

Study Title:

Effects of combined alcohol and cannabis on young drivers' simulated driving

Clinical Trial Site	Centre for Addiction and Mental Health (CAMH), Toronto, Canada
Co-Principal Investigator	Christine Wickens
Co-Principal Investigator	Bruna Brands
Qualified Investigator	Bernard Le Foll
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Sponsor: Bernard Le Foll

Address of Trial Site: Centre for Addiction and Mental Health (CAMH), 33 Russell Street, Toronto Ontario, M5S 2S1

Co-Principal Investigator authorized to sign protocol and amendments for the sponsor:

Christine Wickens, Independent Scientist, Institute for Mental Health Policy Research, CAMH. Tel: 416-535-8501, ext. 34711, Fax: 416-595-6899, Email: christine.wickens@camh.ca

Co-Principal Investigator authorized to sign protocol and amendments for the sponsor:

Bruna Brands, Senior Scientist, Healthy Environments and Consumer Safety Branch, Health Canada; Affiliate Scientist, Institute for Mental Health Policy Research, CAMH. Tel: 416-535-8501, ext. 36860, FAX: 416-595-6899, Email: bruna.brands@camh.ca

Medical Expert for the trial and holder of the Drug Exemption and Qualified Investigator:

Bernard Le Foll, Medical Head, Addiction Medicine Service and Medical Withdrawal Service, Ambulatory Care and Structured Treatments Program; Head, Translational Addiction Research Laboratory, Campbell Family Mental Health Research Institute, CAMH. Tel: 416-535-8501, ext. 34772, Fax: 416-595-6922, Email: bernard.lefoll@camh.ca

Sub-Investigators:

Robert Mann, Senior Scientist, Institute for Mental Health Policy Research, CAMH.
Andriy Samokhvalov, Psychiatrist, Addictions Division; and Clinician-Scientist, Institute for Mental Health Policy Research, CAMH.

Collaborators:

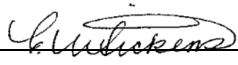
Paul Shuper, Scientist, Institute for Mental Health Policy Research, CAMH.
Jürgen Rehm, Institute for Mental Health Policy Research, CAMH.
Beth Sproule, Independent Clinician Scientist, Pharmacy Department, CAMH.
Gina Stoduto, Institute for Mental Health Policy Research, CAMH.
Marilyn Huestis, Thomas Jefferson University.

Laboratory and Pharmacy involved in the trial:

Clinical Laboratory: Contact: Cristiana Stefan, CAMH, Bell Gateway Building, 2nd floor, 100 Stokes Street, Toronto, ON, M6J 1H4, Tel: 416-535-8501 ext. 32056.

Pharmacy: Contact: Abir Khoury, CAMH, 1001 Queen St. Community Centre, Toronto, ON, M6J 1H4, Tel: 416-535-8501 ext. 33082.

Principal Investigator Signature:  **Date:** June 24 2020
(dd/mm/yy)

Principal Investigator Signature:  **Date:** June 24, 2020
(dd/mm/yy)

Qualified Investigator Signature:  **Date:** June 24, 2020
(dd/mm/yy)

Background Information

Investigational product:

Product name: *Cannabis sativa* (herein referred to as *cannabis*)

Active cannabis will be obtained from Aurora, which bought Cannimed, 1 Plant Technology Road, Box 19A, RR#5 Saskatoon, SK, S7K 3J8, and matching placebo cannabis (<0.1% THC) will be obtained from the National Institute on Drug Abuse (NIDA) in the United States. Each cigarette will contain 750 mg of dried plant material. Cannimed production of cannabis is highly standardized and secure; and the active cannabis cigarette contains $12.5\% \pm 2\%$ (79 – 109 mg) THC.

Information on the cannabis available from Cannimed is available online:

<http://cannimed.ca/pages/our-products>

Summary of findings relevant to the trial:

Alcohol and cannabis are the two most widely used substances of abuse in the world e.g.,¹⁻³, and are the psychoactive substances most often found in seriously and fatally injured drivers⁴⁻¹⁰. The deleterious effects of alcohol on driving and collision risk are well known, with the risk of collision involvement increasing exponentially as blood alcohol concentration (BAC) increases¹¹⁻¹³. However, the effects of cannabis on driving and collision risk have been more controversial. While laboratory studies have identified acute effects of the drug on cognitive and psychomotor measures, earlier epidemiological research on the effects of cannabis on collision risk did not provide consistent findings. In a 1998 review¹⁴, it was concluded that the consumption of cannabis did not increase the risk of culpability for traffic crash fatalities or injuries, and may actually reduce those risks. Since then, it has been suggested that these early results may have been due to methodological difficulties in conducting research on cannabis effects on collisions^{15, 16} and recent meta-analyses have now concluded that driving under the influence of cannabis (DUIC) is associated with significant increases in collision risk^{17, 18}.

Individuals who report driving after using either substance experience a risk of past year collision involvement that is about double that reported by those who do not report driving after substance use¹⁹⁻²¹. In a recent study, we observed that *individuals who reported both driving under the influence of alcohol (DUIA) and DUIC experienced a risk of past year collision involvement that was nearly 4 times that of individuals who reported driving after only one of those drugs*²¹. The prevalence of DUIA and DUIC is becoming very similar in some groups. Recent research in the United States and Canada indicates that the prevalence of DUIC among young drivers of high school and university age and young adults is similar to, or higher than, the prevalence of DUIA^{12, 15-17}. We first reported this in 2003²², when we were able to compare the prevalence of driving after both alcohol and cannabis use among high school drivers in Ontario, Canada, and observed that the prevalence of driving after cannabis use was in fact higher, at 19.7% of drivers, than the prevalence of driving after drinking, at 15.1% of drivers. This is a serious public health issue, given that motor vehicle collisions are the leading cause of death in this age group¹⁹. Drink-driving is known to be one of the major contributors to these deaths, and an unknown but also potentially large proportion of these deaths may be due to cannabis-related impairment of driving skills.

Effects of Alcohol and Smoked Cannabis Alone and Combined on Simulated Driving

There has been extensive simulation and naturalistic study of alcohol impairment effects on driver performance. This vast literature has been fairly consistent in its identification of affected behaviours including increased speed and speed variability, steering error and instability, reduced following distances, increased within-lane position variability and lane departures, slower reaction time, and more crashes²⁷.

Simulation and naturalistic studies of the impairing effects of cannabis have been far fewer and produced less consistent findings. There appears to be some agreement that motorists who drive under the influence of cannabis tend to engage in compensatory behaviour^{28, 29}; driving more slowly³⁰⁻³⁶, with an increased following distance^{30, 31, 34, 37}. They also attempt fewer passes or require a wider gap in traffic before attempting to pass³⁷⁻³⁹. Although researchers generally agree that this type of reduced risk-taking cannot compensate for all cannabis-induced driver impairment, a clear picture of what other dangerous behaviours emerge in cannabis-impaired drivers is still at question. Previous research has demonstrated both improved⁴⁰ and reduced lane control^{30, 31, 33-35, 37, 41}, or failed to find an effect^{32, 36, 42, 43}. Reaction time to unexpected roadway events has generally been greater under the influence of cannabis^{35, 43}, but again this has not been a consistent finding^{30, 34, 42, 44}. Some studies have found an increase in reaction time and other behavioural effects under dual-task conditions^{31, 33, 37, 42}.

