Differences in Cannabis Impairment and its Measurement Due to Route of Administration

NCT03122691

5/18/2018

Johns Hopkins Medicine - eForm A

- **Use the section headings to write the eForm A, inserting the appropriate material in each. If a section is not applicable, leave heading in and insert N/A.**
- **When submitting eForm A (new or revised), enter the date submitted to the field at the top of eForm A.**

****

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.

Over the past decade, there has been a paradigm shift in legal status and social perception of cannabis in the United States. Concurrent with the changing legal status of cannabis, rates of use and potency of available cannabis have increased, while perceived harm related to use has decreased. Not surprisingly, there has been a corresponding increase in prevalence of detecting delta-9-tetrahydrocannabinol (THC) in urine obtained from weekend nighttime drivers. While laws have been established for driving under the influence of drugs (DUID) across a range of drugs, current laws regarding cannabis impairment are either difficult to prosecute or are controversial, and vary widely across states.

Effect-based laws are the most common and least controversial, but are the most difficult to prosecute. These laws often rely on testimony or evidence from the arresting officer or a drug recognition expert (DRE), as well as results from a blood or urine toxicology test, with no clear definition of what constitutes a positive determination of impairment. Per se laws are easier to prosecute because they explicitly define an analyte and a cut-off concentration for that analyte that determines impairment. However, per se laws are controversial because there is a lack of consistency about both which analyte the laws are based on (e.g., THC or one of its metabolites), and the appropriate cut-off concentration to determine impairment. Some states have enacted zero tolerance per se laws, but in states that have legalized cannabis use, zero tolerance laws for cannabis are not practical because common biomarkers of cannabis use can be detected days after a single use and do not correspond with periods of impairment. In fact, there is little scientific evidence from which to determine appropriate objective measures for identifying cases of cannabis impairment and DUID due to cannabis impaired driving.

Currently most law enforcement use a combination of biological and behavioral assessments administered by DREs and blood THC levels to judge cases of suspected DUID involving cannabis. However, behavioral assessments have not been explicitly developed for detecting acute intoxication from cannabis, and blood THC levels do not necessarily correspond with acute impairment. THC blood levels can drop below cutoffs used for drugged driving before the effect of the drug subsides; conversely, THC can be detected for up to a month after use in frequent cannabis users. In addition, the relation between cannabis impairment and THC blood levels varies as a function of route of cannabis administration.

Few controlled studies have assessed the pharmacokinetics and pharmacodynamics of vaporized or orally consumed intact cannabis (e.g., cannabis-containing brownies) on drug test results or behavioral evaluation of performance impairment. The pharmacokinetics and associated pharmacodynamics of cannabis administered via vaporization and oral consumption are currently not well understood and need to be better defined in order to evaluate methods of determining whether or not an individual under the influence of cannabis is impaired. The proposed study will involve acute administration of cannabis via oral ingestion and vaporization. We will evaluate pharmacokinetic outcomes across three biological matrices (blood, urine, oral fluid), in addition to subjective, observer-rated, and objective evaluations of drug effects

and behavioral impairment. This study will directly impact policy related to cannabis impairment and DUID due to cannabis use. This will also help differentiate new from residual cannabis use, which would be a valuable asset in the clinical treatment of cannabis use disorders. Currently, the most effective treatment for cannabis use disorder includes provision of incentives contingent on biologically confirmed abstinence. The problem is that frequent cannabis users often cannot pass a drug test until they have continuously abstained for several weeks. Thus, many folks are not rewarded for initial abstinence success and may relapse prior to having a negative drug test. Improving this methodology may result in increased drug treatment outcomes.

In this study, we will establish behavioral and subjective effect profiles in parallel with pharmacokinetics in order to determine biological concentrations associated with impairment, and will conduct exploratory biomarker evaluation to identify biomarkers that can differentiate new from residual cannabis use. Study results will be used to establish scientifically based cut-off thresholds for impairment and DUID due to cannabis use and new test methods for use in drug treatment clinics.

2. Objectives (include all primary and secondary objectives)

Primary Objective

P1: Determine candidate markers of cannabis use that track with level of impairment, as determined by subjective drug effect reporting, objective performance testing, and subjective DRE assessment.

Secondary Objectives

S1: Analyze effects of cannabis dosing across three biological matrices (blood, urine, oral fluid) within individuals based on route of administration (oral ingestion or inhalation).

S2: Determine ability of oral mucosal biology to convert THC to THC-COOH (and potential impact on oral fluid testing).

S3: Evaluate the sensitivity of existing and novel DRE assessments for detecting impairment following oral and inhaled cannabis dosing.

S4: Identify potential association between cannabis analytes in biological matrices and performance and DRE assessments.

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)

Over the past decade, there has been a paradigm shift in legal status and social perception of cannabis in the United States. Twenty-nine states and the District of Columbia have legalized medicinal use of cannabis, and eight states have legalized adult non-medical (i.e. “recreational”) use (ProCon, 2016). Concurrent with this, rates of use and the potency of available cannabis have increased, and perceived harm related to use has decreased. Past-month use by persons 12 years or older increased from 11.5% in 2011 to 12.1% in 2012 (United Nations Office on Drugs and Crime [UNODC], 2014), and in 2013, there were a reported 19.8 million users, up from 14.5 million in 2007 (Substance Abuse and Mental Health Services Administration [SAMHSA], 2014). Not surprisingly, there has been a corresponding increase in prevalence of detecting delta-9- tetrahydrocannabinol (THC, the primary psychoactive constituent in cannabis) in urine obtained from weekend nighttime drivers (up from 8.6% in 2007 to 12.6% in 2013-2014) (Berning, 2015).

