The Acute and Residual Effects of Cannabis on Driving

and

The Risk of Collision for People Who Drive After Using Alcohol and Drive After Using Cannabis

by

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A thesis submitted in conformity with the requirements for the degree of Master’s of Pharmacology

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Abstract

Although the impairing effects produced by alcohol and their direct effect on the driving task have been well defined for decades, similar information on the effects of Δ⁹-tetrahydrocannabinol (THC) following cannabis use in relation to driving skill is lacking. A combination of experimental and epidemiological studies is presented that examine the effects of THC on driving and collision risk. Preliminary data from a driving simulation study explores how THC impairs driving ability both acutely and residually and consideration is given to the challenges faced when conducting this type of research. Epidemiological data from a population-level survey demonstrate that the self-reported concurrent behaviours of driving under the influence of alcohol (DUIA) and driving under the influence of cannabis (DUIC) impart an increased risk of past-year collision more than 3 times greater than reporting driving after using a single substance, or not driving following substance use.
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Chapter 1

Introduction

1.1 Statement of the Problem

Motor vehicle collisions are a significant public health concern. In 2010, motor vehicle collisions resulted in 2,227 fatalities and another 11,226 serious injuries in Canada alone (Transport Canada, 2012). Driving a motor vehicle is a complex task requiring aspects of physical and behavioural control, and the ability to integrate and process information quickly and accurately from the surrounding environment (Verster and Roth, 2012). Although research over the last 40 years has demonstrated that alcohol impairs these faculties and is a significant contributor to fatal motor vehicle collisions, little is known about how other drugs affect driving skills. Cannabis is the most commonly used illicit drug in Canada, with nearly 40% of the population aged 15 and older having at least tried it within their lifetime and 9.1% of Canadians reporting current (past year) use (Health Canada, 2012). Population-level surveys and traffic violation data show that some people use cannabis before driving (Ialomiteanu et al., 2012; Perrault, 2013). Little evidence exists to assess for how long THC may impair driving capability following use. Furthermore, in Canada, the demographic reporting the greatest prevalence of this behaviour are young drivers under the age of 25 (Asbridge et al., 2005; Ialomiteanu et al., 2012), a group of drivers who may still be acquiring driving skill and experience. Little else is known about people who drive after using cannabis in Ontario. Driving after cannabis use may represent a serious risk to public safety and suggests the need for more research investigating the effects of cannabis on driving skill and risk of collision. Such knowledge is required to inform the creation and direction of public health education campaigns, as well as future legislation, that can deter and prevent these behaviours in Canada.
1.2 Purpose and Objectives

The present study is divided into two subsections – Part A and Part B. Part A represents an experimental study examining the acute and residual effects of smoked cannabis on the driving-related skills of young drivers using a state-of-the-art driving simulator. Part B examines the demographic characteristics of the population of individuals who self-report driving under the influence of cannabis (DUIC) in Ontario, using data from the Centre for Addiction and Mental Health (CAMH) Monitor. Also using this data, the impact of self-reported driving under the influence of alcohol (DUIA) and DUIC on the risk of being involved in a collision is assessed.

1.2.1 Rationale and Hypothesis

1.2.1.1 Part A

With recent advances in technology, driving simulator studies have become a popular means of assessing the impact of driving under the influence of drugs while minimizing the safety risk posed to participants and researchers. Laboratory-based research examining how cannabis affects the driving task is in its infancy. Furthermore, there is little evidence to assess for how long cannabis impairs driving ability. Preliminary research using flight simulators has found evidence of impairment for as long as 24 hours after smoking cannabis (e.g. Leirer et al., 1991; Pope et al., 1995; Yesavage et al., 1985). No studies to date have examined whether driving impairment exists beyond this time frame.

1.2.1.1.1 Objectives

Primary Objective: To examine the acute effects of a moderate dose of cannabis (12.5% THC) on the driving simulator performance of young drivers. Simulated driving performance, tests of cognition, verbal memory, and mood will be measured concurrently with levels of cannabinoids in biological fluids before and after drug administration in male and female drivers aged 19 to 25 years.
Cannabinoids in biological fluids will be measured over a 6-hour period following drug exposure. The relationship of cannabinoid levels to performance measures will be examined in this time frame.

Secondary Objective: To examine the residual effects of a moderate dose of cannabis (12.5% THC) on driving simulator performance of young drivers. Simulated driving performance, tests of cognition, verbal memory, and mood will be measured concurrently with levels of cannabinoids in biological fluids at 24 and 48 hours following acute drug exposure in male and female drivers aged 19 to 25.

1.2.1.1.2 Hypothesis

Cannabis-induced impairment of the driving task will be detectable after smoking, and persist at 24 and 48 hours after a single dose of a 12.5% THC cannabis cigarette.

1.2.1.2 Part B

It is well known that the risk of being involved in a motor vehicle collision increases when driving after drinking (Borkenstein et al., 1964; Movig et al., 2004). Similarly, there is evidence of an increased risk of collision associated with driving following the use of cannabis (e.g. Asbridge et al., 2012; Ramaekers et al., 2004). Little is known about the demographic characteristics of people who self-report DUIC in Ontario. However, it is known that some people who report DUIA also report engaging in DUIC (Ialomiteanu et al., 2012). To date, no population-level survey data exist concerning the risk of collision involvement for drivers who self-report both DUIA and DUIC.

1.2.1.2.1 Objective

The objective of the current report is to describe the demographic characteristics of people who report DUIC in Ontario, and to determine the risk of past-year collision for people who self-report engaging in both DUIA and DUIC.
1.2.1.2.2 Hypothesis

Although a description of the demographic characteristics of people who report DUIC is exploratory, it is expected that people who report both driving under the influence of cannabis and driving under the influence of alcohol will be at a greater risk for involvement in a collision in the past year than people who report only one of these behaviours.

1.3 Review of the Literature

1.3.1 Cannabis use in Canada

While once associated with deviant lifestyles, cannabis has gained significant social acceptance and popularity in Canada over the last 50 years (Duff et al., 2012). Today, nearly 40% of the adult population reports having used cannabis within their lifetime (Health Canada, 2012). Although cannabis remains a controlled substance in Canada, recent developments in other nations that are taking different approaches to the drug have triggered renewed discussion of the issue at home (Tencer, 2013). Decriminalization has been a popular strategy in other jurisdictions as it maintains the status of the drug as illegal, but removes legal consequences from the possession of small amounts (although often replaced by fines or ticketing). Cannabis has been decriminalized in the Netherlands since 1976 (MacCoun et al., 1997), and in 2013, Vermont became the 17th state to decriminalize possession of small amounts of cannabis in the United States (The New York Times, 2013). In November 2012, Colorado and Washington made the unprecedented move of legalizing the recreational use of cannabis (National Post, 2012). Legalization of cannabis takes decriminalization a step further by allowing for the legal growth, sale, and distribution of the drug. In August 2013, Uruguay’s House of Representatives passed a Bill to legalize cannabis, which, if passed by the Senate, would make Uruguay the first country in which cannabis is fully legal (British Broadcasting Corporation, 2013). Cannabis policy has been a candidate for legislative reform in Canada since the 1960’s (Solomon et al., 1983), and these recent developments south of the border have reignited interest in this debate by Canadians (Tencer, 2013).
The purpose of public policy prohibiting the recreational use of cannabis is twofold – to minimize both the safety hazards and the social costs incurred by use of the drug (Single, 1989). Cannabis became illegal in Canada in 1923, though a formal assessment of the safety hazards and social costs associated with its use was not available to guide this decision at the time (Parliament of Canada, 2002). Today, cannabis is a popular drug despite its illegal status, and laws prohibiting cannabis possession have been an ineffective means for deterring use (Soloman et al., 1983). In 2010, 9.1% of Canadians report past-year use of the drug (Health Canada, 2012), compared to just 1% in the early 1970’s (Rootman, 1979). Legal access to cannabis for specific medical purposes was introduced with the Marihuana Medical Access Program (MMAP) by Health Canada in 2001; however, the general legal status of cannabis has not changed since 1923, despite various formal challenges to the law. For example, the most recent challenge, Bill C-38 (2003) sought to decriminalize the possession of small amounts (< 30 g) of cannabis (Hyshka, 2009), making this offence punishable by ticket only. This initiative lacked the necessary parliamentary support, however, and was discarded with the election of a new government in 2006 (Brochu et al., 2011). Nevertheless, the abandonment of this discussion in parliament has not rendered the conversation regarding the legal status of cannabis mute; most recently, the Liberal Party of Canada has included the legalization of cannabis as part of its platform in preparation for the next federal election (Liberal Party of Canada, 2013).

Advocates of legalization highlight that the federal government spends millions of dollars each year enforcing cannabis-related laws that are not only ineffective, but are also poorly understood by the public (Erickson and Murray, 1986). Over the years, cannabis use has become increasingly normalized in Canadian society (Duff et al., 2012), to the extent that a 2004 Toronto-based survey found that 10% of respondents believed cannabis to be currently legal (Hathaway et al., 2007). As such, those in support of legalization or decriminalization also argue that the penalties associated with prohibition of cannabis are disproportionate to the crime, and actively harm society through being a wasteful economic burden. It has been estimated that approximately $300 million dollars are spent each year in Canada to enforce cannabis-related laws (Parliament of Canada, 2002). Furthermore, proponents of legalization or decriminalization argue that when compared to legal recreational drugs (alcohol and tobacco), cannabis is not associated with a comparable degree of morbidity and mortality (Fischer et al., 2009), and should therefore not be subject to stricter control than these substances.
Supporters of the current paradigm, on the other hand, assert that prohibitive laws should be maintained because cannabis is not a harmless drug (Kopala, 2007). Many arguments opposing legalization and/or decriminalization are guided by an anticipated increase in cannabis use and availability, thus leading to a subsequent increase in use-related harms. Cannabis shares properties with other addictive substances and can produce dependence in an estimated 9% of all users (Hall and Degenhardt, 2009). Particular concern for young people is expressed, as this rate may be even higher among young cannabis users. In a study of young cannabis users aged 14 through 24 years, 11% met at least three DSM-IV criteria for cannabis dependence, and 35% met at least one criterion (Nocon et al., 2005). As a result, opponents of legalization argue that any perceived savings from cannabis-related law enforcement would be eclipsed by the costs of cannabis-related social, economic, and healthcare expenses (Joffe and Yancy, 2004). Colorado and Washington will be the first opportunity to directly examine whether an increase in use and related harms can be observed as a result of legalization. Today, evidence is mixed as to whether any change in legal status would prompt an increase in use (Joffe and Yancy, 2004). Surveys conducted in states or other countries where cannabis has been decriminalized have found some evidence that use of the drug is higher (Chaloupka et al., 1999; MacCoun and Reuter, 1997), but this is not a universal finding (Johnston et al., 1981; McGeorge and Aitkens, 1997).

The potential for an increased incidence of driving after cannabis use following any change in legal status is of particular concern. Attitudes already exist, particularly among young drivers, that driving under the influence of cannabis is a relatively harmless activity (Fischer et al., 2006; Terry and Wright, 2005). If cannabis follows the model set by alcohol in terms of regulation and government control, scientific study of how cannabis impairs the driving task is necessary in order to inform legislation to control DUIC. For example, per se limits for $\Delta^9$-tetrahydrocannabinol (THC, the main psychoactive constituent of cannabis) in blood would be a desirable tool to enforce DUIC. However, knowledge of how THC impairs the driving task is still in its infancy, and scientific studies that could inform evidence-based laws are scant.
1.3.2 Driving and Driving Simulation

Driving a motor vehicle is simultaneously regarded as one of the most automatic and necessary every day tasks, and yet also one of the most complex and dangerous (Allen et al., 2011). Driving is an essential part of life for many people across the world, but a range of factors can negatively affect the skills needed to perform safely on the road. The influence of alcohol or drugs represents just one of these factors, which can result in serious consequences including injury and loss of life. From a public safety perspective, an analysis of the risks posed by drivers under the influence of alcohol or drugs is necessary. The introduction of driving simulation technology has offered a safe and cost-effective way to study these factors in a complex and dynamic environment. Any risk of death, injury, property damage, or arrest while driving under the influence is eliminated.

Scientific studies of cognitive psychology and psychomotor performance have extensively explored the impairing effects of drugs on specific tasks deemed important for safe driving (e.g., attention, reaction time). Yet, there is a paucity of literature studying how drugs affect the overall driving task itself. The relatively recent advent of high-fidelity driving simulators can help achieve this goal. The earliest road-driving simulators used analog computers and varying methods of display (Allen et al., 2011). Today, simulators have advanced considerably with improvements in digital computers, electronics, and display technology. Further discoveries and advances in technology will only improve the fidelity of today’s simulators, and allow researchers to more closely replicate the actual driving environment.

Driving simulator technology was first used in the form of flight simulation and was developed initially as a training tool for the use of tactical war machinery during World War II (Blana, 1996). It was not until the late 1950’s and early 1960’s that the applicability of this technology to research was realized, including the study of the effects of alcohol and drugs on driving skill. Driving simulators consist of four basic elements: the simulation computer, the generation of sensory feedback, the sensory display, and the human operator (Allen et al., 2011). Although early simulators differed greatly in terms of what the driver controlled during the simulation and how results were recorded, these elements were usually all present in various degrees of complexity. Because driving is primarily a visual task (Blana, 1996), development of the visual display has been very important. In one of the earliest drugged-driving simulation studies,
participants who were under the influence of cannabis were placed in the front console of a car while they viewed a 23-minute film and ‘drove’ along with the film while under observation by experimenters who recorded driving ‘errors’ (Crancer, 1969). The participant’s operation of the steering wheel and pedals had no effect on the pre-recorded film. Other early display technologies used a moving belt with a closed-circuit television display (Blauuw, 1982) or a cyclorama (a panoramic painting designed to give a 360 degree view to the person in the middle of the cylinder) (Rafaelson et al., 1973) but were unable to provide measurements of driving skill free from experimenter bias. The introduction of digital computer technology and animated graphics has represented a giant leap forward in driving simulation capability.

Today, driving simulators are capable of providing not only a more realistic sensory experience for the participant (for example, moving consoles that respond to the virtual environment) but also unbiased measurements of driving skill that permit better comparisons across studies. Simulators are able to automatically record speed, speed relative to other vehicles, lane deviation (standard deviation of lateral position or SDLP), steering errors, time taken to make a decision, brake time, collisions, and others. Furthermore, the environment can be manipulated to answer specific research questions (e.g., day/night driving, specific hazards) and add complexity to the driving task (e.g., complex signage). Driving simulation has the distinct advantage of being able to provide a safe and risk-free environment to conduct a potentially hazardous driving experiment that incorporates the measurement of these elements (Blana, 1996).

The scientific validity of this technology, however, remains a concern. It is acknowledged that driving simulation can never truly replicate the sensory experience of real driving, and can in some cases provoke reactions that real driving does not. For example, ‘simulator sickness’ is a phenomenon commonly noted in simulated driving experiments, whereby the simulated environment causes real feelings of illness and nausea that can negatively affect driving (Domeyer et al., 2013). Thought to be caused by differences in visual and vestibular sensory cues, simulator sickness can be quite uncomfortable, and it is unknown to what extent it impacts driving (Domeyer et al., 2013). However, simulator sickness has been recognized since some of the earliest simulations (Kennedy et al., 1993), and simulator and study designs can be manipulated to minimize the risk. For example, the use of larger screens and acclimation to the simulator over multiple testing sessions can be used to mitigate the effect (Domeyer et al., 2013; Roe et al., 2007). Driving simulation has also been doubted in its ability to predict actual driving performance in the real world (Hoffman and McDowd,
No standardized validity assessment for driving simulators exists, due in part to the range of differences in simulator types, participants, testing protocols, and data collection methods across studies (Blana, 1996). However, driving simulators can and have been evaluated for their reliability and external validity, and the results so far have been promising (e.g., Mayhew et al., 2011; Shechtman et al., 2009). In a recent study, driving simulation was found to be a valid means of measuring the dose-related increase in standard deviation of lateral position (i.e., lane-weave) while under the influence of alcohol, as compared to real driving on a closed course (Helland et al., 2013). Furthermore, driving simulation has been found to be useful in predicting self-reported automobile accidents 5 years later in older adults (Hoffman and McDowd, 2010). Although to what extent driving simulation replicates real life will likely always be debated, future advances in simulator technology will increase the fidelity of the driving task, and will improve the accuracy of this technology to predict accidents in real scenarios of driving under the influence.

1.3.3 Pharmacology

1.3.3.1 Cannabis

Cannabis is the most widely used illicit substance in the world today (UNODC, 2012). The plant Cannabis sativa contains over 489 chemical compounds, including over 70 cannabinoids (compounds with a similar chemical structure) (ElSohly and Slade, 2005). Cannabinoids can be found in the stalks, leaves, flowers, and seeds of Cannabis sativa, but also in oil extracted from the plant (hash oil) and resin (often pressed into a block, known as hashish) secreted by the female plant (Ashton, 2001). Of these, Δ⁹-tetrahydrocannabinol (THC) has been identified as the main psychoactive constituent of cannabis (Mechoulam, 1970) responsible for the effects that have made the plant popular, although cannabinoid compounds other than THC exhibit varying degrees of psychoactivity, and can alter the effects of cannabis (Grotenherman, 2003). Recent advances in hydroponics and growing techniques may vary the relative amounts of these cannabinoids in the plant, but have most notably caused an increase in the THC concentration found in illicit cannabis over the decades (ElSohly and Slade, 2005). In a study of cannabis products seized in the United States between 1980 and 1997, it was found that the average THC concentration rose from 2.06% to 4.47% during that time (ElSohly et al., 2000). In 2006, analysis of similar seizure material (including...
high potency products such as hash oil and hashish), from the Canada-US border found that the average THC concentration of cannabis products seized in Canada was 10.25%, and even exceeded 30% in some cases (Public Safety Canada, 2008). Similar results have been observed worldwide (McLaren et al., 2008), and Health Canada considers 10% THC to be representative of the cannabis found on the illicit market in Canada today (Health Canada, 2013). In spite of this, most controlled studies to date examining the effects of THC (including the effects of cannabis on driving) have been conducted using cannabis cigarettes with concentrations of THC well below this amount (Ramaekers et al., 2006a).

The pharmacokinetics of THC vary greatly by route of administration. Although ingesting the drug orally is not uncommon, the most popular route of administration of THC from cannabis is by smoking. Smoking is preferred by many users due to the rapid onset of effects and ability to quickly titrate the dose to achieve a desired level of intoxication (Huestis, 2007). Cannabis is typically smoked by rolling the dried, shredded leaves into a cigarette (sometimes mixed with tobacco) or by smoking a small amount of plant material from a pipe. Approximately 50% of the dose contained in a cannabis cigarette is inhaled in the mainstream smoke, while the rest is lost in the side-stream smoke, or destroyed by pyrolysis (Ashton, 2001). When cannabis is smoked, the bioavailability of THC has been estimated at between 2 and 56% (Lindgren et al., 1981). This wide range is largely attributable to the variability in dose received due to extensive inter-and-intra-subject variations in smoking technique (Agurell et al., 1986; Perez-Reyes, 1990). THC is quickly absorbed by the lungs, and is rapidly distributed to all other tissues including the brain. THC appears in the blood almost immediately after the first inhale, but dissipates quickly, with peak concentrations occurring even before smoking has ended, at roughly 3-8 minutes after the start of smoking (Huestis et al., 1992). THC is a highly lipophilic compound, and accumulates in fatty tissues before being released and eliminated. The high lipophilicity of this drug accounts for its high volume of distribution ($V_d = 10\, \text{L/Kg}$) (Huestis, 2007), despite being nearly completely bound to plasma lipoproteins (Hunt and Jones, 1980).

The pharmacokinetic profile of ingested THC differs considerably from smoked THC. Oral absorption of THC is slower, with the peak concentration of THC typically occurring within 1 – 2 hours (Grotenherman, 2003), though this has been observed to occur at up to 6 hours after ingestion in some cases (Ohlsson et al., 1980). Orally administered THC undergoes significant first pass metabolism in the liver, resulting in a low bioavailability estimated at just 6% (Ohlsson et al., 1980).
As a result of this first pass metabolism, lower concentrations of THC and higher concentrations of 11-OH-THC are attained after oral administration than following smoking (Grotenherman, 2003). However, similar to smoked THC, following ingestion of cannabis a disconnect remains between THC concentration in plasma or blood, and the pharmacodynamic effects experienced. The onset of the subjective effects of THC are delayed after ingestion, with psychotropic effects occurring within 30-90 minutes, and reaching a maximum at 2-4 hours (Ohlsson et al., 1980).

THC is metabolized in the liver mainly by oxidation, mediated by cytochrome the P450 enzymes CYP2C9, CYP2C19 and CYP3A4 (Huestis, 2007). Although metabolism of THC results in a wide array of metabolites, of which over 100 have been identified (Huestis, 2007), the major metabolites of interest are 11-hydroxy-Δ⁹-THC (11-OH-THC) and 11-nor-Δ⁹-carboxy-THC (THC-COOH). The 11-OH-THC metabolite retains psycho-activity equal to the parent compound (Perez-Reyes et al., 1972) and appears in blood rapidly with peak concentrations of about 6 to 10% of THC occurring within 45 minutes of the onset of smoking (Huestis et al., 1992). THC-COOH is an inactive metabolite resulting from further oxidation of the psychoactive 11-OH-THC and first appears in blood after several minutes, with peak concentrations of about 30% of the parent THC typically occurring within 1.5 to 2.5 hours (Huestis et al., 1992). Following oxidation, many THC metabolites undergo glucuronidation prior to elimination (Agurell et al., 1986). In vitro data suggests that genetic polymorphism of the cytochrome P450 enzymes involved in the oxidation of THC can have a significant impact its metabolism (Bland et al., 2005). More recently, data from healthy volunteers has demonstrated that individuals who are homozygotic for the CYP2C9*3 allele attain an area under the curve three times higher for THC, and 70% lower for THC-COOH as compared to CYP2C9*1 homozygotes after oral administration of THC (Sachse-Seeboth et al., 2009). It was also found that THC pharmacokinetics did not differ by CYP2C9*2 allele status (Sachse-Seeboth et al., 2009). Furthermore, both homozygotic and heterozygotic individuals who possessed the CYP2C9*3 allele experienced increased sedation following administration of THC, and as such, individuals who possess this allele may attain higher plasma concentrations of THC, and also be at an increased risk of experiencing the adverse effects of THC (Sachse-Seeboth, 2009).

Within 5 days, 80 to 90% of a dose of THC is eliminated via feces and urine as carboxylated and hydroxylated metabolites which are more water-soluble than the parent compound (McGilveray, 2005). Estimates of plasma elimination half lives of THC and THC-COOH have varied widely across studies depending on the dose administered, frequency of smoking, length of detection
window, and sensitivity of the analytical equipment used. For THC, estimates have ranged from 93 and 117 minutes for inexperienced and experienced users (Kelly and Jones, 1992) to up to 12.6 days in the case of a heavy user (Johansson et al., 1989). The plasma elimination half-life of the inactive metabolite THC-COOH is also long, estimated at between 5.2 and 6.2 days for frequent and infrequent users respectively (Kelly and Jones, 1992), although estimates depend strongly on the dose consumed and the time frame of sample collection (Huestis and Cone, 1998). The long terminal half-lives of these compounds are attributed to slow release from lipid compartments and extensive enterohepatic circulation (Huestis and Cone, 1998). A person’s Body Mass Index (BMI) correlates with time taken until the last positive urine specimen (Goodwin et al., 2008) as a high BMI typically represents a greater volume of fat, and hence a larger compartment in which THC can be stored. Such long detection windows for THC and metabolites have complicated studies of driving under the influence – the detection of THC and metabolites in biological samples can occur long after the effects of the drug have dissipated. The terminal urinary excretion half-life of THC-COOH has been estimated at 3.0 ± 2.3 days (range 0.8 to 9.8 days) (Johansson and Halldin, 1989), but the resulting detection window for THC-COOH can be as little as a few hours in naïve users (Huestis et al., 1995) and was detected up to 67 days in the case of a single chronic, heavy user (Ellis et al., 1985). Conversely, THC and 11-OH-THC can be detected in urine following hydrolysis from their glucuronide conjugates, and persist in urine for a shorter time frame than THC-COOH (Lowe et al., 2009). The detection of THC in urine was once thought to be indicative of very recent use within 8 hours (Manno et al., 2001), however, work in heavy users has recently shown detection of THC in urine up to 24 days after last use (Lowe et al., 2009).