Although there is indication that some alcohol and cannabis impairment effects may be similar, at least in the direction of effect (e.g., problems with steering variability and lane control^{31, 33-35, 45, 46}, increased reaction time^{35, 43, 47}), there is also evidence of contrasting impairment effects by the two substances. Alcohol-impaired drivers tend to increase speed and reduce following distance^{48, 49}, whereas cannabis-impaired drivers appear to decrease speed and increase following distance^{31, 34}. Given the frequency with which alcohol and cannabis are consumed together^{50, 51}, it is important to understand their combined effects on driver behaviour.

Simulation studies examining the combined impact of alcohol and cannabis on driver performance are extremely few in number, and differ based on analytical approach. In some cases, an interaction between alcohol and cannabis effects is assessed, whereas in others main effects are examined through direct comparisons between drivers impaired by alcohol or cannabis and drivers impaired by both substances. Of the two studies assessing interaction effects, neither found an effect of combined use on speed, lane control, steering control variability, following distance, or reaction time^{31, 36}. However, Stein et al.³⁶ reported a significant interaction effect of alcohol and cannabis on number of collisions.

Studies examining the combination of alcohol and cannabis as a direct effect report results relative to alcohol or cannabis use alone. Regardless of which comparison is being made, results have been inconsistent. Relative to alcohol use alone, combined use has been associated with both increased³⁰ and decreased^{32, 34} speed, increased³⁴ and decreased³⁰ stopping safety, and an increase³² or no change^{30, 34} in collisions. Findings have generally suggested that relative to alcohol, combined alcohol and cannabis use is associated with worse lane control^{30, 32, 34} but is not associated with changes in reaction time^{30, 44}. Only one study examined how steering control variability³² and following distance³⁰ were impacted, but no effects were found, which is consistent with research assessing interactive effects.

Relative to cannabis use alone, combined use has been associated with increased³⁰ or no change in speed^{32, 34}, reduced^{30, 32} or no change³⁴ in lane control, reduced³⁰ or no change³⁴ in stopping safety, and an increase³² or no change^{30, 34} in collisions. Downey et al.³⁰ reported no change in reaction time, which is consistent with studies assessing interactive effects, but found an increase in following distance, which is inconsistent with interaction effect research. Likewise, a non-significant but suggestive increase in steering control variability was found by Ronen et al.³², which is also inconsistent with interaction effect research.

A few naturalistic studies have provided data examining the combined effects of alcohol and cannabis on specific driver behaviours. Some findings have suggested that combined use results in reductions in lane control relative to alcohol⁵²⁻⁵⁴ or cannabis alone^{52, 53, 55}, although one study suggested an increase in lane control relative to alcohol⁵⁵. There have also been reports of a reduction in speed relative to alcohol⁵⁴, as well as a reduction in following distance⁵² and an increase in reaction time⁵³ relative to alcohol or cannabis alone. Several naturalistic studies have employed assessments of driving proficiency made by professional instructors and of driving impairment made by police, and have identified a reduction in safe driver performance under combined use of alcohol and cannabis⁵⁶⁻⁵⁸.

This highly mixed set of results from both simulation and naturalistic studies is further complicated by the fact that driving skills/behaviours (e.g., lane control) have been measured by a number of different variables (e.g., straddling barrier line, standard deviation of lateral position) both within and across studies, often producing differing results. Moreover, the use of varying dosages of alcohol and cannabis, along with the influence of other measured variables such as simulated time of day, level of driving experience, and frequency of cannabis use makes comparison across studies difficult.

Summary of risks and benefits to subjects:

There is a small risk of an adverse reaction to cannabis. However, participants will have the option to stop smoking whenever they choose.

Minor risks for all participants include:

- An adverse reaction to the cannabis, which can include commonly reported reactions such as decreased blood pressure, increased heart rate and/or increased anxiety.
- Coughing and/or throat irritation due to smoking cannabis or placebo cigarette.
- An adverse reaction to alcohol, which can include commonly reported reactions such as nausea, vomiting, slurred speech, and/or clumsiness.
- Small risk of bruising at the site where blood is drawn.
- Some participants may find driving the simulator system to be frustrating.
- Some participants may feel strange while driving the simulator system (experience “simulator sickness”). If this occurs they will be given a 5 minute rest period to recover and try again. If the participant continues to feel strange or “funny”, their participation will be concluded.

Justification for the route of administration, dosage, dosage regimen and treatment periods:

Cannabis administration. A single cannabis cigarette or a placebo cannabis cigarette (<0.1%THC) will be administered during Test Sessions at least 72 hours apart. The active cigarette represents a moderate dose of cannabis. According to the Health Canada document, Information for Health Care Professionals - Marihuana (available: <http://www.hc-sc.gc.ca/dhp-mps/marihuana/med/infoprof-eng.php>), a typical ‘joint’ contains between 0.5 and 1.0 g of cannabis plant material (average 750 mg), and between 1 and 30% THC (7.5 – 225 mg). The cigarettes we will be using will be of average size, and will therefore contain 750 mg of plant material. At 12.5% ± 2%, the cigarettes will contain approximately 79 – 109 mg THC (average 94 mg), which is a moderate dose. The cigarettes (placebo or cannabis) will be smoked in the Biobehavioural Addictions and Concurrent Disorders Research Laboratory (BACDRL) at CAMH, a dedicated reverse airflow room with external ventilation of expired smoke. Subjects

will be instructed to smoke as they usually do for a maximum of 10 minutes and told that they can stop smoking the cigarette if they are feeling ill or if they are achieving a high greater than they would normally experience. Cigarettes will be weighed before smoking, and remnants after smoking, in order to estimate the amount of cannabis consumed. Smoking is chosen as the route of administration for this study as this is the most common route of administration by recreational users of this drug.

Alcohol administration. Oral administration of an intoxicating dose of alcohol or placebo beverage will occur during Test Sessions at least 72 hours apart. Participants receiving the intoxicating dose of alcohol will receive approximately 1.5 g/L of body water to obtain a target breath alcohol concentration (BrAC) of .08%. This should be roughly equivalent to 3-5 standard drinks in an average woman weighing 66 kg and average man weighing 83 kg. The alcoholic beverage will be mixed in a 1:3 ratio of alcohol (vodka) to tonic water. The placebo beverage will contain tonic water and will include the same volume as the alcoholic beverage. Alcohol and placebo beverages will be divided into three equal portions. Each of the beverage portions will be capped and topped with a few mL of lemon-lime juice. Each of the placebo beverage portions will also have a minimal amount of vodka capped on top and on the rim of the glass to enhance alcohol cues. Participants will be asked to consume each beverage portion over a period of 5 minutes, for a total of 15 minutes.

This trial will be conducted in compliance with the protocol, GCP ICH Topic E6 and Canadian Food and Drug Regulations Division 5.

