Behavioral Pharmacology of Cannabis and Nicotine

NCT04124432

7/15/2022

Date: July 15, 2022
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Application Number: IRB00220975

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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.

Tobacco and cannabis are two of the most commonly abused substances in the United States, with tobacco use being the leading cause of preventable death and disease (Center for Behavioral Health Statistics and Quality, 2015). Further, simultaneous use of both substances is commonplace and is increasing (Schauer et al., 2015; Schauer et al., 2016), primarily due to expanding legalization of cannabis (Borodovsky et al., 2016; Lipperman-Kreda et al., 2014). The upward trend of cannabis and tobacco polysubstance use (CT-PSU) is of particular concern because, compared to use of cannabis without tobacco, CT-PSU is associated with greater cannabis dependence, psychosocial problems, and poorer cessation outcomes (Agrawal and Lynskey, 2009; Baggio et al., 2014; Hindocha et al., 2015; Peters et al., 2012; Ream et al., 2008). Further, cannabis use predicts the onset and escalation of tobacco smoking (Patton et al., 2005; Rubinstein et al., 2014), and cannabis use among tobacco smokers predicts poorer tobacco-cessation outcomes (Amos et al., 2004; Ford et al., 2002). CT-PSU may also be associated with additive health risks relative to either substance alone (Meier and Hatsukami, 2016; Rooke et al., 2013; Schauer et al., 2016).

Mechanistic hypotheses for the etiology of CT-PSU fall into three general categories (which are not mutually exclusive). The first category posits that CT-PSU results from factors that have been shown to play a role in abuse of a single substance (Vanyukov et al., 2012), including genetics (Stringer et al., 2016), impulsivity (Martinez-Loredo et al., 2015), sensation seeking (Meil et al., 2016), and sociocultural environmental factors (Compton et al., 2014). A related hypothesis is that CT-PSU is facilitated by the shared route of administration of the two substances (Agrawal and Lynskey, 2009), including the user-expressed rationale that tobacco enhances the intensity and duration of cannabis effects and thereby delays the need to re-use (Schauer et al., 2016). A second hypothesis is that nicotine and Δ^9-tetrahydrocannabinol (THC), the two primary psychoactive substituents of tobacco and cannabis, respectively, produce enhanced reinforcing effects compared to those produced by either substance alone (Panlilio et al., 2013; Tullis et al., 2003). The final set of hypotheses proposes that CT-PSU may result from one substance modulating the aversive effects of the other substance. For example, tobacco co-use may attenuate the initial aversive effects of THC, THC may attenuate nicotine's withdrawal effects (Balerio et al., 2004), or vice versa (Levin et al., 2010). While empirical support for the role of each of these major factors (i.e., shared liability factors, enhancement of reinforcing effects, and amelioration of aversive effects) has been reported (Agrawal et al., 2012; Kohut, 2016; Rabin and George, 2015), clinical research on CT-PSU is still in its infancy, with relatively few controlled investigations offering specific examination of its effects (vs. single drug use). The primary purpose of the present clinical laboratory study is to determine the extent to which acute cannabis intoxication enhances the effects of nicotine-containing products (both e-cigarettes and tobacco cigarettes) and to determine whether the acute effects of cannabis (versus placebo) alters nicotine/tobacco self-administration patterns (e.g., puffing topography). This study will provide key insights into the mechanisms that underlie CT-PSU and ultimately improve treatment for disordered use of both drugs.

2. Objectives (include all primary and secondary objectives)

Objective 1 (Primary): Evaluate whether administration of THC-containing cannabis (versus placebo cannabis) subsequently influences self-administration patterns (time to first self-administration, amount consumed, puffing topography characteristics) of tobacco cigarettes or e-cigarettes.

Objective 2 (Primary): Evaluate whether administration of THC-containing cannabis (versus placebo cannabis) subsequently influences the acute effects (e.g., subjective effects) of tobacco cigarettes or e-cigarettes, nicotine withdrawal symptoms, or craving.

Objective 3 (Secondary): Evaluate whether administration of THC-containing cannabis (versus placebo cannabis) subsequently influences vital signs (e.g., heart rate, blood pressure).

Objective 4 (Secondary): Evaluate whether administration of THC-containing cannabis (versus placebo cannabis) subsequently influences cognitive performance.

