnancy. Participants with a positive BAL or urine drug screen positive for any drug except THC will be sent home and the session re-scheduled. Participants who have a 2nd positive BAL, 2nd positive urine drug screen or confirmed positive pregnancy test will be immediately discharged from the study. The Time Line Follow Back (TLFB) procedure will be conducted to record substance use since the last study visit (intake assessment or prior experimental session). Concomitant medications**,** including vitamins and herbal supplements taken within 14 days prior to the first experimental session and throughout study participation will be recorded. Changes in medication occurring between the screening assessment and first experimental session, or between subsequent experimental sessions will be reviewed by a study investigator and medical staff prior to starting the session to ensure the volunteer is still eligible to participate.

Baseline Assessments. Prior to drug administration, the following baseline assessments will be completed: 5mL serum blood sample, vital signs (HR, BP), subjective drug effect questionnaire, and a brief cognitive performance battery including tests of working and episodic memory (see below for details).

Experimental Drug Exposure.
Study drugs, pure THC in ethanol, pure alpha-pinene, or placebo (ambient air), will be delivered via vaporization using the Mighty Medic (Storz-Bickel, Tuttlingen, Germany), a commercial vaporizer designed specifically for the delivery of cannabis and THC. Vaporization was selected as the route of administration because THC and pinene have good pulmonary bioavailability, it allows for more precise dose delivery versus smoked or oral routes, this method is most likely to protect the blind of drug conditions between sessions as there are fewer sensory cues associated with inhalation of vapor versus smoked cannabis, inhalation is the most common method of consuming cannabis, and because vaporization has the same pharmacokinetics, but less pulmonary risk, compared with smoking. The Mighty Medic employs hot air at a temperature of 210°C to vaporize THC and terpenoids without combustion, thereby limiting exposure to potentially carcinogenic polyaromatic hydrocarbons, ammonia, and other toxins. Each drug dose is placed in a small dosing capsule (or “pod”). Participants inhale the contents of the capsule by inhaling though a mouthpiece attached to the vaporizer. This activates the heating element and delivers the study drug. A specialized adapter will be used to capture puff topography (e.g. volume and intensity of each puff) during drug administration. A new mouthpiece tip will be used for each experimental session, and a new vaporizer will be used for each study participant to prevent drug contamination across sessions and for sanitary purposes. The Mighty Medic is an approved medical device in the European Union, Canada and Israel and functions similarly to the Volcano Medic, which we have used previously in our laboratory to administer raw cannabis via vaporization. The Mighty Medic and Volcano Medic are made by the same company: Storz-Bickel. Analytical testing conducted by Research Triangle Institute and others has demonstrated that the Volcano Medic reliably and dose-dependently delivers THC and alpha-pinene. Importantly, analytical testing conducted by Stortz and Bickel has revealed that the Volcano Medic and Mighty Medic are equally effective at delivering THC in vapor.

A pharmacist or other qualified technician will apply test substances with a micro-pipette into a dosing capsule, accessories that come with the Mighty Medic. The dose pod will then be placed in a ventilated hood to allow ethanol to evaporate, and then placed into a vaporization device assigned to that study participant. For each experimental test session, a dosing capsule with the assigned dose(s) will be provided for participant self-administration using the Mighty Medic in accordance with the manufacturers operating instructions. When the Mighty Medic is activated, the dosing capsule is heated, vaporizing the substances placed inside it.

Detailed instructions for use of the device are available here: https://www.storz-bickel.com/media/wysiwyg/CRAFTY-MIGHTY/PDF/mighty-vaporizer-instructions-manual.pdf (see annex documents) and are provided in the supplementary materials section of the IRB application. Participants will inhale the contents of one Mighty Medic dosing capsule. Specifically, they will be given 15 minutes to inhale the contents of the capsule *ad libitum* (i.e., at their own pace). Participants will take a minimum of 15 puffs, and if a visible vapor is still observed after 15 puffs, they will continue to take puffs until they no longer exhale visible vapor (this signifies that the dosing capsule is depleted; see detailed instructional materials from Stortz and Bickel). Following each puff, participants will exhale vapor into a hand-held smoke filter; this will ensure that neither the study participants or research staff see the exhaled vapor. We have found in our ongoing study with a different terpene (limonene) that the visibility of exhaled vapor can differ between pure THC, pure terpenes, and placebo. Overall, the puffing procedure will produce THC exposure of 0 or 30mg THC, and alpha-pinene exposure of 0.5mg, 5mg, or 15mg. Participants will be able to halt self-administration of the study drug if they experience adverse effects prior to inhaling the entire dose. Similarly, study staff may halt the drug administration procedure if untoward drug effects are observed. This is not expected at the doses under investigation, but may occur in rare circumstances. Study participants and research staff will be blinded to dose assignment. The conclusion of drug administration will be considered the “0 hour” by which remaining protocol assessments will be scheduled. To prevent issues of cross-contamination, new dosing pods and mouthpieces will be used for every test session, and the vaporizer will be disassembled and thoroughly cleaned according to manufacturers recommended methods between study participants.