Current laws regarding cannabis impairment are either difficult to prosecute or are controversial. Effect-based laws are the most common and least controversial, but are the most difficult to prosecute. They

take into account the totality of circumstances and often rely on testimony or evidence from the arresting officer or a drug recognition expert (DRE), as well as results from a blood or urine toxicology test, with no clear definition of what constitutes a positive determination of impairment. Per se laws are easier to prosecute because they explicitly define an analyte and a cut-off concentration for that analyte; if a person has levels of that analyte above the cut-off concentration, that person is considered intoxicated and no further evidence of impairment need be demonstrated. Per se laws for cannabis impairment are controversial because there is a lack of consistency about both which analyte the laws are based on (e.g., THC or one of its metabolites), and the appropriate cut-off concentration to determine impairment. Some states have enacted zero tolerance per se laws, but in states that have legalized cannabis use, zero tolerance laws for cannabis are not practical because common biomarkers of cannabis use can be detected days after a single use and do not correspond with periods of impairment. In fact, there is little scientific evidence from which to determine appropriate objective measures for identifying cases of cannabis impairment and Driving Under the Influence of Drugs (DUID) due to cannabis impaired driving.

Many controlled laboratory studies have been conducted to evaluate the acute effects of cannabis on various aspects of performance. This research indicates that cannabis reliably impairs attention (both focused and divided attention; see Vandrey & Mintzer, 2009 for review). There is some evidence that cannabis impairs motor ability and memory (short-term/working, episodic), but these effects do not appear to be very robust and are not observed consistently across studies (Chait, 1992). The acute effects of moderate doses of cannabis on motor ability and attention appear comparable to moderate doses of alcohol (BAC approximately 0.05%; Liguori et al., 1998; Ramaekers et al., 2004). In another study, impairment of episodic memory by multiple doses of alcohol and cannabis was shown to be dose-dependent and of comparable severity at parallel points in the dose-response curve (Heishman et al., 1997). With regard to the effects of cannabis on driving, research suggests that cannabis impairs driving ability and increases the risk of getting into an accident (for reviews, see Ramaekers et al., 2004; Asbridge et al., 2012).

Currently, most local law enforcement use a combination of biological and behavioral assessments administered by DREs and blood THC levels, with cutoffs ranging from 1 to 5 ng/mL, to judge cases of suspected DUID involving cannabis. (Governors Highway Safety Association [GHSA], 2016) However, the behavioral assessments have not been explicitly developed to be sensitive for detecting acute intoxication from cannabis (Bosker, 2012; Fierro, 2014; Papafotiou, 2004; Bramness, 2010), and there are significant limitations to the use of blood THC levels as a proxy for impairment. First, THC is present at easily detected levels in the blood of individuals who have recently smoked cannabis but can drop below cutoffs used for drugged driving before subjective drug effects, and likely performance impairing effects, subside. Second, THC can be detected for up to a month after last use in a subset of frequent cannabis users (Bergmaschi, 2013). Also, though smoking remains the most common route of cannabis administration, cannabis is increasingly available in a wide array of “edibles” intended for oral ingestion (Vandrey, 2015).

An estimated 16% to 26% of patients using medical marijuana consume edible products (Grella, 2014; Walsh, 2013), and these types of products accounted for an estimated 40% of sales in Colorado dispensaries in 2014. Cannabinoids are highly lipophilic and subject to presystemic metabolism; thus, orally ingested THC has low bioavailability (6 to 20%) and delayed onset compared to inhaled THC from cannabis smoke (Huestis, 2007). Subjects who have consumed cannabis (or formulations containing active constituents) via oral ingestion can display signs of impairment with THC levels in their blood that are below limits of detection, or below a proposed cutoff value of 5 ng/mL (Ahmed, 2014; Vandrey et al., in press). Similarly, there has been a substantial increase in the use of vaporizers to inhale cannabis products. (Malouff, 2014; Budney/Lee, 2015) Similar to electronic cigarettes, cannabis and related products (e.g., oils, concentrated cannabis resins) can be inhaled using an assortment of hand-held or table-top electronic devices that vaporize cannabis and/or THC for pulmonary self-administration.

Few controlled studies have assessed the pharmacokinetic and pharmacodynamics of vaporized or orally

consumed intact cannabis (e.g., cannabis-containing brownies) on drug test results or behavioral evaluation of performance impairment. The pharmacokinetics and associated pharmacodynamics of cannabis administered via vaporization and oral consumption are currently not well understood and need to be better defined in order to evaluate methods of determining whether or not an individual under the influence of cannabis is impaired.