Trial Objectives and Purpose:

1: Examine the acute effects of a moderate dose of cannabis (12.5% THC) combined with an intoxicating amount of alcohol (BAC=.08%-0.1%) on driving simulator performance of young drivers aged 19-29 years. Driving performance, tests of cognition, verbal memory, and mood, as well as levels of THC and metabolites in biological fluids will be measured within 1 hour of acute cannabis and/or alcohol exposure in male and female drivers aged 19-29 years.

2: Explore the effects of driving history, driving attitudes, and individual difference measures (e.g., demographics, drug and alcohol use, etc.) on the acute effects of alcohol and cannabis on driving simulator performance of young drivers. Exploratory analyses will be undertaken to determine if the acute effects of cannabis and/or alcohol on the driving simulator task are influenced by these measures.

Trial Design

Primary and secondary endpoints measured during the trial:

Primary Outcome Measure:

- **Standard Deviation of Lateral Position.** The driving simulator will objectively measure driving behaviour during a number of pre-programmed driving scenarios.
Approximate Time Frame: Within 2 hours before alcohol-cannabis exposure and 45 minutes after alcohol exposure (conducted 4 times).

Secondary Outcome Measures:

- **Mean speed, standard deviation of speed, maximum speed, minimum time-to-collision, braking latency, number of collisions.** The driving simulator will objectively measure driving behaviour during a number of pre-programmed driving scenarios. *Approximate Time Frame: within 2 hours before alcohol-cannabis exposure and 45 minutes after alcohol exposure (conducted 4 times).*
- **Blood concentration for delta-9-tetrahydrocannabinol, carboxy-tetrahydrocannabinol, and 11-hydroxy-tetrahydrocannabinol.** *Approximate Time Frame: 2 hours before alcohol-cannabis exposure and 45 minutes after alcohol exposure (conducted 4 times).*
- **Breath alcohol reading.** *Approximate Time Frame: 2 hours before alcohol-cannabis exposure and 15, 30, 45 and 75 minutes after alcohol exposure, and then hourly until 5 hours after alcohol exposure (conducted 4 times).*
- **Vital signs.** Blood pressure, pulse, temperature, and respiration rate will be assessed. *Approximate Time Frame: 2 hours before alcohol-cannabis exposure and 15, 30, 45 and 75 minutes after alcohol exposure, and then hourly until 5 hours after alcohol exposure (conducted 4 times).*
- **Subjective alcohol and cannabis effects.** Visual analogue scales will be used to measure subjective pharmacodynamic effects. *Approximate Time Frame: 2 hours before alcohol-cannabis exposure and then 15, 30, 45 and 75 minutes after alcohol exposure, and then hourly until 5 hours after alcohol exposure (conducted 4 times).*
- **Cognitive testing.** Cognitive ability will be assessed using the Digit Symbol Substitution Test; Verbal Free Recall Task; Continuous Performance Test (CPT-X); Useful Field of View Test (UFOV); Grooved Pegboard Test. *Approximate Time Frame: 2 hours before alcohol-cannabis exposure and 75 minutes after alcohol exposure (conducted 4 times).*
- **Urine cannabinoids to creatinine ratio.** *Approximate Time Frame: 2 hours before alcohol-cannabis exposure and 5 hours after alcohol exposure (conducted 4 times).*

Study Design and Duration

This study will be a within-subject, double-blind, double-dummy, placebo-controlled, counterbalanced, randomized clinical trial assessing the impact of alcohol and cannabis, alone and combined, on driver behaviour. The four conditions are: 1) placebo alcohol and placebo cannabis; 2) intoxicating dose of alcohol and placebo cannabis; 3) placebo alcohol and active cannabis, and; 4) intoxicating dose of alcohol and active cannabis.

Participant recruitment will occur through research study posting/postcards, CAMH Research Registry, online sites such as Kijiji and Facebook, and advertisements placed in selected magazines and flyers in Toronto, in Toronto Transit Commission subways/streetcars/buses, and on drink coasters in eating and drinking establishments. In-person recruitment in the community will also be used. Males and females aged 19-29 years old will be included.

Participants will be pre-screened for eligibility by telephone or using the REDCap survey (see REDCap section). During pre-screening participants will be deemed eligible to come for Eligibility Assessment if they meet the inclusion criteria, and deemed ineligible to come for Eligibility Assessment if they report any of the exclusion criteria. The study will consist of an

Eligibility Assessment, a Practice, and 4 Test Sessions, each separated by at least 72 hours. Participants will be asked to refrain from personal use of alcohol for 48 hours before practice and before each test session and from personal use of cannabis for 72 hours before practice and before each test session. Participants will be asked to refrain from use of other drugs not required for medical reasons until their participation in the study is completed. They will be reminded to abstain at each visit and by email prior to visits. Eligibility Assessment and Practice can be completed at any time prior to the 4 Test Sessions.

In certain instances, the Qualified Investigator may ask a participant to return for re-screening, e.g. repeat of urine test or other assessments performed for eligibility assessment. Also, in case of unforeseen delays in scheduling study participation, the Qualified Investigator will determine if there is a need for a participant to repeat some assessments, e.g., physical examination.

Table 1 presents a schedule for biological sampling, assessments and driving trials for eligibility assessment, practice and test sessions.

Eligibility Assessment. Upon arrival at CAMH, study personnel will first verify participants' age and driver's licence status (having valid driver's licence of G2 or G for at least 12 months). The purpose of the study and details of the study procedures will be explained and potential participants will be given time to read the consent form. Study personnel will answer any questions participants might have and participants will be assured that they can withdraw from the study at any time without any consequences. Participants will then be asked to sign a consent form. Participants will be given a breathalyzer test to confirm that their BrAC is zero. To avoid enrolling subjects who have never used cannabis, a urine sample will be taken and point-of-care drug testing will be performed. The urine sample will be sent to the CAMH laboratory for confirmatory analysis. A timeline follow back (TLFB) for 3 months (cannabis) prior to the eligibility session will be administered to determine the pattern of cannabis use. To avoid enrolling subjects who have never before consumed a dose of alcohol similar to that administered in this study, when asked, subjects must self-report consuming a minimum number of drinks (5 for males, 4 for females) on at least one occasion in the last 6 months. Participants will undergo a medical assessment and will be screened for psychiatric disorders using the Structured Clinical Interview for DSM-IV axis I Disorders (SCID-I). All subjects with a psychiatric disorder warranting treatment will be excluded from the study and will be referred for psychiatric evaluation according to their individual needs. Females must use an approved method of birth control for the duration of the study. Urine will be collected for point-of-care pregnancy testing for females. Females who are determined to be pregnant or are breastfeeding will be excluded. Eligible participants will be instructed not to drive to CAMH for test sessions. Participants will be asked to refrain from alcohol use 48 hours before and from cannabis use 72 hours before practice and each test session. Participants will also be asked to refrain from use of all other drugs not required for medical reasons throughout the study, until their participation is completed. Much information on cannabis use characteristics will be collected including: age first started using cannabis, forms of cannabis used (i.e. smoked, oil, edibles), the dose (if known) and the strain used, the amount used per day, the number of days per week that cannabis is used, reason for using cannabis.