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)

Tobacco and cannabis are two of the most commonly abused substances in the United States, with tobacco use being the leading cause of preventable death and disease (Center for Behavioral Health Statistics and Quality, 2015). Further, simultaneous use of both substances is commonplace and is increasing (Schauer et al., 2015; Schauer et al., 2016), primarily due to expanding legalization of cannabis (Borodovsky et al., 2016; Lipperman-Kreda et al., 2014). Additionally, trends in non-cigarette tobacco product use are also changing. For example, in the past 5 years, electronic vapor products (e.g., e-cigarettes) and waterpipe use among youth increased while use of combustible products (e.g., cigarettes) decreased (Singh et al., 2016). Beyond nicotine, vaporizer products are also increasingly being used to consume Δ^9-tetrahydrocannabinol (THC) (Giroud et al., 2015; Lee et al., 2016). The upward trend of cannabis and tobacco polysubstance use (CT-PSU) is of particular concern because, compared to use of cannabis without tobacco, CT-PSU is associated with greater cannabis dependence, psychosocial problems, and poorer cessation outcomes (Agrawal and Lynskey, 2009; Baggio et al., 2014; Hindocha et al., 2015; Peters et al., 2012; Ream et al., 2008). Further, cannabis use predicts the onset and escalation of tobacco smoking (Patton et al., 2005; Rubinstein et al., 2014), and cannabis use among tobacco smokers predicts poorer tobacco-cessation outcomes (Amos et al., 2004; Ford et al., 2002). CT-PSU may also be associated with additive health risks relative to either substance alone (Meier and Hatsukami, 2016; Rooke et al., 2013; Schauer et al., 2016).

Mechanistic hypotheses for the etiology of CT-PSU fall into three general categories *(which are not mutually exclusive)*. The first category posits that CT-PSU results from factors that have been shown to play a role in abuse of a single substance (Vanyukov et al., 2012), including genetics (Stringer et al., 2016), impulsivity (Martinez-Loredo et al., 2015), sensation seeking (Meil et al., 2016), and sociocultural environmental factors (Compton et al., 2014). A related hypothesis is that CT-PSU is facilitated by the shared route of administration of the two substances (Agrawal and Lynskey, 2009), including the user-expressed rationale that tobacco enhances the intensity and duration of cannabis combustion and thereby delays the need to re-use (Schauer et al., 2016). A second hypothesis is that nicotine and THC, the two primary psychoactive substituents of tobacco and cannabis, respectively, produce enhanced reinforcing effects compared to those produced by either substance alone (Panlilio et al., 2013; Tullis et al., 2003). The final set of hypotheses proposes that CT-PSU may result from one substance modulating the aversive effects of the other substance. For example, tobacco co-use may attenuate the initial aversive effects of THC, THC may

attenuate nicotine's withdrawal effects (Balerio et al., 2004) or vice versa (Levin et al., 2010). While empirical support for the role of each of these major factors (i.e., shared liability factors, enhancement of reinforcing effects, and amelioration of aversive effects) has been reported (Agrawal et al., 2012; Kohut, 2016; Rabin and George, 2015), clinical research on CT-PSU is still in its infancy, with relatively few controlled investigations offering specific examination of its effects (vs. single drug use).

To date, only two human laboratory studies have evaluated pharmacological and behavioral mechanisms of CT-PSU. In the first study (Penetar et al., 2005), nicotine was administered via a transdermal patch four hours before smoking a cannabis joint. Nicotine did not alter plasma levels of THC; however, it did enhance cannabis-related increases in heart rate, subject ratings of "stimulated," and scores on the amphetamine scale of the Addiction Research Center Inventory. A second study reported that, compared to blunts, cannabis administered in joints produced greater plasma THC levels and subjective ratings of intoxication, strength and quality; however, lower THC plasma levels after blunt administration was attributed to a procedural limitation in that participants had difficulty drawing smoke from the blunts compared to the joints (Cooper and Haney, 2009). Overall, results from these studies suggest that nicotine may enhance some physiological and subjective effects of cannabis, but results are limited by their use of only a single nicotine dose. Prior research has also yet to examine a key CT-PSU behavior known as "chasing" in which users administer nicotine/tobacco after using cannabis, in an attempt to boost or extend their high. Notably, survey data collected to inform the present clinical research study indicated approximately half of the participants who endorsed recent use of both cannabis and tobacco had engaged previously in "chasing behavior," most commonly with conventional cigarettes or e-cigarettes. The present study seeks to evaluate the impact of acute smoked cannabis effects on nicotine/tobacco self-administration "chasing" behavior in current nicotine/tobacco users. Though nicotine/tobacco "chasing" has been previously reported, controlled studies have not been conducted to elucidate whether pre-exposure to cannabis actually alters nicotine/tobacco use patterns or reinforcement among current, nicotine-tolerant smokers/e-cig user, or whether there are differential changes based on nicotine dose or product type (i.e. tobacco cigarettes vs. electronic cigarettes). This research will be a critical first step towards elucidating the underlying mechanisms responsible for CT-PSU which ultimately may improve treatment outcomes for those with disordered use of cannabis and tobacco products

