UNIVERSITY OF MANITOBA

The utilization of pharmaceutical cannabinoid agents in Manitoba, Canada.

A population-based study using administrative health care data.

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Abstract

Introduction: Pharmaceutical cannabinoids are third-line therapeutic options for several indications, despite the lack of strong evidence to support their efficacy. The extent and patterns of their utilization from a population perspective are unknown.

Methods: A retrospective population-based study using administrative healthcare data from Apr.1, 2004 to Mar.31, 2017, to assess the annual trends, demographic and clinical determinants, and persistence of pharmaceutical cannabinoids use.

Results: The incident and prevalent users of cannabinoid agents increased throughout the study period. Nabilone comprised the majority of dispensations. The percent of users who had a diagnosis for the approved indications was relatively low. Persistence of cannabinoid use was low and influenced by the socio-demographics and medical conditions of users.

Conclusion: Although the rates of pharmaceutical cannabinoid use have increased, the overall low numbers of users and the high discontinuation rates reflect the lack of effectiveness and tolerability to these agents.

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Dedication

To Dr. M.J Alkabbani, the professor I will always look up to,

And

Samia Alshaleh, the woman I aspire to be like.

Thank you, Dad & Mom!

Thesis preface

This thesis is written in a grouped manuscript style (sandwich thesis) and includes five chapters: an introductory background chapter, three papers intended for publication in peer-reviewed journals, and a concluding chapter. Each paper includes its own bibliography at the end of each chapter. A final bibliography for references used in the introductory and concluding chapters is at the end of the thesis.

Student contribution: Researched relevant literature, conducted all analyses, drafted all manuscripts, submitted manuscripts for publication, conducted peer-requested revisions, wrote, combined, and finalized the thesis.

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List of Abbreviations

CB -1R	–	Cannabinoid 1 receptor
CB -2R	–	Cannabinoid 2 receptor
Δ9-THC, THC	–	delta-9-Tetrahydrocannabinol
CBD	–	Cannabidiol
ECS	–	Endocannabinoid System
ACMPR	–	Access to Cannabis for Medical Purposes Regulations
CDSA	–	Controlled Drugs and Substance Act
M3P	–	Manitoba Prescribing Practices Program
CINV	–	Chemotherapy-Induced Nausea and Vomiting
HIV/AIDs	–	Human Immunodeficiency Virus infection and Acquired Immune Deficiency syndrome
MHSHL	–	Manitoba Health, Seniors and Healthy Living
PHIN	–	Personal Health Identification Number
DPIN	–	Drug Program Information Network
ICD-9-CM	–	International Classification of Diseases, Clinical Modification
ICD 10-CA	–	International Classification of Diseases, Canadian
ATC	–	Anatomical Therapeutic Chemical
NSAIDs	–	Non-Steroidal Anti-Inflammatory Drugs
SES	–	Socio-Economic Status
SEFI	–	Socio-Economic Factor Index
SAS	–	Statistical Analysis Software
SD	–	Standard Deviation
95%CI	–	95% Confidence Interval
RR	–	Relative Rate

H	–	Hospitalization
P	–	Physician Claim
Pres	–	Prescription
RCT	–	Randomized Controlled Trial
DIN	–	Drug Identification Number
CAD	–	Canadian Dollar
HR	–	Hazard Ratio
Ref	–	Reference
CTADS	–	Canadian Tobacco, Alcohol and Drugs Survey
CUD	–	Cannabis Use Disorder
GABA	–	gamma-aminobutyric acid
MECIR	–	Methodological Expectations of Cochrane Intervention Reviews
PRISMA	–	Preferred Reporting Items for Systematic Reviews and Meta-analysis
DSM	–	Diagnostic and Statistical Manual of Mental Disorders
TLFB	–	Timeline Follow back
MCQ	–	Marijuana Craving Questionnaire
CWS	–	Cannabis Withdrawal Scale
MWC	–	Marijuana Withdrawal Checklist
WDS	–	Withdrawal Discomfort Score
NR	–	Number Randomized
NC	–	Number Completed
MET	–	Motivational Enhancement Therapy
CBT	–	Cognitive Behavioral Therapy
Sig	–	Significant
SE	–	Side Effects

AE	–	Adverse Effects
Lofex-Dro	–	Lofexidine-dronabinol

Chapter One. Pharmaceutical cannabinoids: Background and research rationale

1.1 Introduction

Cannabinoids are the primary natural chemical constituents of the cannabis plant. Several therapeutic applications of cannabinoids including their use as analgesics, appetite stimulants, and anti-emetics have been reported in the literature.[1,2] Other applications include their use in treating muscle spasticity and epilepsy.[1–3] These compounds exert their effects by binding to the body's own endocannabinoid receptors: the cannabinoid 1 receptor (CB-1R), which is responsible for the psychotropic effects, and the cannabinoid 2 receptor (CB-2R), which primarily plays an immunomodulatory role.[4]

Cannabinoids can be classified into three types based on their origin. The first type is derived naturally from the cannabis plant such as delta-9-tetrahydrocannabinol (THC); the second type is produced endogenously in humans and thus named endocannabinoids, while the third type includes synthetic or pharmaceutically-derived cannabinoids.[5] The pharmaceutically-derived cannabinoids include compounds developed in labs and those that are manufactured by drug companies. Nabilone (Cesamet®), dronabinol (Marinol®) and nabiximols (Sativex®) are the three prescription cannabinoids that have been available in Canada. Research into the appropriate use of these medications is limited and information on their long-term safety and effectiveness in a variety of proposed indications is incomplete. More specifically, there are no estimates of the extent of use of pharmaceutical cannabinoid medications from a population perspective.

An understanding of the extent of utilization in the real-world can be achieved by drug utilization studies that rely on analyzing administrative data that are prospectively collected

for health system management. Characterizing the past trends of cannabinoid use enables a review of the appropriateness of their utilization and establishes baseline measurements. Moreover, identifying population characteristics associated with the use of these agents from a population perspective has the potential to provide policy makers and clinicians with information about which population may be deriving benefit or harms from these agents and guide future policy regarding access to and monitoring of these therapies.

1.2 **History of cannabis**

Cannabis, or marijuana, is a plant that grows naturally in many humid and tropical parts of the world such as central Asia.[6] Historical findings indicate that it was first cultivated in China since 4000 B.C and has been used as a source of fiber for ropes and clothing as well as for recreational and medical purposes, such as rheumatoid arthritis and constipation.[6,7] Cannabis was introduced into Western medicine for several indications, including neuralgia, dysentery, and infectious diseases in the middle of the 19th century and was registered in the United States pharmacopeia in 1850.[7,8] In the 1930's, the use of marijuana started declining due to the appearance of acetylsalicylic acid and injectable morphine as well as to the legal restrictions limiting access and use of marijuana. In Canada, cannabis was added to the schedule of the Opium and Narcotic Act in 1923.[7,9] Moreover, the media and public perception of cannabis use started associating cannabis with crimes and violence, spreading fear about marijuana addiction and its consequences.[9] In the 1960's as a result of a social movement, the recreational use spread among young adults.[7,10] The interest in cannabis research increased in 1964 after the identification of its chemical constituents, which drove the interest of pharmaceutical companies to develop pharmaceutical agents that would exert a similar effect.[7,11] Currently, the recreational and medical use of cannabis is regulated in

several jurisdictions around the world. In Canada, the use of cannabis for medical purposes was legalized in 2001 and as of October of 2018, recreational cannabis is legal in Canada.[12]

1.3 **Chemical constituents of cannabis**

The cannabis plant contains more than 70 cannabinoid compounds and over 400 chemical entities.[13,14] The cannabinoids, which are found exclusively in cannabis, include cannabinol, cannabidiol, and the main psychoactive compound, delta-9-tetrahydrocannabinol (Δ9-THC), or as commonly referred to as THC.[13, 15] The product of THC oxidation, Cannabinol, is a weak psychoactive compound used experimentally as an immunosuppressant. Cannabidiol (CBD) is non-intoxicating and has some medical applications, including a potential role in treatment-resistant epilepsy.[4,15] The exact mechanism of action of these chemical compounds is not currently fully understood; however, it is known that they affect the body's endocannabinoid system (ECS).

1.4 **The Endocannabinoid System**

The term "endocannabinoid system" was first used in the 1990's to describe a signaling pathway involved in several physiological processes, such as metabolism, mood regulation, and analgesia.[16] This system is composed of receptors, endogenous cannabinoid compounds, as well as their synthesizing and degrading enzymes.[16]At least two different types of cannabinoid receptors have been discovered: CB-1R and CB-2R receptors.[16] CB-1R receptor is responsible for the psychotropic effects, such as euphoria and sedation, and is mainly present centrally in various parts of the brain and spinal cord including the cerebral cortex, cerebellum, and hypothalamus.[17] It is also present in lower concentration in the spleen, heart, and leukocytes.[17] CB-2R receptor is present predominantly in the tissue of the immune

system, and plays a role in mediating immune-modulatory effects.[4,18] Endocannabinoids are defined as "endogenous substances capable of binding to and functionally activating the cannabinoid receptors".[19] Anandamide (N –arachidonoylethanolamine) and 2-arachidonoylglycerol (2-AG) are the two most studied endogenous cannabinoids.[19] This system plays a role in various regulatory functions, not only in the central nervous system, but also in the endocrine network, immune system, gastrointestinal system, as well as in metabolism and nociception.[20,21]

1.5 **Therapeutic implications of cannabinoids**

Major therapeutic implications of cannabinoids include their use as analgesics, appetite stimulants, and anti-emetics.[1,22] Cannabinoids have a role in reducing pain and inflammation that is associated with several medical conditions, including cancer and connective tissue disorders, such as arthritis and fibromyalgia.[23,24] Several theories exist to explain the analgesic effect of cannabinoids. The presence of CB-1R receptors in pain control centers is one of the key theories that can explain cannabinoid-induced analgesia by attenuation of synaptic transmission.[24] Moreover, cannabinoids are of therapeutic value against inflammatory pain by inhibiting cell proliferation and cytokine/chemokine production, in addition to the induction of apoptosis.[23] Furthermore, the expression and activation of CB-2R receptors in different types of inflammatory cells generates an anti-nociceptive response in situations of inflammatory hyperalgesia and neuropathic pain.[24] The ECS also has a role in reducing spasticity and producing neuroprotective effect; therefore, cannabinoids are of interest in the management of multiple sclerosis.[25]

Cannabinoid receptors have been identified in tissues of emetic- loci in the gastrointestinal system as well in the brainstem. The activation of CB-1R receptors appears to

decrease the levels of released serotonin (5-HT), a main emetic neurotransmitter.[26] Hence, cannabinoids are of importance in inhibiting emesis evoked peripherally or centrally by drugs, like chemotherapeutic agents, or natural stimuli.[26–28]

Cannabinoids, reduce intraocular pressure, and in mild doses reduce anxiety and cause euphoria; hence they have been studied for their possible role in glaucoma, and anxiety or depression, respectively.[29] However, there is controversy regarding the beneficial claims of cannabinoids in psychiatric disorders. While low doses of a CB-1R receptor agonist are related to an enhanced serotonergic and noradrenergic neurotransmission, leading to reduced anxiety and depression-like behavior; high-level stimulation of the CB-1R receptors can give a paradoxical effect.[30]

The role of ECS in schizophrenia has not been fully elucidated.[31] Pre-clinical studies indicate that CBD may have anti-psychotic properties.[32,33] However, observational studies found an association between the use of cannabis and psychosis.[29,34] Hence, the use of cannabinoids when there is a history of psychosis, is not recommended to avoid a negative long-term prognosis and possible provoking of psychotic episodes.[35–38]

Table 1.1. Summary of commonly reported uses and precautions of cannabinoid use.[39]

Health Canada approved indications	**Possible uses most reported in the literature**	**Contraindications/ Caution**
Chemotherapy-induced nausea and vomiting	Fibromyalgia	History of psychosis/ schizophrenia
Palliative pain	Rheumatoid arthritis	
Multiple sclerosis related neuropathic pain	Osteoarthritis	History of substance use disorder
Anorexia in in Human Immunodeficiency Virus infection and Acquired Immune Deficiency syndrome (HIV/AIDs)	Seizures and epilepsy	
	Glaucoma	History of hypersensitivity to any cannabinoid or to smoke
	Anxiety and depression	

1.6 **Cannabis and prescription cannabinoids in Canada**

Available cannabinoids in Canada for medical use, include the plant-based products (e.g., smoked, vapor, oils), and pharmaceutical products. Access to the plant-derived products has undergone change in the last 20 years. In 2016, "Access to Cannabis for Medical Purposes Regulations" (ACMPR) was implemented. This regulation allows patients access to oils, dried as well as fresh seeds buds or leaves of cannabis from a licensed producer after receiving a medical document from a medical practitioner, who does not prescribe but only authorizes use. Since October 2018, cannabis has become legal in Canada under the Cannabis Act; however, compared to recreational users, those obtaining medical cannabis are still legally protected to carry a 30-day supply rather than an exact amount. Additionally, the public and at work consumption is permitted for them.[40] However, a 10% excise tax that is applied to recreational cannabis will also apply to medical cannabis.[41] There are also no regulations to guarantee supply for the medical market, which has experienced shortages since the legalization.[42,43]

The available pharmaceutical cannabinoid preparations include nabilone, nabiximols, and previously dronabinol. All of these agents exert their pharmacological effects through partial agonist activity at CB-1R and CB-2R receptors. In Canada, these agents are currently Schedule II, i.e., controlled substances, based on the Controlled Drugs and Substance Act (CDSA).[38] In Manitoba, these agents are also under the Manitoba Prescribing Practices Program (M3P), which is a "risk management system to minimize drug diversion for Controlled and Narcotic medications and increase communication regarding drug utilization issues and information."[44] The M3P program requires regulations such as, a special form with

several security features, prescription filling within 3 days, and verification of patient's identity by the pharmacists.[44]

Table 1.2. Comparison of pharmaceutical cannabinoids available in Canada.[45]

Cannabinoid agent	**Nabilone (Cesamet®)**	**Nabiximols (Sativex®)**	**Dronabinol (Marinol®)**
Dosage formulation	Capsules	Oral-Mucosal spray	Tablets
Health Canada approved indications	Chemotherapy-induced nausea and vomiting (CINV)	-Multiple sclerosis related neuropathic pain -Cancer pain	-Chemotherapy-induced nausea and vomiting -Anorexia in in HIV/AIDs
Canadian marketing period	1982-Current	2005-Current	1994-2012
Biochemical description	Synthetic cannabinoid analogue	Extracted THC/CBD (1:1).	Synthetic THC
Price/ month in Canadian Dollar[38]	$110-310	$500-1000	$137- 500

1.7 Efficacy and safety of pharmaceutical cannabinoids

Efficacy

Several systematic reviews and meta-analyses investigated the efficacy of cannabinoids as therapeutic options for a variety of clinical conditions. Herein we chose five recent systematic reviews that covered several possible medical conditions, for which cannabinoids are reported as possible therapeutic options. [46–51]

In 2015, a systematic review and meta-analysis by Whiting*, et al.,* investigated the efficacy and safety of several cannabinoid agents.[50] The review investigated a total of 79 trials comparing the efficacy and safety of cannabinoids versus conventional treatments, placebos, or no treatment for several indications. Most of the trials evaluated chronic pain (28 RCTs), CINV (28), and spasticity in MS (14). Effects on Tourette's syndrome (2), glaucoma (1), sleep disorders (2) and appetite stimulation in HIV/AIDs (4) were also assessed. The trials

also included psychiatric conditions, such as anxiety (1) and psychosis (2). The mostly reported agents were nabilone (20 studies), nabiximols (19 studies), and dronabinol (13 studies). The review also included studies that evaluated smoked and vaporized cannabis and several other cannabinoid extracts.

Most trials did not show a statistically significant improvement in symptoms. The review concluded that among all the conditions included, there is moderate-quality evidence to suggest a beneficial role for cannabinoids for the treatment of chronic neuropathic or cancer pain and spasticity.[50] However, the OR for a 30% reduction in pain failed to reach statistical significance [1.41[95%CI: 0.99-2.00]. Pharmaceutical cannabinoids (nabiximols, dronabinol, and THC/CBD) provided also failed to produce a statistically significant improvement on the Ashworth scale for spasticity compared with placebo [Weighted mean difference, −0.12 [95% CI, −0.24 to 0.01].[50] Other measures used to assess spasticity as an outcome were graded as low quality and also failed to show a statistically significant difference. The evidence to support improvement in nausea and vomiting due to chemotherapy, weight gain in HIV, sleep disorders, and Tourette syndrome was also of low quality.

In 2018, Stockings, *et al*.[52] conducted a systematic review and meta-analysis of controlled and observational studies to examine the evidence of the effectiveness of cannabis-based and pharmaceutical products in chronic non-cancer pain (CNCP). This review included 104 studies (n = 9958 participants) that examined neuropathic pain (48 studies), fibromyalgia (7), rheumatoid arthritis (1), sclerosis-related pain (13), visceral pain (6), and mixed or undefined CNCP (29). The review found eight trials that assessed a 30% reduction in pain across all conditions, and found that cannabinoids were more likely to produce a 30%

reduction in pain compared to placebo, OR, 1.46 [95% CI 1.16-1.84].[52] A smaller number of trials (5) reassessed a 50% reduction in pain. These trials produced a similar OR but this failed to reach statistical significance OR 1.43 [95% CI 0.97-2.11].[52] The change in pain intensity, standardized mean difference, -0.14 [95% CI -0.20 - -0.08] was equivalent to only a 3 mm reduction on a 100 mm visual analogue scale when cannabinoids were used compared to placebo. This is much lower than the 30 mm needed for clinically important reduction in pain intensity.

Safety

Unlike efficacy, with regards to the safety of cannabinoids, there were clear indications of a higher risk of short-term adverse effects when cannabinoids were used. Compared to placebo, cannabinoids produced more adverse effects OR, 3.03 [95%CI: 2.42-3.80] and serious adverse, OR, 1.41 [95%CI: 1.04-1.92].[50] The odds of withdrawing from the trials due to an adverse effect were higher in the group who received cannabinoids compared to placebo, OR, 2.94 [95%CI: 2.18-3.96].[50] These adverse effects were mainly related to the central nervous system. The most reported adverse effects were dizziness confusion, euphoria, drowsiness, and dry mouth. Several other side effects such as diarrhea, paranoia, dyspnea, and somnolence were also reported.[50]

This was in line with results from another systematic review that assessed the literature for the adverse effects of medical cannabinoids.[53] Unlike the systematic review by Whiting *et al*., this review included observational studies in addition to RCTs. The review found a higher rate of non-serious adverse events with cannabinoids, rate ratio (RR), 1.86 [95%CI: 1.57-2.21]. A non-serious event was defined as “any untoward medical occurrence in a patient or participant; the event need not have a causal relation to the treatment”. The review concluded

that risks associated with long-term use of medical cannabinoids were poorly characterized in published clinical trials and observational studies.[53]

Notably, several longitudinal studies have examined the association between the cannabis plant and psychosis.[54–58] A systematic review of cohort studies showed an association between cannabis use and psychotic outcomes, including self-reported psychotic symptoms, hospitalization for psychosis, and a schizophrenia diagnosis.[59] The strength of associations varied across 10 studies, OR [95%CI] ranged from 1.12 [0.76-1.65] to 8.2 [5.1-13.1][59]. Unlike the cannabis plant, other than case reports[60], there are no longitudinal epidemiological studies that looked at the association between pharmaceutical cannabinoids and psychotic outcomes.