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). Participants will complete six outpatient drug administration sessions, each lasting approximately 10 hours and separated by at least 1 week. Participants will receive placebo and two active doses of cannabis via two different routes of administration: orally ingested (0mg, 10mg, 25mg) and inhaled vapor (0mg, 5mg, 20mg). Doses were selected based on prior research at the BPRU; the low active doses are expected to produce discriminative drug effects, but not impair performance, and the high doses are expected to produce both discriminative drug effects and performance impairment. Each dose will be administered to each participant using a within-subjects crossover design. Dosing will be clustered by route of administration (e.g., first three sessions will involve oral administration followed by three sessions of vaporization), and route of administration will not be blinded due to difficulties in estimating the exact time of drug effect onset following oral administration. The order of route of administration will be counterbalanced across participants, and the order of doses within each three-session cluster will be randomized. Research volunteers will be recruited until 20 participants have completed the study.

Participants. We will recruit and consent up to 50 research volunteers in order to obtain 20 study completers. We anticipate that some participants may drop out of the study before completion. Based on recent studies using similar methodology, it is estimated that we will need to enroll 30 participants to achieve 20 study completers.

The target demographic for study participation are healthy adults who: 1) have a history of intentionally consuming cannabis, 2) have not used cannabis in the past month (desire is to have participants free of cannabinoids in biological matrices at the time of initial drug administration), and 3) who are not currently dependent on or seeking treatment for use of cannabis or other psychoactive drugs.

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 a brief screening over the telephone and will be scheduled for an in-person assessment if they meet initial eligibility criteria.

Prior to the in-person assessment, written informed consent to administer the assessment will be obtained. The assessment will be comprised of interviews and self-report surveys that provide participant information regarding health status including physical, mental health, and recreational drug use history (e.g. Medical History Interview, Drug-History Questionnaire, and Time-line Follow-Back [TLFB]). Urine specimens will be obtained and tested for evidence of recent use of commonly abused drugs. Participants must test negative for metabolites of THC, the primary psychoactive constituent of cannabis, and self-report no cannabis use during the prior month. Participants must provide a government-issued photo ID confirming they are 18-45 years old, report prior use of cannabis at least once in their lifetime, and report no allergies to any of the ingredients used to prepare the brownies (e.g., chocolate, egg, wheat, etc.) used as a vehicle for oral cannabis administration. Study participants will also undergo a physical exam including clinical chemistry, hematology, serology, and serum pregnancy test (females only). An electrocardiogram (EKG) reading will be obtained and reviewed by a physician or nurse practitioner to assess current cardiovascular health. Additionally, participants will be required to demonstrate that they

can expectorate at least 3 mL of "native" oral fluid (saliva) over a 5-minute period. Those who appear eligible for participation will receive training on the study assessment measures (e.g. exposure to subjective questionnaires, DRE assessments, and cognitive performance tasks).

Experimental Session Procedures. For all study sessions, participants will be scheduled to arrive early in the morning on the day of cannabis exposure. All participants will complete a breath alcohol test on arrival. Participants with a positive BAL will be immediately discharged from the study. 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. Volunteers must have negative urine drug screens on the day of the cannabis exposure session to participate. Based upon results from previous studies in our laboratory, the one-week minimum interval between sessions should be sufficient for eliminating cannabinoids between test days in such a manner that positive urine drug screens from the prior study exposure is not a concern. Participants will be fed a standardized low fat breakfast (e.g. toast and jam) each morning prior to cannabis administration and will be provided lunch and snacks at predetermined times post drug administration.

Baseline Assessments. Prior to cannabis administration, participants will have an indwelling intravenous catheter inserted for blood collections. Baseline oral fluid, urine, and blood and will be obtained from all participants. Baseline cardiovascular, subjective, DRE, and performance assessments will also be conducted (see below for details), and the TLFB will be conducted to record substance use since the last study visit (intake assessment or prior to experimental session). Concomitant medications**,** including vitamins and herbal supplements taken within 14 days prior to experimental session will be recorded. Changes in medication occurring between the screening assessment and experimental session will be reviewed by a study investigator and medical staff prior to cannabis administration to ensure the volunteer is still eligible to participate.

Cannabis Exposure. After baseline assessments are completed, participants will receive either an oral or an inhaled cannabis exposure. Cannabis will be obtained from the NIDA Drug Supply Program and prepared accordingly for the two routes of administration (see below). For ease of dose calculation, we will obtain cannabis containing approximately 10% THC by volume for active dose administration and placebo cannabis for the "0mg" dose conditions. Because most cannabis available for medical and non-medical use is high in THC and low in minor cannabinoid content, the cannabis used in this study will not contain more than a 3% concentration of cannabinoids other than THC (e.g. CBD, CBG, CBC). Cannabis dose assignment will be blinded in this study; however, route of administration will not be blinded due to difficulties in timing drug onset and peak effects across oral and inhaled cannabis for a double-dummy drug administration procedure.

Oral Administration. Participants will self-administer a brownie containing cannabis measured to produce THC exposure of 0, 10mg, or 25mg. Participants will receive each cannabis dose (one per session) in a randomized order on three consecutive sessions. Cannabis brownies will be prepared using individual baking trays for each dose. Baking will occur using a small oven located in the BPRU pharmacy and a commercial brownie mix. The mix will be prepared according to manufacturer's instructions, with a measured dose of finely ground cannabis added to a portion the brownie batter mixture sufficient to make one cannabis brownie. The plant material will be pre-heated to decarboxylate THCA to free THC. We have prepared brownies individually in this manner for previous studies and verified that this preparation method ensures that target THC cannabis doses can be reliably achieved. Study participants and research staff will be blind to dose assignment. Participants will be provided with cannabis brownies and drinking water approximately 1 hour after finishing their standardized low-fat breakfast, and will be instructed that they need to consume the brownie within 5 minutes. The conclusion of cannabis brownie consumption will be considered the "0 hour" by which remaining protocol assessments will be scheduled.

