Acute Effects of Cannabis on Young Drivers' Performance of Driving Related Skills

by

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for the degree of Master of Science

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Abstract

Impaired driving is a major source of preventable death in Canada, especially among young adults. Although the effects of alcohol on driving are well known, the impact of driving under the influence of cannabis has not been studied as thoroughly. This human laboratory study examines the impact of an acute dose of smoked cannabis on driving-related skills among young drivers who use cannabis regularly. Participants were weekly smokers between the ages of 19 and 25 years who have had an Ontario class G or G2 license for at least twelve months. Measures of driving simulator performance, cognition, mood, and motor skills were collected before and after a single dose of smoked cannabis containing 12.5% Δ^9 -tetrahydrocannabinol (Δ^9 -THC). Although the data presented are based on an interim analysis of an ongoing study, some measures of subjective drug effects, objective physical measures, and driving simulator performance were found to be significantly altered after drug administration.

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Table of Contents

Chapter 1 Introduction	1
1 Introduction	1
1.1 Statement of the Problem.....	1
1.2 Objective and Hypothesis	2
1.2.1 Objective	2
1.2.2 Hypothesis.....	2
1.3 Review of the Literature	2
1.3.1 Endocannabinoid System.....	2
1.3.2 Cannabis.....	8
1.3.3 Cannabis Use in Canada	22
1.3.4 Driving Under the Influence of Cannabis (DUIC)	23
Chapter 2 Methods	49
2 Methods.....	49
2.1 Study Overview	49
2.2 Study Procedures	50
2.2.1 Telephone Screen.....	50
2.2.2 Session One: Eligibility Assessment	50
2.2.3 Session Two: Practice Day	51
2.2.4 Session Three: Drug Administration Day	52
2.3 Participant Selection	54
2.3.1 Inclusion Criteria	54
2.3.2 Exclusion Criteria	55
2.4 Participant Recruitment	55
2.5 Collected Measures	56

2.5.1	Simulated Driving Tests	56
2.6	Driving Simulator	58
2.6.1	Cognitive and Motor Skills Tasks.....	60
2.6.2	Subjective Drug Effects and Mood Questionnaires.....	63
2.6.3	Psychiatric, Behavioural, and Demographic Information.....	65
2.6.4	Biochemical and Physical Measurements.....	66
2.7	Cannabis Cigarettes	69
2.7.1	Cannabis Suppliers.....	69
2.7.2	Preparation of Cigarettes.....	69
2.7.3	Drug Administration	70
2.8	Sample Size Justification	70
2.9	Ethical Considerations	71
2.10	Regulatory Procedures	71
2.11	Data Analysis	71
Chapter 3	Results	74
3	Results	74
3.1	Screening and Enrollment.....	74
3.2	Participant Demographics and Physical Characteristics.....	78
3.3	Adverse Events	78
3.4	Frequency of DUIC as reported on the SRQ	79
3.5	Driving Data.....	79
3.5.1	Overall Mean Speed and SDLP	79
3.5.2	Mean Speed, Standard Deviation of Speed, and SDLP during Straightaway	85
3.5.3	Slow Moving Vehicle Following Distance.....	89
3.5.4	Braking Distance Approaching Risk-Taking Hazard	91
3.6	Cognitive Performance and Motor Skills Data.....	94

3.6.1	CPT-X Commission and Omission errors	94
3.6.2	CPT-X Hit Rate.....	96
3.6.3	HVLT-R Total Recall Score, Percent Retained, and Discrimination Index	97
3.6.4	DSST Completed and Correct Trials	99
3.6.5	DSST Reaction Time	101
3.6.6	Grooved Pegboard Dominant and Non-Dominant Hand Performance	102
3.7	Mood and Subjective Drug Effects Data	104
3.7.1	ARCI Subscales	104
3.7.2	POMS Subscales	107
3.7.3	VAS Subscales.....	110
3.8	Cannabis Cigarette Data	116
3.8.1	Amount of Cigarette Smoked	116
3.8.2	Estimated Δ^9 -THC dose Compared to Peak VAS Effects.....	117
3.9	Physiological Data	120
3.9.1	Heart Rate	120
3.9.2	Blood Pressure	122
3.9.3	Summary	124
Chapter 4 Discussion and Conclusions.....		127
4	Discussion and Conclusions.....	127
4.1	Driving Measures.....	131
4.2	Secondary Outcomes	135
4.3	Challenges and Limitations.....	144
4.4	Conclusions.....	147
4.5	Future Directions	148
References		151
Appendix A: Telephone Pre-Screening Script and Cover Page		178

Appendix B: Consent Form	182
Appendix C: Study Advertisements.....	192
Appendix D: Descriptive Statistics for Analyses.....	199

List of Tables

Table 1. Summary of Measures Collected Throughout the Study	52
Table 2. Reasons for Exclusion Based on the Telephone Screen	73
Table 3. Reasons for Losing Interest	74
Table 4. Reasons for Ineligibility Based on Session One Assessment	74
Table 5. Participant Demographics and Physical Characteristics.....	78
Table 6. Univariate tests from a split-plot repeated-measures MANOVA predicting changes in overall mean speed and SDLP under single-task conditions after smoking	79
Table 7. Descriptive statistics for overall mean speed and SDLP under single-task conditions	80
Table 8. Univariate tests from a split-plot repeated-measures MANOVA predicting changes in overall mean speed and SDLP under dual-task conditions after smoking	81
Table 9. Univariate tests from a split-plot repeated-measures MANOVA predicting changes in overall mean speed and SDLP under dual-task conditions after smoking with BMI as a covariate	82
Table 10. Descriptive statistics for change in speed, change in cigarette weight, and estimated dose of $\Delta 9$ -THC	84
Table 11. Univariate tests from a split-plot repeated-measures MANOVA predicting changes in straightaway mean speed, standard deviation of speed, and SDLP under single-task conditions after smoking	85
Table 12. Descriptive statistics for straightaway mean speed, standard deviation of speed, and SDLP under single-task conditions	86
Table 13. Univariate tests from a split-plot repeated-measures MANOVA predicting changes in straightaway mean speed, standard deviation of speed, and SDLP under dual-task conditions after smoking	87
Table 14. Descriptive statistics for straightaway mean speed, standard deviation of speed, and SDLP under dual-task conditions.....	88
Table 15. Results of a split-plot repeated-measures ANOVA predicting changes in following distance behind a slow-moving vehicle under single-task conditions after smoking	89
Table 16. Descriptive statistics for changes in following distance behind a slow-moving vehicle under single-task conditions after smoking.....	90

List of Tables (Continued)

Table 17. Results of a split-plot repeated-measures ANOVA predicting changes in following distance behind a slow-moving vehicle under dual-task conditions after smoking	90
Table 18. Descriptive statistics for following distance behind a slow-moving vehicle under dual-task conditions	90
Table 19. Results of a split-plot repeated-measures ANOVA predicting changes in stopping distance behind a risk-taking hazard under single-task conditions after smoking	91
Table 20. Descriptive statistics for stopping distance behind a risk-taking hazard under single-task conditions	91
Table 21. Results of a split-plot repeated-measures ANOVA predicting changes in stopping distance behind a risk-taking hazard under dual-task conditions after smoking	92
Table 22. Descriptive statistics for stopping distance behind a slow-moving vehicle under dual-task conditions	92
Table 23. Results of a split-plot repeated-measures ANOVA predicting changes in CPT-X errors after smoking	93
Table 24. Descriptive statistics for CPT-X error type	95
Table 25. Results of a split-plot repeated-measures ANOVA predicting changes in CPT-X hit rate after smoking	96
Table 26. Descriptive statistics for CPT-X hit rate	96
Table 27. Univariate tests from a split-plot repeated-measures MANOVA predicting changes in HVLt-R performance after smoking	97
Table 28. Descriptive statistics for total recall score, percent retained, and discrimination index on the HVLt-R	98
Table 29. Results of a split-plot repeated-measures ANOVA predicting changes in completed and correct trials on the DSST after smoking	99
Table 30. Descriptive statistics for completed and correct trials on the DSST	100
Table 31. Results of a split-plot repeated-measures ANOVA predicting changes in DSST reaction time after smoking	101
Table 32. Descriptive statistics for DSST reaction time	101
Table 33. Results of a split-plot repeated-measures ANOVA predicting changes in grooved pegboard performance after smoking	102

List of Tables (Continued)

Table 34. Descriptive statistics for grooved pegboard performance	103
Table 35. Results of a split-plot repeated-measures ANOVA predicting changes in ARCI subscale scores after smoking	104
Table 36. Descriptive statistics for ARCI subscales.....	105
Table 37. Results of a split-plot repeated-measures ANOVA predicting changes in POMS subscale scores after smoking	107
Table 38. Descriptive statistics for POMS subscales	108
Table 39. Results of a split-plot repeated-measures ANOVA predicting changes in VAS subscale scores after smoking	110
Table 40. Results of a split-plot repeated-measures ANOVA predicting changes in VAS subscale scores after smoking with BMI as a covariate.....	112
Table 41. Results of a One-way Analysis Comparing the Change in Cigarette Weight between the Active and Placebo Groups	116
Table 42. Descriptive statistics for change in cigarette weight	116
Table 43. Pearson Product-Moment Correlations between estimated Δ^9 -THC dose (based on change in cigarette weight) and peak VAS scores for participants in the active condition	117
Table 44. Pearson Product-Moment Correlations between change in cigarette weight and peak VAS scores for participants in the placebo condition	117
Table 45. Descriptive statistics for estimated dose of Δ^9 -THC and peak scores on VAS drug liking and drug effect subscales for participants in the placebo condition	118
Table 46. Linear Regressions on Estimated Δ^9 -THC Dose (Based on Change in Cigarette Weight) and Peak VAS Scores with and without BMI as a Covariate	118
Table 47. Results of a split-plot repeated-measures ANOVA predicting changes in heart rate after smoking.....	120
Table 48. Results of a split-plot repeated-measures ANOVA predicting changes in heart rate after smoking with BMI as a covariate	121
Table 49. Results of a split-plot repeated-measures ANOVA predicting changes in blood pressure after smoking.....	122
Table 50. Descriptive statistics for blood pressure	123

List of Tables (Continued)

Table 51. Descriptive statistics for overall mean speed and SDLP under dual-task conditions.....	199
Table 52. Descriptive statistics for VAS subscales	199
Table 53. Descriptive statistics for peak VAS drug effect and drug liking subscale scores for participants in the active and placebo conditions	204
Table 54. Descriptive statistics for estimated dose of Δ^9 -THC and peak scores on VAS drug liking and drug effect subscales	204
Table 55. Descriptive statistics for heart rate measured in beats per minute.....	204

List of Figures

Figure 1. Virage VS500M driving simulator during a driving scenario.	58
Figure 2. Screening and Enrollment Flow Chart	76
Figure 3. Overall mean speed on simulated driving trials for active and placebo groups under dual-task conditions before and after drug administration.	83
Figure 4. Overall SDLP on simulated driving trials for active and placebo groups under dual-task conditions before and after drug administration.	83
Figure 5 (5.1-5.7). Scores achieved on subscales of the VAS test for subjective drug effects at various times from smoking.	113
Figure 6. Peak VAS subscale score for drug liking versus drug effect for participants in the active condition.	114
Figure 7. Peak VAS subscale score for drug liking versus drug effect for participants in the placebo condition.....	115
Figure 8. Estimated Δ^9 -THC dose versus peak VAS subscale score for “I feel a drug effect”.	119
Figure 9. Estimated Δ^9 -THC dose versus peak VAS subscale score for “I like the drug”	119
Figure 10. Average heart rate in beats per minute over the course of drug administration day for both active and placebo groups.....	121

List of Appendices

Appendix A: Telephone Pre-Screening Script and Cover Page.....	179
Appendix B: Consent Form.....	183
Appendix C: Study Advertisements.....	193
Appendix D: Descriptive Statistics Tables.....	200

Chapter 1

Introduction

1 Introduction

1.1 Statement of the Problem

Motor vehicle collisions are associated with a large societal cost, both financially and in terms of injury and lives lost. In 2013, there were 1,741 collisions in Canada that resulted in the death of at least one person, and these were responsible for 1,923 fatalities. There were 165,306 individuals who were hurt by one of 120,660 crashes causing personal injury, and 10,315 of these injured individuals were hurt seriously enough that they were admitted to hospital for care¹. Operating a motor vehicle is a complex task, requiring both automatic and controlled behaviours². Driving requires a set of skills and abilities such as attention, alertness, vigilance, and psychomotor capabilities. Because of the intricacy of the task, it is not surprising that driving skills can be negatively affected by psychoactive substances. Although the risks associated with driving under the influence of alcohol (DUIA) are fairly well known, driving under the influence of cannabis (DUIC) is widely perceived to be safe^{3,4}. In some populations, DUIC is more common than DUIA⁵. Studies have found that DUIC is associated with an increased risk of collisions, and one study found that driving within three hours of smoking nearly doubled the risk of a crash⁶. It has been more difficult to understand the nature of the impairment in laboratory studies. This may be due to the fact that many of these studies use a lower concentration of delta-9-tetrahydrocannabinol (Δ^9 -THC), the main active ingredient found in cannabis, than what is typically found on the streets. It also could be due to differences in how much drivers are able to compensate based on their driving experience^{7,8,9}. Since young adults have had less driving experience and are more likely to drive under the influence of cannabis, impairing effects may be especially important to understand in this population^{7,8,9}. Given the societal cost associated with impaired driving, it is important to conduct further research to understand how cannabis affects driving behaviour.

1.2 Objective and Hypothesis

1.2.1 Objective

The primary objective of this study was to compare the acute effects of a moderate dose of smoked cannabis (12.5% Δ^9 -THC) to smoked placebo (<0.1% Δ^9 -THC) on simulated driving performance in young drivers aged 19-25 years. Secondary measures of motor skills, mood, subjective drug effects, and cognitive function were also examined.

1.2.2 Hypothesis

Changes in driving behaviour will be detectable thirty minutes after the consumption of a cannabis cigarette containing 12.5% Δ^9 -THC. Attempts at more cautious driving will be seen in a reduction of speed and an increase in stopping distance in participants in the active condition compared to placebo. Loss of control will be seen in an increase in standard deviation of lateral position (SDLP) and standard deviation of speed. Impairment will be more significant in driving tasks completed under dual-task conditions. Tests of isolated cognitive skills will also reflect cannabis impairment.

1.3 Review of the Literature

1.3.1 Endocannabinoid System

The endocannabinoid system is a lipid signalling system found in all vertebrates¹⁰. This ancient, evolutionarily conserved system appears to have important regulatory functions throughout the human body¹⁰. It has been implicated in a wide variety of physiological and pathological processes including neural development, immune function, metabolism and energy homeostasis, cardiovascular function, digestion, bone development and density, synaptic plasticity and

learning, pain, memory, circadian rhythms, and the regulation of stress and emotional state among other things^{11, 12, 13}.

Due to the lipophilic nature of the biologically active ingredients in cannabis, it was thought for a long time that they acted non-specifically, by disrupting lipid membranes¹⁴. This concept was slowly rejected, as researchers continued to study these compounds. In 1964, the correct chemical structure of delta-9-tetrahydrocannabinol (Δ^9 -THC), the main psychoactive component of cannabis, was identified¹⁵. This allowed the production of a range of synthetic analogues throughout the 1970s. It was discovered in 1974 that there was strict structural and stereo-selectivity in the biological effects of Δ^9 -THC and synthetic analogs, which implied that the compounds interact specifically with a drug receptor¹⁶. Evidence for a specific receptor grew, until in 1990, an orphan G protein-coupled receptor (GPCR) was identified as the receptor for cannabinoids in the brain¹⁷. This was later renamed cannabinoid receptor type 1 (CB1)¹⁵.

1.3.1.1 Components of the Endocannabinoid System

There are two known types of cannabinoid receptor: cannabinoid receptor 1 and cannabinoid receptor 2 (CB1 and CB2, respectively)¹². Both of these are G-protein coupled receptors (GPCRs), which signal through secondary messenger cascades¹⁸. The main ligands for these receptors are N-arachidonylethanolamine, also called anandamide or AEA, and 2-arachidonoylglycerol (2-AG)¹². These ligands are synthesized and degraded primarily by two enzymes: fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL)¹². Although anandamide and 2-AG are considered to be the primary mediators in cannabinoid signalling, other endogenous molecules have also been found to exert effects similar to cannabinoids¹⁹. In this category are 2-arachidonoylglycerol ether (noladin ether), N-arachidonoyl dopamine (NADA), virodhamine, N-homo-gamma-linolenylethanolamine (HEA), and N-docosatetraenylethanolamine (DEA)^{12, 20, 21, 22, 23}. Some molecules seem to be able to potentiate the effect of anandamide by competitive inhibition of FAAH and/or by acting allosterically on other receptors, such as the transient receptor potential vanilloid (TRPV1) channel²⁴. These

molecules include palmitoylethanolamide (PEA) and oleoylethanolamide (OEA). Rather than bind to cannabinoid receptors, they bind to an isozyme of the class of nuclear receptors and transcription factors known as peroxisome proliferator-activated receptors (PPARs)²³. Effects of this nature are sometimes referred to as “entourage effects”²⁴.

1.3.1.2 Synthesis of Endocannabinoids

Endocannabinoids are derived from arachidonic acid, and synthesized from membrane phospholipid precursors as needed based on cellular requirements^{12, 25, 26, 27}. In the production of anandamide, arachidonic acid is transferred from phosphatidylcholine to phosphatidylethanolamine by N-acyltransferase (NAT). This results in the production of N-arachidonoylphosphatidylethanolamine (NAPE). NAPE is then hydrolyzed by NAPE-specific phospholipase D, which forms anandamide^{12, 28}. The production of 2-AG occurs through the action of phospholipase C-beta. This hydrolyzes phosphatidylinositol-4,5-bisphosphate with arachidonic acid on the sn-2 position to yield diacylglycerol (DAG). This is hydrolyzed by DAG-lipase to form 2-AG^{12, 28}.

Despite the fact that both anandamide and 2-AG both derive from arachidonic acid, the pathways for their synthesis are distinct from the pathways by which eicosanoids are synthesized. Although they are separate, there may be some cross-talk between the endocannabinoid and eicosanoid pathways²⁹.

1.3.1.3 Genetics and Receptor Signaling

Both CB1 and CB2 are GPCRs which act mainly through Gi/Go-dependent signalling cascades^{18, 30}. Endocannabinoids like anandamide and 2-AG, and phytocannabinoids - such as delta-9-tetrahydrocannabinol (Δ^9 -THC), Δ^8 -THC, cannabinol, and others - bind to and activate these receptors to elicit their effects^{18, 30}. Each ligand binds with a different affinity and efficacy.

In humans, the locus for the CB1 receptor gene (CNR1) is found on chromosome 5q15. The CB2 receptor gene (CNR2) locus is found on a separate chromosome, 1p36²⁹. The coding sequence for CNR1 consists of one exon encoding a protein which is 472 amino acids in length³¹. The coding sequence for CNR2 also consists of one exon, but this encodes a protein containing 360 amino acids³¹. The two genes are more similar in mice than in humans. The mouse CNR1 and CNR2 proteins share 82% sequence identity, while in humans the amino acid sequences are only 48% similar³¹.

Activating the cannabinoid receptors results in a wide variety of cellular responses. One of these is the largely inhibitory action on adenylyl cyclase^{11, 25}. There is also a decrease in the formation of cyclic AMP, which results in decreased protein kinase A activity^{11, 25}. Calcium influx through several types of calcium channels is also inhibited^{11, 25}. Furthermore, activation of these receptors stimulates inwardly rectifying potassium channels, and signalling cascades associated with mitogen-activated protein kinase^{11, 25}. Anandamide binds with a higher affinity to CB1 than CB2, but acts as a partial agonist at both receptors^{12, 32}. 2-AG seems to have a higher potency and efficacy than anandamide at both receptors^{12, 32}. It seems to bind approximately equally well to both CB1 and CB2, but does seem to have a very slightly higher affinity for CB1^{12, 32}.

CB1 receptors are among the most abundant GPCRs found in the central nervous system (CNS)¹⁵. Their overall effect is to inhibit neurotransmitter release, including 5-hydroxytryptamine (5-HT or serotonin), glutamate, acetylcholine, GABA, noradrenaline, dopamine, D-aspartate, and cholecystokinin. This occurs at both excitatory and inhibitory synapses^{12, 30, 33}. They can exert both short- and long-term effects^{12, 30, 33}. Endocannabinoids are synthesized and released from post-synaptic neurons, and diffuse across the synaptic cleft to bind to cannabinoid receptors on the pre-synaptic terminal¹¹. The retrograde signalling mechanism used by this system allows neurotransmission to be tightly regulated, with very precise time and locations of action¹¹. This is a major advantage to paracrine and autocrine signalling.

In immune cells, CB2 receptors can be activated to inhibit the release of cytokines and chemokines, and can act to inhibit neutrophil and macrophage migration¹⁸. These receptors have a complex role in modulating immune system function¹⁹.

1.3.1.4 Receptor Expression and Distribution

Cannabinoid receptors are found throughout the body, but CB1 and CB2 receptors each have a distinct pattern of tissue distribution¹⁹. CB1 receptors are expressed throughout the body, including in organs and tissues such as adipocytes, leukocytes, spleen, heart, lung, gastrointestinal tract (including the liver, pancreas, stomach, small intestine, and large intestine), kidney, bladder, reproductive organs, skeletal muscle, bone, joints, and skin¹⁹. However, they are found primarily at the nerve terminals of central and peripheral nerves, where they are responsible for mediating the release of neurotransmitters^{13, 33, 34}.

In the central and peripheral nervous systems, CB1 is one of the most abundant receptors found. It has been detected in the cerebral cortex, hippocampus, amygdala, basal ganglia, substantia nigra pars reticulata, and in internal and external segments of the globus pallidus and cerebellum in the molecular layer^{13, 33, 34}. Their location in the central nervous system coincides with parts of the brain involved in motor activity, food intake, and pain processing, among other things. It has also been found in central and peripheral levels of the pain pathways which includes the periaqueductal grey matter, rostral ventrolateral medulla, the dorsal primary afferent spinal cord regions (including the peripheral nociceptors), and the spinal interneurons^{13, 33, 34}. Expression of CB1 receptors appears to be sparse in the brainstem region, which controls basic functions such as breathing and heart rate. This could explain the fact that exogenous cannabinoids have not been found to be lethal¹³.

CB2 receptors mainly act on the immune system, although they are found elsewhere in the body as well. They are most highly concentrated in leukocytes, in the spleen, and in other tissues and cells of the immune system^{35, 36}. They can also be found in more moderate numbers in bone, liver, and nerve cells including astrocytes, oligodendrocytes, microglia, and some neuronal sub-populations^{35, 36}.

1.3.1.5 Other Molecular Targets

The endocannabinoid system is further complicated by the fact that several different endocannabinoids are also believed to bind to a number of other molecular targets. One of these is the reputed third cannabinoid receptor, GPR55³⁷. They are also thought to bind to the transient receptor potential (TRP) cation channel family, and the peroxisome proliferator-activated receptor (PPAR) class of nuclear receptors and transcription factors^{22, 23, 32, 38}. This added complexity makes targeting the endocannabinoid system therapeutically a lot more difficult¹⁹.

1.3.1.6 Signal Termination

Endocannabinoids are rapidly broken down to quickly terminate signalling. Fatty acid amide hydrolase (FAAH) is mainly localized post-synaptically, and is primarily responsible for the metabolism of anandamide^{11, 27, 39, 40}. Monoacylglycerol lipase (MAGL) can be found pre-synaptically, and preferentially degrades 2-AG^{11, 27, 39, 40}. This local control allows endocannabinoid signalling to be very precise.

1.3.1.7 Dysregulation

Given the ubiquity of cannabinoid receptors, it is not surprising that dysregulation of the endocannabinoid system has been implicated in many pathological conditions⁴¹. Changes occurring under conditions of disease are either protective, or maladaptive⁴¹. Targeting the endocannabinoid system in treating related pathologies may hold promise. It may be possible to target the endocannabinoid system with molecules that change metabolic pathways, or with molecules that act directly as agonists or antagonists at these receptors²⁵. However, these approaches are complicated by the psychoactive properties of exogenous cannabinoids, and the difficulty of achieving selective targeting of the disease site^{33, 41, 42, 43, 44}.

1.3.2 Cannabis

1.3.2.1 *Cannabis sativa*

The term “cannabis” generally refers to *Cannabis sativa*, a gangly, loosely branched plant that can grow to about twenty feet high, and grows throughout temperate and tropical climates^{45, 46}. *Cannabis sativa* has been cultivated by humans for industrial applications because of its strong fibers⁴⁷, used as a medicine for a variety of therapeutic purposes⁴⁸, and taken recreationally as a result of its psychoactive properties⁴⁹. The leaves and flowering tops of the plant secrete a resin containing cannabinoids. Although the plant contains many cannabinoids, the main ones seem to be Δ^9 -tetrahydrocannabinol (Δ^9 THC), cannabinol (CBN), and cannabidiol (CBD)^{50, 51, 52}. These interact with the endocannabinoid system, producing a variety of effects, many of them in the central nervous system⁴⁷. The psychoactive properties of the plant are mainly attributed to Δ^9 -THC; some other cannabinoids such as Δ^8 -THC also have psychoactive properties, but they are not found in high enough quantities to significantly contribute to cognitive effects^{53, 54}. The highest concentration of these compounds is found in the flowering tops, with a significant but slightly smaller amount also found in the leaves. The stem and roots have considerably less, and the seeds have none. The ratio of various cannabinoids in the plant differs widely depending on the genetic makeup of the plant, as well as where and how it was grown⁴⁷.

Although cannabis will grow in a wide variety of environments, it produces the most resin in very hot climates, as a defense mechanism to trap water. Under these conditions, the quality of the fiber is poor. In contrast, cannabis grown in mild, humid climates produces less resin and stronger, more durable fiber⁵⁵.

The plant can be prepared in a few different ways. Prepared as marijuana, *Cannabis sativa* comes in two different forms. The first of these, bhang, has a lower resin content and consists of the dried leaves and tops of uncultivated plants. Ganja comes from the leaves and tops of cultivated plants, giving it a higher content of resin⁴⁷. Cannabis can also be prepared as Charas,

or hashish, which uses the resin itself, making it approximately 5-10 times stronger than marijuana preparations⁴⁷, or hash oil, a dark liquid containing extracts of the cannabis plant material⁵⁶. These formulations can be chewed, smoked, or consumed in baked goods.

It is believed that the potency of cannabis preparations has been steadily increasing since the 1960s. On average, confiscated cannabis preparations in the late 1960s had approximately a 1.5% content of Δ^9 -THC. By the mid-1980s, this had increased to 3.0-3.5%⁵⁷. Average levels are now estimated to be approximately 10% Δ^9 -THC, with some samples containing as much as 30%¹⁹.

1.3.2.2 Chemistry

Of more than 400 chemical compounds found in cannabis, approximately 60 can be identified as cannabinoids. This category is comprised of aryl-substituted meroterpenes and their transformation products⁵⁴. Not all cannabinoids have effects on the central nervous system. In fact, the psychoactive effects of cannabis can primarily be attributed to one molecule, Δ^9 -THC⁵⁸. Δ^8 -THC has comparable effects on the central nervous system, but is found in smaller quantities in the plant^{53, 54}. The stereoselectivity of this molecule (the (-)-trans isomer is significantly more potent than the (+)-trans isomer) was one of the discoveries which strongly suggested that cannabinoids act specifically through a receptor, rather than non-specifically by disrupting lipid membranes¹⁵.

1.3.2.3 Pharmacological Effects

Although the pharmacology of most cannabinoids is not yet known, some have been studied more extensively. Δ^9 -THC, has been isolated, synthesized, and investigated⁵⁴. Another natural cannabinoid found in the plant is cannabidiol (CBD). It does not have psychoactive properties in

itself, but it appears to influence the actions of Δ^9 -THC either by pharmacokinetic or pharmacodynamic means^{59, 60, 61, 62}. Because of this the amounts of both Δ^9 -THC and CBD in cannabis may change the subjective experience of smoking⁵⁴.

Cannabis is able to elicit a wide range of physiological effects. In the human cardiovascular system, cannabis produces a dose-dependent increase in heart rate, congestion of blood vessels in the conjunctiva (producing red, bloodshot eyes), and orthostatic hypotension (causing light headedness upon standing) because of vascular smooth muscle relaxation^{63, 64, 65}. This drug also produces relaxation of other smooth muscle, including that found in bronchial and gastrointestinal tracts^{66, 67}. It has been observed in mice that administration of Δ^9 -THC causes a reduction in spontaneous locomotor activity⁶⁸. Higher doses of Δ^9 -THC produce a “popcorn” effect, in which mice show hyperreflexia in response to auditory or tactile stimuli⁶⁴. There is some evidence that cannabis may relieve skeletal muscle spasticity and have anti-convulsant effects in humans^{68, 69, 70}. If this is the case, it could be mediated by both central and peripheral action⁵⁶. Intraocular pressure is reduced in humans when cannabis is consumed, but it is unclear what the underlying mechanism is⁶⁵. At high concentrations, the Δ^9 -THC found in cannabis reduces immune function, affecting macrophages, lymphocytes, and natural killer cells^{72, 73}.

Some cannabinoids have potential therapeutic applications. Δ^9 -THC and CBD have both been found to have some antiseizure activity⁷⁴. Cannabis has also been found to have significant analgesic activity, and this effect is seen with pure Δ^9 -THC as well¹⁹. A standardized extract of cannabis containing equal amounts of Δ^9 -THC and CBD, called nabiximols (Sativex[®]), is approved for use in neuropathic pain and spasticity due to multiple sclerosis in patients who have not responded to other medications⁷⁵. It has also been found that cannabis has anti-nausea and anti-emetic properties¹⁹. Dronabinol (Marinol[®]) is a synthetic preparation of Δ^9 -THC which has been approved to treat nausea and vomiting due to anti-cancer and anti-AIDS drugs and radiation⁷⁶.

Many effects of cannabis are in the central nervous system. These effects are mainly sedative⁷¹. Data from humans taken using electroencephalogram (EEG) technology show an increase in alpha waves, which indicate wakeful relaxation⁷⁷. In inexperienced users, cannabis decreases cerebral blood flow although anxiety may be a confounding factor in this observation since these changes were strongly correlated to changes in mood but not to blood levels of tetrahydrocannabinol⁷⁸.

There have been some reports indicating that sensory acuity is sharpened slightly, but this is offset by slower and less accurate thinking⁷⁹. It has been consistently found in both animal and human studies that short-term memory is impaired by cannabis use⁷⁹. Human studies indicate that free recall is more affected than recognition⁷⁹. In animal studies using state-dependent learning tasks, it has been found that memory formation and retrieval are disrupted by Δ^9 -THC. These tasks are based on the fact that it is easier to retrieve the memory of an association in the same condition it was learned in⁸⁰. Impairment from Δ^9 -THC is seen in rats for avoidance learning and conditioned suppression, but it was also noted that tolerance to these effects does develop^{81, 82}.

It is thought that the high density of cannabinoid receptors in the hippocampus may be responsible for the memory impairments seen with the administration of exogenous cannabinoids^{83, 84, 85}. In the delayed match to sample task, administration of Δ^9 -THC in rats produced a disruption that was similar to the disruption seen from a damaged hippocampus, although the effects of Δ^9 -THC administration were reversible within 24 hours of dosing⁸⁶. When assessed using the eight-arm radial maze and the delayed non-match-to-sample task, it was found that although Δ^9 -THC and other exogenous cannabinoids produced an impairment in working memory, the administration of anandamide, an endogenous cannabinoid, did not⁸⁷. Similarly, impairment of spatial memory was seen with Δ^9 -THC but not with anandamide⁸⁸. Cannabidiol did not impair spatial memory when evaluated using the eight-arm radial maze⁸⁸.

Animal studies have also found memory impairment from long-term cannabis exposure in rhesus monkeys. Animals were given one year of training to perform operant tasks, then administered

cannabis for one year. Their task performance was noticeably impaired for over a week after cannabis use was stopped, but levels did eventually return to baseline three weeks after cessation⁸⁹. Although this study did not find long-term behavioural changes, there is evidence that cannabis exposure in humans during cognitive development may have longer lasting behavioural effects⁹⁰.

Emotional reactions tend to be more unstable when under the influence of cannabis⁹¹. Mild euphoria and subjective feelings of relaxation are usually reported as well⁷¹. Individuals tend to become more talkative, and laugh more, similar to alcohol intoxication⁹². Unlike alcohol, cannabis does not seem to contribute to aggressive behaviour⁹³.

Cannabis has been shown to decrease alertness, reduce attention span, impair response times, and reduce the accuracy of motor responses⁷⁹. Because of these effects, activities like driving a motor vehicle while under the influence of cannabis can be very dangerous⁹⁴. The impairing effects of cannabis are additive⁹⁵ and possibly synergistic^{96, 97} with those of alcohol and the two are often taken together for recreational purposes⁹⁸. Cannabis has been found to produce different effects at different times after dosing. When cannabis is first taken by humans, there is some evidence of synergism with amphetamine⁹⁹. As time passes, drowsiness begins to set in, and synergism with sedatives such as benzodiazepines is observed¹⁰⁰.

