The Impact of Oral Cannabis Administration and Co-Administration of Alcohol on Impairment

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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.

Cannabis and alcohol are two of the most commonly used drugs in the world. Among U.S. adults, 15% report using cannabis in the past year (or 1 in 7 adults (Steigerwald et al., 2018), while 70% report using alcohol in the past year (SAMHSA, 2017). Alcohol use has a tremendous toll on public health, in large part because 28% of all fatal automobile accidents are caused by drunk drivers ((NHTSA), 2017). Like alcohol, cannabis is an intoxicating substance that can negatively impact driving performance by acutely impairing psychomotor skills, attention, and cognitive abilities (Arkell et al., 2019; Hartman and Huestis, 2013; Sewell et al., 2009; Spindle et al., 2018). In addition to driving, cannabis is also unsafe to use in safety-sensitive workplace settings because it increases the likelihood of accidental injuries (Goldsmith et al., 2015; Ramchand et al., 2009). Coincident with recent state-led expansions of cannabis legalization for medical and/or non-medical ("recreational") purposes, perceptions of harm associated with cannabis use have decreased (Berg et al., 2015) and the incidence of driving under the influence of cannabis has increased (Johnson et al., 2012; Kelley-Baker et al., 2017; Salomonsen-Sautel et al., 2014). The percentage of U.S. young adults (aged 16-25) who reported driving under the influence of cannabis increased from 3.2% in 2014 to 10.8% in 2018 (Azofeifa, 2019; Azofeifa et al., 2015). Further complicating matters, many alcohol users (8% of all adult users; 15% of young adult users; (Subbaraman and Kerr, 2015; Yurasek et al., 2017)), report regularly using alcohol and cannabis concurrently (i.e., "co-use"), with co-use being most prevalent in states where cannabis is legal (Kim, 2020). Importantly, when administered together, cannabis and alcohol produce additive or synergistic impairment, over and above impairment caused by either substance alone (Ramaekers et al., 2004; Ramaekers et al., 2009; Sewell et al., 2009; Yurasek et al., 2017), and individuals who have ingested both alcohol and cannabis have a greater probability of getting into a car accident, and are more likely to be culpable for the accident, compared to those who have only used one of these substances (Drummer et al., 2019; Drummer et al., 2004).

Controlled human laboratory studies are a valuable method for developing a detailed understanding of the acute impairment profile of cannabis and alcohol, when administered alone and together. However, such studies on cannabis and alcohol co-use are scarce and the few that have been conducted have focused almost exclusively on smoked cannabis. In recent years, many novel methods of cannabis administration have emerged, the two most popular of which are oral cannabis products (*a.k.a.*, "edibles") and cannabis vaporizers (Borodovsky et al., 2016; Borodovsky et al., 2017; Miech et al., 2019; Steigerwald et al., 2018). Data from our laboratory indicates that the time course and magnitude of effects for oral and vaporized cannabis differ markedly from smoked cannabis. For example, vaporized cannabis delivers more THC (the primary psychoactive constituent of cannabis) to users, thus causing greater impairment, relative to the same dose of smoked cannabis (Spindle et al., 2018). Conversely, the acute impairing effects of oral cannabis have a delayed onset and persist for a longer duration compared to inhalable forms of cannabis, including smoked, yet the magnitude of impairment between oral and smoked cannabis is similar

(Schlienz et al., 2020). Overall, these findings suggest that these two novel forms of cannabis may also interact with alcohol in distinct ways from smoked cannabis (e.g., in terms of the overall magnitude of effects and/or duration) and highlight the need for further controlled alcohol/cannabis co-use studies that include non-smoked routes of administration.

This human laboratory study will use cognitive, behavioral, and subjective measures to characterize impairment associated with co-use of alcohol and oral cannabis. Participants (n=32) will complete 7 double-blind, double-dummy outpatient sessions in randomized order. In each session, participants will self-administer placebo (0 mg THC) or active oral cannabis (10 or 25 mg THC, via a chocolate brownie) and a placebo drink (BAC 0.0%) or alcohol drink calculated to produce a breath alcohol concentration (BAC) of 0.05%. Participants will also complete a positive control session in which they administer placebo cannabis and alcohol at a target BAC of 0.08% (the legal threshold for driving impairment in most U.S. states). Participants will always receive both an alcohol drink (active or placebo doses) and cannabis (active or placebo doses). Specific assessments include a state-of-the-art driving simulator, a battery of cognitive/psychomotor performance tasks, field sobriety tests, and subjective drug effect instruments, all of which are sensitive to cannabis and alcohol. Sessions will be conducted at a target rate of once per week for a duration of 7 weeks per participant. This study has many important implications for public health. First, it will elucidate whether impairment from oral cannabis is augmented when used with alcohol; this information will be vital for educating the general public given the unprecedented number of people with legal access to cannabis. This project will also provide data that can be used to inform impairment detection standards for cannabis and alcohol and to help refine a novel cannabis impairment detection tool (the DRUID) that has shown promise in our preliminary research (Spindle TR, 2019); further enhancement of this instrument could improve public safety because there are currently no empirically validated methods for identifying impairment from cannabis and current approaches used to detect cannabis impairment in the real-world (i.e., field sobriety tests and blood *per se* limits for THC) are ineffective (for review see: (Ginsburg, 2019)).

2. Objectives (include all primary and secondary objectives)

Primary Objective 1: Examine the impact of alcohol and oral cannabis on objective impairment (simulated driving, cognitive/psychomotor ability, field sobriety tests) when used alone and concurrently.

Primary Objective 2: Examine the impact of alcohol and oral cannabis on subjective impairment when used alone and concurrently.

Secondary Objective 1: Evaluate whether performance on the DRUID, a novel cannabis impairment detection tool, aligns with driving performance when alcohol and cannabis are used alone and concurrently.

Secondary Objective 2: Examine the impact of alcohol and oral cannabis on cannabinoid/alcohol pharmacokinetics under solo and co-use conditions.

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)

Cannabis and alcohol are two of the most commonly used drugs in the world. Among U.S. adults, 15% report using cannabis in the past year (or 1 in 7 adults (Steigerwald et al., 2018), while 70% report using alcohol in the past year (SAMHSA, 2017). Alcohol use has a tremendous toll on public health, in large part because 28% of all fatal automobile accidents are caused by drunk drivers ((NHTSA), 2017). Like alcohol, cannabis is an intoxicating substance that can negatively impact driving performance by acutely impairing psychomotor skills, attention, and cognitive abilities (Arkell et al., 2019; Hartman and Huestis, 2013;

Sewell et al., 2009; Spindle et al., 2018). In addition to driving, cannabis is also unsafe to use in safety-sensitive workplace settings because it increases the likelihood of accidental injuries (Goldsmith et al., 2015; Ramchand et al., 2009). Coincident with recent state-led expansions of cannabis legalization for medical and/or non-medical ("recreational") purposes, perceptions of harm associated with cannabis use have decreased (Berg et al., 2015) and the incidence of driving under the influence of cannabis has increased (Johnson et al., 2012; Kelley-Baker et al., 2017; Salomonsen-Sautel et al., 2014). The percentage of U.S. young adults (aged 16-25) who reported driving under the influence of cannabis increased from 3.2% in 2014 to 10.8% in 2018 (Azofeifa, 2019; Azofeifa et al., 2015). Further complicating matters, many alcohol users (8% of all adult users; 15% of young adult users; (Subbaraman and Kerr, 2015; Yurasek et al., 2017)), report regularly using alcohol and cannabis concurrently (i.e., "co-use"), with co-use being most prevalent in states where cannabis is legal (Kim, 2020).