Vaporization. Participants will inhale vapor produced from cannabis plant material measured to contain 0, 5mg, or 20mg THC. Vaporization will be achieved using The Volcano desktop vaporizing device (Storz &

Bickel, Oakland, CA). The appropriate amount of cannabis plant material will be vaporized and trapped in an opaque balloon. Participants will be instructed to inhale the air from the balloon ad-libitum until the balloon is empty. This will be repeated for the inhalation of 3 balloons and within a 10-minute time period to ensure the dose is completely delivered and to minimize variability in the time course and magnitude of drug effects. To minimize bias, the placebo dose will be prepared using vaporized "placebo" cannabis (THC and other cannabinoids extracted), so that a visible vapor will still be exhaled after each breath. Participants will receive each cannabis dose (one per session) in a randomized order. Study participants and research staff will be blind to dose assignment. Vaporized cannabis administration will begin approximately 1 hour after finishing their standardized low- fat breakfast. The conclusion of cannabis inhalation period will be considered the "0 hour" by which remaining protocol assessments will be scheduled.

Outpatient Discharge. Participants will be discharged after completing final assessments (approximately 8.5 hours post-exposure). In 3 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 equal to or greater than those use 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 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 include measures of psychomotor ability, working memory and divided attention. If the participant is able to cognitively engage with staff, vital signs are within normative range (HR < 100bpm, SYS BP < 160mmHg, DIA BP < 90mmHg), and performance is not below 10% 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. 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.

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

Screening. During the laboratory screening assessment, a battery of measures will be administered 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, and Time-line Follow-Back (TLFB)). A physical examination will be performed on each subject during the Screening Visit. 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. A 12-lead EKG will be conducted to ascertain cardiovascular health and 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 at baseline, immediately after administration, and 1, 2, 3, 4, 5, 6, and 8 hours post exposure.

Blood sampling (6 mL per specimen) will occur 8 times during each experimental session. For vaporization sessions, blood will be collected at baseline, immediately after administration, and 1, 2, 3, 4, 6, and 8 hours post exposure. For oral administration sessions, blood will be collected at baseline, 1, 2, 3,

4, 5, 6, and 8 hours post exposure. Participants will have an indwelling intravenous catheter inserted prior to the start of the exposure session. Six milliliters of blood will be collected by catheter at designated times into vacutainer tubes (gray top). Blood will be centrifuged and plasma will be divided into three plastic cryotubes, labeled and stored frozen at -80 ºC until shipped frozen on dry ice to a designated laboratory for analysis. 48mL of blood will be obtained per session for a total of 288mL of blood across the 6 outpatient sessions.

Oral fluid sampling will occur at the same time points as blood sampling (see above). Collection of oral fluid specimens will be performed using a Quantisal collection kit (Immunalysis Inc., Pamona, CA). No food or drink will be allowed during collection and for a period of 10 minutes prior to each scheduled collection. Each specimen will be sealed with a plastic screw cap and stored refrigerated until shipped to a designated laboratory.

Spot urine specimens will be collected into empty, clean, plastic collection containers, labeled with the participant's identification number, date, and collection time at baseline, 1, 2, 3, 4, 5, 6, and 8 hours post exposure. Urine will be stored frozen at -20 ºC. A total of 60 urine samples will be collected across the 6 outpatient sessions.

An FDA-approved cardiac monitor will be attached to study participants via disposable electrodes. Participants will be instructed on how and where to place the sensor on their chest and research staff will ensure it is properly placed. The sensor will be applied at baseline and will be worn continuously throughout each session. The device will log 1 lead electrocardiogram and 3-axis accelerometer data to memory. After the device is removed from the participant the data will be uploaded to a computer for analysis.

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, good effect, bad effect) and behavioral/mood states often associated with marijuana 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. This questionnaire will be administered at baseline, immediately after administration and 1, 2, 3, 4, 5, 6, and 8 hours post exposure. It is expected that all subjective drug effects will subside by Hour 8, but if a participant reports a drug effect beyond this time the questionnaire will continue to be administered at other time points until the participant no longer reports a drug effect.

Performance assessments will be conducted on aspects of cognitive/psychomotor functioning known to be sensitive to the acute effects of smoked marijuana and relevant to functioning in the workplace and/or in operating a motor vehicle or heavy machinery. All participants will be trained on the performance tasks to a stable baseline level during the screening session. Tasks include: 1) Divided Attention Task (DAT): Participants simultaneously perform two different simple tasks based on visual stimuli presented on a computer screen. Primary outcome is the accuracy with which they perform the two tasks; 2) Digit Symbol Substitution Task (DSST): Participants must hand type patterns presented to them on a computer screen for 90 seconds. Primary outcomes are accuracy and total number of patterns completed in the allotted time; and 3) a computerized version of the Paced Auditory 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. The primary outcome is a summed score of the number of correct trials during the task. We will also administer a brief (2-minute) cognitive test battery on an iPad. The DRUID App is currently under development as a potential screening tool for identification of impairment in individuals in workplace or roadside settings. The app utilizes tasks that measure similar performance domains as those used in the task battery described above (divided attention, psychomotor ability, working memory), but is much more abbreviated. This will help us determine the relative sensitivity of the app in detecting impairment relative to the more lengthy assessment battery we have traditionally used in our studies. Performance assessments will be completed at baseline, immediately after drug exposure, and 1, 2, 3, 4, 5, 6, and 8 hours post exposure.