When Δ^9 -THC is administered to humans in very high doses, effects mirror those seen with such hallucinogens as mescaline and LSD¹⁰¹. Time and space perception becomes distorted, body image is altered, and people experience depersonalization, hallucinations, spiritual or panic reactions, and acute psychotic episodes^{102, 103, 104, 105}. People sometimes lose partial or full control of body movements, because of selective polysynaptic reflex impairment¹⁰⁶.

1.3.2.4 Mechanism of Action

Although the mechanism of action has not been fully elucidated, enough is known to create at least a partial picture of how cannabis elicits its effects. Δ^9 -THC binds to the CB1 receptor in a stereospecific manner^{17, 107}. This receptor is found to have the highest density in the cerebral cortex, hippocampus, and striatum. It is found in moderate amounts in parts of the hypothalamus, the amygdala, the central grey, and laminae I to III and X of the spinal cord¹⁰⁸. CB1 receptors, like CB2 receptors, are G protein coupled, and tend to decrease adenylyl cyclase activity, inhibit N-type calcium channels, and disinhibit potassium A channels^{11, 25}. Activation of the CB1 receptors increases the firing rate of dopaminergic neurons in the ventral tegmental area, causing the release of dopamine into the nucleus accumbens¹⁰⁹. It is possible that this is accomplished through inhibition of a neuron which acts to decrease dopamine release⁹². This increase in dopamine signalling is believed to play a role in the reinforcing effects of cannabis¹⁰⁹.

The effects of cannabis are complex. Signalling of other neurotransmitters are also affected by cannabis intake^{12, 30, 33}. While changes in dopaminergic signalling are thought to be responsible for the drug's effects on response latency, changes in serotonergic signalling are thought to be behind observed changes in stimulus differentiation¹¹⁰. Although cannabinoids do not interact directly with opioid receptors, the analgesic effects are thought to be due to an interaction with endogenous opioids and actions on thalamic cannabinoid receptors^{19, 111}.

Although cannabis has some hallucinogenic effects, it does not cause generalization of discriminative stimuli¹¹². It also does not produce cross-tolerance with LSD- or amphetamine-like drugs^{113, 114}. When cannabis is used regularly and at high doses, some tolerance develops; however, this does not occur uniformly with all effects¹⁹. Tolerance to mood, intra-ocular pressure changes, EEG, psychomotor performance, nausea, and cardiovascular effects have been reported in normal subjects^{115, 116}. However, some studies have found that tolerance does not develop to the appetite-stimulating effects, and in one case it was reported that tolerance to euphoric effects did not develop in a group of regular cannabis users^{117, 118}.

1.3.2.5 Pharmacokinetics and Pharmacodynamics

1.3.2.5.1 Absorption

Smoked cannabis is absorbed within minutes, leading to higher blood levels of cannabinoids and a shorter duration of action compared to oral administration¹¹⁹. There is a lot of variability in the contents of cannabis cigarettes, depending on where the plant was grown and the ratio of cannabinoids within the plant material. This combined with the variability in the way subjects smoke (for example, how much the cigarette burns between inhalations, how deeply they inhale, and how long each breath is held for) leads to variability in absorption from this route^{119, 120, 121, 122}. The bioavailability from smoking ranges from 2 - 56%, and it is thought that subjects may alter their smoking behaviour to titrate their dose of Δ^9 -THC^{121, 122, 123}. Usually, 25 - 27% of the Δ^9 -THC from smoked cannabis enters the systemic circulation^{106, 124}.

Cannabis can also be vaporized or ingested. Synthetic cannabinoid preparations, such as dronabinol (Marinol[®]), can be taken orally, oral-mucosally, rectally, or topically. Vaporized cannabis reduces the formation of toxic by-products from smoking, and is more efficient at extracting Δ^9 -THC from the plant material^{123, 125, 126}. The plasma concentrations of Δ^9 -THC and the subjective drug effects are similar to those achieved when cannabis is smoked, with one study reporting faster absorption when cannabis is vapourized¹²³. As with smoking, vaporizing has many variables such as the amount and type of cannabis used, the temperature, the duration of use, and the volume of the balloon¹²⁷.

Oral administration of cannabis or medications containing cannabinoids results in a much slower onset of action, lower peak blood levels, and a longer duration of action compared to smoking or vapourizing¹¹⁹. The fact that the subjective “high” occurs much more slowly by the oral route may contribute to the fact that smoking is more popular than oral administration¹²⁸.

Bioavailability also appears to be lower in oral administration because of extensive first pass metabolism¹²⁹. When synthetic Δ^9 -THC, called dronabinol (Marinol[®]), is administered orally, only 10 - 20% of the administered dose enters the systemic circulation⁷⁶. The mean time for peak

plasma concentration ranges from 30 minutes to four hours⁷⁶. Δ^9 -THC can also be ingested through foods containing cannabis, such as baked goods, butters, or oils, or teas prepared using the leaves and flowering tops of the plant¹⁹. There is significant variability in all of these routes. When cannabis containing 20 mg of Δ^9 -THC was administered through a chocolate chip cookie, it was found that only 4 - 12% of the Δ^9 -THC dose was systemically available¹³⁰. Peak plasma concentrations usually took between one and two hours to occur, but for some participants this did not happen until six hours after ingestion. Some participants also had multiple peaks¹¹⁹. In a study comparing delivery of equal amounts of Δ^9 -THC through smoking versus oral administration, it was found that smoking produced peak plasma levels that were five to six times higher¹³¹.

Nabiximols (Sativex[®]) is a synthetic preparation containing equal parts Δ^9 -THC and CBD. When this is administered through the oral-mucosal route, peak concentrations generally occur within two to four hours. With this administration route as well, there is a large amount of inter-individual variability⁷⁵.

While Δ^9 -THC cannot be administered rectally, the pro-drug Δ^9 -THC-hemisuccinate can. Because of reduced first pass metabolism compared to oral administration, bioavailability is much higher, at approximately 52 to 61 percent^{123, 133, 134, 135}. It can take between one and eight hours to reach peak plasma concentrations¹³².

Topical administration of cannabinoids has not been well studied. Because of their hydrophobic nature, the rate-limiting step in their absorption is their transport across the aqueous layer of the skin¹¹⁹. A study examining delivery of 8 mg of Δ^8 -THC through a transdermal patch in a guinea pig found that a steady state concentration of 4.4 ng/ml was reached within 1.4 hours, and maintained for at least 48 hours¹³⁶.

1.3.2.5.2 Distribution

Distribution is fairly similar between different routes of administration, and begins immediately after absorption. Because Δ^9 -THC is highly lipid soluble, it is mainly distributed in the fatty tissues¹¹⁹. It is also primarily taken up by highly perfused organs, including the brain, heart, lungs, and liver¹¹⁹. The fact that Δ^9 -THC is hydrophobic also gives it a large apparent volume of distribution of 10 L/kg¹³⁷. Approximately 97% of Δ^9 -THC and its metabolites are bound to plasma proteins^{138, 139}. Δ^9 -THC is primarily bound to low-density lipoproteins, while 11-OH-THC is strongly bound to albumin^{140, 141}. After drug administration, levels Δ^9 -THC are highest in the heart (ten times the concentration found in plasma) and adipose tissue (1000 times the concentration found in plasma)¹⁴². Although the brain is highly perfused, the blood-brain barrier seems to limit the amount of Δ^9 -THC that can reach the brain or accumulate there^{119, 143, 144}. The time it takes for Δ^9 -THC to cross this barrier may be responsible for the delay between peak plasma concentrations and peak subjective drug effects¹²⁰.

The Δ^9 -THC that is stored in fatty tissue is released into the blood slowly, with a half-life of approximately 56 hours in humans¹⁴⁵. It is not known if Δ^9 -THC is retained in the brain long-term, but the fact that abstinent heavy cannabis users show residual cognitive deficits suggests short-term persistence^{92, 146}. It is also possible that the observed residual cognitive deficits are a result withdrawal, or neurotoxicity causing damage to brain structure or function¹⁴⁷.

1.3.2.5.3 Metabolism

Metabolism mainly occurs in the liver, and will differ depending on the route of administration^{119, 120}. The liver rapidly converts Δ^9 -THC into its major initial metabolites: 11-hydroxy Δ^9 -THC, which is pharmacologically active, and 11-nor-9-carboxy Δ^9 -THC, which is

not¹¹⁹. Plasma levels of 11-hydroxy Δ^9 -THC parallel the duration of observable drug action, and this metabolite is one contributing factor to the fact that drug effects continue even after Δ^9 -THC in the blood is no longer detectable^{148, 149}. First pass metabolism by the liver is especially important in oral administration¹¹⁹, since cannabinoids reach the liver before exerting their biological effects.

Because Δ^9 -THC is oxidized by cytochrome P450 (CYP) 2C9, 2C19, and 3A4, polymorphisms in the CYP isozyme may affect Δ^9 -THC metabolism contributing to inter-individual variability^{119, 150}. Furthermore the expression and activity level of these enzymes is actually influenced by the xenobiotics they metabolize. Therefore, drug-drug interactions, and adverse drug reactions are thought to be largely due to CYP activity¹⁵¹. This also may be related to differences between the effects of cannabis plants with different ratios of cannabinoids; for example, cannabidiol has been found to inhibit CYP3A4 activity, and to a lesser extent CYP2C9, influencing Δ^9 -THC metabolism^{59, 152}.

When cannabis is inhaled, 11-hydroxy Δ^9 -THC appears rapidly. Levels of this active metabolite peak approximately 15 min after the beginning of smoking, shortly after peak levels of Δ^9 -THC are observed¹⁵³. Peak plasma concentrations of 11-hydroxy Δ^9 -THC are about five to ten percent of the parent compound¹⁴⁹. Plasma levels of the inactive metabolite 11-nor-9-carboxy Δ^9 -THC peak approximately 1.5 to 2.5 hours after smoking, and reach about one third of the concentration of Δ^9 -THC¹²⁰.

After an oral dose of Δ^9 -THC, plasma levels of the parent compound and its active metabolite are approximately equal^{122, 154, 155}. Peak concentrations, reached at approximately the same time for both compounds, are seen approximately two to four hours after dosing. They continue to decline over several days⁷⁶.

1.3.2.5.4 Excretion

After smoking is stopped, levels of Δ^9 -THC decline rapidly. From fifteen minutes after smoking, mean plasma concentrations decrease to approximately 60% of peak levels, and by thirty minutes after smoking has stopped, 20%¹⁵⁶. Elimination of Δ^9 -THC and its metabolites mainly occurs through the feces and urine, responsible for 65% and 20% of clearance, respectively¹¹⁹. The majority of the dose (80 - 90%) is excreted within five days, but in chronic smokers a single dose of Δ^9 -THC can still be detected 13 days later^{149, 157}. This is probably due to extensive storage in body fat and subsequent release¹⁵⁷.

Δ^9 -THC and metabolites are also excreted through urine and feces when the drug is administered orally^{119, 149}. Approximately 50% of a radiolabelled dose of Δ^9 -THC was recovered from feces within 72 hours, as compared to 10 - 15% found in urine in this time¹⁴⁹.

The terminal elimination half-life represents the time taken for plasma levels to decrease by 50% when the decrease is fully attributable to elimination¹⁵⁸. For Δ^9 -THC this value appears to vary, but it seems to be approximately four days on average. These levels seem to decline in a multi-phasic way¹¹⁹. Estimates vary considerably due to assay sensitivity and the duration and timing of blood measures¹⁵⁹. It does not seem that the extent of Δ^9 -THC consumption influences its plasma half-life^{120, 160}.

1.3.2.5.5 Relationship between Pharmacokinetics and Pharmacodynamics

The relationship between plasma concentrations of Δ^9 -THC and the associated subjective, cognitive, and motor effects has not been well established¹⁹. These effects are often temporally distanced from peak plasma concentrations of Δ^9 -THC¹⁶¹. In a study of chronic heavy cannabis smokers, psychomotor performance, subjective drug effects, and physiological effects were correlated with concentrations of Δ^9 -THC in whole blood following an acute episode of cannabis

smoking¹⁶². Subjects reported smoking one joint per day on average for the two weeks prior to the study initiation. They were then provided with a cigarette containing approximately 54 mg of Δ^9 -THC. Peak blood concentrations of Δ^9 -THC occurred 15 minutes after the start of smoking on average, and these corresponded to peak visual analog scale scores for subjective drug effects. The authors found that the pharmacokinetic-pharmacodynamic relationship for all measured subjective effects was best described by counter clockwise hysteresis¹⁶². This occurs when pharmacological effects are greater at a given plasma concentration when drug levels in the blood are rising compared to that same concentration as drug levels in the blood are falling¹⁹. This type of relationship indicates that there is a lack of correlation between plasma concentrations of Δ^9 -THC and subjective drug effects.

It has also been found that tolerance can develop to some effects of Δ^9 -THC but not to others. This tolerance is thought to be largely due to pharmacodynamic factors rather than pharmacokinetic ones¹⁶³. This is mainly linked to changes in cannabinoid receptor availability for signalling, primarily CB1. This can result from either receptor desensitization, uncoupling the receptor from downstream events, or receptor downregulation, due to the receptor being internalized and/or degraded¹⁶⁴. There may be tissue-specific mechanisms regulating these processes, possibly explaining differences in tolerance to different effects¹⁶³.

In a study examining the effects of a cigarette containing 9 mg Δ^9 -THC, Jones et al¹⁰² found that the maximum “high” was achieved at approximately 45 minutes after dosing. At approximately 100 minutes following smoking, this had declined to about half of its peak. Another study has reported a peak increase in heart rate and subjective “good drug effect” within seven minutes after smoking¹⁶⁵. Subjects were provided with a cannabis cigarette containing either 18 mg or 39 mg of Δ^9 -THC. Both doses were found to differ significantly from placebo and from each other in terms of subjective measures. The high and low doses were significantly different from placebo but not from each other with respect to physiological measures, such as heart rate. The pharmacokinetic-pharmacodynamic modelling revealed that Δ^9 -THC induced drug effects lag behind plasma concentrations. The subjective effects significantly outlasted the presence of Δ^9 -

THC in the blood. The effects in the central nervous system were found to develop more slowly and last longer than the effects on heart rate¹⁶⁵.

1.3.2.6 Toxicity

Most of the toxicity associated with cannabis occurs with chronic use⁹². The most commonly reported adverse effect from heavy, long-term use is bronchopulmonary irritation caused by cannabis smoke¹⁵². Compared to tobacco smoke, cannabis smoke contains more tar, and this tar contains more irritants and procarcinogens^{166, 167}. Chronic bronchitis, which causes increased airway resistance and impairs gas exchange, is more common among heavy cannabis smokers¹⁶⁸.

Many people who use cannabis also smoke tobacco products, which is at least additive in terms of long-term toxicity¹⁶⁹. After only a few years of smoking hashish or marijuana daily, precancerous mutations have been found in the bronchiolar epithelium¹⁷⁰. Heavy cannabis smokers also seem to have an earlier onset of bronchopulmonary cancer than their tobacco smoking counterparts¹⁷¹.

Chronic heavy cannabis use is associated with several cognitive effects as well^{172, 173}. It is common for such users to experience mental slowing, lack of motivation, and emotional flatness. This is likely due to a constant state of intoxication, since the lipid solubility of cannabinoids render them able to build up in the body and exhibit their effects long after smoking⁹². Usually, these symptoms disappear gradually with abstinence. However, there are some cases where they persist, possibly due to damage to brain structures or functions caused by heavy cannabis use^{92, 147}. This type of damage may be similar to that seen in severe alcoholics, and may be exacerbated by malnutrition, injury, infections, or concurrent use of other drugs⁹². There is evidence in rats that daily injection of a moderately heavy dose (0.75-2.0 mg/kg) of Δ^9 -THC causes learning impairment similar to that seen in hippocampal damage⁸⁶.

Both animal and human studies have demonstrated a decreased output of gonadotropic hormones with heavy cannabis use over several weeks. This is associated with reduced serum testosterone,

and low sperm count or anovulatory cycles as applicable. Tolerance to these effects does seem to develop with time^{174, 175, 176, 177}.

Some chronic toxicity has been reported. For example, it has been reported that in regular cannabis users, there is damage to chromosomes in leukocyte cultures¹⁷⁸. There have also been reports of impaired immune responses, possibly due to suppressed T-lymphocyte function associated with high concentrations of cannabis⁹².

Large doses of cannabis produce effects on perception which can provoke psychiatric problems with prolonged use⁹². Mainly, these consist of brief psychotic episodes of severe anxiety or panic. These episodes usually respond effectively to reassurance and, if necessary, sedation with benzodiazepines; however, it is possible for them to occasionally continue for several days or weeks^{179, 180}. Of more concern are the symptoms of true schizophrenia in those with a history of the disorder or who were previously considered borderline^{181, 182}. Epidemiological evidence supports these observations that heavy cannabis use can precipitate this disorder in susceptible individuals¹⁸¹. Other large-scale studies show a correlation between being a young heavy user of cannabis, and depression and sociopathic behaviour^{71, 95, 183, 184, 185}. However, correlation does not necessitate causation, so these observed effects may be due to other factors, such as socioeconomic conditions.

1.3.2.7 Therapeutic Uses

Historically, cannabis has been used to treat migraines, epilepsy, depression, anxiety, and pain among other conditions⁴⁸. However, it was difficult to control the composition, and so alternatives, such as opioids for pain relief, came to be favoured^{91, 186}. Although cannabis shows therapeutic promise, the body of literature on cannabis use for therapeutic purposes is too limited to draw any conclusions about efficacy and safety. Furthermore, the wide-ranging physiological and psychoactive effects that have been identified so far make it difficult to use as a targeted treatment. Patients in Canada are able to access cannabis for medical purposes through the *Marihuana for Medical Purposes Regulations* (MMPR) when authorized by a healthcare

practitioner; however, cannabis is not currently an approved therapeutic product¹⁸⁷. Despite limited data, there is some evidence suggesting therapeutic uses for cannabinoids¹⁸⁸. Synthetic cannabinoids have been produced to combat some of the challenges associated with using the natural product. Nabilone (Cesamet[®]) is a synthetic cannabinoid prescribed to treat nausea and vomiting associated with cancer treatments in patients who have not responded to other anti-emetic medications¹⁸⁹. Dronabinol (Marinol[®]) is a synthetic preparation of pure Δ^9 -THC which has been approved as an adjunct therapy for AIDS and cancer patients who are experiencing nausea and vomiting which is not responsive to other medications⁷⁶, although it is no longer available in Canada. Nabiximols (Sativex[®]) is approved for use in the treatment of neuropathic pain and muscle spasticity⁷⁵. The fact that the endocannabinoid system functions to moderate appetite gives further clinical applications for targeting this system in the treatment of anorexia and obesity^{190, 191, 192}.

Another possible clinical application for cannabinoids is as an analgesic to treat pain⁷⁵. There is also some evidence suggesting that Δ^9 -THC may reduce muscle spasms associated with multiple sclerosis; however, while findings have suggested that Δ^9 -THC provides subjective relief, objective reduction in muscle spasm has not been conclusively reported^{193, 194, 195}. It is possible that this effect is due to analgesic actions, rather than actions on spasticity⁹². Nabiximols (Sativex[®]), containing equal parts Δ^9 -THC and CBD, is approved for use in the treatment of neuropathic pain and muscle spasticity in patients with multiple sclerosis who have not responded to other medications⁷⁵. In Alzheimer's disease, it has also been found that CB2 receptors are upregulated in activated glia, suggesting a possible future medical application of cannabinoids¹⁹⁶. Currently, work is being done to create more specific cannabinoid drugs which are able to elicit therapeutic effects without unwanted psychoactive properties¹⁹.

1.3.3 Cannabis Use in Canada

Among the general population aged 15 and older, past-year use of cannabis in 2013 was reported to be 10.6% according to the Canadian Tobacco, Alcohol and Drugs Survey (CTADS), with

males (14%) reporting a higher prevalence of the behaviour than females (7%)¹⁹⁷. This is comparable to the 10.3% reported in Ontario on the CTADS¹⁹⁸. Among young adults aged 20-24, past-year use was found to be 26%, more than three times higher than the 8% reported among adults over 25 years of age¹⁹⁷. The age of initiation of cannabis use was found to be approximately 18 years across the sample, although in young adults this was lower at 16.6 years, suggesting earlier initiation of cannabis use over time¹⁹⁷.

Data from the 2013 CAMH Monitor indicates that 7.5% of Ontario adults met the criteria for cannabis use problems, as indicated by the *Cannabis Involvement Score* from the World Health Organization's *Alcohol, Smoking and Substance Involvement Screening Test* (ASSIST V3.0). Males (9.6%) were found to have higher rates of abuse or dependence than females (5.4%)¹⁹⁹. Data from the Canadian Centre on Substance Abuse (CCSA) indicates that in Ontario from 2012 to 2013, 33% of people accessing publicly funded substance abuse treatment identified cannabis as the drug for which they were seeking treatment²⁰⁰.

In Ontario, it has been reported that 23% of students in grades seven to twelve used cannabis in 2013²⁰¹. Males were more likely to use cannabis, with 25% of males reporting use compared to 21% of females²⁰¹. Approximately three percent of these students reported using cannabis daily. Among those who reported using cannabis in the past year, approximately one in ten reported symptoms of dependence²⁰¹.

1.3.4 Driving Under the Influence of Cannabis (DUIC)

Drug-impaired driving is a criminal offence in Canada, and applies to any impairing drug and any type of motorized vehicle²⁰². Despite this, it was reported in the 2012 Canadian Alcohol and Drug Use Monitoring Survey (CADUMS) that 2.6% of Canadian drivers (632,576 individuals) have driven within two hours of using cannabis at least once in the previous 12 months²⁰³. This is estimated to represent 10.4 million trips taken under the influence of cannabis, which averages to 16 trips per person per year among people who drive while high⁹.

On the CADUMS, driving under the influence of cannabis (DUIC) was reported in males three times as often as it was reported in females²⁰³. It also seems that this behaviour was especially prevalent among young drivers²⁰³. In a roadside study conducted in British Columbia, 6.8% of 19-24 year-olds tested positive for cannabis compared to 5.5% of all drivers²⁰⁴. The only age group with a higher prevalence of this behaviour was drivers aged 16-18 years, of whom 7.5% tested positive. This is highlighted by data collected through the CAMH Monitor¹⁹⁹; although rates of driving after cannabis use remained stable at around 2.6% between 2002 and 2013, the prevalence of this behaviour among drivers aged 18 to 29 increased from 7.2% to 8.3%, reaching a peak of 11.9% in 2006.

According to the OSDUHS, driving after cannabis use is reported more often in students than driving after drinking alcohol²⁰¹. Approximately 10% of drivers in grades ten to twelve reported driving within one hour of using cannabis at least once in 2013 compared to 4% driving after consuming two or more alcoholic drinks²⁰¹. In this group, male drivers (13%) are more likely than female drivers (5.8%) to use cannabis and drive²⁰¹.

Riding in a car with a driver who has consumed cannabis is another common behaviour among young Canadians. Data from Beirness et al²⁰⁵ indicates that 15.8% of youth report being a passenger with a driver who had consumed cannabis within the previous two hours.

In Australia, it is illegal to drive with any detectable level of Δ^9 -THC in blood²⁰⁶. Because of this, police are able to randomly test the blood or oral fluid of drivers for Δ^9 -THC²⁰⁶. In the first year of testing, median oral fluid concentrations were found to be 81 ng/ml and median blood concentrations were found to be 6 ng/ml²⁰⁷. A national roadside survey conducted in the United States found that 1,740 drivers were positive for Δ^9 -THC at levels above 1.0 ng/ml, and that of these 76% had blood levels over 2.2 ng/ml²⁰⁸. Median blood concentrations in this study were found to be 3.8 ng/ml. In cannabis only cases, representing 57.7% of the total sample, median blood levels of Δ^9 -THC were found to be higher at 5.8 ng/ml²⁰⁸.

The prevalence of this behaviour is concerning, especially when coupled with the increasing evidence that cannabis-impaired driving makes collisions more likely⁹⁴. Understanding how

cannabis intake affects driving behaviour will be very important for public health and safety. This relationship has been investigated through epidemiological, naturalistic (on-road), and human laboratory studies.

1.3.4.1 Epidemiological Studies

Epidemiological studies are an important way to assess the risks associated with impaired driving in real-world scenarios. Through these types of studies, it has been found that cannabis smokers have demographic characteristics similar to those of other groups with high crash risk⁹⁴. People in this group tend to be male and between the ages of 18 and 25 years, and they tend to have a high tolerance for risk taking and a high incidence of drunk-driving^{209, 210, 211, 212, 213}. There are three general categories of epidemiological studies: cross sectional studies, cohort studies, and case-control studies⁶.

1.3.4.1.1 Cross Sectional Studies

Cross sectional studies examine data from a single point in time to identify possible correlations between smoking cannabis before driving and driving outcomes such as collisions²¹⁴. These studies are used to determine the prevalence of certain behaviours and the correlations between them, but these studies cannot establish causal relationships²¹⁴. This information is useful for identifying possible predictors for motor vehicle collisions, and can generate hypotheses which can be studied in depth using other study designs. Cross sectional studies have generally found that besides alcohol, cannabis is the psychoactive drug most commonly detected in injured or fatally injured drivers, and that people who drive within two hours of using cannabis face increased risk of collision²¹¹. In a study examining collision data from 2000 to 2010, it was found that 16.6% of fatally injured drivers in Canada tested positive for cannabis²¹⁵. Of note was that 40% of these cannabis-positive drivers were between 16 and 24 years of age²¹⁵.

A study by Khiabani and colleagues analyzed the median blood concentrations of Δ^9 -THC in suspected drugged drivers who underwent a Clinical Test for Impairment (CTI) shortly after apprehension²¹⁶. The median blood concentration in samples that contained only Δ^9 -THC was 2.2 ng/ml. The physician conducting the CTI judged 46% of these individuals as impaired. It was found that drivers judged as being impaired had higher blood concentrations of Δ^9 -THC (0.3 - 45.3 ng/ml) than those who were not deemed impaired (0.32 - 24.8 ng/ml). Drivers with blood Δ^9 -THC concentrations exceeding 3 ng/ml were at increased risk of being judged as impaired compared to those below this limit. It was also found that drivers who consumed cannabis regularly were less likely to be judged impaired than occasional smokers with comparable blood concentrations of Δ^9 -THC (OR=1.8, 95% CI 1.2 - 2.7), suggesting that these participants may be displaying tolerance²¹⁶. The large overlap in CTI scores and blood concentrations of Δ^9 -THC indicates that impairment cannot be predicted by these measures.

1.3.4.1.2 Cohort Studies

Cohort studies are those in which distinct groups of drivers who smoke cannabis and drive are compared to drivers who do not, with respect to driving outcomes, such as collisions²¹⁴. Because events are evaluated chronologically, these types of studies are able to suggest cause-effect relationships. A historical cohort study done by Chipman and colleagues²¹⁷ compared associations between cannabis abuse and traffic risk for both at fault collisions and all collisions in a population seeking treatment for their drug abuse. The adjusted relative risk for all crashes prior to treatment in the cannabis only condition was 1.49 (95% CI 1.17 - 1.89), while the adjusted relative risk for culpable crashes was 1.68 (95% CI 1.12 - 2.34). After treatment for cannabis misuse, there was no longer a significantly increased risk of collision, indicating that the increased risk of motor vehicle collisions was probably due to cannabis use patterns²¹⁷.

Fergusson and Horwood²¹⁸ followed a birth cohort of 907 young adults between the ages of 18 and 21 years. The number of collisions to which a driver was found to have contributed was

related to the extent of the driver's cannabis use, measured annually. However, this effect disappeared when other confounding factors were controlled for²¹⁸. This demonstrates one of the difficulties in assessing the effects of cannabis use on collision rates, since it has been shown that cannabis users are more likely to engage in other risk-taking behaviours⁹⁴.

A cohort study by Shope et al²¹⁹ examined driver history data along with a previously collected tenth grade questionnaire which asked about substance use including cannabis. The use of marijuana in the tenth grade was positively correlated with subsequent serious offences ($r=0.11$, $p<0.05$) and crashes ($r=0.07$, $p<0.05$)²¹⁹.

1.3.4.1.3 Case Control Studies

Case control studies are observational studies which examine the relationship between cannabis use and driving outcomes retrospectively. People with driving outcomes of interest are matched with a control group, and exposure to the possible causal agent, cannabis use or cannabis use before driving, is examined in both groups²¹⁴. The results of these studies are expressed in odds ratios, which usually approximate the relative risk²¹⁴. Case control studies can also be broken down by those that differentiate whether the cannabis-impaired driver was at fault (culpability studies), and those that do not⁶. The majority of these studies have found that cannabis consumption before driving is correlated with an increased collision risk⁶.

Some case control studies examine *self-reported* cannabis exposure in their assessment of the impact of cannabis on collisions^{211, 217, 221, 222, 223, 224, 225}. Of these studies, those that examine cannabis consumption rather than driving under the influence of cannabis have tended to produce lower or non-significant odds ratios⁹⁴. However, case control studies examining self-reported data have found that more frequent exposure to cannabis was associated with an increased risk of a motor vehicle collision^{217, 220, 221}. In one such study Mann et al²¹⁷ found that the risk of collision involvement was nearly three times higher in drivers who used cannabis more than once per week compared to those who did not. Case control studies examining risk of collision among those who report driving within an hour after smoking cannabis have found that this behaviour

approximately doubles the risk^{211, 220}. It has also been found that risk of collision was higher in those who reported driving within one hour of using cannabis compared to those reporting driving within two hours²²⁴. Blows et al²²² examined DUIC within two hours of cannabis use among drivers who self-reported a collision-related injury. The initial odds ratio for collision risk of 11.4 (95% CI 3.6 – 35.4) lost significance after adjustment for demographic factors, time of day, number of passengers, and other risky behaviours.

Case control studies using objective measures of cannabis use are well equipped for detecting a link between DUIC and collision risk⁹⁴. In 2011, Gjerde et al²²³ examined 204 driver fatalities with blood Δ^9 -THC greater than 0.6 ng/ml. These were compared to randomly selected control drivers who had levels of Δ^9 -THC in oral fluid that were less than 5 ng/ml. After adjusting for demographics, time period, and season, the odds ratio for fatality was still found to be significant at 8.6 (95% CI 3.9 - 19.3), although there were too few cannabis-only cases to establish an odds ratio for cannabis alone²²³. Other studies which have used urine as the analytical matrix have had less success in establishing a relationship. Studies done by both Movig et al²²⁵ and Woratanarat et al²²⁶ failed to find a significantly increased odds ratio when urine samples were collected from injured drivers to test for the presence of Δ^9 -THC. However, because cannabis has a prolonged detection window in urine, people may have been included who were not actually impaired which would have affected the data⁹⁴.

Culpability studies have also found that drivers who are under the influence of cannabis are more likely to be responsible for a resulting collision. Drummer et al²²⁷ found that drivers who had detectable levels of Δ^9 -THC in their blood, but no other substances, were 2.7 times as likely to be involved in a fatal collision than sober controls (95% CI 1.0 – 7.0). When the level of Δ^9 -THC in blood was over 5 ng/ml, the odds ratio for being culpable for a collision was 6.6 (95% CI 1.5 – 28.0). This is comparable to the likelihood of being responsible for a crash at a blood alcohol level (BAC) of 0.15%²²⁷.

Data based on blood or urine samples collected in the United States through the Fatality Analysis Reporting System (FARS) database has been analyzed to address this question as well²¹². Drivers

who were negative for alcohol but positive for cannabis were more likely to have a potentially unsafe behaviour or action which contributed to a collision (also called a driver-related factor), with a significant adjusted odds ratio of 1.29 (95% CI 1.11 – 1.50)²¹². Since urine samples are included in this database, it is possible that odds ratios are artificially low due to the larger detection window⁹⁴.

A study conducted in France found that drivers who were involved in fatal collisions and had detectable concentrations of Δ^9 -THC were at increased risk of crash responsibility (adjusted odds ratio = 1.78, 95% CI 1.40 – 2.25)²²⁸. As blood concentrations of Δ^9 -THC increased, the odds ratio for driver-responsibility increased as well. These adjusted ratios ranged from 1.57 when Δ^9 -THC levels were less than 1 ng/ml to 2.12 when levels were at or above 5 ng/ml²²⁸. Increasing concentrations of Δ^9 -THC in the blood appear to be associated with an increased risk of culpability in a motor vehicle collision⁹⁴.

1.3.4.1.4 Meta-analyses

Meta-analyses are able to combine the data from many independent studies. In a meta-analysis of epidemiological studies, Asbridge et al⁶ reported that the odds of a collision almost doubled after smoking cannabis relative to other drivers (OR=1.92, 95% CI 1.35 – 2.73). In another meta-analysis of the epidemiological literature, Li et al²²⁹ reported a slightly stronger association (OR=2.66, 95% CI 2.07 – 3.41).

1.3.4.1.5 Challenges with Epidemiological Studies

Epidemiological studies are complicated primarily by two factors. First, cannabis is often not the only drug detected, and is commonly found with alcohol and other psychoactive substances in injured or fatally injured drivers. This leaves a much smaller sample size of cannabis only cases to analyze, making it much more difficult to detect any correlation that may exist. For instance,

Longo et al²³⁰ examined blood samples from 2,500 injured drivers, only 44 of which presented with only Δ^9 -THC and metabolites without other psychoactive substances. When this number is compared to the 1,887 drug-free controls, it is not surprising that no difference was found in collision risk between the two groups. Gjerde et al²²³ examined 204 fatally injured drivers with blood Δ^9 -THC greater than 0.6 ng/ml. These were compared to randomly selected control drivers who had oral fluid Δ^9 -THC less than 5 ng/ml. After adjusting for demographics, time period, and season, the odds ratio for fatality was still found to be significant at 8.6 (95% CI 3.9 – 19.3). However, there were too few cannabis-only cases to establish an odds ratio for cannabis alone.