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). All participants will be healthy adult volunteers who are regular nicotine/tobacco users, and have prior experience with cannabis use. All procedures will be for research purposes. Participants will complete seven outpatient experimental test sessions (see table below; completed in a randomized order), under double-blind conditions, in which they will first self-administer smoked cannabis (containing 10mg THC, 25mg THC or placebo), followed by access to their preferred brand of tobacco cigarette or a commercial e-cigarette device (e.g. JUUL) containing a 3% or a 5% nicotine solution for *ad-libitum* self-administration. The dose of active cannabis will be determined based on the frequency of cannabis use prior to study participation. Individuals who report using cannabis >2 times per week on average in the 3 months prior to the study will be given an active cannabis dose of 25mg THC and participants reporting cannabis use ≤2 times per week on average will be given an active cannabis dose of 10mg THC. Prior research in our lab indicates that these doses will produce a moderate drug effect across all study participants. There will also be one condition in which participants smoke active cannabis and both cigarette and e-cigarette use will be prohibited during the test session. The seven experimental sessions will consist of:

1) Smoked cannabis containing 10mg or 25mg THC + No nicotine/tobacco
2) Smoked cannabis containing 10mg or 25mg THC + ad-libitum use of preferred brand cigarettes

3) Smoked cannabis containing 10mg or 25mg THC + ad-libitum use of low nicotine content E-Cig (3% nicotine JUUL)
4) Smoked cannabis containing 10mg or 25mg THC + ad-libitum use of high nicotine content E-Cig (5% nicotine JUUL)
5) Smoked placebo cannabis + ad-libitum use of preferred brand cigarettes
6) Smoked placebo cannabis + ad-libitum use of low nicotine content E-Cig (3% nicotine JUUL)
7) Smoked placebo cannabis + ad-libitum use of high nicotine content E-Cig (5% nicotine JUUL)

Nicotine self-administration will occur in an *ad-libitum* fashion for 5 hours following cannabis exposure. During the *ad-libitum* nicotine/tobacco-use period, various puffing behaviors (e.g., puff volume, puff duration, puff number, inter-puff-interval) will be measured using specialized equipment. Acute subjective effects of cannabis/nicotine, cannabis/nicotine withdrawal symptoms, craving, vital signs, and cognitive/psychomotor performance will also be assessed throughout the experimental sessions.

Recruitment of study candidates. Research study candidates will be recruited into the study via media advertising (e.g. newspaper, internet) and word-of-mouth communication. Interested individuals will complete screening procedures both over the telephone as well as in person. Participants will provide written informed consent using the Institutional Review Board (IRB) approved form; consent will be obtained by IRB-approved members of the study research and medical team only. Screening procedures will assess participant demographics, alcohol, tobacco, and drug use patterns and associated problems, and medical and mental health status. Specifically, a standard battery of self-report instruments, review of medical history, physical examination, vital signs, standard blood chemistry and hematology laboratory tests, and serum pregnancy test (females only) will occur during screening. 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 21-55 years old, report prior use of cannabis, and be current users of both tobacco cigarettes and e-cigarettes, and use at least one of these daily (see Inclusion Criteria). Those who appear eligible for participation will receive training on the study assessment measures (e.g. exposure to subjective questionnaires and cognitive performance tasks), as well as instruction on using the cannabis pipe and the JUUL/tobacco cigarettes fitted with the specialized puff topography equipment. Participants who successfully complete training will be invited to participate in the study. Based on our recent studies, we anticipate having to consent up to 120 research volunteers in order to obtain 40 people who are fully eligible and who will complete all study procedures (i.e., we will consent up to 3 individuals for each study completer). Study volunteers will be screened for COVID-19 symptoms prior to attending and again on arrival for the laboratory screening assessments. Any volunteer who endorses symptoms will be rescheduled.

Experimental Session Procedures. Once randomized, participants will be scheduled to arrive in the morning on the day of each experimental test session (~8:00am). 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. If a participant reports a positive COVID-19 test during the study, their participation will be stopped until he/she is asymptomatic for 2 weeks and has a negative COVID-19 test result.

Upon arrival, all participants will complete a breath alcohol test, a urine screen to test for commonly abused drugs (e.g. cocaine, opioids, cannabis, MDMA, benzodiazepines), and females will also complete a urine pregnancy test. Volunteers must test negative for all drugs except cannabis and have a negative test for pregnancy in order to participate in the scheduled session. Two failures to meet pre-session alcohol or drug abstinence requirements, or a confirmed pregnancy, will result in removal from the study.