Many laboratory studies have assessed various aspects of performance after administration of alcohol. Alcohol consistently impairs motor coordination, reaction time, and other factors (e.g., information processing; attention) that are key for operating a motor vehicle and performing other complex tasks (Jongen et al., 2016; Martin et al., 2013; Maylor and Rabbitt, 1993). These and other consistent signs of alcohol intoxication (e.g., eye nystagmus), are reliably detected by field sobriety tests. In a similar vein, a person's degree of alcohol impairment can be reliably gauged by their blood alcohol level; blood alcohol can be measured rapidly and non-invasively with a breath test (or "breathalyzer") because breath and blood alcohol levels are highly correlated (Jones, 2010; Peleg et al., 2010). Thus, breath alcohol concentration (BAC) *per se* limits (thresholds that legally constituent impairment) are ubiquitous, with 0.08% being the most common in the U.S. and 0.05% being the most common in Europe (National Academies of Sciences and Medicine, 2018).

In controlled studies, cannabis has also been shown to reliably impair cognitive and psychomotor functioning (Curran et al., 2016; National Academies of Sciences and Medicine, 2017; Spindle et al., 2018; Volkow et al., 2016) and driving performance (both simulated (Arkell et al., 2019; Downey et al., 2013; Hartman et al., 2015b, 2016b; Ronen et al., 2010) and on-road (Bosker et al., 2012a; Ramaekers et al., 2000)). Currently, the two most common methods used to detect impairment from cannabis are blood *per se* limits (assessed via whole blood) and standard field sobriety tests. However, detecting impairment from cannabis is far more difficult than it is for alcohol for several reasons. First, no behavioral tests have explicitly been developed to detect cannabis impairment. Field sobriety tests were developed to identify signs of alcohol intoxication and validated at common *per se* limits (e.g., 0.08% BAC; (Stuster, 2006)) but have shown poor sensitivity to cannabis in controlled studies (Bosker et al., 2012a; Papafotiou et al., 2005). Second, unlike with alcohol, concentrations of THC in blood and other biological matrices (e.g., oral fluid) do not correlate with cannabis impairment. For example, though oral cannabis products (or "edibles") can produce marked impairment (Schlienz et al., 2020), maximum THC levels in blood following cannabis ingestion are often well below common *per se* limits (e.g., 5 ng/mL THC) (Spindle et al., 2020b). Further, chronic cannabis users can have low levels of THC circulating in their blood for weeks after their last use without showing signs of impairment (Bergamaschi et al., 2013). Collectively, these findings suggest that field sobriety tests and *per se* limits for THC may fail to identify individuals who are impaired from cannabis or conversely, may falsely classify individuals as impaired who are not. Despite their limitations, field sobriety tests and blood THC *per se* limits are two of the most common approaches for determining cannabis impairment at the roadside or in the workplace (Ginsburg, 2019; Watson and Mann, 2016), highlighting the need for novel cannabis impairment detection methods.

A few prior laboratory studies have been conducted in which cannabis and alcohol were administered concurrently (e.g., (Belgrave et al., 1979; Bird et al., 1980; Bosker et al., 2012b; Chait and Perry, 1994; Downey et al., 2012; Downey et al., 2013; Hartman et al., 2015b; Manno et al., 1971; Perez-Reyes et al., 1988; Ronen et al., 2010)). These studies have generated important information. For example, in several of these studies, combining cannabis and alcohol resulted in additive (or synergistic) impairment of

cognitive/psychomotor functioning (Belgrave et al., 1979; Bird et al., 1980; Manno et al., 1971) or driving performance (Ramaekers et al., 2000; Ronen et al., 2010) that was greater than that observed from the same doses of alcohol or cannabis alone. Prior co-use studies have also detected pharmacokinetic interactions between the two drugs (e.g., blood THC concentrations are higher following co-use with alcohol, relative to when the same cannabis dose is used alone (Hartman et al., 2015a; Lukas and Orozco, 2001)).

Despite these insights, prior alcohol/cannabis co-use studies are limited because they have virtually all focused on smoked cannabis. Novel forms of cannabis including oral cannabis products (“edibles”) and cannabis vaporizers are now widely used (Borodovsky et al., 2016; Borodovsky et al., 2017; Miech et al., 2019; Steigerwald et al., 2018) but little is known about their interactive effects with alcohol. In fact, no controlled studies have examined co-use of cannabis edibles and alcohol, and only one study (published in several papers (Hartman et al., 2015a; Hartman et al., 2015b, 2016b)) examined co-use of vaporized cannabis and alcohol. Beyond only focusing on smoked cannabis, prior alcohol/cannabis co-use studies are also limited by the inclusion of almost all male participants and examination of only 1 dose of alcohol or cannabis. Moreover, these prior studies are further limited because they were not intended to inform impairment detection standards for individuals suspected of co-use. More specifically, prior co-use studies have dosed alcohol based on body weight (e.g., mg/kg) and thus, did not standardize BAC across participants. Therefore, it is unknown whether established thresholds used to identify alcohol impairment (e.g., 0.08% BAC) should be lowered (e.g., to 0.05%) if a person has recently used alcohol and cannabis. Further controlled research is needed on the co-use of alcohol with oral and vaporized cannabis because in our prior studies, the acute effects of these novel cannabis products have differed markedly from smoked cannabis. For example, peak subjective drug effects and impairment after oral ingestion of cannabis edibles occurs much later compared with smoked cannabis (smoked: ~10 min post-inhalation; oral: ~2-3 hr post-ingestion); these effects also persist for much longer after use of oral cannabis compared to smoked. However, despite differences in the onset of effects, the magnitude of acute drug effects between oral and smoked cannabis is often similar (Schlienz et al., 2020; Spindle et al., 2018). This study will extend prior alcohol/cannabis co-use research to provide vital new knowledge on impairment associated with co-use of alcohol and oral cannabis. It will also address key limitations of prior co-use studies by: dosing participants to BACs with ecological relevance (0.05% and 0.08%), including multiple THC doses, enrolling an equal number of men and women, and including a comprehensive set of impairment assessments (i.e., a sophisticated driving simulator, a diverse battery of cognitive and psychomotor performance tests, field sobriety tests, and various subjective measures of intoxication).