The second problem plaguing epidemiological studies is methodological. Because Δ^9 -THC is highly lipid soluble, it displays pharmacokinetic behaviour which makes it much more difficult to determine if a person is high just based on their blood levels. Although Δ^9 -THC in the blood peaks shortly after smoking, it is very quickly metabolized and distributed throughout the body. Because of this, samples would need to be collected almost immediately to successfully correlate cannabis effects with driving outcomes, which is not always possible²³¹. Blood collection generally occurs approximately 90 minutes after arrest²³¹, and three to four hours after a collision has occurred²¹⁰. This means that even if a sample had been positive when the collision occurred, it could easily be negative by the time it is collected and analyzed.

This can be resolved by using metabolites of Δ^9 -THC which persist in the blood and urine for much longer. However, the caveat is that these metabolites only indicate that cannabis has been used relatively recently, but does not sufficiently limit the time frame of use to determine whether or not the person was experiencing the psychoactive effects of cannabis at the time of the collision. Earlier epidemiological studies often used 11-nor-9-carboxy Δ^9 -THC as a marker of cannabis consumption²²⁷. However, this metabolite has a long window of detection in the blood¹²¹. In cannabis smokers who use less frequently than every day, 11-nor-9-carboxy Δ^9 -THC was detected up to seven days after smoking one cannabis cigarette containing 38 mg of Δ^9 -THC¹⁵³. A study by Drummer and colleagues done in 2004 included subjects in the cannabis-

exposed group who only had this metabolite present in their blood, and was not able to provide strong evidence of a correlation between cannabis use and collisions²²⁷.

Some remain skeptical of the relationship between DUIC and collisions being causative. One of the confounding factors inherent in epidemiological studies is that group differences could be due to other traits intrinsic to each population. One study in which this appears to have occurred was a case control study examining self-reported data. Drivers who reported using cannabis in the three hours prior to the crash were 3.9 times as likely to be involved in a collision, yet after adjusting for other driving behaviours (such as travelling speed and sleepiness), the effect was no longer significant²²². A laboratory study by Bergeron and colleagues²³² evaluated simulated driving performance on young adults aged eighteen to twenty-five years and collected self-reported measures of DUIC and reckless driving. Self-reported DUIC was found to be associated with risky driving style measured by the driving simulator. This suggests that underlying personality traits and driving behaviours inherent to this group are contributing factors to increased collision risk.

Another limitation of epidemiological research arises from differences in tolerance to cannabis effects. In frequent smokers, tolerance may result in less impairment at a given concentration of Δ^9 -THC than in occasional smokers²¹⁶. It is difficult to know how to handle these differences statistically, and failing to account for potential differences in tolerance can make results equivocal. However, many studies which control for confounding factors, such as the influence of other substances, risky driving behaviours, and demographic variables, have found that risk of collision after cannabis consumption is still elevated compared to controls^{94, 227, 233}. These findings make it far less likely that the observed relationship between DUIC and driving outcomes is an artifact of other risk factors.

1.3.4.1.6 Summary

An accumulating number of epidemiological studies continue to lend support to the idea that driving while under the influence of cannabis increases the risk of being involved in a motor

vehicle collision. This growing body of epidemiological evidence suggests that cannabis use prior to driving is a risky activity; however, it is important to examine this relationship through other research methodologies as well.

1.3.4.1.7 Roadside Testing

Although the most accurate measure of Δ^9 -THC concentration in plasma is obtained through blood samples, there has been some evidence suggesting that it may be possible to test drivers for drug-impairment using a roadside saliva test. In these tests, subjects are asked to provide a saliva sample, either stimulated with gum or candy, or with no stimulation²³⁴. Levels of Δ^9 -THC are measured in the saliva samples provided²³⁵. The results of this non-invasive test are thought to correlate with drug effects, and there is some evidence that this is the case. Menkes et al²³⁶ found that there was a significant correlation between Δ^9 -THC concentration in oral fluid and subjective drug effects and heart rate. Significant correlations have also been found in other studies examining mean saliva concentrations and ratings on a ‘feel drug’ scale, digit symbol substitution test, and heart rate²³⁷. However, these correlations have only been found with mean saliva concentrations, not individual ones.

The novel pharmacology of Δ^9 -THC (outlined in Section 1.3.5.2) presents challenges to this approach. Since biological fluid levels do not temporally correlate with subjective effects, it is difficult to gauge the extent to which someone is intoxicated by Δ^9 -THC levels in saliva samples. Furthermore, saliva is not an ideal fluid to analyze for the presence of Δ^9 -THC.

Although saliva is preferred because it is much easier to collect and far less invasive, it is more difficult to get accurate measurements of Δ^9 -THC in saliva than in urine or blood²³⁵. A roadside study of 302 drivers done by Biermann et al²³⁸ evaluated the Toxiquick device which analyzes saliva samples collected on a cotton bud placed in the oral cavity. Oral fluid results of several illicit drugs were compared to corresponding blood samples. The oral fluid test was found to give

20% false negatives for cannabis, which would be very concerning if this were to be used for forensic purposes.

Cannabis consumption may also limit salivation, making sample collection more difficult and potentially resulting in the need to analyze much smaller sample volumes²³⁹. It is possible for samples to be contaminated by food, beverages, or adulteration techniques that have not yet been identified in the literature²⁴⁰. Smoking cannabis may result in the detection of falsely high levels of Δ^9 -THC in oral fluid for approximately 30 to 60 minutes after smoking²⁴¹. The technology continues to be improved in order to resolve technical issues, such as adsorption of drugs to the device which can result in false negative test results; this is especially problematic with lipophilic drugs, such as cannabis²⁴². The biggest problem facing this approach is the inter-individual variation in the relationship between performance impairment, serum concentrations, and oral fluid concentrations of Δ^9 -THC. The fact that a linear relationship between these factors cannot be established makes it problematic to try to predict plasma concentrations based on those found in oral fluid^{243, 244}. A 2015 study concluded that although oral fluid testing has screening value, it poses challenges in interpreting concentration-based effects⁹⁵.

There are several advantages to oral fluid testing. Because saliva is easier to collect, there is less of a lag time between suspected impaired driving and sample collection²³⁵. Furthermore, because saliva can be collected under the direct supervision of the person obtaining it, chances for adulteration are reduced²³⁵. The fact that saliva sampling is non-invasive reduces the risk of infection, and makes it a safer alternative to blood samples where the skin must be broken²³⁵.

Oral fluid testing shows promise and may eventually be widely used to detect cannabis impaired drivers. However, further research is needed to identify new biomarkers, determine drug detection windows, characterize techniques for adulterating oral fluid results, improve sample collection and analysis, and evaluate the stability of analytes before widespread oral fluid testing for the detection of cannabis impaired driving can be implemented²³⁵. In the meantime, it remains an important research tool for epidemiological studies.

1.3.4.2 Human Laboratory Studies

Although epidemiological studies are invaluable for identifying correlations between cannabis use and driving outcomes, human laboratory studies are the most rigorous way to evaluate causality⁹⁴. In impaired driving research, laboratory studies examine psychomotor ability, cognitive performance, capability on a driving task and other outcome measures to see how these change under different drug conditions.

Early laboratory studies were often inconclusive because the measures being used to detect impairment were not sensitive or specific to the effects of Δ^9 -THC^{245, 246}. There is also some evidence suggesting that drivers high on cannabis are aware of their impairment and attempt to compensate by reducing their speed and taking fewer risks^{247, 248, 249, 250, 251, 252}. However, laboratory studies still find impairment under the influence of cannabis. Although driving effort increases with the perceived influence of Δ^9 -THC²⁴⁷, these efforts cannot completely compensate for the loss of control²⁵⁰. This is especially true with complicated processes requiring simultaneous attention to multiple tasks. It has generally been found that performance under the influence of cannabis is impaired by divided attention tasks, where multiple subtasks are being performed simultaneously^{249, 250, 253}; during unexpected events requiring quick decision making²⁵⁴; and during long, monotonous drives where the driver's attention may not stay on the task²⁵⁴.

One variable affecting these types of studies is the driver's prior experience with cannabis use. Research suggests that chronic heavy cannabis users may develop tolerance to some of the impairing effects of Δ^9 -THC, whereas other impairing effects in this population may last beyond the acute period after smoking due to heavy exposure^{216, 255, 256, 257}. This means that the selected study population is important to interpretation of results. Furthermore, the dose of Δ^9 -THC administered²⁵⁸, and the age and level of driving experience of participants may also influence these results and explain many of the apparent discrepancies in study findings. As with epidemiological studies, participant bias may also play a role in these findings.

Laboratory studies have been used to try to determine a connection between blood concentrations of Δ^9 -THC and metabolites, and degree of performance impairment on driving or cognitive tasks. This would be especially useful for determining *per se* limits for driving under the influence of cannabis, similar to the current legal BAC limits. However, because of the novel pharmacology of Δ^9 -THC, this relationship is not an easy one to determine. Menterey et al²⁵⁹ measured Δ^9 -THC in blood concurrently with psychomotor task performance after oral administration of 20 mg dronabinol, or of a cannabis decoction containing 20 mg or 60 mg Δ^9 -THC. It was found that the maximum performance deficits did not coincide with peak blood concentrations of Δ^9 -THC. Variability between people in Δ^9 -THC and cannabinoid concentrations made conclusions about impairment based on Δ^9 -THC concentration impossible. Likewise, Ramaekers et al²⁴³ were unable to identify a linear relationship between Δ^9 -THC levels in serum and level of impairment on a series of tasks. Although it was found that all participants were impaired beyond 30 ng/ml, there was extreme variability in impairment below this level making it difficult to extrapolate from serum levels to dose or impairment.

These studies, when used in combination with epidemiological data, help to provide a more complete picture of impaired driving. However, some laboratory tasks may not translate to real-world driving the way experimenters expect them to, making the predictive validity unknown in many cases. Furthermore, the doses provided are not always representative of what is commonly available on the street, and are often much lower. As research in this area progresses, these problems continue to be addressed. With improvements to driving simulation technology, scenarios can be designed to closely mimic a real driving task. Furthermore, as more confounding variables are identified, it becomes possible to design studies in such a way as to limit these factors.

1.3.4.2.1 Psychomotor and Cognitive Studies

Tests of isolated psychomotor and cognitive abilities are often used in impaired driving research. It is thought that the results of these tests can be extrapolated to driving ability, since they examine many of the skills required for driving. However, not all experts believe that poor performance on these tests will necessarily translate to poor performance on the road. A standard battery of tests specifically designed for testing driving skills has yet to be developed and validated. There is also no standardized set of tests to examine the psychomotor and cognitive aspects of impairing substances which may be important for driving. Despite this, it is possible for researchers to select tests based on the current body of literature. It has been shown that Δ^9 -THC is able to dose-dependently impair faculties from basic motor coordination to complex executive functions²⁴⁶. Cannabis-induced changes have been noted in learning, working memory, perception (specifically space and time estimation), reaction time, fine motor control, and attention^{216, 260}.

The impairing effects of Δ^9 -THC are often dose-dependent. A 2008 study by Weinstein et al²⁵⁸ examined the dose-response effects of two doses (13 mg and 17 mg) of Δ^9 -THC in chronic daily smokers. They found a minor significant impairment in performance of a card-sorting task completed 0.75 hours after smoking either dose, and impairment increased with the higher dose. Since the impairing effects of cannabis are dose-dependent, studies using lower doses of cannabis may not observe impairment. This makes it important to study driving impairment using cannabis with a potency of Δ^9 -THC comparable to what is found on the street.

In this same study, participants tested one hour after smoking were not impaired by either dose in terms of decision making speed in a gambling task²⁵⁸. However, there were a significantly higher number of participants who selected least-likely outcomes after consuming the higher dose as compared to placebo. Participants were also evaluated on their performance in a virtual maze task: a computer game, in which the participants wear virtual reality glasses to see the maze in three dimensions, and navigate it using the arrow keys of a computer keyboard. The 17 mg dose significantly increased the average number of wall collisions (5.5) compared to placebo (2.9)

($t=2.8$, $p<0.05$). In a similar study, recreational cannabis users were administered either 0, 250, or 500 $\mu\text{g/kg}$ Δ^9 -THC in the form of a cannabis cigarette. At 0.75 to 5.75 hours after smoking the 500 $\mu\text{g/kg}$ dose, participants made significantly fewer correct decisions on the Tower of London test, which measures task analysis, working memory, attention, and impulsivity.

One major source of variability in these studies is selection of participants. Another study by Ramaekers and colleagues²⁵⁶ examined cognitive performance of heavy cannabis users after consuming a cigarette containing 400 $\mu\text{g/kg}$ Δ^9 -THC (approximately 28 mg). No significant effects were found in reaction time or the number of correct decisions on the Tower of London test at one hour post-dose. Critical tracking was also not found to be significantly affected by Δ^9 -THC intake in this population. This seems to support the hypothesis that heavy cannabis users are able to develop tolerance to some of the impairing effects of Δ^9 -THC.

The effects of tolerance were explicitly tested in a 2009 study by Ramaekers et al²⁵⁵. Occasional and heavy cannabis users were compared on their neurocognitive performance. After both groups consumed a cannabis cigarette containing 500 $\mu\text{g/kg}$, it was found that Δ^9 -THC significantly impaired occasional cannabis users on measures of critical tracking, divided attention and a stop signal task. However, heavy users were only impaired in the stop signal task, demonstrated by a slowed reaction time. Baseline measures did not suggest intrinsic performance differences between the groups before drug administration, suggesting that tolerance played an important role in the results of laboratory experiments. In the study conducted by Weinstein and colleagues²⁵⁸, neither the 13 mg nor the 17 mg dose produced errors in time or distance perceptions 1.25 hours after smoking. However, this was studied in chronic daily smokers and it is likely that these findings would have been different in a population with less cannabis experience.

It seems that more complicated tasks are more sensitive to the impairing effects of Δ^9 -THC. Cannabis impacted performance during a divided attention task in the study by Ramaekers et al²⁵⁶. Participants were asked to complete a critical tracking test while simultaneously monitoring a central display that put out signals to which the subject was required to respond. The

administration of Δ^9 -THC impaired task performance by increasing the number of times control was lost, slowing reaction time, and reducing the number of correct signal detections. This supports the theory that the impairing effects of Δ^9 -THC cannot necessarily be compensated for during complicated tasks.

Despite these variables which may mask the impairing effects of cannabis, performance deficits are often found. Morrison et al²⁶¹ examined the effects of synthetic intravenous Δ^9 -THC on neuropsychological test performance, and found that measures of immediate recall, attention, working memory, and executive function all showed impairment²⁶¹. Ramaekers and colleagues found that controlled tracking performance was found to be negatively affected after both a 250 $\mu\text{g/kg}$ dose and a 500 $\mu\text{g/kg}$ dose of smoked cannabis²⁴³. Reaction time in a stop signal task was also found to be impacted by cannabis intake²⁴³. A study on individuals who smoked cannabis one or more times per month examined the effects of four standard puffs²⁶² taken from each of two cannabis cigarettes containing 3.6% Δ^9 -THC administered two hours apart²⁵³. Impairment in several measures was found. Perception of time was affected, as participants underestimated 60 and 120 second intervals 1.25 hours after drug administration. Impairment was also noted on a digit-symbol substitution test administered after smoking. Subjects were asked to complete a divided attention task, and cannabis administration was found to significantly increase the number of false alarms.

Overall, these studies provide evidence that cannabis can affect cognitive functions important for complex tasks such as driving. Impairment is more reliably found in slightly higher doses, which are closer to those commonly found on the street. This makes studies including higher Δ^9 -THC doses important for understanding this issue. Many of these findings highlight the importance of studying drug impaired driving in different populations of cannabis users separately, as impairing effects are different in chronic heavy users compared to occasional users, and would likely be different in medical cannabis users as well. However, it seems that with increasing task complexity, impairment is seen even in individuals with prior cannabis experience who may be able to partially compensate. These studies are important for guiding the design of naturalistic

and driving simulator studies, so that they are better able to understand the nature of the effects of cannabis on driving.

1.3.4.2.2 Naturalistic (On-Road) Studies

One of the ways to study the effects of cannabis on driving is by using an instrumented vehicle on a road, and comparing the performance of study participants in various states of sobriety. These cars are often dual controlled, meaning that they have brakes on the passenger's side as a safety feature²⁶³. To further ensure participant safety, these studies are often done on closed-course tracks so that others are not endangered by having intoxicated drivers on public roadways²⁴³.

These studies began to be conducted in the 1970s and 80s. Since that time, not many have been conducted and those that have been performed have had mixed results. Many show that Δ^9 -THC has dose-dependent effects on driving, and that impairment is more prominent with more complex tasks. Some of the variability observed in the results of these studies seems to be attributable to participant bias. Many subjects admit to paying much more attention to their driving than they usually would in order to show that they are able to safely drive while high²⁶⁴.

A study conducted by Hansteen and et al²⁴³ tested the effects of two doses of smoked Δ^9 -THC (1.4 mg and 5.9 mg) or placebo on driving performance in a closed course track. The number of traffic cones hit and the time taken to complete the course were significantly greater for participants who received the higher dose of Δ^9 -THC. No significant findings were observed with the lower dose. A 1983 study done by Sutton et al²⁶⁴ used a similar paradigm to assess impairment, having subjects drive on a closed course track after smoking a cigarette containing 2% Δ^9 -THC or placebo. No significant differences between the active and placebo conditions were found, but participant bias may have played a role in this observation. Researchers were told by study subjects who thought they had received active cannabis that they were much more careful in their driving because they wanted to demonstrate that the drug did not have impairing effects. This situation is actually observed fairly commonly⁹⁴, and has led to the speculation that

cannabis users are aware of their impairment and attempt to compensate by driving more cautiously.

Robbe⁹⁶ used escalating doses of smoked Δ^9 -THC (100, 200, and 300 $\mu\text{g/kg}$) to examine performance deficits in 16 participants on a series of highway driving tasks. Study subjects began driving 45 minutes after the start of smoking, and were asked to complete a 16 km car following task, a 64 km road tracking task, and another 16 km car following task. Dose-dependent increases in standard deviation of lateral position (SDLP) were observed. At the lowest dose, effects were noticeable but not statistically significant. Both the 200 and 300 $\mu\text{g/kg}$ doses produced statistically significant results, with the highest dose showing the most substantial increase relative to placebo. This study also found that the average headway in the car following test increased, but displayed an inverse headway-dose relationship: the lowest dose produced an increase of 8m, the medium dose produced an increase of 6m, and the highest dose produced an increase of only 2m. The authors suggest that this was due to practice effects, where drivers can become less cautious as they become more comfortable with the task. The authors do not believe this observation is due to pharmacodynamic tolerance.

In a study by Ramaekers et al²⁵¹, driving performance was found to be impaired in drivers aged 20 to 28 years by an acute dose of smoked Δ^9 -THC. This was measured using a 40 km car following test, where subjects are asked to maintain a consistent distance behind a car they are following, and a road tracking task. Thirty and seventy-five minutes after smoking cannabis, it was found that participants' SDLP values were significantly increased compared to placebo (2.7 cm for the low dose, 3.5 cm for the higher dose). These values were also found to be higher in the second drive than the first. The standard deviation of headway distance was found to be significantly increased relative to placebo in both doses (2.9 m for the low dose, 3.8 m for the higher dose).

The use of subjective driving evaluation makes detecting impairing effects of cannabis more difficult. In an on-road study by Lamers et al²⁴⁷, subjects between the ages of 21 and 40 who smoke less than daily but more than once per month were assessed by a licensed instructor using

the Driving Proficiency test. They were taken on a 45 minute drive through the city 25 minutes after smoking a cigarette containing either 100 µg/kg Δ^9 -THC or placebo. This study did not find that Δ^9 -THC had significant effects on total score, vehicle checks, handling, action in traffic, traffic observation, or turning.

Increased task complexity makes compensation for impairing effects more difficult, and increases the sensitivity of driving tests. Other on-road studies have tried to increase the cognitive load required for their tasks by incorporating obstacle courses, or using city driving scenarios among other things. These studies have also produced mixed results, but those that have found impairment have noted that drivers under the influence of cannabis display more road tracking errors such as increased SDLP, and failure to maintain following distance²⁵¹. These effects, when noted, seem to be dose-dependent. Some studies, however, have reported no differences between the conditions^{247, 265}. The inconsistency of the results for on-road studies is probably attributable largely to experimenter bias, participant bias, driving courses that are not challenging enough to detect effects, technology that is unable to detect subtle differences in driving measures, and insufficient doses of Δ^9 -THC to mimic intoxication produced in a real-world scenario.

1.3.4.2.3 Driving and Driving Simulation

Researching the potential impact of alcohol and drugs on driver behaviour has become more viable with the advent of driving simulation technology. The precursor to this technology began during World War II, when flight simulators were used to train pilots on how to use tactical war machinery²⁶⁶. In the late 1950s and early 1960s, it became apparent that this technology could be applied to addressing research questions, including those regarding factors that affect driving skill such as impaired driving²⁶⁶. By using simulated driving, it became possible to study these factors in a safe and economical way, while gaining freedom to test more aspects of driving than was possible before. This approach eliminates the risk of death, injury, property damage, or legal consequences.

Driving simulators are composed of four basic parts: the simulation computer, the parts which provide sensory feedback, the display, and the human operator²⁶⁷. Since the advent of these simulators, technology has advanced considerably. It is now possible to incorporate digital computers, and advanced electronics and display technology. Simulations will only continue to get better as technology advances; improvements in the visual display have been and will continue to be especially important for making simulations more realistic, since driving is primarily a visual task²⁶⁶.

One of the earliest simulated driving studies to examine the issue of drugged driving was done by Crancer and colleagues in 1969²⁶⁸. Participants in this study were seated in the front section of a car and asked to view a 23-minute film. Although the controls in the car had no influence over what happened in the scenario, participants were asked to drive along with the video and produce the actions that would result in the visual display being viewed. Experimenters observed participants and recorded driving errors. As technology improved, later studies used more advanced methods. A 1982 study used a moving belt with a closed-circuit black-and-white television display, connected in such a way that the system would respond to participants changing the speed, clutch, and gear shift²⁶⁹. In 1973, Rafaelson and colleagues used a more advanced driving simulator, which included a technology called cyclorama - a panoramic painting giving a 360 degree view to the person in the middle of the cylinder²⁴⁵. Despite advances towards designing a more realistic driving task, the measures of driving behaviour collected in these studies were still subject to experimenter bias.

Now, with the introduction of digital computer technology and animated graphics, driving simulators are capable of providing a much more realistic driving experience. Furthermore, they are able to reduce the risk of experimenter bias by taking automatic measurements of driving skill, such as speed, lane deviations, steering errors, and stopping distances among others. Most simulators are fully programmable, allowing for the development of scenarios that can include day or night driving, distractions such as complicated signage to create a dual-task condition, or hazards designed to test specific driving skills. The fact that this can be done safely removes a major ethical concern with attempting to test these variables on the road²⁶⁶.

One concern that has been expressed with this technology is its scientific validity. Although simulators are designed to imitate driving, the task is still slightly different from driving in a real vehicle on an actual road. Because of this, simulated driving often causes ‘simulator sickness’²⁷⁰. This occurs when the mismatch between visual and vestibular cues causes the driver to become nauseated and feel ill, which may adversely affect driving ability although the extent to which this occurs is unknown²⁷⁰. Simulator sickness has been identified as a problem as far back as the earliest simulations²⁷¹. It is possible to minimize the risk with strategic simulator and study designs; the discomfort seems to be mitigated by the use of larger screens, and by allowing participants to acclimatize over several sessions^{270, 272}.

Concerns have been expressed about the ability of driving simulation to predict real-world performance. Because of the wide range of simulator designs, testing protocols, and data collection methods, a standardized validity assessment has not yet been developed²⁷⁴, although guidelines do exist²⁷³. Despite this, it is possible to evaluate driving simulators themselves for reliability and external validity^{275, 276}. A study comparing naturalistic closed course driving to simulated driving found that the two paradigms were similarly able to measure the increase in SDLP with increasing doses of alcohol²⁷⁷. Another study found that simulated driving performance was a good predictor of self-reported automobile collisions five years later in older adults²⁷⁸. Although driver simulation will improve with advanced technology allowing simulated driving to even more closely mirror an on-road experience, studies thus far have shown that the current technology is valuable for driving research.

1.3.4.2.4 Driving Simulator Studies

1.3.4.2.4.1 Speed

Consistent with the theory that drivers show compensatory behaviour when driving under the influence of cannabis, some measures indicate that these drivers are more cautious. A study conducted by Ronen and colleagues found that speed was reduced during a simulated driving task after consumption of 13 mg of Δ^9 -THC⁹⁷. Participants were 24-29 years of age. In an earlier study, Ronen et al²⁴⁸ assessed the effect of 13 mg and 17 mg of Δ^9 -THC versus placebo on

simulated driving in healthy students (average age 26 years) who use cannabis recreationally. They found that drivers reduced their speed significantly in a dose-dependent manner. Anderson et al²⁵² also found decreases in mean speed after the administration of a single dose of smoked cannabis containing approximately 22.9 mg Δ^9 -THC in participants aged 18-31 years, and Lenné et al²⁵⁰ found the same thing after administering cigarettes containing 19 mg or 38 mg of Δ^9 -THC to participants between the ages of 18 and 21 years. Only one simulated driving study failed to observe an effect on mean speed after administering cannabis cigarettes containing 1.75% or 3.33% Δ^9 -THC to participants aged 21 to 45 years²⁷⁹.

1.3.4.2.4.2 Speed Variability

Although driving speed seems to be reduced when drivers are impaired by Δ^9 -THC, speed variability has been reported to increase in some cases. Rafaelsen et al²⁸⁰ noted this increase in variability after administering 8, 12, and 16 mg of Δ^9 -THC. The effect appeared to be dose-dependent, and only the highest dose was statistically significant. This effect was also noted by Lenné et al²⁵⁰ after administration of 19 or 38 mg of Δ^9 -THC. Some studies have been unable to find this effect^{97, 252, 279}.

1.3.4.2.4.3 Headway

It has also been observed that drivers leave a greater headway when under the influence of cannabis. The study conducted by Lenné et al²⁵⁰ found that smoked doses of 19 and 38 mg of Δ^9 -THC caused significant and dose-dependent increases in mean headway in a car following task. However, standard deviation of headway also increased, suggesting less control over the vehicle.

1.3.4.2.4.4 Reaction Time

Despite this compensatory behaviour, it appears that many effects of Δ^9 -THC are outside of conscious control. Rafaelson et al²⁴⁵ compared the effects of eating small cakes containing 8, 12, or 16 mg of Δ^9 -THC to determine the impact on driving abilities in drivers aged 21 to 29 years. With their simulator, Rafaelson et al were able to assess start and stop times using red and green light signals, and found significant effects. Cannabis intake increased the time required to accelerate and to brake, and reduced the number of gear changes, and these effects were found to be dose-dependent. Ronen et al²⁴⁸ examined 13 mg and 17 mg doses of Δ^9 -THC found that reaction time was slowed in a dose-dependent manner. A number of other simulator studies have replicated this finding^{250, 251, 280}, although two studies failed to find this effect^{252, 281}.

1.3.4.2.4.5 Standard Deviation of Lateral Position (SDLP)

In a recent study by Hartman et al⁹⁵, current occasional cannabis smokers (having used at least once in the past three months and less than three days per week) between the ages of 21 and 55 years were administered vaporized cannabis containing approximately 14.5 mg or 33.5 mg Δ^9 -THC or placebo and allowed to inhale *ad libitum*. In a driving task done 0.5 to 1.3 hours after inhalation, it was found that blood Δ^9 -THC concentrations of 8.2 $\mu\text{g/ml}$ produced increases in SDLP comparable to breath alcohol levels of 0.05 mg/ml. Blood concentrations of 13.1 $\mu\text{g/ml}$ produced increases in this measure that were comparable to breath alcohol levels of 0.08 mg/ml, another common legal limit. Administration of 19 or 38 mg of smoked Δ^9 -THC was found to significantly increase SDLP by 4 cm and 7 cm respectively²⁵⁰. In their 2008 study, Ronen et al²⁴⁸ found that SDLP was significantly impaired by 13mg and 17 mg doses of smoked Δ^9 -THC administration in occasional smokers. However, this group was unable to observe this effect in their 2010 study on occasional smokers who used cannabis one to four times per month⁹⁷, and Anderson et al²⁵² also failed to find significant differences in this measure in smokers who used one to ten times per month.

1.3.4.2.4.6 Road Tracking Measures

Other, less standardized measures are sometimes used to assess impairment by Δ^9 -THC. A study conducted by Ménétrey and colleagues assessed performance after the oral administration of 20 mg dronabinol or a cannabis decoction containing 20 or 60 mg Δ^9 -THC²⁶⁹. They found that road tracking, as measured by the percentage of time spent in the lane, was impaired at 60-330 minutes post-dose, and that visual search in a sign-detection task was also impaired. Papafotiou et al²⁸² found that the consumption of cigarettes containing 1.74 or 2.93% Δ^9 -THC impaired drivers' ability to maintain the car wheels within the dividing lines of the road 80 minutes after smoking, indicating reduced road tracking ability. At 30 minutes post-dose, results did not reach significance but displayed trends towards impairment in how often participants straddled the solid line dividing lanes going in different directions ($p=0.09$) and how often participants straddled the barrier line separating same-direction lanes ($p=0.08$). When Liguori et al²⁷⁹ attempted to measure road tracking by the number of cones knocked over, they were unable to find significant effects.

1.3.4.2.4.7 Divided Attention

Research on cannabis-induced impairment has generally found that the effects of Δ^9 -THC are more prevalent during divided attention tasks. Anderson et al²⁵² examined the effects of a cigarette containing 2.9% Δ^9 -THC (approximately 22.9 mg) on driving performance. During driving assessments, participants were asked to multitask by completing the Paced Serial-Addition Test, which measures auditory processing speed and flexibility. Participants who consumed active cannabis failed to demonstrate practice effects that were observed in the placebo control group, suggesting that drivers under the influence of cannabis may lose some of the benefits gained through prior experiences. Another study by Lenné et al²⁵⁰ found that simultaneously completing car following and sign detection tasks resulted in an increased

headway maintenance and standard deviation of headway maintenance. These findings support the hypothesis that complex tasks are more susceptible to cannabis impairment.

1.3.4.2.4.8 Collisions

Although drivers who have used cannabis exhibit more cautious driving behaviour, evidence still suggests that the impairment is significant enough to overcome this. The 2010 study by Ronen et al⁹⁷ found that three out of twelve subjects had a collision while under the influence of Δ^9 -THC, compared to two out of twelve with a BAC of 0.05% and zero under the placebo condition. Another study found that there was a dose-related pattern in collisions, indicating that more collisions occurred with the high dose of 17 mg Δ^9 -THC (6) than the low dose of 13 mg (3) compared to controls (2)²⁴⁸. Although these numbers are not high enough for rigorous statistical analysis, these patterns suggest that impairment caused by cannabis may translate to unfavourable driving outcomes on the road.

1.3.4.2.4.9 Summary

Overall, these experimental findings shed light on the effects of cannabis on driving, and inform the design of future studies. Studies using driving scenarios that were more applicable to real-world situations have had more consistent findings. The use of unbiased measures of speed, SDLP, and reaction time to assess possible impairment has dramatically improved the validity of simulator study findings. In general there is evidence that despite the apparent effort on the part of study participants to compensate for their impairment, some aspects of driving cannot be consciously controlled. Even with decreased average speed, less risk-taking, and greater headway maintenance reported in many studies, tracking ability, steering, reaction time and tasks requiring divided attention still show dose-dependent impairment after cannabis consumption. It seems that these effects are more prominent in less experienced users. Other effects of cannabis which have not been studied as rigorously are the assessment of unexpected events (for example,

being cut off suddenly by another car), maintaining speed relative to other vehicles on the road, and tasks which increase cognitive load by dividing attention. However, all of these have been found to be impaired by cannabis intake in at least some of the literature^{274, 283, 284}. Further study on these measures is needed.

Given the wide variations in how these studies are conducted, and by extension many of their findings, it is important to continue research in this area to uncover the effects of key variables that affect whether or not impairment is detected, and to have a better understanding of the nature of cannabis impairment on driving.

Chapter 2 Methods

2 Methods

2.1 Study Overview

This human laboratory study was designed to test the acute effects of a single dose of smoked cannabis containing 12.5% Δ^9 -THC or placebo on simulated driving behaviour in young adults. It was a randomized double-blind, placebo-controlled, mixed-design study. The acute pharmacodynamics measures presented here were collected as part of a larger study, in which residual effects were assessed at twenty-four and forty-eight hours after smoking. The larger study also included the collection of biological measures, such as levels of Δ^9 -THC and metabolites in blood and urine. The following analysis focuses only on the acute pharmacodynamic outcomes.