After initial toxicology testing is completed, participants will smoke 1 of their preferred brand cigarettes, *ad-libitum*, under observation in the laboratory. This will standardize the time since last smoking across sessions and across participants. Participants will be informed of this prior to study participation and reminded of this the day before each experimental session. After smoking is completed, participants will be fed a standardized low-fat breakfast of toast and jam.

Baseline Assessments. Prior to drug administration, baseline subjective and cardiovascular assessments will be completed. Participants must meet baseline cardiovascular criteria (HR < 100bpm, SYS BP < 150mmHg, DIA BP < 90mmHg), before an intravenous catheter is placed. The Time-Line Follow-Back (TLFB) assessment will be conducted to record recent use of tobacco, drugs, and alcohol. Concomitant medications**,** including vitamins and herbal supplements, will be also recorded. Any 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. We will also administer a brief battery of cognitive/psychomotor performance tasks (DSST, PASAT, and DRUID App). Prior controlled studies in our laboratory have demonstrated that performance on these tasks are sensitive to acute cannabis-induced impairment. As in our other recent studies (e.g., IRB00199386), performance scores obtained at baseline (prior to drug exposure) will be compared to those obtained 5 hours post-cannabis administration to ensure participants can be safely discharged from the study (see below).

Experimental Drug Exposure. After completion of baseline procedures, approximately 1 hour after the baseline cigarette, participants will self-administer a fixed amount of smoked cannabis, precisely weighed to contain either 0 (placebo), 10 mg THC (active for those who use cannabis ≤ 2 times/week), or 25 mg THC (active for those who use cannabis >2 times/week). Cannabis will be smoked using a custom pipe, fitted with a large “bowl” and screw cap that obscures the contents of the pipe to both the study participants and staff, thereby maintaining the study blind. To ensure complete dose delivery, participants will smoke the pipe until all the plant material has been combusted. We have used this method of cannabis administration in prior studies (Spindle, 2018) to produce orderly dose effects on pharmacodynamic outcomes. The 10 mg and 25 mg THC doses were chosen to balance participant safety and tolerability while maximizing the ability to detect modulation of drug effects by nicotine co-administration in each respective cannabis-use population (i.e., intermittent users who use cannabis ≤ 2 times/week and heavy users who use cannabis >2 times/week). In a recent study of ours (Spindle, 2018), a smoked 10 mg THC dose administered to healthy adults who were intermittent cannabis users, produced a moderate drug effect (Mean peak VAS “Drug Effect” rating = 46 of a possible 100), but no adverse events or untoward drug effects. In another recent study in our laboratory (IRB00101744) that included heavy cannabis users, a smoked 25 mg THC dose produced a moderate drug effect (Mean peak VAS “Drug Effect” rating = 58 of a possible 100) and no adverse events or untoward drug effects were observed. We believe that adjusting the THC dose to account for tolerance to the acute effects of THC in more frequent cannabis users is critical to providing ecologically valid data, and that keeping the dose delivered constant across sessions is critical to the rigor of the study and interpretation of the study findings.

Following cannabis exposure, participants will be free to self-administer the assigned nicotine/tobacco product for that session *ad-libitum* (i.e., at their own pace) over the next 5 hours. Conventional cigarettes available for study participants will be their preferred brand of cigarettes and will be purchased by study staff from a retail tobacco outlet. For the e-cigarette study conditions, participants will be provided with the popular, commercially-available, pod-style e-cigarette called the JUUL. JUUL pods contain tobacco-flavored “e-juice” and come in 2 different nicotine concentrations or “strengths” that are designated as either a low (3%; 35mg/mL) or high (5%; 59mg/mL). All cannabis and nicotine/tobacco administration will occur in a specially ventilated room located within the BPRU designed for the administration of combusted/inhaled drug products.

Participant Discharge. Participants will be discharged after completing final assessments (approximately 5 hours post-drug exposure). At the end of each session, study staff will compare vital signs and cognitive/psychomotor performance (i.e., DSST, PASAT, and DRUID App scores; see *Baseline Assessments* above) with baseline data and engage in face-to-face conversation with the participant to ensure that they are fit to leave the unit. 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 scores on the cognitive tests are within 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. If the participant continues to exhibit behavior indicative of impairment/intoxication, the participant will be asked to remain at the BPRU until the drug effect subsides and their performance on the cognitive test battery is within 20% of baseline. 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. This same protocol will be followed for cases in which a study participant has undergone drug administration but indicates the desire to be discharged from the study early. Based on our prior studies, we do not anticipate the proposed doses of cannabis (10 mg or 25 mg THC) will produce impairment that would prohibit participants from being discharged. That is, using similar participants (i.e., healthy individuals with intermittent cannabis-use patterns; (Spindle, 2018)), we have demonstrated that smoked cannabis with 10 mg THC produces discriminable drug effects (e.g., mean peak rating of 46, on 100-point VAS) which subside within 5 hrs of exposure and does not significantly impair cognitive or psychomotor functioning when compared with placebo. Likewise, in a separate study with daily/near daily cannabis users, 25 mg THC produced discriminable drug effects (e.g., mean peak rating of 58, on 100-point VAS) which subsided within 5 hrs of exposure and did not significantly impair cognitive or psychomotor functioning when compared with placebo. Nicotine/tobacco exposure does not produce functional impairment and any nicotine-induced changes in vital signs are expected to be short-lived and return to baseline before discharge (Spindle et al., 2018).