Although pharmaceutical cannabinoids are controlled substances, strong evidence to support a high risk of abuse is still lacking. Ware, *et al*.[61] and Calhoun, *et al*,[62] assessed the abuse potential of nabilone and dronabinol, respectively. In both studies they searched and evaluated the literature, internet, databases, and popular press to detect signals that these agents were being used or reported as a drug of abuse. In addition to, interviews with medical professionals and law enforcement officials. They also evaluated institutional reports, such as the Canadian Community Epidemiology Network on Drug Use report and the RCMP: Drug situation report. They found that people perceive these agents as more expensive, less effective options compared to cannabis.[61,62] Nabilone had no "street value" and very few incidents of recreational use were found. The study concluded that there is no concern regarding a potential abuse to nabilone.[61] Similarly, abuse or recreational use of dronabiol was not reported, as it showed no street market, and that its use remained to be for therapeutic

purposes only.[62] These results can possibly raise a debate regarding the rationale behind the controlled scheduling of these drugs.

Interestingly, these agents have been associated with decreased drug-taking behavior in a human laboratory model of relapse prevention, which can identify markers of cravings that are predictive of relapse in pre-determined laboratory settings.[63] Pharmaceutical cannabinoids bind to the cannabinoid receptors, affecting them in a similar manner to the cannabis plant.[64,65]

In 2018, Allan, *et al*. published a clinical practice guideline after conducting a detailed systematic review of systematic reviews on the use of cannabinoids for chronic pain, nausea and vomiting, and spasticity, as well as their potential adverse effects.[46] Their recommendations were not in favor of prescribing cannabinoids and that 'their use for neuropathic pain, palliative cancer pain, CINV, and multiple sclerosis- or spinal cord injury-related spasticity should only be considered for patients whose conditions are refractory to standard medical therapies, due to the lack of high quality evidence to support their benefits and their known harms.[66] However, if cannabinoids are to be used, the guideline recommendations are in favor of the pharmaceutically-developed products (nabilone and nabiximols) due to higher consistency in dosing and less bias in available evidence.[66]

1.8 **Pharmaceutical cannabinoids utilization in previous literature**

While estimates regarding the use of medical plant-based cannabis are available, research on the utilization of prescription cannabinoids is lacking.[67] Previous studies that assessed the use of pharmaceutical cannabinoids were on a defined group of users with a specific condition rather than from a general population perspective.

One of the very few studies that considered the utilization of prescription cannabinoid was a retrospective chart review of dronabinol use over a period of 10 years.[68] This was conducted in a pediatric academic oncology hospital to describe the use of dronabinol in pediatric cancer patients and characterize the trend of use with regards to patients' age, sex, diagnosis, and adjunctive chemotherapy and anti-emetic use. The investigators also looked at the response to dronabinol by measuring the number of emesis bouts. The population of interest was hospital patients with a cancer diagnosis, who are ≤ 18 years old and received at least one prescription of dronabinol in an inpatient setting.

Out of 58 patients who used dronabinol for CINV, 30 (52%) were males, and the mean (SD) age of users was 13.9 years (3.2).[68] More than half (57%) of the patients had a high emetogenic risk and 55% of patients received dronabinol as a scheduled regimen while 45% received it as needed.[68] Regarding response to dronabinol, 60% of patients were in the good response group (0-1 emesis), 13% had a fair response (2-3 emesis), and 27% had a poor response to dronabiol (> 4 emesis).[68] With regards to tolerability, 65% of patients received at least one additional course of dronabinol and 62% received an out-patient prescription.[68]

In 2016, Fernandez, *et al*. conducted a retrospective registry-based study in the United Kingdom, Germany, and Switzerland.[69] The purpose of this registry was to evaluate the long-term safety of Sativex® in MS patient, under usual clinical practice conditions. Data were collected between June 2010 and February 2015 from 941 patients using Sativex®; 57% of users were female, the mean (SD) age was 51 (10.8).[69] At one year follow up, 68% of patients continued using Sativex®. It is important to note that reports from only 22% of the 3,493 patients who use Sativex® in the United Kingdom were represented in this study; this was mainly due to the small number of participating clinics and missing data. This might have

introduced a bias towards survival, as several patients might discontinue the drug but fail to report it.

Fernandez, *et al*. also used available data that was prospectively collected from 13 multiple sclerosis centers in Spain to assess the safety of Sativex®. Out of the 204 patients followed, almost 62% were females and the mean (SD) age was 48.6 (9.7) years, and 65% of them continued using Sativex® at one year follow-up.[69] The most commonly reported reasons for discontinuation were lack of tolerability and efficacy. Despite the difference in methods, both studies showed similar results.

In Canada, St-Amant, *et al*. conducted a postal survey involving physicians practicing in Abitibi-Témiscamingue region of Quebec, to identify determinants of prescribing cannabinoids (medical marijuana, nabilone, or nabximols).[70] Although this study focused on prescriber's behavior, data regarding the medical indications, for which cannabinoids were prescribed, were collected. Around one-third (27.3%) of the cannabinoid prescriptions were reported as for "any indication" and 23.0% were for chronic non-cancer pain, followed by cancer pain (9%). The percentage of prescriptions for nausea and vomiting, spasticity, anorexia or weight loss, and anxiety were all as less than 5%.

1.9 **Rationale and research objectives**

Although there is lack of strong evidence to support the long-term efficacy and safety of cannabinoids, these medications are used for a wide range of indications. The current literature, however, does not provide estimates to describe the utilization of these agents from a population prospective. Even less is known about the characteristics of cannabinoid use including persistence. There is a lack of information regarding the "real-word" use of

cannabinoids and the demographics of patients who use these agents. The off-label use of these agents with substance use disorder is of special interest.

This study aims to provide a description of the utilization of pharmaceutical cannabinoids in a Canadian province, using administrative healthcare data. The resulting understanding trends in prescription cannabinoid use may provide foundational knowledge and help guide policy makers, clinicians, patients, and their caregivers in their use of these products. The research period examines prescription cannabinoid use prior the full legalization of cannabis and will create a baseline for future comparison after legalization.

The objectives of this study are to assess the trends in the annual rates of use of pharmaceutical cannabinoids and describe the patient population in terms of their sociodemographic characteristics and medical conditions. The study will also, assess the persistence of the first episode of use of pharmaceutical cannabinoids and explore the determinants of discontinuation among a cohort of incident users. Lastly, a systematic review will be conducted to evaluate the evidence for the efficacy and safety of pharmaceutical cannabinoids in the management of cannabis use disorder.

Chapter Two. Pharmaceutical cannabinoids utilization in Manitoba from 2004-2015

Study classification: A population-based cross-sectional study

Journal: *CMAJOpen*

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The main objective of this study is to determine the utilization of pharmaceutical cannabinoid agents in Manitoba, this includes:

1. To determine the annual incidence and prevalence rates of use from 2004/2005 to 2014/2015.

2. To describe the sociodemographic characteristics of the patient population using pharmaceutical cannabinoids by age, sex, region of residence, socioeconomic status.

3. To report the medical conditions of incident pharmaceutical cannabinoid users.

4. To report the medical specialty of prescribers responsible for initiating pharmaceutical cannabinoids in the patient population.

2.1 **Abstract**

Background: Pharmaceutically-derived cannabinoids are used for several indications, more commonly for pain management. The extent of their utilization from a population perspective is unknown; hence the aim of this study is to evaluate the trends in pharmaceutical cannabinoid use in Manitoba, Canada.

Methods: This was a retrospective population-based cross-sectional study using administrative data from the Manitoba Centre for Health Policy. Pharmaceutical cannabinoid users residing in Manitoba from Apr.1, 2004 to Mar.31, 2015 were identified. We assessed the annual prevalence and incidence of pharmaceutical cannabinoids use, and the socio-demographic characteristics and medical conditions of users.

Results: We identified 5,181 individuals who received at least one prescription for a pharmaceutical cannabinoid. Nabilone accounted for 73,650 (96.0%) of all prescriptions dispensed; dronabinol was discontinued during the study period. The annual prevalence rate of use increased by 527.2%, from 21.5 (95% confidence interval [CI] 21.4–21.6) users per 100,000 person-years in 2004/05 to 134.9 (95% CI 134.7–135.1) users per 100,000 person-years in 2014/15. The annual incidence rate increased by 413.3%, from 12.1 (95% CI 12.1–12.2) users per 100,000 person-years in 2004/05 to 62.2 (95% CI 62.1–62.4) users per 100,000 person-years in 2014/15. The highest use was among older adults aged 46–64 years, females and urban area residents. One-third of incident users (1775 [35.3%]) had a diagnosis of fibromyalgia in a 2-year period before their first cannabinoid prescription. General practitioners initiated almost half (46.7%) of first prescriptions, and anesthesiologists/pain specialists initiated one-quarter (25.8%).

Interpretation: The prevalence and incidence of pharmaceutical cannabinoid use has increased over time. These findings provide insight into the utilization of cannabinoids before the introduction of recreational marijuana that may affect this trend.

2.2 **Introduction**

Cannabis is widely used in Canada; 42.5% of Canadians aged 15 years and older have used cannabis in their lifetime and 17.7% of Canadians who used cannabis reported using it for medical purposes.[1-2] While cannabis has a long history of being used for several conditions such as pain and epilepsy; there is lack of high-level evidence to support its use.[3-5] Pharmaceutically-derived prescription cannabinoids include nabilone, dronabinol and nabiximols. While all three have been available in Canada, currently only nabilone and nabiximols are available.[6] The use of these agents must now be considered in light of recreational cannabis legalization in Canada in October 2018, a move that garnered critical attention regarding the potential economic, social and public health implications.[7-9] One particular concern is the blurring of recreational and medical use, which has been available since 2001, and the potential confusion in healthcare monitoring of those using it medically. Pharmaceutically-prepared cannabinoids may provide better dose standardization and administration consistency compared to raw cannabis when used for therapeutic purposes. Moreover, pharmaceutical cannabinoids pose a lower risk of abuse compared to plant-based cannabis.[10-12]

Nabilone is a cannabinoid receptor agonist approved in 1982 in Canada for chemotherapy-induced nausea and vomiting (CINV) not responding to conventional therapy. Dronabinol, an oral form of tetrahydrocannabinol (THC), was approved in 1994 for CINV and for anorexia associated with human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS), before its discontinuation in 2012. Nabiximols, an extract containing THC and cannabidiol (CBD), was approved in 2005 for central neuropathic pain in multiple sclerosis, and in 2007 for intractable cancer pain. These medications have

also appeared in practice guidelines as third-line alternatives for several off-label indications, such as fibromyalgia and arthritis.[13-15]Several studies have discussed the potential efficacy and possible adverse effects of pharmaceutical cannabinoids; however, there is still a lack of information regarding their use in the population.[3, 17-19] An understanding of the extent of utilization in the real-world can be achieved by drug utilization studies that rely on analyzing drug dispensations and physician claims, prospectively collected for health system management. Characterizing the past trends of cannabinoid use enables a review of their utilization and establishes baseline measurements before recreational cannabis legalization. Therefore, we analyzed the prevalence and incidence of pharmaceutical cannabinoid use in Manitoba, a Canadian province with a relatively stable population of 1, 27 million as of 2016. We also described the demographics and medical conditions of users.

2.3 **Methods**

Data Sources

A retrospective, population-based cross-sectional study was conducted from April/1/2004 to March/31/2015 using data obtained from the administrative databases within the Manitoba Population Research Data Repository located at the Manitoba Centre for Health Policy (MCHP), University of Manitoba.[20] This repository captures the encounters with the health system for > 98% of the Manitoba population that receives health care coverage through the provincial government department, Manitoba Health, Seniors and Healthy Living (MHSHL).[21] These data have been validated and used extensively in health services research.[22,23]

Data were linked across multiple datasets using scrambled personal health identification number (PHIN). Several databases were used, including the Drug Program Information

Network (DPIN) database, which includes the dispensation date, drug name, and medical specialty of the prescriber. DPIN captures all prescription drugs dispensed by community pharmacies to Manitoba residents, regardless of the type of insurance coverage (government-sponsored, private or out-of-pocket). This provides a comprehensive description of non-hospital drug use. The provincial Pharmacare program provides complete coverage for eligible medications for Manitobans after an income-based deductible has been met during the fiscal year.[24] The Medical Services (physician claims) database provided service date and a diagnosis code using the International Classification of Diseases, Clinical Modification (ICD-9-CM); while the Discharge Abstract Database provided hospital admission and discharge dates and several diagnoses using ICD9-CM/10-CA (Canadian) codes. The Manitoba Health Insurance Registry database provided the number of Manitoba residents at the beginning of each interval (one year), user's demographic information, and the dates of their health care coverage.

Study population and exposure definitions

We identified pharmaceutical cannabinoid users living in Manitoba during the 11-year study period, without age restrictions. Prescription dispensations were identified by their Anatomical Therapeutic Chemical (ATC) codes including nabilone (ATC A04AD11), dronabinol (A04AD10), nabiximols (N02BG10). The number of incident and prevalent users was assessed. Incident use was defined as first time use in the study period, with no record of a previous prescription, since the first year of available data, 1995, while prevalent use in a specific year, was defined as receiving at least one cannabinoid prescription in that year throughout the study period. Region of residence was defined as urban (Winnipeg, n=705,244

and Brandon, n=48,859), or rural Manitoba, which includes all other population centers with <16,000 people in each.

The medical conditions of cannabinoid users were identified using algorithms, used in previous research, based on ICD codes from physician claims, hospitalizations, and/or use of prescription medications (Supplementary table 2.1). Medical claims and hospitalizations within two years before the first cannabinoid dispensation were used to ensure a recent diagnosis. We chose 11 medical conditions including the approved indications (multiple sclerosis, HIV/AIDs, and cancer, excluding in situ and skin cancer), and conditions reported in the literature as possible indications for cannabinoid use (glaucoma, epilepsy, rheumatoid arthritis, osteoarthritis, fibromyalgia, mood/anxiety disorders). [4] Schizophrenia and substance abuse disorders were also investigated, as the use of cannabinoids is not recommended in these conditions. Chronic pain was also assessed and defined as a minimum of 180-day supply in at least 2 dispensations of opioids, NSAIDs or acetaminophen and its combinations, excluding psycholeptics and cold preparations, within the year preceding the first cannabinoid prescription.[25]

Last, the medical specialty of prescribers initiating these prescriptions was determined from the de-identified physician identification number reported on the prescription.

Statistical analysis

Annual prevalence rates of cannabinoid use were calculated by dividing the number of prevalent users in a year by the population count on December/31st of that calendar year. Annual incidence rates were calculated by dividing the number of first time users in a year by the population count, excluding prevalent users, in that calendar year. Then the annual incidence rates were calculated for sub-groups based on age, sex, and region of residence.

Multivariable Poisson regression analysis, adjusted for age, sex, area of residence, and socioeconomic status (SES) was used to test for temporal trends in the incident and prevalent rates, which were calculated based on aggregate data for each stratum. To account for health coverage that is less than one year, log person-years was included as an offset in the model. Age was included as a categorical variable and was categorized into ≤ 18, 19-45, 46-64, and ≥65 years. This categorization was based on guidelines requiring caution when prescribing these agents to children and the elderly and to account for the higher risk of conditions like multiple sclerosis and cancer in older compared to younger adults. SES was categorized into 4 groups based on the Socio-Economic Factor Index (SEFI), which is an area level measure derived from Census data. The categorization, according to a validated definition, was based on cut-off points of one standard deviation from the mean into high, middle, middle-low and low SES. [26] A p-value of ≤ 0.05 was considered significant. Data were analyzed using SAS software package for Windows, version 9.4 (SAS Institute, Inc., Cary, NC).

Ethics approval

This study was conducted in full compliance with the Personal Health Information Act of Manitoba and approved by the Health Research Ethics Board at the University of Manitoba and the Manitoba Health Information Privacy Committee (# H2015:271).

2.4 **Results**

Prescriptions

Between April/2004 and March/2015, 76,719 cannabinoid prescriptions were dispensed to 5,181 unique individuals, 5,033 of whom received their first prescription after April/1st, 2004. Nabilone comprised 96% of all cannabinoid prescriptions dispensed. One-third (32.2%) of the incident cannabinoid users received only one prescription. General practitioners were

responsible for initiating 46.7% of first prescriptions, followed by anesthesiologists/pain specialists (25.8%). Only 5.4% of prescriptions were initiated by oncologists.

Incident cannabinoid use

Among all new users, the mean (SD) age was 50.6 (14.7) years and 58.3% were females. The annual incidence rate increased (by 413.3%) from 12.12 (95%CI: 12.06-12.19) to 62.21 (95%CI: 62.08-62.35) users per 100,000 person-years over the study period. The incidence of nabilone use increased (by 475.4%) from 10.76 (95%CI: 10.69-10.82) 2004/2005 to 61.91 (95%CI: 61.77-62.05) users per 100,000 person-years in 2014/2015. The incident use of both nabiximols and dronabinol was low, until dronabinol was discontinued in 2012. (Figure 2.1).

The incident use of cannabinoids by demographics of users is reported in figure 2. Between 2004 and 2015 the incidence rate increased by 242.51% for females and 141.03% for males (Figure 2.2.A). The incidence rate for the older adults (46-64 years) increased by 258.63%. The incidence rate increased by 256.9% and 86.8% for those ≥ 65 years and younger adults (19-45 years), respectively. The youngest segment of the population (0–18 years) showed the lowest incidence of use (Figure 2.2.B). The incident use increased for residents of urban Manitoba by 154.4% and 272.1% for residents of rural Manitoba (Figures 2.2.C).

Prevalent cannabinoid use

The overall rate of use of cannabinoids throughout the 11-year period was 82.4 users per 100,000 person-years. The prevalence of cannabinoid use increased by 527.2% over the study period, from 21.51 users per 100 000 person-years (95% CI 21.41–21.61) in 2004/05 to 134.91 users per 100 000 person-years (95% CI 134.71–135.11) in 2014/15. The prevalence

of nabilone use also increased (by 642.8%) from 18.01 (95%CI: 17.93-18.09) in 2004/2005 to 133.77 users per 100,000 person-years (95%CI: 133.57 – 133.97) in 2014/2015. The prevalent use of both dronabinol and nabiximols was low throughout the study period (Figure 2.3).

Incidence and prevalence rates standardized to the Canadian population based on statistics Canada data in 2016 are reported in supplementary figure 2.2.

The effect of user demographic on incident and prevalent use.