Acute effects of smoked cannabis on motor skills, mood, subjective drug effects, and cognitive function were assessed using a series of tests, many of which are computer-based. Vital signs were also collected as an objective physiological measure of drug effect. Self-reported driving behaviours were documented as well. Participants were asked to come to the Driving Simulator Research Laboratory at the Centre for Addiction and Mental Health (CAMH) for five sessions. Session one was an eligibility assessment which could occur any time prior to the other days, while sessions two through five occurred on consecutive days. Session two was a practice day (baseline measures from this day were not included in the final analysis), session three was an assessment day when the cannabis was administered, and sessions four and five were follow-up testing sessions. Data collected at sessions four and five are not presented here. The timeline describing when various measures were collected during the study is represented in Table 1. As the study was double-blind, treatment conditions were randomized by the CAMH Pharmacy. Permission was obtained by the CAMH REB to conduct an interim analysis of the data (n=54 participants). Study procedures and measures collected are described in more detail in Sections 2.2 and 2.5.

2.2 Study Procedures

2.2.1 Telephone Screen

In order to participate in the study, participants had to complete a telephone screen (Appendix A). This is a brief questionnaire administered by trained study personnel over the telephone using a standardized form. Participants were asked about contact information, and eligibility criteria, i.e. smoking habits, age, and driver's license class. Callers were also asked about pregnancy, drug dependence, use of psychoactive medications, diagnoses of psychiatric disorders, family history of schizophrenia, willingness to abstain from cannabis for the duration of the study, and geographic considerations. Although eligibility criteria were assessed thoroughly at the eligibility assessment, the telephone screen helped to optimize efficiency by only scheduling those who seem likely to be eligible to participate.

2.2.2 Session One: Eligibility Assessment

Potential participants were scheduled for an eligibility assessment following a successful telephone screening. Upon arrival, study personnel verified age and driver's license class, then provided the participant with the consent forms (Appendix B). Participants were given as much time as they needed to read them over and ask questions, and personnel ensured comprehension by asking the subject questions, and explaining any parts the participant did not seem to fully understand. After signing, a photocopy of the forms was provided to the research subject. Participants had their blood alcohol level assessed using a breathalyzer, and this had to be zero in order for them to continue. A urine sample was collected to confirm prior use of cannabis (this needed to be positive for Δ^9 -THC), and also to screen for other psychoactive drugs. These samples were read by study personnel using a drug cup for point of care testing, and sent to the CAMH clinical laboratory for further analysis. When applicable, urine samples were tested for

pregnancy using pregnancy test strips. This test needed to be negative for a participant to be enrolled.

A physical examination was done by a physician to obtain a medical history and check for major medical problems that may have excluded the individual from participating, such as a history of seizures. A Structured Clinical Interview for DSM-IV disorders (SCID-I) was given by qualified personnel to rule out the possibility of mental health concerns that may have put a participant at risk if they had been enrolled. Blood samples were also collected for biochemical analysis to assess for general health. Section 2.5 describes the study procedures listed here in greater detail. All results from tests done during the eligibility assessment were reviewed by the qualified investigator to determine whether or not a subject would be enrolled. Subjects were informed of the result by study personnel once the qualified investigator came to a decision.

2.2.3 Session Two: Practice Day

Those individuals deemed eligible following the assessment in session one were invited to participate in the study and scheduled for the remaining four consecutive study days. The first of these was the practice day (session two). This was an opportunity for participants to gain experience with the cognitive, mood, motor, and driving assessments used in the study to mitigate practice effects. Data collected on practice day was not included in the analysis. Measures included the Addiction Research Centre Inventory (ARCI), the Profile of Mood States (POMS), the Visual Analog Scale (VAS) for cannabis effects, the Hopkins Verbal Learning Test - Revised (HVLT-R), the Continuous Performance Task (CPT-X), the grooved pegboard test, and the Digit Symbol Substitution Task (DSST). Details of these tests are given in Section 2.5. Data from these tests on practice day were not included in the final analysis.

Additionally, baseline information was collected on practice day. This information was used to assist in interpretation of study results. Participants were asked to complete the Self-Report Questionnaire (SRQ) that is described in Section 2.5.2.2. The SRQ collected information about driving behaviour, substance use, and driving experience, and demographic information. At the

end of the questionnaire, a Delayed Discounting task was given to assess how much a reward loses its subjective value when the participant has to wait for it. Participants were also asked to complete the Shipley-IQ test, which measures vocabulary and abstraction. This test is described in detail in Section 2.5.3.1.

2.2.4 Session Three: Drug Administration Day

Session three began with the administration of a breathalyzer to confirm ongoing eligibility. Baseline measures were taken thirty minutes before drug administration, when participants were asked to complete the HVLТ-R, CPT-X, DSST, grooved pegboard, ARCI, VAS, and POMS. Vitals were taken, and participants were asked to provide a urine sample to allow measurements of THC and metabolites to confirm ongoing eligibility. Participants also completed one practice driving trial, and one assessed driving trial (see Section 2.1.5.2) at this time. When the baseline measures were completed, participants were provided with the cannabis or placebo cigarette and given up to 10 minutes to smoke; all of these procedures are described in more detail in Section 2.5.

Blood samples, vital signs, and VAS scores were collected at five minutes, fifteen minutes, and thirty minutes after the end of smoking. At thirty minutes post-smoking, participants completed one assessed driving trial on the simulator. Blood and vitals were taken again at one hour post-dose, and the HVLТ-R, CPT-X, DSST, grooved pegboard, ARCI, VAS, and POMS were repeated. Another set of blood samples, vital signs, and VAS scores was taken at two hours post-dose, and hourly until six hours after smoking. At the end of the study day, at approximately six hours after smoking, participants were asked to provide another urine sample to assess ongoing eligibility.

		Session 1	Session 2	Session 3 (Administration Day)										Session 4	Session 5
Approximate Time from Smoking (time zero)			-24 hr	-30 min	5 min	15 min	30 min	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr	24 hr	48 hr
	Driving Willingness						X							X	X
	Perceived Driving Ability			X			X							X	X
Urine Tests	Point of care testing and Immunoassay	X	X	X									X	X	X
	Pregnancy	X	X												
Blood Tests	Δ^9 -THC and metabolites quantification			X	X	X	X	X	X	X	X	X	X	X	X
	Biochemistry & Haematology	X													

*areas shaded in grey were not used in the presented analysis, although they were part of the larger study

2.3 Participant Selection

2.3.1 Inclusion Criteria

In order to have been included in this study, participants must have met the following criteria:

- Been between ages 19 and 25 years at the time of consent
- Reported using cannabis between one and four times per week on average
- Provided urine that was positive for cannabis at the time of eligibility assessment
- Have held a valid Ontario class G or G2 driver's license (or equivalent) for the past year or longer
- Been willing to abstain from cannabis use for 48 hours prior to session two, and until completion of session five
- Have had the ability to provide written informed consent

- Been using an approved form of birth control if applicable

2.3.2 Exclusion Criteria

In order to have been included in this study, participants must not have met any of the following criteria:

- Reported currently using psychoactive medications on a regular basis (e.g., antidepressants, benzodiazepines, medication for ADHD, stimulants, etc.)
- Had a diagnosis of a severe medical or psychiatric problem, or a diagnosis that made cannabis exposure risky for the participant
- Had a family history of schizophrenia, especially in a first-degree relative
- Was pregnant, trying to become pregnant, or breastfeeding if applicable
- Being unable to provide a urine sample that was positive for cannabinoids at the time of eligibility assessment

The following eligibility criteria were assessed on an ongoing basis throughout the study:

- Providing a breath sample that was positive for alcohol on any study day
- Providing biological samples which suggested recreational use of cannabis outside of the study any time from two days before session two until the end of session five
- Providing a biological sample during study sessions two through five which was positive for additional psychoactive substances

2.4 Participant Recruitment

To recruit participants, the study was advertised in several ways (Appendix C). Online advertisements were posted to Kijiji, Craigslist, and Backpage, and were updated twice per week. The study was also advertised on the Centre for Addiction and Mental Health (CAMH) study recruitment website. Posters were distributed around the city of Toronto, especially on the

University of Toronto St. George campus. Advertisements were published in NOW magazine, and through the advertising space available on Toronto Transit Commission (TTC) vehicles. Interested participants were asked to call the study's CAMH number to get more detailed information about the study, and to complete a telephone screen if they were interested in participating. Trained personnel used the telephone screen to determine whether or not to schedule someone for an eligibility assessment (these are described in Sections 2.2.1 and 2.2.2, respectively; the telephone screen is included in Appendix A).

2.5 Collected Measures

2.5.1 Simulated Driving Tests

Overall driving performance was assessed by simulated driving scenarios. Each one was approximately seven minutes in length, depending on the speed the participant was driving at. Each driving trial consisted of two scenarios, and ran approximately fourteen minutes in length; during the second of the two scenarios, participants were asked to drive and complete a counting task at the same time. This dual-task condition consisted of participants being asked to count backwards by threes from a number between 700 and 999. The number was chosen randomly by study personnel at the beginning of the scenario. This distracting task has been validated as an effective dual-task methodology in previous driving studies^{285, 286}.

Two types of driving trials were done during the study. Initially, participants were given practice trials under both single- (without counting) and dual- (while counting) task conditions, consisting of scenarios with uneventful highway driving. This allowed them to become familiar with the simulator which reduced variability across assessed driving trials. Practice trials were done twice: once on practice day, and once thirty minutes before driving. Assessed trials were done four times throughout the study: once thirty minutes before smoking, and thirty minutes and twenty-four and forty-eight hours after smoking. These were also done under both single- and dual- task conditions, and used scenarios with hazards dispersed throughout them. Each assessed scenario had the same number and types of hazards, but they appeared in different forms and

different orders to reduce the participant's ability to predict them. Assessed driving trials to examine acute effects of cannabis were done thirty minutes before smoking (immediately after practice scenarios) and thirty minutes after smoking.

The assessed driving scenarios were each divided into three primary hazards. These included a straightaway hazard, a stationary obstacle, and a slow moving vehicle. They are described in more detail below. The Virage VS500M driving simulator recorded different driving parameters during each of three hazards, and for overall performance. For overall performance, the main variables examined were mean speed, standard deviation of lateral position, and total collisions. During the straightaway hazard, the main variables of interest were mean speed, standard deviation of speed, and standard deviation of lateral position. During the part of the scenario where the participant was driving behind a slow moving vehicle, the driver's following distance, and the number of oncoming cars the participant allowed through before passing the slow-moving vehicle were the primary variables being examined. During the risk-taking hazard, where there was a stationary obstacle in the road and an oncoming vehicle, where the participant applied his or her foot to the brake in relation to the obstacle was the primary measure of interest.

2.5.1.1 Practice Scenarios

Practice scenarios were done to allow participants to familiarize themselves with the driving simulator before they were actually being assessed. Data from practice scenarios were not used in data analysis, although they can be used to assist study personnel in detecting and interpreting unexpected changes in performance during other baseline scenarios if needed in future analyses. Driving practice was done on the same road as assessed scenarios, but there were no other cars or pedestrians, and there were no hazards. On practice day, these scenarios were done twice in the course of one practice driving trial; the second time was under dual-task conditions, where participants were asked to count backwards by threes from a number chosen by study personnel between 700 and 999. This is the same task that was used during assessed trials.

2.5.1.2 Assessed Scenarios

Assessed scenarios were ones used in the final statistical analysis to measure driving variables for possible impairment. Like the practice driving trials, assessed driving trials consisted of two scenarios. During the second scenario in each trial, participants were asked to count backwards by threes from a number between 700 and 999. Study personnel chose this number at random at the start of the scenario. Scenarios one and two (the first driving trial) were done thirty minutes before smoking. Scenarios three and four (the second driving trial) were done thirty minutes after smoking. Even numbered trials were done under dual-task conditions, and odd numbered trials were done under single-task conditions.

Each of the eight scenarios included a series of hazards that were presented in various orders throughout the study sessions. These hazards always included: a straightaway hazard; one stationary obstacle (“risk taking” hazard) with one oncoming vehicle; and one slow moving vehicle with five oncoming vehicles. The straightaway hazard was a section of the road with no other cars and no obstacles, and thus no cues to drive cautiously or impediments to drive recklessly. Mean speed, standard deviation of speed, and standard deviation of lateral position are measured during the straightaway hazard. The stationary obstacle included situations like a truck pulled over on the side of the road or a collision between two vehicles that partially obstructed the roadway. An oncoming vehicle prevented the participant from moving over into the opposite direction lane in order to safely pass the stationary obstacle. This type of roadway situation warrants slower and more cautious driving; therefore, where the participant actually applied their foot to the brake in relation to the obstacle is the primary variable of interest. The slow moving vehicle travelled at approximately 20 km below the speed limit. The following distance participants left between their car and the slow moving vehicle was recorded.

2.6 Driving Simulator

The driving simulator used was a model VS500M manufactured by Virage Simulations Inc. (Figure 1. See Virage Simulations 2007²⁸⁷ for technical specifications). The cabin consists of the

driver's side console, which replicates an automatic transmission compact model car from General Motors. This includes a seat and seat belt, steering wheel, ignition, hand brake, dashboard, accelerator and brake pedals, and gear shift. The dashboard display includes indicators for speed, RPM, fuel level, warning lights and engine temperature among other things, and displays realistic values, which respond to the virtual environment appropriately.

Figure 1. Virage VS500M driving simulator during a driving scenario.

The instruments and controls, such as the steering wheel, are monitored by the computer and programmed to give realistic feedback throughout the simulation. The ignition key, pedals, gear shift, hand brake, steering wheel, turn signals, and hazard lights are all designed to interact with the participant as they would in a real vehicle. The simulator is also able to provide dynamic force feedback during driving trials. To generate force feedback on the wheel when steering, an electrical DC motor is connected to an amplifier which is operated by a control board to allow for vibration, reactions to potholes, rumble strips, sidewalks, and other obstacles. The accelerator

and brake pedals also provide force feedback in that they are spring-loaded to realistically simulate the feeling of operating a real vehicle.

The front console is mounted on a motion platform. This consists of a compact three-axis platform with motors, and an electric controller and amplifier which provide cues from acceleration, engine vibration, and road texture feedback. This feedback is calibrated based on the car's speed and the surface of the virtual road. Audio feedback provides cues based on acceleration, braking, other vehicles on the road, and environmental hazards. Visual feedback is given through three 50" screens arranged in a semi-circular fashion around the driver's seat. Advanced graphic cards produce realistic images. Blind spots are simulated with two smaller 17" screens located on either side of the driver, slightly behind their seat. Rear-view and side-view mirrors are projected on the 50" screens to allow the driver to monitor their virtual surroundings.

Scenarios used in the study were modified versions of 'stock' driving scenarios, originally developed for driver education purposes. This programming was done by qualified study personnel.

2.6.1 Cognitive and Motor Skills Tasks

2.6.1.1 Shipley-2 IQ Test

The Shipley-2 test is a two-part examination that is able to provide a quick estimate of overall cognitive functioning²⁸⁸. The first of the two parts was a vocabulary test which measured crystallized cognitive ability (the ability to use skills, knowledge, and experience). This consisted of a list of forty words, each of which offered four possible answer options. The participant selected the word from the list of options that had the closest meaning to the word presented. The participant was given ten minutes to complete this task. The second part of the test was the abstraction scale, which measured fluid intelligence (the ability to solve problems in novel situations). In this section, participants were asked to fill in missing items in a presented sequence. The participant had twelve minutes to complete all twenty-five of these problems. The Shipley-2 IQ test was administered only once on practice day.

2.6.1.2 Digit Symbol Substitution Task (DSST)

The Digit Symbol Substitution Test²⁸⁹ is primarily a measure of memory, but also measures speed of processing. In this timed task, participants were shown the numbers from one to nine, each of which had a corresponding pattern. These patterns were different arrangements of black squares in a three-by-three white grid. Each row in the grid had one black square, and two white squares, and each number corresponds to a different arrangement. This legend remained at the top of the screen for reference during the entirety of the test. During the assessment, a large number appeared in the middle of the screen above a blank three-by-three grid. Participants were asked to turn the appropriate squares black by clicking them from the top row to the bottom to produce the pattern that corresponded with that number. When this was done, a new number appeared. The goal of the test was to produce as many correct patterns as possible in 90 seconds, while remembering to fill in the pattern from top to bottom. The test was administered to examine acute cannabis effects once on practice day, and on drug day both thirty minutes before and one hour after drug administration. Practice day data was not included in the final analysis.

2.6.1.3 Hopkins Verbal Learning Test – Revised (HVLTR)

The Hopkins Verbal Learning Test – Revised²⁹⁰ is a test of verbal learning and memory which tests both recall and recognition. Participants were read a list of twelve words which came from three semantic categories. Each category accounted for four words on the list. When the list had been read to the participant at a pace of approximately one word every two seconds, the participant was asked to immediately recall all the words they could remember. This was done three times. After the third time the list had been read and the participants had recalled the words, the test is put aside for 23 minutes. At the end of this time, the participant was asked to recall all the words they could remember without having the list read to them again. Finally, the participant was read a list of 24 words, and asked to identify whether or not each word was on the original list. This test was able to measure the percent of words retained after the delay, the

total number of words recalled (total recall score), and the discrimination index indicating participants' ability to distinguish between words that were on the original list, and those that were not. This test took approximately half an hour to complete, and was administered on practice day, on drug day both thirty minutes before and one hour after smoking to examine acute outcomes. Practice day data was not included in the final analysis.

2.6.1.4 Continuous Performance Test (CPT-X)

The Continuous Performance Test²⁹¹ is a test that measures different aspects of attention. Historically, it has been used as a diagnostic tool for ADHD although that was not its purpose in this study. The test ran for fourteen minutes. During the test, white letters flashed up on a black screen. The participant had to respond as quickly as possible by hitting the spacebar, unless the letter presented was an X. If this was the case, the participant withheld a response and waited for the next letter. The test gave standardized and raw scores for various measures of the participant's success at this task. For analysis, the measures that were of interest were: the number of omission errors, when a letter other than X was presented no response was recorded; the number of commission errors, when the letter X was presented and no response was recorded; and hit reaction time, the speed of response. Acute data from the CPT-X was collected on practice day, and thirty minutes before and one hour after smoking on drug administration day. Practice day data was not included in the final analysis.

2.6.1.5 Grooved Pegboard Test

The grooved pegboard test²⁹² is an assessment of manipulative dexterity and visual motor coordination. The model used in this study was the one offered by Lafayette Instrument Company. The participant was given a board containing twenty five holes, each of which was a randomly rotated version of a circle with a protruding slot. This shape matches the shape of a set of metal pegs which were able to fit into the holes, provided they were rotated to the correct orientation first. In this timed exercise, participants placed all the pegs in the holes using only

one hand and completing the task as quickly as possible. When this test was administered, it was done once with each hand beginning with the dominant one, and the overall time to insert all the pegs was recorded. The grooved pegboard test was given once on practice day, and twice on drug administration day - once thirty minutes before and once one hour after smoking to measure acute effects. Practice day data was not included in the final analysis.

2.6.2 Subjective Drug Effects and Mood Questionnaires

2.6.2.1 Addiction Research Center Inventory (ARCI) 49

This validated, self-report questionnaire was designed to assess the subjective effects of psychoactive drugs, and to differentiate between the effects of different types of drugs^{293, 294}. The full version, developed in the 1960s, contained 550 items to assess positive and negative drug effects on multiple scales²⁹³. This was later shortened to forty-nine items, and modified to include additional scales. This shortened, modified version was the one administered on the computer in this study. Each item on the ARCI was a sentence describing an effect commonly reported by individuals under the influence of a drug. The participant could respond to each of the items as being “true” or “false”. In this version of the ARCI, participants’ answers were coded according to seven subscales based on the drug categories associated with the statements they responded to. The five original scales are the Pentobarbital-Chlorpromazine-Alcohol Group (PCAG), which measures sedation; the Morphine-Benzedrine Group (MBG) which measures euphoria; and measures of dysphoria which are the Benzedrine (BZ), Amphetamine (AMPH), and Lysergic Acid Diethylamide (LSD) scales. The Johns Hopkins School of Medicine modification used here included two additional scales: the Euphoria and Sedation scales. This test was administered on the computer, and took participants approximately five minutes to complete. To collect acute data, the ARCI was administered approximately twenty-four hours prior to smoking (practice day, study session two), and thirty minutes prior to and one hour after smoking (drug administration day, study session three). Practice day data was not included in the final analysis.

2.6.2.2 Visual Analog Scale (VAS)

Visual Analog Scales are questionnaires that allow participants to rate their response on a continuous scale, rather than choosing from a set of discrete answer options. In this study, VASs were used to assess the subjective effects of cannabis. Participants were given seven statements, and asked to rate each on a scale ranging from “not at all” to “extremely” by dragging an indicator to the appropriate place on a horizontal line. The statements were: “I feel a drug effect...” (drug effect), “I feel this high...” (high), “I feel the drug’s good effects...” (good effects), “I feel the drug’s bad effects...” (bad effects), “I like the drug...” (drug liking), “I feel a rush...” (rush), and “It feels like cannabis...” (feels like cannabis). This type of scale is a good way to assess subjective experiences that occur on a spectrum and do not take discreet leaps as may be suggested by the use of categorical ratings. VASs are more sensitive to small changes in subjective feelings than other types of scales²⁹⁵. Acute data from the VAS was collected once on practice day (twenty-four hours prior to drug administration), and ten times on drug administration day. On drug administration day, the VAS was given thirty minutes prior to smoking, and five minutes, fifteen minutes, thirty minutes, and one hour after smoking, and then hourly until six hours after smoking. Practice day data was not included in the final analysis.

2.6.2.3 Profile of Mood States (POMS)

This test was a self-report questionnaire used to evaluate fluctuations in participants’ mood and affective states based on seventy-two adjectives²⁹⁶. The participant rated the extent to which each adjective described their current mood using a five-point Likert scale; their ratings could be zero (not at all), one (a little), two (moderately), three (quite a lot), or four (extremely). Responses were coded into ten subscales: Tension/Anxiety, Anger/Hostility, Depression/Dejection, Friendliness, Fatigue, Confusion, Vigor, Elation, Arousal, and Positive Mood. Arousal and positive mood subscales are both derived measures. The arousal score came from the sum of confusion and fatigue subtracted from the sum of tension/anxiety and vigor, while the positive

mood score came from the depression/dejection score subtracted from elation. This test was administered on the computer, and took participants approximately five minutes to complete. It was done approximately twenty-four hours prior to smoking (practice day, study session two), thirty minutes prior to smoking (drug administration day, study session three), and one hour after smoking (drug administration day, study session three) to evaluate acute cannabis effects on mood. Practice day data was not included in the final analysis.

2.6.3 Psychiatric, Behavioural, and Demographic Information

2.6.3.1 Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)

The SCID-I²⁹⁷ was administered as part of the eligibility assessment, to collect information about participant's psychiatric and drug use history. This semi-structured interview was done by trained personnel to ensure that participants enrolled in the study did not have a history of drug dependence, especially to cannabis, and did not suffer from any condition that might be exacerbated by cannabis consumption. This information was used only to decide if participants meet inclusion or exclusion criteria.

2.6.3.2 Self-Report Questionnaire (SRQ)

The self-report questionnaire was a computer-based test composed of several, independently validated measures. Information about demographics and substance use were collected. The Driver Behaviour Questionnaire (DBQ)²⁹⁸ assessed self-reported driving violations, errors, and lapses. The Driving Vengeance Questionnaire²⁹⁹ assessed driver aggression and vengeance in a handful of driving situations. Driving behaviour was also assessed by the Road Rage Victimization and Perpetration Questionnaire^{300, 301} and the Risk-Taking Behaviour in Traffic Questionnaire³⁰². This survey also evaluated general health using the General Health Questionnaire (GHQ-12)³⁰³. Behavioural measures were evaluated by the Brief Sensation

Seeking Scale (BSSS)³⁰⁴, and the Delayed Discounting task³⁰⁵ which measured impulsivity. The SRQ was only given once on Practice Day, and took approximately twenty minutes to complete.

2.6.4 Biochemical and Physical Measurements

2.6.4.1 Breath Sample for Alcohol

A breath test was given to screen for the presence of alcohol at the start of all sessions, including eligibility. A non-zero reading, indicating that the participant was under the influence of alcohol, would exclude them from the study. At the eligibility assessment, a positive reading would prevent participants from continuing with study-related procedures either indefinitely or until the individual signed a consent form with a blood alcohol level of zero at the discretion of research personnel. The instrument used was the Alert™ J5 breath alcohol testing system, released by Alcohol Countermeasure Systems, Toronto. Before this, the Alert™ J4X model was in use. The breathalyzer used for the study was calibrated annually by the CAMH clinical laboratory.

2.6.4.2 Physical Examination

During session one, the eligibility assessment, a physical examination was done to assess overall physical health. This was to ensure that participants did not have any health problems that would put them at risk if they were enrolled in the study. This assessment was conducted by a qualified physician. Information collected included previous diagnoses (psychiatric and medical), alcohol and illicit drug use history, a general review of health, smoking history, cannabis smoking history, family history, a review of birth control when applicable, vital signs, and weight and height.

2.6.4.3 Vital Signs

Vital signs were collected during the eligibility assessment as part of the medical assessment, and were also monitored throughout study sessions one and two. Vital signs recorded were temperature, heart rate, blood pressure, and respiration rate. Vital signs were taken once on practice day, and ten different times on drug administration day: thirty minutes before smoking, five, fifteen, and thirty minutes after smoking, and hourly beginning at one hour and continuing until six hours after smoking. The analysis presented here focused on heart rate and blood pressure.

2.6.4.4 Serum and Blood Biochemistry

Biochemical analysis was done on blood collected during the eligibility assessment as part of an evaluation of overall physical health. The samples were tested for complete blood count (CBC), sodium, potassium, blood urea nitrogen, creatinine, random glucose, and liver function. Liver function tests included alanine aminotransferase, aspartate transaminase, and gamma glutamyl transpeptidase. These blood samples were analyzed by the CAMH clinical laboratory. Although blood was collected at other times throughout the study, the eligibility assessment was the only time these biochemical tests were done.

2.6.4.5 Urine Toxicology Screening and Pregnancy Testing

Urine toxicology screening was done at each study session to ensure continuing eligibility for the study. This screening is done by study personnel using a drug cup for point of care testing, and then sent to the CAMH clinical laboratory for confirmation of results. At the eligibility assessment, screening was done to ensure that the participant was not under the influence of any substance when they consented, but also primarily to test for the presence of Δ^9 -THC.

Participants were not eligible to be enrolled in the study until it was determined that they already had prior experience with cannabis. If this result was negative, a confirmation test was conducted

by the clinical laboratory. Participants were scheduled to return and provide another urine sample if possible.

During the other study sessions, a positive result for anything other than Δ^9 -THC, or a positive result for Δ^9 -THC that was not consistent with the single cannabis cigarette provided by the study, would have resulted in exclusion from the study. This analysis was done on urine collected thirty minutes before, and six hours after smoking for the purposes of analyzing acute data. A ratio of THC-COOH:creatinine that increased if active cannabis was not provided by the study would have indicated recreational cannabis use outside the study, and the participant would have been excluded.

Pregnancy testing was done as appropriate to ensure that no participants who were exposed to the drug were pregnant at the time. Testing was done at the eligibility assessment, and again on practice day since the two sessions were often separated by a week or more. A positive pregnancy test would have resulted in the participant being discharged from the study.

2.6.4.6 Urine Levels of Δ^9 -THC, THC-COOH, 11-OH-THC, and Creatinine

Urine samples were collected for the purpose of quantifying Δ^9 -THC and metabolites on study sessions two and three, and as needed for determining eligibility. At the eligibility assessment, Δ^9 -THC was quantified in the case of a negative immunoassay result to ensure the participant had been exposed to cannabis prior to being enrolled in the study. Without a laboratory test confirming Δ^9 -THC in the participant's urine, they could not be enrolled. On practice day, urine was collected once to assess baseline levels of Δ^9 -THC. On drug administration day, urine was collected thirty minutes before and six hours after smoking. The ratio of THC-COOH:creatinine was measured to ensure that it only increased after drug administration in the case of participants who were randomly assigned to the active condition. If the ratio had increased in any other case,

it would have indicated that additional recreational cannabis had been consumed during the study and the participant would have been excluded.

2.7 Cannabis Cigarettes

2.7.1 Cannabis Suppliers

During the study, a single dose of smoked cannabis or placebo was given on drug administration day (session three). Active cannabis was obtained from Prairie Plant Systems Inc. in Saskatoon, Saskatchewan. The cannabis is grown under quality control and contains $12.5\% \pm 2\%$ Δ^9 -THC. The placebo cannabis used in this study was obtained from the National Institute on Drug Abuse (NIDA) in Bethesda, Maryland, USA. In the placebo cigarette, Δ^9 -THC was chemically removed from the cannabis. The placebo cigarettes contained $<0.1\%$ Δ^9 -THC, which is considered negligible.

2.7.2 Preparation of Cigarettes

According to Health Canada¹⁹, the average cannabis cigarette can range from 0.5 - 1 g of plant material. Based on this, cigarettes used in the study contained 750 mg of active or placebo cannabis. At this mass, active cigarettes provided a dose of 79 - 109 mg Δ^9 -THC, while the placebo cigarettes provided 0 - 0.75 mg Δ^9 -THC. Active cannabis was received from Plant Prairie Systems Inc. as loose plant material, while the placebo cannabis arrived from NIDA in pre-packaged cigarettes that had to be disassembled and re-rolled by qualified personnel in the CAMH pharmacy personnel. Active and placebo cigarettes were made to be visually indistinguishable for all practical purposes; both weighed 750 mg when they were rolled. Once prepared, cigarettes were stored at -20°C in a secure, locked freezer accessible to designated staff in the CAMH pharmacy. Prior to use, cigarettes were removed from the freezer and re-humidified for at least twelve hours.

2.7.3 Drug Administration

During drug administration, participants were set up in the CAMH Bio-behavioural Addictions and Concurrent Disorders Research Laboratory (BACDRL). This is a dedicated room with external ventilation and a reverse airflow, to ensure that expired smoke is released outside rather than diffusing into the surrounding hallways. Participants were instructed to smoke *ad libitum*, until they felt the high they normally experience, for a maximum of ten minutes. They were also instructed to stop smoking at any time if they felt unwell. During this time, participants were observed by study personnel via a two-way mirror in an adjacent room. This was done to ensure participant safety, and to obtain accurate times for the start and end of smoking without exposing experimenters to the dangers of second-hand smoke. Following smoking, participants were transported back to the clinical exam room using a wheelchair. Cigarettes were weighed before and after smoking to estimate the dose each participant received.

2.8 Sample Size Justification

Because this study used both between- and within- subject comparisons, estimating the effect-size based on previous experiments (which primarily use a within- subjects design) is difficult. The effect size was estimated to be ‘medium’ using Cohen’s terminology ($d=0.5$). In order to increase the scientific yield of the study, a 2:1 randomization of active to placebo was used. Additionally, the first five participants were part of the pilot phase of the study, and all received active cannabis. Based on these factors, the estimated sample size necessary to achieve adequate power ($1-\beta = 0.8$) is 114 participants in total. Of these, 76 would receive active cannabis, and 38 would receive placebo. Allowing for approximately 25% attrition due to people withdrawing from the study or being unable to complete the four days, it is estimated that the sample size required to collect complete data for 114 subjects is 142. Successfully reaching this sample size would make this the largest study of its kind. This interim analysis was based on data collected from fifty-four participants.

2.9 Ethical Considerations

This study was approved by the CAMH Research Ethics Board (REB) and the Health Canada REB. To minimize the risks associated with conducting cannabis and driving research in young people, several safety parameters were in place. Participant identity was kept confidential, as was their status as cannabis users. The study used simulated driving rather than an on-road course. Transportation to and from CAMH was provided in the form of a taxi chit (drug administration day) or TTC tokens (other study days) and participants were instructed not to drive after practice day. These measures protected participants from the potential dangers associated with driving under the influence of cannabis. To ensure that the study was not responsible for exposing participants to cannabis for the first time, a urine drug screen was done prior to enrollment which must have been positive for Δ^9 -THC. Because of the research suggesting a link between cannabis use and psychotic episodes in predisposed individuals³⁰⁶, anyone with a family history of schizophrenia was excluded. Anyone with a history of substance dependence was also excluded.

2.10 Regulatory Procedures

The study was approved by the CAMH and Health Canada REBs. A Clinical Trial Application (CTA) was filed and a No Objection Letter was obtained from Health Canada. Exemptions were obtained for all controlled substances used in the study. The study was registered on clinicaltrials.gov under the NCT number 01592409.

2.11 Data Analysis

Approval was obtained from the CAMH REB to unblind the study after fifty-five participants for an interim analysis. Pharmacodynamic measures were analyzed using split-plot repeated-

measures multivariate analysis of variance (MANOVA), and split-plot repeated-measures analysis of variance (ANOVA). For driving measures collected under both single- and dual-task conditions, split-plot repeated-measures MANOVAs were done on overall mean speed (in km per hour) and overall SDLP (in meters), and on straightaway mean speed, standard deviation of speed, and SDLP. Split-plot repeated-measures ANOVAs were used to examine following distance behind the slow moving vehicle, and stopping distance behind the risk-taking hazard. Pearson product-moment correlations were performed between estimated Δ^9 -THC dose (for participants in the active condition) or change in cigarette weight (for participants in the placebo condition) and driving measures found to have a significant interaction effect from baseline to after smoking in the placebo and active groups separately. All driving measures analyzed compared changes from baseline performance to driving performance thirty minutes after smoking between participants in the placebo and active conditions.