Post-Drug Administration Procedures.
Following the “0-hour” time point (last exhalation of study drug), participants will complete a battery of assessments that includes:

1) Serum specimen collection at 0min, 15 min, 60 min, 120 min, and 180 min.
2) Subjective drug effect and mood ratings on computerized questionnaires and vital signs assessments at 0 min, 15 min, 30 min, 60 min, 90 min, 120 min, 180 min, 240 min, 300 min, and 360 min.
3) Cognitive performance tests at 0, 30 min, 60 min, 90 min, 120 min, 180 min, 240 min, 300 min, and 360 min (Episodic memory tests will only be administered at 30 min and 360 min).

Use of medication or tobacco products will not be allowed during the study sessions. Study participants who regularly use tobacco products will be provided a nicotine patch upon request.

Outpatient Discharge. Participants will be discharged after completing final assessments (approximately 6 hours post-exposure). In prior studies conducted in our laboratory, this timeline has been adequate for healthy adults to resolve any effects from acute doses of cannabis that are similar to those used in the present protocol. If a study participant indicates the desire to be discharged from the study early, BPRU medical staff will review the self-reported rating of “drug

effect" on the most recent subjective drug effect assessment, performance on the cognitive test battery, and conduct a brief interview with the participant prior to discharge. At the end of each session, study staff will compare vital signs and cognitive performance assessments with baseline data and engage in face-to-face conversation with the participant to ensure that they are fit to leave the unit. Cognitive performance tasks obtained measure psychomotor ability, working memory, higher-order cognitive functioning and attention. If the participant is able to cognitively engage with staff, vital signs are within normative range (HR < 100bpm, SYS BP < 150mmHg, DIA BP < 90mmHg), and performance is not below 20% of baseline, the participant will be cleared to leave without further evaluation. If any of these parameters are not met, medical staff will assess the participant and a formal field sobriety test will be conducted. Note, that multiple members of the BPRU cannabis lab have received formal training on administering filed sobriety tests by a Maryland State Police Drug Recognition Expert (DRE). If the participant reports a drug effect or exhibits behavior indicative of impairment/intoxication, the participant will be asked to remain at the BPRU until the drug effect subsides and they can pass a field sobriety test. If vital signs are out of range, then medical staff will evaluate and make a determination with regards to whether it is safe for participant to be discharged or remain under observation. Participants will not be allowed to drive home; instructions will be provided at the screening session regarding the need to make alternative transportation arrangements. If a participant fails to arrange a ride, taxi transportation home will be coordinated by study staff and provided free of charge.

For ease of scheduling, we will target conduct of sessions on a weekly basis. Because there are 6 total sessions, some participants may want to complete at an accelerated rate. A minimum of 48 hours will separate each study session and no more than 2 sessions will be completed in a calendar week. These timing parameters will allow for adequate elimination of study drugs between sessions and keeps the frequency of exposure to acceptable levels given that the study population will be infrequent cannabis users at the time of study participation.

Study Measures. A battery of measures will be used to assess participant characteristics and drug effects during the study.

Screening. Initial study screening will be completed over the telephone. During the phone screening assessment, staff will conduct assessments to collect background demographic data (age, gender, self-reported race and ethnicity, height, and weight) and to determine study eligibility (e.g. Medical History Interview, Drug-History Questionnaire, Time Line Follow Back (TLFB) assessment of all substance use for the prior 90 days, self-report of adverse effects following cannabis use). If the volunteer appears eligible based on this interview, a physical examination will scheduled to be completed at the BPRU by medical staff. All major organ systems, including head, eyes, ears, nose, and throat (HEENT); cardiovascular system; lungs; abdomen (liver/spleen); extremities; skin; central nervous system (CNS); musculoskeletal system, and general appearance will be assessed. Biological specimens will be tested for routine clinical chemistry, hematology, serology, serum pregnancy test (females only), and for evidence of recent illicit drug use.