Study Measures. A battery of measures will be used to assess participant characteristics, nicotine/tobacco use patterns/behaviors, subjective effects of nicotine/tobacco and cannabis, cognitive and psychomotor performance, and nicotine/cannabis withdrawal symptoms (e.g., craving).

Screening. During the 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)). The Mini-International Neuropsychiatric Interview (MINI, v.7) (Sheehan et al., 1998) for DSM-5 will be used to assess cannabis and tobacco-use disorders, other substance use disorders, and psychiatric disorders. A physical examination will be performed on each participant during their 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 will be evaluated. Biological specimens (blood and urine) will be tested for routine clinical chemistry, hematology, serology, serum pregnancy test (females only), and for evidence of recent illicit drug and tobacco use. A study physician will review any incidental findings with the study participant and referral for additional testing completed as appropriate. Breath samples will also be tested for recent use of alcohol (BAC; must be negative) and combustible tobacco (CO). Breath CO must be ≥8ppm or urine cotinine >200ng/mL to confirm current nicotine use status.

Experimental Sessions. Puff topography variables including puff volume, duration, number, inter-puff interval (IPI), and flow rate will be measured during cannabis and tobacco-product use with topography recording equipment developed and manufactured at the American University of Beirut (AUB).

Specifically, the mouth-end of the cannabis pipe and the tobacco product (either tobacco cigarettes or the JUUL) is inserted into a specialized mouthpiece (custom-made to firmly fit either product) and users inhale the product through the mouthpiece; a sensor inside the mouthpiece detects puff-induced pressure changes which are then used to derive data for the various topography variables (e.g., puff duration, puff volume). This topography-recording equipment has been used in several other clinical laboratory examinations of cannabis, conventional cigarettes, and e-cigarettes (McClure et al., 2012; Ramoa et al., 2016; Spindle et al., 2018) and has been demonstrated to not interfere with acute e-cigarette effects when compared to e-cigarette use without the equipment present (Spindle et al., 2017).

Vital signs (heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP)) will be measured in the seated position before (i.e., baseline), and approximately 5, 30, 60, 90, 120, 180, 240-and 360-min after cannabis exposure.

The Drug Effect Questionnaire (DEQ) (Spindle, 2018; Vandrey et al., 2017) will be used to obtain subjective ratings of drug effects. Individual items include ratings of general positive/negative drug effects (e.g. drug effect, good effect, bad effect, liking) and behavioral/mood states often associated with cannabis intoxication (e.g. relaxed, paranoid, hungry/have munchies). The DEQ will be administered before (i.e., baseline), and approximately 5, 30, 60, 90, 120, 180, 240-and 360-min after cannabis exposure. We expect that all subjective drug effects will subside within 5 hours (360 min) of cannabis exposure based on recent and ongoing studies in our laboratory.

The Direct Effects of Tobacco Use scale (Spindle et al., 2018) will be used to assess subjective effects specific to tobacco cigarettes or e-cigarettes. Example items from this questionnaire include: “Did the cigarette/e-cigarette make you feel more awake?,” “ Did the cigarette/e-cigarette help calm you down?,” “Did the cigarette/e-cigarette make you dizzy?,” “Was the cigarette/e-cigarette pleasant?,” “Did the cigarette/e-cigarette reduce hunger?,” “Would you like another cigarette/e-cigarette right now?,” “Was the cigarette/e-cigarette satisfying?,” “Did the cigarette/e-cigarette make you sick?,” and “Did the cigarette/e-cigarette taste good?” This questionnaire will be administered before (i.e., baseline), and approximately 5, 30, 60, 90, 120, 180, 240-and 360-min after cannabis exposure.

The Tobacco (Heishman et al., 2003) and Cannabis Craving Questionnaires (Heishman et al., 2001) will assess cravings/withdrawal symptoms for tobacco/nicotine and cannabis, respectively. These questionnaires will be administered before (i.e., baseline), and approximately 5, 30, 60, 90, 120, 180, 240-and 360-min after cannabis exposure.