This human laboratory study will characterize impairment associated with co-use of alcohol and oral cannabis. Participants (n=32) will complete 7 double-blind, double-dummy outpatient sessions in randomized order. In each session, participants will self-administer placebo (0 mg THC) or active oral cannabis (10 or 25 mg THC), via a chocolate brownie, and a placebo drink (BAC 0.0%) or alcohol drink calculated to produce a breath alcohol concentration (BAC) of 0.05%. Participants will also complete a positive control session in which they administer placebo oral cannabis and alcohol at a target BAC of 0.08% (the legal threshold for driving impairment in most U.S. states). Specific assessments include a state-of-the-art driving simulator, a battery of cognitive/psychomotor performance tasks, field sobriety tests, and subjective drug effect instruments. Sessions will be conducted at a target rate of once per week for a duration of 7 weeks per participant. Participants will always receive both an alcohol drink (active or placebo doses) and cannabis (active or placebo doses). This study has many important implications for public health. First, it will elucidate whether impairment from oral cannabis is augmented when used with alcohol; this information will be vital for educating the general public given the unprecedented number of people with legal access to cannabis. This project will also provide data that can be used to inform impairment detection standards for cannabis and alcohol and to help refine a novel cannabis impairment detection tool (the DRUID) that has shown promise in our preliminary research (Spindle TR, 2019); further enhancement of this instrument could improve public safety because there are currently no empirically

validated methods for identifying impairment from cannabis and current approaches used to detect cannabis impairment in the real-world (i.e., field sobriety tests and blood *per se* limits for THC) are ineffective (for review see: (Ginsburg, 2019)).

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).

Study 1 (N=32)	
Oral Cannabis (mg THC)	Alcohol (BAC %)
0	0
10	0
25	0
0	.05
10	.05
25	.05
0	.08 -> pos. control

Protocol Overview. This study will be conducted at the Johns Hopkins Behavioral Pharmacology Research Unit (BPRU). Participants will complete a screening visit, and, if eligible, will then complete 7 experimental drug administration sessions in randomized order where they will consume a cannabis-infused brownie (containing 0, 10, or 25mg THC) with a drink that contains no alcohol or alcohol (alcohol-containing drinks will be calculated to produce a breath alcohol concentration, BAC, of 0.05%). There is also a positive control session where participants will ingest placebo cannabis with an alcohol drink calculated to produce a BAC of 0.08%. Each session will last approximately 10 hours and will be separated by at least 1 week to allow for sufficient drug washout. Drugs will be administered in a double-blind and double-dummy fashion (i.e., participants will always receive both active or placebo cannabis and active or placebo alcohol). During each session, a battery of assessments including blood collection, subjective questionnaire administration, cognitive performance testing, and simulated driving will be conducted. The 7 study conditions are depicted in the Table above.

Participants. In total, we will recruit and consent up to 90 research volunteers in order to obtain 32 study completers. We anticipate that some participants may drop out of the study before completion. It is estimated that we will need to randomize 45 participants to achieve 32 total completers. Participants who drop out of the study prior to completion will be considered “incomplete” and replaced.

The target demographic for study participation are individuals who: 1) are 21-55 years old, 2) in good general health based on screening procedures (e.g., physical exam, blood testing, psychiatric evaluation), 3) for women, are not pregnant or breast feeding, 4) are experienced and regular alcohol drinkers, but who do not meet criteria for severe alcohol use disorder, 5) have experience using cannabis, and 6) have experience using cannabis and alcohol in combination, 7) are not seeking treatment for alcohol, cannabis, or other drug use.

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 use alcohol and cannabis products and are not currently trying to quit. Interested participants will receive an initial screening over the telephone that includes interviews and self-report questionnaires that provide participant information (e.g., physical and mental health status and drug use history), to determine initial eligibility. Individuals who meet initial eligibility criteria will then be scheduled for a more thorough in-person screening evaluation which will occur over 2 days (see below).

Prior to the in-person assessment, written informed consent to participate in the study will be obtained. During in-person assessment, study participants will undergo a physical exam including clinical chemistry, hematology, serology, and serum pregnancy test (females only) and provide a urine specimen which will be tested for evidence of recent use of commonly abused drugs.

The screening visit will also include interviews and self-report surveys to evaluate physical and mental health, drug-use history, recent drug use and current substance use disorders, alcohol dependence, and

literacy (see Study Measures below for list of specific screening assessments). Those who appear eligible for participation after this initial training visit will be invited for another screening visit where they will receive training on the study assessment measures (e.g. exposure to subjective questionnaires and cognitive/simulated driving performance tasks). Participants who successfully complete training will be invited to participate in the study.

Experimental Session Procedures Overview. Participants will arrive in the morning for each session in a fasted state; they can consume no more than 100mg of caffeine before arrival. Upon arrival, they will be fed a standard, calorie-controlled, high-fat breakfast and self-report, via the timeline-follow-back (TLFB) (Sobell, 1992), their drug/alcohol use since the last visit (either screening or prior session). Recent concomitant medication use**,** including vitamins and herbal supplements, will be recorded before each session. Medication changes occurring between the screening visit and first session, or between sessions, will be reviewed by medical staff prior to the session to ensure the volunteer is still eligible to participate. Next, participants provide a breath sample (to test for alcohol) and a urine sample (to test for recent drug use and pregnancy). Participants who test positive for alcohol, drugs (aside from cannabis), or pregnancy, will be discharged immediately. Participants who are tobacco users and who meet criteria for tobacco use disorder (based on the MINI for DSM-5) will be given a nicotine patch to wear during sessions to prevent the occurrence of aversive nicotine/tobacco withdrawal symptoms (these symptoms could influence study outcomes such as subjective drug effects and cognitive performance). Participants will have an intravenous catheter inserted into a forearm vein before each session to enable repeated blood sampling. Following baseline procedures, participants will first consume a cannabis-infused brownie (containing 0, 10, or 25mg THC) and 45 min after oral cannabis ingestion, they will begin consuming their alcohol or placebo drink (they will be given 15 min to consume their entire drink, meaning they will finish their drink 1 hour after brownie consumption). The point immediately after the brownie is consumed is considered time “0” by which remaining study assessment time points will be scheduled. After drug administration, participants will complete study assessments again at 15-60 min intervals until they are discharged (see below for specific outcome assessment timepoints and for a description of discharge procedures).

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.

Baseline Assessments. Prior to drug administration, baseline blood specimens will be obtained from all participants. Baseline cardiovascular, subjective, and performance assessments will also be conducted (see below for details). Self-reported sleep quality the night before each experimental session will also be assessed at baseline.