A battery of DRE assessments will include currently practiced assessments that have been found to be most sensitive to effects of cannabis impairment (e.g., walk-and-turn, one-leg stand, lack of convergence, and horizontal gaze nystagmus). Eye movements will be recorded using an eye-tracking camera during the assessment, which will include measures of eye convergence, horizontal gaze nystagmus, and pupil size. Note: this eye-tracking camera will gauge which tracking paths produce characteristic involuntary eye movements that a trained officer could observe without the aid of a recording device. We are not proposing that the camera itself would be used in a roadside testing environment. All DRE assessments will be recorded using a web camera which will be set up by the research staff member running the session. The purpose of these recordings is to assure valid ratings on the DRE assessments and to allow for re-coding performance of study completers if new "clues" about impairment are established during the course of the study. Consent for videotaping will be obtained from all study volunteers and video recordings will not be shared outside the study team without additional written consent of the individual study participant. These assessments will be completed at baseline, immediately after exposure, and 1, 2, 3, 4, 5, 6, and 8-hours post exposure.

The eye-tracking camera (e.g. DAX Evidence Recorder) automatically quantifies and assesses the involuntary eye movements (e.g. gaze nystagmus) that occur when a user is asked to visually follow an object (e.g. a pencil moved back and forth). We will evaluate whether cannabis administration impacts gaze nystagmus, eye convergence, and changes in pupil size when ambient room lighting is brightened/darkened. The eye convergence test involves asking the participant to follow the test administrator's finger (or a pencil) with their eyes as it moves from far to close to the nose (without touching the participant).

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

All participants will complete a visit for screening evaluation. Participants meeting eligibility criteria will be enrolled in the study and complete 6 outpatient drug administration sessions, lasting approximately 10 hours each, and spaced at least one week apart.

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

Cannabis dose assignment will be blinded in this study, but route of administration will not. It is standard procedure for appropriate scientific control in studies evaluating dose effects of psychoactive drugs to blind dose assignment. Blinding of route of administration is not necessary and would be difficult to manage in this study given the immediacy of effects via inhaled routes and the unpredictable delay in drug onset effects following oral administration.

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

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

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

A placebo dosing session 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.

f. 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.

g. 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 45
3. Be in good general health based on a physical examination, medical history, vital signs, 12-lead ECG and screening urine and blood tests
4. Test negative for recent cannabis use in urine at the screening visit (confirmed by GC/MS laboratory test) and at clinic admission
5. Test negative for other drugs of abuse, including alcohol at the screening visit and at clinic admission
6. Demonstrate ability to expectorate 3-5 mL of "native" oral fluid over a 5-minute period
7. 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.
8. Have a body mass index (BMI) in the range of 19 to 36 kg/m2
9. 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
10. Have no allergies to any of the ingredients used to prepare cannabis brownies (chocolate, eggs, wheat, etc.).
11. Report prior experience inhaling cannabis (either via smoking or vaporization).
12. Have not donated blood in the prior 30 days.

Exclusion Criteria

1. Non-medical use of psychoactive drugs other than, nicotine, alcohol, or caffeine 3 months prior to the Screening Visit;
2. History of or current evidence of significant medical or psychiatric illness 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 hemp seeds or hemp oil in any form in the past 3 months.
6. Use of dronabinol (Marinol) within the past 6 months.

7. History of xerostomia (dry mouth), or the presence of mucositis, gum infection or bleeding, or other significant oral cavity disease or disorder that in the investigator's opinion may affect the collection of oral fluid samples.
8. History of clinically significant cardiac arrhythmias or vasospastic disease (e.g., Prinzmetal's angina).
9. Abnormal EKG result that in the investigator's opinion is clinically significant.
10. Epilepsy or a history of seizures.
11. Enrolled in another clinical trial or have received any drug as part of a research study within 30 days prior to dosing.
12. Individuals who have a recent history of traumatic brain injury diagnosed by CT/MRI and have current sequela from prior brain injury, as determined by the study physician
13. Individuals with anemia