THC exerts its psychoactive effects by binding to specific cannabinoid receptors in the brain. Two cannabinoid receptor subtypes have been discovered (CB1 and CB2) (Matsuda et al, 1990; Munro et al., 1993), and recent evidence has suggested the existence of a third and phylogenetically distinct cannabinoid receptor (GPR55, or ‘CB3’) (Ryberg et al., 2007), although its pharmacology is not well elucidated (Balenga et al., 2011). Cannabinoids have also been found to bind to other receptor types including the transient receptor potential cation family (De Petrocellis et al., 2011). CB1 is expressed widely in the CNS but can also be found in certain peripheral organs including the heart and gastrointestinal tract. On the other hand, CB2 is highly expressed in the periphery in immune cells, the spleen, and the tonsils (Pertwee, 1997), but is also expressed in important brain regions such as the cerebellum, brainstem (Van Sickle et al., 2005), cerebral cortex, striatum, and
Endogenous ligands have been discovered for the CB1 and CB2 receptors and comprise a family of lipid signaling molecules constituting a novel class of intercellular messengers known as the ‘endogenous cannabinoids’, or endocannabinoids (Grotenhermen, 2003). The endocannabinoids serve as part of the ‘endocannabinoid system’ which is thought to have appeared early in evolution and is now known to play an important regulatory function in all vertebrates (De Fonseca et al., 2005). Thus far, at least four endocannabinoids have been discovered, all of which derive from arachidonic acid and have varying affinity for CB1 and CB2 receptors (De Fonseca et al., 2005; Pertwee et al., 2010). Of these, the most important and well studied are arachidonylethanolamide (anandamide, AEA) and 2-arachidonylglycerol (2-AG). Both are thought to serve as neurotransmitters and neuromodulators with roles in mood, cognition, emotion, and pain (De Petrocellis et al., 2000) by serving as retrograde messengers at GABAergic and glutamatergic synapses, as well as through interactions with other neurotransmitters (e.g., dopamine) post-synaptically (De Fonseca et al., 2005). AEA and 2-AG are released on-demand from cells (i.e., in a stimulant-dependent manner) by the cleavage of a membrane-lipid precursor, and are actively regulated by the enzymes fatty acid amide hydrolase (FAAH) (De Fonseca et al., 2005) and monoacylglycerol lipase (MAGL), respectively (Puighermanal et al., 2012). However, despite these advances in knowledge, the highly complex actions of the endocannabinoid system remains poorly understood.

The cardiac and subjective effects of THC are largely blocked by a compound known as rimonabant, a CB1 antagonist/inverse agonist, indicating that THC’s interaction with the CB1 receptor is responsible for the bulk of the effects of smoked cannabis in humans (Huestis et al., 2001). CB1 and CB2 receptors are G$_i$-protein coupled receptors, which inhibit the formation of cyclic adenosine monophosphate (cAMP) and are positively coupled to mitogen-activated protein (MAP) kinase. CB1 receptors are also positively coupled to calcium and potassium ion channels, increasing inward ion flux upon activation, resulting in an overall increase in neuronal activity (Howlett et al., 2002). The activation of cannabinoid receptors has a neuromodulatory function, mediating interactions with neurotransmitter systems such as GABA, dopamine, endogenous opioids, and the monoamines (Howlett et al., 2002). Specifically, it has been demonstrated that THC increases the release of dopamine from the nucleus accumbens and prefrontal cortex, which may
account for its reinforcing effects and ability to produce a dependence syndrome in up to 10% of users (Hall and Degenhardt, 2009).

The widespread and varied effects of cannabis have defied its classification as a depressant, stimulant, or hallucinogen exclusively. At doses as low as 2.5 mg, a THC ‘high’ can be induced, characterized by euphoria, increased sociability, decreased anxiety, feelings of intoxication and increased appetite (Ashton, 2001). However, the nature of the effects produced by THC can be strongly influenced by the user’s own personality, their experience with the drug, their expectations, and their immediate surroundings (Metrik et al., 2009). With increased dosage, unpleasant reactions can result, ranging from dysphoria, anxiety, paranoia, hallucinations, and in extreme cases, a psychosis syndrome can occur (Channabasavanna et al., 1999). Aggravation and/or precipitation of schizophrenia has been reported (Moore, 2007). Smoking cannabis also produces perceptual changes that may be seen as pleasant or unpleasant; colours or sounds may be intensified (Ashton, 2001) and distortion of time and space (where users often perceive time as passing more quickly than it is) is common (Sewell et al., 2013). Cannabis impairs aspects of cognition and psychomotor skills including deficits in attention and concentration, short-term memory difficulties, incoordination and slowed reaction time (Ramaekers et al., 2004). These effects are dose-dependent and additive with other central nervous system depressants. Effects can begin to be felt almost immediately after smoking begins, but do not reach peak intensity until 30 minutes to 1 hour after smoking (Grotenherman, 2003), by which time blood THC concentrations have fallen dramatically. The dissociation between blood concentration and effect makes concentration-effect estimations difficult for THC, resulting in a counterclockwise hysteresis when relating effects to plasma or blood concentration (Huestis, 2007). See Figure 1 for a graphical representation of this phenomenon following oral administration of cannabis, as adapted from Grotenhermen (2003).
Figure 1. From Grotenherman (2003). Phase plot of the subjective ‘high’ versus plasma $\Delta^9$-tetrahydrocannabinol (THC) concentration after oral ingestion, showing counter-clockwise hysteresis. Every point in the figure marks 30 minutes of time. Maximum THC concentration occurs at 60 minutes, which does not coincide with maximum subjective effect, which is delayed, occurring at 180 minutes.

In addition to psychoactive effects, THC produces an array of other systemic effects on the body. THC increases heart rate and blood pressure almost immediately after smoking, although tolerance to these effects can develop with repeated use (Ashton, 2001). THC produces widespread vasodilation resulting in reddening of the conjunctivae, a symptom often seen as characteristic of cannabis use. Tachycardia, increased appetite, and dryness of the mouth are induced as a result of THC’s effects on the release and turnover of acetylcholine (Grotenherman, 2003). Other non-psychoactive effects of cannabis have been found to have therapeutic applications. Cannabis has been supplied Health Canada’s Marihuana Medical Access Program since 2001 for the treatment of a range of conditions including chemotherapy induced nausea and vomiting, multiple sclerosis, as well as cancer and non-cancer pain (Health Canada, 2013). Using cannabis to treat these conditions takes advantage of the anti-nausea (Machado Rocha et al., 2008), anti-spasmodic (Leussink et al., 2012), and anti-nociceptive (Lee et al., 2013; Ware et al., 2010) properties of cannabis, respectively. THC has also demonstrated some positive effects on the respiratory system, by increasing airway conductance through short-term bronchodilation and decrease of bronchospasm (Tashkin, 2001). However, treatment of respiratory disorders with smoked marijuana is likely not a viable option, as harmful compounds are produced from the pyrolysis of cannabis that can cause cancer or damage to
the respiratory system (Owen et al, 2013), and long-term use can lead to extensive injury of the airway (Tashkin, 2001). Long-term heavy use of cannabis has also been linked to an increased likelihood of depression (Lev-Ran et al., 2013) and a lower BMI (Le Strat and Le Foll, 2011). The prevalence of toxicity produced from THC intoxication is extremely low, and no deaths solely attributed to THC have been confirmed. However, it is speculated that people who have compromised cardiovascular systems may be more susceptible to the tachycardia produced by THC, and could suffer fatal cardiovascular complications as a result of intoxication (Bachs and Morland, 2001).

1.3.3.2 Alcohol (Ethanol)

Alcohol (ethanol) is a commonly consumed drug worldwide; over 40% of the world’s population are current drinkers (Shield et al., 2013) and most Canadians (80%) report current use of alcohol (Health Canada, 2012). Alcohol is also one of the world’s oldest drugs, with consumption by humans dating back to at least 10,000 BC (Hanson, 1995). Ethanol is naturally produced from the fermentation of grains or fruit, and typical concentrations of alcohol in beverages can vary from 4 to 6% for beer, 10 to 15% for wines, and 40% and above for distilled spirits (Pohorecky and Brick, 1988).

Ethanol is a very simple molecule with a simple pharmacokinetic profile in comparison to a more complex drug like THC. After ingestion, ethanol is rapidly absorbed from the stomach (20%) and the small intestine (80%) into the bloodstream and subsequently distributed to all other parts of the body (Paton, 2005). Ethanol is highly soluble in water and distributes quickly into the body’s entire water content by passive diffusion (Norberg et al., 2003). The pharmacokinetics of ethanol are therefore described by a one-compartment model. Ethanol has low lipid solubility and does not bind to plasma proteins, and as a result, the volume of distribution is highly related to body water content (Norberg et al., 2003). For example, the volume of distribution of alcohol has been found to range from 0.4 L/kg for an obese female to 0.85 L/kg for a lean male (Jones, 2007). This property of alcohol contributes to age and sex related differences in pharmacokinetics (Norberg et al., 2003) as females and older adults typically have higher body fat and lower body water, and thus can attain a
higher blood alcohol concentration (BAC) after consuming the same volume of alcohol as their male or younger counterparts (Holford, 1987).

The time to tissue equilibrium is a function of tissue perfusion and blood flow. When consumed orally, ethanol undergoes first-pass metabolism, dependent on hepatic blood flow and the absorption rate of ethanol (Holford, 1987). Despite this, bioavailability is high and is estimated at 80% (Holford, 1987). Following absorption, BAC typically peaks at approximately 30 minutes after ingestion; however, this is highly variable (Norberg, 2003) and depends greatly on dose, and the consumption of food before or with the beverage (Holford, 1987; Shuckit, 2011). Because absorption occurs more rapidly from the small intestine than the stomach, the presence of food will delay gastric emptying and peak BAC (Paton, 2005). Only a small amount of ethanol is excreted unchanged in urine, sweat, and breath, and the vast majority of a dose of ethanol is removed from the body via hepatic metabolism (Holford, 1987; Paton, 2005). Ethanol is oxidized by hepatic alcohol dehydrogenase to acetaldehyde, and subsequently to acetate by aldehyde dehydrogenase. Acetate is further oxidized to carbon dioxide and water. When higher doses are consumed, cytochrome P450 enzyme CYP2E1 is recruited to oxidize excess alcohol (Shuckit, 2011). The rate of metabolism and elimination of alcohol can be explained by Michaelis-Menten saturation kinetics (Wilkinson, 1980). Doses of alcohol consumed are relatively large compared to other substances and hepatic enzymes are saturated quickly. As such, ethanol is considered to undergo zero-order metabolism at physiologically meaningful concentrations (Holford 1987). Ethanol is removed from the blood at a constant rate, as only a constant amount can be removed per unit of time regardless of the amount consumed. A rate of 10 to 20 mg/dL/hour from blood is applicable to most of the population (Jones, 2010). However, this rate can vary with age, experience with alcohol, and/or disease states (Jones, 1996). For example, in people with alcohol dependence, the rate of elimination of alcohol from blood can increase to 35 mg/dL/hour through the achievement of pharmacokinetic (metabolic) tolerance and the induction of CYP2E1 enzymes (Jones, 2010).

Ethanol is a central nervous system depressant that produces a wide range of effects on a variety of systems in the body. It should be noted that there exists no specific “ethanol receptor” in the brain, and that the pharmacodynamic effects of ethanol are attributed instead to the disruption of the balance between excitatory and inhibitory events (Shuckit, 2011) through interaction with a number of neurotransmitter systems (Faingold, et al., 1998). Ethanol is thought to exert its main effects in two ways; by enhancing the effects of the main inhibitory neurotransmitter, GABA, at
GABA<sub>A</sub> receptor sites, and by preventing the action of glutamate, an excitatory neurotransmitter, at NMDA receptors (Faingold et al., 1998). Dopamine and serotonin (Daws et al., 2006), as well as other neuromodulatory systems such as the endocannabinoids (Cho et al., 2012) and endogenous opioids (Schulz, 1980; Herz, 1997) are also affected by ethanol. Effects are dose-dependent and correlate directly with BAC. Reflecting its nature as a social drug, at low concentrations (50 mg/dL) ethanol mimics the effects of some stimulatory drugs through disinhibition of emotions, increased talkativeness, and improvements in mood and sociability (Pohorecky and Brick, 1988). With increasing BAC (100 mg/dL), the less desirable effects of alcohol such as sedation, loss of muscle control and in-coordination, are observed. At even higher concentrations (200 to 300 mg/dL), slurred speech, unsteady gait and impairments in attention are noticeable as ethanol begins to effect lower brain functions (Shuckit, 2011).

Chronic use of alcohol can result in pharmacodynamic tolerance to its effects, mediated in part by desensitization and down-regulation of GABA<sub>A</sub> receptors. These effects also contribute to physical dependence and withdrawal symptoms, which have been well described to range from mild (insomnia, tremulousness) to severe and life threatening (seizures, delirium tremens) (Bayard et al., 2004). Tolerance to alcohol can have a significant effect on the dose and blood concentration at which toxicity is produced. Toxicity to alcohol is characterized by severe depression of the central nervous system, resulting in respiratory depression, coma, and death. Other complications resulting in fatality such as accidents, positional asphyxia, or aspiration of vomit are also common and can occur at lower BACs (Kelly and Moyzani, 2012; Pohorecky and Brick, 1988). In the general population, BACs in excess of 400 mg/dL are associated with toxicity. However, blood concentrations in excess of 500 mg/dL have been recorded in ambulatory drinking drivers who showed no outward signs of toxicity due to a high tolerance to alcohol (Jones, 1999). Although tolerance to the intoxicating and toxic effects of alcohol is clearly demonstrable, tolerance to the impairing effects of alcohol, such as those that negatively impact complex tasks like safe driving, are not similarly observed. This phenomenon is described in greater detail under section 1.3.4.2.
1.3.4 Impaired Driving

1.3.4.1 Cannabis Use and Driving

1.3.4.1.1 Epidemiological Findings

Next to alcohol, cannabis is the most frequently detected drug in injured or fatally injured drivers (Cimbura et al., 1990; Stoduto et al., 1993). Just as alcohol has been demonstrated to cause an exponential rise in crash risk with increasing blood alcohol concentration (BAC) (Borkenstein et al., 1964), similar attempts have been made to quantify the risk of crash involvement for cannabis use alone. However, unlike alcohol, findings from these studies have been less clear. Epidemiological studies have been less consistent in providing proof of an elevated risk of crash following cannabis use. Epidemiological studies of crash risk following DUIC typically fall within three main study types; cohort, cross-sectional, and case-control studies, with case-control studies being further divided into those which make attempts to assess whether the person under the influence was at-fault in the collision (culpability studies) and those that do not (Asbridge et al., 2012). Results from all three study types have been mixed, although case-control studies are best able to provide direct evidence of an effect of cannabis on driving, and will be discussed in greatest detail here.

DUIC appears to be particularly popular among young people, with an estimated prevalence of 5 to 9% of young drivers reporting this behaviour (Fischer et al., 2006), compared to just 2.4% of drivers of all ages (Simpson et al., 2006). In the general population, rates of DUIC among drivers who identify as cannabis users may be as high as 23% (Walsh and Mann, 1999). Though young age is common among DUIC drivers, little is known about the other demographic characteristics that comprise this group. It has been suggested that the high rate of DUIC among cannabis users may be influenced by commonly held beliefs, particularly by young cannabis users, that DUIC is a relatively safe activity (Fischer et al., 2006; Jones et al., 2007). Epidemiological study of collision risk following the acute use of cannabis is an important tool used to educate the public and inform policy in response to this potentially dangerous activity. Among the epidemiological studies that exist to date, some report an increase in collision risk as a result of recent cannabis use (e.g., Drummer et al., 2004; Laumon et al., 2005; Terhune, 1992), however, others find no significant association (Elvik, 2012; Longo et al., 2000; Movig et al., 2004). Much of this discrepancy may be attributed to methodological challenges and other complicating factors due to the unique pharmacology of THC.
In cases of fatally injured drivers, cannabis is often not the only drug detected. The detection of other psychoactive substances (in particular alcohol) in combination with THC makes the identification of THC-only cases infrequent. In this situation, the likelihood of detecting an effect of THC, if it truly exists, is relatively low. For example, in a large study by Longo and colleagues (2000) examining the blood of 2500 injured drivers, a mere 44 cases were recorded with only THC and metabolites in blood. This represents a severely limited sample size in comparison to drug-free controls (n = 1887), and as such this study failed to find an increased risk of collision as a result of cannabis use. The pharmacology of THC does not lend itself well to this type of study design. Levels of the active drug, THC, fall quickly in blood after smoking, making timeliness of sample collection essential, though it cannot often be guaranteed (Jones et al., 2008). To circumvent this challenge, other studies use the pharmacologically inactive metabolite, THC-COOH, as an alternate analyte because it has a longer terminal half-life and is therefore more likely to be detected (e.g., Drummer, 1994). However, THC-COOH is of limited forensic value because of this longer half-life; the detection of THC-COOH can only establish prior use of cannabis, and not recent use of cannabis. THC-COOH can remain detectable in blood long after the intoxicating effects of THC have dissipated. Similarly, because blood samples are often difficult to obtain, some studies have chosen to collect urine samples for testing (e.g. Movig et al., 2004). However, the longer detection window of THC and its metabolites in urine likewise makes it difficult to establish any relationship between THC use and crash risk. For case-control studies, THC in blood is the only type of biological analysis that can establish a link between DUIC and crash risk. A well-designed study by Drummer et al. (2004) that was able to obtain blood samples found that THC-only drivers were 2.7 times more likely to be involved in a fatal collision than controls. Similar studies by Mura and colleagues (2003) and Biecheler and colleagues (2008) replicate this finding, with the odds of being involved in a crash when THC is detected in blood being calculated at 2.5 and 2.3 times greater than controls, respectively. Other studies have similarly found that drivers under the influence of cannabis are more likely to be at-fault in a collision when blood is used (e.g., Laumon et al., 2005, OR = 3.3).

Although case-control studies offer what is perhaps the most convincing epidemiological evidence for an increased risk of collision following cannabis use, some authors are skeptical that this increased risk can be explained by other factors that may be inherent to this group of drivers. In a case-control study of self-reported recent cannabis use (Blows et al., 2005), the risk of collision involvement was found to be higher among cannabis users than among controls (OR = 3.9, 95% CI
1.2 - 12.9). However, after adjustment for other risky behaviours at the time of driving, the results lost significance, leading to speculation that any increase in crash risk related to self-reported cannabis use could instead be attributed to other risky behaviours or personality traits. However, further research controlling for DUIA, other risky behaviours, and demographic factors, has revealed that self-reported driving after recent use of cannabis still imparts a greater risk of collision as compared to controls (Mann et al., 2010; Richer and Bergeron, 2009). It is therefore unlikely that the risk of crash can be solely attributed to other confounding factors.

Well-designed studies (e.g., Drummer et al., 2004) and literature reviews (Ramaekers et al., 2004) on this topic lend increasing confidence to an elevated risk of crash following the acute use of cannabis. The weight of the evidence is increasingly in favour of a rise in collision risk following acute cannabis use (e.g., Laumon et al., 2005; Terhune, 1992). Asbridge and colleagues (2012) conducted a meta-analysis of the epidemiological literature and found that the pooled risk of collision while under the influence of cannabis was nearly twice the risk of driving sober (OR 1.92, 95% CI 1.35-2.73). A review by Ramaekers and colleagues (2004) of the relevant epidemiological, psychomotor, and simulator studies also concluded that the risk of motor vehicle crash after cannabis use is dose-dependent. Epidemiological studies have highlighted the risky nature of using cannabis and driving, although other types of studies (i.e., laboratory, driving simulator, and on-road) are necessary to further elucidate the nature of this increased risk of crash.

1.3.4.1.2 Laboratory Studies

Epidemiological studies, while helpful in estimating the risk of becoming involved in a crash after consuming drugs and/or alcohol are limited in their ability to establish a direct cause-and-effect relationship. In this way, experimental laboratory studies of psychomotor ability, cognitive performance, and in some cases the driving task itself (driving-specific studies are discussed in further detail under section 1.3.4.1.3) are better able to provide information on effects of the drug as they relate directly to safe driving on the road. The results of psychomotor and cognitive tests are extrapolated to the driving task, as poor performance in the laboratory is expected to translate to poor performance on the road. However, many experts have misgivings about how well the measurement of isolated skills in laboratory translates to actual driving performance (Verster and Roth, 2012).
No standard battery of tests exists to examine the psychomotor and cognitive effects of cannabis as they relate to driving. Similarly, no standard exists describing which aspects of psychomotor function and cognition are the ones that are essential for driving. Tests can range from simple to fairly complex, and assess a variety of psychomotor and cognitive processes that are estimated to affect driving skill. Despite this, research over the last 50 years has demonstrated that THC impairs faculties from basic motor coordination to complex executive functions (i.e., planning, problem solving) in a dose-dependent manner (Crean et al., 2011). Studies to date have demonstrated deficiencies in learning, working memory (the ability to remember information after a short delay), perceptual distortions (space and time estimation), reaction time, tracking (fine motor control), and attention (e.g., Khiabani et al., 2006; Ramaekers et al., 2006a).

The experience the user has with THC seems to play a significant role in the level of impairment seen when testing certain faculties. Recent work has established that chronic heavy users of cannabis can develop tolerance to some of the impairing effects of THC (Ramaekers et al., 2009, 2011; Theunnissen et al., 2012). This finding may help explain the discrepancy in research findings when occasional or light versus heavy users are used in studies. For example, some studies examining attention (simple versus divided) in daily cannabis smokers have found either no difference (e.g., Hart et al., 2001; Ramaekers et al., 2009) or a slight improvement (Haney et al., 1999) of scores after smoking as compared to controls. On the other hand, studies examining attention in occasional smokers have found clear impairment of these same faculties (e.g., Morrison et al., 2009; Ramaekers et al., 2009). Other cognitive measures may be less sensitive to the tolerance and experience of the user. Working memory and impulsivity remain impaired in both occasional (Heishman et al., 1997; McDonald et al., 2003) and chronic users (Ramaekers et al., 2009; Hart et al., 2001). This effect may also be dose-dependent, as Weinstein and colleagues (2008) found performance deficits in daily users only after a high dose (17 mg) THC cigarette, but did not detect any impairment of performance in the low dose condition (13 mg).

While the acute effects of THC are well described, how long these effects last is not yet known. Studies examining the acute effects of the drug typically examine a time period of up to 6 hours after use. Few studies looking at residual effects of the drug beyond this time frame exist, although work that has been completed to date notes that the residual effects of the drug also seem to vary with frequency of use and experience of the user (Pope et al., 1995). Following acute use in occasional users, cognitive and psychomotor deficits generally resolve within 6 to 8 hours (Huestis,
Some effects have been detected at 24 hours after use (Huestis, 2002; Pope et al., 1995), but this has not been a consistent finding (Chait and Perry, 1994; Kurzthaler et al., 1999) likely due in part to the varying sensitivity of tests used to assess these skills. Heavy users have demonstrated poorer performance on tasks relating to attention and decision-making well beyond 6 hours (Bolla et al., 2002), although it is unclear for how long these deficits can persist. Other studies examining residual effects of THC as they relate to the driving task specifically are described under section 1.3.4.1.3.

Psychomotor and cognitive studies have attempted to determine a connection between the concentration of THC and metabolites in blood and degree of impairment. However, the nature of this relationship remains elusive. In a comprehensive study by Menterey and colleagues (2005), blood THC and cannabinoid concentrations were measured concurrently with performance on psychomotor tasks after oral administration of a range of doses of THC. They found that peak deficits in performance did not coincide with peak blood THC concentrations, and that inter-individual variability in THC and cannabinoid concentrations precluded concrete conclusions about THC concentration and degree of impairment. Similarly, Ramaekers and colleagues (2006b) could not conclude that a linear relation between serum THC and impairment existed following a series of tasks following smoking. Although the authors of this study were able to conclude that 100% of participants were impaired at > 30 ng/mL THC in serum, this did not preclude significant impairment at much lower concentrations in some individuals, making generalizations about dose, serum concentration, and impairment, difficult (Ramaekers et al., 2006b). In a further study in a naturalistic setting, a physician was used to perform a Clinical Test for Impairment (CTI) shortly after the apprehension of suspected impaired drivers (Khiabani et al., 2006). The researchers found that drivers who were believed to be impaired had higher blood THC concentrations (range 0.3 to 45 ng/mL) than those who were not deemed impaired (range 0.32 to 24.8 ng/mL), however there remained considerable overlap in blood THC concentration and performance on the CTI.