Drug Administration Procedures. Participants will first consume a cannabis-infused brownie (containing 0, 10, or 25mg THC). They will be asked to consume the entire brownie with a 5 min period. Each brownie will be baked individually to ensure accurate dosing (precisely weighed amounts of ground cannabis will be included in each brownie; see Section 6 below for additional drug preparation information). Active and placebo brownies will be made with the same quantity of cannabis to assist with blinding.

Forty-five minutes after oral cannabis ingestion, participants will begin consuming their alcohol or placebo drink; doses will be spread out over 3 small drinks to assist with blinding (see section 6 for details). Active drinks will include alcohol doses calculated to produce a breath alcohol concentrations (BACs) of 0.05% or 0.08%; doses of alcohol needed to produce these BACs for each participant will be determined using the Computerized Blood Alcohol Calculator (CBAC©) (Fisher et al., 1987); see section 6 for further details. Alcohol drinks will be made by mixing an exact amount of pure alcohol (minus 1 mL for blinding, see

below) with a non-caloric sweetened beverage (e.g., Crystal Lite) to achieve a volume of 4 oz per individual drink. Placebo drinks will be prepared by floating 1 mL of alcohol on top of the 4 oz of sweet beverage immediately prior to dosing as part of blinding procedures; to further facilitate blinding, an alcohol-soaked wristband will be placed around each glass, delivering a strong alcohol odor for placebo and active drinks. Participants will be asked to try to consume their full drink within a 15 min window (i.e., 5 min for each of the three individual 4 oz drinks).

Post-Dose Assessments. Following cannabis dosing, participants will complete a battery of assessments that includes biological specimen collection, subjective ratings on computerized questionnaires, simulated driving, field sobriety tests, and cognitive performance tasks for 7.5 hours. Participants will thus be discharged 7.5 hours after oral cannabis ingestion (approximately 6.5 hours after alcohol consumption). Participants must have a BAC of 0.03% or less in order to be discharged. Prior to discharge, 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. If the participant is able to cognitively engage with staff, vital signs are within normative range (HR < 100bpm, SYS BP < 150mmHg, DIA BP < 90mmHg), and performance is not below 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 must remain under observation. This same protocol will be followed for cases in which a study participant indicates the desire to be discharged from the study early. Given that on average, individuals metabolize alcohol at a rate of 0.016% per hr when in a fasted state (Wilkinson et al., 1977), participants should approach a BAC of 0.0% 5 hrs after alcohol ingestion at the highest dose (0.08%); thus, 6.5 hrs should be more than sufficient for participants to fall below a 0.03% BAC. In our prior studies, the intoxicating effects of oral cannabis (up to 50mg THC) have not typically persisted past 7.5 hours (Schlienz et al., 2020; Spindle et al., 2018; Vandrey et al., 2017). If a participant reports a drug effect, exhibits impairment, or has a BAC >0.03% when it is time to be discharged, they will be asked to remain at the BPRU until these effects subside and/or their BAC falls below 0.03%. Participants will not be allowed to drive home. Taxi transportation home (e.g., Uber; Lyft) will be provided for participants.

The risk of serious adverse events related to cannabis or alcohol exposure in this study is minimal because participants are experienced users of both substances and will be administering doses of each drug that we have previously shown to have a favorable safety profile. In a recent cannabis study with 20 infrequent cannabis users (IRB00122849), we administered 20 mg THC via vaporization and 25 mg THC via oral ingestion and in other studies, we have administered cannabis containing up to 25 mg THC via vaporization and up to 50 mg THC via oral ingestion (Schlienz et al., 2020; Vandrey et al., 2017); no serious or unexpected adverse events occurred in any of these studies, and we did not have any participant stop participation or be removed from the study due to cannabis side effects. Thus, we feel participants will be able to tolerate the maximum possible oral THC dose in this study (25 mg THC) without incident. In prior alcohol studies, we have dosed individuals to BACs higher (e.g., 0.10%) than what we propose in this research (i.e., 0.05% or 0.08%) without incident and with a high degree of precision. For example, in one study of 127 young adult social drinkers (comparable inclusion criteria as in proposed research) (Weerts et al., 2017) participants were dosed to a terminal BAC of 0.10%; no sessions were terminated early due to adverse alcohol effects or untoward alcohol effects. Given the lack of adverse alcohol effects at 0.10% BAC in that study, and lack of adverse cannabis effects in our prior studies that used similar doses of THC to what we propose, we are confident that co-administration of alcohol (at BAC of 0.05%) and cannabis (high THC dose: 25mg) in this study will also not elicit adverse effects or untoward drug effects and will be well-tolerated by study participants.

Study Measures:

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

Screening. Initial study screening will be completed over the telephone. During the phone screening assessment, staff will conduct assessments to collect background demographic data (age, gender, self-reported race and ethnicity, height and weight) and to determine study eligibility (e.g. Medical History Interview, Drug-History Questionnaire, etc.). If the volunteer appears eligible based on this interview, an in-person screening visit be scheduled to be completed at the BPRU. The screening visit will be comprised of interviews and self-report surveys that provide participant information regarding physical and mental health and drug-use history, and driving history. The screening visit will be split into two parts: day 1 and day 2. At day 1, written informed consent will be obtained before any procedures and demographics, general health, and prescription/non-prescription medication use will be obtained via locally developed forms. Recent alcohol and drug use will be assessed via the 90-day Time Line Follow Back (TLFB) (Sobell, 1992). An interview will be completed to evaluate current psychiatric and substance use disorders using the Mini-International Neuropsychiatric Interview (MINI) for DSM-5 (Sheehan et al., 2010); the Alcohol Use Disorders Identification Test (AUDIT) and clinical institute withdrawal assessment for alcohol, revised (CIWA-Ar) (Bush et al., 1998; Sullivan et al., 1989); Literacy will be confirmed with the Shipley-2 (Shipley, 2009). Urine 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. The brief sensation seeking questionnaire (Stephenson et al., 2003) and Eysenck Impulsivity Questionnaire (Eysenck et al., 1985) will also be given at screening. They will also undergo a physical exam by a physician or nurse practitioner. 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. Routine blood tests will be conducted including clinical chemistry, hematology, serology, and serum pregnancy (for females). Individuals who still appear eligible after day 1 of the screening procedures will be invited to return to the BPRU on a separate day. At screening day 2, participants will undergo training on the various performance measures (e.g., DRUID, driving, field sobriety tests, etc.). They will be trained on each measure until reaching a stable baseline. Participants who successfully complete this training visit and demonstrate mastery of the tasks will be invited to participate in the study.

Experimental Sessions

Vital signs (heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP)) will be measured in the seated position. Vitals will be measured at baseline (prior to drug administration) and again 0.5, 1, 1.25, 1.5, 2.5, 3.5, 4.5, 5.5, 6.5, and 7.5 hours after oral cannabis ingestion.