6. Drugs/ Substances/ Devices

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

All cannabis will be obtained specifically for use in this study from the Federal Drug Supply System. For oral administration, brownies will be made by the BPRU pharmacy and will contain target THC doses of 0, 10mg, or 25mg, (e.g., 100 or 250mg of cannabis material that is approximately 10% THC by volume; or 250mg cannabis for which THC and other cannabinoids has been extracted). For vaporization, THC doses of 0, 5mg, and 20mg will be administered. Cannabis will be vaporized using a commercial vaporizer called The Volcano (Storz and Bickel, GmbH & Company (Oakland, CA). To preserve the blind, we will mix active and placebo cannabis so that the same amount of plant material is placed in the vaporizer at each session. For example, if we obtain cannabis with 10% THC, the placebo dose will contain 200mg cannabis for which THC and other cannabinoids has been extracted. The 5mg THC dose will contain 50 mg cannabis with 10% THC and 150mg cannabis for which THC and other cannabinoids has been extracted. The 20mg dose will contain 200mg cannabis with 10% THC. Selection of doses was conducted to balance participant safety and tolerability based on our previous experience, and to administer 2 active doses the are expected to produce subjective drug effects via each route of administration, but only one that produces significant impairment of performance ability. This will help test the sensitivity of the biological and behavioral assessments for detecting impairment versus discriminable drug effects. We have experience safely delivering acute cannabis doses within the range utilized in this study with healthy adult volunteers who are not frequent cannabis users.

Potential risks of consuming cannbis in the present study are stomach/gastrointestinal irritation and adverse effects associated with cannabis intoxication. We have considerable experience administering smoked, vaporized, and oral cannabis in our laboratory. Recently, using essentially the same protocol, we have administered up to 50mg THC via oral cannabis ingestion and up to 25mg THC via cannabis vaporization. Following 25mg oral THC administration to 23 healthy adults, one participant vomited and one participant experienced a brief period of anxiety. The participant who vomited experienced immediate relief of discomfort and the case of anxiety was resolved within about one hour of onset without the need for medical intervention. In both the oral cannabis study as well as a recently completed study of vaporized cannabis exposure, transient experiences of dizziness and nausea were reported by a minority of participants, the effects were dose-dependent, but did not result in the need for intervention and no participants withdrew participation as a result. In fact, half of the participants who completed the oral cannabis study volunteered for and completed the protocol extention involving smoked and vaporized cannabis administration one year later (those who elected not to return did so because of work conflicts or because they moved). By reducing the maximum doses administered in this study, we believe that we will still achieve our target behavioral outcomes, and maintain safety and tolerability of doses for study volunteers. That said, we still have adequate procedures in place to handle adverse events. The research space has multiple restrooms and bio-hazard waste containers for use in cases of vomiting. 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. Acute cannabis exposure is expected to result in a time-limited increase in heart rate and orthostatic hypotension. If heart rate increases above 120bpm, blood pressure increases above 160/90mmHg or drops below 90/50mmHg, a nurse practitioner or physician will be notified and will evaluate the study participant. The NP/MD will determine whether there is a need for urgent care versus continued observation and evaluation. In the case of an extreme adverse reaction, study staff will call 911 and EMTs will take participants across the street to the Johns Hopkins Bayview ER for treatment.

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.

Not applicable to this protocol.

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

Not applicable to this protocol. An IND has been obtained for the administration of cannabis.

Study Statistics

a. Primary outcome variable.

The primary outcome variables are the quantitative levels of THC and its metabolites in biological matrices (oral, urine, blood), subjective rating of “Drug Effect” on the DEQ, and performance on DRE and cognitive/psychomotor assessments.

b. Secondary outcome variables.

Secondary outcome variables include subjective drug effect and mood ratings on additional items of the DEQ and vital signs.

c. Statistical plan including sample size justification and interim data analysis.

The sample size estimate for this study was based on previous work in our 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, 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. This sample selection methodology has been consistent in our long history of studies investigating dose-effects comparisons of different drugs, which have demonstrated excellent external validity and have become the FDA recommended standard for human abuse liability assessment. Subjective drug effect and mood ratings, vital signs, DRE assessments 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).

d. 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 cannabis exposure include dizziness, change in blood pressure, red or irritated eyes, drowsiness, easy laughing, euphoria, rapid heart rate, dry mouth, jitters, headache, nausea, vomiting, increased appetite, perceptual difficulties, memory lapse, hallucinations, confusion, depression, paranoid reaction, depersonalization, and rash. Additional potential risks of orally consuming cannabis are stomach/gastrointestinal irritation. We feel that the risk of serious adverse events related to cannabis exposure in this study is minimal, participants are experienced users and the doses we are administering are within the range by which most participants in our prior studies have had good tolerance to the drug.

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. The only risk associated with oral fluid collection is dryness of the mouth.

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.

The cardiac sensor should not be worn by subjects with a pacemaker or defibrillators.

The eye-tracking camera will include exposure to flashing lights and light patterns. Some people with photosensitive epilepsy are susceptible to epileptic seizure or loss of consciousness when exposed to certain flashing lights or light patterns in everyday life. While the illumination of the eye tracking camera is continuous and invisible to the subjects, we will exclude from testing subjects with epilepsy or a history of seizure. The safety of the near-infrared lighting source was assessed using the guidelines set forth in the *IEC 62471/CIES009-2006, Photobiological Safety of Lamps and Lamp Systems Optical Standard*. The power output of the lighting source was measured with a commercial calibrated powermeter (Thorlabs PM100D) and used to determine irradiance and radiance. The standard specifies an irradiance safety limit of 100 W/m^2, this is the maximum recommended irradiance for day-long continuous exposure by ACGIH, *American Conference of Governmental Industrial Hygienists*; the RTI custom system measured 44.1 W/m^2. The standard also specifies a maximum radiance limit of 60 $mW/mm^2/sr$, and our system measured a radiance of 0.36 $mw/mm^2/sr$.