Experimental Sessions. Vital signs (heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP)) will be measured in the seated position using an automated monitor.

Six milliliters of blood will be collected by venipuncture or IV catheter insertion at baseline and again at the 0, 15, 60, 120, and 180-minute post-inhalation time points into vacutainer tubes. Blood will be spun to separate plasma, which will be labeled and stored frozen at -80 ºC until

shipped frozen on dry ice to a designated laboratory for analysis. The maximum amount of blood to be collected is 36 mL per session, and 216 mL over the course of the 6 study sessions (226 mL including the screening visit), which is less than the amount typically collected during a single routine blood donation (473ml). Quantitative levels of THC and its metabolites (e.g. 11-OH-THC and THCCOOH) will be obtained. Additional analytical testing (e.g. markers of pinene) may be conducted as deemed appropriate to the current study.

A 21-item Drug Effect Questionnaire will be used to obtain subjective ratings of intoxication. Individual items include ratings of drug effects (i.e. drug effect, pleasant drug effect, unpleasant drug effect) and behavioral/mood states often associated with cannabis intoxication (i.e. relaxed, paranoid, hungry/have munchies). Participants will rate each item using a 100mm visual analog scale (VAS) anchored with “not at all” on one end and “extremely” on the other. At the end of each session, participants will also complete a brief hypothetical purchasing questionnaire in which they estimate how much they would purchase of the dose they just received if it were to cost different prices.

The Profile of Mood States (POMS) questionnaire is a 65-item questionnaire that is commonly used to assess state-dependent changes in mood on 7 different domains: anger-hostility, confusion-bewilderment, depression-dejection, fatigue-inertia, tension-anxiety, vigor-activity, and friendliness.

A brief battery of cognitive performance assessments will be conducted on aspects of functioning known to be sensitive to the acute effects of THC and cannabis, and which are relevant to functioning in the workplace and/or in operating a motor vehicle. All participants will be trained on the performance tasks to a stable baseline level during the screening session. Tasks include: 1) the Digit Symbol Substitution Task (DSST): Participants must hand type patterns presented to them on a computer screen for 90 seconds and outcomes include accuracy and total number of patterns completed in the allotted time (measures psychomotor performance); 2) a computerized Paced Serial Addition Task (PASAT): Participants are provided a string of single digit numbers on the computer and must add the total of the prior to integers presented and respond by selecting the answer using the computer mouse on the screen, primary outcome is a summed score of the number of correct trials (out of 90) during the task. This task measures working memory performance; 3) The DRIUD App: participants complete a brief (2 minute) task using an iPad that incorporates measures of memory, divided attention, reaction time and balance. Participants will be required at screening to demonstrate competency on and comprehension of the cognitive tasks in order to be eligible for the study. Recent studies in our laboratory (Vandrey et al. 2017, Spindle et al., 2018, Spindle et al., in press) have shown that these 3 tasks are sensitive to cannabis dose effects.

Finally, we will assess episodic memory impairment using a simple delayed verbal recall task called the international shopping list test (Thompson et al. 2011). Performance on this test has been shown to decrease as a result of cannabis exposure in prior controlled studies (Bidwell et al., 2018). In this task, participants are shown a 12-item grocery list and asked to recall as many items from that list as possible at a later time. In each condition of the present study, participants will be shown such a list at baseline (before drug administration) and will be asked to recall items from the list post-drug administration (during peak drug effects). Following recall of the initial list, participants will be presented with a new list of 12 items that they will be asked to memorize. Recall of this second list will be measured at the end of the experimental session (6 hours-post dosing). The second list will contain non-grocery store items to avoid confusion with the first list. Testing verbal recall twice in this manner (once during peak drug effects, once

again at the end of the session) will allow us to test whether pinene mitigates THC-induced memory impairment at two memory stages: the memory retrieval phase (list 1) and the memory encoding/consolidation phase (list 2). Participants will be presented with new lists at each experimental session.

b. Study duration and number of study visits required of research participants.