Cognitive and motor skills measures consisted of the CPT-X, HVLT-R, DSST, and grooved pegboard tests. For the CPT-X, the percent of omission errors and commission errors were analyzed together using a split-plot repeated-measures ANOVA, and hit rate in milliseconds was analyzed separately with the same type of test. Measures collected using the HVLT-R that were analyzed include total recall score (in number of words), percent retained, and discrimination index. These were analyzed together using a split-plot repeated-measures MANOVA. Completed trials and correct trials from the DSST were analyzed together using a split-plot repeated-measures ANOVA, and reaction time in milliseconds was analyzed separately using the same test. Dominant and non-dominant hand performance from the grooved pegboard test, measured in milliseconds, were analyzed together using a split-plot repeated-measures ANOVA. Analysis of all cognitive measures compared changes in performance from baseline to one hour after smoking between participants in the placebo and active conditions.

Measures of mood and subjective drug effects were comprised of data collected using the ARCI, POMS, and VAS. Each test was analyzed separately in a split-plot repeated-measures ANOVA that included scores from all subscales entered as a percentage of the full scale score. Pearson product-moment correlations were performed between peak VAS scores reported on subscales

measuring drug liking and drug effect in the placebo and active groups separately. Analyses from the POMS and ARCI compared changes in subscale scores between baseline and one hour after smoking in participants in placebo versus active conditions. VAS subscale scores were compared between participants in placebo and active conditions at baseline, five minutes, fifteen minutes, thirty minutes, one hour, and hourly until six hours after smoking.

Laboratory data analyzed included the change in weight of the cigarette from before to after smoking, and the estimated dose of Δ^9 -THC based on this change in weight. Change in cigarette weight in milligrams was compared between participants in the active versus placebo conditions using a one-way ANOVA to determine if there were significant differences in the amount of cigarette smoked between the two groups. Pearson product-moment correlations were performed between estimated Δ^9 -THC dose or change in cigarette weight and peak VAS scores reported on subscales measuring drug liking and drug effect in the placebo and active groups separately. Significant correlations were further explored using linear regressions. Because Δ^9 -THC is highly lipophilic and can be deposited in body fat, significant regressions were repeated using BMI as a covariate.

Physiological measurements analyzed were heart rate in beats per minute, and systolic and diastolic blood pressure in mmHg. These were examined using split-plot repeated-measures ANOVAs. Heart rate was analyzed alone, while systolic and diastolic blood pressures were analyzed together. Vital signs were compared between participants in placebo and active conditions at baseline, five minutes, fifteen minutes, thirty minutes, one hour, and hourly until six hours after smoking.

All ANOVA and MANOVA analyses yielding significant interaction effects between condition and time were repeated using BMI as a covariate.

Chapter 3 Results

3 Results

3.1 Screening and Enrollment

Between July 2012 and April 2015, 549 calls were received from individuals responding to advertisements for this study. Of these, 119 were deemed eligible to come for session one, 259 did not meet inclusion criteria, and 171 lost interest or were lost to follow-up. Reasons for exclusion are outlined in Table 2. Reasons for losing interest are outlined in Table 3. The telephone pre-screening interview script can be found in Appendix A.

Table 2. Reasons for Exclusion Based on Telephone Screen

Reason for Ineligibility	Number
Smokes too frequently (> 4 days per week)	170*
Smokes too infrequently (< 1 day per week)	6*
Does not currently smoke cannabis	8
Over 25 years of age	79*
Under 19 years of age	2*
Does not meet driver licensing requirements	8*
Resides outside geographical limits	10
Regular user of psychoactive medication	2*
Diagnosis of a psychiatric disorder	2
Family history of schizophrenia	2

* These numbers include 30 participants who were excluded for two reasons

Table 3. Reasons for Losing Interest

Reason for Losing Interest	Number
Time commitment	29
Discomfort around blood draws	2
Felt compensation was inadequate	2
Other (called about wrong study, etc.)	3
Did not specify	30

Of the 119 individuals meeting inclusion criteria, 101 were enrolled in the study and assessed for eligibility in the clinic. Forty-five of these were excluded: twenty did not meet inclusion criteria after a more extensive screen, nine declined to participate, and sixteen were lost to follow up. Fifty-six were enrolled as eligible to participate. Reasons for not being enrolled in the study are outlined in Table 4.

Table 4. Reasons for Ineligibility Based on Session One Assessment

Reason for Ineligibility	Number
Met DSM-IV criteria for lifetime substance use disorders (except nicotine) or cannabis dependence	13*
Had a diagnosis of a severe medical or psychiatric condition	6*
Was unable to provide a urine sample positive for Δ^9 -THC	6
Did not use cannabis one to four times per week	1

*These numbers include one subject who was excluded for more than one reason

No participants were deemed ineligible after session one because of a positive alcohol breathalyser reading; having a first degree relative diagnosed with schizophrenia; current use of a psychoactive medication; or a positive pregnancy test, reports of trying to become pregnant, or

reports of currently breastfeeding where applicable. All participants included in this analysis were found at their first session to be 19 to 25 years of age; have a valid Ontario class G2 or full G license or equivalent for at least twelve months; and to use an approved form of birth control where applicable.

Of the fifty-six participants enrolled in the study, five of these were run as pilot subjects, all of whom received active cannabis. Fifty were randomized to receive either the active drug or the placebo. Of the fifty who were randomized, one person was excluded from analysis on the grounds that they were observed by study personnel to have made obvious attempts at skewing the data, and openly admitted to wanting to “prove” that cannabis does not impair driving ability. No participants were lost to follow-up. Information about screening and enrollment is summarized in Figure 2.

Figure 2. Screening and Enrollment Flow Chart

Data presented here is based on an interim analysis, conducted on participants enrolled as of April 10, 2015. The analysis includes fifty-four people: five pilot participants, and forty-nine randomized participants. Urine results were evaluated by the CAMH laboratory to detect recreational substance use during study participation, but no participants were deemed to have violated this criterion.

3.2 Participant Demographics and Physical Characteristics

The demographic and physical characteristics of participants in the active and placebo group are presented in Table 5. The two groups were similar in age, body mass index (BMI), and had a similar percentage of males and females. No participants run as of this analysis identified as being gender non-binary or trans-gendered.

Table 5. Participant Demographics and Physical Characteristics

	Active Cannabis (n=39)	Placebo Cannabis (n=15)	Total (n=54)
Sex N (%)	27 male (69%)	9 male (60%)	36 male (67%)
	12 female (31%)	6 female (40%)	18 female (33%)
Age (SD)	22.1 (2.0)	22.5 (2.1)	22.2 (2.0)
Body Mass Index (SD)	24.3 (4.8)	24.7 (4.6)	24.4 (4.7)
Smoking Frequency in days per week (SD)	2.56 (0.9)	2.60 (1.1)	2.6 (1.0)

3.3 Adverse Events

In total, there were sixty adverse events reported throughout the study. None of these were considered serious adverse events. Twenty-three were considered possibly or probably related to the study protocol, and thirty-seven were considered unrelated. Unrelated adverse events often occurred before drug administration (often between the eligibility assessment and practice day),

and included such occurrences as a nasal infection or the common cold. The most frequently reported adverse events that were considered possibly or probably related to the study were headache (six), fatigue (two), insomnia (two), light-headedness (two), and simulation sickness (two). The severity of these symptoms ranged from mild to moderate, and none were considered reportable to the REB. It was not possible to compare the frequency and type of adverse events between the placebo and active groups since this would have compromised the blind.

3.4 Frequency of DUIC as reported on the SRQ

On the SRQ, thirty participants included in this analysis reported DUIC at least once in the twelve months prior to their participation in the study. These participants took an average of four trips each over the twelve month period. Twenty-four did not report this behaviour.

3.5 Driving Data

3.5.1 Overall Mean Speed and SDLP

For single- and dual- task conditions, overall mean speed and overall SDLP in metres were analyzed together using a split-plot repeated-measures MANOVA. Under single-task conditions, multivariate effects were found to be significant for time [$F(2,51)=5.01$, $p=0.01$]. No other multivariate effects were found to be significant ($p>0.49$). Results of univariate tests are presented in Table 6. Main effects for time were found to be significant ($p=0.01$) Interaction effects were not found to be significant. Descriptive statistics are presented in Table 7. Baseline differences were not found to be significant ($p>0.34$).

Table 6. Univariate tests from a split-plot repeated-measures MANOVA predicting changes in overall mean speed and SDLP under single-task conditions after smoking

Source	Measure	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Observed Power
Condition	Mean Speed	37.80	1	37.80	.29	.60	.01	.08
	SDLP	.01	1	.00	.34	.56	.01	.09
Error (condition)	Mean Speed	6882.64	52	132.36				
	SDLP	.13	52	.00				
Time	Mean Speed	220.61	1	220.61	8.75	.01	.14	.83
	SDLP	.00	1	.00	2.14	.15	.04	.30
Time*Condition	Mean Speed	27.63	1	27.63	1.10	.30	.02	.18
	SDLP	.00	1	.00	.48	.49	.01	.11
Error (time)	Mean Speed	1311.07	52	25.21				
	SDLP	.07	52	.00				

Table 7. Descriptive statistics for overall mean speed and SDLP under single-task conditions

	Active			Placebo			Full Sample		
	Mean	Standard Deviation	n	Mean	Standard Deviation	n	Mean	Standard Deviation	n
Mean speed (km/h)			39			15			54
Baseline	82.20	8.41		82.40	9.93		82.30	8.76	
After Smoking	77.88	7.11		80.33	12.55		79.11	8.89	
	80.04	8.04		81.37	11.17				
SDLP (m)			39			15			54
Baseline	.26	.04		.28	.04		.27	.04	
After Smoking	.28	.04		.28	.06		.28	.05	
	.27	.04		.28	.05				

Under dual-task conditions, multivariate effects were found to be significant for the interaction between time and condition [$F(2,51)=3.49$, $p<0.05$] and time [$F(2,51)=3.93$, $p<0.05$]. No other multivariate effects were found to be significant ($p>0.89$). Results of univariate tests are presented in Table 8. Interaction effects for mean speed were found to be significant. Interaction effects for SDLP were observable but not significant. Descriptive statistics are presented in Appendix D, Table 50. They are summarized in Figures 3 and 4. Baseline differences were not found to be significant ($p>0.25$).

Table 8. Univariate tests from a split-plot repeated-measures MANOVA predicting changes in overall mean speed and SDLP under dual-task conditions after smoking

Source	Measure	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Observed Power
Condition	Mean Speed	40.37	1	40.37	.22	.64	.00	.08
	SDLP	.00	1	.00	.13	.72	.00	.06
Error (condition)	Mean Speed	9360.47	52	180.01				
	SDLP	.25	52	.01				
Time	Mean Speed	17.81	1	17.81	.54	.47	.01	.11
	SDLP	.01	1	.01	5.88	.02	.10	.66
Time*Condition	Mean Speed	173.05	1	173.05	5.20	.03	.09	.61
	SDLP	.01	1	.01	3.86	.06	.07	.49
Error (time)	Mean Speed	1729.40	52	33.26				
	SDLP	.10	52	.00				

Since significant interaction effects were found, this analysis was repeated using BMI as a covariate. Multivariate effects for the interaction between time and condition were found to be significant [$F(2,49)=3.51$, $p<0.05$]. No other multivariate effects were found to be significant ($p>0.32$). Results of univariate tests are presented in Table 9. Interaction effects for mean speed were found to be significant. Interaction effects for SDLP were observable but not significant. Changes in mean speed between active and placebo groups after smoking are summarized in Figures 3 and 4. Descriptive statistics are presented in Appendix D, Table 50. Baseline differences were not found to be significant ($p>0.25$).

Table 9. Univariate tests from a split-plot repeated-measures MANOVA predicting changes in overall mean speed and SDLP under dual-task conditions after smoking with BMI as a covariate

Source	Measure	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Observed Power
BMI	Mean Speed	14.09	1	14.09	.08	.79	.00	.06
	SDLP	.00	1	.00	.50	.48	.01	.11
Condition	Mean Speed	43.44	1	43.44	.23	.63	.01	.08
	SDLP	.00	1	.00	.12	.73	.00	.06
Error (condition)	Mean Speed	9323.86	52	186.48				
	SDLP	.25	52	.01				
Time	Mean Speed	40.69	1	40.69	1.23	.27	.02	.19
	SDLP	.00	1	.00	.01	.91	.00	.05
Time*BMI	Mean Speed	55.94	1	55.94	1.69	.20	.03	.25
	SDLP	.00	1	.00	.15	.70	.00	.07
Time*Condition	Mean Speed	189.09	1	189.09	5.72	.02	.10	.65
	SDLP	.01	1	.01	3.50	.07	.07	.45
Error (time)	Mean Speed	1654.08	50	33.08				
	SDLP	.10	50	.00

Figure 3. Overall mean speed on simulated driving trials for active and placebo groups under dual-task conditions before and after drug administration. Mean speed under dual-task conditions was significantly reduced for participants in the active condition compared to placebo at thirty minutes after smoking ($p=0.02$).

Figure 4. Overall SDLP on simulated driving trials for active and placebo groups under dual-task conditions before and after drug administration. At thirty minutes after smoking, SDLP was reduced for participants in the placebo condition, but not in the active condition. This finding is observable but not significant ($p=0.07$).

A Pearson Product-Moment Correlation was performed on change in overall mean speed while counting from baseline to after smoking (speed in km per hour after smoking minus speed at baseline) and estimated dose of Δ^9 -THC for participants in the active condition. The correlation was not found to be significant ($r=0.15$, $p=0.36$, $n=39$). A Pearson Product-Moment Correlation was also performed on change in overall mean speed while counting from baseline to after smoking and amount smoked for participants in the placebo condition. The correlation was not found to be significant ($r=0.15$, $p=0.60$, $n=15$). Descriptive statistics are presented in Table 10.

Table 10. Descriptive statistics for change in speed, change in cigarette weight, and estimated dose of Δ^9 -THC

	Mean	Standard Deviation	n
Change in Cigarette Weight (mg)	641.33	126.59	15
Change in Speed (km/h) (placebo)	1.92	8.20	15
Estimated Dose of Δ^9 -THC (mg)	78.22	23.59	39
Change in Speed (km/h) (active)	-3.73	8.14	39

3.5.2 Mean Speed, Standard Deviation of Speed, and SDLP during Straightaway

For single- and dual- task conditions, straightaway mean speed in km per hour, standard deviation of speed, and overall SDLP in meters were analyzed together using a split-plot repeated-measures MANOVA. Under single-task conditions, multivariate effects were found to be significant for time [$F(3,50)=23.18$, $p<0.001$]. No other multivariate effects were found to be significant ($p>0.27$). Results of univariate tests are presented in Table 11. Interaction effects were not found to be significant. Descriptive statistics are presented in Table 12. Baseline differences were not found to be significant ($p>0.09$).

Table 11. Univariate tests from a split-plot repeated-measures MANOVA predicting changes in straightaway mean speed, standard deviation of speed, and SDLP under single-task conditions after smoking

Source	Measure	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Observed Power
Condition	Mean Speed	12.89	1	12.89	.06	.81	.00	.06
	Standard Deviation of Speed	15.61	1	15.61	2.07	.16	.04	.29
	SDLP	.00	1	.00	.30	.59	.00	.08
Error (condition)	Mean Speed	11495.88	52	221.08				
	Standard Deviation of Speed	392.67	52	7.55				
	SDLP	.23	52	.00				
Time	Mean Speed	115.98	1	115.98	2.06	.16	.04	.29
	Standard Deviation of Speed	13.42	1	13.42	6.26	.02	.11	.69
	SDLP	.11	1	.11	51.20	<.001	.50	1.00
Time*Condition	Mean Speed	22.11	1	22.11	.39	.53	.01	.09
	Standard Deviation of Speed	1.70	1	1.70	.79	.38	.02	.14
	SDLP	.00	1	.00	1.27	.27	.02	.20
Error (time)	Mean Speed	2930.56	52	56.36				
	Standard Deviation of Speed	111.52	52	2.15				
	SDLP	.11	52	.00				

Table 12. Descriptive statistics for straightaway mean speed, standard deviation of speed, and SDLP under single-task conditions

	Active			Placebo			Full Sample		
	Mean	Standard Deviation	n	Mean	Standard Deviation	n	Mean	Standard Deviation	n
Mean speed (km/h)			39			15			54
Baseline	90.16	11.22		89.92	11.26		82.30	11.13	
After Smoking	86.84	10.35		88.62	16.48		79.11	12.21	
	88.50	10.85		89.27	13.88				
Standard deviation of speed			39			15			54
Baseline	4.03	2.38		2.90	1.35		3.47	2.19	
After Smoking	4.54	2.46		3.97	1.58		4.25	2.25	
	4.29	2.41		3.44	1.54				
SDLP (m)			39			15			54
Baseline	.17	.05		.17	.07		.17	.06	
After Smoking	.23	.05		.25	.08		.24	.06	
	.20	.06		.21	.09				

Under dual-task conditions, multivariate effects were found to be significant for time [$F(3,50)=21.79$, $p<0.001$]. No other multivariate effects were found to be significant ($p>0.29$). Results of univariate tests are presented in Table 13. Interaction effects were not found to be significant. Descriptive statistics are presented in Table 14. Baseline differences were not found to be significant comparisons ($p>0.38$).

Table 13. Univariate tests from a split-plot repeated-measures MANOVA predicting changes in straightaway mean speed, standard deviation of speed, and SDLP under dual-task conditions after smoking

Source	Measure	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Observed Power
Condition	Mean Speed	92.77	1	92.77	.39	.53	.01	.09
	Standard Deviation of Speed	7.06	1	7.06	.82	.37	.02	.14
	SDLP	.00	1	.00	.15	.70	.00	.07
Error (condition)	Mean Speed	12261.14	52	235.79				
	Standard Deviation of Speed	447.31	52	8.60				
	SDLP	.19	52	.00				
Time	Mean Speed	63.50	1	63.50	9.27	.34	.02	.16
	Standard Deviation of Speed	29.1	1	29.10	4.81	.03	.09	.58
	SDLP	.09	1	.09	58.84	<.001	.53	1.00
Time*Condition	Mean Speed	217.16	1	217.16	3.17	.08	.06	.42
	Standard Deviation of Speed	4.18	1	4.18	.69	.41	.01	.13
	SDLP	.00	1	.00	.93	.34	.02	.16
Error (time)	Mean Speed	3560.40	52	68.47				
	Standard Deviation of Speed	314.39	52	6.05				
	SDLP	.08	52	.00				

Table 14. Descriptive statistics for straightaway mean speed, standard deviation of speed, and SDLP under dual-task conditions

	Active			Placebo			Full Sample		
	Mean	Standard Deviation	n	Mean	Standard Deviation	n	Mean	Standard Deviation	n
Mean speed (km/h)			39			15			54
Baseline	85.40	6.78		84.30	11.84		84.85	8.38	
Post-dose	83.94	12.87		89.18	20.39		86.56	15.30	
	84.67	10.24		86.74	16.57				
Standard deviation of speed			39			15			54
Baseline	5.22	2.36		5.08	2.46		5.15	2.36	
After Smoking	4.49	3.37		3.48	1.58		3.99	3.00	
	4.85	2.91		4.28	2.19				
SDLP (m)			39			15			54
Baseline	.16	.05		.14	.05		.15	.05	
After Smoking	.21	.05		.21	.06		.21	.05	
	.18	.06		.18	.06				

3.5.3 Slow Moving Vehicle Following Distance

For single- and dual- task conditions, following distance behind a slow moving vehicle was analyzed using a split-plot repeated-measures ANOVA. Results of this analysis for single-task conditions are presented in Table 15. Interaction effects were not found to be significant ($p=0.08$). Descriptive statistics are presented in Table 16. Baseline differences were not found to be significant ($p=0.57$).

Table 15. Results of a split-plot repeated-measures ANOVA predicting changes in following distance behind a slow moving vehicle under single-task conditions after smoking

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Observed Power
Condition	31.52	1	31.52	4.31	.04	.08	.53
Error (condition)	380.13	52	7.31				
Time	35.84	1	35.84	8.11	.01	.14	.80
Time*Condition	14.06	1	14.06	3.18	.08	.06	.42
Error (time)	229.92	52	4.42				

Table 16. Descriptive statistics for following distance behind a slow-moving vehicle under single-task conditions

	Active			Placebo			Full Sample		
	Mean	Standard Deviation	n	Mean	Standard Deviation	n	Mean	Standard Deviation	n
Following distance (m)			39			15			54
Baseline	9.95	1.75		9.55	3.34		9.75	2.28	
After Smoking	9.47	2.11		7.46	3.46		8.46	2.68	
	9.71	1.94		8.50	3.51				

Results of this analysis under dual-task conditions are presented in Table 17. Interaction effects were not found to be significant ($p=0.94$). Descriptive statistics are presented in Table 18.

Baseline differences were not found to be significant ($p=0.91$).

Table 17. Results of a split-plot repeated-measures ANOVA predicting changes in following distance behind a slow-moving vehicle under dual-task conditions after smoking

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Observed Power
Condition	.04	1	.04	.01	.94	.00	.05
Error (condition)	335.52	52	6.45				
Time	119.03	1	119.03	15.83	<.001	.23	.97
Time*Condition	.04	1	.04	.01	.94	.00	.05
Error (time)	391.09	52	7.52				

Table 18. Descriptive statistics for following distance behind a slow-moving vehicle under dual-task conditions

	Active			Placebo			Full Sample		
	Mean	Standard Deviation	n	Mean	Standard Deviation	n	Mean	Standard Deviation	n
Following distance (m)			39			15			54
Baseline	8.47	2.18		8.56	3.02		8.51	2.41	
After Smoking	10.86	3.02		10.86	2.25		10.86	2.81	
	9.67	2.88		9.71	2.87				

3.5.4 Braking Distance Approaching Risk-Taking Hazard

For single- and dual-task conditions, braking distance approaching a risk-taking hazard was analyzed using a split-plot repeated-measures ANOVA. Results of this analysis for single-task conditions are presented in Table 19. Interaction effects were not found to be significant

($p=0.13$). Descriptive statistics are presented in Table 20. Baseline differences were not found to be significant after a Bonferroni correction for multiple comparisons ($p=0.03$).

Table 19. Results of a split-plot repeated-measures ANOVA predicting changes in braking distance approaching a risk-taking hazard under single-task conditions after smoking

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Observed Power
Condition	4985.22	1	4985.22	4.71	.04	.08	.57
Error (condition)	55042.88	52	1058.52				
Time	95897.05	1	95897.05	121.42	<.001	.70	1.00
Time*Condition	1907.06	1	1907.06	2.42	.13	.04	.33
Error (time)	41069.96	52	789.81				

Table 20. Descriptive statistics for braking distance approaching a risk-taking hazard under single-task conditions

	Active			Placebo			Full Sample		
	Mean	Standard Deviation	n	Mean	Standard Deviation	n	Mean	Standard Deviation	n
Following distance (m)			39			15			54
Baseline	54.14	37.51		78.69	33.65		61.00	37.83	
After Smoking	130.05	24.69		135.84	16.11		131.66	22.64	
	92.10	49.54		107.26	38.94				

Results of this analysis under dual-task conditions are presented in Table 21. Interaction effects were not found to be significant ($p=0.95$). Descriptive statistics are presented in Table 22. Baseline differences were not found to be significant ($p=0.95$).

Table 21. Results of a split-plot repeated-measures ANOVA predicting changes in braking distance approaching a risk-taking hazard under dual-task conditions after smoking

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Observed Power
Condition	1.44	1	1.44	.00	.97	.00	.05
Error (condition)	39726.58	52	763.97				
Time	2017.36	1	2017.36	2.83	.10	.05	.38
Time*Condition	2.63	1	2.63	.00	.95	.00	.05
Error (time)	37111.35	52	713.68				

Table 22. Descriptive statistics for braking distance approaching a slow-moving vehicle under dual-task conditions

	Active			Placebo			Full Sample		
	Mean	Standard Deviation	n	Mean	Standard Deviation	n	Mean	Standard Deviation	n
Following distance (m)			39			15			54
Baseline	125.54	31.68		124.94	38.91		125.38	33.46	
After Smoking	115.55	19.11		115.64	16.13		115.57	18.18	
	120.54	26.47		120.29	29.64				

3.6 Cognitive Performance and Motor Skills Data

3.6.1 CPT-X Commission and Omission errors

Commission and omission errors made during the CPT-X were analyzed together using a split-plot repeated-measures ANOVA. Results of this analysis are presented in Table 23. The three way interaction effect was not found to be significant ($p=0.20$), nor was the interaction effect of time and condition ($p=0.10$). Main effects for time (0.001) and CPT-X error type ($p<0.001$) were both found to be significant. Descriptive statistics are presented in Table 24. Baseline differences were not found to be significant ($p>0.22$).

Table 23. Results of a split-plot repeated-measures ANOVA predicting changes in CPT-X errors after smoking

Source	Type III Sum of Squares	df	Mean Square	F	Sig	Partial Eta Squared	Observed Power
Condition	1700.03	1	1700.03	3.13	.08	.06	.41
Error (condition)	28270.94	52	543.67				
Time	1095.23	1	1095.23	11.82	.001	.19	.92
Time*Condition	260.97	1	260.97	2.82	.10	.05	.38
Error (time)	4817.34	52	92.64				
CPT-X Error Type	101209.52	1	101209.52	198.97	<.001	.79	1.00
CPT-X Error Type*Condition	1139.25	1	1139.25	2.24	.14	.04	.31
Error (CPT-X error type)	26450.50	52	508.66				
Time*CPT-X Error Type	816.27	1	816.27	7.93	.01	.13	.79

Source	Type III Sum of Squares	df	Mean Square	F	Sig	Partial Eta Squared	Observed Power
Time*CPT-X Error Type*Condition	175.91	1	175.91	1.71	.20	.03	.25
Error (time*CPT-X error type)	5354.97	52	102.97				

Table 24. Descriptive statistics for CPT-X error type

	Active			Placebo			Full Sample		
	Mean	Standard Deviation	n	Mean	Standard Deviation	n	Mean	Standard Deviation	n
Omissions			39			15			54
Baseline	1.26	2.07		.56	.94		1.06	1.84	
After Smoking	2.39	4.02		.81	1.11		1.94	3.52	
	.68	3.23		1.82	1.02				
Commissions			39			15			54
Baseline	48.36	22.64		41.43	26.96		46.43	23.86	
After Smoking	62.19	26.23		46.33	24.32		57.79	26.48	
	55.27	25.32		43.88	25.35				

3.6.2 CPT-X Hit Rate

Hit rate during the CPT-X was analyzed using a split-plot repeated-measures ANOVA. Results of this analysis are presented in Table 25. Interaction effects were not found to be significant ($p=0.32$). Descriptive statistics are presented in Table 26. Baseline differences were not found to be significant ($p=0.56$).

Table 25. Results of a split-plot repeated-measures ANOVA predicting changes in CPT-X hit rate after smoking

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Observed Power
Condition	433.01	1	433.01	.08	.78	.00	.06
Error (condition)	276397.23	52	5315.33				
Time	51.44	1	51.44	.13	.73	.00	.06
Time*Condition	410.52	1	410.52	1.00	.32	.02	.17
Error (time)	21399.41	52	411.53				

Table 26. Descriptive statistics for CPT-X hit rate

	Active			Placebo			Full Sample		
	Mean	Standard Deviation	n	Mean	Standard Deviation	n	Mean	Standard Deviation	n
Hit Rate (ms)			39			15			54
Baseline	315.88	39.26		324.70	70.44		318.33	49.31	
After Smoking	321.77	50.32		321.89	72.48		321.80	56.60	
	318.82	44.93		323.29	70.24				

3.6.3 HVLT-R Total Recall Score, Percent Retained, and Discrimination Index

Total recall score, percent retained, and discrimination index measured using the HVLT-R were analyzed together using a split-plot repeated-measures MANOVA. No multivariate effects were found to be significant ($p>0.12$). Results of univariate tests are presented in Table 27.

Descriptive statistics are presented in Table 28. Baseline differences for total recall score and percent retained were not found to be significant after a Bonferroni correction for multiple comparisons ($p>0.04$). Baseline differences were found to be significant for discrimination index ($p=0.02$).

Table 27. Univariate tests from a split-plot repeated-measures MANOVA predicting changes in HVLT-R performance after smoking

Source	Measure	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Observed Power
Time	Total Recall Score	26.22	1	26.22	2.31	.14	.04	.32
	Percent Retained	177.30	1	177.30	1.02	.32	.02	.17
	Discrimination Index	.00	1	.00	.00	.99	.00	.05
Time*Condition	Total Recall Score	6.96	1	6.96	.61	.44	.01	.12
	Percent Retained	616.58	1	616.58	3.56	.07	.06	.46
	Discrimination Index	1.48	1	1.48	.27	.61	.01	.08
Error (time)	Total Recall Score	591.20	52	11.37				
	Percent Retained	9008.75	52	173.25				
	Discrimination Index	284.19	52	5.47				

Table 28. Descriptive statistics for total recall score, percent retained, and discrimination index on the HVLT-R

	Active			Placebo			Full Sample		
	Mean	Standard Deviation	n	Mean	Standard Deviation	n	Mean	Standard Deviation	n
Total recall score			39			15			54
Baseline	29.18	4.12		31.67	3.52		29.87	4.09	
After Smoking	27.51	6.03		31.13	4.58		28.52	5.85	
	28.35	5.20		31.40	4.02				
Percent retained			39			15			54
Baseline	96.10	11.43		95.96	7.45		96.06	10.40	
After Smoking	87.91	21.89		98.44	10.54		90.83	19.89	
	92.00	17.83		97.20	9.06				
Discrimination index			39			15			54
Baseline	22.46	2.27		23.60	1.12		22.78	2.07	
After Smoking	22.21	3.69		23.87	.52		22.67	3.23	
	22.33	3.05		23.73	.87				

3.6.4 DSST Completed and Correct Trials

The numbers of completed and correct trials during the DSST were analyzed together using a split-plot repeated-measures ANOVA. Results of this analysis are presented in Table 29. The three-way interaction effect was not found to be significant ($p=0.10$). Descriptive statistics are presented in Table 30. Baseline differences were not found to be significant ($p>0.51$).

Table 29. Results of a split-plot repeated-measures ANOVA predicting changes in completed and correct trials on the DSST after smoking

Source	Type III Sum of Squares	df	Mean Square	F	Sig	Partial Eta Squared	Observed Power
Condition	47.31	1	47.31	.21	.65	.00	.07
Error (condition)	11676.77	52	224.55				
Time	10.89	1	10.89	3.10	.08	.06	.41
Time*Condition	.19	1	.19	.05	.82	.00	.06
Error (time)	182.52	52	3.51				
DSST Trials	178369.08	1	178369.08	977.71	<.001	.95	1.00
DSST Trials*Condition	195.56	1	195.56	1.07	.31	.02	.17
Error (DSST trials)	9486.63	52	182.44				
Time*DSST Trials	.98	1	.98	.27	.61	.01	.08
Time*DSST Trials*Condition	10.12	1	10.12	2.75	.10	.05	.37
Error (time*DSST trials)	191.40	52	3.68				

Table 30. Descriptive statistics for completed and correct trials on the DSST

	Active			Placebo			Full Sample		
	Mean	Standard Deviation	n	Mean	Standard Deviation	n	Mean	Standard Deviation	n
Completed trials			39			15			54
Baseline	30.87	3.08		31.53	3.67		31.06	3.23	
After Smoking	30.10	3.44		31.60	4.15		30.52	3.67	
	30.49	3.27		31.57	3.85				
Correct trials			39			15			54
Baseline	96.82	11.57		94.20	19.46		96.09	14.05	
After Smoking	96.72	10.79		93.00	19.80		95.69	13.78	
	96.77	11.11		93.60	19.30				

3.6.5 DSST Reaction Time

Reaction time during the DSST was analyzed using a split-plot repeated-measures ANOVA.

Results of this analysis are presented in Table 31. Interaction effects were not found to be significant ($p=0.26$). Descriptive statistics are presented in Table 32. Baseline differences were not found to be significant ($p=0.99$).

Table 31. Results of a split-plot repeated-measures ANOVA predicting changes in DSST reaction time after smoking

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Observed Power
Condition	47825.12	1	47825.12	.32	.58	.01	.09
Error (condition)	7870531.26	52	151356.37				
Time	11674.76	1	11674.76	.31	.58	.01	.08
Time*Condition	50310.09	1	50310.09	1.32	.26	.03	.20
Error (time)	1978970	52	38057.12				

Table 32. Descriptive statistics for DSST reaction time

	Active			Placebo			Full Sample		
	Mean	Standard Deviation	n	Mean	Standard Deviation	n	Mean	Standard Deviation	n
Reaction time (ms)			39			15			54
Baseline	2341.46	251.55		2342.67	332.83		2341.80	273.19	
After Smoking	2366.44	330.52		2271.27	352.81		2340.00	336.24	
	2353.95	292.06		2306.97	338.95				

3.6.6 Grooved Pegboard Dominant and Non-Dominant Hand Performance

Dominant and non-dominant hand performances on the grooved pegboard were analyzed together using a split-plot repeated-measures ANOVA. Results of this analysis are presented in Table 33. The three way interaction effect was not found to be significant ($p=0.26$). Descriptive statistics are presented in Table 34. Baseline differences were not found to be significant ($p>0.40$).