Breach of confidentiality about self-reported drug use, biological tests indicating recent drug use, and study participation is a risk.

b. Steps taken to minimize the risks.

Participants are not a "vulnerable population" as defined by human subjects 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, participants will be taken for immediate care. The Principal Investigator will be immediately notified of any serious adverse events that arise.

If participants develop nausea or vomiting after consuming cannabis, study staff will assist the affected participant(s) appropriately and contact a study physician located in the building should the PI and/or study staff decide the participant would benefit from medical attention.

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. Placement of indwelling venous catheters poses a risk of infection or thrombophlebitis, which increases with duration of placement. This risk is minimized by use of careful sterile techniques and catheter placement by experienced nursing staff. The risk of anemia is negligible because the total amount of blood to be collected during the study (5 mL at screening and 288mL during sessions) 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.

Individuals with a pace maker or defibrillator will not be given a heart rate monitor to wear during sessions. It is unlikely that any study volunteer with such devices would meet study eligibility requirements.

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 ingest cannabis brownies and vaporized cannabis 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.

Confidentiality will be maintained by using study specific identifiers, rather than participant names, on all study-related documents as possible, following standard human subjects practice for protecting PHI, and keeping all documents and video with PHI in secure physical and digital environments.

c. Plan for reporting unanticipated problems or study deviations.

The PI 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.

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. Video footage of the field sobriety assessments will be stored internally on password protected computers and servers that conform to JHU IT standards and will not be shared outside the study team. 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 relative biological, subjective and behavioral dose effects of exposure to cannabis administered orally, or via vaporization. The knowledge will be used to advise the establishment of new drug testing guidelines across different biological matrices, and will inform the relevance of oral administration vs. inhalation on interpretation of workplace or roadside drug testing. The study will also extend the extant literature investigating the acute dose effects of cannabis, including subjective effects, cognitive performance, and their correlation with biological cannabinoid levels. 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. Compensation for full participation is $2030. Compensation of this magnitude is appropriate given the length and nature of this study.

Screening Visit:	$30
Sessions:	$300/session ($1800 total)
Completion Bonus:	$500
Total Compensation:	$2330

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.

Reference List

Abrams, D.I., Vizoso, H.P., Shade, S.B., Jay, C., Kelly, M.E., & Benowitz, N.L. (2007). Vaporization as a smokeless cannabis delivery system: a pilot study. *Clinical Pharmacology & Therapeutics, 82*, (5), 572-8.

Ahmed, A.I.A., van den Elsen, G.A.H., Colbers, A., van der Marck, M.A., Burger, D.M., Feuth, T.B., Rikkert, & M., Kramers, C. (2014). Safety and pharmacokinetics of oral delta-9-tetrahydrocannabinol in healthy older subjects: A randomized controlled trial. Eur. *Neuropsychopharmacology., 24*, (9), 1475-1482.

Asbridge, M., Hayden, J.A., & Cartwright, J.L. (2012). Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. *BMJ, 344*.

Bergamaschi, M.M., Karschner, E.L., Goodwin, R.S., Scheidweiler, K.B., Hirvonen, J., Queiroz, R.H., & Huestis, M.A. (2013). Impact of prolonged cannabinoid excretion in chronic daily cannabis smokers' blood on per se drugged driving laws. *Clinical Chemistry, 59*, (3), 519-26.

Berning, A., Compton, R., & Wochinger, K. (2015). Results of the 2013-2014 National Roadside Survey of alscohol and drug use by drivers. (Traffic Safety Facts Research Note. Report No. DOT HS 812 118). National Highway Traffic Safety Administration: Washington, DC.

Bosker, W.M., Theunissen, E.L., Conen, S., Kuypers, K.P., Jeffery, W.K., Walls, H.C., Kauert, G.F., Toennes, S.W., Moeller, M.R., & Ramaekers, J.G. (2012). A placebo-controlled study to assess Standardized Field Sobriety Tests performance during alcohol and cannabis intoxication in heavy cannabis users and accuracy of point of collection testing devices for detecting THC in oral fluid. *Psychopharmacology (Berlin), 223*, (4), 439-46.

Bramness, J.G., Khiabani, H.Z., & Morland, J. (2010). Impairment due to cannabis and ethanol: clinical signs and additive effects. *Addiction, 105*, (6), 1080-7.

Caulkins, J.P., Kilmer, B., MacCoun, R.J., Pacula, R.L., & Reuter, P. (2012). Design considerations for legalizing cannabis: lessons inspired by analysis of California's Proposition 19. *Addiction, 107*, (5), 865-871

Chait, L., & Pierri, J. (1992). Effects of smoked marijuana on human performance: A critical review. In *Marijuana/cannabinoids: Neurobiology and neurophysiology,* Murphy, L., Bartke, A., Eds. CRC Press: Boca Raton, FL, 387-423.

Fant, R.V., Heishman, S.J., Bunker, E.B., & Pickworth, W.B. (1998). Acute and residual effects of marijuana in humans. *Pharmacology Biochemistry and Behavior, 60*, (4), 777-84.