Blood Samples will be collected at baseline (prior to drug administration) and again 1, 1.25, 1.5, 2.5, 3.5, 4.5, 5.5, and 7.5 hours after oral cannabis ingestion. Six mL of whole blood will be collected at designated times listed above into vacutainer tubes. Blood will be divided in half and transferred to two plastic cryotubes, labeled and stored frozen at -80 ºC until shipped frozen on dry ice to a designated laboratory for analysis. An additional 2.5 mL of whole blood will be collected at baseline, 1.5, 3.5, 5.5, and 7.5 into PAXgene blood RNA tubes. The blood RNA tubes will be labeled and stored frozen at -80 ºC and an RNA sequencing analysis of these specimens will be conducted to probe for possible biomarkers of cannabis impairment; deidentified sequencing results will be uploaded to a genomic repository (dbGaP). Additionally, deidentified pharmacodynamic data collected in this study (e.g., simulated driving data) will be uploaded to dbGaP, along with the sequencing files. Each study participant will provide a total of 14 blood specimens in each of the 7 study sessions (465.5 mL total throughout the study) and will provide and additional 5mL at screening. Thus, the total amount of possible blood collected from participants who complete the study will be 470.5 mL. This amount is less than the amount typically provided at a single blood drive donation (473 mL) and also less than the amount recommended by the National Cancer

Institute (NCI) to be drawn over an 8-week period for healthy non-pregnant adults. The spacing of blood collection timepoints over 7 weeks is adequate for blood to be replaced by healthy adults without negative health consequences.

Breath Samples. Breath alcohol concentration (BAC) will be measured via the Alco-Sensor IV breathalyzer. Measuring BAC is needed to confirm that participants reached the targeted BAC for a given session and adhered to pre-session alcohol abstinence requirements. BAC readings will not be viewable to participants to maintain dose blinding. Breath samples will be taken at baseline (prior to drug administration) and again 1, 1.25, 1.5, 2.5, 3.5, 4.5, 5.5, 6.5, and 7.5 hours after oral cannabis ingestion.

The Drug Effect Questionnaire, DEQ, (Spindle et al., 2018; Vandrey et al., 2017) will be used to obtain subjective drug effects. Individual items include ratings of 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). Additional DEQ items added for this protocol will evaluate subjective effects specific to driving (e.g., confidence to drive; willingness to drive). 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. The DEQ will be given at baseline (prior to drug administration) and again 0.5, 1, 1.25, 1.5, 2.5, 3.5, 4.5, 5.5, 6.5, and 7.5 hours after oral cannabis ingestion. The **Subjective High Assessment Scale (SHAS)** (Martin et al., 1993) and the **Biphasic Alcohol Effects Scale (BAES)** (Schuckit, 1980) will assess alcohol-specific subjective effects. For the SHAS, participants rate alcohol effects on a 10-point line (0=normal; 10=extremely); they are told to assume their ratings are "normal" before receiving a beverage. Example items include: muddled/confused, slurred speech, dizzy, drunk, distorted sense of time, and difficulty concentrating. Items are summed to produce an overall score (the primary SHAS outcome). The BAES measures stimulant (e.g., energized, excited, stimulated) and sedative (e.g., inactive, sedated, sluggish) effects of alcohol with 14 items. Participants rate each item on a scale from 1 (not at all) to 10 (extremely). Overall stimulant and sedative scores are calculated from the individual items (two primary BAES outcomes). These questionnaires will be given at baseline (prior to drug administration) and again 0.5, 1, 1.25, 1.5, 2.5, 3.5, 4.5, 5.5, 6.5, and 7.5 hours after oral cannabis ingestion.

Cognitive/Psychomotor performance. Participants will complete the **DRUID application**, which is comprised of a battery of computerized performance tasks which test aspects of cognitive/psychomotor functioning known to be sensitive to the acute effects of cannabis and relevant to functioning in the workplace and/or in operating a motor vehicle or heavy machinery. All participants will be trained on the DRUID to a stable baseline level during the screening session. 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. Scores on each of the four tasks are integrated to yield a global impairment score (our primary outcome for this task). The DRUID battery will be given at baseline (prior to drug administration) and again 1, 1.5, 2.5, 3.5, 4.5, 5.5, 6.5, and 7.5 hours after oral cannabis ingestion.

Driving Simulator. The STISIM Drive® M4000-R Console system will be used to assess driving performance, a state-of-the-art technology that has been independently validated to reflect real-world driving conditions (Mayhew et al., 2011; Shechtman et al., 2009). This model includes a cab/console engineered to conform to automotive ergonomics. Seat positioning, monitor positioning, monitor size, turning signals, responsiveness of gas/brake pedals and steering wheel, and viewing angles have all been engineered to simulate the driver experience one would have if driving in an actual vehicle. The system includes a fully interactive virtual reality driving simulator software suite that offers the driver a 135-degree field-of-view. participants will complete simulated drives that assesses key aspects of driving that are most affected by acute cannabis/alcohol impairment: divided attention, vigilance, lane position, maintenance of speed, adherence to traffic laws, maintaining appropriate distance to other cars, response to unexpected

stimuli, and avoidance of collisions. Programmed drive simulations that encompass each of these features will be utilized during each session (each simulation will last about 25 min). Specific driving outcomes include: lateral control (i.e., SDLP), longitudinal control (i.e., standard deviation of speed, SDSP, mean speed, number of speed exceedances), total accidents (sum of number of collisions, pedestrians hit, etc.), total rule violations (sum of number of missed stop signs, illegal turns, etc.), and distance to lead vehicles. SDLP (a composite index of lane weaving, swerving, and over-correcting) is the primary outcome measure because it is widely considered the gold standard for evaluating driving performance and quantifying the extent of drug/alcohol-induced driving impairment (Jongen et al., 2017; Verster and Roth, 2011). Drives will be performed at baseline (prior to drug administration) and again 1.5, 3.5, 5.5, and 7.5 hours after oral cannabis ingestion.

Field Sobriety Tests. A battery of field sobriety tests commonly used at the roadside to detect impairment from drugs and alcohol will be administered. The battery includes: The Walk-and-Turn (W&T), One-Leg Stand (OLS), Horizontal Gaze Nystagmus (HGN), Vertical Gaze Nystagmus (VGN), Modified Romberg Balance (MRB), Finger-To-Nose test, and Lack of Convergence test. Together, these tests take 6-7 min to complete. These tests were designed specifically to detect various aspects of alcohol-related impairment such as difficulty balancing, motor coordination, and involuntary eye movements (e.g., nystagmus) at 0.08% BAC and lower (Stough et al., 2006; Stuster, 2006). While performing each test, the task administrator looks for distinctive behavioral indications (or "clues") that indicate impairment; clues are either scored as present (1) or not present (0). The number of clues observed are summed to produce an overall score for the task, with higher scores indicating more impairment. For example, on the W&T test, the participant is asked to take 9 heal-to-toe steps down a straight line and on the 9th step, to take 9 identical steps back in the other direction; the administrator looks for 8 distinct clues (e.g., stepping off of the line, using arms to balance, etc.); 0/8 clues indicate no impairment; 8/8 clues indicate maximum impairment. The primary outcome is the cumulative clues across all tests. Secondary outcomes include scores on the individual tests. Tests will be video recorded to allow another study team member (aside from the person scoring during the session) to score them at a later time; agreement between raters will be calculated. Mr. Thomas Woodward, an external collaborator on the project, will also review/score the performance of a subset of participants (via recorded videos) to ensure study staff are maintaining proper technique during the study and assist with interpretation of participants' performance. As a retired police officer and former certified Drug Recognition Expert, DRE, Mr. Woodward is an expert in field sobriety tests and is ideal for this role. This level of oversight by a trained DRE is necessary to ensure the validity of the data and will provide confidence in the study findings. The task battery will be given at baseline (prior to drug administration) and again 1.5, 3.5, 5.5, and 7.5 hours after oral cannabis ingestion.