Table 33. Results of a split-plot repeated-measures ANOVA predicting changes in grooved pegboard performance after smoking

Source	Type III Sum of Squares	df	Mean Square	F	Sig	Partial Eta Squared	Observed Power
Condition	1058116.33	1	1058116.33	.01	.94	.00	.05
Error (condition)	8074689978.47	52	155282499.59				
Time	148924611.11	1	148924611.11	5.14	.03	.09	.60
Time*Condition	35687941.67	1	35687941.67	1.23	.27	.02	.19
Error (time)	1507196658.91	52	28984551.13				
Performance	1542181175.79	1	1542181175.79	51.50	<.001	.50	1.00
Performance*Condition	5029943.38	1	5029943.38	.17	.68	.00	.07
Error (performance)	1557059279.42	52	29943447.68				
Time*Performance	19946392.31	1	19946392.31	.66	.42	.01	.13
Time*Performance*Condition	38244957.31	1	38244957.31	1.27	.26	.02	.20
Error (time*performance)	1562915566.94	52	30056068.60				

Table 34. Descriptive statistics for grooved pegboard performance

	Active			Placebo			Full Sample		
	Mean	Standard Deviation	n	Mean	Standard Deviation	n	Mean	Standard Deviation	n
Dominant hand performance (ms)			39			15			54
Baseline	57277.05	6262.98		57060.67	6482.82		57216.94	6263.75	
Post-dose	58420.49	7154.16		58268.00	4818.49		58378.13	6544.79	
	57848.77	6704.29		57664.33	5645.74				
Non-dominant hand performance (ms)			39			15			54
Baseline	61284.08	8518.25		63628.00	10440.64		61935.17	9052.17	
Post-dose	65663.33	8854.35		64313.33	8825.27		65288.33	8783.90	
	63473.705	8908.23		63970.67	9505.02				

3.7 Mood and Subjective Drug Effects Data

3.7.1 ARCI Subscales

Scores from all subscales of the ARCI (AMPH, MBG, LSD, BZ, PCAG, euphoria, and sedation) were analyzed together using a split-plot repeated-measures ANOVA. Results of this analysis are presented in Table 35. The three-way interaction effect was not found to be significant ($p=0.39$). Descriptive statistics are presented in Table 36. Baseline differences were not found to be significant ($p>0.44$).

Table 35. Results of a split-plot repeated-measures ANOVA predicting changes in ARCI subscale scores after smoking

Source	Type III Sum of Squares	df	Mean Square	F	Sig	Partial Eta Squared	Observed Power
Condition	5737.43	1	5737.43	4.80	.03	.08	.58
Error (condition)	62216.38	52	1196.47				
Time	8461.88	1	8461.88	15.01	<.001	.22	.97
Time*Condition	2100.67	1	2100.67	3.73	.06	.07	.47
Error (time)	29306.21	52	563.58				
Subscale	72301.99	6	12050.33	26.95	<.001	.34	1.00
Subscale*Condition	2522.21	6	420.37	.94	.47	.02	.37
Error (subscale)	139502.44	312	447.12				
Time*Subscale	3518.51	6	586.42	2.53	.02	.05	.84
Time*Subscale*Condition	1480.60	6	246.77	1.06	.39	.02	.42
Error (time*subscale)	72457.47	312	232.24				

Table 36. Descriptive statistics for ARCI subscales

	Active			Placebo			Full Sample		
	Mean	Standard Deviation	n	Mean	Standard Deviation	n	Mean	Standard Deviation	n
AMPH			39			15			54
Baseline	40.46	24.11		37.04	20.00		39.50	22.91	
Post-dose	49.00	25.71		40.74	21.28		46.71	24.65	
	44.73	25.13		38.89	20.37				
MBG			39			15			54
Baseline	30.77	25.10		27.50	21.23		29.86	23.94	
Post-dose	39.90	24.78		25.00	19.05		35.76	24.11	
	35.34	25.20		26.25	19.86				
LSD			39			15			54
Baseline	18.50	8.47		19.05	5.83		18.65	7.78	
Post-dose	35.35	19.66		23.81	9.98		32.14	18.18	
	26.92	17.26		21.43	8.39				
BZ			39			15			54
Baseline	50.89	17.44		50.26	16.92		50.71	17.14	
Post-dose	46.15	22.25		51.28	15.84		47.58	20.66	
	48.52	20.00		50.77	16.11				

	Active			Placebo			Full Sample		
	Mean	Standard Deviation	n	Mean	Standard Deviation	n	Mean	Standard Deviation	n
PCAG			39			15			54
Baseline	25.30	15.91		23.11	10.95		24.69	14.63	
Post-dose	38.97	17.67		30.67	16.87		36.67	17.70	
	32.14	18.07		26.89	14.49				
Euphoria			39			15			54
Baseline	20.88	25.56		16.19	20.82		19.58	24.24	
Post-doe	39.20	28.52		20.00	25.21		33.86	28.74	
	30.04	28.44		18.10	22.80				
Sedation			39			15			54
Baseline	10.02	15.15		6.67	11.12		9.09	14.13	
Post-dose	26.57	20.90		14.54	16.04		23.23	20.26	
	18.30	19.95		10.61	14.14				

3.7.2 POMS Subscales

Scores from all subscales of the POMS (tension/anxiety, anger/hostility, depression/dejection, friendliness, fatigue, confusion, vigor, elation, arousal, and positive mood) were analyzed together using a split-plot repeated-measures ANOVA. Results of this analysis are presented in Table 37. The three way interaction effect was not found to be significant ($p=0.25$). Descriptive statistics are presented in Table 38. Baseline differences were not found to be significant ($p>0.07$).

Table 37. Results of a split-plot repeated-measures ANOVA predicting changes in POMS subscale scores after smoking

Source	Type III Sum of Squares	df	Mean Square	F	Sig	Partial Eta Squared	Observed Power
Condition	2008.58	1	2008.58	1.98	.17	.04	.28
Error (condition)	52883.04	52	1016.98				
Time	141.22	1	141.22	1.27	.27	.02	.20
Time*Condition	261.03	1	261.03	2.34	.13	.04	.32
Error (time)	5793.17	52	111.41				
Subscale	485144.23	9	53904.92	232.67	<.001	.82	1.00
Subscale*Condition	1507.39	9	167.49	.72	.69	.01	.36
Error (subscale)	108426.72	468	231.68				
Time*Subscale	1446.01	9	160.67	3.18	.001	.06	.98
Time*Subscale*Condition	580.83	9	64.54	1.28	.25	.02	.63
Error (time*subscale)	23661.80	468	50.56				

Table 38. Descriptive statistics for POMS subscales

	Active			Placebo			Full Sample		
	Mean	Standard Deviation	n	Mean	Standard Deviation	n	Mean	Standard Deviation	n
Tension/anxiety			39			15			54
Baseline	11.75	7.17		8.52	4.51		10.85	6.66	
Post-dose	14.67	7.86		9.07	10.31		13.12	8.87	
	13.21	7.61		8.80	7.82				
Anger/hostility			39			15			54
Baseline	4.75	8.01		2.78	4.57		4.21	7.23	
Post-dose	4.11	7.53		3.19	7.08		3.86	7.36	
	4.43	7.73		2.99	5.86				
Depression/dejection			39			15			54
Baseline	2.91	5.92		4.56	11.26		3.36	7.69	
Post-dose	3.63	8.93		4.33	13.18		3.83	10.15	
	3.27	7.53		4.45	12.05				
Friendliness			39			15			54
Baseline	54.25	20.93		50.00	22.29		53.07	21.19	
Post-dose	54.81	22.32		45.00	25.05		52.09	23.29	
	54.53	21.50		47.50	23.43				
Fatigue			39			15			54
Baseline	13.46	12.47		7.14	7.01		11.71	11.51	
Post-dose	14.01	11.16		12.14	13.28		13.49	11.69	
	13.74	11.76		9.64	10.74				

	Active			Placebo			Full Sample		
	Mean	Standard Deviation	n	Mean	Standard Deviation	n	Mean	Standard Deviation	n
Confusion			39			15			54
Baseline	14.10	8.74		9.76	7.45		12.90	8.57	
Post-dose	17.40	12.88		8.33	7.23		14.88	12.23	
	15.75	11.06		9.05	7.25				
Vigor			39			15			54
Baseline	33.56	19.43		32.71	22.16		33.10	20.01	
Post-dose	27.81	18.07		24.17	22.02		26.10	19.10	
	30.53	18.84		28.44	22.13				
Elation			39			15			54
Baseline	35.47	16.22		35.00	21.81		35.34	17.73	
Post-dose	37.71	21.75		29.44	20.86		35.42	21.64	
	36.59	19.10		32.22	21.16				
Arousal			39			15			54
Baseline	50.93	6.33		52.26	6.47		51.30	6.34	
Post-dose	49.50	5.62		49.41	7.22		49.48	6.04	
	50.22	5.99		50.83	6.89				
Positive Mood			39			15			54
Baseline	79.79	6.47		78.17	11.70		79.12	8.16	
Post-dose	79.61	9.87		76.75	12.88		78.81	10.74	
	79.55	8.29		77.46	12.12				

3.7.3 VAS Subscales

Scores from all subscales of the VAS (drug effect, high, good effects, bad effects, drug liking, rush, and feels like cannabis) were analyzed together using a split-plot repeated-measures ANOVA. Results of this analysis are presented in Table 39. Since the assumption of sphericity was violated, the Greenhouse-Geisser correction was used. The three-way interaction effect was found to be significant [$F(10.47, 481.54) = 3.95$, $p < 0.001$]. Figure 5 summarizes these findings. Descriptive statistics can be found in Appendix D, Table 52. Baseline measures were zero for both conditions on all subscales except drug liking. Baseline differences on the drug liking subscale were not found to be significant ($p = 0.38$).

Table 39. Results of a split-plot repeated-measures ANOVA predicting changes in VAS subscale scores after smoking

Source	Type III Sum of Squares	df	Mean Square	F	Sig	Partial Eta Squared	Observed Power
Condition	436541.65	1	436541.65	50.82	<.001	.53	1.00
Error (condition)	395137.09	46	8589.94				
Time	509489.22	3.17	160756.76	69.57	<.001	.60	1.00
Time*Condition	174716.53	3.17	55127.49	23.86	<.001	.34	1.00
Error (time)	33.6883.84	145.79	2301.77				
Subscale	179873.49	3.27	55053.50	31.97	<.001	.41	1.00
Subscale*Condition	51402.50	3.27	15732.66	9.14	<.001	.17	1.00
Error (subscale)	258788.57	150.29	1721.89				
Time*Subscale	66251.79	10.47	6328.87	7.91	<.001	.15	1.00
Time*Subscale*Condition	33073.30	10.47	3159.41	3.95	<.001	.08	1.00
Error (time*subscale)	385354.48	481.54	800.26				

Since interaction effects were found to be significant, the analysis was repeated using BMI as a covariate. As the assumption of sphericity was violated, the Greenhouse-Geisser correction was used. Interaction effects were still found to be significant [$F(10.32,454.03)=3.89$, $p<0.001$]. These results are presented in Table 40. Figure 5 summarizes these findings. Descriptive statistics can be found in Appendix D, Table 52.

Table 40. Results of a split-plot repeated-measures ANOVA predicting changes in VAS subscale scores after smoking with BMI as a covariate

Source	Type III Sum of Squares	df	Mean Square	F	Sig	Partial Eta Squared	Observed Power
BMI	11676.83	1	11676.83	1.36	.25	.03	.21
Condition	420623.93	1	420623.93	49.12	<.001	.53	1.00
Error (condition)	376762.27	44	8562.78				
Time	38953.76	3.09	12626.19	5.24	.002	.11	.93
Time*BMI	8372.12	3.09	2713.68	1.13	.34	.25	.30
Time*Condition	171660.60	3.09	55640.82	23.08	<.001	.34	1.00
Error (time)	327211.87	135.75	2410.46				
Subscale	14855.04	3.22	4615.13	2.61	.05	.06	.65
Subscale*BMI	1493.26	3.22	463.92	.26	.87	.01	.10
Subscale*Condition	48795.22	3.22	15159.57	8.56	<.001	.16	1.00
Error (subscale)	250770.84	141.63	1770.66				
Time*Subscale	14965.48	10.32	1450.31	1.83	.05	.04	.85
Time*Subscale *BMI	12421.97	10.32	1203.82	1.52	.13	.03	.77
Time*Subscale *Condition	31907.97	10.32	3092.21	3.89	<.001	.08	1.00
Error (time*subscale)	360702.83	454.03	794.45

Figure 5.1. VAS responses to “I feel a drug effect...”

Figure 5.2. VAS responses to “I feel this high...”

Figure 5.3. VAS responses to “I feel the drug’s good effects...”

Figure 5.4. VAS responses to “I feel the drug’s bad effects...”

Figure 5.5. VAS responses to “I like the drug...”

Figure 5.6. VAS responses to “I feel a rush...”

Figure 5.7. VAS responses to “It feels like cannabis...”

Figure 5 (5.1-5.7). Scores achieved on subscales of the VAS test for subjective drug effects at various times from smoking. All VAS subscale scores were significantly higher for participants who smoked active cannabis compared to those who smoked placebo cannabis. Differences in subscale scores retained significance until between three and six hours after smoking. * $0.005 < p < 0.001$, ** $p < 0.001$ based on independent samples t-tests with a Bonferroni adjustment for multiple comparisons.

A Pearson Product-Moment Correlation was performed on peak VAS scores for drug effect and drug liking subscales for participants in the active and placebo conditions separately. The correlation was found to be significant in both the active ($r=.41$, $p=0.01$, $n=38$) and placebo ($r=0.65$, $p=0.01$, $n=15$) groups. Figures 6 (active) and 7 (placebo) summarize these findings. Descriptive statistics are presented in Appendix D, Table 53.

Figure 6. Peak VAS subscale score for drug liking versus drug effect for participants in the active condition. Participants in the active condition who reported higher peak drug liking also reported a higher peak drug effect. $R=0.41$.

Figure 7. Peak VAS subscale score for drug liking versus drug effect for participants in the placebo condition. Participants in the placebo condition who reported higher peak drug liking also reported a higher peak drug effect. $R=0.65$.

3.8 Cannabis Cigarette Data

3.8.1 Amount of Cigarette Smoked

A one-way ANOVA was performed to compare the amount of cigarette consumed between the active and placebo groups. No significant differences were found ($p=0.77$). The results of this analysis are presented in Table 41. Descriptive statistics are presented in Table 42.

Table 41. Results of a one-way ANOVA comparing the change in cigarette weight between the active and placebo groups

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	2624.28	1	2624.28	.09	.77
Within Groups	1577334.26	52	30333.35		
Total	1579958.54	53			

Table 42. Descriptive statistics for change in cigarette weight in milligrams

	Mean	Standard Deviation	n
Active	641.33	126.59	39
Placebo	625.77	188.69	15
Total	630.09	172.65	54

3.8.2 Estimated Δ^9 -THC dose Compared to Peak VAS Effects

Pearson Product-Moment Correlations were performed on estimated dose of Δ^9 -THC compared to peak VAS scores on drug effect and drug liking for participants in the active condition only. Estimated dose of Δ^9 -THC was calculated based on the change in cigarette weight. Significant correlations were found for both measures. The results of these analyses are presented in Table 43. Descriptive statistics are presented in Appendix D, Table 54. Figures 8 (drug effect) and 9 (drug liking) summarize these findings.

Table 43. Pearson Product-Moment Correlations between estimated Δ^9 -THC dose and peak VAS scores for participants in the active condition

VAS measure	r	p	n
Drug effect	.35	.03	38
Drug liking	.38	.02	38

Pearson Product-Moment Correlations were also performed on amount smoked and peak VAS scores on drug liking and drug effect for participants in the placebo condition only. No significant correlations were identified. These results are presented in Table 44. Descriptive statistics are presented in Table 45.

Table 44. Pearson Product-Moment Correlations between change in cigarette weight and peak VAS scores for participants in the placebo condition

VAS measure	r	p	n
Drug effect	.11	.70	15
Drug liking	-.13	.65	15

Table 45. Descriptive statistics for change in cigarette weight and peak scores on VAS drug liking and drug effect subscales for participants in the placebo condition

	Mean	Standard Deviation	n
Change in Cigarette Weight (mg)	641.33	126.59	15
Peak VAS Drug Effect	20.13	27.18	15
Peak VAS Drug Liking	38.07	37.94	15

Linear regressions were performed to further explore the relationship between peak VAS score and estimated dose of Δ^9 -THC for participants in the active condition. A significant relationship was found between peak scores on both VAS subscales and estimated Δ^9 -THC dose. These findings are presented in Table 46. Descriptive statistics are presented in Appendix D, Table 54. Figures 8 (drug effect) and 9 (drug liking) summarize these findings.

Table 46. Linear regressions on estimated Δ^9 -THC dose and peak VAS Scores with and without BMI as a covariate for participants in the active condition

		R	R ²	β	B	SE	CI 95% (B)	P
Drug effect	No Covariates	.35	.12	.35	.33	.15	.03/.62	.03
	BMI as a Covariate	.35	.13	.36	.34	.15	.03/.65	.03
Drug liking	No Covariates	.38	.15	.38	.38	.15	.07/.67	.02
	BMI as a Covariate	.39	.15	.38	.38	.16	.06/.70	.02

Figure 8. Estimated Δ^9 -THC dose versus peak VAS subscale score for “I feel a drug effect...”. Participants in the active condition who smoked more of their cigarette reported higher peak VAS scores this subscale. $R=0.35$.

Figure 9. Estimated Δ^9 -THC dose versus peak VAS subscale score for “I like the drug...”. Participants in the active condition who smoked more of their cigarette reported higher peak VAS scores this subscale. $R=0.38$.

3.9 Physiological Data

3.9.1 Heart Rate

A split-plot repeated-measures ANOVA was performed on heart rate to compare participants in the placebo condition to participants in the active condition before and after smoking. The time by condition interaction effect was found to be significant [$F(9,432)=7.23$, $p<0.001$]. These results are presented in Table 47. Descriptive statistics are presented in Appendix D, Table 55. Figure 10 summarizes these findings. Baseline differences were not found to be significant after a Bonferroni correction for multiple comparisons ($p=0.03$).

Table 47. Results of a split-plot repeated-measures ANOVA predicting changes in heart rate after smoking

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Observed Power
Condition	12405.39	1	12405.39	12.07	.001	.20	.93
Error (condition)	49351.11	48	1028.15				
Time	7725.87	9	858.43	7.21	<.001	.13	1.00
Time*Condition	7745.37	9	860.60	7.23	<.001	.13	1.00
Error (time)	51404.47	432	118.99				

Significant interaction effects were explored by repeating the analysis using BMI as a covariate. The time by condition interaction effect was still found to be significant [$F(9,414)=7.92$, $p<0.001$]. These results are presented in Table 48. Descriptive statistics can be found in Appendix D, Table 55. Figure 10 summarizes these findings. Baseline differences were not found to be significant after a Bonferroni correction for multiple comparisons ($p=0.03$).

Table 48. Results of a split-plot repeated-measures ANOVA predicting changes in heart rate after smoking with BMI as a covariate

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Observed Power
BMI	2211.07	1	2211.07	2.18	.15	.05	.30
Condition	12865.10	1	12865.10	12.68	.001	.22	.94
Error (condition)	46683.05	46	1014.85				
Time	1053.67	9	117.08	1.02	.43	.02	.51
Time*BMI	1689.18	9	187.69	1.63	.10	.03	.76
Time*Condition	8200.18	9	911.13	7.92	<.001	.15	1.00
Error (time)	47628.43	414	115.05

Figure 10. Average heart rate in beats per minute over the course of drug administration day for both active and placebo groups. For several hours after smoking and especially for the first hour, participants in the active condition had a significantly increased heart rate compared to those in the placebo condition. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ based on independent samples t-tests. * $0.005 < p < 0.001$, ** $p < 0.001$ based on independent samples t-tests with a Bonferroni adjustment for multiple comparisons.

3.9.2 Blood Pressure

A split-plot repeated-measures ANOVA was performed to analyze systolic and diastolic blood pressure together to compare placebo and active groups before and after smoking. The results of this analysis are presented in Table 49. The three-way interaction effect was not found to be significant ($p=0.14$). Descriptive statistics for this analysis are presented in Table 50. Baseline differences were not found to be significant ($p>0.66$).

Table 49. Results of a split-plot repeated-measures ANOVA predicting changes in blood pressure after smoking

Source	Type III Sum of Squares	df	Mean Square	F	Sig	Partial Eta Squared	Observed Power
Condition	14.30	1	14.30	.01	.91	.00	.05
Error (condition)	61400.82	48	1279.18				
Time	1806.67	9	200.74	1.79	.07	.04	.80
Time*Condition	852.99	9	94.78	.84	.58	.02	.42
Error (time)	48531.89	432	112.34				
Blood Pressure	501176.58	1	501176.58	2329.69	<.001	.98	1.00
Blood Pressure*Condition	141.53	1	141.53	.66	.42	.01	.13
Error (Blood Pressure)	10326.02	48	215.13				
Time*Blood Pressure	1064.54	9	118.28	2.77	.004	.06	.96
Time*Blood Pressure*Condition	583.71	9	64.86	1.52	.14	.03	.72
Error (time*Blood Pressure)	18428.94	432	42.66				

Table 50. Descriptive statistics for blood pressure

	Active			Placebo			Full Sample		
	Mean	Standard Deviation	n	Mean	Standard Deviation	n	Mean	Standard Deviation	n
Systolic			35			15			50
Baseline	117.34	11.83		117.60	12.86		117.96	12.00	
5 min post-dose	122.71	17.80		122.27	12.71		122.80	16.43	
15 min post-dose	115.51	15.57		120.20	13.64		116.81	15.08	
30 min post-dose	117.63	16.00		113.73	7.98		116.11	14.19	
1 hr post-dose	116.83	15.30		116.13	14.18		117.30	14.88	
2 hrs post-dose	115.69	13.63		117.20	10.27		116.56	12.70	
3 hrs post-dose	117.09	12.76		118.87	17.15		118.02	13.97	
4 hrs post-dose	116.49	12.01		119.27	9.41		117.51	11.30	
5 hrs post-dose	118.14	13.06		122.67	10.77		119.32	12.54	
6 hrs post-dose	120.69	12.31		121.00	9.36		120.71	11.45	
	118.08	14.16		118.89	12.05				
Diastolic			35			15			50
Baseline	69.66	11.30		69.67	7.99		68.65	10.43	
5 min post-dose	73.17	10.39		71.00	10.79		72.13	10.42	
15 min post-dose	71.91	12.23		67.87	10.18		70.47	11.71	
30 min post-dose	71.43	11.96		67.40	6.79		69.96	10.81	
1 hr post-dose	71.77	10.40		69.33	11.02		70.98	10.52	

	Active			Placebo			Full Sample		
	Mean	Standard Deviation	n	Mean	Standard Deviation	n	Mean	Standard Deviation	n
2 hrs post-dose	67.83	12.13		73.07	9.51		69.96	11.54	
3 hrs post-dose	66.71	8.70		65.73	11.18		66.87	9.38	
4 hrs post-dose	68.09	9.45		67.80	11.71		68.02	10.02	
5 hrs post-dose	68.03	8.18		68.27	9.85		67.94	8.59	
6 hrs post-dose	69.20	9.77		72.07	7.61		69.90	9.23	
	69.60	10.58		69.22	9.74				

3.9.3 Summary

The main effect of time was significant for overall mean speed under single-task conditions ($p=0.01$), with speed being reduced after smoking. Significant interaction effects were only noted when participants were driving under dual-task conditions. Overall mean speed [$F(1,52) = 5.72$, $p=0.02$] was found to be significantly reduced in participants who received active cannabis. Those in the active condition had higher overall SDLP, but this result was not statistically significant ($p=0.07$). The main effect of time was significant for SDLP ($p=0.02$), with SDLP being reduced after smoking. The correlation between change in speed and estimated dose of Δ^9 -THC or amount of cigarette consumed was not found to be significant for participants in active or placebo conditions. Main effects of time ($p=0.01$) and condition ($p=0.04$) were significant for following distance behind a slow moving vehicle under single task conditions. Following distance behind a slow moving vehicle under dual-task conditions showed significant effects of time ($p<0.001$). Braking distance approaching a risk-taking hazard under single-task conditions showed significant main effects of time ($p<0.001$).

No measures on the CPT-X, HVLT-R, DSST, or grooved pegboard were found to have statistically significant interaction effects. Main effects of error type ($p<0.001$) and time ($p=0.001$) were found to be significant on the CPT-X. The main effect of trial type (completed versus correct) was found to be significant for the DSST ($p<0.001$). The main effect of time was found to be significant for the grooved pegboard test ($p=0.03$).

Interaction effects for subjective drug effects as recorded by all subscales of the VAS were found to be significant. Subjective effects were increased after smoking in participants who received active cannabis compared to placebo [$F(10.32,454.03)$, $p<0.001$]. Subscale scores for drug effect and drug liking were found to be significantly correlated in both active ($r=.41$, $p=0.01$, $n=38$) and placebo ($r=0.65$, $p=0.01$, $n=15$) groups. Subscales on the ARCI and POMS were not found to differ significantly between active and placebo groups after smoking ($p>0.25$). An interaction effect between time and subscale was found to be significant for the POMS ($p=0.001$). A main effect for time was found to be significant for both the ARCI ($p<0.001$) and POMS ($p<0.001$). The main effect of subscale was also very significant for the ARCI ($p<0.001$).

Analysis of laboratory data did not yield significant difference between active and placebo groups in terms of the amount of cigarette smoked. There were significant positive correlations between estimated dose of Δ^9 -THC and peak VAS subscale scores for drug effect ($r=0.35$, $n=38$, $p=0.03$) and drug liking ($r=0.38$, $n=38$, $p=0.02$) for participants in the active condition. No significant correlations between amount of cigarette smoked and peak VAS subscale scores were identified for participants in the placebo condition. Linear regressions were calculated to predict peak VAS subscale scores for drug effect and drug liking based on Δ^9 -THC dose. Significant regression equations were found for both subscales. Estimated dose of Δ^9 -THC accounted for 13% of the variance in the perceived drug effect and 15% of the variance in drug liking.

Objective measures of cannabis effects were noted in that heart rate was significantly increased in participants who smoked active cannabis compared to placebo [$F(9,414)=7.92$, $p<0.001$]. This effect seems to have lasted for an hour beyond drug administration. The three-way interaction effect was not found to be significant for blood pressure, although the time*blood pressure

interaction was found to be significant ($p=0.004$). The main effect of blood pressure (systolic vs. diastolic) was also found to be significant ($p<0.001$).

Chapter 4 Discussion and Conclusions

4 Discussion and Conclusions

In North America, policies dealing with legalizing or decriminalizing cannabis are gaining in popularity. Harms associated with legal drugs tend to be greater than those associated with illegal drugs, simply because use is more widespread³⁰⁷. It is important to understand the risks associated with cannabis impaired driving before more jurisdictions adopt policies to make cannabis legal, in order to prevent harms due to impaired driving before they occur.

The majority of studies on cannabis-impaired driving to date suggest that driving under the influence of cannabis is a dangerous behaviour, but this is disputed by some studies^{Section 1.3.5}. Studies with negative findings are often cited by the general population as proof that cannabis does not impair driving^{308, 309, 310}. Although epidemiological studies help to identify driving outcomes that may be associated with cannabis use, naturalistic and human laboratory studies are necessary to clarify the nature of the relationship. While epidemiological studies are very useful in determining the prevalence of driving under the influence of cannabis and its relationship to collision risk, they suffer from an intrinsically biased sample selection because they examine drivers who have already had a collision, and are often unable to support a causative relationship. Data from naturalistic and human laboratory studies have been varied. Some have found changes in reaction time^{245, 246, 250, 251, 280}, headway maintenance²⁵⁰, road tracking^{95, 248, 250}, and speed^{97, 248, 250, 252}, while others have not observed these effects^{97, 252, 279, 281}. This may be attributable to differences between study populations (arguably the most notable ones being the age and cannabis use history of participants) and dosing protocols.

This study addresses some of these issues by limiting the study population to young adults aged 19 to 25 years who smoke cannabis weekly. Young drivers are the focus of this study because they are more likely to drive under the influence of cannabis^{7, 8, 9} and they have not had as much driving experience as older drivers. Of the fifty-four participants included in this analysis, thirty reported having driven under the influence of cannabis at least once in the past twelve months

prior to their participation in the study. These participants took an average of four trips while intoxicated over the twelve month period. It is possible that this study attracted a disproportionate number of cannabis users who also drive while high. However, the fact remains that over half of the participants recruited for this study reported driving under the influence of cannabis, underscoring the importance of researching driving behaviours under the influence of cannabis in young adults. By limiting the sample to this demographic, variability in years of driving experience is reduced making it easier to interpret the outcomes of cannabis impaired driving.

In order to be eligible to participate in the study, participants had to smoke one to four days per week. This group is unlikely to display tolerance to the effects of cannabis the way chronic, heavy cannabis smokers have been found to in previous studies^{19, 216, 255, 256}. So far, the preliminary findings of this study have supported this hypothesis, with significant effects on driving being observed despite the fact that less than half of the target sample size has been included in the analysis.

In addition, the dosing procedure allowed participants to smoke a cigarette containing 12.5% Δ^9 -THC which is similar to street cannabis, currently estimated to be approximately 10% and found to be as high as 30%¹⁹. Participants were asked to smoke *ad libitum*, i.e. until they experienced the high they would normally feel. This helped to control for inter-individual variability, by ensuring that participants who were more sensitive to cannabis effects could titrate their dose to smoke less and vice versa. This made the smoking procedure very relevant to the way cannabis is consumed recreationally. Therefore, by addressing speculation around possible reasons for variable findings between studies on how cannabis affects driving, the results of this study may provide a significant contribution to the current body of literature.

Developments in simulator technology have improved the ability of simulators to objectively collect driving measures. While driver simulation used to rely on experimenter observations of participant behaviour, interactive state-of-the-art simulators like the one used in this study take precise measurements automatically as participants drive. This new technology reduces another source of error by significantly reducing experimenter bias. Furthermore, the experience of

operating the simulator is more realistic than what has been possible in other such research. In a 1969 study by Crancer et al²⁶⁸, participants were asked to follow along with a video, even though their actions did not affect the visual stimulus they were receiving. Technology has improved since then, and the simulator used in this study consists of the driver's seat, surrounding controls, and instrumented dashboard, and responds to driver control in an interactive way. The speedometer is able to indicate the participants' driving speed, and the motion platform provides feedback based on the surface the car is driving on, the driver's speed, and level of acceleration. Visual feedback is provided via three large television monitors that project the view in front of the vehicle and display the virtual environment behind the vehicle through rear- and side-view mirrors. Two smaller computer screens are placed behind the driver to allow participants to monitor blind spots. The fact that the simulator is able to replicate driving so realistically makes the findings of this study very important for understanding the effects of cannabis on driver behaviour.

There are some concerns that simulated driving is not generalizable to on-road driving tasks. Because driving does not take place in the real world, simulator drivers do not face the risks of real consequences associated with dangerous driving on an actual roadway. However, although there are certainly differences between simulated driving and real driving, driving simulators have been validated as a good predictor of on-road outcomes^{275, 276, 277, 278}. Simulated driving also allows for consistency between scenarios which is not possible in the real world. Furthermore, a large amount of data can be objectively measured by the simulator rather than relying on experimenter observation. Along with these logistical benefits, simulated driving addresses the safety and ethical concerns associated with allowing impaired drivers to operate a real vehicle. These benefits outweigh the risk to external validity.

An important outcome of research on impaired driving is in deciding the best way to reduce harms through legislation. There are several ways to legislate impaired driving, and these differ between countries and within countries, between states or provinces. A zero-tolerance policy has been adopted by many places including Sweden and Finland, where having any detectable level of Δ^9 -THC or metabolites in urine can result in charges^{311, 312}. This may be problematic because

metabolites can persist in the blood and other biological fluids long after the impairing effects of cannabis have worn off. Another zero-tolerance policy that attempts to address this is the one used in Delaware, USA, where detectable blood levels of psychoactive cannabinoids Δ^9 -THC or 11-OH-THC are enough for a charge of driving under the influence of drugs (DUID)³¹³. Another strategy relies on police observations of erratic driving behaviour to apprehend someone, and this is the one currently used in Canada. This form of apprehension sidesteps challenges associated with measurements of biological fluids, but is not objective and is subject to error and uncertainty.

In 2007³¹⁴, it was determined by an international working group of experts on drug use and traffic safety that the best approach would be to use a validated *per se* limit, similar to the ones implemented in Norway and some states in the USA³¹⁵. This would mean setting a legal limit above which a driver is deemed impaired, such as the current legal blood alcohol limit of 0.08 ng/ml. This poses a challenge however because of the novel pharmacology of Δ^9 -THC. Since levels of Δ^9 -THC in biological fluid do not correlate temporally with impairment, it is challenging to try to determine what this limit might be. It is undesirable to apprehend people who are not impaired, but it is also very dangerous to allow drivers to get behind the wheel if it puts them and others at risk. For this reason, more work needs to be done to determine what a limit might be that will selectively target drivers who are still impaired by cannabis. The study presented here uses an *ad libitum* smoking protocol, where participants are told to smoke until they experience the high they normally feel. Because of this, varying doses are observed which can potentially be correlated to pharmacodynamic outcomes. This may aid in the determination of a *per se* limit which is as fair as possible by identifying doses at which most participants were impaired, accounting for inter-individual differences. Although the current analysis focused specifically on the dose, levels of Δ^9 -THC and metabolites in biological fluids were collected throughout the study, and future analyses of these measures will assist in the determination of an appropriate *per se* limit when the study has recruited its full sample size.