The Digit Symbol Substitution Task (DSST) will measure psychomotor ability. Participants view a series of nine geometric patterns. Each pattern is numbered (1-9) and consists of three highlighted squares on a 3x3 grid. When the number associated with a particular pattern appears in the center of the screen, participants must replicate the shape of that pattern using an assigned 3x3 section on the keyboard. Task duration is 90 seconds. DSST outcomes include: number of trials attempted, number correct, and percentage of attempted trials completed correctly (Jaeger, 2018). This task will be administered before (i.e., baseline), and approximately 5, 30, 60, 90, 120, 180, 240-and 360-min after cannabis exposure.

The Paced Auditory Serial Addition Task (PASAT) will measure working memory performance. Participants are shown a string of single digit integers and calculate the sum of each successive pair of integers presented; they select the correct answer from a list of displayed choices, ranging from 2-10. Each integer appears for 2.8 seconds during an initial set of 30 trials. After a 30-sec break, a second set of 60 additional trials is completed and integers appear every 2.4 seconds. Task duration is 5 min. PASAT outcomes include: total number of trials correct and reaction time on correct items (Gronwall, 1977). This task will be administered before (i.e., baseline), and approximately 5, 30, 60, 90, 120, 180, 240-and 360-min after cannabis exposure.

The DRUID® app ("DRiving Under the Influence of Drugs") has been developed as a novel screening tool to detect impairment from cannabis and other sources (e.g., alcohol). The DRUID requires users to perform four 30-45 sec tasks (total time is 2.5 min), measuring reaction time, decision making, hand-eye coordination, time estimation, balance, and/or divided attention. These performance domains are the most reliable predictors of driving impairment caused by cannabis/alcohol. Scores on each of the four tasks are summed to yield a global impairment score. This task will be administered before (i.e., baseline), and approximately 5, 30, 60, 90, 120, 180, 240-and 360-min after cannabis exposure.

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

All potential participants will complete a visit for screening evaluation. Those who are eligible and enrolled in the study will complete seven experimental drug administration sessions, lasting approximately 6 hours each, and spaced 1 week apart. Because there are 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. missing cognitive testing time points, equipment failure), or protocol deviation that impacts data integrity. This is not expected to occur for most participants.

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

Dose assignment (for both cannabis and the JUUL) will be blinded in this study. It is standard procedure for appropriate scientific control in studies evaluating the effects of psychoactive drugs to blind dose assignment.

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.

Placebo cannabis dosing sessions will be included to help interpret subjective and performance effects of cannabis and tobacco. Placebo dosing provides a control for expectancy effects on these outcomes and 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 tobacco 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 21 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 aside from cannabis (via urine sample) and alcohol (via breath sample) at the screening visit and upon arrival for each experimental session.
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 not donated blood in the prior 30 days.
9. Report prior experience inhaling cannabis.
10. Report using cannabis at least 5 times in the past year.
11. Meet criteria for past month e-cigarette/cigarette dual user defined as either:

    a) Smoke ≥5 tobacco cigarettes per day on average in the past 30 days and used an e-cigarette (with nicotine) at least once in the past 30 days
    OR
    b) Used an e-cigarette (with nicotine) every day for the past 30 days and smoked tobacco cigarettes at least once in the past 30 days

13. Have a breath CO of ≥8ppm or urine cotinine >200ng/mL to confirm current nicotine use status.

Exclusion Criteria

1. Non-medical use of psychoactive drugs (aside from cannabis) other than, nicotine, alcohol, or caffeine in the month prior to the Screening Visit;
2. History of or current evidence of significant medical or psychiatric illness which, in the opinion of the investigator or sponsor, will interfere with the study results or the safety of the subject.
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 results 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 results or the safety of the subject.
5. History of clinically significant cardiac arrhythmias or vasospastic disease (e.g., Prinzmetal's angina).
6. Enrolled in another clinical trial or have received any drug as part of a research study within 30 days prior to dosing.
7. Epilepsy or a history of seizures.
8. 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
9. Individuals with anemia.
10. Prior history of allergic or serious adverse reaction to either cannabis or tobacco/nicotine.

To determine eligibility, the clinical assessments conducted during the screening process will be reviewed by study physicians with JHBMC privileges (e.g., Drs. Antoine, Umbricht) and psychological assessments and full inclusion/exclusion criteria will be reviewed by Dr. Vandrey or another senior Co-investigator (e.g., Dr. Elise Weerts). Dr. Annie Umbricht or other JHBMC credentialed study physician will review all health information to determine study eligibility. Annie Umbricht, MD is a board certified internist with 14 years of experience with research participants at the BPRU, including cannabis users.