Although helpful in determining cause and effect relationships between THC and psychomotor and cognitive impairment, experimental laboratory studies suffer limitations in their applicability to real-world driving. Even though controlled doses are administered, due to ethical and practical considerations, the doses of THC used in these studies often do not approach the doses found in real-world driving scenarios. Furthermore, the predictive validity of these findings to real driving remains unknown. For this reason, driving simulation studies have become a popular method
for studying the effects of cannabis on driving by combining the power of determining a cause-and-effect relationship with a task more reflective of real-world driving.

1.3.4.1.3 On-road and Driving Simulator Studies

The best way to test the impact of drugs on driving skill is to directly test the driving task itself. Some researchers have been able to test real driving in an instrumented vehicle during on-road studies using dual-controlled cars (often equipped with passenger-controlled breaks as a safety feature) and closed-course tracks (e.g., Hansteen et al., 1976). However, with technological advances in driving simulation and virtual reality, more and more researchers are taking advantage of testing drug-impaired driving using this approach. Together, these attempts at demonstrating the psychomotor and cognitive impairments found in the laboratory using real or near-real driving have produced mixed results. While some researchers have found performance decrements under the influence of THC, this has not been universal. Much of this variability, however, can be attributed to the evolution of simulation technology, and the variability in doses used and types of participants. Many studies attempt to compare the effects of THC with the effects of alcohol, a substance that is already known to have a detrimental effect on driving skill.

Very few true on-the-road studies exist in the literature. Those that are available tend to demonstrate the dose-dependent nature of the effects of THC, its sensitivity to the complexity of the task, and participant bias. The earliest on-road studies assessing driving under the influence of cannabis were performed in the 1970’s and 80’s. In 1976, Hansteen and colleagues used a closed driving course and two doses of THC (1.4 mg and 5.9 mg). Although significant findings were reported in the number of traffic cones hit and time to complete the course, this was only noted for the higher THC dose; no significant differences in driving were seen with the lower dose of THC. Similarly, Sutton (1983) found no significant differences in subjects’ driving performance on a closed-course track following administration of a single 2% THC cigarette. However, this author noted that some participants disclosed that they paid much greater attention to their driving than they normally would, in order to prove that the drug has no effect on driving. This study highlights the common effect observed in subsequent work that cannabis users are aware of their impairment and make attempts to compensate in their driving (Hartman and Huestis, 2013). Other on-road studies have attempted to incorporate obstacle courses or city driving tasks in an effort to increase
the complexity and demand placed on the participant, and subsequently improve the sensitivity of the test. Findings in these instances have been mixed, with some authors reporting no change or even an improvement in driving among some individuals (Klonoff, 1974; Lamers and Ramaekers, 2001), while other studies have found dose-dependent increases in road tracking error (e.g., Standard Deviation of Lateral Position, SDLP) and failure to maintain distance (Ramaekers et al., 2000). Experimenter bias, participant bias, overly simple driving courses, and the use of doses of THC that may not be high enough to detect an effect could all contribute to the discrepancy in results among on-road driving studies.

Driving simulation studies represent a simple way to increase task complexity while avoiding the ethical challenges that can be problematic with on-road experiments using instrumented vehicles. However, the earliest driving simulation experiments using cannabis were limited in the aspects of driving that could be assessed. In 1969, Crancer and colleagues compared the effects of alcohol and marijuana on driving using a driving simulator consisting of a mock up for the front console of a car. Participants viewed a 23-minute video and ‘drove’ along with the scenario while experimenters recorded driving errors. They found that participants who smoked cannabis demonstrated significantly more speedometer errors than participants in the control condition. No significant differences were found, however, in accelerator, brake, signal, steering, or total errors. Kalant (1969) pointed out in a reply to this study that it suffered serious design flaws that made it subject to bias and more difficult to detect impairment by cannabis. After expressing similar concerns, Rafaelson and colleagues (1973) used a modified driver-training instrument complete with cyclorama (description available under section 1.3.2) to study the effects of three doses of THC on driving. Using red and green light signals, they found significant effects of cannabis on start and stop (braking) time, an aspect of driving Crancer (1969) could not assess. They found that cannabis increased the time required to brake and start, and decreased the number of gear changes in a dose-dependent manner.

Advances in technology have increased the sensitivity of driving simulation to detect specific effects of THC (Hartman and Huestis, 2013), although results remain equivocal. Using a computerized driving simulator (AGC mobile model SV5000LE), Liguori and colleagues (1998) measured brake latency (simple reaction time to stop in front of a randomly appearing fence) and judgment (drivers must choose the widest of three laneways and drive through it while maintaining current speed) and found only marginal impairment in brake latency with the highest dose (3.95%
THC) condition. The judgment task was not affected. It should be noted, however, that these tasks are dissimilar to real driving scenarios, and further work by this group found no effect of THC on brake latency using the same tests (Liguori et al., 2002). Other studies using more realistic driving scenarios have been more consistent. Studies using unbiased measures of speed, SDLP, and reaction time have generally found dose-dependent decreases in speed, and increases in SDLP, headway, and reaction time, and have reported that these effects are typically more pronounced in less experienced users (Lenné et al., 2010; Ronen et al., 2008, 2010). Less common measurements including assessment of unexpected (e.g., pulling out) events, speed relative to other vehicles, and tasks of divided attention have found performance impairments under the influence of cannabis (e.g., Anderson et al., 2010; Downey et al., 2013; Sexton et al., 2002).

Overall, driving simulation studies demonstrate that participants are often aware of their condition and make efforts to compensate, as demonstrated by slower average speed, greater headway, and less risk-taking (Ronen et al., 2008; Smiley, 1999). However, despite this, there is evidence that not all aspects of driving may be compensated for equally. Tracking ability, steering, and tasks requiring divided attention do not seem to be as susceptible to conscious control and compensation after use of THC (Anderson et al., 2010; Lenné et al., 2010). As task complexity increases, the ability to compensate decreases, and this inability to compensate may be particularly pronounced when combined with alcohol (Downey et al., 2013). Future driving simulation research (such as presented in this thesis) should address how long the driving task may be impaired following cannabis use. Automotive driving simulator studies conducted to date have only tested the acute use of cannabis on driving skills using the most recent technology. Preliminary research conducted more than 20 years ago using flight simulation found evidence of impairment for as long as 24 hours after smoking cannabis, although participants reported no longer feeling any effect of the drug (Leirer et al., 1991; Yesevage et al., 1985). It is possible impairment may exist beyond this time frame.
1.3.4.2 Alcohol and Driving

Research over the last 40 years has demonstrated that intoxication due to alcohol (ethanol) impairs the safe operation of a motor vehicle. Although rates of drinking and driving in Canada declined sharply in the 1980’s and early 1990’s, today, the percentage of fatally injured drivers in Canada who are found to have had a BAC > 0 mg/dL has remained roughly steady at approximately 35% (Transport Canada, 2012). Similarly, in the United States, 20% of the population aged 16 and older reported driving within 2 hours of drinking alcohol (Drew et al., 2010), and 2.2% of weekend nighttime drivers were found to be driving with an illegal BAC, in 2008 (Compton and Berning, 2009). Drinking and driving represents a serious and ongoing threat to public safety.

The first observation of a correlation between alcohol consumption and risk of motor vehicle collision occurred as early as 1904 (Voas and Fell, 2011). Since then, numerous epidemiological and experimental studies have firmly established the role of alcohol consumption on traffic accidents. In the landmark Grand Rapids Study (so named for being conducted in Grand Rapids, Michigan) by Borkenstein and colleagues (1964), the researchers demonstrated quantitatively that as BAC rises, the risk of crash involvement increases exponentially. The team conducted roadside interviews of, and collected breath samples from, nearly all accident-involved drivers in this area over a one-year period (n = 9,353). The interviewees were then matched with a control group (n = 8,008) of drivers based on demographics. The main findings were (1), that blood alcohol levels greater than 0.04 mg/dL are associated with increased accident involvement; (2), that the probability of a collision increases rapidly at 0.08 mg/dL; and; (3), that the probability of collision becomes extremely significant at 0.15 mg/dL. Similar studies conducted in Long Beach, California, and Fort Lauderdale, Florida between 1997 and 1999 (Bloomberg et al., 2009) found nearly identical results to those obtained in 1964, demonstrating that the role of alcohol in traffic collisions has remained unchanged over time.

Experimental studies have confirmed and supported the epidemiological data that alcohol consumption is incompatible with safe driving. The impairment caused by alcohol as it relates to driving is generally considered to fall into two categories: (1), physical deficits in motor control; and; (2), disinhibition of behaviour (Weafer and Fillmore, 2012). The former category is thought to account for the types of driving errors that typically come to mind when imagining an intoxicated
driver; the sedating effects of alcohol can result in motor incoordination and subsequent increases in lane deviation (swerving, crossing the line). The latter category can result in driving errors that when combined with decreased motor control may become particularly insidious. For example, behavioural disinhibition of alcohol can result in increased confidence in one’s driving and a propensity for risk taking, producing speeding behaviour, excessive lane changes, and a disregard for traffic signals. Increased confidence and risk taking also influences a drivers’ decision to begin driving after drinking (Weafer and Fillmore, 2012). The sedation caused by alcohol further causes decreased attention resulting is slower reaction time and a decreased ability to respond to unexpected events.

Laboratory studies examining the effects of alcohol on driving have found a dose-dependent increase in impairment on a variety of faculties (Moskowitz and Fiorentino, 2000). However, many of the isolated skills tested to assess driving capability after alcohol intoxication differ in their sensitivity, and some skills are observable only at high BACs. For example, studies testing divided attention, drowsiness, and tracking, have demonstrated impairment by alcohol in the laboratory starting at low BACs (0.01 to 0.02 mg/dL) (e.g., Roehrs et al., 1994a; 1994b). Other faculties such as choice reaction time and vigilance begin to show evidence of impairment by alcohol when a person’s BAC is greater than 0.02 mg/dL (e.g., Vermeeren & O’Hanlon, 1998). Others still, such as simple reaction time and critical fusion flicker (the ability to determine the frequency at which a flickering light becomes steady), and are only observable at BACs in excess of 0.05 mg/dL (e.g., Tzambazis et al., 2000; Hindmarch et al., 1991). As a result, as BAC increases, the number of faculties impaired is also expected to increase, and complex tasks like driving become increasingly more difficult. It has been suggested that the vast majority of persons are expected to show a decrease in at least one faculty necessary for driving at a BAC of 0.08 mg/dL and higher (Moskowitz and Fiorentino, 2000). On-road and driving simulation studies have confirmed these results, and as expected, find the sum total of impairment on various faculties leads to subsequent increases in driving errors and collisions (e.g., Christoforou et al., 2013; de Waard and Brookhuis, 1991; Gawron and Ranney, 1988; Mets et al., 2011).

To quote Borkenstein and colleagues (1964), “the evidence all points in one direction – that alcohol in significant levels in the blood increases the probability that the driver will be involved in an accident”. As a result of this finding, countries around the world have addressed the problem of drinking and driving by setting limits on the amount of ethanol that can be present in a person’s
blood while operating a motor vehicle. However, in many cases, alcohol may not be the only drug detected. The study of how other drugs (e.g., THC) interact with alcohol is in its infancy, although preliminary research suggests the combination is severely detrimental to driving safety.

1.3.4.3 The Effects of Combining Alcohol and Cannabis

Cannabis and alcohol are a popular combination of recreationally used drugs (Earleywine and Newcomb, 1997). Unsurprisingly, it follows that alcohol and cannabis are the most frequently detected combination of drugs in the blood of seriously and fatally injured drivers worldwide (Biecheler et al., 2008; Blencowe et al., 2012; Drummer et al., 2003; Poulsen et al., 2012; Simonsen 2012;). In 1990, Cimbura and colleagues found evidence of cannabis use in 11% of 1,100 fatally injured drivers in Ontario, 84% of whom had also been drinking alcohol. Similar results have been found in studies examining suspected impaired drivers (Palmentier et al., 2009) although it has been suggested that the prevalence of combined alcohol and cannabis intoxication may be underestimated in living drivers due to the nearly universal practice of law enforcement agencies to omit testing for other drugs if the alcohol detected is above the legal limit (Compton et al., 2009). In a United States national survey of alcohol users, 10% reported concurrent use of cannabis (using at the same time in their lives), and nearly as many (7%) reported episodes of simultaneous (within the same episode) use (Midanik et al., 2007). This behaviour appears to be even more common among young people and adolescents (Collins et al., 1998), with a recent study reporting that nearly a third of Quebec high school students described engaging in this behaviour (Brière et al., 2009). In a further study, 15.5% of adolescents who reported simultaneous cannabis and alcohol use also stated that they would be likely to drive after consuming both (Fischer et al., 2006). Although some drivers report both DUIC and DUIA, little is known about the risk of collision experienced by this group.

Epidemiological studies analyzing the blood of crash-involved drivers have found that alcohol and cannabis are a dangerous combination behind the wheel, and that the combination of THC and alcohol in blood elevates the risk of crash more than the detection of either of these drugs alone (Sewell et al., 2009). For example, Biecheler and colleagues (2008) conducted a large study in France on fatally injured drivers who were found to be responsible for the collision. They found that drivers who were under the influence of cannabis, alcohol, and combined alcohol and cannabis were
2.3, 9.4, and 14.1 time more likely to be responsible for a crash, respectively, suggesting that the impairment produced by this combination is beyond that of either substance used alone. This relationship holds true even in studies that fail to detect impairment for THC alone. For example, in a retrospective study examining 589 impaired driving cases positive for THC in blood and 894 cases positive for THC and ethanol combined, no relationship was found between THC and performance on a physical impairment test, however, when THC and alcohol were combined, the risk of being judged impaired increased substantially (Bramness et al., 2010).

Some of the earliest experimental work on cannabis and driving performance recognized the popularity of combining cannabis with alcohol, and hence the necessity of testing both substances together (e.g., Sutton, 1983). Although the evidence on the combined effects of cannabis and alcohol on driving performance from human laboratory studies remains limited, in the few studies where alcohol and cannabis are co-administered, results have shown that performance on psychomotor or driving tasks are consistently inferior to each drug condition tested separately. In several on-road studies conducted in the Netherlands over the last 15 years, the effects of alcohol and THC alone were found to be moderate given the doses used (BAC 0.04 - 0.05 mg/dL, THC 100 – 300 µg/kg), but when combined, the impact on driving performance was dramatic on measures of SDLP, time out of lane, and simple reaction time (Ramaekers et al., 2000; Robbe, 1998). Similarly, in a recent driving simulator study, it was found that the condition of using THC and alcohol together at either low or high doses produced the greatest impairment compared to either drug alone (Downey et al., 2013). Early work using real driving tasks that failed to find impairment of performance following THC or low doses of alcohol often still found that the combination of alcohol and cannabis demonstrably impaired driving performance (Stein et al., 1983; Sutton et al., 1983). This further emphasizes the severity of this combination, even in the face of insensitive testing procedures, and at low doses. More recent studies continue to note this effect, and highlight the need for further studies using more realistical concentrations of THC to tease out the relationship between THC, alcohol, and driving performance (Lenné et al., 2010).

The combination of alcohol and THC is negatively related to driving performance, however, whether the combined effects of these drugs are additive (produces impairment expected from the sum of either dose alone) or synergistic (produces impairment greater than the sum of each alone) remains equivocal (Liguori et al., 2002). Although most researchers agree that the effects demonstrated are at least additive, and may be synergistic (Bramness, et al., 2009; Chait and Perry,
to others the relationship does not appear to be this simple. A recent study using sub-threshold doses of oral THC (by capsule) and alcohol failed to find an additive effect of these substances (Ballard and de Witt, 2011). Inconsistent findings may point to the contribution of other cannabinoids when THC is smoked, as in most other studies where additive or synergistic effects have been noted (Ballard and de Witt, 2011).

The effects of THC and alcohol have often been compared to each other in the driving literature. In studies examining alcohol alone, more significant impairment is observed on tasks that require greater cognitive control (e.g., decision making) as compared to those that are more automatic (e.g., road tracking) (Fillmore et al., 1999). On the other hand, studies examining THC alone demonstrate the opposite; impairment of automatic functions seems to be more pronounced than the impairment of functions requiring greater cognition (Sewell et al., 2009). This has been offered as a reason why cannabis does not demonstrate an impairing effect as easily as alcohol in some epidemiological studies and laboratory tests. The idea that cannabis users tend to be better judges of their impairment, and consequently make active attempts to compensate for their impairment through reductions in speed and risk-taking (Sexton et al., 2002) remains in contrast to drinking drivers who commonly underestimate their level of impairment and overestimate their fitness to drive (e.g., Bierness, 1987). This finding has led to the hypothesis that the combination of alcohol and THC is particularly hazardous because alcohol reduces the compensatory behaviour of cannabis intoxication, and therefore results in performance deficits that are particularly severe (Sexton et al., 2002). An alternate hypothesis is based on some evidence that the consumption of alcohol increases the blood concentration and subjective effects of THC (Lukas and Orozco, 2001), and in turn, leads to greater driving impairment (Downey et al., 2013). However, this theory warrants further examination as it is unclear whether alcohol alters THC blood levels through pharmacokinetic means, or through increased intake of THC through alterations in smoking topography (Lukas and Orozco, 2001).
1.4 Linking the knowledge

Research on the effects of THC on driving skill is in its infancy. Epidemiological, cognitive/psychomotor, and on-road testing have been valuable tools to assess the impact of THC on driving to date, driving simulation technology is now capable of more closely replicating the driving task and is increasingly being used to overcome the limitations of previous work. Despite this, knowledge in this area remains preliminary. Although it is known that cannabis and alcohol are frequently used together, there are few experimental studies examining the effects of cannabis on driving, whether alone or in combination with alcohol. A study of this nature examining the acute and residual effects of cannabis alone is before the combined effects of these drugs can be properly evaluated. Epidemiological literature, on the other hand, is more robust in its examination of the impact cannabis alone on driving. As such, information on how the combination of alcohol and cannabis impacts driving represents a relatively new area of research. These gaps in the experimental and epidemiological literature are addressed through a combination of experimental and epidemiological studies presented in the following chapter. Together, these studies examine how THC impairs driving ability both acutely and residually, and whether the self-reported concurrent behaviours of DUIA and DUIC impart an increased risk of collision.

1.5 Restatement of the Hypothesis

It is expected that the acute effects of THC will negatively impact the driving task up to 6 hours after administration, and that residual effects of the drug will be observable beyond this time frame at 24 and 48 hours post dose. In addition, it is expected that individuals who self-report both DUIA and DUIC behaviours will be more likely to have been involved in a collision within the last year than those who do not engage in either behaviour, or only one behaviour.
Chapter 2
Materials and Methods

2.1 Part A: Cannabis and Driving Simulator Study

2.1.1 Study Design

This study is a human laboratory experiment designed to test the acute and residual effects of a single dose of smoked cannabis on the simulated driving of young adults. Cognitive functioning and subjective effects are assessed using a battery of computer-based tests. Serial blood samples are collected to allow pharmacokinetic and pharmacodynamic (PK/PD) modeling following cannabis administration. The study is a double-blind, placebo-controlled mixed-design study, and includes a randomized between-subjects comparison of the acute effects of smoked cannabis, and a between-and-within-subjects examination of the residual effects of cannabis at 24 and 48 hours following a single drug administration of a 12.5% THC cigarette. The study will evaluate a variety of driving measures (SDLP, speed, relative speed, collision frequency, and others), cognitive/psychomotor performance, self-reported behaviour, as well as pharmacokinetic and pharmacodynamic data. The study is carried out over 5 Sessions. Each participant is paid $200 upon completion of the study, although payment can be pro-rated for those who do not complete all study sessions. An eligibility assessment (Session 1), a practice day (Session 2), and three consecutive testing days (Sessions 3, 4, and 5) are included. Although Session 1 can be completed at any time prior to the remaining study sessions, Sessions 2 through 5 must be performed on consecutive days. The cannabis or placebo cigarette is administered during Session 3. Table 1 represents a timetable of measures that are taken throughout the study. To maintain the blind of the study, randomization of the treatment condition is determined by the CAMH Pharmacy. All laboratory results are faxed directly to the Russell Street CAMH pharmacy, and reviewed by designated staff. Only laboratory data that results in an exclusion of the participant (e.g., positive pregnancy, evidence of supplementary cannabis use) is communicated to experimenters. Measurements collected are explained in greater detail under section 2.1.1.1. Detailed study procedures by study session are described under section 2.1.2.
This experiment is ongoing and is currently in the pilot phase of testing. During the pilot phase, a total of five participants will receive the active cannabis. Preliminary data from the first two pilot participants who received the active drug will be presented in Chapter 3.

2.1.1.1 Measures Collected

A data collection scheme is depicted in Table 1. The data collected in this experiment are divided into categories of physical, behavioural, cognitive, subjective, and other measures. All subjective measures have been validated and are suitable for use in this study. A brief description of each measurement is provided.

Physical Measurements

1. Breath sample for alcohol

A breath sample is obtained at the start of each session using the Alert™ J4X breath alcohol testing system (Alcohol Countermeasure Systems, Toronto) in order to eliminate the possibility of testing the driving performance of an individual who is under the influence of alcohol. A positive breath sample excludes the subject from further testing and analysis. Breath testing instruments are calibrated yearly by the CAMH Clinical Laboratory.

2. Physical examination

A physical examination is conducted during the eligibility screening visit (Session 1) by a qualified physician. Relevant medical history and drug use history are obtained. Measures of height and weight are used to calculate BMI.

3. Vital signs

Temperature, pulse rate, blood pressure, and respiration rate are collected during the medical screening in Session 1, at baseline (30 minutes prior to drug exposure), and at 5, 15, 30 minutes and
hourly thereafter for 6 hours during Session 3, and at 24 and 48 hours respectively during Sessions 4 and 5.

4. Serum and blood biochemistry

Serum and blood samples are taken during the medical examination. Tests administered include complete blood count (CBC), sodium, potassium, blood urea nitrogen, creatinine, glucose, and liver function tests (alanine aminotransferase, aspartate transaminase, and gamma glutamyl transpeptidase). All analyses are conducted by the CAMH Clinical Laboratory.

5. Blood levels of THC, THC-COOH, and 11-OH-THC

Quantitation of THC, THC-COOH, and 11-OH-THC are performed in blood for pharmacokinetic analysis. Whole blood samples are extracted using a solid-phase extraction technique (see Appendix A) and analyzed using gas-chromatography mass-spectrometry (GC-MS). Quantitation is performed at baseline (30 minutes prior to drug exposure), at 5, 15, 30 minutes and hourly thereafter for 6 hours during Session 3, and at 24 and 48 hours during Sessions 4 and 5, respectively. All analyses are conducted by the CAMH Clinical Laboratory.

These samples are used in conjunction with pharmacodynamic measures collected (ARCI, VAS, POMS – described below) to predict an appropriate PK/PD model. Because of the delayed onset of effects of THC and counter-clockwise hysteresis of the time course of concentration versus effects (see Figure 1), an indirect link, indirect response, soft link, time-variant model can be used. (Derendorf and Meibohm, 1999). The concentration-time curve for THC, 11-OH-THC and THC-COOH can be used to calculate $C_{\text{max}}$, $T_{\text{max}}$, AUC, and $T_{1/2}$. 


Table 1. Testing Matrix for Part A – Cannabis and Driving Human Laboratory Driving Simulation Study

<table>
<thead>
<tr>
<th>Examination</th>
<th>Session 1</th>
<th>Session 2</th>
<th>Session 3 (Administration Day)</th>
<th>Session 4</th>
<th>Session 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time pre/post smoking</td>
<td>-24 hr</td>
<td>-30 min</td>
<td>5 min</td>
<td>15 min</td>
<td>30 min</td>
</tr>
<tr>
<td>Driving Trial</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Examinations</td>
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<tr>
<td>Breath Sample</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Physical Exam</td>
<td>X</td>
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<tr>
<td>Psychiatric Exam (SCID)</td>
<td>X</td>
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<tr>
<td>Vital Signs (temperature, pulse, blood pressure, respiration rate)</td>
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<tr>
<td>Examinations</td>
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<tr>
<td>Toxicology Screen</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>THC and metabolites</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Pregnancy</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Blood Tests</td>
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<tr>
<td>THC and metabolites</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Biochemistry (CBC, electrolytes, liver and renal function tests)</td>
<td>X</td>
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<tr>
<td>Examinations</td>
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<tr>
<td>Demographics</td>
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<tr>
<td>Driver Behaviour</td>
<td>X</td>
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<tr>
<td>Driving Vengeance</td>
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<tr>
<td>Road Rage Victimization &amp; Perpetration</td>
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<tr>
<td>Risk-Taking Behaviour in Traffic</td>
<td>X</td>
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<td>General Health</td>
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<td>Brief Sensation Seeking</td>
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<td>Impulsivity</td>
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<tr>
<td>Delayed Discounting</td>
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<td>Questionnaires</td>
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<td>Cognitive Tests</td>
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<td>Shipley-2 IQ</td>
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<td>HVLT-R</td>
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<td>DSST</td>
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<td>CPT</td>
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<td>Grooved Pegboard</td>
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<tr>
<td>ARCI</td>
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<td>VAS</td>
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<tr>
<td>POMS</td>
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</table>
6. Urine levels of THC, THC-COOH, 11-OH-THC, and creatinine.