Practice. The session will commence with a breathalyzer test to confirm that the participant's BrAC is zero and a point-of-care urine test to rule out any drug use. A urine sample will be collected and sent to the clinical laboratory for semi-quantitative analysis of THC. THC will also be detected through saliva. Cognitive, psychomotor, self-report measures of mood and driver

behaviour will be collected. A TLFB (cannabis) for the past week will be administered. Participants will perform a practice driving simulation trial. If the practice driving trial induces simulation sickness symptoms, such as mild dizziness or nausea, the practice driving trial will be stopped and the participant will be given a 5-10 minute rest period to recover. Participants will be offered water and/or a snack if needed. They may withdraw from the study at this point if they wish. Simulator sickness is uncommon among young participants; therefore, we do not anticipate this to be a frequent occurrence. Participants will be given the opportunity to do the practice driving trial one more time. However, if they experience simulation sickness again they will not be allowed to continue with other measurements and their participation will be concluded. Participants will be reminded not to eat for 3 hours before each test session and not to drive to CAMH.

Test sessions. Participants will come to the lab for four test sessions. They will undergo one of these alcohol and cannabis exposure conditions: 1) placebo alcohol and placebo cannabis; 2) intoxicating dose of alcohol and placebo cannabis; 3) placebo alcohol and active cannabis, and; 4) intoxicating dose of alcohol and active cannabis. The order of these conditions will be randomly assigned. The alcohol and cannabis exposure sessions will be separated by at least 72 hours.

Alcohol and cannabis exposure sessions: The sessions will commence with a breathalyzer test to confirm that the participant's BrAC is zero and a point-of-care urine test to detect recent drug use. THC will also be detected through saliva. Participants will be asked when they last smoked tobacco and cannabis. The participant will be weighed, vital signs recorded, and urine collected for point-of-care pregnancy testing (females). The urine sample will be sent to the CAMH laboratory for THC semi-quantification. Urine THC semi-quantification will be repeated at 5 hours after Time 0. A blood sample will be collected to measure THC and its two major metabolites, 11-OH-THC and THCCOOH, at baseline and approximately 45 minutes after alcohol exposure is completed. Breathalyzer measurements will be made at approximately 15, 30, 45 and 75 minutes, and then hourly until 5 hours after alcohol exposure. A TLFB (cannabis) will be administered for the past week.

Before alcohol and cannabis exposure, participants will first complete a five-minute practice driving trial in order to assess whether participants experience any driving simulation sickness and this will be followed by a Driving Trial. Approximately 45 minutes after alcohol exposure participants will perform another Driving Trial. The point-of-care saliva test will be administered approximately 30 minutes following cannabis smoking for detection of THC; corresponding to immediately before administration of the post-drug-exposure Driving Trial. The saliva test will be administered again approximately 5 hours following drug exposure. The Standardized Field Sobriety Test (SFST)⁵⁹ will be administered approximately 75 minutes following alcohol exposure. Cognitive, psychomotor and mood effects measurements will be collected before alcohol and cannabis exposure and approximately 75 minutes following alcohol exposure. Questions designed to assess the participants' perceived driving ability and willingness to drive, and to determine the magnitude of placebo effects will be administered (see Table 1). Vital signs will be measured before alcohol and cannabis exposure and approximately 15, 30, 45 and 75 minutes, and then hourly until 5 hours after alcohol exposure. Subjective assessment of alcohol and cannabis effects will be measured using Visual Analog Scales (VAS) before alcohol and cannabis exposure and approximately 15, 30, 45 and 75 minutes, and then hourly after alcohol exposure. For the remainder of the day (until participants are sent home) they will be in the lounge where television, DVDs, and video games will be available. All participants will be offered a meal during the day, but will not be offered caffeinated beverages. Participants will not

be permitted to leave CAMH until 5 hours following alcohol exposure at which time a final urine sample will be collected for THC semi-quantification analysis. If participants' BrAC is still greater than 0.04% 5 hours following alcohol exposure, participants will be required to stay at CAMH until their BrAC has dropped below this level. Upon completion of the session participants will be provided with a taxi chit and study personnel will ensure that they get in the taxi to be taken home.

Determination of cannabis smoking from semi-quantification of THC in urine

All urine collected for semi-quantification of THC (from eligibility, practice, and test sessions) will be sent to the clinical lab. Not to break the blind, the profile of each person (labs and self-report) will be examined to determine whether additional cannabis was smoked between sessions. For this reason, as much information about dose and frequency of cannabis use will be collected at each visit.

Alcohol manipulation:

Participants will be taken into a unique laboratory barroom facility at CAMH, where they will undergo beverage administration procedures. These procedures will be based on methods used successfully in past experimental investigations involving acute alcohol consumption.⁶⁰⁻⁶⁸ Participants receiving the intoxicating dose of alcohol will be administered approximately 1.5 grams of alcohol per litre of body water to obtain a target BrAC of .08%. This should be roughly the equivalent of 3-5 standard drinks in an average woman weighing 66kg and average man weighing 83kg. The amount of body water will be determined using the equations outlined by Watson et al.⁶⁹ Alcohol will be provided in the form of a chilled beverage of 80-proof vodka mixed with tonic water in a 1:3 ratio. Participants receiving the placebo alcohol will be administered beverages containing chilled tonic water. One quarter of the total volume of the placebo beverage will be in the form of flat tonic water poured from a vodka bottle. The placebo alcohol group will receive a volume of beverage equivalent to what they would have received in the alcohol condition. All beverages will be capped with a few mL of lemon-lime juice with a minimal amount of vodka capped on top and on the rim of the glass to enhance alcohol cues. As well, all beverages will be divided into three equal portions, and participants will be asked to consume each portion over a period of 5 minutes, for a total of 15 minutes. This marks **Time 0**.

Immediately after finishing their third drink, participants will rinse their mouths with water, and approximately 15 minutes later, will complete a breathalyzer test to assess BrAC. Placebo alcohol participants will go through these same procedures in which the timing and frequency of BrAC tests will be yoked to corresponding alcohol condition participants. Once the alcohol manipulation has been completed, participants will be asked to complete Visual Analog Scales measuring subjective alcohol effects. Participants will then undergo the cannabis manipulation procedures.

Cannabis manipulation:

Cannabis (at a potency of 12.5% THC) will be obtained through Cannimed/Aurora, a licensed dealer approved by Health Canada. Placebo cigarettes (<0.1% THC) will be obtained from NIDA. Participants will be taken into a unique laboratory smoking facility (BACDRL) at CAMH, specially constructed with negative-pressure ventilation of expired smoke, where they will undergo cannabis administration procedures. The research personnel will observe the participant from another room (through one-way mirror). Participants will be instructed to smoke the cannabis until they achieve a high that they would normally experience (maximum 10

minutes). They will also be told that they may stop smoking the cigarette if they are feeling ill. Any cigarette remnants will be weighed in order to estimate the amount of THC consumed. Following the cannabis administration procedures, participants will complete Visual Analog Scales measuring subjective alcohol and cannabis effects.

Driver Simulator Testing.

The CAMH Virage VS500M simulator features the driver's side instrument cluster, steering wheel, controls, and centre console of a GM compact car. The steering wheel provides dynamic force feedback, as do the brake and accelerator pedals. The visual system consists of three 50-inch screens providing a 180° field of view in the front, and two 17-inch side displays providing visual feedback for the left and right blind zones.