4.1 Driving Measures

In the analysis of driving measures, cannabis did not significantly affect simulated driving performance in the single-task driving assessment (Section 3.5). This finding was surprising, given that mean speed^{97, 248, 250, 252}, speed variability^{250, 280}, and road tracking^{95, 248, 250} have been previously reported to be sensitive to the effects of cannabis. However, as of this analysis the study had only recruited half of the target sample size, and this may be responsible for many of the non-significant results. Another possibility is that these aspects of driving are not affected in the paradigm used in this study. Several other studies have not found effects in these measures^{97, 252, 279}, so it is likely that experimental set up plays a role in the ability to detect impairment. The driving task used in this study was relatively simple, involving a two lane highway in a rural setting. Since it has been reported that more complicated tasks are more sensitive to the effects of cannabis^{249, 250, 253}, the driving task used in this study may have been too simple. However, there is speculation that cannabis effects may be more prominent on long, monotonous drives²⁵⁴. Findings of the current analysis support the literature indicating that more complex tasks are more sensitive to cannabis impairment, and do not support the speculation that long, monotonous drives may also be sensitive to cannabis intake.

Although the analysis did not indicate that cannabis significantly affected driver behaviour under single-task conditions, some main effects were significant. Overall mean speed under single-task conditions was significantly reduced in trials done after smoking for both groups (Table 6). This this could have been due to the fact that the first driving trial was the first time participants had encountered hazards. This may have caused all participants to be subsequently more cautious knowing that the driving trial done after smoking was likely to have hazards as well.

Straightaway SDLP and standard deviation of speed under single-task conditions both increased significantly after smoking in the both the active and placebo groups (Table 11). This could have been due to practice effects, where participants became more comfortable handling the car by the second assessed trial.

All participants had significantly reduced following distance behind a slow moving vehicle after smoking under single-task conditions (Table 16). Those in the placebo condition left less following distance at both baseline and after smoking. It is possible that differences between the placebo and active groups after smoking will become significant when the study reaches full recruitment, especially given the fact that the time*condition interaction had an alpha level of 0.08. Differences between baseline and after smoking in both placebo and active groups are probably attributable to participants becoming more comfortable with the driving scenarios and exhibiting less cautious behaviour.

Braking distance approaching a risk-taking hazard under single-task conditions was significantly increased in both placebo and active groups after smoking (Table 19). The differences in stopping distance before and after smoking could have resulted from more cautious driving behaviour after being exposed to the hazards in the first trial. The hazards in each scenario were designed so that they were not identical, to reduce the participants' ability to predict them during the scenarios. These slight differences between risk-taking hazards may also be responsible for the increase in stopping distance in the second scenario compared to the first. Participants in the placebo group left more braking distance compared to those in the active group at both time points assessed. This can likely be attributed to chance, since the difference was present at baseline as well as after smoking. It is also possible that cannabis effects will be detected when the full sample size is reached.

Under dual-task conditions, where participants were asked to count backwards by threes while driving, overall mean speed was found to decrease significantly in the active group after smoking (Table 8). Overall SDLP was higher in participants under the active condition after smoking compared to participants in the placebo condition, but this did not reach significance in the current analysis. However, future analyses may find this measure to be significantly affected. The fact that more driving measures were affected by cannabis intake in the dual-task condition compared to the single-task condition was not surprising, given the increased complexity of the task. The fact that more measures were not found to be significant was surprising, but could be due to the relatively simple driving scenario, in which it may have been easier for participants to

compensate even while multitasking. It is also possible that the relatively small sample size is masking driving outcomes which may become significant once the full sample size is recruited.

Under dual-task conditions, some driving measures were found to have significant main effects. Overall SDLP under dual-task conditions was significantly reduced after smoking (Table 8), especially in the placebo group. This likely indicates practice effects, which were not as visible in the group who received active cannabis.

Following distance behind a slow moving vehicle under dual-task conditions was significantly increased after smoking across both placebo and active groups (Table 17). This suggests that the counting task designed to distract participants made the driving task more difficult, resulting in more cautious driving behaviour.

Since the effects of cannabis have been demonstrated to be dose-dependent²⁴⁶, it was surprising that a significant correlation was not found between estimated dose of Δ^9 -THC and change in overall mean speed under dual-task conditions in participants assigned to the active condition (Table 10). However, since the smoking paradigm required participants to smoke enough so that they feel the high they normally feel, inter-individual differences in cannabis sensitivity may have been responsible for the absence of a significant correlation.

When examining changes in driving behaviours observed during simulated scenarios, one consideration is the generalizability or external validity of findings. Driving simulation does not take place in the real world. Simulator drivers do not face the risk of property damage costs, liability, legal prosecution, injury, or death that is associated with actual unsafe roadway behaviour. Therefore, it is possible that participants may have driven differently knowing there was no real danger associated with risky driving or with having a collision. However, they may also have driven more carefully knowing that they were being observed. Nonetheless anecdotally, participants appeared to put great effort into avoiding collisions. The only exception to this was the one individual whose data was removed from analysis on the basis of deliberately trying to skew study results. This was immediately noticed by study personnel, and is the only case in the study where someone clearly did not behave in the simulator the way they would on a

real roadway. Data collected from this participant was subsequently omitted from the analysis. It is important to remember that the potential threat to external validity posed by simulator technology is outweighed by numerous benefits, including that driving simulation addresses many ethical concerns regarding safety, has been validated as being a good predictor of on-road outcomes, allows collection of objective measures that could not be taken in a real car, and allows consistency in roadway scenarios that would not otherwise be possible.

All driving simulations were set on a rural, two-lane highway, which may limit the generalizability of the results to city driving. However, it is likely that results from a rural setting will provide at least some insight into driving skills relevant to all roadway environments. Rural scenarios on a two-lane highway were chosen for three reasons. The first is that there has been some speculation that long, monotonous drives may be especially affected by cannabis consumption, by contributing to driver inattention²⁵⁴, although this was not observed in the current analysis. Secondly, the use of a road with a single lane in each direction ensured consistency in the primary measure of SDLP. Lane changing on a roadway with two lanes in each direction would have impacted calculation of the SDLP measure and potentially confounded its interpretation. Finally, simulator sickness (described in Section 1.3.5.2.3) is occasionally experienced by people when operating a driving simulator, and results from a mismatch between visual and vestibular cues²⁷⁰. When the study was being designed, the investigators were informed by personnel from Virage Simulations that simulator sickness is far more common in city driving scenarios, presumably because of the frequent stopping and turning. Because nausea and other feelings associated with simulator sickness can negatively impact driving, it was thought that a rural scenario would yield more accurate data. Furthermore, it was predicted that by using a rural highway scenario, fewer participants would have to withdraw from the study due to simulator sickness. This appears to have been the case so far; only two people reported an adverse reaction to simulated driving, and this was easily managed by turning on the car fan, providing water, and taking short breaks between scenarios.

It is difficult to determine the extent to which the simplicity of the driving scenarios used has been responsible for the lack of significant changes in driving behaviour observed thus far.

However, it is important to remember that the findings of this analysis do not indicate that most driving behaviours are unaffected by acute cannabis consumption. These findings only indicate that this type of driving task may not be as sensitive to cannabis impairment. This is an important consideration for future studies examining the effects of cannabis on driving.

4.2 Secondary Outcomes

When tests of cognitive performance and motor skills were analyzed, no significant three way interaction effects were found in performance on the CPT-X, HVLT-R, DSST, or grooved pegboard (Section 3.6). The fact that these results did not reach significance in the current analysis may be the result of the sample size being approximately half of the sample size estimated for sufficient power to detect cannabis effects.

There have been mixed findings in the literature on the effects of cannabis on isolated cognitive and motor skills. D'Souza et al³¹⁶ administered 2 mg of Δ^9 -THC intravenously over twenty minutes, and evaluated measures of sustained attention using the CPT approximately 65 minutes after dosing. They found significant increases in omissions, and near significant increases in commissions. This group also had the same findings in another study using a similar drug administration paradigm¹¹⁷. Ramaekers et al²⁶⁰ found that omission errors, commission errors, and reaction time all increased on a stop-signal task (similar to the CPT-X) after 250 or 500 $\mu\text{g/kg}$ of smoked Δ^9 -THC. In contrast, Hooker et al³¹⁷ found that attention, measured using the digit span task and the Paced Auditory Serial Attention Task (PASAT), was not affected by acute consumption of cigarettes containing 1.2% Δ^9 -THC in moderate cannabis users aged 19 to 26 years. Wilson et al³¹⁸ failed to observe significant changes in CPT performance after the administration of 1.75% or 3.55% smoked Δ^9 -THC. Weil et al³¹⁹ did not observe changes in CPT performance after 4.5 mg or 18 mg of smoked Δ^9 -THC. In this interim analysis, significant changes in CPT performance were not found (Tables 23 – 26), which would seem to support the

work done by Hooker et al³¹⁷, Wilson et al³¹⁸, and Weil et al³¹⁹. However, significant differences may be found when the study is fully powered.

Both commission and omission errors on the CPT-X increased after smoking in all participants (Table 23). This may have been due to fluctuations in circadian rhythms throughout the day. It also may have been partially attributable to the fact that the testing day lasted several hours and involved many assessments, which may have caused participants to be less focused by the time the post-smoking CPT-X administration was done. There were also significant main effects of error type, indicating that commission errors were much more common than omission errors. This indicates that participants generally prioritized speed over accuracy.

This study used the HVLT-R as a measure of immediate and delayed free recall. D'Souza et al found that both immediate and delayed free recall measured by the HVLT-R was impaired after 2 mg³¹⁶, 2.5 mg¹¹⁷, and 5 mg¹¹⁷ of Δ^9 -THC administered intravenously. However, other studies have not observed this effect. Chait and Perry²⁵³ found no differences between participants in the active and placebo conditions on a free recall task performed one hour after two administrations of smoked Δ^9 -THC, in which participants followed a paced smoking protocol for five minutes. Weinstein and colleagues²⁵⁸ also did not observe an effect of cannabis on free recall performance following intravenous administration of 13 mg or 17 mg Δ^9 -THC. An effect could not be detected in this interim analysis (Table 27). When the study is fully powered, an analysis of the full sample size will allow more concrete conclusions regarding HVLT-R performance after acute cannabis consumption.

Performance on the DSST has been previously reported to be impaired by cannabis intake. Chait and Perry²⁵³ found that participants who smoked active cannabis had a lower percent of correct responses compared to placebo controls one hour after two paced five-minute smoking sessions spaced two hours apart. Heishman et al³²⁰ found that the number of correct and attempted responses was reduced after eight or sixteen puffs of a cigarette containing 3.55% Δ^9 -THC compared to placebo. In contrast, Wilson et al³¹⁸ found that neither 1.75% nor 3.55% smoked Δ^9 -THC resulted in significant changes in DSST performance compared to placebo. There is

some evidence indicating that cannabis use history may play a role in the acute effects of cannabis on DSST performance. Weil et al³¹⁹ found that cannabis naïve subjects had significant performance decrements 15 and 90 minutes following administration of 4.5 mg and 18 mg of smoked Δ^9 -THC. However, chronic cannabis users in the study were able to improve their scores slightly even after administration of 18 mg of Δ^9 -THC. This indicates that tolerance to cannabis effects may be able to reduce cannabis effects on DSST performance. Results of the study presented here did not indicate changes in DSST performance after smoking in the active condition compared to placebo (Tables 29 – 32), and so seem to be in agreement with the work by Wilson et al³¹⁸. Given the number of studies that have found impairment in this measure, this finding is somewhat surprising; however, differences in drug administration protocols and participant selection may play a role in this observation.

Although there was no difference in DSST performance between active and placebo groups, a main effect of trial type was found (Table 29). Since the two types of trials were those completed and those correct, this was expected as the number of correct trials would always be equal to or less than the number of completed trials.

Peters et al³²¹ found that motor skills as assessed by a finger oscillation test were unaffected by an oral dose of 0.2, 0.4, or 0.6 mg/kg Δ^9 -THC 3.5 hours after drug administration. Beautrais and Marks³²² used the Minnesota Rate of Manipulation – Block Turning Task to measure fine motor skills after smoking a cannabis cigarette containing 1.0% Δ^9 -THC, and did not observe any significant interaction effects between condition and time. Milstein et al³²³ also found no impairment in motor skills measured by either finger or toe tapping after the administration of 7.8 mg Δ^9 -THC by smoking. It was hypothesized that impairment would be detected on the grooved pegboard since it has been reported that single automatic motor abilities are more sensitive to cannabis effects³²⁴. However, the fact that the study findings presented here did not show significant differences in performance between subjects in the active and placebo conditions after smoking (Table 33) supports the findings of some other studies examining cannabis impairment.

The time taken to complete the grooved pegboard test was increased after smoking in both placebo and active groups (Table 33). This probably indicates a certain amount of fatigue after completing so many cognitive and driving tests throughout the day, and may also be reflective of circadian rhythm fluctuations throughout the day. In all participants at both time points, the non-dominant hand performed worse than the dominant hand, which was expected.

Reaction time in the study presented was measured using both the CPT-X and the DSST (Tables 25 and 31). The fact that neither of these measures has been significantly different between active and placebo groups after smoking is somewhat surprising, given that a slower reaction time after cannabis intake has been reported previously^{245, 248, 250, 251, 280}. Ramaekers et al²⁵⁶ did not observe a change in reaction time measured by a stop signal task in heavy cannabis users after administration of 400 µg/kg Δ^9 -THC by smoking. However, the fact that heavy cannabis users were being studied indicates that the lack of effects observed may be due to tolerance. The lack of effects in reaction time in the study presented here may be due to the level of task complexity. Drug impairment is more easily detected when tasks are complex^{249, 250, 253}, and it may be that the CPT-X and DSST are too straightforward for impairment to be evident.

The level of task complexity may be responsible for the fact that no isolated measures of cognition were found to be significant in this study. It has been reported that more complex tasks are especially sensitive to cannabis impairment^{249, 250, 253}. The tests used to measure cognitive skills in this study may have been sufficiently simple so that that impairment may not have been detected. Since aspects of cognition were tested one at a time, participants were able to focus completely on the task at hand. This may have made it possible for participants to compensate for their impairment by increasing their effort into completing the task. Compounding this, it is possible that a small degree of tolerance may have developed from weekly cannabis exposure in the population being studied. Jones and Stone³²⁵ found that tolerance occurred after only four days of 10 mg doses. The cannabis cigarettes used in the study were designed to be representative of average street values¹⁹, and contained approximately 94 mg Δ^9 -THC. If participants smoked this amount four days per week, they may have begun to develop some degree of tolerance to some of the impairing effects of cannabis. This may have made it possible

for them to compensate for cannabis impairment on relatively simple cognitive tests. This may be an important consideration for future studies seeking to elucidate the effects of cannabis on isolated cognitive and motor skills.

When mood and subjective drug effects were examined, several significant findings were noted. Subscales on the ARCI were not found to change significantly in the active group compared to placebo after drug administration (Table 35). This finding was surprising, given that the ARCI has been previously demonstrated to be sensitive to the effects of cannabis. Statistically significant increases in sedation and decreases in stimulation have been noted in prior literature^{262, 326, 327}. It has also been reported that smoked cannabis has neither effect²⁵³, and the study presented here seems to support this finding. Previous studies have been mixed with respect to euphoric effects, with some finding a significant increase³²⁷, and some failing to observe this^{262, 328, 329}. The fact that the current study did not find significant changes in ARCI subscales after smoking in the active condition compared to placebo may have been related to when the questionnaire was administered relative to smoking. For example, Lukas et al³³⁰ found that euphoria occurred in several short episodes during the first fifteen minutes after smoking cannabis. In this study, the ARCI was administered at one hour post-dose, at which point euphoric effects may have dissipated based on the findings of Lukas et al³³⁰. Although it was expected that the ARCI subscale scores would change with cannabis administration, the fact that this was not observed does not undermine the validity of the drug administration paradigm. A contributing factor to the lack of significant effects observed on the ARCI may have been the clinical setting of the study, which could have influenced levels of euphoria by making participants feel less relaxed than they would in normal smoking situations. The ARCI was also administered alongside other cognitive tests. The fact that participants had a task to focus on immediately before completing the ARCI may have diminished any sedative effects of cannabis. The lack of observed effects may also have been due to the fact that a specific subscale for cannabis was not used. Although cannabis effects often show up on the standard subscales used here, one has been specifically developed to detect marijuana effects³³¹, and this scale may have been more successful at detecting impairment by cannabis. These factors should be considered for future studies seeking to measure the subjective drug effects of cannabis.

ARCI subscale scores generally increased in placebo and active groups after smoking as compared to baseline (Table 35). Only the BZ group score dropped slightly, while AMPH, MBG, LSD, PCAG, euphoria, and sedation all increased after smoking. This finding was somewhat unexpected, since responses that increase scores in some subscales decrease scores in others, but it is possible that participants responded “true” to more statements after smoking which would have led to a general increase in subscale scores. This could possibly be attributed to circadian rhythm fluctuations throughout the day, and the large number of tests done over the several hours prior to the second ARCI administration. The effect of subscale was very significant, meaning that changes in scores were different on the different subscale. This was expected, since each subscale measures a different type of drug effect.

Subscales on the POMS did not show significant interaction effects (Table 37). This finding was unexpected. It has been reported that the POMS confusion subscale is significantly increased in participants who receive cannabis³³². Mathew et al³³³ found that in experienced users who smoked at least ten joints per week, the tension/anxiety subscale score was reduced, and a significant increase in the confusion score was noted after smoking a cannabis cigarette containing 2.2% Δ^9 -THC. The study did not note any changes in anger, fatigue, depression, or vigor in experienced users. However, these findings were different for cannabis naïve users indicating that history with the drug influences changes in mood state after smoking. It is possible that in cannabis users who smoke one to four days per week, significant changes in mood after cannabis consumption do not occur. Heavier users may experience withdrawal effects such as anxiety which may be relieved by smoking, whereas naïve users may feel anxiety associated with being unaccustomed to the feeling of being high. Another possibility is that the clinical setting used in the study reduced any relaxation or euphoria participants normally experience when smoking cannabis. The fact that subscale scores were not found to change significantly after smoking may be attributed to a variety of factors, all of which should be considered for future studies examining mood changes with acute cannabis consumption.

POMS subscale scores were significantly different from each other in both active and placebo groups prior to and after smoking (Table 37). This was expected, since each subscale measures a

different aspect of mood. The effect of time*subscale was also significant, indicating that for all participants, subscale scores were significantly different after smoking. This could possibly be related to the relatively intense testing procedures on drug administration day, and fluctuations in circadian rhythms throughout the day.

Changes to VAS subscale scores after smoking were found to be significantly different between placebo and active groups (Table 39). Although scores increased slightly in the placebo group after smoking, participants in the active condition reported near-maximum scores for most subscales. VASs are commonly used to detect cannabis impairment, and scores on these scales are reliably reported to increase after cannabis consumption¹⁰⁶. Drug liking is an especially important subscale, since it is indicative of abuse liability³³⁴. The very significant increase in VAS subscale scores in the active group compared to the placebo after smoking is consistent with previous literature, and indicates that participants who received active cannabis were feeling the effects while undergoing testing day procedures. This demonstrates that the drug administration paradigm employed in this study was successful, and would be a viable option for future studies. It also demonstrates that the lack of significant effects on ARCI and POMS subscales do not result from a lack of cannabis effects, and are instead attributable to other factors.

The significant correlation between VAS drug liking and drug effect subscales (Figures 6 and 7) was expected, especially given the high scores on the good effects subscale, and the relatively low scores observed on the bad effects subscale. This indicates that the majority of the drug effect being experienced was enjoyable for participants, and that the stronger the effects were, the more participants liked them. Since the drug liking subscale is a good predictor of abuse liability³³⁴, this is especially interesting to note. It implies that the more heavily someone uses cannabis, the more likely they may be to take it again. Although this observation is not directly relevant to the effects of cannabis on driving behaviour, it may provide some insight into the factors that motivate people to use cannabis. The fact that this relationship was found to be significant for participants in the placebo condition as well indicates that this relationship depends as much on perceived drug effects as it does on actual dose.

The significant findings on VAS subscale scores highlight a limitation of all double-blind studies using psychoactive substances, which is that participants are often able to correctly guess which condition they were in. Although there is no way to completely avoid this issue, several factors reduced the impact on the study. Participants would only have been likely to be able to guess their condition after smoking. Because of this, it is likely that data collected at baseline measures were not affected by a participant's condition assignment, limiting the extent to which data can be confounded. Furthermore, the smoking instructions inform participants that the cannabis provided may be stronger or less strong than what they normally smoke. This reminder helped to create some uncertainty for participants about whether they received the placebo, or the cannabis provided was less strong than that to which they are accustomed. It is also possible that those in the active group may actually be accustomed to smoking more potent cannabis, and may have believed that they were in the placebo group. Because smoking is done *ad libitum*, participants may have also attributed a lack of effect to simply not consuming enough of the cigarette. Participants in the active group may also have smoked too little, and believed that they received placebo. As with any placebo control, placebo effects do occur, and this was seen on several of the VAS measures which had non-zero values for participants in the placebo group, especially immediately after smoking. This speculation is supported by the fact that study personnel received several requests from participants at the end of the five sessions to know which group they were actually in, indicating that there was at least some uncertainty among participants about their condition. A way to further reduce this effect for future studies would be to inform participants that they will be getting either a high or very low dose of the substance, so that all participants expect at least some effects. Although placebo conditions in such studies have negligible amounts of the psychoactive substance in terms of producing impairment, the trace amounts that are present are enough to reasonably refer to this as a very low dose.

In the analysis of the change in cigarette weight, it was found that there was no significant difference between active and placebo groups in terms of the amount they smoked (Table 41). This indicates that participants may not have been able to guess to their condition at the time of smoking. The study was designed such that there should have been no difference in the way the active and placebo cigarettes taste, look, feel, or smell, and this finding indicates that this was the

case. It has been reported by Chait et al³³⁵ that participants are able to visually distinguish active from placebo cigarettes. This effect is somewhat mitigated by assigning different people to the active and placebo groups, rather than using a within-subjects design. The results of the study presented did not find significant differences between the two groups in terms of the amount smoked, suggesting that the between-subjects condition assignment was sufficient to overcome participants' ability to guess their condition while smoking.

Statistically significant correlations were also found between the estimated dose of Δ^9 -THC, based on the change in cigarette weight before and after smoking, and the peak VAS drug effect and drug liking scores in participants assigned to the active condition (Table 43). Regression analyses revealed significant linear relationships for both drug liking and drug effect subscales, and this was unchanged when BMI was included as a covariate (Table 46). Significant relationships between the amount of cigarette smoked and peak VAS subscale scores for drug effect and drug liking were not observed for participants assigned to the placebo condition (Table 44). This indicates that placebo effects were not “dose-dependent”, an observation which may result from the fact that the smoking instructions remind participants that the potency of the cannabis they are smoking may be different from the cannabis they are used to. The uncertainty introduced by this may have reduced the relationship between heightened expectations and amount smoked.

In examining the effects of cannabis on physiological measures, significant interaction effects between condition and time were only observed for changes in heart rate; participants who received active cannabis had an increased heart rate after smoking compared to those who received placebo (Table 47). An increase in heart rate has been described as being the most reliable physiological sign of acute cannabis intoxication³²⁰, so this finding was not surprising and indicates that the effects observed in this study align with those in previous studies. The fact that an objective, physiological outcome of cannabis intake was measureable in this study supports the appropriateness of the drug administration paradigm used.

Analysis of blood pressure readings throughout the day did not yield significant interaction effects, but two significant main effects were noted (Table 49). Systolic and diastolic blood

pressure values were significantly different from each other as expected. There was also a significant interaction between time and blood pressure, with fluctuations both up and down throughout the day. This could have been the result of blood pressure changes with circadian rhythm as the day progressed.

4.3 Challenges and Limitations

Although the findings of this study are very important for understanding the nature of cannabis impairment on a driving task, there are some limitations. A limitation of the study as it is presented here is that it is based on an interim analysis. This resulted in the sample size used for this analysis being smaller than that initially calculated to detect an effect of this nature, reducing the power. As data collection continues and the study is more strongly powered, many of the results of the analyses may become statistically significant.

One limitation relates to the way driving scenarios were designed. Each scenario included a risk taking hazard, where the virtual roadway was partially obstructed and there was an oncoming vehicle. The measure taken from this is braking distance, which is the distance from the hazard where the participant applies their foot to the brake pedal. While this was a good approximation of cautious driving behaviour, it does not account for participants who may simply take their foot off the gas and let the car slow down on its own for a few seconds. For the design of scenarios in the future, it may be prudent to also measure the distance at which the participant removes their foot from the acceleration before applying the brake.

Another potential limitation involves the external validity of driving simulation technology. As simulated driving does not take place in the real world, simulator drivers do not face the risk of serious consequences associated with actual unsafe roadway behaviour. It is possible that participants may have driven differently under these conditions; however, the use of a driving simulator has numerous benefits, and the advantages gained in safety, consistency, and objective data collection outweigh the potential alterations in driving behaviour^{274, 275, 276, 277}.

The fact that driving scenarios were set on a rural, two-lane highway may have limited the generalizability of results to city driving. However, changes in driving behaviour observed in this setting may still inform our expectations in other roadway environments. This setting was chosen to minimize potential simulator sickness (described in Section 1.3.5.2.3) and to ensure an accurate measure of SDLP, necessitating a single lane in each direction. The rural, two-lane highway also allowed this study to test the hypothesis that long, monotonous drives may be especially affected by cannabis intake²⁵³, although this hypothesis was not supported by the current data.

As with any double-blinded study using a drug which has psychoactive properties, maintaining the blind posed many challenges. Several measures were implemented to mitigate this effect. Because multiple personnel were available to run participants, tasks were divided among them strategically. Tasks that could potentially provide clues as to which condition the participant was assigned, such as administering the VAS or reading urine results, were carried out by one team member, while tasks requiring full objectivity, such as interpreting qualitative components of simulated driver behaviour were carried out by another team member. The fact that many of the measures were objectively collected, either by the computers or by the driving simulator, helped to maintain objectivity. Furthermore, participants were asked not to disclose what condition they believed they were in to any of the study personnel in order to assist with blinding. Since the data presented in this thesis were part of an interim analysis which required breaking the blind, one study personnel who does not interact with the participants was nominated to receive the unblinding code. This team member entered laboratory data and ran all statistical analyses received as SPSS syntax. Statistical output was sent back without any indication of the designated condition for each participant.

A limitation inherent to research conducted using psychoactive substances is that the participants often correctly guess the condition to which they were assigned. However, several measures in this study were in place to reduce this effect. The fact that participants were blinded when baseline measures were taken reduced their ability to deliberately alter the data they provided. Furthermore, the cannabis provided in this study may have had a different potency from the

cannabis participants were accustomed to. Instructions reminding participants of this fact may contribute to participants being more uncertain about their condition assignment. The *ad libitum* smoking procedure may also have resulted in participants being less accurate in guessing their assigned condition.

An *ad libitum* smoking procedure has limitations associated with it as well. Participants may generally experience different levels of cannabis high, and some smokers included in the study may normally smoke very moderate amounts. This may mean that some participants are below a level where they would be considered impaired. However, since the effects of cannabis on driving occur in the real world where this variability exists, the *ad libitum* smoking procedure is more representative of actual impairment experienced by regular cannabis users.

In the case that participants may have felt that they knew their condition assignment, there are various factors which made them less likely to intentionally influence study results. Since the study requires a significant amount of time, personnel are able to build a rapport with participants. Most participants seemed to be fairly honest with study personnel; however, one participant was removed from the analysis based on their conduct after smoking. It became apparent to study personnel that this individual thought they had received the placebo, and was intentionally trying to drive as poorly as possible to reduce any effects seen in the study. This participant had also previously mentioned that they were excited to participate because they wanted to “prove” that smoking marijuana and driving was a safe activity. The fact that this only happened once, and that study personnel became aware of it supports the idea that the measures put in place to prevent this were largely successful. For future studies, a way to further reduce this effect is to tell participants that they may receive a high dose or a very low dose, rather than explicitly telling them that the very low dose is low enough to be considered a placebo.

One possibility that cannot be completely discounted is that there may be some learning occurring throughout the study. Participants were performing tests that were new to them, and driving on a simulator with which they had not had prior experience. In order to minimize potential practice effects, participants were given the opportunity to practice all procedures during session two, before data collection began. Furthermore, two practice driving scenarios

were performed on drug administration day immediately prior to baseline driving measures being collected. This amount of practice seems to have been adequate as everyone appeared to be performing at an acceptable level at the start of data collection; however, it must be acknowledged that variation in operator skill may have resulted in differential learning effects. Although additional opportunities for practice with the simulator may have further reduced the potential for learning effects, this would have necessitated more study sessions. Since the time commitment required was already the primary reason people lost interest in the study (see Table 3), this would likely have made recruitment even more difficult, and attrition more likely. Furthermore, those who participated may have been a less varied group, since the time commitment would have likely required that they be unemployed and not in school at the time of their participation. Although some learning may have occurred throughout the study, any resulting error would have been randomly distributed, and probably does not represent a large confound.

4.4 Conclusions

Overall, the preliminary findings of this study support the hypothesis that the acute consumption of smoked cannabis had a potentially detrimental effect on driving behaviour of young adults who use cannabis weekly. This was especially apparent in driving measures collected under dual-task conditions, where speed was significantly reduced in the group that received active cannabis. This may make driving activities like keeping up with traffic or merging onto the highway difficult for individuals driving under the influence of cannabis. Effects on the SDLP may achieve statistical significance when data is collected from the full sample.

The findings of this interim analysis highlight some of the difficulties associated with legislating driving under the influence of cannabis. The measures that were found to be significant in this study would be difficult to translate into practical means to detect impairment. Subscales on the VAS were very significant, but these require self-report and are thus not useful for legislation. An increase in heart rate is a reliable, objective, physiological measure of impairment, but

requires baseline readings to make meaningful comparisons. As well, elevated heart rate can be caused by other factors besides cannabis consumption. While a reduction in speed is not a reliable way to detect cannabis-impaired drivers on its own, it may be a useful consideration. For instance, police officers may be able to look for drivers travelling well below the speed limit as a guide for when to administer further roadside tests or collect biological samples.

It is also informative to note that drivers may be at the most risk when driving tasks are more complicated. While alcohol impairment generally results in a single-driver collision³³⁶, crashes that occur when a driver is under the influence of cannabis may be more likely on a busy road with other cars and pedestrians. Focusing law enforcement on roadways such as these may do more to reduce collisions associated with cannabis consumption than directing attention to all roadways equally. However, further research is needed to determine how frequently cannabis-impaired drivers use busy roadways to examine this possibility further.

It is possible that when the study reaches its full sample size, other driving behaviours will be found to be significantly altered by acute cannabis intake. If this is the case, it may be possible to identify a profile of driving behaviours associated with cannabis. While any one behaviour alone may not reliably predict cannabis impairment, behaviours taken together could be found to be strongly associated with driving under the influence of cannabis. Despite the challenges associated with enforcing policies to combat cannabis impaired driving, more research to bridge knowledge gaps and suggest future initiatives may eventually reduce collisions associated with this behaviour. The study presented here contributes to this body of research, and suggests areas where more work needs to be done.

4.5 Future Directions

An important extension to the present study is currently underway to evaluate driving impairment caused by alcohol using the same protocol described here. This will aid in the interpretation of findings when the current study is completed by demonstrating that the protocol

being used is well equipped to detect impairment, and providing the opportunity to compare cannabis effects with those of a drug that has more well-known effects on driving performance.

Although it is hoped that the results of this study will make important contributions to the current body of literature on this issue, there are still questions about impaired driving that will need to be answered by future studies. More research will need to focus on specific age groups and groups with a limited range of smoking frequencies to explore some of the factors that may be causing variation in the literature on cannabis impaired driving. It will be important to examine heavy cannabis smokers, those who use for therapeutic purposes, and those who smoke less often than once per week. Each of these groups may display a different tolerance to cannabis, and may show different levels of impairment as a result. Furthermore, cannabis is often not the only drug detected in impaired drivers, and may have additive or synergistic effects with other drugs^{96, 97, 99, 100}. It will be important to examine the effects of cannabis in combination with the most commonly co-administered drugs (such as alcohol) to see if driving performance is differently affected. With all of these studies, the potency of the cannabis used should be taken into account and be representative of the potency of cannabis routinely confiscated by police. This will make study findings more applicable to real-world impairment.

Future research should also explore the effects of synthetic Δ^9 -THC on driving as these effects may be different from natural cannabis. Exploration of different routes of administration for cannabis and synthetic cannabinoids may also yield different effects on driving, since the pharmacokinetics would be different than those of smoking. These areas of research could also help in determining appropriate *per se* limits and may contribute to an understanding of how best to measure impairment.

The current interim analysis of about half of the target sample size has so far only indicated that mean speed under dual-task conditions was significantly reduced, and was unable to identify changes in other driving behaviours. Because of this, it was not possible to identify a profile of driving behaviours that are highly predictive of cannabis intake. However, in future studies or when this study has recruited its full sample size and is fully powered, identifying a set of

behaviours that indicate cannabis impairment would be very useful for identifying drivers who are under the acute influence of cannabis and reducing cannabis-related collisions.