Urine toxicology screening and pregnancy testing

Urine is collected for quantitation at baseline in Session 3, and a sample is collected at 6 hours post administration. Additional samples are collected at 24 and 48 hours (Sessions 4 and 5). Urinary quantitation of THC and metabolites is accompanied by quantitation of urinary creatinine. The ratio of THC-COOH: creatinine will inform experimenters if additional recreational cannabis has been consumed between testing days.

7. Urine toxicology screening and pregnancy testing

Urine is collected for screening at each session for determination of ongoing eligibility of participants. A positive immunoassay result for any drug class other than cannabinoids results in disqualification from the study. A positive pregnancy test for females likewise results in disqualification.

**Behavioural Information**

8. Psychiatric exam: Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)

A semi-structured clinical interview for DSM-IV axis I disorders (First et al., 2002) is conducted by trained personnel in order to rule out pre-existing psychiatric conditions which may predispose a participant to harm during the study. Data collected from this interview is used for exclusionary purposes only.

9. Demographics and Driving Behaviour Questionnaire

A computer-based questionnaire is administered during Session 2 (practice day), which takes approximately 30 minutes to complete and encompasses a variety of independently validated measures. The questionnaire collects basic demographic information, as well as assessing other self-reported measures of driving behaviours. The questionnaire includes the Driver Behaviour
Questionnaire (DBQ) (Reason et al., 1990) assessing self-reported driving violations, errors, and lapses, the Driving Vengeance Questionnaire (DVQ) (Wiesenthal et al., 2000) assessing driver aggressiveness and vengeance in common driving situations, the Road Rage Victimization and Perpetration Questionnaire (Butters et al., 2006; Smart and Mann, 2002), and the Risk-Taking Behaviour in Traffic Questionnaire (Ulleberg and Rundmo, 2003). Additional constructs assessed include general health status using the General Health Questionnaire (GHQ-12) (Goldberg et al., 1997), Brief Sensation Seeking Scale (Stephenson et al., 2003), as well as impulsivity using a delayed discounting task (Bickel and Marsch, 2001).

**Cognitive Tests**

Cannabis users have demonstrated impairment of cognitive function during intoxication (Crean et al., 2011). The following measures are collected to examine the acute and residual effects of cannabis on cognition.

10. Shipley-2 for IQ measure

The Shipley-2 IQ test (Kaya and Dehlan, 2012) is administered to assess overall cognitive functioning and to detect cognitive impairment. The test specifically measures crystallized knowledge (gained through education) and fluid reasoning (ability to adapt to new information). While the data collected from this test will be used for subsequent analyses, the primary purpose of administering this test is for exclusionary purposes. Should a low score (< 80) be obtained and there is question as to whether a participant is capable of fully understanding the study procedures, the individuals will be excluded from further participation.

11. Digit Symbol Substitution Test (DSST)

The computer-based Digit-Symbol Substitution Test (DSST) is a sub-measure of the Wechsler Adult Intelligence Scale and is useful for measuring overall cognitive ability, associations, and reaction time (McLeod et al., 1982). Participants are presented with a series of block patterns all associated with a number. Below this legend, participants are presented with a number and asked to
replicate the pattern associated with the number as quickly as possible. The DSST is collected during Session 2, as well as at baseline (30 minutes prior to exposure), 1 hour after exposure during Session 3, and at 24 and 48 hours during Sessions 4 and 5, respectively.

12. Hopkins Verbal Learning Test Revised (HVLTR)

The computer-based HVLTR is a measure of verbal learning, memory, and delayed recall (Benedict et al., 1998). Participants are read a list of words by the experimenter and asked to repeat back as many as can be remembered on four separate occasions; three times immediately after the list is read, and a fourth time following a 23 minute delay. Participants are then read a second list of words and after each word are asked to indicate if the word appeared on the original list, or not. The HVLTR is administered in Session 2, as well as at baseline (30 minutes prior to exposure), 1 hour after exposure in Session 3, and at 24 and 48 hours during Sessions 4 and 5, respectively.

13. Connors’ Continuous Performance Test II (CPT-X)

The CPT-X is a test of attention (Connors et al., 2003) that has been previously used as a diagnostic test for ADHD, although it will not be used for that purpose in this study. The test is designed to assess sustained attention and impulsivity. During this computer-based test, a letter flashes on a black screen. Participants are asked to press the space bar after every letter that appears, unless that letter is an X. The CPT-X is administered during Session 2, as well as at baseline (30 minutes prior to exposure), 1 hour after exposure in Session 3, and at 24 and 48 hours during Sessions 4 and 5, respectively.

14. Grooved Pegboard Task (Lafayette Model 32025)

The grooved pegboard test is a test of fine motor control and hand-eye coordination. The test consists of a board with 25 holes with randomly positioned slots and pegs equipped with a protruding groove along one side. The pegs must be rotated to fit the hole before they can be inserted (Lafayette Instruments, 2002). The time taken to insert all the pegs is recorded for both the dominant and non-dominant hands. The test is administered during session 2, at baseline (30
minutes prior to drug exposure), and at 30 minutes and 1 hour after exposure in Session 3, and at 24 and 48 hours post drug administration in Sessions 4 and 5, respectively.

**Subjective Drug Effects**

15. Addiction Research Centre Inventory (ARCI) Short Form

The ARCI is a standardized questionnaire developed by the Addiction Research Centre. The test is used for assessing the subjective effects of psychoactive drugs, and for differentiating between the effects of different types of drugs (Haertzen, 1963; Hill, 1963). The full ARCI consists of 550 true/false statements based on a method of sentence completion (Haertzen, 1963). The short-form (49 items) used in this study is derived from the full version, is computer-based, consists of true or false questions, and uses 4 different drug-like effect scales. The morphine-benzedrine group scale (MBG) assesses morphine-like euphoric effects, the benzedrine (BG) scale measures stimulant effects, the LSD scale measures hallucinogenic effects, and the pentobarbital, chlorpromazine, and alcohol-like group (PCAG) measures sedating effects of the drug. The ARCI is administered during Session 2, at baseline (30 minutes prior to drug exposure), at 30 minutes, and at 1 hour in Session 3, and at 24 and 48 hours post administration during Sessions 4 and 5, respectively.

16. Self-reports of drug effects using Visual Analog Scales (VAS)

Computer-based visual analog scales are used to assess subjective drug effects. A horizontal line scale from 0-100 is presented to participants beneath a word or phrase describing how they might feel, and they are asked to move a pointer along the scale to correspond to how much they do or do not currently agree with the statement based on how they are feeling. Participants are asked to provide a rating on feelings of “Drug Effect”, “High”, “Good Effect”, “Bad Effect”, “Rush”, “Drug Liking” and “Feels Like Cannabis”. Visual analog scales are more sensitive to small changes in subjective feelings than are other types of scales (Paul-Dauphin, et al., 1999). VASs to assess subjective drug effects are administered on Session 2, at baseline (30 minutes prior to drug exposure), and at 5, 15, and 30 minutes, 1 hour and hourly thereafter for 6 hours in Session 3. VASs
are administered to assess residual effects at 24 and 48 hours post dose in Sessions 4 and 5, respectively.

17. Profile of Mood States (POMS)

The computer-based POMS represents a list of 72 items designed to measure fluctuations in mood and affective states (McNair et al., 1981). The questionnaire is self-administered and uses a 5-point Likert scale with response options of not at all; a little; moderately; quite a lot; and, extremely. The scale assesses eight mood clusters and two derived mood clusters. Mood clusters include: tension/anxiety, depression/dejection, anger/hostility, vigor, confusion, friendliness and elation. Derived measures include: arousal (sum confusion and fatigue subtracted from sum of tension/anxiety and vigor), and positive mood (depression/dejection subtracted from elation). Subjects are given a score for each trait. The POMS is administered in this study during session 2, as well as at baseline (30 minutes prior to drug exposure), 30 minutes and 1 hour post drug administration in Session 3, as well as at 24 and 48 hours in Sessions 4 and 5, respectively.

Other

18. Driving simulation tests

The main outcome measure - overall driving performance - is assessed through four driving trials of 2 x 10 minutes each in duration, conducted at baseline (30 minutes prior to drug administration), and at 1, 24, and 48 hours following drug administration. Opportunity to practice on the simulator is given on the practice day (session 2) and prior to each experimental driving task. This is accomplished in order to mitigate potentially poor driving performance that may be observed due to unfamiliarity with the simulator, and/or to diminish the contribution of significantly improved performance across testing days due to practice effects. The practice driving scenarios consist of uneventful rural highway driving, and are designed to maximize familiarity with the driving simulator system. To better simulate the cognitive demand of real-world driving conditions, during each testing opportunity one of the two 10-minute driving simulations is conducted under a dual-task condition. The participant is asked to count backwards by threes from a three-digit number chosen by
the investigator, and audio recordings are taken with permission. Each scenario driven by the participant is altered slightly, so as to mitigate the effects of practicing the same driving scenario multiple times across study days.

Five main categories of driving skill are assessed: overall performance across the session and performance in response to four separate driving hazards within the session. Overall performance includes measures of mean speed, SDLP, and total number of collisions across the entire driving session. The four hazards within each scenario includes: (1) a straightaway (open road with no traffic); (2) a slow moving vehicle with traffic in the oncoming lane; (3) a reaction time hazard where a pedestrian or other vehicle suddenly blocks the way, and; (4) a risk-taking hazard where risk should be anticipated and caution exercised (e.g., a pedestrian standing next to a disabled vehicle at the side of the highway). Different dependent variables are measured for each hazard. The straightaway hazard measures mean speed, SD of speed, and SDLP. As no traffic is present in this zone, it is anticipated that risky behaviour is more likely to occur. The slow moving vehicle hazard measures the participant’s following distance in seconds to the rear of the slow moving vehicle. The reaction time hazard measures simple reaction time (braking distance in meters) to the hazard (e.g., immovable object in the road). Finally, the risk-taking hazard measures the braking distance (in meters) to the risky stimulus.

2.1.1.2 Dosage Regimen

This experiment tests the acute and residual effects of a single dose of cannabis or placebo administered in the morning of Session 3 (Drug Administration Day) on cognition, psychomotor skill, and driving ability. Active cannabis was obtained from Health Canada (Ottawa, ON), and matching placebo cannabis was obtained from the National Institute on Drug Abuse (NIDA) in Bethesda, Maryland, USA. The cannabis provided by Health Canada is the same as that provided for the Marihuana Medical Access Program throughout Canada, and is grown under strictly controlled conditions by Prairie Plant Systems, Inc. (Saskatoon, Saskatchewan). Production of the active cannabis is highly standardized and secure, with a guaranteed potency of 12.5% ± 2% THC (Health Canada, 2013). The placebo cannabis is obtained directly from NIDA. The chemical removal process of THC from the placebo cannabis provides results of a guaranteed potency of < 0.1% active THC, and is therefore considered to be negligible.
The volume of plant material contained in each cigarette was chosen to reflect that of an ‘average’ cigarette, which can range in mass from 0.5 to 1.0 g of plant material according to Health Canada (Health Canada, 2013). As such, each cigarette is weighed to contain 750 mg of plant material. At 12.5% ± 2%, this results in dosage range of 79 – 109 mg THC in the active condition, and a maximum of 0.75 mg in the placebo condition (< 0.1% THC). Cannabis is received as loose plant material from Health Canada, and placebo cannabis in pre-packaged cigarettes 713 mg in mass from NIDA. NIDA placebo cigarettes are re-assembled into 750 mg cigarettes by the CAMH Pharmacy, visually indistinguishable from the active cigarettes.

All cannabis cigarettes (active and placebo) are stored frozen at -20°C in a secure, locked freezer accessible only to designated CAMH Pharmacy staff, and re-humidified for at least 12 hours prior to use according to NIDA recommendations (NIDA, year unknown). Smoking of the cigarette by participants is conducted in the CAMH Bio-behavioural Addictions and Concurrent Disorders Research Laboratory (BACDRL), a dedicated reverse airflow room with external ventilation of expired smoke. The one-time dosing regimen consists of instructing subjects to smoke as they normally would for a maximum of 10 minutes while being observed by experimenters and medical staff via two-way mirror in an adjacent room. Participants are instructed to smoke until they achieve a “high” similar to that which they normally would achieve, and that they may stop smoking at any time if they are feeling ill, or are achieving a high greater than they would normally experience.

2.1.1.3 Participant Selection

Participants were selected for inclusion in this study based on strict inclusion and exclusion criteria, as outlined below.
**Inclusion Criteria**

- Aged 19 to 25 years
- Self-reported use of cannabis between 1 and 4 times per week (prior use of cannabis confirmed via positive immunoassay cannabinoids in urine collected during Session 1)
- Valid G2 or G class driver’s licence (or equivalent from another province or country with similar driving culture)
- Willing to abstain from cannabis use for 48 hours prior to Session 2, and until completion of Session 5
- Ability to provide written and informed consent
- Use of an approved form of birth control (abstinence, physical barriers, or hormonal methods) (females only)

**Exclusion Criteria**

- Self-reported regular use of psychoactive medication (e.g., antidepressants, benzodiazepines, stimulants)
- Any severe or contraindicated medical or psychiatric diagnoses, including current or lifetime DSM-IV substance use disorders
- A first degree family history of schizophrenia
- Pregnant, trying to become pregnant, or breastfeeding (females only)

**Ongoing Exclusion Criteria**

- A positive breath sample for alcohol at any time
- Negative Session 1 urine screen for cannabinoids (e.g., cannot confirm regular cannabis use)
- Any evidence of supplemental cannabis use between study days, including urine toxicology screening
- Urine toxicology screen at any time positive for additional psychoactive substances
2.1.2 Study Procedures

2.1.2.1 Session 1: Screening Day

Following initial eligibility assessment via telephone, participants are invited to attend a medical screening eligibility assessment (Session 1). Informed consent is obtained prior to commencement of any study procedures. Participants are given the opportunity to ask questions and are required to demonstrate their understanding of the study prior to signing the consent form, after which time they are provided with a photocopy of the signed version to keep. A sample of breath is collected to measure alcohol. A urine sample is also collected and sent to the CAMH Clinical Laboratory for pregnancy testing (females only) and general drug screen analysis to confirm the presence of cannabinoids and absence of other psychoactive substances. Participants then undergo a physical examination by a physician, and a Structured Clinical Interview (SCID) is performed by qualified personnel. Blood samples are drawn by the physician or other qualified personnel for biochemistry analysis. In order to proceed with subsequent testing days, a medical doctor reviews the laboratory, medical and SCID results to confirm eligibility.

2.1.2.2 Session 2: Practice Day

Participants who satisfactorily complete Session 1 are invited to complete the remainder of the study. Breath and urine samples are taken to confirm ongoing eligibility. Participants then are asked to complete a series of computer-based questionnaires providing information on demographics, substance use, and driving behaviour. The Shipley-2 IQ test is administered (on paper), followed by a series of computer-based tasks. The Driver Behaviour Questionnaire is administered, along with cognitive tests (DSST, HVLT-R, CPT-X) and psychomotor testing (grooved pegboard). Subjective measures of drug effects and mood (ARCI, VAS, POMS) are also completed. All computer tasks are also practiced in order to mitigate potential practice effects that may be seen in the absence of the ability to practice. Participants have the opportunity to perform two practice driving simulator trials (2 x 10 minutes, one under full attention, and the other under the dual-talk condition) on this day in order to gain experience and mitigate practice effects on the simulator.
2.1.2.3 Session 3: Administration Day

Breath and urine samples are taken to confirm ongoing eligibility. Blood samples are taken for baseline THC and metabolites measurement. At 30 minute prior to drug administration, vital signs are recorded, and participants are asked to complete baseline measures of cognitive tests (DSST, HVLT-R, CPT, grooved pegboard) and subjective measures (ARCI, VAS, POMS), and to complete two 10-minute driving trials (full attention and dual-task conditions) preceded by a 5-minute practice session. Participants are then asked to smoke a single cannabis cigarette (12.5% THC or placebo) in the BACDRL lab, and instructed to smoke as they normally would to achieve a high no greater than they would normally achieve for a maximum of 10 minutes. Vital signs are taken, sequential blood samples are drawn, and VAS are completed to permit characterization of cannabinoid levels for time-effect estimation over a 6-hour period beginning at 5, 15, 30 minutes and 1 hour after administration, then hourly thereafter for 6 hours. Another two 10-minute driving trials (full attention and dual task conditions) are completed at 30 minutes post administration, preceded by a 5-minute practice opportunity. Cognitive tests and some subjective assessment (DSST, HVLT-R, CPT, grooved pegboard, ARCI, POMS) are performed at 1 hour after administration. Urine samples are collected prior to smoking, and pooled throughout the day.

2.1.2.4 Sessions 4 and 5: Follow-up Procedures at 24 and 48 hours

The procedures for follow-up at Sessions 4 and 5 (24 and 48 hours) are identical. Breath and urine samples are taken to confirm ongoing eligibility. Participants are asked to complete a driving simulator trial (two 10-minute trials preceded by 5 minutes of practice). Vital signs are taken along with blood and urine samples collected for cannabinoid analysis. Participants' mood and cognitive functioning are also measured (DSST, HVLT-R, CPT, grooved pegboard, ARCI, VAS, POMS) to assess residual effects.
2.1.3 Sample Size Justification

The effect size of cannabis’ residual effects on driving simulator performance is difficult to determine, as this is a relatively new area of research. Most studies examining the effects of drugs on driving use within-subjects designs. This research is unique in that a between-and-within-subjects design is proposed in order to provide better and more numerous comparisons of driving measures, and to maximize the scientific yield of the study. As such, a 2:1 allocation ratio of the active to placebo is used, and the sample size estimated to be necessary to achieve adequate power ($1-\beta = 0.8$) is based on a ‘medium’ effect size of 0.5. The estimated sample size for this study is 114 participants in total, with 76 receiving active cannabis and 38 receiving placebo. Because attrition is anticipated with this population, an estimated 25% dropout/non-completion rate is assumed, and therefore a total of 142 individuals are needed to achieve this sample size. This sample size is larger than any other study to date assessing the impact of cannabis on simulated driving performance and residual drug effects. The first five participants recruited are part of the pilot phase of testing, and will receive the active drug.

2.1.4 Participant Recruitment

In order to recruit participants in the target age group (19 to 25 years), advertisements for the study are placed in NOW magazine, the Metro newspaper, and on the CAMH study recruitment website (see Appendix B). Additionally, posters are placed around the University of Toronto campus and other community poster boards in the area (see Appendix B). Initial contact with potential participants was made via telephone, and study personnel conduct an initial telephone screen for eligibility (see Appendix C). Upon positive eligibility screening by telephone, participants are invited to attend CAMH for a medical eligibility assessment (Session 1). Details of the results of recruitment for the study so far can be found under section 3.1.1.
2.1.5 The Simulator

Greater technical detail for the simulator can be found in Virage Simulations (2007). The Virage driving simulator model VS500M (Figure 2) cabin features only the driver’s side console. The console replicates a General Motors automatic transmission compact model car. The console contains a front seat, seatbelt, steering wheel, ignition, hand brake, indicators, accelerator, gear shifter, and brake pedals. All displays (e.g., speed, RPM) and display lights are operational and responsive to the virtual environment. Fuel level and engine temperature also display realistic values, and warning lights can alert the driver to mechanical emergencies. The position of the instruments and controls (e.g., steering wheel), are monitored by a computer and are used by the simulation to provide realistic feedback of the vehicle’s behaviour. These include the ignition key, accelerator and brake pedals, gear, hand brake, and steering wheel, as well as left and right signals, hazard signals, and seatbelt on or off position.

The simulator provides dynamic force feedback during the simulation. Specifically for steering, an electrical DC motor connected to an amplifier is used, and a control board generates the force feedback on the wheel. This force feedback allows for vibration and special effects associated with pot holes, rumble strips on a highway, sidewalks, and other obstacles. The accelerator and brake pedals also provide force feedback. The pedals are spring-loaded and able to realistically simulate the feel of acceleration and braking. The motion and vibration system consists of a compact three-axis platform with electric actuators (motors), an electronic controller and amplifier. The system provides cues from acceleration, engine vibration, and road texture feedback as they relate to the car’s speed and the road surface. Audio feedback gives appropriate auditory cues in relation to acceleration, braking, the presence of other cars, and environmental hazards.

The visual display is generated using technically advanced graphic cards for maximum realism. The display system consists of three 50” screens in a curved configuration in front of the console. Two smaller 17” computer screens are located to the rear sides of the driver console to allow for blind spot checking. The rear view and side mirrors are simulated in the display as an insert in the main screens. ‘Stock’ driving scenarios originally developed for driver education purposes were modified by qualified personnel for the purpose of this study.
Figure 2. The Virage VS500M driving simulator. Photo courtesy of Virage Simulations, Montreal QC.

2.2 Part B: Epidemiological Study

2.2.1 The CAMH Monitor

The CAMH monitor is a yearly population-based survey of Ontario adults aged 18 years and older. The survey monitors issues related to alcohol, tobacco, and other drug use in addition to gambling and general mental health. The survey has been ongoing at CAMH (and formerly, the Addiction Research Foundation) since 1977 when it began as the Adult Drug Use Series (1977-1991). The survey is the longest study of adult drug use in Canada. Early versions of the survey were conducted using labor-intensive in-person interviews, which were discontinued in 1991. Since 1992, the CAMH Monitor has been administered by the Institute for Social Research at York University in Toronto using computer-assisted telephone interviews (CATI). The data analyzed in Part B of this
study were collected using only CATIs. CATI interviews are conducted over the telephone with a person, although a computer provides the human interviewer with the specific questions to be asked. A ‘core’ set of questions are asked of all interviewees, and a selection from two separate panels of additional questions (panel A and panel B) are asked of different interviewees. The computer is able to assist in removing subsequent sections in a series, particularly when a ‘no’ response renders a following set of questions irrelevant or unanswerable.

The CAMH Monitor sample for years 2002 - 2010 is based on an annual, monthly, continuous (“rolling”) sampling procedure (explained in further detail under section 2.2.2.1). The number of respondents are stratified equally by region. This type of monthly survey, as compared to a cross-sectional survey of a population at a particular point in time, allows for a better detection of seasonal trends, provides statistical advantages through the use of repeated measures, provides timely information and increases the potential for rapid evaluation of trends (Ialomiteanu and Adlaf, 2013). However, limitations of the design should also be noted. As with all survey data, the CAMH Monitor cannot truly capture the population of Ontario without sampling every individual. The CAMH Monitor does not sample all sub-populations within the province, as it does not include individuals who are phoneless, who are of no fixed address, or are institutionalized in prisons or hospitals. Individuals who do not converse adequately in English are unable to participate in the survey, as are the too ill or aged. Self-report data collected by the CAMH Monitor may underestimate true drug and alcohol usage within a population. Although, any underestimation inherent in the CAMH Monitor dataset is likely to remain consistent over time, and thus retain the survey’s ability to detect trends within the population. Finally, although it is estimated that alcohol and drug use may be higher among the populations who are not captured by the survey (e.g., prison populations), the size of these populations are sufficiently small so as not to impact the survey excessively. Further information on the CAMH Monitor is available from Ialomiteanu and Adlaf (2013).

2.2.2 Study Design

In 2002, two important items were introduced to the CAMH Monitor asking about DUIC and past-year collision involvement. Specifically, these questions asked “during the past 12 months, have you driven a motor vehicle within an hour of using cannabis, marijuana, or hash?” and, “during the
past 12 months, how often, if at all, were you involved in an accident or collision involving any kind of damage or injury to your or another person or vehicle while you were driving?”.

Responses to these questions and other demographic measures from the CAMH Monitor in the years 2002 through 2010 were merged for this study. Examination of self-reported collision involvement in the past 12 months among the general-population sample of Ontario adults was carried out to determine the relationship between DUIA, DUIC and past-year collision involvement. Methods of statistical analysis are described in section 2.2.4.