Eight study visits will be required. One visit for screening evaluation, and 6 outpatient experimental sessions lasting approximately 7 hours each. Because there are so many experimental testing sessions in this trial, and interpretation of data is contingent on a complete data set, participants may be invited to repeat a study session should circumstances arise that result in the loss of data during a session (e.g., failure to obtain blood specimens or missing cognitive testing time points), or protocol deviation that impacts data integrity. This is not expected to occur for most participants. Because the study involves repeated collection of blood samples, participants may not repeat more than 4 testing sessions, as this would result in cumulative blood collection that would exceed what is typically collected during a single routine blood donation (473mL); see Risks, Section 7, below. That said, it would be very unlikely for a participant to repeat more than 1 test session.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

THC/terpenoid dose assignment will be double-blinded in this study. That is standard procedure for appropriate scientific control in studies evaluating the dose effects of psychoactive drugs.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

e.

Participants in this study will be healthy volunteers. Routine care for any medical illness that may arise during participation will not be affected.

f. Justification for inclusion of a placebo or non-treatment group.

A placebo dosing session (no THC, no pinene) will be included to help interpret active drug effects on pharmacodynamic outcomes. Placebo dosing provides a control for expectancy effects on subjective reports and cognitive performance as well as non-pharmacological factors such as fatigue, hunger, and learning effects on performance tasks. Placebo dosing is standard for research studies involving evaluation of acute drug effects.

g. Definition of treatment failure or participant removal criteria.

This is not a treatment study. Participants may quit participation at any time of their own volition. The study investigators will discharge study participants for failing to attend their scheduled session, failure to follow the protocol requirements, or for other reasons not known at this time.

h. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

This is not a treatment trial; there is no direct course of therapy related to the participant population being targeted. We are recruiting healthy adults with experience using cannabis and who are not seeking treatment for substance use problems. Should any report the desire for treatment they will be referred to appropriate community service centers. Premature termination of participation may result in the need to recruit additional research volunteers, but should have no impact on the study volunteer directly.

5. Inclusion/Exclusion Criteria

Participants will meet the following eligibility criteria:

Inclusion Criteria

1. Have provided written informed consent
2. Be between the ages of 18 and 55
3. Be in good general health based on a physical examination, medical history, vital signs, and screening urine and blood tests
4. Test negative for drugs of abuse other than cannabis, including breath alcohol at the screening visit and at clinic admission
5. Not be pregnant or nursing (if female). All females must have a negative serum pregnancy test at the screening visit and a negative urine pregnancy test at clinic admission.
6. Have a body mass index (BMI) in the range of 18 to 36 kg/m2
7. Blood pressure at Screening Visit does not exceed a systolic blood pressure (SBP) of 150 mmHg or a diastolic blood pressure (DBP) of 90 mmHg
8. Have no allergies to any of the ingredients used to prepare vapor (THC, pinene).
9. Demonstrate competency on cognitive performance measures at screening visit (e.g., PASAT score of 75/90).

Exclusion Criteria

1. Non-medical use of psychoactive drugs other than, nicotine, alcohol, or caffeine 3 month prior to the Screening Visit;
2. History of or current evidence of significant medical (e.g. seizure disorder) or psychiatric illness (e.g. psychosis) judged by the investigator to put the participant at greater risk of experiencing an adverse event due to exposure or completion of other study procedures.
3. Use of an OTC, systemic or topical drug(s), herbal supplement(s), or vitamin(s) within 14 days of experimental sessions; which, in the opinion of the investigator or sponsor, will interfere with the study result or the safety of the subject.
4. Use of a prescription medication (with the exception of birth control prescriptions) within 14 days of experimental sessions; which, in the opinion of the investigator or sponsor, will interfere with the study result or the safety of the subject.
5. Use of dronabinol (Marinol®) within the past month.
6. Average use of cannabis more than 2 times per week in the prior 3 months.
7. History of clinically significant cardiac arrhythmias or vasospastic disease (e.g., Prinzmetal's angina).
8. Enrolled in another clinical trial or have received any drug as part of a research study within 30 days prior to dosing.
9. Having previously sought medical attention to manage adverse effects following acute cannabis use.
10. Individuals with anemia or who have donated blood in the prior 30 days