The order of assessments will be as follows: vitals, subjective measures, driving, field sobriety tests, cognitive tasks, blood draws and breathalyzer.

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

All participants will complete an outpatient visit for screening evaluation. Those who are eligible and enrolled will complete 7 experimental sessions, each separated by 1 week. Thus, the total duration of the study will be 7 weeks.

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

Cannabis/alcohol dosing will be blinded in this study. It is standard procedure for appropriate scientific control in studies evaluating the effects of potentially 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 doses of alcohol and cannabis will be included to help interpret active drug effects on pharmacodynamic outcomes. Placebo dosing provides a control for expectancy effects on subjective reports and performance tasks 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 may discharge study participants for failing to attend their scheduled sessions, 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 alcohol and who are not seeking treatment for substance use problems. Should any participants 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. 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 each study visit.
5. Have a body mass index (BMI) in the range of 19 to 38 kg/m2
6. 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
7. Have not donated blood in the prior 30 days.
8. Report at least 1 day of binge drinking in the past 90 days (greater than 4 or 5 drinks on a single occasion for women and men, respectively)
9. Report at least one use of cannabis in the past year
10. Provide negative urine test for illicit drug use (excluding THC) and negative breath alcohol test (0% BAC) at screening and before study sessions
11. Report at least 1 lifetime instance of simultaneous alcohol and cannabis use (i.e., "co-use").
12. No uses of OTC drugs, supplements/vitamins, or prescription medications (aside from birth control and acetaminophen) in the past 14 days or within 5 half-lives for that specific drug before study sessions.

13. For women of children bearing potential and men with female partners of child-bearing potential, must be willing to use an effective form of contraception during the study and for at least 30 days after the last drug administration session.

Exclusion Criteria

1. Psychoactive drug use (aside from cannabis, nicotine, alcohol, or caffeine) in past month
2. History of or current evidence of significant medical condition
3. Evidence of current psychiatric condition (MINI for DSM-V)
4. Meet criteria for severe alcohol use disorder (MINI for DSM-V)
5. CIWA-Ar score > 9
6. Been in treatment previously for alcohol or cannabis use disorder
7. Use of cannabis, on average, more than 2 times/week over past 3 months
8. Liver function tests more than 2x normal range
9. Enrollment in another clinical trial or receiving of any drug as part of research within past 30 days
10. Shipley vocabulary score <18 (corresponds to 5th grade reading level).

6. Drugs/ Substances/ Devices

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

All placebo and active cannabis will be obtained from the National Institute on Drug Abuse (NIDA) Drug Supply Program. Preparation of cannabis brownies will consist of: (1) grounding cannabis into fine powder; (2) baking cannabis at 250°C so that tetrahydrocannabinolic acid (THC-A) will decarboxylate to THC, and (3) mixing decarboxylated cannabis with a commercial brownie batter, along with other ingredients (eggs, vegetable oil, etc.). Each brownie will be baked individually to ensure accurate dosing (precisely weighed amounts of ground cannabis will be included in each brownie). In prior studies, we have ensured that these methods reliably yield targeted THC doses (Schlienz et al., 2020; Vandrey et al., 2017). Active and placebo brownies will be made with the same quantity of cannabis to assist with blinding; placebo cannabis is plant material from which THC has been extracted with ethanol. In each session, participants will be instructed to consume their entire brownie within a 5 min period. THC doses (10 and 25mg THC) were chosen based on our recent prior studies. We have conducted 3 prior studies using these exact doses (Schlienz et al., 2020; Spindle TR, 2019; Vandrey et al., 2017). In these studies, the 10mg THC dose elicited discriminable subjective drug effects, but had little impact on impairment. Conversely, the 25mg THC dose increased subjective drug effects, while also producing impairment of cognitive/psychomotor performance. Thus, these two doses will enable proper sensitivity testing of the impairment measures included. Also, of note, these two doses were generally well tolerated in our prior studies and no participants experienced unexpected or serious adverse events.

Alcohol suitable for human consumption will be obtained from Spectrum Chemical (New Brunswick, NJ, USA); a certificate of analysis is provided with each order to ensure the purity of the alcohol. Alcohol drinks with doses targeted to produce peak breath alcohol concentrations (BACs) of 0.05% or 0.08% will be prepared by the BPRU pharmacy and self-administered by participants. Targeted BACs were selected based on our prior research and *per se* limits for driving under the influence (DUI) of alcohol in most U.S. states (0.08%) and most of Europe (0.05%). Dosing participants to a 0.05% BAC in alcohol and cannabis co-use conditions will avoid ceiling effects on study outcomes and mitigate potential untoward drug effects (e.g., emesis) that may potentially be present if higher alcohol doses were administered with cannabis. This study design will also allow us to assess whether cannabis and alcohol (at a BAC below the U.S. legal limit for intoxicated driving) have additive or synergistic drug effects when combined that meet or exceed the effects produced by alcohol alone at a higher BAC (0.08%) that does constitute DUI in the U.S. Alcohol drinks will be made by mixing an exact amount of pure alcohol (minus 1 mL for blinding, see