2.2.2.1 Participant Recruitment and Selection

The sampling procedure used to collect data for years 2002 to 2010 used a two-stage stratification design, with the sample divided by six regional area codes. The sample is equally allocated between regions. Although this procedure results in a disproportionate percentage of respondents based on region (e.g., despite most of Ontario’s population being located in the Greater Toronto Area, an equal number of respondents are chosen from the Greater Toronto Area as from any other region), this strategy has the advantage of ensuring adequate participation from less-populated regions, and can be accounted for by weighting of the sample prior to analysis.

The primary sampling unit of the survey (first stage) is the selection of the household for sampling. Households are selected each month using list-assisted random digit dialing (RDD) (described below). The secondary sampling unit (second stage) involves selection of an English-speaking resident within the household, aged 18 years and older, by selecting the person within the household whose birthday had passed most recently. This ensures an unbiased selection. Although the CAMH Monitor aims to survey a representative sample of Ontario adults, in reality, the population is based only on adult Ontario landline or cellular telephone subscribers and their household members. Excluded are residents who are phoneless, of no fixed address, those who are too ill or aged to be interviewed, and people who are unable to communicate sufficiently in English. Excluded are people who are institutionalized or in custody in hospitals or prisons; however, military personnel are not excluded from the population.

The RDD sampling procedure uses the structure of 10-digit telephone numbers in Ontario. First, a list of valid, residential, Ontario telephone numbers are constructed from CD-ROM telephone
directories and other commercially available lists of telephone numbers. Numbers pulled from these sources are supplemented by the numbers between, or on either side, of listed numbers. For example, if a published telephone number ends in a 2585, all similar numbers from 2580 through 2589 are included in sampling. Numbers are excluded only if known to be inactive or not in service. Following this procedure, a computer is used to generate a random sample of telephone numbers from which each monthly sample is drawn. This strategy increases the probability of including active numbers that are unpublished, and reduces the bias of the sample. Unanswered numbers are re-tried a minimum of 12 times before replacement with another number. Households that refuse participation on the first contact are re-contacted in an attempt to gain participation.

2.2.3 Sample Size

Survey data from 2002 to 2010 were merged for the analysis. Since 2002, the CAMH Monitor has included an item on collision involvement in the past 12 months, thus for purposes of the current study data from 2002 to 2010 were merged (N=16,224). Each annual cycle used a randomly selected sample ranging between 2,005 and 3,030 adults aged 18 years and older. The weighted sample is representative of the Ontario general adult population (response rates: 51% to 58%).

2.2.4 Data Analysis

Data were analyzed using SPSS 15.0 software, in two parts. First, demographic characteristics (gender, age, marital status, income, region) were examined between people who report DUIC and people who do not report DUIC within the population. Chi-square analyses were used to determine an association between demographic variables and DUIC behaviour followed by logistic regression analysis to assess the impact of these variables on the likelihood of reporting DUIC. Second, the self-reported collision involvement in the past 12 months was examined in three groups (no DUIA or DUIC, either DUIA or DUIC, both DUIA and DUIC). The association between collision involvement and substance use group was first examined using Chi-square analysis. Logistic regression analysis further assessed the impact of reporting either DUIA or DUIC, and
reporting both DUIA and DUIC, on collision risk while controlling for demographic characteristics that significantly affect collision risk. All analyses are based on the weighted sample size.
Chapter 3
Results

3.1 Part A
3.1.1 Regulatory Requirements

Prior to commencement of screening and enrollment for this study, considerable efforts were
directed towards obtaining the necessary regulatory approvals for use of a controlled substance
(cannabis) in research. Table 2 represents a simplified timeline of the procurement of these
requirements. Re-submissions to research ethics and an amendment to the clinical trial application
(CTA-A) were required following any significant changes to the protocol, consent form, or any
change resulting in an increased burden to participants or change in the target study population
(inclusion/exclusion criteria). Over the course of the study, such changes included the separation of
participant screening and data collection by study day (in order to minimize wasted time and
resources in the event of an exclusion), changes in the battery of cognitive tests used, increasing the
volume of blood collected, and most notably, expanding the allowable age range to 25 years, and
allowable days of smoking to four days per week or less. With the exception of the initial grant
submission and obtaining the active drug, the writer took the lead responsibility for drafting and
submitting these regulatory documents.
Table 2. Timeline of approval for regulatory requirements for Part A

<table>
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<tr>
<th>Requirement Type</th>
<th>Regulatory Body</th>
<th>Original or Amended Document</th>
<th>Approval Date</th>
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<td>CAMH</td>
<td>Amendment</td>
<td>June, 2013</td>
</tr>
<tr>
<td>Research Ethics</td>
<td>Health Canada</td>
<td>Amendment</td>
<td>June, 2013</td>
</tr>
</tbody>
</table>

CIHR = Canadian Institutes of Health Research, N/A = Not Applicable, CAMH = Centre for Addiction and Mental Health, CDSA = Controlled Drugs and Substances Act, NIDA = National Institute on Drug Abuse (Bethesda, Maryland)

3.1.2 Screening and Enrollment

Between July 2012 and July 2013, 156 people called the telephone extension advertised on the study flyers. Of those, 132 were pre-screened for inclusion in the study. The remainder are waiting to be pre-screened (n = 10), lost interest upon call-back (n = 6), could no longer be reached after multiple attempts, including providing an incorrect return number (n = 7), or called about the wrong study (n = 1). Of the 132 people pre-screened by telephone, 29 met the initial eligibility criteria (21.9%). For those who were found to be ineligible following telephone pre-screening, various reasons for exclusion emerged (see Table 3). No individuals were excluded for reporting a family history of schizophrenia, or due to pregnancy, intent to become pregnant, or breastfeeding. Many individuals were excluded for multiple reasons (most commonly aged over 25 years and smoking > 4
times per week). The telephone pre-screening interview script (Version 1.0; July, 2012 – December 2012, and Version 2.0; January 2013 – July 2013) can be found in Appendix C.

Table 3. Frequency of and reasons for exclusion of study participants following initial telephone pre-screening. Frequencies include individuals who were excluded under multiple criteria.

<table>
<thead>
<tr>
<th>Reason for Exclusion</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of smoking greater than 4 times per week</td>
<td>77</td>
</tr>
<tr>
<td>Age over 25 years</td>
<td>40</td>
</tr>
<tr>
<td>Invalid licensure</td>
<td>8</td>
</tr>
<tr>
<td>Frequency of smoking less than once per week, or does not use cannabis</td>
<td>7</td>
</tr>
<tr>
<td>Self-reported lifetime diagnosis of psychiatric illness</td>
<td>4</td>
</tr>
<tr>
<td>Age under 19 years</td>
<td>1</td>
</tr>
<tr>
<td>Current use of other psychoactive medication(s)</td>
<td>1</td>
</tr>
</tbody>
</table>

Of the 29 people who were found to be eligible, 10 were enrolled in the study and gave informed consent. Of the remaining 19 people, nine are awaiting scheduling for screening (Study Session 1). Ten people could not be scheduled due to loss of interest (n = 3), because they were unable to be reached again after multiple attempts (n = 6), or due to declining to sign the consent form upon attendance for Session 1 (n = 1). Of the 10 people who were enrolled in the study (took part in Session 1), four were excluded following medical screening due to the absence of cannabinoids in urine (n = 1), history of alcohol dependence as assessed from the SCID (n = 1), admission of smoking greater than four times per week (n = 1), and medical ineligibility (low blood pressure, n = 1). At the time of writing, n = 4 have completed Session 1 and are to waiting be scheduled for the remainder of the study, n = 1 dropped out of the study after dosing, and n = 1 has completed the study in its entirety. Figure 3 is a graphical depiction of the flow of screening and enrollment in this study. The average age of the individuals screened by telephone thus far is 25.8 years (range 18 to 69 years), and the majority are male (28.8% female).

Enrollment has presented a significant challenge for this study. The inclusion and exclusion criteria, methods of advertising, and telephone screening questions all required revision in order to address low recruitment. Advertisement of the study commenced on July 19th, 2012 through a print ad featured in the classified section of NOW magazine (see Appendix B). Print 8.5 x 11” posters were placed around the University of Toronto St. George campus concurrently (see Appendix B).
Participants who called were screened using version 1.0 of the Telephone Pre-Screening form (See Appendix C). This screening form captured the inclusion criteria of a previous version of the protocol, restricting age of participant to 19 and 20 years, and allowable frequency of smoking to only one or two times per week. Between July 2012, and December 2012, 97 people were screened, and only six people were found to be eligible (6.2%). The majority of people who responded to the advertisements were found to be ineligible due to being aged over 20 years (n = 32) and/or for self-reported use of cannabis more than one or two times per week (n = 57). Of the six respondents who were found to be eligible, two were enrolled in the study. Both participants were subsequently excluded following medical eligibility screening (n = 1 due to no evidence of prior cannabinoid use in urine, n = 1 due to alcohol dependence as assessed by the SCID), with the remainder of eligible respondents losing interest in participation prior to enrollment. To address low enrollment, and using this data as justification, an amendment to the protocol was approved expanding the allowable age of participants to up to 25 years, and the allowable frequency of smoking up to four times per week. The telephone pre-screening procedure was updated to reflect these changes (version 2.0, see Appendix C). Re-analysis of respondents pre-screened using version 1.0 revealed an additional nine participants who were eligible using the new criteria, who had previously been excluded due to admission of smoking between three and four times per week (n = 6), age of 21 to 25 years (n = 2), or both (n = 1). These respondents were re-contacted. Of these potential participants, four could not be reached after multiple attempts, and two had lost interest in participating. Further to this, two from this group were subsequently enrolled in the study, although one has been excluded, and the other has to date completed Session 1 only. Finally, a single person from this cohort is currently waiting to be scheduled for Session 1.

Since expansion of the inclusion criteria for this study, 43 people have been screened using Telephone Screening Form 2.0, and 13 people (30.2%) have met the expanded criteria for eligibility. This represents a substantial improvement in recruitment as a result of expansion of eligibility criteria over the previous protocol. Due to the complex nature of the study and challenges with recruitment and enrollment, this thesis includes information on the first 2 pilot participants who received the active drug, for information only. Demographic, pharmacokinetic, cognitive and driving data for these participants are presented in the subsequent sections for preliminary descriptive purposes. These participants will herein be referred to as participant #1 (P1) and participant #2 (P2). Disjointed lines represent missing data points.
Figure 3. Flow chart of participant enrollment for Part A

- Waiting for call-back: 10
  - Lost interest: 10
    - Lost Interest: 3
    - Cannot reach: 6
    - Refused Consent: 1

- Total Called: 156
  - Not Screened: 14
    - Cannot reach: 7
    - Not interested following explanation of study: 6
    - Other: 1

  - Total Screened: 132
    - Eligible: 29
      - Not eligible: 103
        - Frequency of smoking > 4x/wk: 77*
        - Above age 25 years: 40*
        - Invalid licensure: 8*
        - Frequency of smoking <1x/wk: 7*
        - Psychiatric history: 4*
        - Below age: 1*
        - Concomitant medication: 1*
        - History of drug dependence: 1*

- Completed Session 1 (enrolled): 10
  - Ineligible following first visit: 4
    - No evidence of cannabinoids: 1
    - Alcohol dependence: 1
    - Too frequent smoking: 1
    - Medical ineligibility: 1

  - Received Dose: 2
    - Dropped Out: 1
    - Completed: 1

* Frequencies include individuals who were excluded under multiple criteria.
3.1.3 Participant Profiles: Demographic and Physical Characteristics

The demographic and physical characteristics of P1 and P2 are presented in Table 4. Both participants were male and students. They were similar in age, height, weight, BMI, and frequency of cannabis use per week. The more substantial differences were that P1 and P2 differed in IQ by 33 points, and that P1 completed the protocol, whereas P2 did not complete the protocol and voluntarily ended participation mid-way through Session 3. P2 chose to end his participation as the result of an adverse emotional reaction after smoking cannabis. Both participants were recruited during the pilot phase of testing (first five participants), and as such, each received the active drug.

Table 4. Demographic and physical characteristics of participants who received the study drug.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>P1</th>
<th>P2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>Sex</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>Frequency of cannabis use per week</td>
<td>3</td>
<td>2-3</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>173</td>
<td>174</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71</td>
<td>66.5</td>
</tr>
<tr>
<td>BMI (kg/cm2)</td>
<td>23.7</td>
<td>22</td>
</tr>
<tr>
<td>IQ</td>
<td>135</td>
<td>102</td>
</tr>
<tr>
<td>Occupation</td>
<td>Student</td>
<td>Student</td>
</tr>
<tr>
<td>Completed Protocol</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

3.1.4 Pharmacokinetic Data

Presented are the pharmacokinetic data for THC, 11-OH-THC and TH-COOH for both participants. Not all of the time-sensitive blood samples for THC and metabolite quantitation could be collected for either participant due to participant refusal, or because of delays in completing other study procedures. As such, detailed data describing the time course of peak concentrations of THC and metabolites is not available. Regardless, it can be seen from the data collected that THC and metabolites peak shortly after smoking, that metabolites 11-OH-THC and TH-COOH reach only a
fraction of the concentration of the parent drug, and that all compounds continue to be present in trace amounts after 24 and 48 hours. Figures 4 and 5 depict the time course of THC and metabolites in blood for P1 and P2, respectively. Table 5 displays the pharmacokinetic data for these compounds for both participants.

Figure 4. Concentration and time course of THC, THC-COOH, and 11-OH THC prior to, and for 48 hours after smoking for P1. Concentrations are in ng/mL. Concentrations < 0.2 ng/mL are recorded as zero.
**Figure 5.** Concentration and time course of THC, 11-OH-THC and THC-COOH prior to, and for 30 minutes after smoking for P2. Concentrations are in ng/mL. Concentrations < 0.2 ng/mL are recorded as zero.

**Table 5.** Concentrations of THC, THC-COOH, and 11-OH-THC for P1 and P2 from baseline (30 minutes before drug administration) through total participation in the study (48 hours for P1 and 3 hours for P2). Concentrations are in ng/mL. NA = sample not collected.
3.1.5 Physiological Data

Figures 6 and 7 represent the physiological data collected throughout the study, before and after dosing, for each participant. A sharp increase in pulse rate is seen following cannabis administration. No other trends in blood pressure, respiration rate, or temperature are readily apparent from these two participants. Missing data points are the result of participant refusal, or delays in administering other study procedures.

**Figure 6.** Vital signs (blood pressure, pulse rate, temperature, respiration rate) for P1. Blood pressure is recorded in mm/Hg, pulse rate in beats per minute, temperature in degrees Celsius, and respiration rate (RR) in breaths per minute.
Figure 7. Vital signs (blood pressure, pulse rate, temperature, respiration rate) for P2. Blood pressure is recorded in mm/Hg, pulse rate in beats per minute, temperature in degrees Celsius, and respiration rate (RR) in breaths per minute.

3.1.6 Cognitive Data – HVLT-R, DSST, CPT-X, and the Grooved Pegboard

The following table (Table 6) summarizes all cognitive and psychomotor measures collected throughout the study for both participants. A small effect of the drug may be seen for the HVLT-R Total Recall score, DSST completed trials, and DSST time to complete trials for P1 only. For the CPT-X, a slight increase in omission errors and Hit Reaction Time (Hit RT) can be seen before and after administration for P1 and P2. A dramatic increase in commission errors is observed after drug administration, but only for P2. A slight increase in time taken to complete the grooved pegboard following drug administration for both participants is also observed.
Table 6. Data from cognitive and psychomotor testing for P1 and P2 before and after drug administration. Scores for the Hopkins Verbal Learning Test-Revised (HVLT-R), Digit Symbol Substitution Test (DSST), Continuous Performance Task-X (CPT-X) and grooved pegboard are presented. NA = data not collected.

<table>
<thead>
<tr>
<th></th>
<th>Practice Day</th>
<th>Before Drug</th>
<th>After Drug</th>
<th>24 hours</th>
<th>48 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(-24 hours)</td>
<td>(-30 mins)</td>
<td>(+1 hour)</td>
<td>(+24 hours)</td>
<td>(+48 hours)</td>
</tr>
<tr>
<td><strong>HVLT-R</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Recall Score</td>
<td>33</td>
<td>34</td>
<td>31</td>
<td>33</td>
<td>34</td>
</tr>
<tr>
<td>Learning Score</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Percent retained</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Discrimination Index</td>
<td>24</td>
<td>24</td>
<td>24</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>P2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Recall Score</td>
<td>24</td>
<td>25</td>
<td>28</td>
<td></td>
<td></td>
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<tr>
<td>Learning Score</td>
<td>5</td>
<td>7</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent Retained</td>
<td>90</td>
<td>91.7</td>
<td>100</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Discrimination Index</td>
<td>24</td>
<td>24</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DSST</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed Trials</td>
<td>33</td>
<td>37</td>
<td>29</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>Correct Trials</td>
<td>33</td>
<td>37</td>
<td>29</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>Mean RT</td>
<td>2143</td>
<td>1918</td>
<td>2373</td>
<td>1989</td>
<td>1948</td>
</tr>
<tr>
<td>P2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed Trials</td>
<td>30</td>
<td>31</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct Trials</td>
<td>30</td>
<td>28</td>
<td>32</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mean RT</td>
<td>2257</td>
<td>2412</td>
<td>2264</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CPT-X</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Omissions</td>
<td>0</td>
<td>0</td>
<td>0.3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>% Commissions</td>
<td>30.6</td>
<td>25</td>
<td>30.6</td>
<td>30.6</td>
<td>33.3</td>
</tr>
<tr>
<td>Hit Reaction Time</td>
<td>307.4</td>
<td>310.4</td>
<td>325.0</td>
<td>300.3</td>
<td>302.6</td>
</tr>
<tr>
<td>P2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Omissions</td>
<td>0.3</td>
<td>0</td>
<td>3.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Commissions</td>
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<td>41.7</td>
<td>94.4</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hit Reaction Time</td>
<td>310.1</td>
<td>311.8</td>
<td>336.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Grooved Pegboard</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominant hand time (s)</td>
<td>58.65</td>
<td>55.84</td>
<td>57.00</td>
<td>44.00</td>
<td>57.59</td>
</tr>
<tr>
<td>Non-dominant hand time (s)</td>
<td>62.06</td>
<td>61.31</td>
<td>68.00</td>
<td>51.93</td>
<td>51.78</td>
</tr>
<tr>
<td>P2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominant hand time (s)</td>
<td>55.9</td>
<td>47.65</td>
<td>56.71</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Non-dominant hand time (s)</td>
<td>56.5</td>
<td>61.35</td>
<td>65.60</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
3.1.7 Subjective Drug Effects Measures

Below are presented the subjective effects data (ARCI, POMS, VAS) collected from participants P1 and P2.

3.1.7.1 ARCI

Scores on the Addiction Research Centre Inventory (ARCI) short form for effects of psychotropic drugs demonstrate some before and after drug effects on the subscales presented. Specifically, the scales measuring sedation (PCAG) (Figure 8.2) and hallucination/depersonalization (LSD) (Figure 8.3) show the greatest effect after drug administration. Although some effects are seen on the BG (Figure 8.1) and MBG scales (Figure 8.4), these are less easily interpretable, although they seem to demonstrate a slight decrease in arousal (BG) for both participants, and a decrease in euphoria (MGB) for P2 only.

Figure 8 (8.1-8.2). Scores achieved on the Addiction Research Centre Inventory (ARCI) scales for P1 and P2 before and after drug administration.
Figure 8 (8.3-8.4). Scores achieved on the Addiction Research Centre Inventory (ARCI) scales for P1 and P2 before and after drug administration.

3.1.7.2 VAS - Visual Analog Scales

The visual analog scales give detailed information on subjective drug effects before and after dosing. The data show that subjective drug effects are detectable at 5 minutes after dosing, peak within one to two hours and decline thereafter. Data show resolution of subjective effects at 6 hours post dose, and no residual subjective effects 24 and 48 hours later. Scales of Drug Effect (Figure 9.1), High (Figure 9.2), Bad Effects (Figure 9.4), and Rush (Figure 9.5) show clearly the time course of these effects following dosing. Other scales of Good Effects (Figure 9.3), Drug Liking (Figure 9.6), and Like Cannabis (Figure 9.7) less clearly demonstrate the time course of these effects, although some effect of the drug before and after dosing is detectable.
Figure 9 (9.1 - 9.4). Visual Analog Scales are presented for measurement of subjective drug effects, before and after administration for P1 and P2.
Figure 9 (9.5 - 9.7). Visual Analog Scales are presented for measurement of subjective drug effects, before and after administration for P1 and P2.

3.1.7.3 POMS – Profile of Mood States

Figure 10 presents scores from the Profile of Mood States for both participants. Effects of the drug are most strongly detected for both P1 and P2 on the scales of elation (Figure 10.1), fatigue (Figure 10.2), friendliness (Figure 10.5) and vigor (Figure 10.9). The direction of the effect on these
scales demonstrates that the negative effects of the drug were the ones most acutely experienced by participants. Other scales showing a weaker before and after drug effect are confusion (Figure 10.4), tension/anxiety (Figure 10.7), anger/hostility (Figure 10.8), and arousal (Figure 10.10), which generally showed an increase in these measures. Some scales show effects more strongly for P2 than P1. These include depression/dejection (Figure 10.3), positive mood (Figure 10.6), and friendliness (Figure 10.5). The higher scores on negative affect scales (depression/dejection) and lower scores on positive affect scales (positive mood, friendliness) for P2 are a reflection of a negative emotional state attained post drug administration that resulted in this participant concluding their participation in the study.

**Figure 10 (10.1 – 10.6).** Profile of Mood States scores before and after drug administration for P1 and P2
**Figure 10 (10.7 - 10.10).** Profile of Mood States scores before and after drug administration for P1 and P2
3.1.8 Driving Measures

Table 7 displays overall driving performance for full and divided attention tasks, and Table 8 displays the four hazard scenarios under full and divided attention conditions. Overall observations of the driving data suggest a decrease in mean driving speed from before to after drug administration, and between focused and dual task driving conditions for P1 only. No trends are immediately apparent for SDLP or collisions. Collisions in the driving scenarios are thus far a highly infrequent event as only a single collision was observed. For the hazard scenarios, following distance to a slow moving vehicle may decrease following cannabis use, and under condition of divided attention. Possible trends as a result of the other hazard scenarios are not readily apparent. Any residual effects that may have been experienced by P1 are difficult to assess. Although P1 maintained a slightly slower driving speed and higher SDLP 24 and 48 hours later as compared to the before drug condition, it is difficult to conjecture if this represents an effect of the drug.

**Table 7.** Overall driving performance measures (mean speed, SDLP, and collisions) for P1 and P2 under full and divided attention conditions, before and after drug administration. Speed is measured in km/h.

<table>
<thead>
<tr>
<th></th>
<th>P1</th>
<th>P2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T-30 mins</td>
<td>T+1 hour</td>
</tr>
<tr>
<td><strong>Driving Only</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Speed</td>
<td>89.77</td>
<td>70.49</td>
</tr>
<tr>
<td>SDLP</td>
<td>0.21</td>
<td>0.25</td>
</tr>
<tr>
<td>Collisions</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Dual Task</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Speed</td>
<td>86.11</td>
<td>66.44</td>
</tr>
<tr>
<td>SDLP</td>
<td>0.26</td>
<td>0.23</td>
</tr>
<tr>
<td>Collisions</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 8. Driving performance measures on four different hazard scenarios are presented for P1 and P2 under full and divided attention conditions, before and after drug administration. Speed is measured in km/h.