The sociodemographic characteristics of incident users are reported in (Table1). After adjusting for age, sex, area of residence, and the SES, the annual rate of prevalent and incident cannabinoid use increased by 1.15 and 1.09 per 100,000 person-years, respectively. The upward trend was significant for both models. The effect of user demographics on use is reported in (Table 2.2).

Medical conditions of incident cannabinoid users

We identified 1,775 incident cannabinoid users (35.26%) who had received a diagnosis of fibromyalgia, and 1,116 with a diagnosis of mood and anxiety disorders (22.17%). The percent of users who had a diagnosis for the approved indications: cancer, multiple sclerosis, and HIV/AIDS were 18.21%, 4.23%, 1.01%, respectively (Table 2.1). Moreover, 50.46% (n=2,540) of cannabinoid users were being treated for chronic pain in the year before their first cannabinoid prescription.

2.5 **Interpretation**

This population-based study found an increase in the number of pharmaceutical cannabinoid users in Manitoba over an 11-year period, driven almost entirely by nabilone use. In 2009, there was a slight temporary decrease in nabilone use. Considering that there were no

alternatives to Cesamet® (nabilone) by *Valeant Pharmaceuticals* International, Inc., this drop might be explained by a recall of Cesamet® due to a mislabeling incident identified nationally by Health Canada.[27]

The rates of use were higher for females; several factors can affect this trend, possibly because conditions like fibromyalgia, osteoarthritis, and mood/anxiety disorders are more common in women. As expected, the lowest rate of use was among the youngest age group as the use of cannabinoids in those <18 years is not recommended due to lack of safety data. The highest rate of use was among individuals between ages 46 to 64 followed by those ≥65 years; where conditions like multiple sclerosis and cancer are more prevalent. There was a difference in the rates of use among urban vs rural residents, possibly due to difference in access and use of health care.

The majority of medical conditions identified were pain-related conditions such as fibromyalgia, osteoarthritis, cancer, and multiple sclerosis (Table 2.1). Almost half of the incident cannabinoid users met the study definition of chronic pain. This pattern of use is consistent with the growing evidence regarding the potential role of cannabinoids in pain management and the safety of chronic opioid use, which may have influenced the pattern of cannabinoid use during this study period.[4, 28,29] Despite the caution required, we found that 8.3% of incident users received a diagnosis of substance use disorder; this could be due to prescribers looking for an alternative to medical cannabis among those who have a history of substance use disorder. The number of users with diagnosis for schizophrenia was very low as these agents are contraindicated when there is history of psychosis. The percentage of users who met the study definition for the approved indications was low. Furthermore, one third of incident users only filled one prescription. This could be a reflection of the real-world

effectiveness of these agents; however, the underlying reason to explain this trend requires further investigation.

Regarding the overall increase in nabilone use over time, this might be related to a general increased interest in medical marijuana, as nabilone represents an option that is easier to access and covered by the provincial drug program, in contrast to nabiximols.[30] Furthermore, prescribers may prefer nabilone over raw medical cannabis because it generally causes less euphoria than marijuana, hence is less prone to abuse, and because of its consistent, standardized dosing, which is highly variable with the natural cannabis products.[12,31-32]

However, it is unknown if this trend will continue after the legalization of recreational cannabis as several patients may favor purchasing cannabis over a physician visit and filling a prescription. This will be determined by the cost, age, quantity limits, and other administrative regulations associated with legalization.[7]

2.6 **Strengths and limitations**

This is an observational, population-based database study that captures nearly every encounter between Manitoba residents with a universal health care system, allowing for a complete assessment of the real-world drug utilization, without sampling errors. Despite the advantages of observational studies using administrative data, there are recognized limitations. These include potential misclassification of medical conditions using data not intended for research purposes; however, algorithms validated in other studies were used to minimize misclassifications. It is impossible to fully determine the intended indication for the use of cannabinoids, which have a number of potential uses. Thus, even when an associated condition is correctly identified, the clinical indication for cannabinoid use cannot be

confirmed. This is especially difficult in chronic pain as there is no consensus on a validated definition for identifying pain patients using administrative data, despite the fact that numerous painful conditions can be identified. Moreover, other factors that we were not able to examine, such as ethnicity, might influence cannabinoid use.

2.7 **Conclusion**

Incident and prevalent cannabinoid use increased over the study period. Nabilone comprised the majority of dispensed cannabinoids. Incident use was higher throughout the 11-year period among females and older adults. Pain and pain-related conditions represented the highest percent among the possible indications for cannabinoids. These findings provide insight into the utilization of these agents before policies regarding access to cannabis change. The introduction of recreational marijuana and its legal availability may affect this trend.

2.8 **Acknowledgment**

This study is supported by funding from the College of Pharmacy, University of Manitoba. The authors thank the Manitoba Centre for Health Policy for use of data contained in the Manitoba Population Research Data Repository under project (HIPC 2015/2016–22). The results and conclusions are those of the authors and no official endorsement by the Manitoba Centre for Health Policy, Manitoba Health, Seniors and Healthy Living, or other data providers is intended or should be inferred. The authors would like to thank and acknowledge Heather Prior and Natalia Dik for retrieving the data.

2.9 **Figures and tables**

Figure 2.1: Annual incidence of cannabinoid users (2004/05-2014/15).

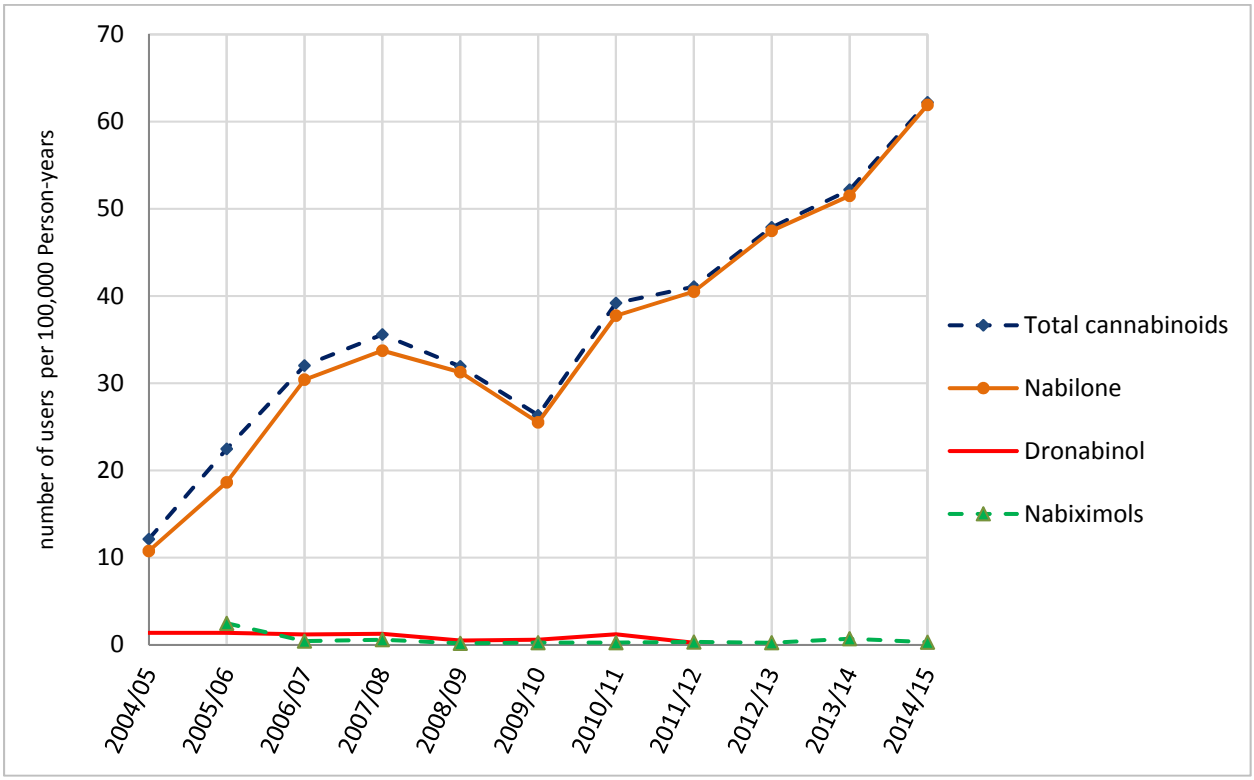


Figure 2.2.A: Annual incidence rate of cannabinoid use by age group (2004/05-2014/15).

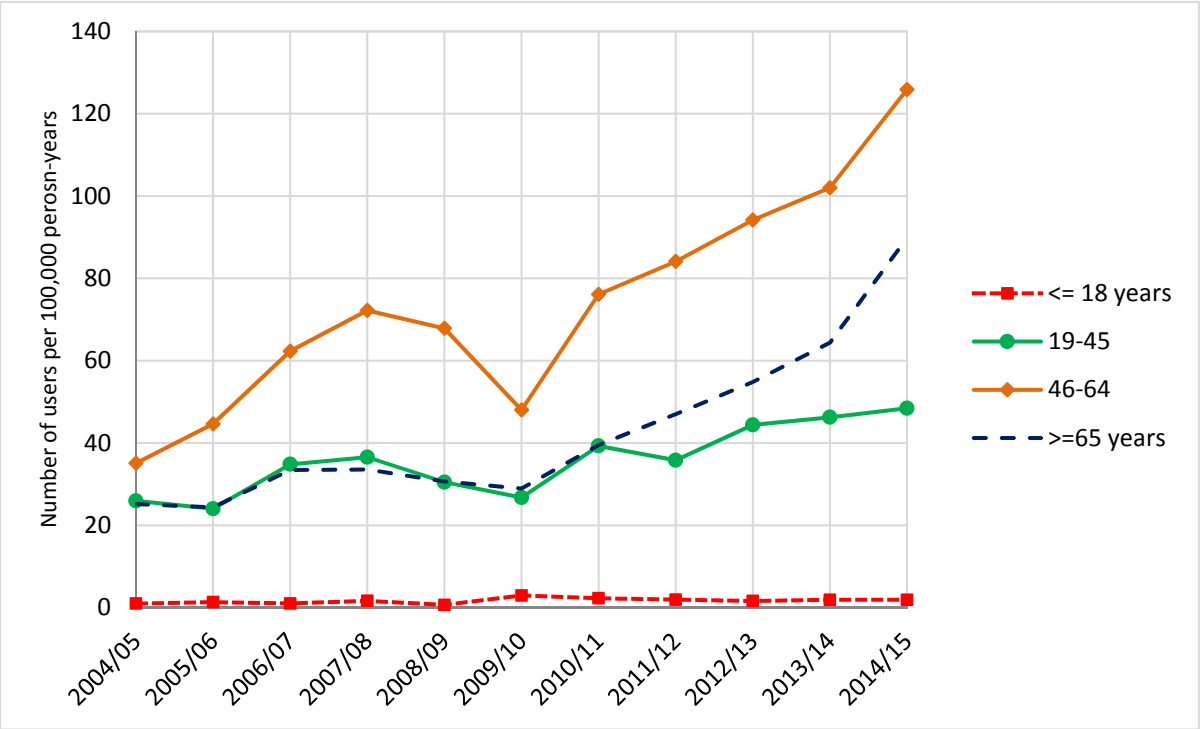


Figure 2.2.B: Annual incidence rate of cannabinoid use by sex (2004/05-2014/15).

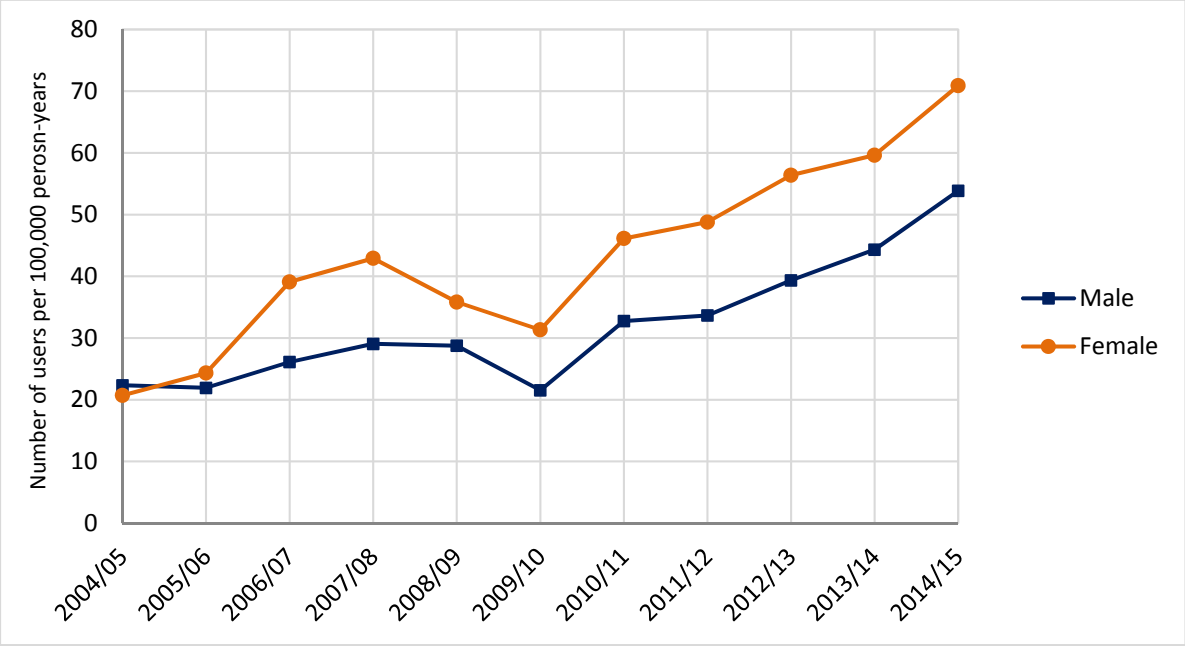


Figure 2.2.C: Annual incidence rate of cannabinoid use by area of residence (2004/05-2014/15).

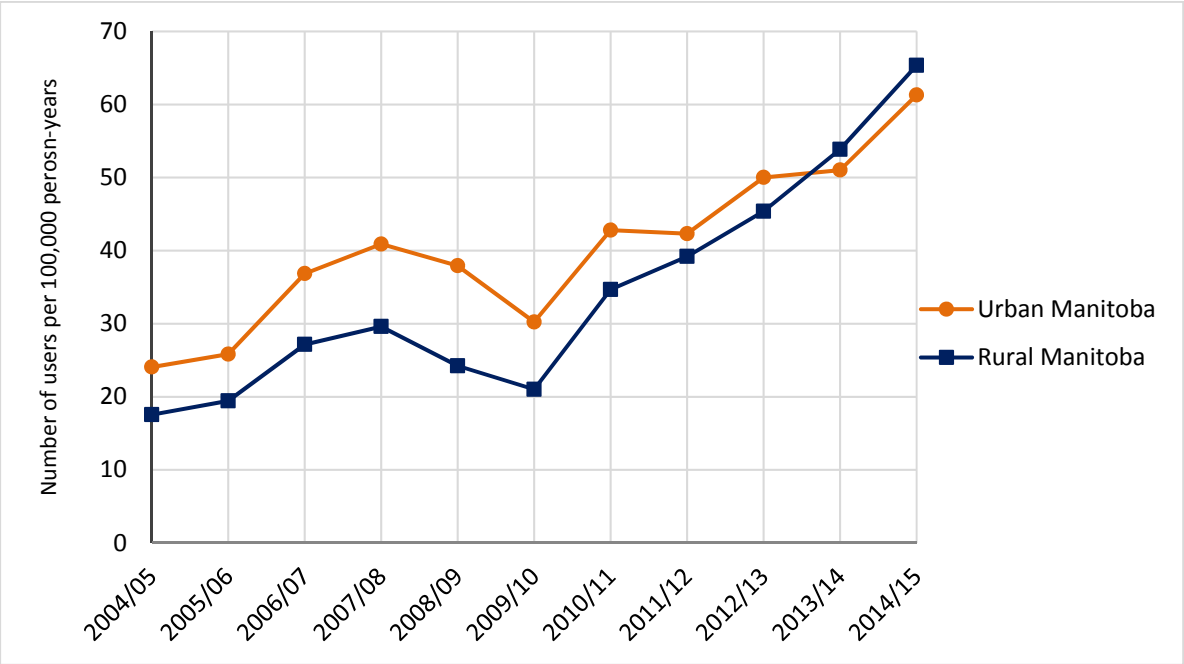


Figure 3: Annual prevalence of cannabinoid users (2004-2015).

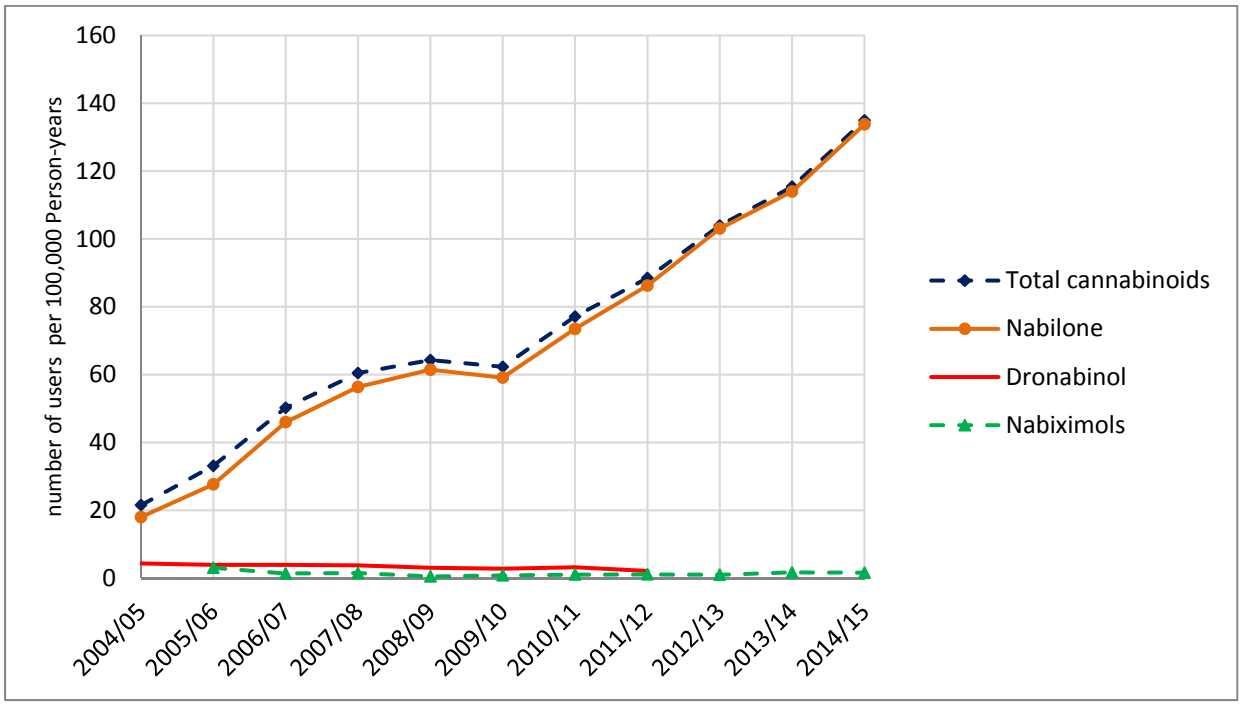


Table 2.1: Demographics and medical conditions of new cannabinoid users.