Participants will receive a series of simulator training trials at the start of the study session. These practice simulations will allow the participant to become familiar with the simulated vehicle's steering, accelerator, and braking controls. The driving simulations to be used for main effects testing are comprised of a series of driving events designed to assess mechanisms by which alcohol/drug consumption may impact driver performance. Dependent measures of driver performance will be based on global performance throughout the entire simulation as well as event-specific performance, and will be measured precisely using the simulator software. Risk-taking behaviour will be assessed by measuring average speed throughout the simulation and in a straightaway section of road without other traffic, as well as examining the minimum distance (measured as time-to-collision) at which participants pass a slower moving vehicle with an oncoming vehicle approaching. Reaction time will be measured by brake pedal latency. Number of crashes across simulations will also be measured.

To better simulate the cognitive demand of real-world driving conditions, and to further assess participants' driving skill, one of the testing trials will be conducted under dual-task conditions. The secondary task will require participants to count backwards by threes as they drive, which has been validated as a distracting task in previous driving studies e.g.,^{70, 71}. To improve interpretation of performance, participants will also perform the counting task independent of driving for a two-minute period immediately after the driving while counting task.

All subjective measures have been sufficiently validated and are suitable for use in this study.

Physical Measurements

- 1) Breath sample for alcohol (BrAC)
- 2) Physical examination
- 3) Vital signs (temperature, pulse, blood pressure, respiration rate)
- 4) Blood samples to measure biochemistry and haematology (e.g., complete blood count (CBC), glucose, renal and liver function tests)
- 5) Blood sample to measure THC and metabolites quantification (THC-COOH and 11-OH-THC)
- 6) Urine sample for toxicology screening for drugs of abuse (point-of-care testing);
- 7) Urine sample for pregnancy testing (point-of-care testing);
- 8) Urine sample to measure cannabinoids (THC and metabolites) (immunoassay with semi-quantitative THC and THC metabolites normalized to creatinine). The lab may perform mass spectrometry analysis if the results of the semi-quantitative analysis need confirmation.
- 9) Saliva sample for detection of THC (point-of-care testing)

Behavioural Information

- 1) Psychiatric examination: Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)

- 2) Individual Difference measures (demographics, substance use, impaired driving, collisions)
- 3) Driver Behaviour Questionnaire^{72, 73} to assess driving errors, lapses, and violations
- 4) Driving Anger Scale – short form⁷⁴
- 5) Driving Anger Expression Inventory⁷⁵
- 6) Road Rage Victimization and Perpetration Questionnaire^{76, 77} to measure driver anger and aggression
- 7) Optimism Bias for Accident Risk and Driving Skill questionnaire⁷⁸ to assess driver confidence (including DUIC and DUA items)
- 8) K6 screening scale⁷⁹ to measure psychological distress
- 9) Brief Sensation Seeking Scale⁸⁰
- 10) Impulsivity Questionnaire⁸¹
- 11) Brief Comprehensive Effects of Alcohol Questionnaire^{82, 83} to assess anticipated effects of alcohol
- 12) Marijuana Effect Expectancy Questionnaire-Brief⁸⁴ to assess anticipated effects of cannabis
- 13) Timeline Follow Back (TLFB) for 3 months at eligibility assessment and for 7 days at each of the practice and test sessions. In the TLFB participants report their use of a substance each day for a number of days prior to the assessment. The TLFB has been shown to have good validity between self-report measures and those reported by collaterals. It has also been shown to have good reliability.

Cognitive/Psychomotor Tests

- 1) Digit Symbol Substitution Test (DSST⁸⁵) for cognitive function
- 2) Verbal Free Recall Task⁸⁶ for verbal learning and memory
- 3) Continuous Performance Test (CPT-X⁸⁷) for attention, vigilance and reaction time
- 4) Useful Field of View Test (UFOV⁸⁸) for visual processing speed, selective and divided attention
- 5) Grooved Pegboard⁸⁹ for physical dexterity
- 6) Standardized Field Sobriety Test (SFST)⁵⁹

Subjective Assessment for Cannabis and Alcohol Effects

- 1) Addiction Research Centre Inventory (ARCI) short form for effects of psychotropic drugs⁹⁰
- 2) Self-reports of alcohol and cannabis effects using Visual Analog Scales (VAS)
- 3) Profile of Mood States – short (POMS^{91, 92}) to measure general mood, including fatigue and vigour

Other

- 1) Placebo alcohol and cannabis effects questions
- 2) Perceived driving ability question
- 3) Willingness to drive under ‘normal’ circumstances question
- 4) Driving simulation tests (including audio recording of dual-task driving)
- 5) Observational recording of tobacco smoking frequency on testing days (if required). For participants who are tobacco smokers, the number of cigarettes smoked will be recorded.

Table 1: Schedule for biological sampling, assessments and driving simulation trials

	Eligibility Assessment	Practice	Test Sessions									
			alcohol exposure: Time 0		cannabis exposure							
Approximate Time pre/post alcohol exposure (Time 0)			-2 hr	-30 min	15 min	30 min	45 min	75 min	2, hr	3 hr	4 hr	5 hr
Driving Trial		x		x			x					
Breathalyzer	x	x	x		x	x	x	x	x	x	x	x
Physical Exam, Psychiatric Exam (SCID)	x											
Vital Signs	x		x		x	x	x	x	x	x	x	x
Urine: point-of-care drug screen	x	x	x									
Urine: immunoassay with semi-quantitative THC and THC metabolites normalized to creatinine	x	x	x									x
Urine: point-of-care pregnancy test	x		x									
Blood: Biochemistry, Hematology	x											
Blood: THC and metabolites quantification ^a			x				x					
Behavioural Information ^c		x										
Cognitive/Psychomotor ^d , ARCI ^e , POMS ^f		x	x					x				
VAS ^g		x	x		x	x	x	x	x	x	x	x
Saliva: point-of-care THC test		x	x				x					x
Standardized Field Sobriety Test (SFST)								x				
Placebo questions												x
Driving willingness							x					x
Timeline Follow Back	x ^h	x ⁱ	x ⁱ									
Perceived driving ability				x			x					x
Reminder to refrain from driving for 24 hours												x

Notes:

Time 0 in the table is completion of the alcohol exposure procedure.

Cannabis exposure begins 15 minutes following alcohol exposure completion (Time 0).

^a THC-COOH and 11-OH-THC

^c Individual difference measures (demographics, substance use, impaired driving, collisions); Driver Behaviour Questionnaire^{72, 73}, Driving Anger Scale – short form⁷⁴; Driving Anger Expression Inventory⁷⁵, Road Rage Victimization and Perpetration Questionnaire^{76, 77}; Optimism Bias for Accident Risk and Driving Skill questionnaire⁷⁸; K6 screening scale⁷⁹; Brief Sensation Seeking Scale⁸⁰; Impulsivity Questionnaire⁸¹; MEEQ; CEA

^d Digit Symbol Substitution Test⁸⁵, Verbal Free Recall Task⁸⁶, Continuous Performance Test⁸⁷; Useful Field of View Test⁸⁸, Grooved Pegboard⁸⁹

^e Addiction Research Centre Inventory⁹⁰

^f Profile of Mood States – short^{91, 92}

^g Visual Analog Scales to measure subjective alcohol and cannabis effects

^h For the past 3 months

ⁱ For the past week

Randomization:

The CAMH Research Pharmacy will maintain randomization codes for study participants. The randomization codes are recorded on slips that bear the participant ID# and randomization group. The slips are individually placed in envelopes and envelopes bear a label with the following information: Study Title, REB #, Participant ID#, Emergency Contact, Emergency Contact Number, and the statement “Open envelope to unblind study drug assignment only in the event of an emergency with the research participant”.