6. Drugs/ Substances/ Devices

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

Participants will smoke a fixed dose of cannabis (containing either 10mg or 0mg THC) using a small commercial pipe. Placebo (<1% THC by dry weight) and active cannabis (approximately 10-13% THC by dry weight) will be obtained from the NIDA drug supply program for this study. All cannabis will be precisely prepared and dispensed by the BPRU pharmacy. Participants will be given the pipe and instructed to smoke its entire contents *ab-libitum* (i.e., at their own pace), within 10 minutes. The pipe will be fitted with a metal top to obstruct the participants' and experimenters' view of its contents. This procedure has been demonstrated to reliably deliver doses of THC from dried cannabis and adequately blinds study conditions (Spindle, 2018).

We have administered smoked cannabis containing 10mg THC in a prior study (Spindle, 2018) (IRB00035394). In that study, 10mg THC produced discriminative drug effects but did not produce substantial impairment or other negative effects which is why it was selected for this study. This dose also did not produce any adverse events. Following inhalation of smoked cannabis containing 10mg THC, participants self-reported an increase in pleasant drug effects (e.g., mean peak rating of 42.4 for "pleasant drug effect", on 100-point VAS) but subjective ratings of negative effects (e.g., "anxious/nervous", "unpleasant drug effect") remained largely unchanged; 10 mg THC also did not impair cognitive or psychomotor functioning compared with placebo. In another recent study in our laboratory (IRB00101744) that included heavy cannabis users, a smoked 25 mg THC dose produced a moderate drug effect (Mean peak VAS "Drug Effect" rating = 58 of a possible 100) and no adverse events or significant impairment of cognitive function was observed.

Participants will administer nicotine *ad-libitum* in this study using their preferred brand of tobacco cigarettes or the JUUL, the most popular e-cigarette on the market today (King et al., 2018). Tobacco cigarettes and JUUL e-cigarettes will be purchased by study staff from commercial retail tobacco outlets. JUUL pods will be tobacco flavored and will contain nicotine concentrations of either 3% (35mg/mL) or 5% (59mg/mL). Since participants in this study will be regular cigarette smokers and e-cigarette users, and since they will be able to titrate their nicotine dosage during the *ad-libitum* period, we do not anticipate untoward effects from the nicotine doses we will administer. To our knowledge, there is no evidence that the simultaneous administration of nicotine and cannabis will put participants at increased risk of experiencing adverse events.

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

An IND application has been submitted to the FDA for the administration of cannabis in this protocol (see IRB application).

Study Statistics

a. Primary outcome variable.

Primary outcome variable is the amount of nicotine used (determined by total volume of cigarette smoke or JUUL vapor inhaled) after cannabis exposure in each session. We hypothesize that exposure to active cannabis will result in greater nicotine use compared with placebo cannabis.

b. Secondary outcome variables.

Secondary outcome variables include other nicotine use behaviors (amount self-administered and puff topography outcomes), subjective drug effect ratings, cognitive and psychomotor performance, and vital signs (HR, BP). We hypothesize that nicotine use will increase subjective drug effect ratings and decrease cognitive performance after exposure to active cannabis compared with the experimental session in which no nicotine/tobacco products are consumed. We also expect that active cannabis will increase self-reported drug effects compared with placebo cannabis.

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

The proposed sample size of 40 study completers was estimated based on limited prior studies. One study found significant effects of transdermal nicotine and smoked cannabis on subjective drug effects with a sample size of N=20, suggesting that the proposed sample size for this study is adequate to detect interactive effects of nicotine and cannabis on subjective drug effects using a within subjects design (Penetar et al., 2005). Evaluation of pharmacodynamic drug effects using a within-subjects design reduces variability across dose administration sessions and significantly increases statistical power to detect differences on the proposed study outcomes. However, because we have a greater number of dose conditions, and because a primary outcome is amount of drug self-administration rather than self-reported drug effects, we expect the need for a greater sample size in this study.