Variable	No.	%
Age Group (y)		
≤18	55	1.09
19-45	1698	33.74
46-64	2455	48.78
≥65	825	16.39
Sex		
Female	2934	58.30
Male	2099	41.7
Area of residence		
Urban	3207	63.7
Rural	1826	36.3
Socioeconomic status		
High	458	9.1
Middle	1712	34.0
Mid-low	2028	40.3
Low	835	16.6
Medical conditions*		
Chronic pain	2540	50.46
Fibromyalgia	1775	35.26
Mood/Anxiety	1116	22.17
Cancer	917	18.21
Osteoarthritis	662	12.35
Substance abuse	418	8.30
Multiple sclerosis	213	4.23
Glaucoma	169	3.35
Rheumatoid arthritis	155	3.07
HIV/AIDS	51	1.01
Schizophrenia	29	0.57
Epilepsy	27	0.53

*user can belong >1 group

Table 2.2: Effect of time and socio-demographics on the prevalence and incidence of cannabinoid use in Manitoba, 2004/2005-2014/2015.

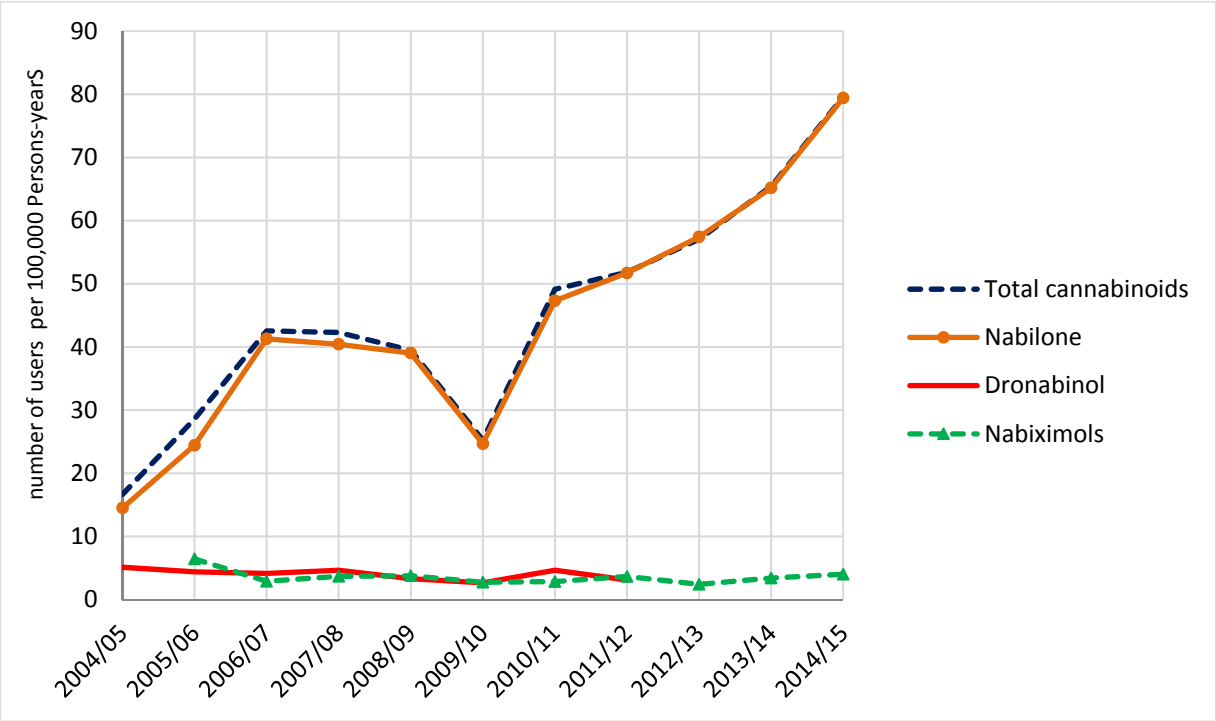
Variable	PREVALENCE		INCIDENCE	
	Relative rate	95% CI	Relative rate	95% CI
Change in annual rate	1.15	1.14-1.16	1.09	1.08-1.10
Sex				
Female vs male	1.38	1.30-1.46	1.33	1.23-1.42
Age				
≤18 vs ≥65	0.03	0.02-0.04	0.04	0.03-0.06
19-45 vs ≥65	0.96	0.88-1.06	0.82	0.74-0.91
46-64 vs ≥65	2.28	2.09-2.49	1.70	1.53-1.89
Region				
Urban vs rural	1.17	1.10-1.24	1.11	1.04-1.19
Socioeconomic status				
Low vs high	0.62	0.55-0.71	0.79	0.68-0.92
Mid-low vs high	0.73	0.66-0.80	0.84	0.74-0.95
Middle vs high	0.92	0.89-1.08	1.06	0.94-1.19

Supplementary Table 2.1: Algorithms for identification of medical conditions among prescription cannabinoid users. [33-38]

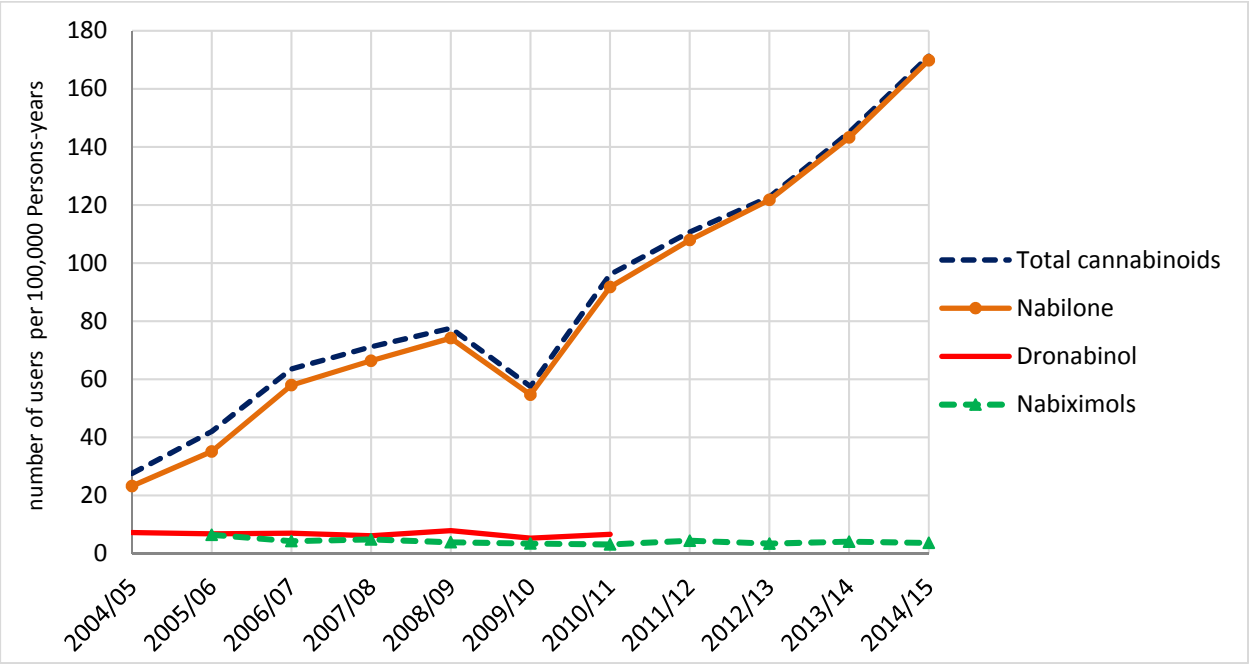
Condition	Definition*	ICD 9	ICD 10
Epilepsy	1H and/or 3P**	345	G40,G41
Cancer	1H and/or 2P	140-172, 174-209	C00-C43, C45-C97
Schizophrenia	1H and/or 2P	295	F20-F25
HIV/AIDS	1H and/or 3P	042-043	B20-B24
Rheumatoid Arthritis	1H and/or 2P	714	M05,M06
Osteoarthritis	1H and/or 2P	715	M15,M16
Fibromyalgia	1H and/or 2P	729	M79
Multiple sclerosis	1H and/or 3P	340	G35
Substance abuse/misuse	1H and/or 1P	291,292,303,304,305	F10-F19,F55
Glaucoma	2 P	365	N/A
Mood/Anxiety disorders	A. 1H for (mood disorders), (stress and adjustment disorders), (mental and behavioral disorders), (emotional disorders).	A. (296.1,296.8), (300.4 309,311).	A. (F33, F36,F38), (F43),(F53),(F93).
	B. 1H for anxiety disorders, depressive disorder, mood disorders, obsessive-compulsive disorders dissociative disorders somatoform disorders + 1 Pres for antidepressant/mood stabilizer*	B. (300.0)	B. (F40, F41), (F32), (F34.1), (F42), (F44), (F45.0, F45.1).
	C. 3P for mood disorders, reaction to stress and adjustment disorders, depressive disorders.	C.(296),(309),(311)	
	D. 3P for anxiety disorders + 1 pres for antidepressant/ mod stabilizer.	D. 300	

Abbreviations: H, hospitalization; P, physician claim; Pres, prescription.
* Within two years before the first cannabinoid prescription dispensation.
** physician claims separated by 30 days.

Supplementary figure 2.1: Annual incidence of cannabinoid users (2004/05-2014/15) standardized to the Canadian population (2016).



Supplementary figure 2.2: Annual prevalence of cannabinoid users (2004/05-2014/15) standardized to the Canadian population (2016).



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Chapter Three. Persistence of use of pharmaceutical cannabinoids in Manitoba.

Study classification: A population-based cohort study.

Journal: *Addiction,* under review (Submitted Nov 14, 2018)

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The main objectives of this study are:

1- To assess the persistence of the first episode of use of pharmaceutical cannabinoid agents in an outpatient setting.

2- To explore the relationship between cannabinoid persistence and socio-demographic characteristics and medical conditions of incident pharmaceutical cannabinoid users.

3.1 **Abstract**

Background and aims: Despite the mixed evidence to support their efficacy and their well-characterized side effects, pharmaceutical cannabinoids are used for a variety of conditions, such as pain. Randomized controlled trials are not able to measure the 'real-world' persistence of medication use. Hence, this study aimed to assess the persistence of use of pharmaceutical cannabinoid agents and assess the potential socio-demographic characteristics and medical conditions associated with the discontinuation of these agents in a naturalistic setting.

Design and setting: A retrospective, population-based, cohort study using administrative data from the Manitoba Population Research Data Repository located at the Manitoba Centre for Health Policy.

Participants: Incident pharmaceutical cannabinoid users from April 1st, 2004 to April 1st, 2016 were included and followed for one year from the date of first prescription dispensation.

Measurements: Persistence was defined as continuous use without a gap exceeding 60 days. Data were analyzed, using a competing risk regression model (Cause-specific hazards model), with death from any cause as the competing risk, to assess factors that may influence discontinuation rates.

Findings: Among 5,881 pharmaceutical cannabinoid users, 5,452 were incident users, of whom only 18.1% continued using cannabinoids at one year. The final regression model showed that age and income status had a significant effect on persistence of cannabinoid use. Fibromyalgia, osteoarthritis, and substance use disorder were associated with lower discontinuation rates with hazard ratios (95%CI) of 0.89 (0.84-0.95), 0.91 (0.82-0.97), 0.85 (0.76-0.94), respectively, while cancer was associated with higher discontinuation rates 2.73(2.02-3.67).

Conclusions: In a naturalistic setting, persistence of prescription cannabinoid use was low and affected by age, income, and specific medical conditions of the incident user. The reason for these observed differences and the effects of the recent legalization of recreational cannabis in Canada warrant further investigation.

3.2 **Introduction**

Despite the limited research regarding the efficacy and appropriateness of medical cannabinoids, they are used for a variety of conditions. Specifically, little research has been carried out on the population use of pharmaceutical cannabinoid medications.[1] Three pharmaceutical cannabinoids have been available in Canada for therapeutic use: nabilone (Cesamet®), a CB1 cannabinoid receptor agonist, dronabinol (Marinol®), a synthetic delta-9-tetrahydrocannabinol (THC), and nabiximols (Sativex®®), an extract containing THC and cannabidiol (CBD).[2] Nabilone is an oral medication that has been available in Canada since 1982 and has a Health Canada-approved indication for the treatment of severe chemotherapy-induced nausea and vomiting.[1,3] Dronabinol is another oral medication that was available in Canada (Dec, 31, 1994 to Feb, 24, 2012), approved for the treatment of severe chemotherapy-induced nausea and vomiting and weight loss associated with acquired immune deficiency syndrome (AIDS)-related anorexia.[4] Nabiximols is an oromucosal spray that entered the Canadian market in 2005 as an adjunctive treatment for spasticity or neuropathic pain in adult patients with multiple sclerosis and for intractable cancer pain.[2,5] While these agents have approved indications for very specific conditions, they have also been used for several off-label indications, such as fibromyalgia, arthritis, epilepsy, and anxiety disorders.[6-8]

Since their development, several studies have examined the efficacy and safety of cannabinoids for a wide array of conditions but with conflicting results.[9, 10] While evidence supporting their efficacy is mixed, the adverse effects have been well characterized and include somnolence, euphoria, disorientation, drowsiness, confusion, loss of balance, and hallucination.[9,10] The user's experience with respect to benefits and harmful effects can greatly influence their persistence of use. When medications fail to provide the anticipated

effect or induce intolerable adverse effects, users may discontinue the treatment.[11] Discontinuation rates of medications in randomized controlled trials (RCT) are possibly lower than routine clinical practice due to more motivation to endure adverse events in RCTs than in a primary clinical setting.[12] Moreover, RCTs are for a short period of time (2-15 weeks [9]) and tend to exclude patients with comorbid medical problems and polypharmacy that are commonly encountered in routine clinical practice.[13] In addition there are also theoretical concerns with these products, that misuse may increase persistence, however, there is limited research regarding the abuse potential of these medications.[14,15]

Observational studies using administrative databases better reflect the 'real-world' duration of use. Very few observational studies have examined the duration of pharmaceutical cannabinoid use and the discontinuation rates in a naturalistic setting.[1] Consequently, this study aimed to assess the persistence of use of pharmaceutical cannabinoid agents in an outpatient setting using administrative health data. The relationship between cannabinoid persistence and socio-demographic characteristics and medical conditions was also explored.

3.3 **Methods**

Data Sources

We conducted a retrospective, population-based cohort study in Manitoba, a centrally located Canadian province with a population of approximately 1.27 million, as of 2016.[16] The universal health care system in Manitoba provides health care services at no charge to all residents, while the provincial Pharmacare program provides complete coverage for eligible medications for residents after an income-based deductible has been met during the fiscal year. All administrative data that include hospital, physician, and prescription claims are electronically captured at the time of service and collected by the Manitoba Population

Research Data Repository located at the Manitoba Centre for Health Policy at the University of Manitoba. These data have been validated and used extensively in health services research.[17,18]

We acquired data from April 1st, 1995 to March 31st, 2017 to assess the persistence of cannabinoid use in Manitoba. Several databases from the repository were used for this study. The Drug Program Information Network (DPIN) database captures all outpatient prescription drug dispensation information, regardless of insurance coverage, providing a comprehensive description of non-hospital drug use. DPIN provided the date of dispensation, drug name, drug identification number (DIN), and day supply. The DINs of pharmaceutical cannabinoids are linked to their ATC codes, which were used to identify the agents, (nabilone (Cesamet® and generics) (ATC Code A04AD11), nabiximols (Sativex®) (ATC Code N02BG10), and dronabinol (Marinol®) (ATC Code A04AD10).19 The Manitoba Health Insurance Registry database provided the dates of health care coverage and the users' demographic information (e.g., dates of birth, sex, area of residence (postal codes)). The Medical Services (physician claims) database provided the service date and a diagnosis code recorded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The Hospital Discharge Abstract Database provided information on hospitalizations, including the admission and discharge dates, as well as diagnoses using ICD-9-CM or ICD-10-Canadian (CA) codes. Last, the Vital Statistics database provided the dates of death of the cannabinoid users.

Study design and definitions

Incident users of any cannabinoid agent, i.e. the first cannabinoid agent used, from April1st, 2004 to April 1st, 2016 were identified. Incident use was defined as first time use in

the study period, with no record of a previous cannabinoid prescription, since the first year of available data, 1995.These individuals were followed for a one-year period starting from the date they received their first prescription. If the agent used was dronabinol, the last date of incident use allowed in the cohort was Feb, 24th, 2011, to allow for at least one -year of follow-up. All prescriptions were given an 'index date', the date on which the prescription was filled, and an 'end date', the date which corresponds to the starting date of the prescription plus the number of days supplied by the prescription. When prescriptions overlapped (i.e. when a patient filled an additional prescription before the end date of the preceding prescription), residual days were added to the end date of the next prescription. The status of the user's persistence to cannabinoids was categorized as either 'non-persistent', or 'persistent'. If the user had a gap of more than 60 days between the calculated end date of a prescription and a refill, the patient was classified as 'non-persistent'. The 'discontinuation date' was the date of the last calculated end date, and time to discontinuation was the time from the first index date to the discontinuation date. We restricted our analysis to the first episode of use, without allowing users to re-enter the cohort after being classified as 'non-persistent'. If therapy was not discontinued, before the end of the follow up period, the user was classified as 'persistent'. In-patient medication use of cannabinoids during hospitalizations was assumed. Last, as sensitivity analyses, these calculations were repeated using 30-day and 90-day gaps.

Potential factors associated with persistence

Patient-related characteristics (age, sex, area of residence, socioeconomic status, and medical conditions) were examined to assess their associations with rates of discontinuation. We included eight medical conditions that have been reported in the literature as possible

indications for cannabinoid use (multiple sclerosis, epilepsy, rheumatoid arthritis, osteoarthritis, fibromyalgia, HIV/AIDs, mood/anxiety disorders, and cancer, excluding in situ and skin cancer).[9] We also included substance abuse disorder to examine any possible association with persistence or any possible abuse. The medical conditions were identified using algorithms based on ICD codes from physician claims, hospitalizations, and/or use of prescription medications. These algorithms used have been validated, or used in previous research, (Supplementary table 3.1).[20-25] Medical claims and hospitalizations within two years before the first cannabinoid prescription dispensation were used to ensure individuals were actively receiving care for these conditions when they received their first cannabinoid prescription.