Unblinding:

In the instance of a medical emergency, the QI will determine whether unblinding is required to ensure appropriate medical care is rendered. If unblinding is required, procedures outlined in study specific SOP # DRIV2, Alcohol-Cannabis and Driving Study – Medical Emergencies and Unblinding Procedures Version 1.0, will be followed. The PI will ask to be unblinded in order to conduct interim analyses approximately midway through the study.

Pilot Testing

A pilot testing phase will be undertaken in order to determine if changes to the study protocol need to be made due to practical/logistical considerations. Five (5) participants will be recruited for the pilot phase and will participate in all study procedures as outlined in this document.

Subsequent to analysis of our pilot data, it was determined that there were some irregularities in levels of THC in blood; some participants did not show an increase in blood THC after smoking cannabis. Analysis of the cigarette remnants revealed that the cigarettes were indeed positive for cannabis and analysis of heart rate revealed no increase suggesting minimal inhalation of THC. To further ensure that all of our processes in place are working properly, we would like to unblind after 3-4 subsequent participants to allow us to analyse the levels of THC in blood.

To unblind, the Pharmacy will send the unblinding information directly to one study staff (likely Dr. Di Ciano) who will be unblinded to compile the data. The clinical lab will remain blinded, and all other study staff directly involved with the participants will remain blinded. The unblinding code will remain confidential (not accessible to other staff). The QI and PI may be unblinded, but they do not have regular contact with study participants so this will not compromise the integrity of the study.

Selection and Withdrawal of Subjects

Inclusion criteria.

- Use of cannabis at least once a week, confirmed by urine point-of-care testing;
- Males who report consuming at least 5 drinks and females who report consuming at least 4 drinks in about 2 hours in the past 6 months and at least one episode of rapid alcohol consumption in the past 6 months (3 or more drinks over a span of one hour)
- 19-29 years of age;
- Holds a class G or G2 Ontario driver's licence (or equivalent from another jurisdiction) for at least 12 months;

- Willing to abstain from using alcohol for 48 hours and cannabis for 72 hours prior to Practice and Test Sessions.
- Willing to abstain from all other drugs not prescribed for medical purposes for the duration of the study;
- Provides written and informed consent.

Exclusion criteria.

- Urine toxicology screens negative for cannabis upon eligibility assessment;
- Diagnosis of severe medical or psychiatric conditions;
- Females: Pregnancy or breastfeeding;
- Meets criteria for Alcohol or Substance Dependence (current or lifetime) (DSM-IV);
- Is a regular user of medications that affect brain function (i.e., antidepressants, benzodiazepines, stimulants);
- Taking medications or have any medical condition for which alcohol is contraindicated;
- First-degree relative diagnosed with schizophrenia;
- Severe allergy to citrus (lemon-lime).

Individuals will also be excluded if at the beginning of any Test Session:

- A breathalyzer test for alcohol is positive;
- A drug toxicology screen indicates the presence of a psychoactive substance, except for cannabis ;
- Females: pregnancy test is positive.
- Saliva test indicates use of cannabis

Maintenance of ongoing eligibility: Due to the detection windows of THC in saliva (6-14 hours) or urine (up to 7 days), both saliva and urine will be collected to determine ongoing eligibility and compliance with the 72 hours abstinence from use of cannabis. At the Practice and Test Sessions, if saliva is positive for THC, participants will be withdrawn or re-scheduled. If urine is negative or positive, they will still be considered eligible and the urine will be sent to the clinical lab for semi-quantification to allow for the post hoc determination of eligibility along with the TLFB.

Subject Withdrawal Criteria and Procedures:

- a) When and how to withdraw subjects: Subjects may be withdrawn from the study at any time by study staff should ongoing exclusion criteria be met or safety concerns exist. For example:
 - Positive breath test for alcohol
 - Positive drug toxicology screen, except for cannabis
 - Positive pregnancy test
 - Simulator sickness
 - Positive saliva test for THC
- b) Type and timing of the data to be collected for withdrawn subjects: No additional data will be collected from withdrawn subjects.
- c) Whether and how subjects will be replaced: Withdrawn subjects will be replaced using approved study recruitment procedures.

Procedures for monitoring subject compliance with respect to drug use: Abstinence from additional psychoactive drug use will be monitored between testing days by point-of-care testing. Use of non-study cannabis will be confirmed by measuring the ratio of THC and metabolites in the urine. The lab may perform mass spectrometry analysis if the results of the semi-quantitative analysis need confirmation.

Treatment of Subjects

During test sessions participants will be randomized to one of four experimental conditions: 1) placebo alcohol and placebo cannabis; 2) intoxicating dose of alcohol and placebo cannabis; 3) placebo alcohol and active cannabis, and; 4) intoxicating dose of alcohol and active cannabis.

Participants will be given a cannabis cigarette, 750 mg (active $12.5\% \pm 2\%$ THC or placebo $<0.1\%$ THC) in each test session. Participants receiving the active cannabis cigarette will receive a maximum of 79-109 mg THC. All subjects will be instructed to smoke as they usually do for a maximum of 10 minutes and told that they can stop smoking the cigarette if they are feeling ill or if they are achieving a high greater than they would normally experience. Any cigarette remnants will be measured in order to estimate dosage.

Participants will be given a beverage containing an intoxicating dose of alcohol (approximately 1.5 grams of alcohol per litre of body water to obtain a target BrAC of .08%; roughly the equivalent of 3-5 standard drinks in an average woman weighing 66 kg and average man weighing 83 kg) or placebo in each of the test sessions. The amount of body water will be determined using the equations outlined by Watson et al.⁷⁰.

The alcoholic beverage will be mixed in a 1:3 ratio of alcohol (vodka) to tonic water. The placebo beverage will contain only tonic water and will include the same volume as the alcoholic beverage. All the beverages will be capped and topped with a few mL of lemon-lime juice. The placebo beverage will also be capped with a minimal amount of vodka on top and on the rim of the glass. All beverages will be chilled prior to administration. All beverages will be divided into three equal portions, and participants will be asked to consume each portion over a period of 5 minutes, for a total of 15 minutes. Approximately three minutes after completing their last drink, all participants will be asked to rinse their mouths with water.

The follow-up period for all participants in this double-blind study will continue until the end of the fourth test session, after which testing is completed. Participants will be provided with a wallet card listing a pager number for the Qualified Investigator, should they experience any negative effects. They are free to access this number beyond the study testing follow-up period.

Concomitant Medications:

Identification of medications that specifically interact with cannabis is a largely unexplored area of research, and appropriate rescue medications have not been identified. However, during screening, individuals will be asked about any medical conditions that require use of medications with psychoactive properties (e.g., ADHD medication). Individuals taking such medications may be excluded by the Qualified Investigator.