Initial data analyses will examine whether study completers differ from non-completers with regard to demographic or cannabis use variables. This will inform the generality of the results. We will also examine the data for missing values. When missing data are found in self-report measures we will impute scores by averaging the closest pre and post values when applicable, otherwise missing data will be treated as missing in analyses. Missing data is expected to be rare given that all assessments are conducted via computer and individual items cannot be skipped. However, it is possible that a time point could be missed due to severe drug effects. Data will be evaluated for normal distribution, skewness, kurtosis and appropriate modifications will be made for data that is not normally distributed. All hypothesis tests will be two-sided; α will be set at 0.05. Nicotine/tobacco self-administration data will be analyzed using 2-tailed t-tests comparing the consumption of each nicotine/tobacco product after active versus placebo cannabis pre-treatment. Additional planned comparisons will then be conducted to compare consumption of 3% versus 5% nicotine E-Cig use following active cannabis. Secondary analyses will be conducted using repeated-measures multiple regression to evaluate the effects of nicotine/tobacco product type (None, conventional cigarette, low dose E-Cig, and high dose E-cig) and time as within-subjects factors on subjective drug effect ratings, cardiovascular effects, craving, and cognitive performance effects during sessions in which active (10mg or 25mg THC) cannabis was administered. If sufficient variability in pre-study cannabis use exists in our final study sample, we will conduct exploratory analyses comparing less frequent vs heavy (e.g. daily) cannabis users on primary and secondary outcomes.

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.

A potential risk of smoking cannabis is irritation of the throat/lungs. Acute administration of cannabis can produce tachycardia, intoxication, altered mood, impaired coordination, and cognitive deficits. Given that the dose of cannabis we will administer has demonstrated a favorable safety profile in our prior research, and given that the participants will be experienced with smoking cannabis, the risk of these negative cannabis-related effects or serious adverse events in the laboratory setting is minimal. There is no known risk of overdose or death related to cannabis /THC. In the unlikely event 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. In the case of an extreme adverse reaction, we will call 911 for emergency treatment. Note that the BPRU is located directly across the street from the Johns Hopkins Bayview ER.

Participants may experience some mild discomfort when not using tobacco/nicotine in the present study. Symptoms of nicotine/tobacco withdrawal are time-limited and typically resolve without clinically significant problems. In case of an adverse event, a study physician is available via pager for assistance. Unpleasant side effects associated with using nicotine/tobacco may include sweating, lightheadedness, dizziness, nausea, and nervousness, though these effects are unlikely to be experienced by participants in the present study because they will be regular users of tobacco products and use will be self-titrated. Given that participants will be regular users of both tobacco cigarettes and e-cigarettes, they will also be familiar with the other more positive acute effects associated with using nicotine/tobacco (e.g., feelings of euphoria, and heightened arousal). We are not aware of any evidence that would suggest simultaneous administration of nicotine and cannabis will put participants at increased risk of experiencing adverse events than use of either drug alone, and, as highlighted in the background, these two substances are widely co-administered in the real-world (Schauer et al., 2015; Schauer et al., 2016).

Exposure to COVID-19 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 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. 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.

We feel that the risk of serious adverse events related to cannabis/nicotine exposure in this study is minimal – participants are experienced users of tobacco cigarettes, e-cigarettes, and cannabis, and thus they will be familiar with any acute drug effects they may experience in this study. The doses of THC we are administering (10 mg or 25 mg THC) are on the low end of the ranges used in prior studies and has demonstrated a favorable safety profile (i.e., produced mostly mild subjective drug effects without eliciting adverse effects) among individuals with the cannabis use profile we will recruit in this study. The cannabis doses are expected to produce positive discriminable drug effects without causing impairment of cognitive functioning or adverse events. Given that these individuals regularly use nicotine, they are not expected to experience negative nicotine-related side effects (e.g., nausea). Participants will be able to halt self-administration of either study drug (cannabis or nicotine) if they experience adverse effects. Similarly, study staff may halt the drug administration procedure if untoward drug effects are observed. Such effects

are not expected for either nicotine or cannabis at the doses under investigation.

It is unlikely that any adverse event should arise that requires immediate medical 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, we will call 911 for immediate care. The Principal Investigator will be immediately notified of any serious adverse events that arise.

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 and tobacco products (cigarettes and e-cigarettes). Any participant who expresses an interest in receiving immediate treatment for cannabis, tobacco, 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.

The PI will 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 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, a Certificate of Confidentiality has been obtained for this study.

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 interactive effects of cannabis and nicotine/tobacco. The knowledge can be used to advise the treatment for disordered use of either of these drugs and provide insights into the mechanisms underlying the high rates of co-use of tobacco and cannabis. Because we anticipate relatively minor risks to these cannabis and nicotine-experienced healthy study volunteers, 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. Participants will be compensated $200 for completion of each of the seven experimental sessions and will be paid an additional $300 for completing the study. Total possible earnings for each participant is $1730. Compensation of this magnitude is appropriate given the nature of this study.

Screening Visit:	$30
Experimental Sessions	$200/visit (7 visits = $1400 total)
Study Completion Bonus	$300
Total Compensation:	$1730

Study participants will receive an additional $200 for any test session that is repeated due to data loss. 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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