below) with a non-caloric sweetened beverage mixer (e.g., Crystal Lite) to achieve a volume of 12 oz which are then spread out evenly over three 4 oz drinks. Placebo drinks will be prepared by floating 1 mL of alcohol on top of the three 4 oz drinks of sweet beverage immediately prior to dosing as part of blinding procedures; to further facilitate blinding, an alcohol-soaked wristband will be placed around each glass, delivering a strong alcohol odor for placebo and active drinks. Spreading doses out over 3 drinks will assist with blinding and further reduce the chances of emesis. Participants will be asked to try to consume their full drink within a 15 min window (i.e., 5 min for each of the three individual drinks). Given that many factors can affect BAC after alcohol use (e.g., differences in total body water content between men and women (Fisher et al., 1987)), we will calculate alcohol doses for each participant with the Computerized Blood Alcohol Calculator (CBAC©) created by Dr. Bushan Kapur (Addiction Research Foundation (Fisher et al., 1987)). The CBAC uses a regression equation derived from controlled alcohol dosing studies of 500 males and 265 females. The dose of alcohol needed to produce a given BAC is calculated by factoring in a person's total body water and by correcting for age, percent body fat, and time spent drinking. We have used the CBAC to safely administer alcohol to hundreds of research volunteers in prior studies (McCaul et al., 2018; Uhart et al., 2013; Weerts et al., 2017) and have confirmed that we can reliably produce specific BACs (e.g., 0.05% or 0.08%) in a diverse range of individuals (e.g., males and females with high and low body fat percentages) with a high degree of precision. For example, in one study of 127 young adult social drinkers (comparable inclusion criteria as in proposed research) (Weerts et al., 2017) participants were dosed to a terminal BAC of 0.10%; no sessions were terminated early due to adverse alcohol effects or untoward alcohol effects. Given the lack of adverse alcohol effects at 0.10% BAC in that study, and lack of adverse cannabis effects in our prior studies that used similar doses of THC to what we propose, we are confident that co-administration of alcohol (at BAC of 0.05%) and cannabis (high THC dose: 25mg) in this study will also not elicit adverse effects or untoward drug effects and will be well-tolerated by study participants.

Alcohol and cannabis dosing will be performed in a double-blind, double-dummy manner. All drug products will be stored in the secure Johns Hopkins BPRU pharmacy, a satellite of the Johns Hopkins Investigational Drug Service (IDS) research pharmacy, and BPRU pharmacy staff will handle all drug dispensing and blinding.

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 will be obtained for this study.

Study Statistics

a. Primary outcome variable.

Primary outcomes include: (1) Driving performance (standard deviation of lateral position, SDLP). (2) Cognitive task performance (number correct on the PASAT and DSST; DRUID global impairment score). (3) Cumulative clues detected across all field sobriety tests. (4) "feel drug effect" and "high" on the DEQ. (5) subjective driving items (e.g., "confidence to drive") and (6) overall SHAS score, overall stimulant and sedative BAES scores.

b. Secondary outcome variables.

Secondary outcomes include: (1) standard deviation of speed, mean speed, number of speed exceedances, total accidents, total rule violations, and distance to lead vehicles on driving tasks. (2) Number attempted and percentage correct on DSST; reaction time on correct trials on PASAT. (3) Clues detected on individual field sobriety tasks. (4) positive (e.g., “like”; “want more”) and negative DEQ items (e.g., “dislike”) and cannabis-specific DEQ items (e.g., “paranoid”; “munchies”).

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

Demographics will be summarized and compared across males and females using t-tests. For each outcome, descriptive statistics (means and standard deviations) will be generated. Linear mixed models will be used to test for differences across experimental conditions. Hypothesis tests will be two-sided and significance will be set at $p<.05$. Factors entered into these models will include: time (number of levels will differ depending on outcome variable), alcohol dose (0%, 0.05%, and 0.08%), cannabis dose (0, 10, and 25mg THC), and sex (male or female). Time, alcohol dose, and cannabis dose will be within-subject factors (i.e., repeated measures); sex will be a between-subject factor. Maximum concentration (Cmax) and area under the curve (AUC) for THC and THC metabolites (11-OH-THC; THCCOOH) will be entered as covariates. Holm-Bonferroni corrections will be used to control for multiple comparisons. Data will be inspected for normality (skewness, kurtosis, outliers) and, where necessary, data transformations will be applied. Missing data is expected to be rare, as tasks/instruments are computerized, and field sobriety tasks will be video recorded.

A-priori planned comparisons will be conducted to compare mean peak change-from-baseline scores for each outcome (i.e., impairment outcomes and subjective effects) for: (1) alcohol alone (BAC 0.05%) to alcohol with cannabis (BAC 0.05% + 10mg THC and 25mg THC); and 2) cannabis alone (10mg THC and 25mg THC) to cannabis with alcohol (BAC 0.05% + 10mg THC and 25mg THC). Additional planned comparisons will compare impairment (e.g., DRUID scores) between cannabis with alcohol (BAC 0.05% + 10mg THC and 25mg THC) to the positive control condition (alcohol alone: BAC 0.08%). Correlations will be conducted to assess the relations between DRUID and driving performance and sensitivity/specificity analyses will be conducted to characterize the effectiveness of the DRUID for determining driving impairment. Specifically, we will plot the sensitivity (true positive rate) and specificity (true negative rate) of the DRUID at identifying impaired driving by comparing various DRUID cutoffs to established cutoffs for driving simulator data that are indicative of clinically meaningful impaired driving in real-world settings (e.g., SDLP change-from-placebo ≥ 2.4 cm (Jongen et al., 2017)).

Power analyses for each primary outcome were conducted in R, using the SIMR package (Green and MacLeod, 2016) which estimates power for linear mixed models by fitting a regression model multiple times under different scenarios, or simulations (100 simulations were performed for each power calculation). Effect sizes (Cohen’s d) and data (means and SDs) were obtained from prior alcohol/cannabis co-use studies and/or prior studies conducted in our laboratory that administered the proposed doses of oral/vaporized cannabis or alcohol alone. In prior studies, greater driving impairment (i.e., SDLP, (Hartman et al., 2015b; Ramaekers et al., 2000; Ronen et al., 2010)) (Cohen’s d range: 0.15-1.13) and impairment on field sobriety tests (Bosker et al., 2012b) (Cohen’s d=0.46) and cognitive/psychomotor performance tasks (Belgrave et al., 1979; Bird et al., 1980; Manno et al., 1971) (Cohen’s d range: 0.28-0.53), has been observed following co-use of cannabis and alcohol compared to the use of these substances alone. Several studies (Belgrave et al., 1979; Bird et al., 1980; Hartman et al., 2016a) have similarly shown increases in subjective ratings of intoxication (e.g., ratings for “high”, “feel drug effects”, or “feel stoned”; effect sizes range: d=0.71-1.11) and for ratings of “stimulated” or “sedative” (Hartman et al., 2016a) following co-use of cannabis and alcohol compared to solo use of these

substances. Overall, all power analyses revealed that 32 participants in each study would provide sufficient power (≥ 0.80 power for all 100 simulations) to test the study hypotheses stated in the primary aims. Also, of note, we have conducted several within-subject crossover studies with sample sizes between N=17-20 (i.e., 8-10 males and 8-10 females) (Spindle et al., 2020a; Spindle et al., 2018; Spindle TR, 2019) and detected significant sex differences and differences across drug conditions (e.g., doses of 0, 10, 25 mg THC) on the same measures as the proposed study, further highlighting that a sample size of N=32 (16 males/16 females) in each study is adequate.

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.