Procedures for monitoring subject compliance:

Due to the fact that some of the cannabinoid measures cannot be obtained quickly, data from participants that have used additional cannabis during the study will be excluded from the final data analysis.

The expectation is that no additional cannabis or additional alcohol will be used for 72 hours prior to each alcohol-cannabis exposure session, and therefore it is expected that only the administration of active cannabis will result in a significant increase of the cannabinoid to creatinine ratio following cannabis administration. Levels of THC in the urine will be monitored throughout the study and a determination made, based on these values, as to whether a participant was compliant during the study. This will help determination of eligibility in addition to saliva tests. For those that are deemed non-compliant, data will not be entered into the final analysis.

The quantification of blood for THC and its two major metabolites (11-OH-THC and THC-COOH) involves purification by solid phase extraction followed by derivatization and analysis by mass spectrometry. Samples will be stored frozen at -20° C. and in plastic cryotubes. Periodically, the batch of samples will be forwarded to the CAMH clinical laboratories for analysis. Upon receipt of samples, the clinical lab will store the samples at -80° C after test is completed. Internal standards used are the deuterated compounds for each analyte.

Assessment of Safety

Safety parameters:

The Qualified Investigator is responsible for ensuring subject safety and will report serious adverse events to the CAMH REB. Regular meetings will be held with the research team to assess and identify problems and potential solutions, and measures will be taken to ensure safety.

Several issues require special consideration.

- 1) There is the risk of enrolling a participant who has never used cannabis into the study. In order to minimize this risk, a urine sample will be taken on the Eligibility Assessment and analyzed for the presence of THC and/or THC metabolites. The lab may perform mass spectrometry analysis if the results of the semi-quantitative analysis need confirmation. Any individual with a urine screen negative for cannabinoids will not be enrolled into the study.
- 2) In order to minimize the risk of exposing a participant who has never experienced an episode of heavy drinking, only participants who report consumption of at least one heavy drinking episode (according to NIAAA criteria of 5 drinks for males and 4 for females within an occasion) in the 6 months prior to eligibility assessment will be included. As well, we will not include any participants who have not had one episode of rapid alcohol consumption in the preceding 6 months (3 or more drinks over a span of one hour). This criterion is used to ensure that we recruit drinkers who have achieved a peak target BrAC level used in this study (.08%-0.1%).
- 3) There is a risk of residual effects of alcohol and/or cannabis at the end of test sessions. Participants will be instructed not to drive to CAMH for any of the test sessions. Public

transit tokens will be provided for transportation to CAMH. Taxi chits will be provided at the end of test sessions for participants' return home.

Methods and timing for assessing, recording, and analyzing safety parameters:

Participants will be monitored for any side effects or adverse effects using study SAFTEE guidelines from the time they attend the first test session until the final study visit. Side effects will be recorded on a SAFTEE Log. Adverse events will be recorded on an Adverse Event Log. The Qualified Investigator will be consulted by the medical professional delegated to provide medical monitoring of participants to make a determination on the reasonable causal relationship to the study intervention or investigational product and the seriousness of the event. Study personnel will follow the guidelines as outlined in CAMH Standard Operation Procedures (SOPs): SOP # HSR 205, Identifying, Documenting, Reporting and Managing Adverse Events in Health Canada Regulated Human Subject Research and SOP # HSR 207, Serious Adverse Event Reporting.

Procedures for eliciting reports of and for recording and reporting adverse events:

In the event of an adverse reaction to cannabis, medical staff will be called to intervene and supportive care given, as appropriate. Where the case is deemed a Serious Adverse Event (SAE), whether related to the study drug or not, the Principal Investigator and Qualified Investigator will notify the REBs (CAMH and Health Canada). A SAE Form will be sent to the REBs. Only SAEs will be reported to the REBs (CAMH and Health Canada); however, every adverse event will be assessed and recorded in the subject's file by the Qualified Investigator or another physician involved in the study. The Qualified Investigator will report all Serious and Unexpected Adverse Drug Reactions (SUADR) to Health Canada as per Division 5 regulations.

Type and duration of the follow-up of subjects after adverse event:

The Qualified Investigator is responsible for determining the duration of follow-up required for any adverse event dependent on the seriousness of the event.

Statistics

Descriptive statistics, simple bivariate tests, repeated measures analyses of variance (ANOVA) and covariance (ANCOVA, including potentially important covariates such as gender, body weight, driving experience, and substance use history), and multivariate analyses of variance (MANOVA) tests will be used to assess acute drug effects. Analyses of drug effects will be performed with ANOVAs, ANCOVAs and MANOVAs. 2 (alcohol vs. placebo) X 2 (cannabis vs. placebo) X 4 (test sessions) ANOVAs and ANCOVAs will be conducted comparing post-baseline driving simulator measures, particularly the average speed measure. Subsequently, MANOVAs will be conducted including all simulator measures for more comprehensive analyses. A similar analytic strategy will be applied to mood and cognition measures. Post-hoc tests will be used to identify significant mean differences. Measures of Breath Alcohol Content and serum THC will be reported for descriptive purposes and may be used as covariates.

Level of statistical significance to be used in statistical analysis: $p < .05$

Number of subjects planned to be enrolled:

Seventy participants will be recruited, in order to achieve the **target sample of 50** participants. This sample size will provide power of .89 to detect a medium effect size (in Cohen's⁹³ terminology) in a two-tailed *F*-test of a within-subjects main effect of one drug following drug administration. It will also provide power >.90 to detect a significant interaction with a medium effect size. We also note that this sample size is similar to or larger than those in most other studies of the individual and combined impact of alcohol and cannabis on simulator performance and residual effects e.g.,^{31, 32}.

Criteria for termination of the trial:

If after 3 years the study is unable to recruit the desired target sample we will consider termination of the trial or seek continuation for a period of time to increase the sample.

We recently analyzed data from a driving study (REB# 125/2011) on the effects of cannabis on simulated driving. With that data, we conducted a power analysis to determine the minimal number of participants needed to obtain a significant effect. Assuming 80% power, with an alpha of 0.05, it was determined that 16 participants are required to see a significant decrease in speed after smoking a 12.5% THC cannabis cigarette. Speed was chosen as the variable of interest, because it is a robust variable, and many reports have found decreased speed after smoking cannabis (see Background section).

In view of this, we would like to unblind this study after collecting data from 20 participants. The purpose of this would be to determine if significant effects are obtained, which would warrant stopping the trial. If, after unblinding, the decision to continue is made, we will then conduct further sample size calculations and subsequently unblind again after completing more participants. The subsequent number of participants would be dependent on the results of the sample size calculations.

Publication of the data

Upon completion of data collection in January 2020, inspection of the data revealed to the Investigators that the data from this study may be better communicated as a series of publications. These publications will, as a whole, include all of the data and cover several themes.