Further work will also need to be done in implementing these findings into policy. A current barrier to this is a lack of objective measure (e.g., a metabolite level in biological fluids, a meaningful physiological measure, etc.) which will correlate with impairment by cannabis. If such a measure could be identified through research, it would allow laws regarding cannabis use and driving to be implemented fairly. It could also allow the determination of a *per se* limit for cannabis use, similar to that currently implemented for alcohol.

Gender differences with respect to cannabis effects on driving were not analyzed, since the two-to-one randomization schedule and the fact that more males were enrolled left only six females in the placebo group. However, when more participants are recruited, it will be important to explore this. Although this will likely not contribute to policy, it will be important for the design and interpretation of future studies examining cannabis impairment of driving behaviour.

One possible interpretation of this data is that in addition to having decreased driving abilities, subjects who are under the acute influence of a dose of cannabis behave in such a way that they become less predictable to other drivers. This may contribute to an increase in collision risk. This speculation could be more thoroughly explored with future studies examining the behaviour of other drivers when confronted with driving behaviours typical of a driver who is under the influence of cannabis. This hypothesis could also be examined by studies evaluating the types of collisions most often occurring when drivers are under the influence of cannabis. If it is found that these collisions mainly involve other cars, it would support this hypothesis.

Further research will need to determine how cannabis impairs driving in other populations of cannabis users, especially medical cannabis users. It will also be important to examine the effects of cannabis in combination with other drugs such as alcohol, since cannabis is often used with other psychoactive substances. Finally, it will be important to explore how other drivers respond to driving behaviours typical of drivers under the influence of cannabis.

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Appendix A: Telephone Pre-Screening Script and Cover Page

SCREEN ID:	Name:
Date of first contact:	
Telephone #:	Okay to leave a message? ☐ Yes ☐ No
Okay to contact via email? ☐ Yes ☐ No	
Email:	
Address:	
How did you find out about this study?	
May we pass on your contact information to researchers conducting other studies at CAMH for which you may be eligible? ☐ Yes ☐ No	

Comments:

Caller Contact Log		
Date/Time	Phone/Email/Other	Comments

Form Completed by (print): _____ Initials: _____

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.

Do you smoke Cannabis?

- ☐ No (ineligible)
☐ Yes

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

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
☐ Yes

Do you live in an area which is TTC accessible?

- ☐ No
☐ 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? ☐ Yes ☐ No

Assessment Date and Time: _____

Additional Notes:

Appendix B: Consent Form

STUDY INFORMATION and INFORMED CONSENT

Name of Study: Acute and residual effects of cannabis on young drivers' performance of driving-related skills.

Responsible Investigators: Robert E. Mann 416-535-8501 ext. 34496
Bernard Le Foll 416-535-8501 ext. 34772
Bruna Brands 416-535-8501 ext. 36860

This study will take place at the Centre for Addiction and Mental Health at 33 Russell St., Toronto, Ontario. One-hundred forty-two subjects will take part in this study. This study is funded by the Canadian Institutes of Health Research (CIHR).

Please take the time to read this information sheet carefully and ask any questions that you may have before deciding whether you wish to participate in this study.

Study Drug Administration

During the course of this study you will be asked to smoke a cannabis or placebo cigarette. A placebo is an inactive substance that is made to look and taste like the real substance. The placebo cannabis does not contain the active drug THC. You will have a 2-to-1 chance of receiving a cannabis or placebo cigarette. Please inform the medical doctor of any medications or natural health products that you are taking. If you are a woman with the ability to have children, you will be required to use an approved method of birth control for the duration of the study. These methods include abstinence, hormonal contraceptives, and barrier devices or having a partner who has had a vasectomy or is using male contraceptives. Pregnancy testing after sessions 1 and 2 must be negative in order to proceed with the study. If you are eligible for the study you will also be asked not to drive to CAMH on sessions 3, 4, and 5. You will be provided with a taxi chit or TTC tokens.

Purpose

The purpose of this study is to examine driving behaviour under the influence of cannabis using a driving simulator system.

Study Procedures

The study will involve five (5) sessions with different procedures required for each study day. Completion of all 5 sessions will require a total of about 17 hours of your time.

If you choose to withdraw from the study at any time or you are withdrawn from the study by us, you must let study staff know if you wish to have any data, blood or urine samples you have provided destroyed.

You will be asked to refrain from personal use of cannabis, alcohol or other drugs not required for medical reasons, outside of the laboratory, for 48 hours prior to Session 2, and until your participation in this study is completed.

Session 1 (Eligibility Screening Day): On the screening day you will undergo an assessment to determine whether you are eligible to participate in the study. You will undergo a physical exam by a medical doctor, and you will be asked for information about

- your past and present drug use (including when you last used cannabis)
- current medications
- psychiatric symptoms and history

As well you will be asked to give some samples of blood (total about 15 mL or 3 teaspoons) for biochemistry and haematology, and urine for drug screening. If you are female, you will be asked to also provide a urine sample for pregnancy testing. The blood sample(s) will be drawn by a needle from a vein in your arm. You will be asked to submit to a breathalyzer test for alcohol, and vital signs will be taken (e.g. blood pressure, heart rate).

Completion of procedures will take about 2 ½ hours of your time.

Session 2 (Practice Day):

You will be asked to provide a urine sample to confirm your ongoing eligibility.

You will be asked information about demographics (age, education, occupation), and to complete a series of questionnaires designed to assess driving behaviour and individual difference as well as mood and cognitive functioning (e.g. memory and attention).

You will be given two 10-minute driving simulator practice sessions in the CAMH driving laboratory. During one of these sessions, you will be asked to complete a counting task, and if you agree an audio recording of your voice will be taken.

Please initial one of the two following alternatives:

I agree to have my voice recorded _____
 I do not agree to have my voice recorded _____

Completion of procedures will take about 2 ½ hours of your time.

Session 3 (Testing Day 1):

You will return to CAMH the following morning and be asked to give blood and urine samples for drug screening, to submit to a breathalyzer test for alcohol, and vital signs will be taken. You will have a small tube inserted into your vein by a nurse (intravenous catheter) so that blood can be taken throughout the day. The blood samples will be analyzed to determine the quantity of THC (the active drug found in cannabis) in your blood. Blood samples and vital signs will be taken before smoking, and 5 minutes after smoking the cannabis or placebo cigarette, then 15, 30 minutes, and hourly thereafter. After the 6th hour measurement, the intravenous catheter will be removed. A total

of 10 blood samples will be collected of 10mL (or 2 teaspoons) each, for a total of 100 mL (or less than ½ cup) for the whole day.

If you agree to participate in the supplemental study on genetic influences, an additional sample of blood (about 20mL or 4 teaspoons) will be collected for these analyses at the time other blood is drawn.

Before smoking, you will be given a 5-minute practice driving simulator session followed by two 10-minute driving simulation testing sessions in the CAMH driving laboratory, where your driving will be recorded by the simulator system.

You will then be given a cannabis or placebo cigarette and will be asked to smoke it in the CAMH smoking laboratory.

You will be asked to complete a questionnaire to measure drug effects as well as mood and cognitive functioning (e.g. memory and attention).

After smoking, you will be given two 10-minute driving simulation testing sessions in the CAMH driving laboratory, where your driving will be recorded by the simulator system. During one of these sessions, you will be asked to complete a counting task, and if you agree, an audio recording of your voice will be taken.

You will be asked again to complete a questionnaire to measure drug effects as well as mood and cognitive functioning (e.g. memory and attention).

Completion of procedures will require approximately 8 hours of your time.

Session 4 (Testing Day 2): You will return to the lab the following morning to complete the 24 hour measurements.

You will be asked to give blood (about 10mL or 2 teaspoons) and urine samples for drug screening and to measure THC. The blood sample will be drawn by a needle from a vein in your arm. You will be asked to submit to a breathalyzer test for alcohol, and vital signs will be taken.

You will be asked to complete a questionnaire to measure drug effects as well as mood and cognitive functioning (e.g. memory and attention).

You will be given two 10-minute driving simulation testing sessions in the CAMH driving laboratory, when your driving will be recorded by the simulator system. During one of these sessions, you will be asked to complete a counting task, and if you agree an audio recording of your voice will be taken.

Completion of procedures will require approximately 2 hours of your time.

Session 5 (Testing Day 3): You will return to CAMH the following morning to complete the 48 hour measurements.

You will be asked to give blood (about 10mL or 2 teaspoons) and urine samples for drug screening and to measure THC. The blood sample will be drawn by a needle from a vein in your arm. You will be asked to submit to a breathalyzer test for alcohol, and vital signs will be taken.

You will be asked to complete a questionnaire to measure drug effects as well as mood and cognitive functioning (e.g. memory and attention).

You will be given two 10-minute driving simulation testing sessions in the CAMH driving laboratory, when your driving will be recorded by the simulator system. During one of these sessions, you will be asked to complete a counting task, and if you agree an audio recording of your voice will be taken.

Completion of procedures will require approximately 2 hours of your time.

Ongoing Eligibility

To participate in this study you must be between 19 and 25 years old, must have held a valid Ontario class G2 or G driver's licence (or the equivalent from another province, state, or country) for at least twelve months, and must use cannabis between one and four times per week.

You must not have a history of substance dependence or be currently dependent on cannabis or other substances of abuse.

You must not be a regular user of medications that affect brain function (e.g., antidepressants, benzodiazepines, stimulants).

If you have a psychiatric disorder needing treatment, or have a family history of schizophrenia you will be excluded from the study and will be referred to the psychiatric evaluation centre.

You will be excluded from the study at any point if you test positive for alcohol based on a breathalyzer test or if your laboratory results after the screening day indicate that you have used a substance that affects brain function other than cannabis.

You will be excluded from the study if you are pregnant, trying to become pregnant, or currently breastfeeding.

Confidentiality

You have been invited to participate in this study because you are a cannabis user. Although we have received permission from Health Canada to use cannabis in this study, cannabis remains an illegal substance. Your identity will be kept confidential to the full extent provided by law. In addition, neither your name nor any other personal identifier will be used in any reports or publications arising from this study. The data produced from this study will be stored in a secure, locked location and on anonymized datasets on a password-protected computer file. Only members of the research

team will have access to the data. Following completion of the research study the data will be kept as long as required by CAMH and then destroyed. Published study results will not reveal your identity.

As part of continuing review of the research, your study records may also be assessed on behalf of the Research Ethics Board and, if applicable, by the Health Canada Therapeutics Products Programme. A person from the research ethics team may contact you (if your contact information is available) to ask you questions about the research study and your consent to participate. The person assessing your file or contacting you must maintain your confidentiality to the extent permitted by law. Furthermore, as part of the Research Services Quality Assurance Program, this study may be monitored and/or audited by a member of the Quality Assurance Team. Your research records and CAMH records may be reviewed during which confidentiality will be maintained as per CAMH policies and extent permitted by law.

If you agree, you will be registered in a centralized, secure database used to connect people interested in participating in studies with CAMH researchers. The CAMH Research Registry is used to help researchers identify individuals who may be interested in participating in approved research studies. By sharing your experiences with researchers, we will gain new insights into issues that may be important to you and to others who share similar experiences. If you choose to join, you will be asked to complete a separate informed consent form.

- ☐ I am interested
- ☐ I am not interested

You can also authorize us to keep your contact information in our lab database and contact you regarding the participation in future studies. If you consent to participate in another study, to avoid repeating the same assessments and reduce your time commitment, we may share the results of common assessments completed within the past 3 months. If you decline sharing information, you can still consent to participate in this study.

- ☐ I agree
- ☐ I decline

Compensation

You will receive \$200 for completing the study. If you decide not to continue in the study or if the study physician withdraws you from the study you will receive up to \$25 for completing each of sessions 1 and 2, and up to \$50 for completing each of sessions 3, 4, and 5.

Risks

Although we do not foresee serious risks or discomfort arising from your participation, some minor risks that may occur are:

- An adverse reaction to the cannabis, which can include commonly reported reactions such as increased heart rate, decreased blood pressure, drowsiness, and/or increased anxiety.
- Coughing and/or throat irritation due to smoking cannabis.
- Small risk of bruising at the site where blood is drawn.
- Small risk of infection at the site where blood is drawn.
- Some participants may find driving the simulator system to be frustrating.
- Some subjects may feel strange or funny while driving the simulator system.

Epidemiological studies have linked cannabis use with other mental health issues such as psychosis and schizophrenia. There is a potential risk that exposure to cannabis would trigger some mental health problems. Those conditions could require long term treatment. For this reason, we are recruiting only participants that are already using cannabis and we are excluding participants that have schizophrenia or for whom there is a high risk due to family history. Schizophrenia and psychosis is a chronic condition requiring long term treatment.

Benefits

There are no direct benefits to you for participation in this study. However, some participants may find driving the simulator system to be fun or exciting. Also, there may be societal benefits if results of this study aid in reduction of collisions.

Voluntary Participation

Your participation in this study is voluntary. You may choose to withdraw from the study at any time. In addition, the investigators or their staff responsible for this study may, at their discretion, end your participation at any time. This could be due to medical reasons or for not following study procedures. If your participation ends early for whatever reason, you will be compensated as described above. Your choice to withdraw or your dismissal by us will not affect any treatment needs that you might have at the Centre for Addiction and Mental Health now or in the future. If you choose to withdraw from the study or you are withdrawn from the study by us, you must make it known to study research staff if you wish to have any data, blood or urine samples you have provided destroyed.

Supplemental Participation in Study of Genetic Influences on Cannabis Effects

We are also asking if you would agree to provide an additional 2 samples of blood (about 20 mL or 4 teaspoons) on the Screening Day for an investigation of how your genes can affect your response to cannabis, including how genes may influence your performance on the driving simulator task and other measures we will collect. You may choose to withdraw from this supplemental study at any time. If you choose to withdraw from this study or you are withdrawn from the study by us, you must make it known to study research staff if you wish to have the data and blood sample you have provided for this purpose destroyed. If you agree to participate in this substudy, please indicate your approval below, and also complete the additional consent form for the Supplemental Study of Genetic Influences on Cannabis Effects. Otherwise, please indicate that you do not want to participate in this supplemental study and the additional sample of blood will not be collected.

Please initial one of the two following alternatives:

I agree to participate in the supplemental study of genetic influences on cannabis effects. _____

I do not wish to participate in this supplemental study. _____

New Information

If any changes are made to the study or new information becomes available, you will be informed in a timely fashion.

Additional Information

A description of this clinical trial will be available on <http://www.clinicaltrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

If you have questions about the study that are not answered in these Information Sheets, please ask us. In addition, if you have questions in the future you may contact the study investigators at these telephone numbers: Robert E. Mann 416-535-8501 ext. 34496; Bernard Le Foll 416-535-8501 ext. 34772; Bruna Brands 416-535-8501 ext. 36860. Dr. Pdraig Darby, Chair, Research Ethics Board, Centre for Addiction and Mental Health, may be contacted by research subjects to discuss their rights. **Dr. Darby may be reached by telephone at 416-535-8501 ext. 36876.**

INFORMED CONSENT

I, _____, have read (or had read to me) the Information Sheet for the study named 'Acute and residual effects of cannabis on young drivers' performance of driving-related skills.' The purpose of this study is to examine driving behaviour under the influence of cannabis using a driving simulator system. My role in the study is as a research volunteer to help the investigators collect information on cannabis effects on driver behaviour by smoking a cannabis or placebo cigarette, acting as a driver, providing urine and blood samples, and completing some questionnaires. My questions, if any, have been answered to my satisfaction. By signing this consent form I do not waive any of my rights.

If I have any further questions I understand that I can contact the study investigators: Robert Mann 416-535-8501 ext. 34496; Bernard Le Foll 416-535-8501 ext. 34772; Bruna Brands 416-535-8501 ext. 36860. Dr. Pdraig Darby, Chair, Research Ethics Board, Centre for Addiction and Mental Health, may be contacted by research subjects to discuss their rights. **Dr. Darby may be reached by telephone at 416-535-8501 ext. 36876.**

I voluntarily consent to participate in this research study.

Research Volunteer:

Signature: _____

Date: _____

Name: _____
Please Print

Person Obtaining Consent:

Signature: _____

Date: _____

Name: _____
Please Print

I have been given a copy of this form to keep.

SUPPLEMENTAL INFORMED CONSENT – GENETIC INFLUENCES FOR THE CANNABIS AND DRIVING STUDY

I, _____, have read (or had read to me) the Information Sheet for the study named ‘Acute and residual effects of cannabis on young drivers’ performance of driving-related skills.’ The purpose of this study is to examine driving behaviour under the influence of cannabis using a driving simulator system. My role in the study is as a research volunteer to help the investigators collect information on cannabis effects on driver behaviour by smoking a cannabis or placebo cigarette, acting as a driver, providing urine and blood samples, and completing some questionnaires. I also understand that the investigators will be conducting a supplemental study of genetic influences on the effects of cannabis, including how it affects performance on the driving simulator task and other measures. I understand that by agreeing to participate in this supplemental study I allow the investigators to collect an additional 20 mL (or 4 teaspoons) of my blood to conduct these analyses on the Screening Day, and these samples and/or genetic data extracted from me may be shared with other authorized collaborators. My questions, if any, have been answered to my satisfaction. By signing this consent form I do not waive any of my rights.

If I have any further questions I understand that I can contact the study investigators: Robert Mann 416-535-8501 ext. 34496; Bernard Le Foll 416-535-8501 ext. 34772; Bruna Brands 416-535-8501 ext. 36860. Dr. Pdraig Darby, Chair, Research Ethics Board, Centre for Addiction and Mental Health, may be contacted by research subjects to discuss their rights. **Dr. Darby may be reached by telephone at 416-535-8501 ext. 36876.**

I voluntarily consent to participate in this research study.

Research Volunteer:

Signature: _____

Date: _____

Name: _____
Please Print

Person Obtaining Consent:

Signature: _____

Date: _____

Name: _____
Please Print

I have been given a copy of this form to keep.

Appendix C: Study Advertisements

Flyer

*CAMH is a Pan American Health Organization/ World Health Organization Collaborating Centre
Affiliated with the University of Toronto*

Study Volunteers Needed

Do you smoke cannabis every week?

Are you 19 to 25 years old?

Do you 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 ext: 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

Cannabis and Driving Study

(416) 535 8501 ex 6032

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Postcards

Front:

camh
Centre for Addiction and Mental Health

**Cannabis
and
Driving**

RESEARCH SUBJECTS NEEDED
Do you smoke cannabis every week?
Are you 19 to 25 years old?
Do you have a G2 or G driver's 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: 36587

camh
Centre for Addiction and Mental Health

**Cannabis
and
Driving**

RESEARCH SUBJECTS NEEDED
Do you smoke cannabis every week?
Are you 19 to 25 years old?
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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: 36587

Back:

WE INVITE YOU TO TAKE PART IN A RESEARCH STUDY

Do you smoke cannabis every week?
Are you 19 to 25 years old?
Do you 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.

The Study will involve:

- answering questions
- several hours over 4 days
- undergoing a physical
- smoking a cannabis cigarette which may or may not contain THC
- driving a state-of-the-art driving simulator
- providing samples of blood and urine
- completing cognitive tasks

*The study is held at CAMH 33 Russell Street
 Compensation will be provided*

*If you are interested,
 please call for more information
416-535-8501 ext: 36587*

camh
 Centre for Addiction and Mental Health

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

NOW Magazine

RESEARCH SUBJECTS NEEDED

Do you smoke cannabis every week?

Are you 19 to 25 years old?

Do you have a G2 or G driver's 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: 36587

camh
 Centre for Addiction and Mental Health

Toronto Transit Commission

Wide poster:

TAKE PART IN A RESEARCH STUDY

Do you smoke **Cannabis** every week?
 Are you **19-25** years old?
 Do you have a **valid driver's 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 36587
REG# 125/2011

camh
Centre for Addiction and Mental Health

Tall poster:

TAKE PART IN A RESEARCH STUDY

Do you smoke **Cannabis** every week?
 Are you **19-25** years old?
 Do you have a **valid driver's licence**?

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

This study will involve several hours over 4 days.
 Compensation will be provided if you participate in this study.

For more information please contact 416.535.8501 ext 36587
REG# 125/2011

camh
Centre for Addiction and Mental Health

Online

CAMH Website:

Study Details

Title: Cannabis and driving study

What is the purpose of the study?

Using a high-fidelity driving simulator we will assess if the effects of cannabis on driving-related skills will be observed in young drivers 24 hours and 48 hours following a single dose of smoked cannabis, as well as the immediate effects of cannabis on those skills.

Who is needed?

Individuals with: Valid driver's licence, Smoke cannabis regularly, Willing to abstain from cannabis use during study

Individuals without a mental health or addiction problem: Yes

Age range: 19 - 25

Gender: All

Ethnicity:

Other:

What does the study involve?

Number of contacts: total of 5 visits

Time period: 1 eligibility day and 4 consecutive study days

Length of contacts: 2.5hr, 2.5hr, 8hr, 2hr, 2hr

Treatment offered: No

Location: 33 Russell St.

Investigators: Robert Mann, Bernard Le Foll, Bruna Brands

Contact information:

Phone: 416-535-8501 ext 36587

e-mail: jiefei.pan@camh.ca

Website:

Flyer: [Download](#)

Study end date: 31 Aug 2015

REB number: 125/2011

Full study title: Acute and residual effects of cannabis on young drivers' performance of driving-related skills

Keywords: cannabis, driving, driving simulator

PLEASE NOTE:

- Research staff cannot give medical advice over the phone.
- If you have specific questions regarding your health care, please contact your family physician.
- We regret that not everyone screened for a study will be eligible to participate
- For more information about other treatment options for mental illness or addiction offered by CAMH, visit www.camh.ca or call 416-535-8501.

Backpage:

[backpage.com](#) > [Toronto community](#) > [Toronto volunteers](#)

Report Ad

Cannabis and Driving Study

Posted: Thursday, August 6, 2015 9:36 AM

Reply

RESEARCH SUBJECTS NEEDED

Do you smoke cannabis every week?
Are you 19 to 25 years old?
Do you have a G2 or G driver's license?

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 ext. 36587](tel:416-535-8501)

All queries are strictly confidential.

Compensation provided.

33 Russell Street, M5S2S1 [google map](#) | [yahoo map](#)

- Location: Toronto, Centre for Addiction and Mental Health
- Post ID: 29347204 toronto

[Enlarge Picture](#)

camh
Centre for Addiction and Mental Health

[Enlarge Picture](#)

Kijiji:

[Ontario](#) > [Toronto \(GTA\)](#) > [City of Toronto](#) > [community](#) > [volunteers in City of Toronto](#) > Ad ID 1092774406

Cannabis and Driving Study

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Centre for Addiction and Mental Health

Cannabis and Driving

RESEARCH SUBJECTS NEEDED
Do you smoke cannabis every week?
Are you 19 to 25 years old?
Do you have a G2 or G driver's 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. 36587

View larger image

camh
Centre for Addiction and Mental Health

Date Listed 06-Aug-15
Address 33 Russell Street, Toronto, ON M5S 3B1
 [View map](#)

RESEARCH SUBJECTS NEEDED

Do you smoke cannabis every week?
Are you 19 to 25 years old?
Do you have a G2 or G 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 ext. 36587
All queries are strictly confidential.

Compensation provided.

Visits: 56

Poster Contact Information

416-535-8501 ext. 3XXXX Click to show

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Verification code

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Craigslist:

★ Cannabis and Driving Study (33 Russell Street)

camh
Centre for Addiction and Mental Health

Cannabis and Driving

RESEARCH SUBJECTS NEEDED
Do you smoke cannabis every week?
Are you 19 to 25 years old?
Do you have a G2 or G driver's 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. 36587

camh
Centre for Addiction and Mental Health

RESEARCH SUBJECTS NEEDED

Do you smoke cannabis every week?
Are you 19 to 25 years old?
Do you have a G2 or G driver's license?

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 ([show contact info](#)) ext. 36587
All queries are strictly confidential.

Compensation provided.

- do NOT contact me with unsolicited services or offers

Appendix D: Descriptive Statistics for Analyses

Table 51. Descriptive statistics for overall mean speed and SDLP under dual-task conditions

	Active			Placebo			Full Sample		
	Mean	Standard Deviation	n	Mean	Standard Deviation	n	Mean	Standard Deviation	n
Mean speed (km/h)			39			15			54
Baseline	79.71	7.30		78.25	11.59		79.30	8.61	
Post-dose	75.98	9.80		80.17	15.89		77.14	11.80	
	77.84	8.79		79.21	13.70				
SDLP (m)			39			15			54
Baseline	.28	.05		.30	.10		.28	.07	
Post-dose	.27	.05		.26	.05		.27	.05	
	.28	.05		.28	.08				

Table 52. Descriptive statistics for VAS subscales

	Active			Placebo			Full Sample		
	Mean	Standard Deviation	n	Mean	Standard Deviation	n	Mean	Standard Deviation	n
Drug effect			33			14			47
Baseline	.00	.00		.00	.00		.00	.00	
5 min post-dose	72.85	22.79		11.86	17.12		54.68	35.28	
15 min post-dose	67.33	23.23		14.86	21.48		51.70	33.03	
30 min post-dose	59.39	26.74		12.86	21.52		45.53	33.03	

	Active			Placebo			Full Sample		
	Mean	Standard Deviation	n	Mean	Standard Deviation	n	Mean	Standard Deviation	n
1 hr post-dose	53.30	26.69		12.14	24.69		41.04	32.09	
2 hrs post-dose	38.52	26.96		6.43	16.08		28.96	28.26	
3 hrs post-dose	23.03	24.21		6.14	15.15		18.00	23.10	
4 hrs post-dose	15.58	22.68		3.07	8.65		11.85	20.31	
5 hrs post-dose	6.42	15.14		.07	.27		4.53	12.96	
6 hrs post-dose	2.67	9.54		.00	.00		1.87	8.05	
	34.60	33.30		7.59	20.29				
High			33			14			47
Baseline	.00	.00		.00	.00		.00	.00	
5 min post-dose	69.97	19.46		10.14	18.51		52.15	33.54	
15 min post-dose	65.70	24.61		11.29	16.24		49.49	33.59	
30 min post-dose	59.45	24.29		12.21	21.29		45.38	31.87	
1 hr post-dose	50.97	25.97		8.93	21.29		38.45	31.23	
2 hrs post-dose	38.88	26.93		5.86	14.85		29.04	28.28	
3 hrs post-dose	21.15	24.60		3.36	8.41		15.85	22.55	
4 hrs post-dose	10.30	18.44		1.93	4.94		7.81	16.08	
5 hrs post-dose	5.36	13.73		.00	.00		3.77	11.71	
6 hrs post-dose	2.55	9.19		.00	.00		1.79	7.75	
	32.97	32.77		6.25	18.31				
Good effects			33			14			47

	Active			Placebo			Full Sample		
	Mean	Standard Deviation	n	Mean	Standard Deviation	n	Mean	Standard Deviation	n
Baseline	.00	.00		.00	.00		.00	.00	
5 min post-dose	66.94	22.17		19.00	26.35		52.66	32.08	
15 min post-dose	67.94	19.04		16.29	21.98		52.55	30.97	
30 min post-dose	63.73	23.28		16.86	24.62		49.77	31.90	
1 hr post-dose	62.15	23.59		12.07	23.43		47.23	32.84	
2 hrs post-dose	46.33	31.10		6.93	15.15		34.60	32.70	
3 hrs post-dose	29.30	28.01		6.79	15.64		22.60	26.90	
4 hrs post-dose	14.21	22.86		.79	2.00		10.21	20.08	
5 hrs post-dose	8.45	19.38		.00	.00		5.94	16.63	
6 hrs post-dose	5.64	14.77		.00	.00		3.96	12.59	
	36.11	33.22		10.87	25.49				
Bad effects			34			15			49
Baseline	.00	.00		.00	.00		.00	.00	
5 min post-dose	21.39	20.07		1.79	5.21		15.55	19.23	
15 min post-dose	19.91	22.42		4.07	13.35		15.19	21.30	
30 min post-dose	16.85	19.76		3.93	13.33		13.00	18.91	
1 hr post-dose	14.76	17.65		1.07	3.73		10.68	16.15	
2 hrs post-dose	10.94	14.59		.14	.53		7.72	12.15	
3 hrs post-dose	5.73	11.14		.00	.00		4.02	9.66	
4 hrs post-dose	5.91	12.09		.00	.00		4.15	10.45	

	Active			Placebo			Full Sample		
	Mean	Standard Deviation	n	Mean	Standard Deviation	n	Mean	Standard Deviation	n
5 hrs post-dose	3.76	9.66		.00	.00		2.64	8.24	
6 hrs post-dose	2.12	8.93		.00	.00		1.49	7.51	
	10.08	16.53		1.22	6.35				
Drug liking			33			14			47
Baseline	1.42	8.18		.00	.00		1.00	6.86	
5 min post-dose	70.55	24.64		36.86	36.18		60.51	32.17	
15 min post-dose	69.09	21.24		29.43	27.13		57.28	29.29	
30 min post-dose	67.70	18.38		22.64	25.29		54.28	29.15	
1 hr post-dose	67.24	20.36		22.00	28.27		53.77	30.85	
2 hrs post-dose	61.70	27.10		12.07	20.99		46.91	34.08	
3 hrs post-dose	49.76	29.37		12.43	21.25		38.64	32.02	
4 hrs post-dose	38.06	32.96		10.93	21.74		29.98	32.35	
5 hrs post-dose	21.67	31.10		3.50	13.10		16.26	28.13	
6 hrs post-dose	21.67	31.10		3.5	13.10		16.26	28.14	
	45.19	33.34		21.53	32.93				
Rush			33			14			47
Baseline	.00	.00		.00	.00		.00	.00	
5 min post-dose	47.85	27.10		5.36	8.2		35.19	30.26	
15 min post-dose	43.33	28.55		7.86	12.69		32.77	29.69	
30 min post-dose	33.67	27.39		6.57	15.72		25.60	27.36	

	Active			Placebo			Full Sample		
	Mean	Standard Deviation	n	Mean	Standard Deviation	n	Mean	Standard Deviation	n
1 hr post-dose	25.64	24.86		4.50	13.48		19.34	24.01	
2 hrs post-dose	19.94	22.63		4.50	13.37		15.34	21.40	
3 hrs post-dose	6.39	11.05		.43	1.60		4.62	9.66	
4 hrs post-dose	3.79	8.46		.00	.00		2.66	7.27	
5 hrs post-dose	2.42	7.73		.00	.00		1.70	6.55	
6 hrs post-dose	2.52	8.66		.00	.00		1.77	7.31	
	19.46	25.89		3.35	12.96				
Feels like cannabis			33			14			47
Baseline	.00	.00		.00	.00		.00	.00	
5 min post-dose	73.27	27.94		21.14	37.14		57.74	38.90	
15 min post-dose	65.45	27.95		13.71	24.24		50.04	35.80	
30 min post-dose	67.09	27.13		15.79	28.05		51.81	36.01	
1 hr post-dose	65.76	27.63		17.79	35.74		51.47	37.20	
2 hrs post-dose	54.21	33.89		7.07	16.04		40.17	36.70	
3 hrs post-dose	37.18	35.62		5.64	15.44		27.79	34.10	
4 hrs post-dose	32.24	35.63		.43	1.09		22.77	33.16	
5 hrs post-dose	20.15	34.61		.00	.00		14.15	30.33	
6 hrs post-dose	14.48	30.61		.00	.00		10.17	26.39	
	36.58	40.76		16.67	34.90				

Table 53. Descriptive statistics for peak VAS drug effect and drug liking subscale scores for participants in the active and placebo conditions

		Mean	Standard Deviation	n
Active	Peak VAS Drug Effect	74.66	22.19	38
	Peak VAS Drug Liking	77.82	23.27	38
Placebo	Peak VAS Drug Effect	20.13	27.18	15
	Peak VAS Drug Liking	38.07	37.94	15

Table 54. Descriptive statistics for estimated dose of Δ^9 -THC and peak scores on VAS drug liking and drug effect subscales

	Mean	Standard Deviation	n
Estimated Dose (mg)	79.09	24.51	39
Peak VAS Drug Effect	74.66	22.19	38
Peak VAS Drug Liking	77.82	23.27	38

Table 55. Descriptive statistics for heart rate measured in beats per minute

	Active			Placebo			Full Sample		
	Mean	Standard Error	n	Mean	Standard Error	n	Mean	Standard Error	n
Heart rate (bpm)			34			15			49
Baseline	75.94	10.58		68.47	7.38		73.65	10.24	
5 min post-dose	101.03	31.05		75.60	12.13		93.24	29.09	
15 min post-dose	96.85	16.41		72.13	10.15		89.29	18.65	

	Active			Placebo			Full Sample		
	Mean	Standard Error	n	Mean	Standard Error	n	Mean	Standard Error	n
30 min post-dose	90.65	13.63		69.67	7.62		84.22	15.49	
1 hr post-dose	82.88	14.81		70.73	8.36		79.16	14.25	
2 hrs post-dose	76.41	12.71		73.67	11.61		75.57	12.33	
3 hrs post-dose	82.09	13.15		76.47	13.08		80.37	13.26	
4 hrs post-dose	83.59	12.43		77.07	10.92		81.59	12.26	
5 hrs post-dose	79.71	11.31		79.53	14.09		79.65	12.08	
6 hrs post-dose	78.44	12.06		73.60	5.96		76.96	10.75	