<table>
<thead>
<tr>
<th></th>
<th><strong>Driving Only</strong></th>
<th><strong>Dual Task</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Straightaway</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Speed</td>
<td>P1</td>
<td>P2</td>
</tr>
<tr>
<td>T-30 mins</td>
<td>101.33</td>
<td>85.17</td>
</tr>
<tr>
<td>T+1 hour</td>
<td>72.62</td>
<td>83.93</td>
</tr>
<tr>
<td>T+24 hours</td>
<td>102.69</td>
<td></td>
</tr>
<tr>
<td>T+48 hours</td>
<td>99.37</td>
<td></td>
</tr>
<tr>
<td>SD Speed</td>
<td>2.77</td>
<td>2.37</td>
</tr>
<tr>
<td>SDLP</td>
<td>0.11</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>Slow moving vehicle</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Following Distance (s)</td>
<td>11.32</td>
<td>10.27</td>
</tr>
<tr>
<td></td>
<td>8.44</td>
<td>8.64</td>
</tr>
<tr>
<td></td>
<td>12.12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12.40</td>
<td></td>
</tr>
<tr>
<td>Reaction Time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Braking distance (m)</td>
<td>0</td>
<td>32.35</td>
</tr>
<tr>
<td></td>
<td>29.13</td>
<td>28.34</td>
</tr>
<tr>
<td>Risk Taking</td>
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</tr>
<tr>
<td>Braking distance (m)</td>
<td>47.36</td>
<td>70.92</td>
</tr>
<tr>
<td></td>
<td>150.36</td>
<td>146.12</td>
</tr>
<tr>
<td></td>
<td>142.32</td>
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</tr>
<tr>
<td></td>
<td>160.66</td>
<td></td>
</tr>
<tr>
<td><strong>Straightaway</strong></td>
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</tr>
<tr>
<td>Mean Speed</td>
<td>P1</td>
<td>P2</td>
</tr>
<tr>
<td>T-30 mins</td>
<td>83.12</td>
<td>78.92</td>
</tr>
<tr>
<td>T+1 hour</td>
<td>78.53</td>
<td>81.90</td>
</tr>
<tr>
<td>T+24 hours</td>
<td>89.57</td>
<td></td>
</tr>
<tr>
<td>T+48 hours</td>
<td>87.72</td>
<td></td>
</tr>
<tr>
<td>SD Speed</td>
<td>5.54</td>
<td>6.61</td>
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<td>SDLP</td>
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<td>0.16</td>
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<td><strong>Slow moving vehicle</strong></td>
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<tr>
<td>Following Distance (s)</td>
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<td>7.33</td>
</tr>
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<td></td>
<td>0</td>
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<tr>
<td></td>
<td>11.11</td>
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<tr>
<td>Reaction Time</td>
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<tr>
<td>Braking distance (m)</td>
<td>52.98</td>
<td>136.76</td>
</tr>
<tr>
<td></td>
<td>147.44</td>
<td>88.25</td>
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<td></td>
<td>56.13</td>
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<tr>
<td>Risk Taking</td>
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<td></td>
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<tr>
<td>Braking distance (m)</td>
<td>92.32</td>
<td>150.39</td>
</tr>
<tr>
<td></td>
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<td>120.11</td>
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</tr>
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<td></td>
<td>144.02</td>
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</table>
3.2 Part B

3.2.1 Demographic Characteristics of Individuals who self-report DUIC in Ontario

Of the 16,224 individuals who responded to the survey, the number of valid cases on which demographics are reported is \( n = 16,110 \). This population encompasses respondents who answered “yes” or “no” to the item “Have you driven a motor vehicle within an hour of using cannabis, marijuana, or hash?”. The remainder did not drive or were not licensed \( (n = 83) \), responded that they did not know \( (n = 4) \), refused to answer \( (n = 9) \), or the data was not collected \( (n = 18) \). Within this subset, sample sizes were reduced for the variables of marital status \( (n = 15,980 \text{ valid cases}, n = 21 \text{ answered don’t know}, n = 109 \text{ refused}) \), drinking and driving \( (n = 16,054 \text{ valid cases}, n = 10 \text{ don’t know}, n = 56 \text{ refused}) \) and age category \( (n = 15,762, n = 355 \text{ values missing}) \).

Chi-square analysis revealed significant associations between all variables assessed, with the exception of region, which approached but did not reach significance \( (p = 0.052) \). Table 9 shows the results of these analyses using weighted data. Un-weighted sample sizes are shown.
Table 9. Demographic characteristics of respondents to the CAMH Monitor who self-report DUIC (2002-2010).

<table>
<thead>
<tr>
<th>DEMOGRAPHIC</th>
<th>DUIC N (%)</th>
<th>NO DUIC N (%)</th>
<th>X²(df)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>259 (4.0)</td>
<td>7107 (96.0)</td>
<td>145.29(1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>69 (1.0)</td>
<td>8675 (99.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-25</td>
<td>124 (10.2)</td>
<td>1092 (89.8)</td>
<td>518.71(1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>25+</td>
<td>203 (1.4)</td>
<td>14343 (92.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metro</td>
<td>52 (3.0)</td>
<td>2197 (97.0)</td>
<td>10.96(5)</td>
<td>0.052</td>
</tr>
<tr>
<td>Central East</td>
<td>63 (2.8)</td>
<td>2687 (97.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central West</td>
<td>56 (2.6)</td>
<td>2634 (97.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>West</td>
<td>57 (2.3)</td>
<td>2781 (97.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>East</td>
<td>38 (1.7)</td>
<td>2666 (98.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>North</td>
<td>62 (2.6)</td>
<td>2817 (97.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marital Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/Partner</td>
<td>118 (1.3)</td>
<td>10340 (98.7)</td>
<td>378.75(2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previously Married</td>
<td>49 (1.8)</td>
<td>2886 (98.2)</td>
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<td></td>
</tr>
<tr>
<td>Never Married</td>
<td>160 (7.5)</td>
<td>2427 (92.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Income</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;$30,000</td>
<td>37 (2.4)</td>
<td>1791 (97.6)</td>
<td>19.34(4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>$30,000-$49,000</td>
<td>53 (2.7)</td>
<td>2385 (97.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$50,000-$79,000</td>
<td>91 (2.9)</td>
<td>3354 (97.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$80,000 +</td>
<td>120 (2.9)</td>
<td>5120 (97.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DK/Refused</td>
<td>27 (1.5)</td>
<td>3132 (98.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drinking and Driving</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>130 (12.1)</td>
<td>944 (87.9)</td>
<td>582.25(1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>189 (1.3)</td>
<td>14791 (98.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Descriptive statistics revealed that self-reported DUIC was more prevalent among certain sub-populations. Table 9 and Figures 11 through 16 show the prevalence of DUIC among the demographic characteristics assessed. Of those reporting DUIC, 80.4% were males (19.3% female) compared to a nearly 50/50 split (50.4% male, 49.6% female) among those who did not report DUIC (Figure 10). Nearly half (49.2%) of respondents who reported DUIC were between the ages of 18
and 25 years (Figure 12). Although the prevalence of DUIC by region ranged from 1.7 – 3.0% of all respondents (see Table 9), self-reported DUIC was found to be most commonly reported among people living in the Central East region (25.9% of respondents reporting DUIC were from the Central East) and least reported among those in Northern Ontario (7.7% of respondents reporting DUIC were from the North). However, a similar distribution by region is observed among those who did not report DUIC (See Figure 13). Most people reporting DUIC (57.1%) were never married, 35.1% and 7.7% were married/partnered and previously married, respectively (Figure 14). The most commonly reported household income bracket among the DUIC group was $80,000+ (42.8%), with only 8% reporting earnings of less than $30,000. This was similar to the No DUIC group, 37.4% of whom reported earnings of greater than $80,000, although more from this group reported that they did not know or declined to disclose their income (20.3% compared to 11.8% of the DUIC group; Figure 15).

Of those who did not self-report DUIC, most were over the age of 25 (88.4%), married or with a partner (70.4%; 10.9% previously married and 18.7% never married). Finally, of those who reported DUIC, 38% reported also drinking and driving, compared to just 6.4% of the No DUIC group (Figure 16).

![Figure 11](image.png)

**Figure 11.** Distribution by gender of people who self-report DUIC or NO DUIC in the past year in Ontario.
**Figure 12.** Distribution by age of people who self-report DUIC or NO DUIC in the past year in Ontario.

**Figure 13.** Distribution by region of people who self-report DUIC or NO DUIC in the past year in Ontario.
**Figure 14.** Distribution by marital status of people who self-report DUIC or NO DUIC in the past year in Ontario.

**Figure 15.** Distribution by income group of people who self-report DUIC or NO DUIC in the past year in Ontario.
Figure 16. Distribution by self-reported DUIA of people who self-report DUIC or NO DUIC in the past year in Ontario.

Logistic regression analysis revealed that certain demographic characteristics predict self-reported DUIC within the last year (Table 10). These include males more likely than females (OR = 3.15, 95% CI 2.42 - 4.10, p < 0.001); people who are 18-25 more likely that those over the age of 25 (OR = 4.07, 95% CI 3.01 - 5.49, p < 0.001); regional differences with people in Eastern Ontario less likely to report DUIC (OR = 0.48, 95% CI 0.31 - 0.72, p = 0.001) than people in metro Toronto; people who are previously married (OR = 1.90 95% CI 1.27 - 2.85 p < 0.01) or never married (OR = 2.41, 95% CI 1.77 – 3.27, p < 0.001) more likely than married or partnered people; and people who do not know or refused to provide their income less likely than people who have a household income of < $30,000 to report this behaviour (OR = 0.50, 95% CI 0.32 - 0.82, p < 0.01). Finally, people who report drinking and driving are at a substantially increased risk of also reporting DUIC (OR = 6.04, 95% CI 4.80 - 7.60, p < 0.001).
Table 10. Logistic regression analysis of the risk of reporting DUIC by demographic. **p< 0.01, ***p<0.001.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Self-Reported DUIC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>8744</td>
</tr>
<tr>
<td>Male</td>
<td>7366</td>
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<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>25+</td>
<td>14546</td>
</tr>
<tr>
<td>18-25</td>
<td>1216</td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
</tr>
<tr>
<td>Toronto</td>
<td>2197</td>
</tr>
<tr>
<td>Central East</td>
<td>2687</td>
</tr>
<tr>
<td>Central West</td>
<td>2634</td>
</tr>
<tr>
<td>West</td>
<td>2838</td>
</tr>
<tr>
<td>East</td>
<td>2666</td>
</tr>
<tr>
<td>North</td>
<td>2817</td>
</tr>
<tr>
<td><strong>Marital Status</strong></td>
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</tr>
<tr>
<td>Married/Partner</td>
<td>10458</td>
</tr>
<tr>
<td>Previously Married</td>
<td>2935</td>
</tr>
<tr>
<td>Never Married</td>
<td>2587</td>
</tr>
<tr>
<td><strong>Income</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;$30,000</td>
<td>1828</td>
</tr>
<tr>
<td>$30,000-$49,000</td>
<td>2438</td>
</tr>
<tr>
<td>$50,000-$79,000</td>
<td>3445</td>
</tr>
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<td>$80,000+</td>
<td>5240</td>
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<td>DK/Refused</td>
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<td><strong>DUIA</strong></td>
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<tr>
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<td>14980</td>
</tr>
<tr>
<td>Yes</td>
<td>1074</td>
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</table>

3.2.2 Risk of Collision

The prevalence of collisions among three groups of drivers (no DUIA or DUIC, self-reported DUIA or DUIC, and self-reported DUIA and DUIC) was assessed (Figure 17). Additionally, the risk of past-year collision involvement for the group of drivers reporting both DUIA and DUIC was determined using logistic regression analysis while controlling for demographic variables (Table 11).
Significant differences in the prevalence of self-reported collision involvement by driving after substance use were found (Figure 17). Drivers reporting neither DUIA nor DUIC (91.3% of the sample) had the lowest prevalence of collisions (6.7%). Those reporting either DUIA or DUIC (7.7% of the sample) reported a significantly higher prevalence of collision involvement of 9.6%. The highest prevalence of collision involvement (30.5%) was found among drivers reporting both behaviours (0.9% of the sample). Chi-square analysis revealed that these differences were statistically significant ($\chi^2(2) = 61.3$, $p < 0.001$). Logistic regression analysis further revealed that, after controlling for demographic factors, drivers who reported engaging in both DUIA and DUIC within the past year had the highest risk of collision, with more than 3 times greater odds of collision involvement than those who reported only one substance used before driving (OR = 3.40, 95% CI 2.23 - 5.07, $p < 0.001$). Though drivers who reported no substance use before driving trended towards a lower risk of collision than drivers reporting DUIA or DUIC, this did not reach statistical significance (OR = 0.83, 95% CI 0.67 - 1.02, $p = 0.07$).

**Figure 17.** Prevalence of past-year self-reported substance use before driving, by group. No driving after substance use (No DUIA/DUIC), one substance used before driving (DUIA or DUIC) and both driving after alcohol and driving after cannabis use (DUIA and DUIC). Vertical bars represent 95% confidence intervals.
Demographic variables shown to predict risk of self-reported DUIC (Table 10) were also found to be significant predictors of the risk of past year collision. Gender was shown to be a significant predictor of collisions, with males at an increased risk (OR = 1.16, 95% CI 1.02 - 1.31, p < 0.05) as compared to females. The youngest age (18-34 years) and middle age groups (35-54 years) were found to be at an increased risk of collision (18-34 years OR = 1.53, 95% CI 1.26 - 1.86, p < 0.001; 35-54 years OR = 1.18, 95% CI 1.00 – 1.39, p < 0.05) as compared to drivers aged 55 years and over. Respondants from Western (OR = 0.72, 95% CI 0.57-0.90, p < 0.01) or Northern Ontario (OR = 0.73, 95% CI, 0.55 - 0.97) were at a decreased risk of collision as compared to respondants from the Toronto area. Individuals who were previously married (OR = 1.42, 95% CI 1.15 - 1.74, p = 0.001) or never married (OR = 1.44, 95% CI 1.21 - 1.71, p < 0.001) were found to be at an increased risk of collision as compared to people who were married or with a partner. Finally, individuals who did not know or refused to disclose income were found to be at a decreased risk of collision as compared to those making less than $30,000 per year (OR = 0.74, 95% CI 0.56 - 0.97, p< 0.05).
Table 1. Logistic regression analysis of the risk of collision involvement after controlling for variables known to independently influence risk of collision. * p<0.05, **p<0.01, ***p<0.001.

<table>
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<tr>
<th></th>
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<th>Collision involvement *</th>
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<td></td>
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<td>%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>16224</td>
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</tr>
<tr>
<td><strong>Gender</strong></td>
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<td></td>
</tr>
<tr>
<td>Female</td>
<td>8799</td>
<td>6.4</td>
</tr>
<tr>
<td>Male</td>
<td>7425</td>
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<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-54</td>
<td>6906</td>
<td>6.7</td>
</tr>
<tr>
<td>55+</td>
<td>5798</td>
<td>5.4</td>
</tr>
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<td><strong>Region</strong></td>
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<td>Toronto</td>
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<td>8.1</td>
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<td>Central East</td>
<td>2766</td>
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</tr>
<tr>
<td>Central West</td>
<td>2708</td>
<td>7.5</td>
</tr>
<tr>
<td>West</td>
<td>2852</td>
<td>5.7</td>
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<tr>
<td>East</td>
<td>2722</td>
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<td>North</td>
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<td>Previously Married</td>
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<td>10.8</td>
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<tr>
<td><strong>Income</strong></td>
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<tr>
<td>&lt;$30,000</td>
<td>1851</td>
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<tr>
<td>$30,000-$49,000</td>
<td>2457</td>
<td>7.3</td>
</tr>
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<td>$50,000-$79,000</td>
<td>3462</td>
<td>7.8</td>
</tr>
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<td>$80,000+</td>
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<td>8.1</td>
</tr>
<tr>
<td>DK/Refused</td>
<td>3201</td>
<td>5.0</td>
</tr>
<tr>
<td><strong>Driving after cannabis/alcohol use in the last 12 months</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No driving after cannabis/alcohol use</td>
<td>14791</td>
<td>6.7</td>
</tr>
<tr>
<td>Driving after one substance only</td>
<td>1133</td>
<td>9.6</td>
</tr>
<tr>
<td>Driving after cannabis plus alcohol use</td>
<td>130</td>
<td>30.5</td>
</tr>
</tbody>
</table>

Note: * At least once in the last 12 months
Statistical significance * p<.05, ** p<.01, ***p<.001
R = reference category
Chapter 4
Discussion and Conclusions

4.1 PART A

4.1.1 Towards a per se Limit for THC: The Importance of Human Laboratory Studies

In the absence of conclusive evidence attributing cases of acute toxicity and/or death due to THC intoxication, and debate over the severity of the long-term consequences of cannabis use, it has been suggested that the most pressing health risk posed to cannabis users is the risk of motor vehicle collision involvement (Hall and Solowij, 1998). Although epidemiological evidence is accumulating that demonstrates an increased risk of crash following the acute use of cannabis, the body of experimental literature examining how and at what dose cannabis impairs a person’s ability to safely operate a motor vehicle is in its early stages. Considerable mythology and false information exists among cannabis users that driving after cannabis use is safe, or at the very least, safer than driving after drinking (Lenné et al., 2001; Terry and Wright, 2005). These attitudes will likely persist unless public education and/or appropriate deterrent methods are put in place within the community. The majority of evidence that has accumulated to date on the risky nature of driving after cannabis use has been gained from epidemiological studies. While valuable, such evidence should be supplemented by experimental human laboratory studies in order to inform evidence-based per se laws and other public policies aimed at protecting the public from cannabis-impaired drivers. Human laboratory studies, such as the one presented in this thesis, are needed to fill the knowledge gaps that currently exist, and to inform laws that can deter and penalize instances of DUIC.

Very recent (unpublished) data from Colorado suggests that in the wake of Amendment 64, rates of cannabis use have increased (Booth, 2013), with use in Denver now reaching 12% of the population, as compared to the national average of 6% use in the USA (Booth, 2013). Along with an increase in general use of the drug, preliminary data from Denver also suggests that rates of DUIC have likewise increased, and furthermore, that DUIC among cannabis users in the city is extremely widespread; 86% of medical users, and 73% of recreational users in Denver report that they have driven while intoxicated by cannabis (Booth, 2013). However, the science behind DUIC has not been
fully elucidated, making the prosecution and deterrence of DUIC very difficult in Colorado, or in any other jurisdiction. In anticipation of potentially increased rates of DUIC in Colorado as the result of legalization, Bill 13-1325 was passed in the US Senate on May 8\textsuperscript{th}, 2013. This Bill introduced a 5 ng/mL (in whole blood) legal \textit{per se} limit for THC.

Driving under the influence of drugs (DUID) policies vary from country to country, state to state, province to province, and include zero-tolerance laws, “effect-based” laws (e.g., witnessed evidence of impairment by an officer), \textit{per se} limits in biological samples, or a combination thereof. They differ still in the types of biological samples and analytes used for forensic confirmation of intoxication, further illustrating the lack of consensus on this topic. Some states, for example, impose zero-tolerance of THC or any metabolite thereof in urine (e.g., Arizona, Illinois, and Indiana), while others impose zero-tolerance only of active THC or 11-OH-THC (e.g., Delaware and Michigan). Nevada and Ohio have introduced \textit{per se} limits on THC of 2 ng/mL and 10 ng/mL in blood and urine, respectively. Similar \textit{per se} limits are in effect in Norway. Finland has adopted what is perhaps the strictest approach; detection of the inactive THC-COOH in urine can result in penalties for DUIC, but also in penalties for the use of a prohibited substance (Knochne et al., 2011). Given the large inter and intra individual variability of pharmacokinetic parameters seen in studies of THC, limits such as these may be premature. For the moment, Canada has chosen not to adopt \textit{per se} limits for THC or its metabolites, instead relying on demonstrable evidence of impairment to prove guilt in cases of DUID. However, this option may be a more costly alternative to \textit{per se} or zero tolerance limits in effect elsewhere (Grotenhermen et al., 2007).

In 2004 and 2005 an expert panel convened to review the literature and provide a scientifically defensible \textit{per se} limit for THC in serum or blood. Although a consensus was reached among the group (based largely on epidemiological data) that 7 to 10 ng/mL in serum (3.5 - 5 ng/mL in blood) would reasonably discriminate between impaired versus unimpaired persons, they also noted that “inadequate evidence from epidemiological studies renders this limit preliminary and suggests the need for review and possibly revision in the future” (Grotenhermen et al., 2007). In 2012, the DRUID (DRiving Under the Influence of Drugs) Project - a 5-year multi-national European scientific working group, whose purpose was to give scientific support to the European Union Transport Policy and establish guidelines to combat impaired driving - drafted a final report. One of the recommendations that resulted from this working group was to set \textit{per se} limits for THC and other drugs (Knoche and Schumacher, 2011). However, unlike Grotenhermen and colleagues,
this group focused on analyzing only experimental laboratory data. The group reached a similar conclusion, proposing a *per se* limit of 3.8 ng/mL in blood from the analysis of 78 experimental studies (Knoche and Schumacher, 2011). This limit was chosen because it produced impairment in experimental work similar to impairment produced by a BAC of 0.05 mg/dL. Other reviewers comparing the effects of THC to alcohol have concluded that a THC concentration in blood of 11 ng/mL was the minimum to produce significant impairment, and is therefore more appropriate (Kruger and Berghaus, 1995). While these limits are excellent starting points, it is important to remember that neither epidemiological data nor most experimental studies directly measure the driving task, and those that do often find more modest impairment that is likely the result of the compensatory mechanisms used by the driver who is aware of his or her intoxication (Hall and Solowij, 1998). More focused studies will be needed to better inform *per se* limits in the future. Zero-tolerance laws could improperly convict users for whom the drug persists in biological fluids for significant periods of time (Bergamashi et al., 2013), and could prove to be particularly problematic for users of medical marijuana. However, because little is known about how long the impairing effects of THC last, laws allowing even small amounts of THC in blood or urine could allow impaired drivers to avoid prosecution.

An issue of particular importance to the study of THC is that little information exists to guide estimates for how long impairment by this drug lasts. Although experimental laboratory psychomotor studies have suggested that the impairing effects of THC are resolved at 6 hours, laboratory testing of airline pilots has suggested that some effects may persist up to 24 hours (Leirer et al., 1991; Yesevage et al., 1985). No studies to date have tested beyond this time frame. Part A of this study is poised to address both of the preceding questions by being the first of its kind to directly link performance on a high-fidelity driving simulator to levels of THC and metabolites in blood, before, during, and after driving, up to 48 hours post dose. However, the data collected to date are limited.

### 4.1.2 Interpretation of Results

Preliminary data from the two participants who received the drug are presented. Although too few participants received the drug to draw any conclusions from the data, some very basic and
preliminary observations are noted. The suitability of these tests to detect an effect of THC is assessed. Unfortunately, not all data points were collected for these two participants; logistically, some data points were not feasible to collect, or the participant refused to provide a sample or submit to testing. This is an important point to consider, as both participants experienced anxiety post smoking, making subsequent and timely blood draws particularly difficult to obtain. P2 withdrew from the study 3 hours after drug administration due to an adverse emotional reaction following cannabis smoking, and as such data points beyond this time are not available for this participant.

Both participants, although instructed to only smoke as much as they needed to achieve a level of ‘high’ that they normally would, smoked all or nearly all of the cannabis provided. It has been suggested in the literature that some cannabis users will naturally titrate their dose to compensate for differences in THC concentration (Kelly et al., 1993; Lane et al., 2005). However this was not our preliminary experience in this study, and has not been a universal finding. In a study by Chait (1989), participants who were asked to self-administer THC cigarettes of varying doses failed to taper their dose in response to increasing THC content. Both participants in this instance remarked after smoking that they had achieved a high greater than they were accustomed to. This was associated with an adverse emotional state following smoking in both participants that resulted in the refusal to submit to some testing (e.g., blood sample collection) immediately following smoking, and this consequently limited the amount of data that is presented here. Such adverse emotional reactions may be common among cannabis users; a study by Cheung and colleagues (2010) found an association between cannabis use and the risk of comorbid anxiety and mood disorders. The adverse emotional state was more severe for the second participant (P2), and resulted in the conclusion of this participant’s interest in the study. As such, the detailed characterization of the pharmacokinetic and pharmacodynamic effects of THC immediately following smoking is not possible using this data. In future studies, a slow, paced smoking procedure, or perhaps allowing greater than 10 minutes for smoking may be more favourable than ad lib smoking in 10 minutes, as participants may feel less pressure to complete smoking in such a short time frame. However, a lengthier smoking window would likely also decrease the likelihood of detecting peak THC concentrations after smoking, and increase the likelihood that the Cmax would be reached before the smoking session has ended and blood collection begins. In addition, although a lower dose of THC could avoid adverse emotional reactions, one of the unique features of this work is the more realistic ‘street-level’ concentration of THC used. Using a lower dose could diminish the likelihood of
detecting any residual effects of the drug. All measures that were collected are based on before and after effects of administration within subjects. A comparison to a placebo condition is not possible, as both participants received the active drug, and any residual effects of THC cannot be ascertained as only a single participant completed the protocol.