Statistical analysis

We conducted survival analyses using Kaplan–Meier estimators for any cannabinoid and then stratified by the cannabinoid agent. In the survival analysis, patients were censored in case of death, health coverage ending before the discontinuation date, or if the user reached the end of the follow-up period (one year) without discontinuing the cannabinoid agent. Then, we used a competing risk regression model (Cause-specific hazards model), with death from any cause as the competing risk, to assess if age, sex, area of residence, socioeconomic status (SES), and all the medical conditions identified were associated with discontinuation rates. Time to discontinuation, in days, was the dependent variable. Age was based on the date of the first cannabinoid prescription fill and was treated as a categorical variable in the analysis. We categorized age into 4 groups (≤18, 19-45, 46-64, and ≥65 years). Region of residence was defined as urban that included the two largest cities in the province, Winnipeg (population > 700,000) and Brandon (population > 48,000), or rural, which included the

remainder of the province. SES was included as a categorical variable in the model. The categories were based on the Socio-Economic Factor Index (SEFI), which is an area level measure derived from Census data. SEFI uses four variables to calculate an overall score: the average household income, percent of single parent households, unemployment rate, and high school education rate.[26] SEFI creates four categories: high, middle, middle-low and low SES, using cut off-points of one standard deviation from the mean. The proportional hazards assumption for each categorical variable was tested.[27] Cancer diagnosis violated the assumption and was treated as a time-dependent covariate and incorporated to the model as the interaction between each level of cancer (yes/no) and time.

A p-value of ≤ 0.05 was considered statistically significant. Data were analyzed using SAS software package for Windows, version 9.4 (SAS Institute, Inc., Cary, NC).

Ethics approval

This study was conducted in compliance with the Personal Health Information Act of Manitoba and approved by the Health Research Ethics Board at the University of Manitoba and the Manitoba Health Information Privacy Committee.

3.4 **Results**

Out of 5,881 pharmaceutical-cannabinoid users between April 1st, 2004 and April 1st, 2016, 5,452 were incident users and included in the cohort. Nabilone was the most used agent (n=5307; 97.3%), followed by dronabinol (n=77; 1.4%) and nabiximols (n=68; 1.2%).The mean (SD) age of users was 51.2 (15.0) years and 59% were females. Their characteristics at entry into the cohort are reported in Table 3.1 and their medical conditions are reported in Table 3.2.

Approximately one-third (33.6%) of the included users received only one prescription for a pharmaceutically-derived cannabinoid agent. The percentage of those who persisted (i.e. there was no gap > 60 days between dispensations) to use cannabinoids for one year from their first prescription dispensation was only 18.1%. The proportion of users persisting on therapy at one year differed by cannabinoid, being 18.4%, 10.9%, 5.9% for nabilone, dronabinol, and nabiximols, respectively. The median (IQR) duration of use, in days, during the one-year follow up period was 31(25-193) for all cannabinoids, 33(25-199) for nabilone, 30 (16-134) for dronabinol, and 20 (7-30) for nabiximols. The Kaplan-Meier curves of non-persistence differed for patients prescribed nabilone, dronabinol, and nabiximols (Log-rank x^2= 46.8; p = <0.0001) (Figure 2.2). These overall trends of persistence remained the same when 30- and 90-day refill gaps were applied. The percentage of those who persisted to use cannabinoids for one year from their first prescription was 13.7% for a 30-day gap and 19.8% for a 90-day gap. The Kaplan-Meier curves stratified by the drug used also differed significantly for both gaps (P= <0.0001).

The final regression model, adjusted for socio-demographic factors and medical conditions, showed that discontinuation of cannabinoid therapy was related to the agent used. Compared to patients prescribed nabilone, patients prescribed nabiximols (Sativex®) were more than twice as likely to discontinue therapy (Table 3.3).

The effect of sociodemographic characteristics and clinical conditions on persistence

Sex was not associated with discontinuation of cannabinoid use. Compared to those 65 years and older, those aged 19-64 years had lower rates of discontinuation. While region of residence was not associated with rates of discontinuation, the socio-economic status was. Only those among the low-income group had significantly higher rates of discontinuation

compared to those among the high-income group. Among all medical conditions included, only having cancer (versus not having cancer) was associated with higher discontinuation rates. Having fibromyalgia, osteoarthritis, or substance abuse was associated with lower discontinuation rates as compared to not having these conditions (Table 3.3).

3.5 **Discussion**

This study found low persistence of use with pharmaceutical cannabinoid agents. These findings raise questions about the efficacy and the tolerability of these agents but provide reassurance about any possible abuse. There was no significant difference in the rates of discontinuation among those who used dronabinol (89.1%) and nabilone (81.6%); however, the rates of discontinuation were higher for nabiximols (Sativex® 94.1%) with reference to nabilone. Nabilone and dronabinal were covered by the provincial drug insurance program ($110-500 Canadian Dollar (CAD)/month). [28] Nabiximols (Stativex®) is more expensive ($500-1000 CAD per month.[28]) and not covered by the provincial drug insurance program. Drug cost and coverage may therefore be a factor explaining the higher discontinuation rate with nabiximols (Stativex®).

Results from a retrospective registry report in the United Kingdom (UK), Germany and Switzerland, in which safety data were collected on more than 900 patients, showed that there was a positive risk-benefit profile for Sativex® during long-term use and that the long-term rates of discontinuation were 32% over a mean follow-up time of one 1 year.[29] In addition, a prospective registry study involving 207 Sativex® users in Spain showed that more than one-third of patients (35%) discontinued Sativex® during the one-year study period.[30] The main reported reasons for discontinuation were lack of tolerability and/or lack of effectiveness in roughly equal proportions during the first six months. The real world Canadian data in this

study showed a dramatically higher discontinuation rate (94.1%) than found in these European registry studies. These differences could be due to different access and drug coverage regulations and the differences in the availability of whole-plant cannabis for medical purposes. The literature has registry data on over 1000 patients, but the cost and lack of insurance coverage in Manitoba resulted in only a small number of individuals using nabiximols. This may have contributed to the differences found in discontinuation rates. In addition, medical cannabis is readily available in Canada, but it was not an available option in the UK, restricted and difficult to access in Germany, and Spain continues to lack a program for medical cannabis and laws to distinguish recreational and medical use.[31-33]

Among the different sociodemographic characteristics of users, only age and socioeconomic status were associated with persistence. The rates of discontinuation among younger (19-45) and older (46-64) adults were lower than among those 65 years and older. The monographs for these medications require caution when they are used among older adults. Reported adverse effects such as drowsiness and vertigo impose a risk of falls, which is a concern among this population, may have contributed to the higher rate of discontinuation in the group. This can also be explained by the continuous efforts to minimize polypharmacy in this age group.[34] The difference seen in rates of discontinuation among those in the high and low income status may be explained by the financial burden to continue meeting the cost of these relatively expensive products ($110 to $1000 CAD per month).

Regarding the different medical conditions, the higher rates of discontinuation among cancer patients might possibly be explained by the patterns of cyclic use when these agents are used only for chemotherapy-induced nausea and vomiting. This may also be related to their progressive disease, as they get closer to death or unable to swallow, unnecessary drugs

are stopped. In contrast, lower rates of discontinuation among those who have osteoarthritis and fibromyalgia, may relate to regular use and their possible benefit in chronic non-cancer pain management. It is notable that fibromyalgia has lower discontinuation rates without having an official indication for any of the cannabinoids studied. The rates of discontinuation are lower among patients who had a diagnosis of substance use disorder compared to those who did not. Practice guidelines require caution in prescribing and strict monitoring of use of these medications among those who have a history of substance use disorder. However, new literature suggests a possible role for them in the management of cannabis use dependence.[35,36]

Limitations and strengths

This study was based on pharmacy dispensation data, hence the actual consumptions of the dispensed medications can only be assumed. Additionally, data regarding medication use during hospitalization are not available. The exact reason for treatment discontinuation was impossible to ascertain as patients may have discontinued treatment for reasons other than lack of tolerability and efficacy. The low utilization of both dronabinol and nabiximols compared to nabilone that comprised the majority of cannabinoids used is another limitation. We were also unable to measure either the recreational or the medical use of plant-based cannabis, which might have been an alternative option for some users. Last, because the data used are collected for administrative purposes, misclassification of the medical conditions is possible; however, we used algorithms validated or used in other studies to minimize misclassifications. Despite these limitations, this was a population-based database study allowing for a complete assessment of the real-world use, without sampling errors. Moreover,

Manitoba population is relatively stable, allowing us to follow individuals longitudinally over time with limited loss of follow-up.

3.6 **Conclusion**

In a naturalistic setting, we observed high rates of discontinuation of pharmaceutical cannabinoids within the first year of incident use. Typically, high discontinuation rates are found when patients experience limited efficacy or adverse effects with medications.[11]There were also differences in discontinuation times among users with different sociodemographic characteristics and the persistence of use was affected by the medical conditions of users. Fibromyalgia, osteoarthritis and substance use disorder were associated with low discontinuation rates while cancer was associated with higher rates of discontinuation. The reason for these observed differences and the effect of the recent legalization of recreational cannabis in Canada warrant further investigation.

3.7 **Acknowledgment**

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3.8 **Figures and tables**

Table 3.1: Baseline sociodemographic characteristics of pharmaceutical cannabinoid users compared to the Manitoba population.

Variable	Pharmaceutical Cannabinoid Cohort	Manitoba Population*
	N=5,452	N=1,242,428
Age (years), mean (SD)	51.9 (15.0)	37.9 (22.9)
Age group (years), n (%)		
≤ 18	53 (0.97)	307,009 (24.7)
19-45	1,684 (30.9)	447,969 (36.1)
46-64	2,688 (49.3)	315,328 (25.4)
≥ 65	1,027 (18.8)	172,122 (13.8)
Females, n (%)	3,217 (59.0)	628,654 (50.6)
Urban residents, n (%)	3,426 (62.8)	782,729 (62.9)
Socioeconomic status, n (%)		
High	473 (8.7)	143,150 (11.5)
Middle	2,028 (37.2)	404,928 (32.6)
Mid-low	2,243 (41.1)	531,251 (42.8)
Low	708 (13.0)	158,728 (12.8)
NF**	-	4,371 (0.35)

*Manitoba population at study mid-point, year= 2010.

**NF, not found, includes individuals to whom neighborhood income could not be assigned (i.e., personal care home residents, residents of psychiatric facility and prisons, wards of the public trustee or child and family services).

Table 3.2: Medical Conditions of cannabinoid users.

Medical Condition, n (%)*	N=5452
Fibromyalgia	1,894 (34.7)
Mood and anxiety	1,275 (23.4)
Cancer	1,008 (18.5)
Osteoarthritis	781 (14.3)
Substance abuse disorder	474 (8.7)
Rheumatoid arthritis	176 (3.2)
HIV/AIDS	59 (1.1)
Epilepsy	32 (0.59)

*Can belong to more than one group

Table 3.3: Association between potential predictors and discontinuation of pharmaceutical cannabinoids use.

Cohort	Crude		Adjusted	
	Hazard Ratio (95% CI)	**P-Value**	**Hazard Ratio (95% CI)**	**P-Value**
Cannabinoid agent				
Dronabinol	1.19 (0.93-1.52)	0.1488	1.14 (0.89-1.45)	0.2993
Nabiximols	2.31 (1.81-2.97)	<0.0001	2.31 (1.80-2.79)	<0.0001
Nabilone	1.00	ref	1.00	Ref
Age group (years)				
≤ 18	1.07 (0.79-1.45)	0.6501	1.04 (0.77-1.40)	0.7885
19-45	0.71 (0.65-0.77)	<0.0001	0.73 (0.67-0.80)	<0.0001
46-64	0.72 (0.67-0.77)	<0.0001	0.74 (0.67-0.79)	<0.0001
≥ 65	1.00	ref	1.00	Ref
Sex				
Females	0.94 (0.88-0.99)	0.0500	0.98 (0.93-1.05)	0.6212
Males	1.00	ref	1.00	Ref
Area of residence				
Rural	1.03 (0.97-1.10)	0.0258	1.04 (0.97-1.10)	0.2631
Urban	1.00	ref	1.00	Ref
Socioeconomic status				
Low	1.36 (1.19-1.55)	<0.0001	1.24(1.08-1.40)	0.0015
Middle-low	1.17 (1.05-1.30)	0.0069	1.09(0.97-1.22)	0.1192
Middle	1.16 (1.04-1.30)	0.0087	1.12(0.99-1.26)	0.519
High	1.00	ref	1.00	Ref
Medical conditions				
Fibromyalgia				
Yes	0.85 (0.79-0.90)	<0.0001	0.89 (0.84-0.95)	<0.0001
No	1.00	ref	1.00	Ref
Cancer*				
Yes	3.40 (2.59-4.59)	<0.0001	2.73 (2.02-3.67)	<0.001
No	1.00	ref	1.00	Ref
Osteoarthritis				
Yes	0.97 (0.89-1.00)	0.0500	0.91 (0.82-0.97)	0.028
No	1.00	ref	1.00	Ref
Substance abuse disorder				
Yes	0.79 (0.70-0.88)	<0.0001	0.85 (0.76-0.94)	0.00136
No	1.00	ref	1.00	Ref

Univariate analyses are presented as crude HR. Multivariate analyses are adjusted for age, sex, area of residence, socioeconomic status, medical conditions (fibromyalgia, cancer, osteoarthritis, substance abuse disorder). Abbreviations: HR, hazard ratio; ref, reference.

*HR at time=365days

Figure 3.1.1: Kaplan-Meier curve of persistence (time to discontinuation) among users of all cannabinoids.

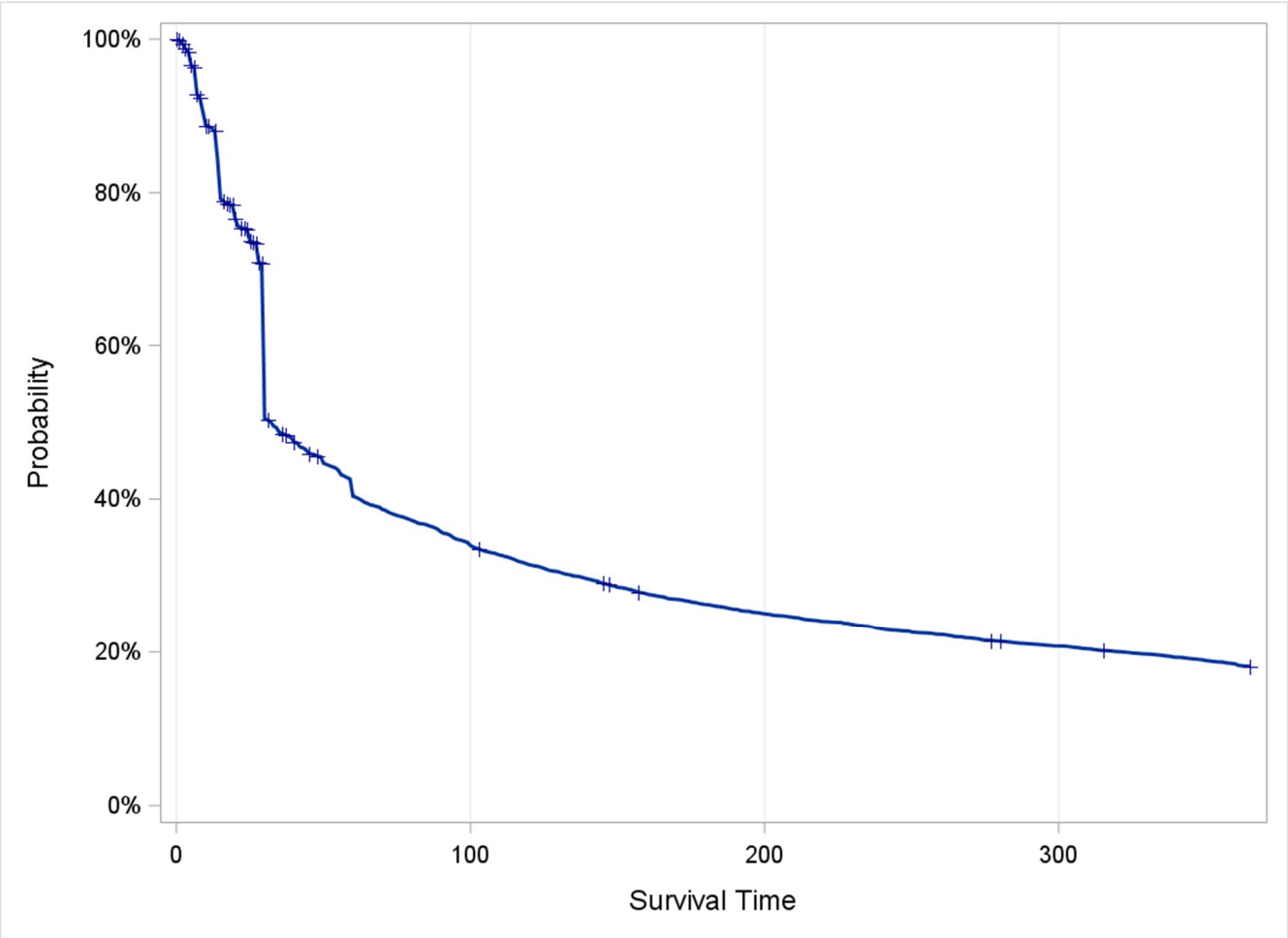
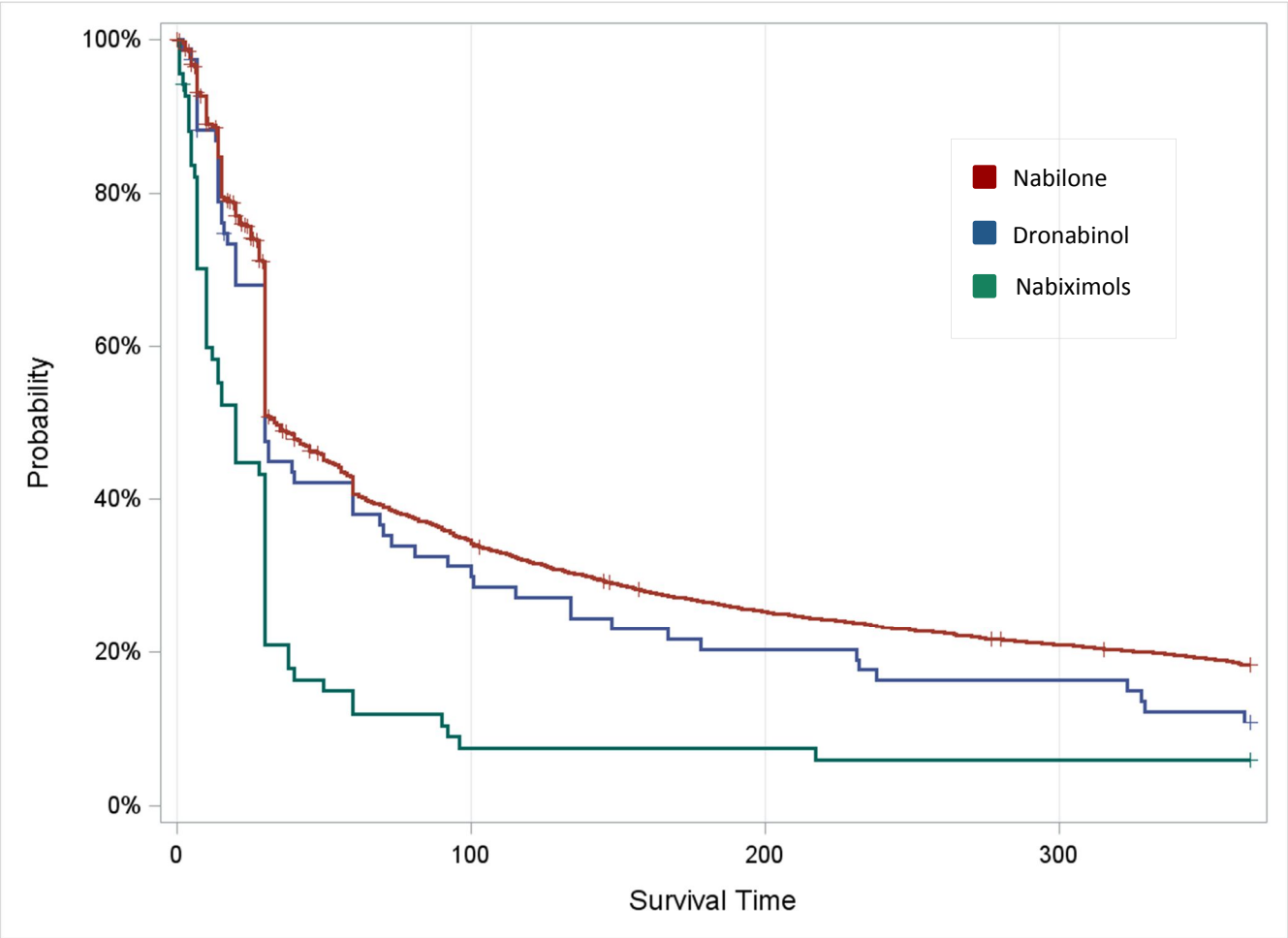


Figure 3.1.2: Kaplan-Meier curve of persistence (time to discontinuation) among users stratified by the three cannabinoid agents.