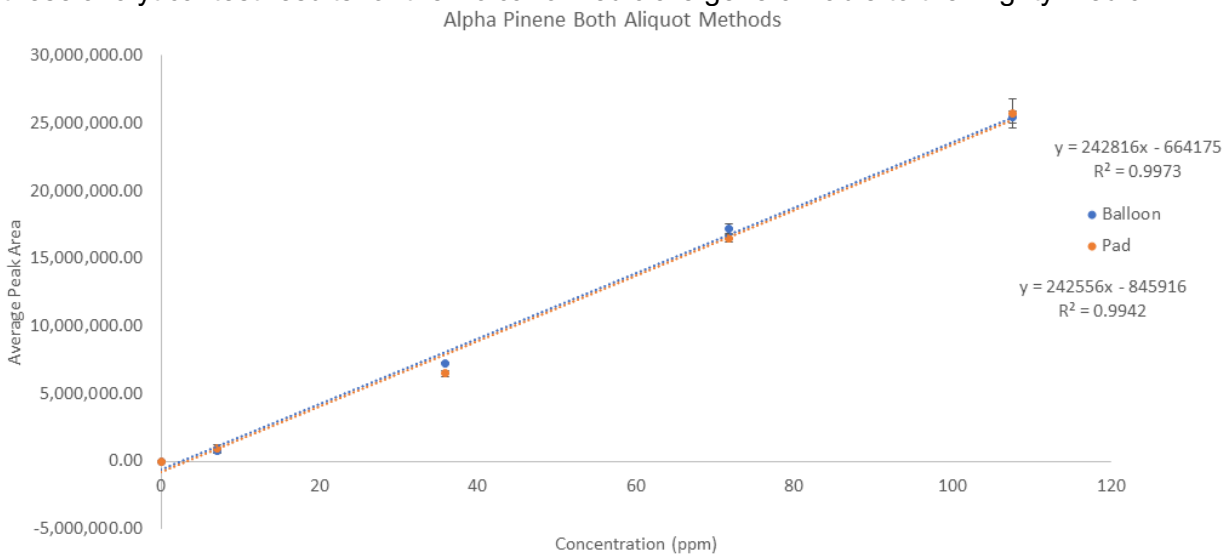
6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

The THC for this study will be of GMP quality and manufactured and distributed to JHU by THC Pharm GmbH (Frankfurt, Germany) in accordance with federal regulations. THC Pharm GmbH will supply pure THC in a resinous form. The THC will be suspended in pharmacy-grade ethanol (190 proof) to create a solution that is approximately 10% THC/ 90% ethanol (this will increase the ease and precision of dosing measurements for THC, given the small doses that will be used). The ethanol solution will be purchased from Spectrum Chemical (product code: ET108; see appendix materials for product specifications), and meets standards for use in drug preparations intended humans. Prior to pulmonary administration, the ethanol will be dissipated from the heating pad used for THC administration under a ventilated hood in the BPRU Pharmacy. These procedures mirror those of our ongoing study which utilizes essentially the same protocol to examine the individual and interactive effects of the terpene limonene and THC (IRB00085652).

The Mighty Medic is an approved medical device for administration of THC in Germany and Canada and can reliably deliver cannabinoids with similar effectiveness to the Volcano Medic device (made by the same manufacturer), which has been used to deliver THC in research studies elsewhere (including in our laboratory).

The alpha-pinene for this study is >99% purity, meets GMP specifications, and will be obtained from True Terpenes. Analytical testing conducted by Brian Thomas, PhD, at RTI International indicates that the Volcano Medic reliably delivers alpha-pinene in a linear dose-response manner, and that recovery of pinene from the Volcano Medic balloons via GC/MS has little variability and does not differ whether the terpene is injected directly into the balloon and equilibrated with laboratory air or vaporized at 210°C as will be done in the current study (see below Figure for triplicate testing via both methods). Given that the Mighty Medic and Volcano Medic are demonstrated to deliver comparable levels of cannabinoids and given that we will use the same temperature settings (210°C) for the Mighty Medic to vaporize THC and alpha-pinene, these analytical test results for the Volcano Medic are generalizable to the Mighty Medic.