The vital signs and pharmacokinetic data presented are consistent with results reported in other studies. Increases in pulse rate are noted for both participants following drug administration, and represents a consistent finding across THC administration studies (Ashton, 1999). Changes in systolic and diastolic blood pressure appear to be variable over time in this study. Typically, a mild increase in blood pressure is seen following acute administration of THC (Sidney, 2002). Temperature and respiration rate appear to be unaffected. Although cannabis use may cause a decrease in body temperature (Ashton, 1999), this is not a universal finding (Heishman et al., 1990), and previous studies have not demonstrated an increase in respiration rate (Schwope et al., 2012). The pharmacokinetic data collected indicate that THC appears quickly in blood and peaks shortly after smoking. The most proximal data point collected is 15 minutes after smoking, and represents the peak concentrations of THC and metabolites detected in this study. However, previous studies have indicated that peak concentrations of THC can occur even before smoking has concluded (Huestis et al., 1992). As such, the true $C_{\text{max}}$ of THC likely occurred prior to 15 minutes post smoking in this study, although this data was not captured.

The subjective effects data collected (ARCI, VAS, POMS) suggest that most of these measures are sensitive to THC. Scores achieved on the Addiction Research Centre Inventory (ARCI) short form demonstrate some effect before and after drug administration. Specifically, the scales measuring sedation (PCAG) (Figure 8.2) and hallucination (LSD) (Figure 8.3) show the greatest effect after drug administration. Some effects are observable on the BG (Figure 8.1) and MBG scales (Figure 8.4), demonstrating a slight decrease in arousal (BG) for both participants, and a decrease in euphoria (MGB) for P2 only. Previous studies have shown that the MBG and LSD scales of the ARCI Short Form are most sensitive to THC administration (Haertzen and Hickey, 1987); however, for these two participants, only a modest rise in MBG score was observable following drug administration while a sharp rise in LSD score was seen for only P2. The PCAG scale, measuring the sedating effects of the drug, showed the strongest effect for both participants in this study. This is consistent with previous studies of the effects of THC, as THC can cause feelings of drowsiness (Grotenhermen, 2003).
For the VAS, most measures show clear before and after administration effects, with peak effects occurring between 5 minutes and 2 hours for most scales. Measures of Drug Effect (Figure 9.1), High (Figure 9.2), Bad Effects (Figure 9.4), and Rush (Figure 9.5), show a clear peak shortly following drug administration, and a tapering of effects as time increases. Measures of Good Effects (Figure 9.3), Drug Liking (Figure 9.6) and Feels Like Cannabis (Figure 9.7) are less easily interpretable. These scales maintain a clear before and after drug effect, but seem to fluctuate over time.

Together, the ARCI and POMS scores reflect the more complex moods and emotions experienced following administration. The POMS measures reflect most clearly the negative emotions experienced by the participants. Lower scores on Elation (Figure 10.1), Friendliness (Figure 10.5), and Positive Mood (Figure 10.6) are suggestive of this. It is also noted that although most measures show an effect of dosing with THC, scores on some scales seem to differ between P1 and P2. While P2 showed a clear before and after effect of THC on most scales, the effect was much more subtle for P1. This could suggest that the effects of THC were highly individualized and variable during this study. As a result, the POMS may prove to be a less effective means of detecting an effect of THC on mood than other measures (e.g., VAS) as the study progresses. Previous studies have demonstrated a significant increase in the POMS scale for confusion (Lex et al., 1984; Watchel et al., 2002). In this study only a very slight increase has been observed on the scale of confusion, and more data are needed to assess an effect of the drug on this measure.

The cognitive measures evaluated in this study give some information on the effects of acute THC administration. It has been demonstrated that THC impairs both working memory and verbal learning acutely (Heishman et al., 1997) and chronically (Solowij et al., 2011), however, no trends are readily apparent using the HVLT-R test of verbal learning and working memory as yet. The DSST is a test of overall cognitive performance. Although a previous study using a battery of cognitive tests following THC administration found the DSST to be the most sensitive measure used (Wilson et al., 1994), an after-drug effect is only potentially observable for P1 using this test. P1 completed fewer trials and took longer to complete the trials after cannabis administration suggesting a slowed rate of cognition. Increases in time to perform the DSST, the number of trials completed, and the number of incorrect trials following cannabis use have been demonstrated in previous research (Heishman et al., 1988; Kelly et al., 1993; Wilson et al., 1993). Scores on the measure of sustained attention and impulsivity used in this study, the CPT-X, showed potential drug effects. The
measure of % omissions (how many times the bar was not pressed when it should have been) shows a slight increase before and after drug administration, indicating a potentially decreased level of attention. The % commission errors (pressing the bar when it should not be pressed) showed a dramatic increase for P2 after drug administration. This could be attributed to an acute effect of the drug on impulsivity. However, the hit RT (mean time taken to press the bar between letters), another measure of impulsivity, although showing a slight increase for P1 and P2 post drug administration, did not approach the dramatic increase that % commission errors did for P2. It is expected that an effect of the drug using this test will be observed following the analysis of more participants, as THC has been shown to impair sustained attention acutely (Solowij and Battisti, 2008). A small number of previous studies have failed to show an effect of THC using previous versions of the CPT-X, specifically (Vachon et al., 1974; Wilson et al., 1993). Similarly, although a decrease in the number of correct presses (demonstrating decreased sustained attention) using the CPT-X was observed among adolescent cannabis smokers as compared to their non-smoking peers (Jacobsen et al., 2004), no effect was observed in an adult twin study comparing regular users to non-users (Agarwal et al., 2004). To our knowledge, no studies have used the CPT-X specifically to measure sustained attention following acute administration of THC. With respect to the grooved pegboard test, cannabis has demonstrated a detectable and dose-dependent effect on fine psychomotor skills and manual dexterity in previous research using this instrument (Klonoff et al., 1973). For both participants, a trend towards increasing time taken to complete the test using both dominant and non-dominant hands is observed. It is expected that further research will demonstrate a dose-dependent increase in time taken to perform the task, based on findings of previous studies using this measure (Klonoff et al., 1973). It is expected based on findings from both participants for this test that it may be more sensitive to the effects of THC than the previously discussed tests, which demonstrated a potential effect only for P1 or P2.

The driving data are presented in two parts: overall driving performance and performance during potentially hazardous scenarios. For both participants, before drug and after drug data are available. Some basic trends are observable from the overall driving performance data. As expected, driving performance was diminished under the dual task condition on measures of overall speed and SDLP. However, it is impossible to determine as yet whether this effect is worsened following the administration of THC. Because only one participant completed the 24 and 48 hour driving tasks, no conclusions or observations can be made regarding whether residual effects of THC exist in this time
frame. The main observation that can be presented is that under the THC condition, driving may be slower, a finding that is consistently demonstrated across other studies of this kind (Lenné et al., 2010; Ronen et al., 2008; 2010), although was only observable in one of the two participants in this study thus far. Although previous studies have demonstrated that SDLP (lane weave) increases following THC administration (Ramaekers et al., 2000), no trends are as yet apparent in this dataset. Collisions have thus far been a rare event, and as such may not provide a reliable measure of driving performance. However, a single collision was recorded during the dual-task condition at 48 hours post drug administration, and may be a reflection of the complexity of the dual-task condition, or may be evidence of a residual effect of THC.

Little information can be gleaned from performance during the hazard scenarios completed to date. It should be noted that the zero value indicated on the hazard scenario for P1 is the result of the participant driving above the speed limit, and thus driving past the hazard scenario that was meant to be presented (a car unexpectedly pulling out onto the road) at a certain point in the course. This is a flaw in the programming of the system that should be rectified in future to avoid the accumulation of un-interpretable data and a potential reduction in the number of participants who do not complete this scenario. It is worth reiterating that these are preliminary observations based on two participants, only one of whom completed the protocol with the active drug. No comparison with a placebo condition is possible, nor is it possible to draw any conclusions about any residual effects of the drug that may exist. As the study progresses, the preliminary observations that are noted here may not hold, and new observations and effects of THC administration may become clear.

4.1.3 Limitations: Challenges and Lessons Learned

Human laboratory experiments such as Part A of this study are scarce in the literature, and this may be due in part to the complexity of conducting such studies. Since obtaining the grant to perform this research from the Canadian Institutes of Health Research (CIHR) in 2011, significant efforts have been made to bring this study to the participant recruitment and data collection phase. Approval from numerous regulatory bodies had to be obtained prior to recruitment of the first participant, and this study faced special challenges from a regulatory perspective.
Since September, 2011, significant efforts have been focused on obtaining ethical approval from two separate Research Ethics Boards (REBs). It was necessary to obtain approval for this work from both within CAMH, and also from the REB at Health Canada in Ottawa, due to the employment of an investigator working on this project within that organization. Additionally, because the study involved administration of a drug to human participants for an indication for which it is not intended (e.g., recreationally, to test driving skill), it was necessary to file a Clinical Trial Application with the Therapeutic Products Directorate of Health Canada, following dual REB approval in December, 2011. Due to the status of the research drug as a controlled substance under the Controlled Drugs and Substances Act, additional regulatory paperwork was required, and obtaining an exemption to section 56 of the Controlled Drugs and Substances Act was mandatory prior to procurement of the drug for use in the study. Subsequently, although obtaining the active drug from Prairie Plant Systems, Inc. with the assistance of Health Canada was a straightforward process, procurement of the placebo from NIDA required further regulatory documentation and navigation of the processes and procedures for importing a controlled substance from the US into Canada. Although absolutely necessary, these initial regulatory requirements proved to be very time consuming. By the time the first advertisement was placed in NOW magazine to recruit the first participant, 11 months had elapsed. Future studies, particularly in a Canadian context, can benefit from this experience by taking this time frame into consideration during project planning.

Another major challenge faced by this project was the recruitment of study participants. Described here are the three major challenges that will need to be overcome in this and other studies of this kind in the future in order to increase the chance of success. Firstly, the initial target population (19 or 20 years of age, use of cannabis 1 or 2 times per week) was not as abundant in the community as was initially anticipated. It was expected from the time of initial study design that interest in this study from potential participants from the community would be very high, and as such, people who met the very narrow initial inclusion criteria would be available. However, through the initial phase of recruitment, it was discovered that only 6.2% of callers eligible after telephone pre-screening. The reason for this was that smoking one to two times per week was significantly less common among callers than was smoking more frequently. This could be because smoking greater than twice per week is more common among the general population of cannabis users, that it is more common among young users, or that it is more common among the type of cannabis user that would be interested in participating in this study. Information is not available in the literature to guide
researchers on this topic, although experience gained from the initial phase of this research may guide future projects. As a result of the infrequency of eligible callers, the inclusion criteria were expanded to accommodate a less specific population of cannabis users, while still maintaining the goals and objectives of the study. Although daily cannabis use was frequently reported by callers, the expansion of the allowable frequency of smoking was capped at up to four times per week in order to minimize the risk of including participants who may be cannabis dependent, for whom abstinence would be challenging, or for whom residual effects could be problematic. Increasing the age limit to 25 years allowed a greater number of eligible participants to be found, as the majority of callers throughout the study were above 20 years of age. Although the mean age of callers as of July, 2013 was 25.8 years (range 18 to 69 years), the age range allowable for this study was capped at 25 years in order to maintain another objective of the study - to test cannabis and driving among young people, a population for whom DUIC may be most dangerous, as they may still be acquiring driving skill. In future studies, inclusion criteria should begin (and remain) as inclusive as possible without jeopardizing the scientific requirements of the study. Setting inclusion criteria that are too narrow, and therefore requiring revision in the future, jeopardizes valuable study time and creates additional regulatory/administrative requirements that further impacts the time required to conduct research.

Another challenge of recruitment was maintaining interest among this group of young cannabis users. Although expansion of the inclusion criteria resulted in an increased number of eligible participants, maintaining their interest after initial pre-screening was difficult. Scheduling a participant to attend the study is a complex task requiring the cooperation, coordination, and availability of a number of different parties (e.g., medical assistance, use of a specialized smoking room, pharmacy assistance, clinical laboratory, etc.), and as such, making an appointment immediately following initial telephone pre-screening was not always feasible or practical. Although email and telephone messages were always left for those individuals who had agreed to be re-contacted following initial pre-screening, re-contact, particularly via telephone, was not always straightforward. Some participants would not return messages left nor pick up the phone when called. For those whom re-contact was possible, some would indicate that they had changed their mind about their participation. The most often cited reasons for this were due to the time commitment required, or because they felt that compensation was not sufficient upon second thought. For those who could not be re-contacted, the inability to re-establish contact could be the result of an unwillingness to pick up a blocked telephone number from CAMH, apprehension about
making a return phone call due to having changed their mind without wanting to express this directly, or both. In any case, in future, efforts should be made to simplify scheduling for the study in order to increase the number of appointments that can be made immediately, which will hopefully minimize or avoid call-backs and loss of interest. In a study where eligible participants are already in short supply, any loss of interest among eligible individuals is particularly problematic and impacts recruitment goals considerably.

Finally, the time commitment required for completion of study procedures on an individual basis represents a significant obstacle to recruitment. Although it was initially anticipated by the research group that finding participants who would agree to be abstinent for the study week would present the greatest challenge to recruitment, it was found that nearly all who were asked easily agreed to be abstinent for the week of the study. Instead, a greater barrier to participation was scheduling participants for four consecutive study days. This has proven to be very challenging. To date, only two participants have received the drug, and both were postsecondary students scheduled during the winter break (“Reading Week”) from their respective institutions. It has not been possible to schedule other eligible participants for the remaining study sessions beyond this time frame due to work and school commitments faced by this group. For the future, one suggestion would be to try to recruit university/college aged participants in the summertime (April through September) as there is a greater likelihood that academic commitments will be fewer, and hence potential participants may be more amenable to attending CAMH for all study sessions consecutively. Alternatively, arrangements could be made to allow participants to attend on weekends during the year, in order to increase chances that they will complete the study.

4.1.4 Future Directions

Moving forward, researchers should be mindful of the challenges experienced by this study to date and take whatever steps are possible to avoid them. Although regulatory documentation and processes are a necessary component of this work that cannot and should not be circumvented, additional time should be budgeted during project planning to account for this. Secondly, inclusion criteria should be made as inclusive as possible, and every effort should be made to make attending the study sessions as easy and as desirable as possible for participants. Because increasing
compensation for the study is not financially feasible, and could be ethically problematic (there is a risk of exposing financially vulnerable members of the public to harm through the incentive of monetary gain), efforts should be focused on recruiting and scheduling processes that remove barriers to participation. This could include modifying the study design to decrease the time commitment required per session (e.g. shortening the battery of cognitive testing), and improved coordination of the scheduling process in order to minimize attrition. Future studies may consider using a within-subjects design. Although this would increase the length of participation for participants overall because each participant would be required to complete both arms of the study, this design may prove more efficient as fewer research participants would need to be recruited.

The data that will be produced by this project in the future will address gaps in current cannabis and driving knowledge through the direct measurement of THC in blood and concurrent evaluation of driving ability, as well as determining what, if any, residual effects of THC exist at 24 and 48 hours post smoking. Although this study is designed to test the effects of cannabis on driving in recreational users, the issue of cannabis and driving remains particularly problematic for users of medical marijuana for whom no exception is granted under current laws. The impairing effects of cannabis on driving have a direct impact on the independence and lifestyle of this population. Entangled in the issue of medical usage are issues of tolerance and chronic use of the drug. Although tolerance to cannabis has been well documented in the literature (e.g., Ramaekers et al., 2011), to what degree, if any, tolerance attenuates the negative effects of cannabis on driving performance remains a largely unexplored area of research. Future studies should examine the effects of cannabis on driving in tolerant users, and particularly medical users, in order to determine if it is safe for this sub-population of users to be driving when using their medication as prescribed.

4.2 Part B
4.2.1 Significance of Findings

Part B of this study examines the demographic characteristics of Ontarians who report smoking cannabis and driving within the past year. Although the general demographic characteristics of drinking and drug-using drivers in Canada have been described elsewhere (Bierness and Beasley, 2011; Bierness and Davis, 2008), little information exists describing the demographic characteristics
of people who self-report driving after smoking cannabis, and to our knowledge, none exists describing the characteristics of drivers in Ontario who report DUIC. Such knowledge is important in order to inform to whom public health education strategies should be targeted within the province, in order to be most effective. Through this analysis, it was discovered that people who smoke and drive share some of the same demographic characteristics as people who drink and drive, although some important differences are also noted.

In our sample, smoking drivers were more likely to be male (OR 3.15, 95% CI 2.47 - 4.10, p < 0.001), under age 25 (OR 4.07, 95% CI 3.01 - 5.49, p < 0.001), be previously (OR 1.90, 95% CI 1.27 - 2.85, p < 0.01) or never married (OR 2.41, 95% CI 1.77 - 3.27, p < 0.001) and less likely to not know or refuse to disclose their income (OR 0.50, 95% CI 0.32 - 0.82, p < 0.05). Some characteristics of cannabis using drivers have been described by Mahindoretep and colleagues (2013). Although this group of researchers sought to characterize drugged-drivers versus wrongly accused drivers who had an interaction with law enforcement in a French sample, the vast majority of these motorists were drivers who had used cannabis only (n = 201; 98%). It was found that the mean age of drug-using drivers was lower than wrongly accused or drinking drivers (26 years, versus 31 and 34 years, respectively). All groups were mostly male. Although the work by Mihindhoretep and colleagues (2013) did not assess variables of income or marital status, the finding that younger males are largely responsible for this behaviour in the population is congruent with the current findings.

Drinking drivers in Canada and elsewhere have also been shown to be a largely male population (Bierness and Davis, 2008; Drew et al., 2010; Gjerde et al., 2011). However, some differences between drinking drivers and drivers in this analysis may exist. For example, drinking drivers may be older. In a roadside sample of drivers in British Columbia, the majority of drivers who tested positive for alcohol were over age 25 (9.3% of 19-24 years category tested positive for alcohol, versus 12.6% and 12.7% of 25-34 and 35-44 years categories, respectively). Similarly, in the 2004 Canadian Addiction Survey (a Canada-wide household telephone survey similar to the CAMH Monitor) people who reported drinking and driving tended to be older than our sample (mean age 39.8), although they were still younger than non-drinking drivers (mean age 43.4 years) (Bierness and Davis, 2008). It has been suggested that although younger people may not be more likely to drink alcohol and drive overall (defined as two or more drinks within an hour of driving), they may be overrepresented in the population of DUIA drivers with higher BACs (Bierness and Beasley,
In the same BC roadside survey by Bierness and Beasley (2011), testing positive for alcohol above 80 mg/dL was more common among the youngest age category. Similarly, the Centre for Disease Control (CDC) reports that although young men comprised only 11% of the US population in 2010, they accounted for 32% of impaired driving charges (CDC, 2011). However, other studies have not confirmed these findings. In a study of drivers with ‘unusually’ high BACs (> 400 mg/dL) in Sweden and Wisconsin, the average age of offenders was nearly 44 years (Jones and Harding, 2013). Furthermore, in Finland, a recent report described the ‘average’ drinking driver to be male, 40 to 49 years of age, employed, married or partnered, and driving without a passenger (Portman et al., 2013).

The marital status of smoking drivers in this study shows that they are more likely to be previously or never married than they are to be married or partnered. Findings on drinking drivers in Canada have shown that drinking drivers are likewise less likely to be married (OR 0.55, p < 0.01; Bierness and Davis, 2008), although studies in other countries have found drinking drivers are more often married or partnered (Portman et al., 2013). This may be a reflection of the young age of respondents who self-reported DUIC in the CAMH Monitor, who are therefore less likely to be married due to their age. In terms of income, the sample of drinking drivers in the Canadian Addiction Survey reported a personal income greater than that of non-drinking drivers. In this analysis of DUIC drivers, the income bracket most frequently reported by the cannabis and driving group was > $80,000 (42.8%). However, upon logistic regression analysis it was found that DUIC drivers are less likely to report not knowing or refusing to disclose income, than they are to report a household income in any other bracket. The reason for this finding is not clear, and may be due in part to the small number of respondents in either group (DUIC, or no DUIC) that reported not knowing or refusing to provide information on household income. This finding may warrant further investigation. As part of the DRUID project, Meesman and Boets (2011) reported that individuals of lower socio-economic status were more likely to use illicit drugs and drive, although it is seen from this analysis that individuals who reported a low income (< $30,000) were not more likely to report DUIC than any other group. This difference could be attributed to Meesman and Boets’ choice not to differentiate cannabis use from other illicit drug use, and/or not specifying personal income or household income in their analysis. The CAMH Monitor specifies household income only. The greater frequency of respondents in the DUIC group in this analysis who reported greater than > $80,000 may be because people who use cannabis and drive earn more on average than those who
don’t report this behaviour, although more likely, it is again a direct result of the lower age of this group; some of these individuals may still be living at home and therefore would report a higher household income.

A critical finding of the demographic assessment of this population is that people who report DUIC in the province of Ontario were found to be very highly likely (OR = 6.04, 95% CI 4.80 - 7.60, p < 0.001) to also report drinking and driving. This suggests that the population of individuals who report DUIC may overlap significantly with the population of drinking drivers in Ontario. This may be a group for whom education regarding substance use and driving would be most effective. Further analysis of all drivers captured in the CAMH monitor from 2002 to 2010 revealed that nearly one third of drivers (30.5%) who reported both DUIA and DUIC reported a motor vehicle collision within the past year. After adjustment for demographic factors via logistic regression, an elevated risk of crash remained for this population of drivers (OR 3.65, 95% CI 2.12 - 6.28, p < 0.001) at more than 3 times greater risk relative to drivers who reported only one behaviour (DUIA or DUIC). Drivers who reported neither DUIA nor DUIC were found to have a slightly decreased risk of collision involvement compared to drivers who reported DUIA or DUIC (OR 0.83, 95% CI 0.67 – 1.02, p = 0.07) although this did not reach statistical significance. These data are similar to data from epidemiological studies of seriously and fatally injured drivers demonstrating that the risk of crash under combined influence is greater than either substance when used alone (e.g., Biecheler et al., 2008). This is the first report of living drivers who self-report this behaviour and the associated risk of collision. These data demonstrate that drivers reporting both DUIA and DUIC are more frequently involved in collisions than drivers who report neither, or only one of these behaviours. This finding suggests that these drivers may represent a small segment of the population who are overrepresented in collision statistics, and public health education strategies may be most effective when targeting this group.

4.2.2 Limitations

There are several limitations to this analysis that need to be considered. These limitations are in addition to the limitations in data collection and survey design as noted in sections 2.2.1 and 2.2.2.1. Firstly, although the CAMH Monitor survey is administered anonymously, there are
limitations inherent to any self-reported dataset that should be noted. Some types of information can only be obtained by asking, and any process that involves a behaviour over which an individual has a high degree of control (e.g. drug-use) is likely to require self-report of that information (Baldwin, 2000). In fact, self-report may be the only way that information about past drug use and behaviour can be gained (Baldwin, 2000). Such data, however, is frequently influenced by psychological processes that affect the storage and recall of information (Baldwin, 2000). Furthermore, while self-report presents the advantage of obtaining information directly from the source, there can be problems with the validity of the information obtained (Barker et al., 2002). People are not always truthful, and they do not always recall past events perfectly. Typically, self-reported data on sensitive topics (i.e., drug use) underreport the frequency and severity of these behaviours (Paulhus and Vazire, 2007). Although anonymous, participants may minimize their drug use, or hide any instances of drinking and/or drugged driving in an effort to ‘look good’, or due to a sense of personal shame over their behaviour. As such, the proportion of the population that reports DUIA, DUIC, or both, and/or collisions reported within the past year may be higher.

How survey questions are phrased or asked can also greatly influence the information gained from self-report. Interpretation of the data from this analysis should be interpreted with caution based on how the questions of interest were phrased in the CAMH Monitor. As outlined in Chapter 2, apart from standard questions assessing demographic characteristics, three main questions of interest emerged from the dataset: (1), In the past year have you been involved in a collision?; (2), Have you driven after 2 or more drinks of alcohol?; and; (3), Have you driven within 2 hours of smoking cannabis? The answers to these questions were in the form of “yes”, “no”, or a refusal to answer. Only “yes” or “no” responses were included in the analysis. From the way these questions are phrased, it is impossible to determine if the collisions reported within the past year were the result of driving under the influence. Information regarding the severity of each collision is similarly not gathered. A “yes” response to the collision item could be for a collision that was not at all related to the driver, or alternatively, it could be for a serious collision that was directly related to drinking or drug use. The number of collisions experienced by respondents per year is also not assessed.