Supplementary Table 3.1: Algorithms for identification of medical conditions among incident pharmaceutical cannabinoid users.[19-24.]

Medical condition	Definition*	ICD 9-CM	ICD 10-CA
Epilepsy	1H and/or 3P**	345	G40,G41
Cancer	1H and/or 2P	140-172, 174-209	C00-C43, C45-C97
HIV/AIDS	1H and/or 3P	042-043	B20-B24
Rheumatoid Arthritis	1H and/or 2P	714	M05,M06
Osteoarthritis	1H and/or 2P	715	M15,M16
Fibromyalgia	1H and/or 2P	729	M79
Multiple sclerosis	1H and/or 3P	340	G35
Substance abuse/misuse	1H and/or 1P	291,292,303,304,305	F10-F19,F55
Mood/Anxiety disorders	A. 1H for (mood disorders), (stress and adjustment disorders), (mental and behavioral disorders), (emotional disorders).	A. (296.1,296.8), (300.4 309,311).	A. (F33, F36,F38), (F43),(F53),(F93).
	B. 1H for anxiety disorders, depressive disorder, mood disorders, obsessive-compulsive disorders dissociative disorders somatoform disorders + 1 Pres for antidepressant/mood stabilizer*	B. (300.0)	B. (F40, F41), (F32), (F34.1), (F42), (F44), (F45.0, F45.1).
	C. 3P for mood disorders, reaction to stress and adjustment disorders, depressive disorders.	C.(296),(309),(311)	
	D. 3P for anxiety disorders + 1 pres for antidepressant/ mod stabilizer.	D. 300	

Abbreviations: H, hospitalization; P, physician claim; Pres, prescription.
* Within two years before the first cannabinoid prescription dispensation.
** physician claims separated by 30 days.

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4. Chapter Four. The efficacy and safety of pharmaceutical cannabinoids in the management of cannabis use disorder

Study classification: A systematic review.

Journal: *NA*

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The main objective of this study is to review the literature to assess the evidence to support the efficacy and safety of pharmaceutical cannabinoid agents as therapeutic options for the clinical management of cannabis use disorder.

4.1 **Abstract**

Background: Cannabis use disorder has become a concern as a result of increased availability of cannabis and reduced perceived risk of harm. The use of psychosocial approaches has been associated with high rates of relapse, suggesting a possible need for pharmacotherapy. Cannabinoid replacement therapy with pharmaceutical cannabinoid agents is a possible therapeutic option.

Objective: The objective of this review is to assess the evidence for the efficacy and safety of the use of pharmaceutical cannabinoid agents as clinical management options of cannabis use disorder.

Methods: In August 2018, we searched MEDLINE, EMBASE, IPA, and the Cochrane library Databases, for randomized controlled trials that compared the use of a pharmaceutical cannabinoid agent with placebo or other interventions for the management of cannabis use disorder. Two reviewers independently screened abstracts. One reviewer abstracted data using a standardized form. Two reviewers assessed the quality and risk of bias across studies using the Cochrane tool.

Results: This review included six trials with a total of 403 participants and the duration of treatment ranged from 6 days to 12 weeks. All trials showed no statistical difference between pharmaceutical cannabinoids or placebo in increasing abstinence rates or decreasing cannabis consumption. There is some limited evidence to support their efficacy in managing withdrawal symptoms and cravings. Pharmaceutical cannabinoids seem to be well-tolerated.

Conclusion: In the currently available literature, evidence to support the use of pharmaceutical cannabinoids for cannabis use disorder management is still lacking.

4.2 **Introduction**

The use of cannabis in North America has increased, and public acceptance of recreational cannabis has been on the rise notwithstanding many years of prohibition.[1] In 2015, the Canadian Tobacco, Alcohol and Drugs Survey (CTADS) estimated that the prevalence of cannabis use among Canadians aged 15 years or older in 2014 was 12%.[2] The prevalence of use was highest among young adults aged 20 to 24 years (24%).[2] Approximately 9% of those who used cannabis had developed dependence, and the transition from cannabis use to dependence was highest among those aged 15-24 years (15.3%).[3,4] The Canadian National Treatment Indicators Report for 2014 to 2015 identified cannabis as the second most used substance among those seeking publicly funded substance use treatment services in several Canadian provinces, including Ontario, Manitoba, Saskatchewan, and Alberta.[5] Clinicians have also continuously warned about the increase in the development of cannabis use disorder (CUD) as a result of increased availability and reduced perceived risk of harm, which may increase use especially among young people. Cannabis users are also more likely to use other substances of abuse.[6]

According to the DSM-5 criteria, CUD is a 'problematic pattern of cannabis use leading to clinically significant impairment or distress occurring within a 12-month period'.[7] The most common manifestations of this impairment include tolerance and withdrawal, an increase in the amounts of cannabis used over time, and the inability to control consumption.[7] Symptoms of cannabis withdrawal start to appear and peak within the first week of abstinence, and subside within a few weeks.[7-9] Cannabis withdrawal syndrome is diagnosed if at least three symptoms develop.[7] These symptoms include irritability, aggression, and nervousness. In addition to sleep problems, weight loss and a reduced appetite as well as

restlessness, feeling depressed or significant discomfort from one of the following: stomach pain, tremors or shakes, sweating, hot flashes, chills, headaches.

Evidence-based psychosocial approaches have been associated with high rates of relapse, suggesting a possible need for pharmacotherapy.[7] Currently, there is no Health Canada-approved agent for the management of CUD; however, several approaches have been studied. These include the use of antidepressants, such as bupropion and mirtazapine or anxiolytics such as buspirone to manage specific withdrawal symptoms, such as anxiety or irritability.[7,10-12] Moreover, the suggested role of the gamma-aminobutyric acid (GABA) system might indicate a possible role of gabapentin and baclofen in the management of CUD.[13] Cannabinoid replacement therapy, with pharmaceutical cannabinoid agents, has also been reported as a possible therapeutic option.[14,15] These agents include nabilone, a cannabinoid receptor agonist, dronabinol, a synthetic tetrahydrocannabinoid (THC), and nabiximols, which contain equivalent amounts of THC and cannabidiol. These agents bind to the cannabinoid receptors, CB1 and CB2, affecting them in a similar manner to the cannabis plant. Cannabinoid agents have been associated with decreased drug-taking behavior in human experimental models of relapse prevention.[16, 17] These models identify markers of cravings that are predictive of relapse in pre-determined laboratory settings.[18]

Marshall *et al.*[19] conducted a systematic review in 2014 that assessed the effectiveness and safety of 14 pharmacological interventions for cannabis dependence. However, this review did not limit the studies included to those in which individuals who were diagnosed as cannabis dependent and included a wide variety of medications and study outcomes. Furthermore, a systematic review by Bahji and Mazhar in 2016 [20] has assessed the efficacy of pharmaceutical cannabinoids for cannabis dependence, however; it did not address the safety

of cannabinoids and did not evaluate the trials for the risk of bias. Hence, we conducted a systematic review to assess the evidence for the efficacy and safety of the use of pharmaceutical cannabinoid agents as a clinical management option of CUD.

4.3 **Methods**

This study was conducted in accordance with the Methodological Expectations of Cochrane Intervention Reviews (MECIR) guidelines and reported as per the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[21,22] This review was registered to PROSPERO (#CRD42018116300).

Inclusion criteria

We included randomized controlled trials (RCT), published in the English language, which compared the use of a pharmaceutical cannabinoid agent with placebo or other interventions for individuals who met the cannabis dependence criteria, as determined by the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* as a diagnostic criteria manual, (DSM-IV) or the recent DSM-5 criteria for CUD, available since 2013.[8] No limitations were placed on age, gender or severity of dependence or the presence of comorbid conditions. We included studies that primarily evaluated rates of abstinence, defined as the number of participants abstinent from cannabis at the end of treatment as determined by self-report or urine drug screens. In addition we included several other efficacy outcomes, including: 1-the average amount or sessions of cannabis used; 2- cravings of cannabis as determined by scores for different craving scales (e.g., Marijuana Craving Questionnaire (MCQ); and 3- intensity of withdrawal as determined by scores on different withdrawal scales. We also included trials that assessed secondary outcomes including: 1-self-related parameters, such as quality of life; 2- changes in levels of anxiety and or depression and any

other symptoms associated with cannabis withdrawal or the development or worsening of mental health disorders; and 3- further treatment engagement to prevent relapse, following withdrawal treatment. Safety was determined by assessing the nature, incidence and frequency of adverse effects, including serious adverse events. A serious adverse event was defined as "any event that results in death, is life threatening, requires prolong hospitalization, results in persistent of significant disability or incapacity or result in congenital anomaly or birth defects."

Other study designs including, observational studies, review articles, case reports, abstracts, and letters were not included. Only full publications in peer-reviewed journals were considered for inclusion in the review.

Data sources and searching

A research librarian experienced in the conduct of systematic reviews was consulted regarding the search strategy. One author (WA) conducted a literature search to retrieve RCTs on the efficacy and safety of pharmaceutical cannabinoids as a therapeutic option for cannabis use disorder. The search included four databases MEDLINE (inception – Aug/2018), EMBASE (inception - Aug/2018), International pharmaceutical Abstracts (IPA) (inception - Aug/2018), and the Cochrane library (inception- Aug/2018). The search included different combinations of the following MeSH headings(/) and keyword terms: (nabilone, Cesamet®, nabiximols, Sativex®, THC:CBD, dronabinol/, Marinol®, synthetic THC, synthetic delta-9-tetrahydrocannabinol, cannabinoids/, or cannabinoid receptor agonists/) AND (marijuana abuse/, marijuana, marihuana, cannabis, dependence, abuse, misuse, or addiction) and different combinations of these terms. This search was further supplemented by various combinations of truncated keywords that described the type of publication, such

as random, double-blind, random allocation, placebo, clinical trial, and comparative study. Full search strategies are included in the supplemental material (Supplementary table 1). Pharmaceutical manufacturers and authors were not contacted.

Screening

First, any duplicates were removed. Second, two reviewers screened each abstract independently. One reviewer (WA) screened all abstracts, while (KL, JL, and KG) each screened one-third of the abstracts. Disagreements were checked and resolved by a third reviewer (CL).

Data extraction

One reviewer (WA) extracted the data from each study onto a predesigned form, adapted from Cochrane Public Health Group Data Extraction and Assessment Template and developed in MS Excel 2016 (Microsoft Corporation, Redmond, WA, USA) to include: study details, study population, intervention and comparator, and efficacy and safety outcome details.

Quality assessment

Two reviewers (WA and DJ) independently assessed the risk of bias for each included study using the Cochrane Risk of Bias Tool. This tool assigns a judgment of high, low or unclear risk of bias for each of the following domains: selection bias, performance bias, detection bias, attrition bias, and reporting bias. Disagreements were resolved by discussion between the two reviewers.

4.4 **Results**

Studies

Figure 1 shows the flow of studies through the review process. The search yielded 486 citations after duplicates were removed, 17 of which were assessed as full-text. Finally, this review included 6 trials [23-28], which looked at the efficacy and/or safety of pharmaceutical cannabinoids as therapeutic options for CUD. Duration of treatments ranged from 6 days to 12 weeks and the duration of follow-up after treatment ranged from 28 days to 6 months.

Participants

In total, 403 participants were randomized and participated in the 6 trials, most of whom were males and all participants were ≥18 years old. All studies excluded those with current psychiatric disorders, such as schizophrenia or bipolar disorder, or alcohol or any other substance addiction, excluding nicotine and caffeine. Pregnant and breastfeeding women were not included in any of the studies. In all studies, except for one, participants received the intervention as outpatients but in Allsop 2014 [24], they received the treatment as inpatients and were followed as outpatients for abstinence assessment. The characteristics of the trials are reported in Table 1.

Interventions

Nabiximols (Sativex®) was the intervention in three of the trials [24, 26,28]. Target doses used in these trials ranged from 86.4 THC: 80 CBD to 113.4 THC: 105 CBD mg/day. Nabilone 2 mg/day was given in one study[27] and dronabinol 40 mg/day was used in one study[23]. Only one study assessed a combination of agents (dronabinol+ lofexidine) [25]. All trials were placebo controlled. Psychosocial or behavioral interventions were implemented to both arms of the treatment in five studies, while Trigo 2016 [26] did not have any non-pharmacological interventions.

Main outcomes

Efficacy

Several efficacy outcomes were assessed in the trials, including abstinence rates, cannabis use, effects on cravings and withdrawal symptoms. All 6 studies used the Timeline Follow back (TLFB) method to assess cannabis use weekly or biweekly. Four trials [23,25,26,28] evaluated cannabis abstinence, which was assessed at different post-intervention times across the studies. All trials assessed cannabis use, which was defined, as days of cannabis use per week, or number of inhalations or sessions per day. Except for Hill 2017 [27], all studies assessed withdrawal, using different scales: the withdrawal discomfort score (WDS) [23,25,27], Marijuana withdrawal checklist[26,28] , or cannabis withdrawal scale (CWS),[24] a 19-item scale measuring withdrawal symptom severity in the previous 24 hours. While craving was assessed by 5 trials,[23, 25-28] all of which used the marijuana craving questionnaire (MCQ), which is a modification of the Cocaine craving questionnaire.

Nabiximols was statistically significant in reducing cannabis withdrawal symptoms in two trials [24, 26]and levels of cannabis cravings over time in two trials [24,28]. Nabiximols did not have a statistically significant effect on abstinence rates or cannabis use in any of the studies. Dronabinol was statistically significant in reducing withdrawal symptoms and increasing retention in treatment (time to dropout), but had no effect on cravings or abstinence. Dronabinol and lofexidine combination did not promote cannabis abstinence, and had no significant reduction on cravings or withdrawal. Nabilone had no effect on cannabis use or cravings. A summary of the main efficacy outcomes is reported in Table 2.

Safety

Safety outcomes and the risk of adverse effects and serious adverse effect were assessed by all studies. Nabiximols was well-tolerated in all three studies. The combination of dronabinol-lofexidine significantly increased side effects, including dry mouth and hypotension. Both dronabinol and nabilone were well-tolerated. A summary of the main safety outcomes is reported in table 2.

Quality

Three of the six studies were of good quality with low risk of bias [23-25], while three were of poor quality with a high risk of bias [26-28]. While Hill 2017[27] mentioned randomization, there was not enough information explaining the methods of randomization. Three trials [26-28] did not have enough information regarding allocation concealment. There was unclear information regarding blinding of intervention in Hill 2017 [27] and participants in Trigo 2016 [26] reported feeling "high" under Sativex® conditions compared to placebo, which might have compromised blinding. In Hill 2017[27], differential imbalance in loss to follow-up between intervention groups might have introduced a high risk of incomplete outcome data. Both Hill 2017[27] and Trigo 2018[28] had a high risk of bias for selective reporting, as multiple outcomes were reported in the protocol without reporting results in the publication. Detailed results of the quality assessment using the Cochrane Collaboration tool for assessing risk of bias are reported in table 3.

4.5 **Discussion**

This review described the evidence for the use of pharmaceutical cannabinoid agents as a potential therapeutic intervention for CUD. Several studies suffered from several limitations, including small sample size in Trigo 2018[28] and a short intervention period in Allsop 2014[24]. All studies assessed cannabis use based on self-reports. Moreover, different scales were used to assess withdrawal and there was no consentient timing used when assessing abstinence. Although the majority of the studies included psychological interventions in the design, none of the studies compared the effects of pharmacological vs non-pharmacological interventions. In fact, several studies reported significantly lowers rates of cannabis use over time that did not differ between treatment groups. Since in many of these trials both arms received the psychological interventions, this may provide some indirect evidence of the impact of these interventions.

There was not enough evidence to support a significant effect of cannabinoids on cannabis abstinence. All 6 studies showed no significant effect of cannabinoids on abstinence rates or average cannabis use. THC containing preparations, dronabinol and nabiximols, showed a possible role in managing withdrawal symptoms, nabiximols also had a significant effect on cravings over time. Nabilone was assessed by a single study with a small sample size and poor quality, indicating a need for bigger and higher quality trials to assess its role.

Although pharmaceutical cannabinoids have been associated with an increased risk of adverse effects,[29] herein cannabinoids seem to be well-tolerated. Five trials showed no significant difference between cannabinoids and placebo in adverse effects. The side effects of these agents, such as euphoria, confusion and thought distortion, are similar to the effects

of cannabis, hence this group of regular cannabis users might be tolerant or used to these effects.

Only the combination of dronabinol and lofexidine increased the risk of a number of adverse effects, such as hypotension and dry mouth, which might be due to the addition of lofexidine, an α-agonist.

Therapies that are based on agonist replacement provide some similar effects of a drug of abuse, and are used to attenuate the effects of withdrawal and cravings. This has been a successful therapeutic strategy for some addictions, including smoking and opiate dependence. However, it is unclear if the approach that works for nicotine and opioids actually applies in CUD. There is no indication of reduced use with pharmaceutical cannabinoid treatment and the evidence for the reduction in withdrawal symptoms is limited. Findings from our review are in line with several other reviews that evaluated the literature regarding the risk and benefit of pharmaceutical cannabinoids for cannabis dependence management.[19,20,30] These reviews also found some evidence for a potential role for THC containing agents to minimize withdrawal symptoms and found cannabinoids to be tolerable.