The selection of doses was conducted to balance the study aim, participant safety and tolerability based on previous experience, and ensuring that doses are ecologically valid. In our laboratory, tolerant daily cannabis users have safely self-administered up to 3 grams of smoked cannabis containing 10% THC (300mg THC) within one hour (protocol NA_00082269). More recently, acute oral, smoked and vaporized administration of 5mg to 30mg THC to infrequent cannabis users (as will be recruited here) resulted in dose-dependent drug effects (IRB00035394, IRB00122849, IRB00085652). At doses of 10-15mg THC, participants reported an increase in pleasant drug effects with few unpleasant side effects and mild impairment of working memory was observed for a subset of participants. At 25-30mg THC doses, there was ratings of pleasant drug effects were comparable to the 10-15mg doses, but working memory performance was significantly impaired; there were also no unanticipated or serious adverse events in this dosing condition. Moreover, inspection of the individual-level data showed that 14/17 study completers exhibited a decrease in performance of 10 or more correct responses compared with baseline on the PASAT following administration of the 25 mg THC vaporized whole plant cannabis and the mean reduction in PASAT scores after 30mg pure THC was also about 10 correct responses (this magnitude of change signifies moderate impairment of working memory). Thus, based on prior studies and pilot testing of this protocol, we believe that a 30 mg THC dose will be sufficient to produce moderate to high memory impairment in most participants in the present study, thus allowing us to examine our proposed hypothesis, but this dose should still be well tolerated by study participants without putting them at risk of significant discomfort or danger.

If initial testing in this study indicates difficulty with dose tolerability of either drug then we will revise the proposed doses accordingly. Adverse events beyond anxiety, memory impairment, sedation, or nausea (vomiting in rare instances) are unlikely given the relatively safe pharmacological profile of THC (partial agonist), which has no history of being directly associated with fatalities. In cases where a participant experiences panic and or paranoid reactions, research staff will engage the person in relaxation exercises and will suspend research procedures until the volunteer has regained comfort. These types of effects are typically of short duration and our staff is well practiced in helping manage these types of effects. In the case of an extreme adverse reaction, we will call 911 and participants will be taken by emergency responders to the Johns Hopkins Bayview ER for treatment.

The pinene doses employed in this study (0.5, 5, or 15 mg) were derived based on previous experiments outlined in the background (Falk et al. 1990) and the known ratios of terpenes and THC in cannabis currently being used in legal markets in the U.S. and Canada. We are not aware of any serious adverse events occurring after acute inhalation of pinene. It is commonly inhaled in ambient air due to exposure to household cleaners or air fresheners, candles, or a variety of other products containing pinene/turpentine essential oils. Beyond commercial products, humans are also exposed regularly to pinene in the ambient air of forested areas, where they form one component of ambient volatile organic compounds (Guenther et al., 1994). In a similar vein, the indoor ambient environment is also rich in pinene and other terpenoids (Krol, Namiesnik, and Zabiegala 2014) due to emissions from wood building materials and furniture.

The Mighty Medic is an approved medical device in the European Union, Canada and Israel for inhalation of THC or cannabis (see certificate in Annex documents). The rationale behind its use is to volatilize cannabinoids and cannabis terpenoids at a temperature below that which combusts the material, and produces polyaromatic hydrocarbons (Abrams et al. 2007, Hazekamp et al. 2006, Zuurman et al. 2008).

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

THC is FDA approved as an oral formulation (dronabinol; Marinol). Pinene is Generally Recognized as Safe (GRAS) for oral consumption. Neither THC or pinene is FDA approved via the pulmonary route. As detailed above, we believe that the THC and pinene administration in this study will be safe for cannabis-experienced participants. The route of administration (vaporization) is common for cannabis self-administration and the doses of both THC and pinene are within the range of what would be expected in real-world cannabis use scenarios. We have submitted an IND application to the FDA for the conduct of this experiment.

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

N/A

Study Statistics

a. Primary outcome variable.

The primary outcome measure for this study is the total correct on the PASAT (test of working memory).

b. Secondary outcome variables.

Secondary outcome measures include total correct on the International Shopping List Test (test of episodic memory), Reaction Time for Correct Trials on the PASAT, Number Correct on the DSST, self-reported rating of “Trouble With Memory” on the DEQ, and composite score of the Confusion-Bewilderment sub-scale of the POMS.