- 1) Main driving paper: The flagship manuscript will include all of the driving variables, as well as the blood results (THC and metabolites), VAS, subjective measures and physiological measures. This paper will highlight the additive effects of combining alcohol and cannabis on driving. This paper builds on our stated objectives and falls within the scope of the present protocol.
- 2) Cognition: The effects of alcohol and/or cannabis on cognition is a stated outcome of the present protocol and therefore this manuscript falls within the present protocol.
- 3) Sex differences: There is increasing interest in the Scientific community in understanding the contribution of sex to health-related outcomes. This is now an explicit stated objective of the CIHR, the funding body that has provided support for this study. The emphasis on sex differences has emerged largely in the past couple of years and has come about mostly after the present protocol was prepared. We are now analyzing the data and it

appears that we may be able to publish 1-3 papers on sex differences. One paper would look at differences between males and females in subjective and physiological variables. The other paper would look at sex differences in driving and the third paper would look at sex differences in cognition. While we are fairly confident that our data supports the first mentioned manuscript, we are currently exploring the possibility of the second and third papers. It will be decided if the findings are robust enough to warrant these additional papers.

- 4) Standardized Field Sobriety Tests (SFSTs): Since writing this protocol we received funding from the Ministry of Transportation Ontario (MTO) to explore the effects of cannabis and/or alcohol on SFST. MTO has also provided the funds to determine whether certain saliva tests are sensitive enough to detect impairment. The SFST and saliva tests were added to the present protocol in an amendment. We are currently analyzing that data to determine whether it is possible to publish.
- 5) Equivalencies between alcohol and cannabis: Roadside testing for impairment employs fairly validated techniques for the detection of breath alcohol levels. For alcohol, it is known that 0.05% or 0.08% breath alcohol levels produce significant impairment in driving. By comparison, the relationship of impairment to THC levels in blood is not as well characterized. There is considerable interest in determining the blood levels of THC that produce the same level of impairment as the standard roadside cut-offs of 0.05% or 0.08% for breath alcohol. In this paper, we will use statistical methods to equate breath alcohol levels with blood THC levels for different degrees of impaired driving.
- 6) Dose-response of cannabis on driving: This next paper will use predictive modelling to determine the effect of dose of cannabis on driving. Our participants all smoked different amounts of cannabis and it is possible to use mathematical models to estimate peak THC levels in blood after smoking cannabis. THC levels in blood can then be related to changes in driving.

Procedure for accounting for missing, unused, and spurious data:

In the final report the procedures used to deal with missing, unused or spurious data in statistical analyses will be described.

Procedures for reporting deviations from the original statistical plan:

Any deviation from the planned statistical analyses will be described in the final report.

Direct Access to Source data/documents

The PI and QI will permit trial-related monitoring, audits, REB review, and regulatory inspections, by providing direct access to source data/documents. This is outlined in the study information and informed consent form. Monitoring will be conducted according to the study monitoring plan.

Ethics:

Prior to commencing the study, study documents will be submitted to the CAMH and Health Canada Research Ethics Boards for approval.

The ethical implications of conducting alcohol, cannabis, and driving research in young people have been extensively considered by the research team. Safety parameters are in place to minimize the risk to participants to the greatest degree possible. For example:

- The identity of all participants and their status as cannabis users are kept confidential.
- A driving simulator is used to eliminate the risk of exposing participants to real dangers in traffic.
- Taxi chits and/or public transit tokens are provided for transportation to and from study testing sessions. Participants are instructed not to drive before and after each testing session until participation is completed.
- To avoid exposing young people to a controlled substance for the first time, a urine drug screen for cannabinoids must be positive prior to enrollment.
- To avoid the possibility of precipitating a first psychotic episode in a cannabis user, we exclude individuals who have a family history of schizophrenia.
- To avoid exposing young people to an intoxicating level of alcohol for the first time, males who have not consumed at least 5 drinks and females who have not consumed at least 4 drinks on at least one occasion in the past 6 months are excluded from the study.
- To avoid exposing participants to rapid alcohol consumption to achieve intoxication for the first time, participants will only be recruited if they report having consumed 3 or more drinks over a span of one hour at least once in the preceding 6 months.
- Individuals with a history of substance dependence (including cannabis and alcohol dependence) are excluded from the study.

Active and placebo investigational products used in this study are to be obtained through Cannimed/Aurora or NIDA. Upon expiry of the current exemption to hold cannabis, the Sponsor, QI or PI will apply for a license to hold cannabis, consistent with current regulations (using the CTLS system if necessary).

Data handling and record keeping:

Participants will be given a unique identifier number, and only this number will be present on questionnaires and blood and urine samples. Participants will not be identified by name in any data collection documents, analysis of the data, or in any presentation or publication resulting from the analysis of these data. Only the research staff directly involved in the study will have access to individually identifiable private information about human subjects.

The CAMH clinical laboratory will perform analyses of blood and urine samples during study sessions, and each measurement will be faxed to the Qualified Investigator. Any study specific documents generated by the lab will be transferred to the Qualified Investigator at the end of the study to ensure they are retained for the required 25 year period.

Recruitment data will be maintained in a locked cabinet in an office located at CAMH. Access to such information will be restricted to key project personnel. At the end of the recruitment process, eligible subject files will be separated from those failing to meet eligibility criteria. Records of ineligible recruitment subjects will be anonymized. Any computerized data will be password protected and stored on a secure server at CAMH. Data transfer and storage procedures will be in strict accordance with REB guidelines (e.g., driving simulation data will be copied to USB memory drives or external hard drives with encryption capabilities, and transferred to a password-protected folder on a secure server at CAMH). In accordance with Health Canada regulations, files will be maintained for a 25 year period.

Source data:

Data collected on participants during each study session include electronic data files (captured on laptop computers and the driving simulator computer) and questionnaires completed on paper by participants and data collected by study personnel on data collection tools developed for study purposes. Side effects will be recorded on a SAFTEE Log. Adverse events will be recorded on an Adverse Event Log. Serious Adverse Events will be recorded on the SAE Log. The Vital Signs Sheet (source document) will serve as a CRF.

REDCap will be used as an electronic data capture tool for some questionnaires and cognitive tasks. REDCap will also be used as a survey for recruitment purposes. For recruitment, the survey will be a stand alone site where participants will answer preliminary questions to determine eligibility. To gain access to the survey, participants will respond to our advertisement by email or telephone. Staff will reply to them with a unique Study ID that the participant will use to gain access to the survey. .

Transcription from source data to case report forms:

Case report forms (CRFs) developed for the study will ensure that essential endpoint data collected in Excel will be transcribed for each participant. Where not indicated below, all data is collected directly onto hardcopy, REDCap or is in a form that allows for a full audit trail.

Information to be transcribed onto CRFs on REDCap include:

Driving trial overall performance measures (Standard Deviation of Lateral Position, Mean Speed, Standard Deviation of Speed, Maximum Speed, Total Collisions) and Zone/Hazard performance measures (Standard Deviation of Lateral Position, Mean Speed, Standard Deviation of Speed, Maximum Speed, Minimum Time-To-Collision when passing slow moving vehicle, and braking latency).

Financing and insurance

The study is funded by the Canadian Institutes of Health Research (CIHR). This study is performed under usual arrangements for studies that are conducted at CAMH. No specific insurance has been taken.

Publication policy

Scientific publications of study data will be sought in peer reviewed journals and authorship will be in accordance with journal policies.

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