Limitations

All of the trials that looked into the role of pharmaceutical cannabinoids in the management of cannabis use disorder excluded those with current psychiatric disorders, such as schizophrenia or bipolar disorder, or alcohol or any other substance addiction, excluding nicotine and caffeine. This limits the generalizability of the results, as cannabis use disorder is of concern among these specific populations.[31-33]

In this thesis, we did not seek any unpublished data and there was no quantitative pooling of study results carried out, representing limitations of the review. Moreover, all differences in efficacy outcomes are assessed statistically and we were not able to conclude if they can provide a clinically important difference.

4.6 **Conclusions**

The idea of using pharmaceutical cannabinoids to treat CUD remains theoretical. There is no evidence on the benefit of cannabinoids on increasing abstinence rates or lowering the average amount of cannabis consumption. However, there is some limited evidence to support the efficacy of pharmaceutical cannabinoids in managing withdrawal symptoms and cravings for patients suffering from cannabis use disorder. In addition, there is some evidence that the use of pharmaceutical cannabinoids to treat CUD is well tolerated. Future research aimed to assess the benefit and risk of cannabinoids as a possible option for the management of CUD should consider these findings and limitations.

4.7 **Acknowledgment**

We would like to thank Ms. Me-Linh Le for her help with the research strategy. We would also like to acknowledge Kara Lipski, Kiana Gozda, and Joyce Leung for their help with abstract screening process.

4.8 **Figures and tables**

Figure1. Systematic review on the efficacy and safety of pharmaceutical cannabinoids in cannabis use disorder: flow chart of articles found through the review process.

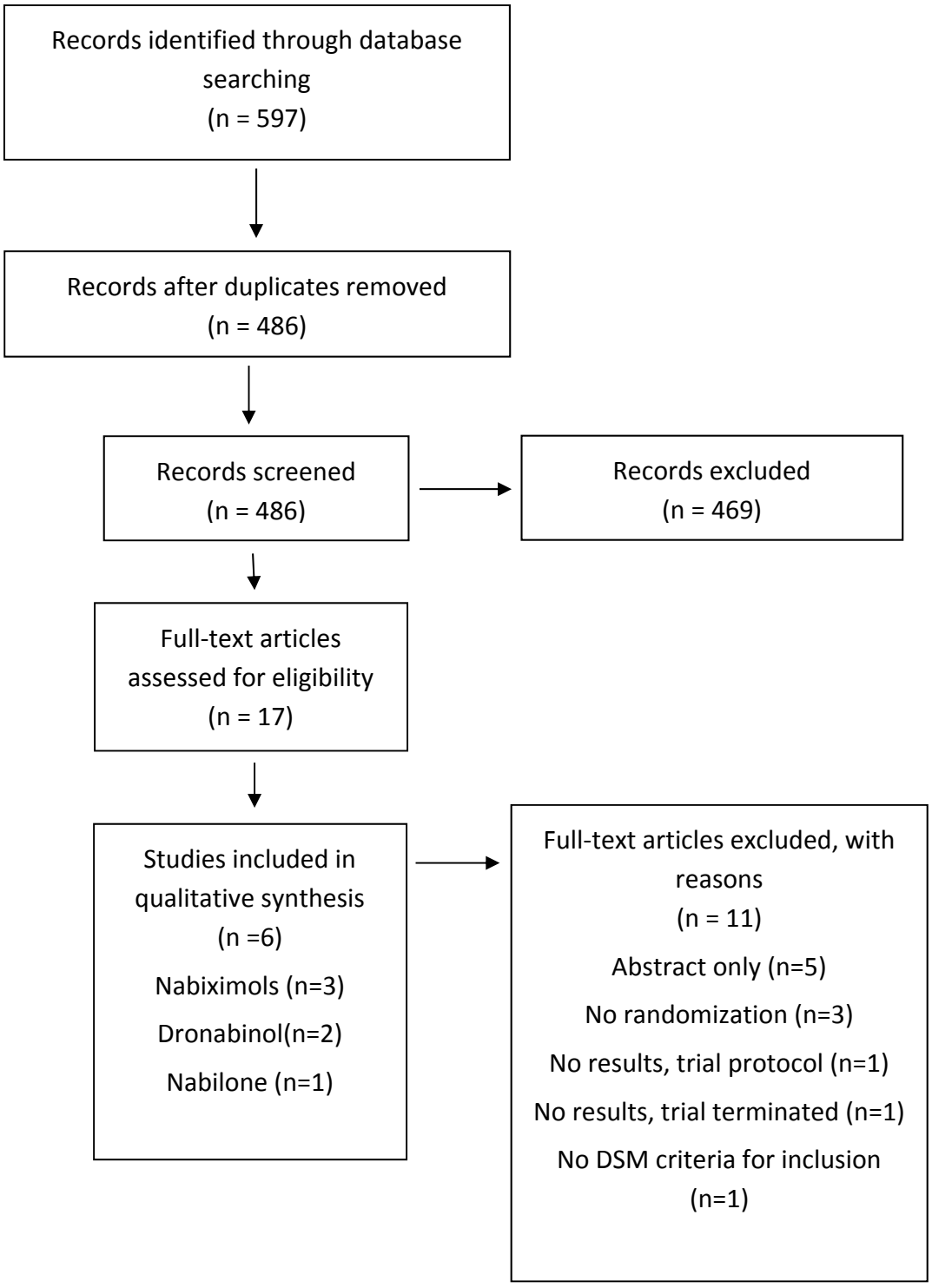

Table 4.1. Systematic review on the efficacy and safety of pharmaceutical cannabinoids in cannabis use disorder: characteristics of included studies.

Study, year, location	Setting & design & duration	[NR] NC	Intervention (max dose/day) vs comparator	Participants mean (SD) age	% of females
Levin 2011, NY,USA[23]	Outpatient, randomized, double-blinded. Parallel (5 phases) 1→ placebo (1wk), 2→ titration (1wk), 3→ maintenance (6wks), 4→ dose tapering (2wks), 5→ placebo (2wks).	[156] 99	Dronabinol 40 mg vs placebo. psychotherapy (MET) in both groups	Total NA; intervention 36.9(10.8); placebo 38.4(9.2)	Total: 18 Intervention: 15.2 Placebo: 20.8
Allsop 2014, Sydney & NSW, AUS [24]	Inpatient, Randomized, Double-Blinded. Parallel (3 phases) 1→ intervention (6 days), 2→ washout (3 days), 3→ outpatient follow-up (28 days).	[51] 27	Nabiximols (86.4 THC:80CBD mg) vs placebo. CBT in both groups	Total:35.39(8.89); Intervention:34.96 (9.70); placebo: 35.88(8.05)	Total: 24 Intervention: 33 Placebo: 22
Levin 2016, NY,USA[25]	Outpatient, randomized, double-blinded. Parallel (6 phases) 1→ placebo (1wk), 2→ titration (2wks), 3→ maintenance (6wks), 4→ tapering (2wks), 5→placebo (1wks).	[122] 67	(Lofex-Dro)1.8/60 mg vs placebo. Manualized MET +CBT / relapse prevention therapy in both groups	Total NA; intervention 34.8(11.2); placebo 35.4.(10.8)	Total: 31.15 Intervention: 36.1 Placebo: 26.2
Trigo 2016, GTA, Canada[26]	Outpatient, randomized, double-blinded. Crossover (8 phases) (5 days each). 4 phases→ smoking as usual; 4 phases → abstinence (A: washout, B: intervention (Fixed dose), C: intervention (self-titrated dose), D: placebo 1, E: placebo 2).	[16] 9	Fixed and self-titrated nabiximols (108 THC:100 CBD mg) vs placebo.	Total: 35.9 (11.5) Intervention: NA; Placebo: NA	Total: 10.1 Intervention: NA; Placebo: NA
Hill 2017, Boston, USA[27]	Outpatient, randomized. Parallel (5 phases) 1→initiation (1wk), 2→ titration (2wks), 3→ maintenance (4wks) 4→tapering (3wks), 5→ follow-up (4wks).	[18] 12	Nabilone 2 mg vs placebo. Behavioral therapy (1st session 45-min; subsequent 15-25 mins in both groups	Total: 26.4(6.5); Intervention 24.4 (5.2); placebo 28.9 (7.5).	Total: 33 Intervention: 30 Placebo: 37
Trigo 2018, GTA, Canada[28]	Outpatient, randomized, double-blinded. Parallel 1→ self-titration (3wks), 2→ maintenance (9wks), 3→ follow-up (6 months)	[40] 27	Nabiximols (113.4THC/105 mg CBD) vs placebo. MET + CBT in both groups	Total: NA intervention: 30.7 (10.4); control: 35.3 (13.1)	Total: NA Intervention: 25 Placebo: 30

Abbreviations: NY, New York; NSW; New South Wales; GTA, Greater Toronto Area; NR, number randomized; NC, number completed; SD, standard deviation; wk, week; MET, motivational enhancement therapy; NA, not available; THC, tetrhydrocannabinoil; CBD, cannabidiol, CBT, cognitive behavioral therapy.

Table 4.2. Systematic review on the efficacy and safety of pharmaceutical cannabinoids in cannabis use disorder: summary of main results.

Study	Efficacy outcome results summary	Safety outcome results summary
Levin 2011[23]	1ry: The proportion of patients achieving two-weeks of continuous abstinence in weeks 7 and 8, was not sig different between Dronabinol (17.7%) and placebo (15.6%) (p=0.69). 2ndry: WDS was sig lower for dronabinol over time (p=0.02). Group retention of treatment (time to dropout) was sig better on dronabinol (77% vs 61%) (p=0.02). Max days (Median, [IQR]) of consecutive abstinence were not sig between dronabinol (6[1-13]) and placebo (5[2-16]) (p=0.79). The days per week of use were not sig different among the groups (p=0.54).	No sig differences in AE between groups (p>0.05). Dronabinol was well tolerated (89%) reached max dose. 4 serious AE: hospitalizations: worsening of asthma at follow up (1); altercation with police (1); stomach virus (1); worsening of DM (1); 3 w/ dronabinol and 1 w/ placebo (detailed information NA)
Allsop 2014[24]	1ry: Nabiximols sig reduced CWS scores (mean 66% decrease from baseline) compared to placebo (mean 52% increase from baseline) (p = .01). 2ndry: Nabiximols group showed sig lower levels of cannabis cravings over time (p = 0.04). No sig advantage of nabiximols on self- reported cannabis use (p=0.75), cannabis-related problems (p=0.14), or cannabis dependence (p=0.89) at follow-up.	No sig differences between dronabinol and placebo in number of severity of AE (p>0.05). Serious AE: 1 participant w/ suicide attempt and 1 w/ suicidal thoughts both in placebo group.
Levin 2016[25]	1ry: Dichotomous any 21-days consecutive abstinence was not sig effect on achieving abstinence between Lofex-Dro (27.9%) and placebo (29.5%) (p=0.68) 2ndry: Marijuana abstinence during last 2 weeks of maintenance medication phases was not sig different between Lofex-Dro (19.7%) and placebo (19.7%) (p=0.89). Withdrawal scores (WDS) were not sig difference between groups (p=0.83). Retention in treatment (time to drop out) was not sig different between Lofex-Dro (p=0.24).	Dry mouth (44.3% vs 9.8%) (p<0.001), intoxication (21.3% vs 3.3%) (p=0.004) and hypotension (16.4% vs 1.6%) (p=0.008) were sig higher with Lofex-Dro, but anxiety was sig lower with Lofex-Dro (4.9% vs 18%) (p=0.44). Serious AE: 2 hospitalizations during placebo lead in phases.

Table 4.2. Systematic review on the efficacy and safety of pharmaceutical cannabinoids in cannabis use disorder: summary of main results.

Study	Efficacy outcome results summary	Safety outcome results summary
Trigo 2016[26]	2ndry: There was no sig deference in abstinence among nabiximols conditions (77.7%) compared to placebo conditions (77.7%) (p>0.05). Cannabis withdrawal (MWC) score was sig lower under fixed-nabiximols (3.6) compared to placebo (7.4) conditions under abstinent conditions (p<0.01). No sig difference in reducing craving (MCQ) score between fixed-nabiximols (10.8) and placebo (10.8) conditions (P>0.05).	1ry: well tolerated in high fixed doses. No differences in nausea sleep problems and diarrhea between treatment conditions (p>0.05) Serious AE→ None.
Hill 2017[27]	2ndry: No significant difference in cannabis use; sessions/day (mean [SD]) between nabilone (2.55 [0.86]) and placebo (3.14 [1.91]) (p=0.29). No significant difference in percent of days of use (mean [SD]) between nabilone (91.7% [12.6]) and placebo (89.0 [10.7]) (p=0.22). No significant difference in cannabis use inhalations/day (mean [SD]) between nabilone (42.5 [34.6]) and placebo (28.0 [20.5]) (p=0.28). No sig difference in reducing craving (MCQ) score between nabilone and placebo at end of treatment (P=0.74) and end of follow-up (p=0.69)	1ry: 8 reported by 2 participants in nabilone group; 6 AE reported by 4 participants in placebo group. Significance of difference in AE between groups was not reported. Serious AE: None.
Trigo 2018[28]	1ry: 7-day abstinence rate was not sig different between nabiximols (30.8%) and placebo (42.9%). 2ndry: No significant difference in % reduction in cannabis use; g/day between nabiximols (70.5%) and placebo (42.6%) (p=0.98). Nabiximols sig reduced cannabis craving scores (MCQ) over time (p < .05). No significant differences between groups on withdrawal scores (MWC) (p=0.59)	No sig differences in rates of AE between groups (p>0.05) Serious AE: None.

Abbreviations: sig, statistically significant;1ry, Primary; 2ndry, secondary; WDS, withdrawal discomfort score; SE, side effects; AE, adverse events; DM, diabetes mellitus; CWS, cannabis withdrawal scale; MWC, Marijuana withdrawal checklist w/, with; Lofex-Dro, lofexidine-dronabinol; MCQ, Marijuana craving questionnaire; NA, not available.

Table 4.3. Systematic review on the efficacy and safety of pharmaceutical cannabinoids in cannabis use disorder: quality/bias assessment using the Cochrane Collaboration tool for assessing risk of bias.

	Random sequence generation	Allocation concealment	Blinding of intervention	Blinding of outcome	Incomplete data outcome	Selective reporting
Levin 2011						
Allsop 2014						
Levin 2016						
Trigo 2016						
Hill 2017						
Trigo 2018						

 Low  High  Unclear

Supplementary table 4.1. Search strategy used in MEDLINE and EMBASE for capturing trials assessing the use of pharmaceutical cannabinoids in cannabis use disorder.

MEDLINE:	EMBASE:
nabilone.tw,kf. Cesamet.tw,kf. Lilly 109514.tw,kf. 1 or 2 or 3 nabiximols.tw,kf. sativex.tw,kf. THC:CBD.tw,kf. GW-1000.tw,kf. GW 1000.tw,kf. tetrahydrocannabinol-cannabidiol combination.tw,kf. 5 or 6 or 7 or 8 or 9 or 10 DRONABINOL/ marinol.tw,kf. synthetic Tetrahydrocannabinol.tw,kf. synthetic THC.tw,kf. 12 or 13 or 14 or 15 exp CANNABINOIDS/ Cannabinoid Receptor Agonists/ 4 or 11 or 16 or 17 or 18 marijuana abuse/ "cannabis use disorder*".tw,kf. ((cannabis or hashish or marijuana or marihuana) adj3 (abuse* or disorder* or depend* or addict* or misuse or mis-use*)).tw,kf. 20 or 21 or 22 19 and 23 (controlled clinical trial or randomized controlled trial or equivalence trial or pragmatic clinical trial).pt. clinical trials as topic.sh. (randomi#ed or randomly or randomi#ation? or RCT$1 or placebo).tw,kf. ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kf. trial.ti. 25 or 26 or 27 or 28 or 29 24 and 30 limit 31 to english language 33.limit 32 to humans	nabilone/ cesamet.tw,kw. Lilly 109514.tw,kw. 1 or 2 or 3 nabiximols/ Sativex®.tw,kw. THC:CBD.tw,kw. GW-1000.tw,kw. GW 1000.tw,kw. tetrahydrocannabinol-cannabidiol combination.tw,kw. 5 or 6 or 7 or 8 or 9 or 10 dronabinol/ marinol.tw,kw. synthetic Tetrahydrocannabinol.tw,kw. synthetic THC.tw,kw. 12 or 13 or 14 or 15 exp cannabinoid/ cannabinoid receptor agonist.tw,kw. 4 or 11 or 16 or 17 or 18 cannabis addiction/ "cannabis use disorder*".tw,kw. ((cannabis or hashish or marijuana or marihuana) adj3 (abuse* or disorder* or depend* or addict* or misuse or mis-use*)).tw,kw. 20 or 21 or 22 19 and 23 randomized controlled trial/ or controlled clinical trial/ exp "clinical trial (topic)"/ (randomi#ed or randomly or RCT$1 or placebo*).tw. (randomi#ed or randomly or RCT$1 or placebo*).tw. 25 or 26 or 27 or 28 24 and 29 31. limit 30 to (human and english language)

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5. Chapter Five. Major conclusions and future directions

5.1 Major conclusions

This population-based study showed an increase in both the annual prevalence and incidence rates of the use of pharmaceutical cannabinoids. However, despite this increase in use over time, overall the rates of use of these agents in the population are low. Out of three available cannabinoids in Canada during the study period, nabilone was the mostly used agent (96%), nabiximols had very low rates of use, which is possibly due to its high price and lack of coverage. Dronabinol use was also low before it was discontinued in 2012. The increase in the overall use of pharmaceutical cannabinoids might reflect the increased interest in cannabis and cannabis-based medications as a therapeutic option. This trend might also reflect the limited therapeutic options for certain conditions, such as chronic pain and fibromyalgia. Despite the increase in rates of use, the persistence of use of these agents was low. The majority (81.9%) discontinued these agents within the first year of use and one third of incident users received only one prescription and never filled a second one. Although the rates of use have increased, the overall low numbers of patients receiving these agents and the high discontinuation rates might indicate a "real-world" reflection of the lack of effectiveness and tolerability to these agents.

When we assessed the medical conditions of those receiving cannabinoids, we found that almost half of the incident users suffered from chronic pain and more than third had a diagnosis of fibromyalgia. Likewise, discontinuation rates among those who have fibromyalgia and osteoarthritis were lower compared to those who did not. These findings provide some indirect evidence of a possibly beneficial role for cannabinoids in chronic pain management.[50,52,71–73] On the other hand, the percentage of users who met the study definition

for the approved indications, cancer, multiple sclerosis, HIV/AIDS was low. Moreover, discontinuation rates were significantly higher among cancer patients. These findings, in addition to the lack of strong evidence to support their benefit, raise questions about the effectiveness of cannabinoids for these conditions.