The sample size estimate for this study was based on previous work in this laboratory evaluating dose effects of acute drug administration using a within-subjects design. A meta-analysis was previously conducted comparing the statistical power of 13 drug effect assessments from six dose-effect studies, with 14 participants each, evaluating a range of abused drugs in our laboratory (Felch, Di Marino, and Griffiths 1996). The analysis showed that average effect size for primary measures (i.e. subjective drug effect ratings, staff ratings and behavioral/cognitive performance measures) ranged from approximately 0.87 to 1.0. Based on this estimate of effect size, the proposed sample size of 20 should be adequate to assess the expected effects and to differentiate low from high doses. This sample selection methodology has been consistent in our long history of studies investigating acute dose-effect comparisons of cannabis/THC. These methods have excellent external validity and have become the FDA recommended standard for human abuse liability assessment. Subjective drug effect and mood ratings, vital signs and cognitive performance outcomes will be assessed using multiple regression analyses appropriate for repeated measures testing based on the final characteristics of the data set (e.g. normal distribution, skewness, kurtosis).

c. Early stopping rules.

The study will be stopped if new information is learned that indicates a serious risk to study participants.

7. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

Potential risks of THC exposure include dizziness, change in blood pressure, red or irritated eyes, drowsiness, easy laughing, euphoria, rapid heart rate, orthostatic hypotension, dry mouth, jitters, headache, nausea, vomiting, increased appetite, perceptual difficulties, memory lapse, hallucinations, confusion, depression, paranoid reaction, depersonalization, and rash. An additional potential risk of THC and/or terpenoid inhalation is coughing. Available preclinical and clinical evidence indicates that the doses of pinene we intend to administer are non-toxic risk to humans. In a prior clinical study involving pulmonary inhalation of pinene in the ambient air (Falk et al., 1990), pinene exposure was not associated with any discomfort in the eyes, nose, or throat, and no CNS-related symptoms (e.g., “headache,” “fatigue,” “sick,” “dizziness,” “difficulty breathing”) were different from placebo at the doses examined that approximated those in the present study. Pinene exposure also produced minimal pulmonary function changes, with a tendency toward bronchodilation rather than constriction (Falk et al., 1990).

Exposure to pinene with THC may modulate or accentuate certain effects, and there is always the possibility of paradoxical reactions. However, we feel that the risk of serious adverse events related to THC or pinene exposure in this study is minimal, inasmuch as participants are experienced cannabis users and the doses we are administering are within the range by which most participants are likely to have encountered these substances through naturalistic cannabis use.

Venous blood sampling may cause pain, tenderness, bruising, or bleeding at the needle puncture site. Some subjects may feel transient lightheadedness or dizziness, or lose consciousness (syncope), because of anxiety and vasovagal reaction.

A further risk is that participants may mistake the proposed studies as treatment or may delay treatment seeking in order to participate, although this is unlikely since we are targeting occasional users.

Breech of confidentiality about self-reported drug use and biological tests indicating recent drug use is also a risk.

Exposure to COVID-19 is a risk.

b. Steps taken to minimize the risks.

Participants are not a "vulnerable population" as defined by human subject protection guidelines; that is, they are not minors, pregnant women, under legal coercion or restriction, or mentally impaired. They are competent adults who provide their voluntary informed consent. Participants will be recruited via media advertisements and posters that clearly state the nature and intent of the study. The consent process will inform the participant in detail of the procedures, time involvement, compensation, risk, and treatment options other than participation in our study. Particular emphasis will be given to providing information regarding

the potential risks involved with taking the study drugs. Volunteers will also be instructed that they may withdraw from participation at any time without losing any of the compensation that they have earned to that point.

It is unlikely that any adverse event should arise that requires immediate medical or psychiatric treatment. However, in case of an adverse event, participants will be under the supervision of medical/nursing staff throughout the study. The medical and nursing staff at BPRU are trained in CPR and mobile emergency crash carts are available on the same corridor where all experimental procedures will be conducted. The research facility (BPRU) is located directly across the street from the Johns Hopkins Bayview Medical Center Emergency Department, and, in case of an adverse event, staff will call 911 and participants will be taken by EMTs for immediate care. The Principal Investigator will be immediately notified of any serious adverse events that arise.

If participants develop nausea or vomiting after vaporization, study staff will assist the affected participant appropriately and contact the study PI and BPRU medical staff. Nursing staff will be on site during all experimental test sessions and a physician is always on call.