Felch, L., Di Marino, M., & Griffiths, R. (1995). A meta-analysis of psychomotor, subject- and observer-rated effects in abuse liability studies of anxiolytics. In *Problems of Drug Dependence*, Harris, L. S., Ed. Government Printing Office: Washington, DC, 1996.

Fierro, I., Gonzalez-Luque, J.C., & Alvarez, F.J. (2014). The relationship between observed signs of impairment and THC concentration in oral fluid. *Drug and Alcohol Dependence, 144*, 231-8.

GHSA Drug-Impaired Driving Laws. http://www.ghsa.org/html/stateinfo/laws/dre_perse_laws.html (accessed January 6, 2016).

Grella, C.E., Rodriguez, L., & Kim, T. (2014). Patterns of Medical Marijuana Use Among Individuals

Sampled from Medical Marijuana Dispensaries in Los Angeles. *Journal of Psychoactive Drugs, 4*6, (4), 263-272.

Heishman, S.J., Arasteh, K., & Stitzer, M.L. (1997). Comparative effects of alcohol and marijuana on mood, memory, and performance. *Pharmacology Biochemistry and Behavior, 58*, (1), 93-101.

Huestis, M.A. (2007). Human Cannabinoid Pharmacokinetics. *Chemistry & Biodiversity, 4*, (8), 1770-1804.

Huestis, M.A., & Smith, M.L. (2014). Cannabinoid pharmacokinetics and disposition in alternative matrices. In *Handbook of Cannabis,* Pertwee, R. G., Ed. Oxford University Press: Oxford, UK.

Kilmer, B., Caulkins, J.P., Pacula, R.L., MacCoun, R.J., & Reuter, P. (2010). *Altered state? Assessing how marijuana legalization in California could influence marijuana consumption and public budgets*. RAND Drug Policy Research Center: Santa Monica, CA.

Lee, D. C., Crosier, B. S., Borodovsky, J. T., Sargent, J. D., & Budney, A. J. (2016). Online survey characterizing vaporizer use among cannabis users. *Drug and alcohol dependence*, 159, 227-233.

Liguori, A., Gatto, C.P., & Robinson, J.H. (1998). Effects of marijuana on equilibrium, psychomotor performance, and simulated driving. *Behavioural Pharmacology, 9*, (7), 599-609.

Malouff, J.M., Rooke, S.E., & Copeland, J., (2014). Experiences of marijuana-vaporizer users. *Substance Abuse, 35*, (2), 127-8.

Papafotiou, K., Carter, J.D., & Stough, C. (2004). An evaluation of the sensitivity of the Standardised Field Sobriety Tests (SFSTs) to detect impairment due to marijuana intoxication. *Psychopharmacology (Berlin), 180*, (1), 107-114.

Pomahacova, B., Van der Kooy, F., & Verpoorte, R. (2009). Cannabis smoke condensate III: the cannabinoid content of vaporised Cannabis sativa. *Inhalation Toxicology, 21*, (13), 1108-12.

Procon.org 28 Legal medical marijuana states and DC: laws, fees, and possession limits. http://medicalmarijuana.procon.org/view.resource.php?resourceID=000881 (accessed 12/21/16).

Ramaekers, J.G., Berghaus, G., van Laar, M., & Drummer, O.H. (2004). Dose related risk of motor vehicle crashes after cannabis use. *Drug & Alcohol Dependence,* 73, (2), 109-119.

Substance Abuse and Mental Health Services Administration (SAMHSA). (2014). *Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings*.

United Nations Office on Drugs and Crime (UNODC). (2014). *World Drug Report*. United Nations Publication, Sales No. E.14.XI.7.

Vandrey, R., Raber, J.C., Raber, M.E., Douglass, B., Miller, C., Bonn-Miller, M.O. (2015). Cannabinoid dose and label accuracy in edible medical cannabis products. *Journal of the American Medical Association, 313*, (24), 2491-2493.

Vandrey, R., Cone, E.J., Herrmann, E.S., Mitchell, J.M., Flegel, R., LoDico, C., & Bigelow, G.E. (2015b). *The pharmacodynamic dose effects of oral cannabis administration*. Society of Forensic Toxicologists Annual Meeting, Atlanta, GA, October 18-23.

Vandrey, R.G., & Mintzer, M.Z. (2009). Performance and cognitive alterations. In L. Cohen, F.L. Collins, A.M. Young, D.E. McChargue, & T.R. Leffingwell (Eds.), *The Pharmacology and treatment of*

substance abuse: an evidence-based approach (pp. 41-62). Mahwah, NJ: Lawrence Erlbaum Associates, Inc.

Walsh, Z., Callaway, R., Belle-Isle, L., Capler, R., Kay, R., & Lucas, P., Holtzman, S. (2013). Cannabis for therapeutic purposes: Patient characteristics, access, and reasons for use. *International Journal of Drug Policy, 24*, (6), 511-516.

Zuurman, L., Roy, C., Schoemaker, R.C., Hazekamp, A., den Hartigh, J., Bender, J., Verpoorte, R., Pinquier, J.L., Cohen, A.F., & van Gerven, J.M.A. (2008). Effect of intrapulmonary tetrahydrocannabinol administration in humans. *Journal of Psychopharmacology, 22*, (7), 707- 716.