Furthermore, although we are reporting on a population of individuals who report both DUIA and DUIC, it is unclear from the phrasing of the questions whether these individuals had simultaneously consumed alcohol and cannabis before driving, or if they had consumed only one of either substance and drove on more than one occasion. It is reasonable to assume given what the
literature reveals regarding the prevalence of the simultaneous use of alcohol and cannabis (Midanik et al., 2007), that at least some of the individuals in this study would have driven under the combined influence of these substances at least some of the time. However, it is impossible to determine how many and what the frequency of this behaviour would be. The experimental literature suggests that cannabis and alcohol have additive or possibly synergistic effects when used together (Bramness, et al., 2009; Chait and Perry, 1994; Drummer et al., 2004), and as such the large number of individuals reporting collisions within the group reporting both DUIA and DUIC may be a result of the combined effects of these drugs. However, alternative explanations are viable. For example, the large effect size seen from this group of drivers who report both DUIA and DUIC may be the result of an underlying predisposition of this group to engage in risky behaviour. There is a relationship between individual personality differences and driving style (Poó and Ledesma, 2013). People who demonstrate personality traits such as high sensation-seeking, aggression, and social deviance have shown generally poorer and riskier performance on the road (Ulleberg and Rundmo, 2003). The individuals reporting DUIA and DUIC in this analysis may therefore be at a higher risk of collision involvement regardless of intoxication status. However, it should be noted that previous research has shown an increase in collision risk among cannabis using drivers after controlling for other risky behaviours (Mann et al., 2010; Richer and Bergeron, 2009).

The phrasing of driving and substance use questions asked by the CAMH Monitor present further limitations. The questions “Have you driven after 2 or more drinks of alcohol?” and “Have you driven within 2 hours of smoking cannabis?” are unable to gather much information about the amounts of these substances used prior to driving. Certainly, the impact and subsequent risk of collision following two standard drinks in one hour for a 100 lb. older female would be different than that of a 250 lb. younger male, and yet, the same question is asked of all participants. Similarly, a “yes” response captures equally those individuals who had two drinks prior to driving, and those who had ten drinks (for example) before driving. Furthermore, no attempt to assess the dose of cannabis ingested prior to driving is made. Recall bias, particularly when under the influence, may make accurate estimates of the amount of alcohol or cannabis used before driving difficult to obtain. However, the absence of this information should be considered in the interpretation of this data.
4.2.3 Future Directions

Future epidemiological research on crash risk following cannabis use should focus on addressing some of the limitations presented by the current study. In this instance, the data were extracted from a general drug use and mental health monitoring survey. A targeted survey able to ask a greater variety of, and more specific questions about, cannabis and alcohol use in conjunction with driving habits in the population would be better able to answer some of these questions. The questions posed by the CAMH Monitor were only able to be answered as a simple “yes” or “no”. A targeted qualitative study using a semi-structured interview format would be able to gain more detailed information about driving under the influence of alcohol, cannabis, or both, and uncover themes that may exist. In particular, the questions asked could focus on whether individuals report driving under the combined influence of substances, and whether or not the collisions they are reporting within the past year occurred during an episode of substance use. This type of study would be better able to directly provide information on collision risk following acute substance use. Self-report data is an important addition to the driving literature because it gives direct access to the population demonstrating this behaviour.

4.3 Conclusions

Cannabis and driving research that directly measures the driving task in a human laboratory setting will be important in informing future evidence-based policies that protect the public from the threat posed by cannabis-impaired drivers, who have demonstrated evidence of an increased risk of collision in the epidemiological literature. This research will become increasingly important if more jurisdictions worldwide (including Canada) move to decriminalize or legalize cannabis in the future. However, the challenges inherent in conducting this type of research are many. Researchers should be mindful of the timeframes needed to meet the necessary regulatory requirements and the availability of the target population, and take steps to ensure that participation is easy for interested parties in order to increase participation and sample size. Epidemiological research has long demonstrated an elevated risk of crash following the acute use of alcohol, and is now able to show an
increased risk of crash following the acute use of cannabis. In Ontario, people who report DUIC are more likely to be male, under age 25, previously or never married, and to also report drinking and driving. As such, public education campaigns aimed at reducing the incidence of DUIC behaviour may be most effective when targeted towards this demographic. Furthermore, nearly a third of individuals who report both behaviours also report being involved in a collision within the past year and are more than 3 times as likely to be involved in a collision as people who report only DUIA or DUIC. This finding represents a significant health risk to this group of individuals. In addition, this finding identifies an opportunity for clinicians to engage patients who disclose these behaviours in discourse about the risk posed to their health by using substances before driving. An educational intervention of this nature could improve not only the health and safety of these drivers, but also the health and safety of drivers who share the road with this group.
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APPENDIX A

Method for the Solid Phase Extraction and Quantitation of THC, 11-OH-THC, and THC-COOH
Quantitation of THC, OH-THC, and COOH-THC by GC/MS

<table>
<thead>
<tr>
<th>Prepared By</th>
<th>Authorized By</th>
<th>Current Revision Date</th>
<th>Date of Issue</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. Giesbrecht</td>
<td></td>
<td>Mar 27, 2012</td>
<td></td>
</tr>
</tbody>
</table>


Intended use:
For measuring levels of delta-9-tetrahydrocannabinol and its two major metabolites in whole blood, serum, and urine.

Principles of Procedure:
Solid phase extraction (SPE) is used for sample clean up. The extract is then analyzed by GC/MS.

Reagents and Supplies:

1. Standards:
   A: stock solutions
   THC 1 mg/ml in MeOH (T-005 from Cerilliant), stored in fridge.
   COOH-THC 100 ug/ml in MeOH (T-018 from Cerilliant), stored in fridge.
   OH-THC 100 ug/ml in MeOH (H-026 from Cerilliant), stored in fridge.

   B: 10 ug/ml diluted standard in MeOH
   Into a 5 ml volumetric flask, combine 50 ul of stock THC, 500 ul of stock COOH-THC, and 500 ul of stock OH-THC. Make to 5 ml with MeOH.
   Store in glass tube at -20C.

   C: 100 ng/ml in appropriate matrix (serum, EDTA whole blood, or urine).
   Into a 5 ml volumetric flask add 50 ul of std B, 150 ul water, then to volume with matrix material. Blood, serum or urine must be from a volunteer with no exposure to cannabinoids. Aliquot (1 ml) in glass tubes and store frozen.

   D: 10 ng/ml.
   On the day of assay, thaw an aliquot of Std C and make a 1/10 dilution (50 ul plus 450 matrix material).
Internal Standards: 1 ug/ml in 30% MeOH (Store in fridge in glass bottle.)
Stock stds purchased from Cerilliant and stored in the fridge:
- THC-D3 (T-003) 100 ug/ml in MeOH
- OH-THC-D3 (H0041) 100 ug/ml in MeOH
- COOH-THC-D3 (T008) 1mg/ml in MeOH

- 250 ul of THC-D3, OH-THC-D3, and 25 ul of COOH-THC-D3 is combined in a 25 ml volumetric flask and made to volume with 30% MeOH.
- 25 ul (25 ng) is added to each sample.

2. For hydrolysis of urine samples:
   a. 0.2M Sodium acetate buffer, pH 5.0 FW 82.03. From Aldrich (24,124-5)
      Weigh 8.2 grams, dissolve in dist water, adjust pH to 5.0 with glacial acetic acid and make to 500 ml with distilled water. Store in a brown bottle.
   b. Beta-glucuronidase, Type HP-2 from Helix pomatia. Purchased from Sigma (G7017-25 ml). Store in the fridge and mix very well before use.

3. 0.1M sodium acetate buffer pH 6.0, FW 82.03 From Aldrich (24,124-5)
Weigh 8.2 grams, dissolve in dist. Water, adjust pH to 6.0 with acetic acid and make to 1 litre with distilled water. Store in a brown dispenser in the fridge.

4. acetonitrile: (Omnisolv) from VWR. Store in a glass bottle in the fridge.

5. Certify 2 cartridges, 200 mg from Agilent # 121102080
   (C8 and anion exchange mixed mode)

6. methanol (Omnisolv) from VWR

7. hexane (Omnisolv) from VWR

8. ethyl acetate (Omnisolv) from VWR

9. conditioning, washing and elution solutions:
   a. 95% sodium acetate buffer pH 6.0 and 5% MeOH
   b. 95% hexane and 5% ethyl acetate (Prepare fresh daily)
   c. 50% MeOH and 50% water
   d. 75% hexane, 25% ethyl acetate, and 1% acetic acid (Prepare fresh daily)

10. BSTFA with 1% TMCS from Cerilliant (B-023)
Precautions
For in vitro diagnostic use

Reagent Preparation
See instructions under Reagents.

Storage Instructions
See instructions under Reagents.

Expiration
All stock standard solutions are used before the expiry date.

Specimen Collection
For whole blood samples: draw at least 4 ml blood in an EDTA vial, mix and store frozen at -80C.
For serum samples: draw 10 ml blood without additives or gel separators, allow to clot, centrifuge, and store the serum at -80C.
For urine samples, pour an aliquot of urine (4 ml) into a 13x100 glass vial, cap, and store at -80C.
Patient preparation: none
Specimen type: see above
Handling: Handle specimens as a biohazardous material
Storage: several months to years at -80C.

Known interfering substances:
Any medications or preparations containing hemp or cannabinoids.
Eg. Sativex, Marinol
URINE SAMPLES

Hydrolysis of Urine samples:
1. All urines must have creatinine levels done.
2. Make serial dilutions (x10, x100, x1000) of the urine sample with blank urine (not water) and analyze by immunoassay to determine the appropriate dilution for analysis. Hydrolyze and analyze the sample neat and also at the appropriate dilution.
3. Hydrolysis: for std curve and samples.
   a. Pipette 1 ml of urine (and also an appropriate dilution) each into 13x100 glass tubes.
   b. Add 150 ul sodium acetate buffer pH 5.0
   c. Add 30 ul beta glucuronidase.
   d. Cap, vortex to mix, and place in 37C water bath overnight.
4. Hydrolyze a Urine standard curve as well:

<table>
<thead>
<tr>
<th>Std Conc.</th>
<th>Volume of std</th>
<th>Volume of Blank</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 0 (U1)</td>
<td>0</td>
<td>1000 ul urine</td>
</tr>
<tr>
<td>2. 1 (U2)</td>
<td>100 ul D</td>
<td>900</td>
</tr>
<tr>
<td>3. 5 (U3)</td>
<td>50 ul C</td>
<td>950</td>
</tr>
<tr>
<td>4. 10 (U4)</td>
<td>100 ul C</td>
<td>900</td>
</tr>
<tr>
<td>5. 25 (U5)</td>
<td>250 ul C</td>
<td>750</td>
</tr>
<tr>
<td>6. 50 (U6)</td>
<td>500 ul C</td>
<td>500</td>
</tr>
<tr>
<td>7. 100 (U7)</td>
<td>1000 ul C</td>
<td>0</td>
</tr>
</tbody>
</table>

5. The next morning remove the tubes, allow to cool and proceed with step 5 in the procedure.
Procedure – Sample Preparation for serum or whole blood.

1. Thaw samples, QC, and Std C.

2. Obtain at least 10 ml of blank matrix.

3. Prepare Std D (see under Reagents), then prepare calibration curve in 13×100 glass tubes with screw caps: (try to deposit sample half-way down tube, especially stds)

<table>
<thead>
<tr>
<th>Std Conc</th>
<th>Volume of Std</th>
<th>Volume of blank</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 ng/ml (S0)</td>
<td>0</td>
<td>1000 ul</td>
</tr>
<tr>
<td>0.2</td>
<td>20 ul D</td>
<td>980</td>
</tr>
<tr>
<td>0.5</td>
<td>50 ul D</td>
<td>950</td>
</tr>
<tr>
<td>1.0</td>
<td>100 ul D</td>
<td>900</td>
</tr>
<tr>
<td>2.0</td>
<td>200 ul D</td>
<td>800</td>
</tr>
<tr>
<td>5.0</td>
<td>50 ul C</td>
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<tr>
<td>10.0</td>
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<tr>
<td>25.0</td>
<td>250 ul C</td>
<td>750</td>
</tr>
<tr>
<td>50.0</td>
<td>500 ul C</td>
<td>500</td>
</tr>
</tbody>
</table>

4. Pipette 1 ml of QC and of all samples.

5. Add 25 ul of the combined internal std (1μg/ml) to each tube, using a repeater pipette. Try to deposit material half-way down the tube. Vortex samples to mix.

6. Add 2 ml cold acetonitrile while vortexing. Use a 2 ml glass pipette, set mixer to setting 6, then vortex on HIGH after solvent has been added. Cap tubes.

7. Centrifuge tubes at 2500 rpm for 10 minutes.

8. Immediately decant the supernatant to 10 ml tubes (16×100), and add 5 ml of 0.1M acetate buffer pH 6.0 to each. Use the dispenser.

9. Condition Certify 2 cartridges with 2 ml MeOH, followed by 2 ml 95% 0.1M acetate buffer pH 6.0 / 5% MeOH (dispenser). Do not allow columns to dry before addition of sample.

10. Mix samples with plastic pipette before transferring to cartridges; allow sample to slowly pass through cartridge while adding the remaining sample.

11. Wash with 2 ml 0.1M sodium acetate buffer pH 6 (dispenser), then increase the vacuum for 5 minutes to allow cartridges to dry.

12. Wash with 1 ml hexane (dispenser).
13. Elute THC
   Place blue labeled 13x100 glass tubes under the cartridges and elute the THC slowly with 2 ml 95:5 hexane/ethyl acetate. (Dispenser) Remove the tubes.

14. Wash the columns with 5 ml (2x2.5 ml) 50% MeOH (dispenser), then increase the vacuum for 5 mins. To allow the cartridges to dry.

15. Wash with 1 ml hexane.

16. Elute metabolites:
   Place re labeled 13x100 glass tubes under the cartridges and elute OH-THC and COOH-THC slowly with 2 ml 75:25 hexane/ethyl acetate containing 1% acetic acid. (Dispenser) Remove the tubes.

17. Evaporate extracts under nitrogen no higher than 40C. Ensure dryness.

18. Derivatization:
   Add 50 ul BSTFA with 1% TMCS, vortex, and heat at 70C for 30 minutes.

19. Cool the tubes, vortex to mix, centrifuge at 2500 rpm for 5 minutes.

20. Transfer extract to injection vials with glass pipettes, being careful to no transfer any residue. Load samples on GC/MS (DSQ).
   The 2 sets of extracts (THC, metabolites) are injected separately, with their respective instrumentation methods and processing methods.
   If analyzing more than one matrix, choose the correct processing method for each matrix; note that the concentration of the stds may be different.

**Instrumentation:**

Column TR-5MS (from Thermofisher); 0.18um ID x 20 meters.
Injection volume: 2ul
Run time:
Retention times:  THC: approx 7 mins  
OH-THC: approx 7.8 mins  
COOH-THC: approx 8.4 mins
SIM mode. Ions used for quantitation:  THC: 386 (371, 343)  
   THC-D3: 389 (374, 346)  
   OH-THC: 371 (459, 474)  
   OH-THC-D3: 374 (462, 477)  
   COOH-THC: 371 (473, 488)  
   COOH-THC-D3: 374 (476, 491)

See Instrument Method Print-out for more details.
**Procedure Notes**

Helpful hints: Avoid storage in plastic, especially aqueous solutions.
Backup method: None
Clinical application: various applications
Turn around time: as needed
Other:

**Calibration**

Assay Range (Dynamic Range):
- linear: Blood, serum: 0.2-50 ng/ml
  - Urine: 1-100 ng/ml

Reference Material: See Reagents
Calibration Scheme: Calibration curve with each batch;
must be matrix appropriate.
LOQ: Blood or serum: 0.2 ng/ml
  - Urine: 1 ng/ml

**Quality Control**

QC product: Patient pool, frozen aliquots, run 1 per batch
Preparation/handling: same as patient samples
Corrective action: see performance characteristics.

**Results and Reporting**

The computer calculates results based on the calibration curve. All analytes are calculated using the ratio of the signal generated by the specific analyte divided by the signal of the specific deuterated compound.
See example of chromatography.
Results less than the LOQ are reported as such.
Urine results are normalized for 8.8 mmol/L creatinine (= 100 mg/dl)

**Limitations of procedure:**

Manual dilution: Appropriate blank matrix must be used for dilution.
LOQ: see calibration and reporting.
This method is used for serum, whole blood (EDTA) and urine. It has not been tried for saliva samples.

**Reference Interval:**

Reference Range: none
Repeat analysis for values greater than the highest calibrator.

**Specific Performances Characteristics**

Acceptable CV is less than 10. Between batch CV: to be determined
Reproducibility: see performance characteristics

<table>
<thead>
<tr>
<th>Material</th>
<th>Mean nmol/L</th>
<th>Between Run CV</th>
</tr>
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</table>

Correlation

Regression Statistics

<table>
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</tr>
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<tbody>
<tr>
<td>not applicable</td>
<td></td>
<td></td>
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</table>

Analytical specificity
See Known Interfering Substances for details

Bibliography;
APPENDIX B

Study Advertisements
**RESEARCH STUDIES**

**Camh**

Centre for Addiction and Mental Health

**RESEARCH SUBJECTS NEEDED**

**Are you a regular Cannabinoid user?**

Are you 18 or 20 years old?
Do you have a Q2 or G licence?

CAMH is conducting a study on the effects of cannabis on driving using a state-of-the-art driving simulator.

For more information

**PLEASE CONTACT:**

416-535-8501 ext. 6032

**Lake Simcoe Waterfront**

1 & 2 bdrm. fully equipped cottages, 10 min. from town, half price Fri. & Sat. 1-800-964-5680

**OUT OF TOWN**

**Boscayland**

Beautiful waterfront apt., Stouffville. Lake Couch, 10 min. from Toronto. Big boats go in/wind 705-718-1580

**Accommodations**

**Family/friends visiting?**

Need a place to stay? cross this out.

www.rentals.com/rentals/144547

**Singles $30**

2013 Dundas West. Call John 416-516-8994

**FOR RENT - GENERAL**

**College / Spadina**

Daily, weekly, monthly (from $500)

Pay weekly (416-603-1243)

**FOR RENT - BACH**

**Church/Wellesley**

Clean, fully furnished bachelor, @ 7pm/day to 7pm/day.

Price: $700 inc. 416-603-1243

**STUDIO FOR RENT**

**Artist & Prof. lofts**

Dundas + Roncesvalles 2 bdrm., 2+1, 2+1. Excellent location, open concept, lots of natural light, $1150.

**Dundas/Lansdowne**

Charm, 2 bdrm., 2+1. East side, 2 bdrm., 2+1, 1 bath, $1050.

**Dupont/Lansdowne**

Stylish, 2 bdrm., 2+1 with roof deck, 2 bdrm., 2+1, 1 bath, $1200.

**Dupont/Lansdowne**

Call 416-516-8994 for details.

**Have You Been Diagnosed With High Blood Pressure?**

Manna Research is looking for subjects who are available to participate in a 3-month clinical research trial.

This trial involves a medication approved by Health Canada for high blood pressure.

**IF YOU ARE 18 YEARS AND OLDER AND WOULD LIKE TO PARTICIPATE PLEASE CALL:**

**Manna Research**

Canadian Clinical Trials

416-740-2895

Or visit: www.mannaresearch.com
Study Volunteers Needed

Are you a regular Cannabis user?

19 or 20 years old?

Have a valid driver’s licence?

If so, you might be eligible to participate in a research study examining driving behaviour under the influence of cannabis using a state-of-the-art driving simulator.

If you are interested, please call for more information 416-535-8501 ex: 6032

Compensation provided.

CAMH provides other treatment options for mental illness or addiction. For more information call CAMH at 416-535-8501.

ALL QUERIES ARE STRICTLY CONFIDENTIAL
APPENDIX C

Telephone Pre-Screening Script
Telephone Screener - Cannabis and Driving Simulator Study

This research study is examining driving behaviour under the influence of cannabis using a driving simulator system.

This study will take place at the Centre for Addiction and Mental Health at 33 Russell St., Toronto and requires participants to come for four consecutive days. As a participant in the study you would be randomly assigned to smoke either a cannabis or placebo cigarette. The placebo cigarette is made to look and taste like a real cannabis cigarette but it does not contain the active drug THC. You will operate a state-of-the-art driving simulator during the study. You will be paid for your participation in this study. After each study day you will receive $50 for a total of $200 for completing all 4 days.

I will now ask you questions to determine if you meet the criteria to participate in the study.

Do you smoke Cannabis?
- No (ineligible)
- Yes

How often do you smoke Cannabis in a typical week? ______________________

How old are you? ______________________

What class of driver's licence do you have?
- G1 (ineligible)
- G2
- Full G

How long have you held that licence? ______________________

Are you pregnant or breast feeding?
- No
- Yes (ineligible)

Do you have a history of drug dependence, or are you currently dependant on a drug?
- No
- Yes (ineligible)

Do you regularly use medications such as anti-depressants or benzodiazepines?
- No
- Yes (ineligible)

Have you ever been diagnosed with a psychiatric disorder?
- No
- Yes (ineligible)

☐ Thank you, you are not eligible to participate in this study.

☐ Thank you, you are eligible to participate in this study.

Study details you should know before you decide whether to participate or not:
• You will undergo an assessment to be sure you are eligible for the study that includes a physical examination, laboratory investigations including blood and urinalysis, and a urine drug screen.
• Also information will be collected about demographics (e.g., your age, education), your past and present drug use, current medications, psychiatric symptoms and history, and your driver behaviour.
• Two study days are brief (day 3 and 4) approximately 1-2 hours, Day 2 is approximately 5 hours and Day 3 is approximately 7 hours.
• You will be asked to refrain from driving a motor vehicle on Day 2, 3 and 4.
• You will be asked to refrain from personal use of cannabis, alcohol or other drugs not required for medical reasons, outside of the laboratory, until your participation in this study is completed.
Telephone Screening Questionnaire Version 2.0

Revised Sept 10, 2012

Date: __________________________
First name: _____________________
Phone #: _______________________
Screened by: ____________________
Heard about us?: ________________

Telephone Screener - Cannabis and Driving Simulator Study

This research study is examining driving behaviour under the influence of cannabis using a driving simulator system.

This study will take place at the Centre for Addiction and Mental Health at 33 Russell St., Toronto and requires participants to attend for five sessions, four of which occur on consecutive days. As a participant in the study you would be randomly assigned to smoke either a cannabis or placebo cigarette. The placebo cigarette is made to look and taste like a real cannabis cigarette but it does not contain the active drug THC. You will operate a state-of-the-art driving simulator during the study. You will be paid for your participation in this study. You will receive $200 for completing all 5 sessions.

I will now ask you questions to determine if you meet the criteria to participate in the study.

Do you smoke Cannabis?
☐ No (ineligible)
☐ Yes

How many days of the week do you use cannabis? ____________________________

When do you usually smoke? ________________

When you smoke, approximately how much do you smoke (in grams, for example)? ____________________________

How old are you? ____________________________ what is your birth date?: ________________

What class of driver’s licence do you have?
☐ G1 (ineligible)
☐ G2
☐ Full G

How long have you held that licence? ____________________________

Are you pregnant, looking to become pregnant, or breast feeding?
☐ No
☐ Yes (ineligible)

Have you ever been, or are you currently dependent on any drug?
☐ No
☐ Yes (ineligible)

Do you regularly use medications such as anti-depressants, medication for anxiety, or for ADHD?
☐ No
☐ Yes (ineligible)

Have you ever been diagnosed with a psychiatric disorder?
☐ No
☐ Yes (ineligible)

Have any family members, (e.g., mother, father, brothers, sisters), been diagnosed with schizophrenia?
☐ No
☐ Yes (ineligible)

Are you willing to abstain from using cannabis for 48 hours prior to, and for the duration of the study?
☐ No (ineligible)
☐ Yes

Do you live in an area which is TTC accessible?
☐ No (ineligible)
☐ Yes

Closest major intersection or postal code: ____________________________
☐ Thank you, you are not eligible to participate in this study.

☐ Thank you, you are eligible to participate in this study.

Study details you should know before you decide whether to participate or not:

- You will undergo an initial assessment (session 1) to be sure you are eligible for the study that include a physical examination, some questions about psychiatric symptoms and drug use, and a urine drug screen. This can be completed at any time prior to the remaining sessions, which must be completed on consecutive days.
- During the study, information will be collected about demographics (e.g., your age, education), your past and present drug use, current medications, psychiatric symptoms and history, and your driver behaviour. Blood samples will be collected.
- Of the 5 sessions, session 3 is long (approximately 8 hours) and the rest (1, 2, 4 and 5) are short (2 – 3 hours).
- You will be asked to refrain from driving a motor vehicle on and before sessions 3, 4 and 5.
- You will be asked to refrain from personal use of cannabis, alcohol or other drugs not required for medical reasons for 48 hours prior to session 2, and until your participation in this study is completed.

Okay to send information sheet by email? If yes, address _________________________________

Assessment Date and Time: _________________________________

Okay to leave a message? ☐ Yes ☐ No