Oral THC exposure is associated with risk of 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. There is no known risk of overdose or death related to cannabis/THC exposure. Alcohol may produce mood and behavioral effects that are dysphoric and that can result in impairment of cognitive/psychomotor abilities, divided and sustained attention, coordination, and judgment. Use of alcohol can also cause vomiting, drowsiness, slurred speech, distorted vision/hearing, increased heart rate/blood pressure, and upset stomach. In cases of overdose, ethanol can produce medically serious toxic effects (this is not expected at the proposed alcohol doses).

We feel that the risk of serious adverse events related to cannabis exposure or alcohol exposure in this study is minimal for several reasons. First, participants are experienced cannabis users (they must have used cannabis at least five times in the year prior to screening in order to be eligible) and regular alcohol users (they must report one recent binge drinking episode and also must consume ≥ 7 drinks/week for women and ≥ 14 drinks/week for men). Moreover, participants must also report co-using alcohol/cannabis on at least one occasion in the past year to be eligible. Second, we have administered doses of THC or alcohol comparable to the doses we propose to administer, as well as higher doses, to similar study populations without incident in several prior studies (see above). Thus, we believe that the study volunteers will be able to tolerate the proposed doses of THC and alcohol without incident and the risk of serious adverse events in the laboratory is minimal. In the unlikely event a participant experiences untoward cannabis effects (e.g., panic and/or paranoid reactions) or alcohol effects, research staff will engage the person in relaxation exercises and will suspend research procedures until the participant has regained comfort. These types of effects are time-limited and typically of short duration. In the case of an extreme adverse reaction, participants will be taken to the Johns Hopkins Bayview ER for treatment.

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 total amount of blood drawn is comparable to what we have collected in prior studies, and we feel will not pose a significant health risk to participants given that we are screening for anemia and total blood count at the screening assessment and the study medication is not known to interfere with blood production.

A further risk is that participants may mistake the proposed studies as treatment or may delay seeking treatment in order to participate.

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

Exposure to COVID-19 is a risk.

b. Steps taken to minimize the risks.

Participants are not a "vulnerable population" as defined by human subject's protection guidelines; that is, they are not minors, pregnant women, under legal coercion or restriction, or mentally impaired. They are competent adults who provide 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 using 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.

To reduce the likelihood of serious adverse events during experimental sessions, we will have several early stopping rules in place. First, drug administration will be withheld for any participant with a resting heart rate above 120 beats per minute, systolic blood pressure >150 or <100, or diastolic blood pressure >100 or <40 during vital signs assessments, which will occur throughout each drug administration session. It will be also made clear to participants that they may discontinue administration of either drug at any point during study sessions (e.g., they may decline the alcohol drink following cannabis administration). As described above, the risk of serious adverse events related to cannabis or alcohol exposure in this study is minimal because participants are experienced users of both substances and will be administering doses of each drug that we have previously shown to have a favorable safety profile. In a recent cannabis study with 20 infrequent cannabis users, we administered 20 mg THC via vaporization and 25 mg THC via oral ingestion and in other studies, we have administered cannabis containing up to 25 mg THC via vaporization and up to 50 mg THC via oral ingestion; no serious or unexpected adverse events occurred in any of these studies, and we did not have any participant stop participation or be removed from the study due to cannabis side effects. Thus, we feel participants will be able to tolerate the maximum possible THC dose in this study (25mg THC) without incident. In prior alcohol studies, we have dosed individuals to BACs higher (e.g., 0.10%) than what we propose in this research (i.e., 0.05% or 0.08%) without incident and with a high degree of precision. For example, in one study of 127 young adult social drinkers (comparable inclusion criteria as in proposed research), participants were dosed to a terminal BAC of 0.10%; no sessions were terminated early due to adverse alcohol effects or untoward alcohol effects. Given the lack of adverse alcohol effects at 0.10% BAC in that study, and lack of adverse cannabis effects in our prior studies that used similar doses of THC to what we propose, we are confident that co-administration of alcohol (at BAC of 0.05%) and cannabis (high THC dose: 25mg) in this study will also not elicit adverse effects or untoward drug effects and will be well-tolerated by study participants, who will be experienced alcohol and cannabis users.

In case an adverse event of any magnitude occurs, participants will be under the supervision of medical/nursing staff throughout the study, and access to medication dose information will be readily available. The medical and nursing staff at BPRU are trained in CPR and mobile emergency crash carts are available near the session room where all drug administration will occur. The research facility (BPRU) is located directly across the street from the Johns Hopkins Bayview Medical Center Emergency Department, and, in case of a serious adverse event, participants will be taken there for immediate care. Dr. Spindle (PI) and study medical monitors (Antoine, Strain, Umbricht) will be immediately notified of any serious adverse events that arise. If participants develop nausea or vomiting after consuming cannabis or alcohol, 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 technique and flushing the catheter after each blood draw. The amount of blood collected for the study (383 mL) is less than a standard blood donation (473 mL) and should be readily replaced without harm to study participants.

All advertisements and the informed consent process will clearly indicate that this research is designated only for those not seeking treatment, that participation is not a substitute for treatment, and that participation offers no clinical benefit. They will be clearly informed that they will be asked to consume alcohol and cannabis. Any participant who expresses an interest in receiving immediate treatment for cannabis, alcohol, 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.

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 members who come in contact with any single participant to the extent possible based on duties to be performed and staff availability. Our goal 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). In addition, prior to arrival for any study visit, participants will be asked about potential COVID-19 symptoms and possible recent exposure to COVID-19. Any participant who reports symptoms indicative of COVID-19 per the JHU clinical screening algorithm will not be allowed to visit the lab and participation will be paused for at least 2 weeks after which a health care professional must clear a return to participation (e.g., with a negative COVID-19 test).

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 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, aside from external collaborator Mr. Thomas Woodward. Mr. Woodward

will review participants' performance on field sobriety tests (via recorded videos) to ensure study staff are maintaining proper technique during the study and assist with interpretation of their performance. He will only view these recordings on site at the BPRU on JHU computers (thus, no video files will be shared electronically with Mr. Woodward). 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.

There will be no direct benefit to subjects who participate in the study. The primary benefit of the proposed research is in the knowledge gained regarding the relative biological, subjective and behavioral impairment effects of exposure to alcohol and oral cannabis. The knowledge may be used to inform impairment detection standards for alcohol and cannabis and assist in interpretation of drug tests across different biological matrices, such as those conducted at the roadside or in the workplace. Because we anticipate relatively minor risks to these cannabis and alcohol 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 and $30 for completing the task training visit. Compensation for each of the 7 study sessions is $300. Additionally, participants will receive a $500 completion bonus for completing all 7 sessions. Total possible earnings for each participant is $2630. Compensation of this magnitude is appropriate given the length and nature of this study.

Screening Visit:	$30
Task Training Visit	$30
Outpatient sessions:	$300/session ($2100 total)
Study Completion Bonus:	$500
Total Compensation:	$2660

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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