Blood collection risk will be minimized by performing venipuncture while participants are sitting down, and by having them remain under staff observation until it is clear that no acute adverse effects occur as a result of the procedure. The risk of infection is negligible because standard sterile technique will be used. Venipuncture poses a risk of infection or thrombophlebitis, which increases with duration of placement. This risk is minimized by use of careful sterile technique, having nursing staff check the venipuncture site (with prompt attention if there are clinically significant signs or symptoms such as tenderness, swelling, or redness). The risk of anemia is negligible because the total amount of blood to be collected during the entire completed study is less than the amount (473 mL) collected within one hour during a single blood donation session. The amount of blood loss will be readily replaced without harm to study participants.

All advertisements and the informed consent process will clearly indicate that this research is designated only for those not seeking treatment, that participation is not a substitute for treatment, and that participation offers no clinical benefit. They will be clearly informed that they will be asked to inhale cannabis components during their participation. Any participant who expresses an interest in receiving immediate treatment for cannabis or other substance use will be referred to a community treatment clinic. If this occurs during the study, their participation in the study will be terminated. As previously described, participants will be instructed that should they withdraw from the study at any point to pursue treatment they will still be compensated for their participation up until that point in the study.

Until risk of exposure to COVID-19 is no longer a public health concern, we will maintain social distancing throughout the study procedures to the extent possible. All staff and study participants will be required to wear PPE appropriate to the nature of the tasks being completed and distance to others (e.g. face masks when maintaining social distancing, face masks, face shields, and disposable gloves when closer than 6ft). We will also minimize the number of staff who come in contact with any single participant to the extent possible based on duties to be performed and staff availability. Our target will be to have each participant only interact with 3 staff (medical staff member for physical evaluation, nurse for blood draws, research staff member for all other procedures).

c. Plan for reporting unanticipated problems or study deviations.

Study personnel will also follow ICH regulations (detailed in *Clinical Safety Data Management, Definitions, and Standards for Expedited Reporting)* regarding reporting of adverse events and all study deviations to the IRB and study sponsor. The study PI and medical team will work together to determine the severity of each AE and relatedness to the study procedures.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

Participants' names will be recorded only on the screening, informed consent, and necessary medical and payment forms. Anonymous participant identification numbers will be used on all other forms and labeling of biological fluids and test results. All information gathered will be kept in locked research staff offices or file cabinets. All medical information obtained will be handled in accordance with HIPAA regulations. Only research staff will have access to participant records. The limits of confidentiality (e.g. suspected child abuse or neglect, or harm to self or others) will be discussed in detail with the participants during the informed consent process. To reduce the likelihood of patient records disclosure we have obtained a Certificate of Confidentiality.

e. Financial risks to the participants.

This study does not involve patients receiving treatment; therefore, the financial risks are minimal. Participants will be fairly compensated for their time and effort in complying with the study protocol.

8. Benefits

a. Description of the probable benefits for the participant and for society.

The primary benefit of the proposed research is in the knowledge gained regarding the pulmonary inhalation of THC and pinene alone and in combination. This knowledge will advance our basic scientific understanding of both substances and may guide policy and regulations related to cannabis. The study will also extend the extant literature investigating the acute dose effects of inhaled THC, including subjective effects, cognitive performance, and their correlation with biological cannabinoid levels. These experiments may objectively demonstrate synergy of cannabis components and the modulating and even beneficial effects of cannabis terpenoids on THC. The results could benefit the research community in finding and developing selected cannabis chemovars with unusual cannabinoid and terpenoid contents and ratios for improved efficacy and optimized therapeutic index. Because we anticipate relatively minor risks to these cannabis experienced study participants, we feel that the proposed research has a positive risk-benefit ratio.

9. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

All participants will be compensated $30 for completing the screening assessment, up to $1800 for completing each of 6 outpatient sessions, and $500 in completion bonuses resulting in $2330 of total possible earnings for completing the entire study. Compensation of this magnitude is appropriate given the length and nature of this study. Calculations are as follows:

Screening Visit:	$30
Outpatient Sessions 1-6:	$300/day ($1800 total)
Completion Bonus:	$500
Total Compensation:	$2330

Study participants will receive an additional $300 for any test session that is repeated due to data loss or for participants invited back to completed additional doses added as a study amendment. There will not be any change to the study completion bonus for repeat testing.

10. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

The only direct costs to the participants will be their transportation to and from Bayview for each study visit. That cost has been factored into the compensation for participating.

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