Interestingly, although guidelines recommend against the use of pharmaceutical cannabinoids in this patient population due to concerns about the risk of abuse, a small percent of incident cannabinoid users met the study definition of substance use disorder. These users had significantly lower discontinuation rates compared to patients who do not have a diagnosis of substance use disorder. This might signal concerns about prescribing among some, but can also be related to opioid use disorder among those who suffer from chronic pain and received a cannabinoid prescription as well. Recent literature from trials suggests a possible role for these agents as a replacement therapy in cannabis use disorder. However, when we systematically evaluated the literature, we did not find evidence to support their efficacy in initiating or maintaining abstinence or in reducing cannabis consumption.

5.2 **Future directions**

Although this study has provided estimates to describe the use of pharmaceutical cannabinoids among a Canadian population, and provided insight for their use in different medical conditions, there are several questions yet to be answered. The legalization of recreational cannabis in Canada might have several impacts on different health outcomes and on the use of these medications. This will mainly depend on several factors related to patient behavior, cannabis regulations, social acceptance, and cost. Moreover, the controlled scheduling of pharmaceutical cannabinoid agents, after cannabis has become legal, is

debatable. Hence, the possible post-legalization changes in rates of use of this class of medications and the determinants of utilization need to be further analyzed.

The long term safety and effectiveness of these agents also require more analyses, including the association between the use of these agents and the risk of psychosis, in addition to their effectiveness and trend in use for chronic pain management.

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Appendix

Examples of programming code for data analysis

Data access and Ethics approval documentations

```
/* example 1: Poisson model for prev use */

option mergenoby='error';
data dpin;
set project.Wajd_thesis_dpin1996_2015;
run;
/* cbs main is the main table for all prescriptions of cannabinoids from
DPIN, including info regading the date, phin, brand name, atc code,
postal code, prescriber specialty */

data cbs_main;
set dpin;
keep SCRPHIN brand_name fiscalyear ATC PRVDDT POSTAL muncode;
where ATC in ('A04AD11' 'A04AD10' 'N02BG10');
run;

/* made a new var called drug to include only one name for each
cannabinoid with the same ATC code*/
data cbs_main;
set cbs_main;
length drug $10;
if ATC='A04AD11' then drug='Nabilone';
if ATC='A04AD10' then drug='Dronabinol';
if ATC='N02BG10' then drug='Nabiximols';

run;


data cbs_main;
set cbs_main;
%assign_iq(muncode=muncode, postal=postal, year=2012, iqvar=incomeq);
if incomeq in('U1' 'U2' 'U3' 'U4' 'U5') then area=1;
if incomeq in('R1' 'R2' 'R3' 'R4' 'R5') then area=2;
sefi = input(postal,sefi11f.);
if sefi=<-1 then income=4;
if  -1 < sefi < 0 then income=3;
if   0< sefi < 1 then income=2;
if sefi => 1 then income=1;
run;


/* the following steps are to get the date of birth and then merge it
with the cbs dataset and the sex of users and then sort them by the
phin*/
proc sort data=cbs_main;
by SCRPHIN;
run;
data DOB;
set project.Wajd_thesis_regcov;
keep BIRTHDT SCRPHIN SEX area;
run;
proc sort data= dob;
by SCRPHIN;
run;
```

```
data Cbs_main ;
merge Dob (in=m1)
cbs_main (in=m2);
by SCRPHIN;
run;

/* the followinf step is to keep first prescription of any cannabinoid in
each year  in the cbs data set. i.e only one prescreption per person per
year*/
proc sort data=cbs_main ;
by fiscalyear  SCRPHIN;
run;
data cbs_year;
set cbs_main ;
by   fiscalyear  SCRPHIN;
if first.SCRPHIN;
run;

/* the following steps are to assign users to 3 different age groups and
then remove the date of birth because I dont need it anymore */
data cbs_year ;
set cbs_year ;
age=(fiscalyear- year (BIRTHDT));
if age=<18 then agegrp=1;
if  19 <= age <= 45 then agegrp=2;
if  46 <= age <= 64 then agegrp=3;
if age => 65 then agegrp=4;
run;
data cbs_year;
set cbs_year;
drop BIRTHDT;
run;


/*the following step is to get the people living in Manitoba  ( Jan-Dec)
for the years 2004 to 2014*/
data pop2004_2014;
set common.MHpop_1975dec;
where 2003< popyear <2015;
%assign_iq(muncode=muncode, postal=postal, year=2012, iqvar=incomeq);
if incomeq in('U1' 'U2' 'U3' 'U4' 'U5') then area=1;
if incomeq in('R1' 'R2' 'R3' 'R4' 'R5') then area=2;
sefi = input(postal,sefi11f.);
if sefi=<-1 then income=4;
if  -1 < sefi < 0 then income=3;
if   0< sefi < 1 then income=2;
if sefi => 1 then income=1;
run;

data pop2004_2014;
set pop2004_2014;
if age=<18 then agegrp=1;
if  19 <= age <= 45 then agegrp=2;
```

```
if  46 <= age <= 64 then agegrp=3;
if age => 65 then agegrp=4;
run;
/* the following is to keep the names of the results table in order to
use that name to use the ods output option to make a dataset for that
result table*/

ods trace on / listing ;
/* using that ods option, I made a table for the frequency of the
population to get the number of ppl (in each strata) living in maniotba
for each year 2004-2014 */
title 'MB population 2004-2014';
proc freq data=pop2004_2014;
tables popyear*agegrp*sex*area*income;
ods output CrossTabFreqs=MB_pop(keep= popyear sex agegrp area income
frequency
  rename=(popyear=fiscalyear frequency=Numofppl));
run;

data mb_pop;
set mb_pop;
where fiscalyear>2003;
where sex in ( '1' '2')&  agegrp>0 & area>0 & income>0;
run;


title'number of users by sex_age_income';
proc freq data=cbs_year;
tables fiscalyear*sex*agegrp*area*income;
where fiscalyear>2003;
ods output  CrossTabFreqs=cbs_sex_age;
run;

data cbs_sex_age;
set cbs_sex_age;
keep fiscalyear sex area agegrp income frequency;
where fiscalyear>2003;
where sex in ( '1' '2')&  agegrp>0 & area>0 & income>0;
run;

proc sort data= cbs_sex_age ;
by fiscalyear sex agegrp area income;
run;

proc sort data= mb_pop ;
by fiscalyear sex agegrp area income;
run;


data Cbs_pois ;
merge cbs_sex_age (in=m1)
Mb_pop(in=m2);
by fiscalyear sex agegrp area income ;
log_pop= log (numofppl);
```

```
run;

proc genmod data=cbs_pois;
class sex(ref='1') agegrp(ref='4') area (ref='2') income
(ref='1')/params=ref;
model frequency= fiscalyear sex agegrp area income / offset=log_pop
dist=poisson link=log pscale;
run;


/* end of example 1 */


/*-------------------------------------------------------------------------
---------------*/

/*example 2: algorthims for medical conditions (ex: epilepsy)*/


option mergenoby='error';
/*the following macro is to get rid of the work data sets that i no
longer need*/
%macro rid (datast);
proc datasets library=work noprint;
delete &datast; run;
%mend rid ;
/*&&&&&&&NOTE: THIS IS ONLY MED CLAIMS AND MUST ASSESS AnD ADD HOSPITAL
AND PRESCRIPTIONS BEFORE DECIDING ON MORBIDITY */
/*this data set MED is to bring the medical claims of cannabinoid users
and clean it keeping only their phin numbers, the date of  the serviece
and their ICD 9 code/Diagnosis*/
data MED;
set project.Wajd_thesis_med;
run;
data morbid;
set med;
keep SCRPHIN SERVDT DIAG ;
run;
Proc sort data=morbid;
by SCRPHIN;
run;
/*data set Pres is  from dpin to know which cannabinoid they used and the
providing date of that drug, I merged the first prescription of
cannabinoids for each person with all their */
/*medical claims*/
data pres;
set project.Wajd_thesis_Dpin1996_2015;
run;
data first_Pres;
set pres;
keep PRVDDT SCRPHIN ATC fiscalyear;
where ATC in ('A04AD11' 'A04AD10' 'N02BG10');
run;
data first_pres;
```

```
set first_pres;
length drug $10;
if ATC='A04AD11' then drug='Nabilone';
if ATC='A04AD10' then drug='Dronabinol';
if ATC='N02BG10' then drug='Nabiximols';
drop ATC palliative;
run;

proc sort data=first_pres;
by SCRPHIN;
run;
data first_pres;
set first_pres;
by SCRPHIN ;
if first.SCRPHIN;
run;

/* This step is very important to keep only the claims that are 2 years
before the first prescription*/
data morbid;
set morbid;
if (prvddt)=> servdt => (PRVDDT- 2*365);
run;

/*the data set epilepsy has only medical claims for epilepsy */

data epilepsy;
set morbid;
where DIAG='345';
run;
proc sort data=epilepsy;
by Scrphin Servdt ;
run;
/*this step is to ensure I have only one vist per day and no double
visits for the same code on the same day */
data epilepsy;
set epilepsy;
by SCRPHIN servdt;
if first.servdt;
run;
/*this step is to count the number of epilepsy codes per person */
data epilepsy;
set epilepsy;
epilepsy_ICD +1 ;
by SCRPHIN;
if  first.SCRPHIN then epilepsy_ICD=1;
run;
/*this step is to create a variable called prev date which basically
carries the date of the previous serv date for the same perosn, */
/*note: the first serv and prev date are the same for one person, because
there is no prev date to carry  */
 data epilepsy;;
 set epilepsy;
 format prevdt YYMMDDD10.;
```

```
by SCRPHIN;
 prevdt= lag(servdt);
 if first.SCRPHIN then prevdt=servdt;
run;
proc sort data=epilepsy;
by SCRPHIN ;
run;
/*this step will compare the first date and find the next sev date that
is 30 days away and the then make that date the first date and so on*/
data epilepsy2;
set epilepsy;
format firstdt YYMMDD10.;
by SCRPHIN;
retain firstdt;
if first.SCRPHIN then firstdt= servdt;
else if (servdt-firstdt>30) then do; episode=1;
firstdt=servdt; end;
run;
/*in the data set epilepsy_episodes I have the total number of epilpesy
episodes ( ie that are 30 days apart ) for each person as well as the
date of the first diagnosis as the First_code and
the date of the last diagnosis as the last_code*/
proc sql ;
create table epilepsy_med
as select  SUM (episode) as numofepisodes, PRVDDT, scrphin, max(servdt)
as last_code format YYMMDD10. , min (servdt) as first_code format
YYMMDD10. from epilepsy2
group by SCRPHIN;
run;

/* now in addition to that I have the variable epilepsy which is either
yes ( if the person has at least 3 episodes ( again episode is when the
ICD codes are 30 days apart) )
or no if the person doesnt have 3 episodes  */

data epilepsy_med;
set epilepsy_med;
if numofepisodes =>3   then epilepsy = 'yes' ;
run;
proc sort data=epilepsy_med;
by SCRPHIN;
run;
data epilepsy_med;
set epilepsy_med;
by SCRPHIN;
if first.SCRPHIN;
run;
%rid (epilepsy);
%rid (epilpesy2);


/* end of example 2 */
```

```
/*-------------------------------------------------------------------------
---------------*/

/* example 3: creating KM graph ( black colour only with different
patterns)  */


ods trace on / listing ;

/* this step to create a KM, the level of sig is 0.05, not stratified by
anyhting at this point */
proc lifetest data=surv alpha=0.05 plots=(s);
      time time_to_event*event(0);
      ods output productlimitestimates= km_all;
      run; quit;

data km_all; set km_all;
      if survival = . then delete;
      if censor = 0 then ctime= time_to_event;
run;

footnote "";
ods graphics= on;
ods dpi=300/height= 800 width= 1100;
proc sgplot data= km_all noautolegend;
      yaxis min=0 max= 1 label= 'Survival Probability' ;
      xaxis label= 'Time to Discontinuation in Days' max= 365 grid
labelattrs=(size=10);
      step x= time_to_event y= survival/lineattrs= (thickness= 1 pattern=
1 color=black) legendlabel= "All Cannabinoids" name= '1';
/*    scatter x= ctime y= survival/markerattrs= (symbol = circle size=3 )
;*/
run;


      proc sort data=surv;
      by drug;
      run;

      proc lifetest data=surv alpha=0.05 plots=(s);
      time time_to_event*event(0);
      strata drug;
      ods output productlimitestimates= km;
run; quit;

data km2; set km;
      if survival = . then delete;
      if drug =: 'Dron' then do;
            if censor = 0 then d_ctime= time_to_event;
            d_time= time_to_event;
            d_surv= survival;
      end;
      if drug =: 'Nabil' then do;
            if censor = 0 then nb_ctime= time_to_event;
```

```
            nb_time= time_to_event;
            nb_surv= survival;
      end;
      if drug =: 'Nabix' then do;
            if censor = 0 then Nx_ctime= time_to_event;
            nx_time= time_to_event;
            nx_surv= survival;
      end;
run;

data test; ;
      drug= 'Nabiximols';
      nx_time= 400;
      nx_surv= 0.058;
run;
data km3; set km2 test; run;

footnote "";
ods graphics= on;
ods dpi=300/ height= 800 width= 1100;
proc sgplot data= km3 noautolegend;
      yaxis min=0 max= 1 label= 'Survival Probability' ;
      xaxis label= 'Time to Discontinuation in Days' max= 365 grid
labelattrs=(size=10);

      step x= d_time y= d_surv/lineattrs= (thickness= 1 pattern= 4
color=black) legendlabel= "Dronabinol" name= '1';
/*    scatter x= d_ctime y= d_surv/markerattrs= (symbol = circle size=3 )
;*/

      step x= nb_time y= nb_surv/lineattrs= (thickness= 1 pattern=1
color=black) legendlabel= "Nabilone" name= '2';
      scatter x= nb_ctime y= nb_surv/markerattrs= (symbol = x size= 1) ;

      step x= nx_time y= nx_surv/lineattrs= (thickness= 1 pattern=3
color=black) legendlabel= "Nabiximols" name= '3';
/*    scatter x= nx_ctime y= nx_surv/markerattrs= ( symbol = square
size=3) ;*/

      keylegend "1" "2" "3";
run;

/* end of example 3 */
```

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Winnipeg, Manitoba
Canada, R3E 0W3
Telephone : 204-789-3255
Fax: 204-789-3414

UNIVERSITY OF MANITOBA | Bannatyne Campus
Research Ethics Board

HEALTH RESEARCH ETHICS BOARD (HREB)
CERTIFICATE OF FINAL APPROVAL FOR NEW STUDIES
Delegated Review

PRINCIPAL INVESTIGATOR:	INSTITUTION/DEPARTMENT:	ETHICS #:
Dr. Christine Leong	U of M/College of Pharmacy	HS 18824 (H2015:271)
APPROVAL DATE: September 1, 2015	**EXPIRY DATE:** September 1, 2016	
STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (If applicable): N/A		

PROTOCOL NUMBER:	PROJECT OR PROTOCOL TITLE;
N/A	Trend Prescription Synthetic Cannabinoid Medication and Health Outcomes in Manitoba (2004-2014)
SPONSORING AGENCIES AND/OR COORDINATING GROUPS: College of Pharmacy Start-up Fund and Manitoba Medical Services Foundation(pending) and American Pain Society (pending)	

Submission Date of Investigator Documents:	HREB Receipt Date of Documents:
June 19 and August 28, 2015	June 23 and August 28, 2015

THE FOLLOWING ARE APPROVED FOR USE:

Document Name	Version(if applicable)	Date
Protocol: Revised submission		received Augsut 29, 2015
Consent and Assent Form(s):		
Other: Data Capure Sheet		June 16, 2015

CERTIFICATION

The above named research study/project has been reviewed in a ***delegated manner*** by the University of Manitoba (UM) Health Research Board (HREB) and was found to be acceptable on ethical grounds for research involving human participants. The study/project and documents listed above was granted final approval by the Chair or Acting Chair, UM HREB.

HREB ATTESTATION

The University of Manitoba (UM) Research Board (HREB) is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulations of Manitoba. In respect to clinical trials, the HREB complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations of Canada and carries out its functions in a manner consistent with Good Clinical Practices.

QUALITY ASSURANCE
The University of Manitoba Research Quality Management Office may request to review research documentation from this research study/project to demonstrate compliance with this approved protocol and the University of Manitoba Policy on the Ethics of Research Involving Humans.

CONDITIONS OF APPROVAL:

1. The study is acceptable on scientific and ethical grounds for the ethics of human use only. ***For logistics of performing the study, approval must be sought from the relevant institution(s).***
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to the research study/project, and for ensuring that the authorized research is carried out according to governing law.
4. **This approval is valid until the expiry date noted on this certificate of approval. A Bannatyne Campus Annual Study Status Report** must be submitted to the HREB within 15-30 days of this expiry date.
5. Any changes of the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be reported to the HREB for consideration in advance of implementation of such changes on the **Bannatyne Campus Research Amendment Form.**
6. Adverse events and unanticipated problems must be reported to the HREB as per Bannatyne Campus Research Boards Standard Operating procedures.
7. The UM HREB must be notified regarding discontinuation or study/project closure on the **Bannatyne Campus Final Study Status Report**.

Sincerely,

[redacted]

Chair, Health Research Ethics Board
Bannatyne Campus

Please quote the above Human Ethics Number on all correspondence.
Inquiries should be directed to the REB Secretary **Telephone:** [redacted]

UNIVERSITY OF MANITOBA | Research Ethics - Bannatyne
Office of the Vice-President (Research and International)

P126-770 Bannatyne Avenue
Winnipeg, Manitoba
Canada, R3E 0W3
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Fax: 204-789-3414

HEALTH RESEARCH ETHICS BOARD (HREB)

CERTIFICATE OF ANNUAL APPROVAL

PRINCIPAL INVESTIGATOR: Wajd Alkabbani	**INSTITUTION/DEPARTMENT:** U of M/Pharmacy	**ETHICS #:** HS18824 (H2015:271)
HREB MEETING DATE (If applicable):	**APPROVAL DATE:** August 22, 2017	**EXPIRY DATE:** **September 1, 2018**
STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (If applicable): Dr. Christine Leong		

PROTOCOL NUMBER: NA	**PROJECT OR PROTOCOL TITLE:** Trend in Prescription Synthetic Cannabinoid Medication and Health Outcomes in Manitoba (2004-2015)
SPONSORING AGENCIES AND/OR COORDINATING GROUPS: NA	

Submission Date of Investigator Documents: July 10, 2017	**HREB Receipt Date of Documents:** July 10, 2017

REVIEW CATEGORY OF ANNUAL REVIEW: **Full Board Review** ☐ **Delegated Review** ☒

THE FOLLOWING AMENDMENT(S) and DOCUMENTS ARE APPROVED FOR USE:

Document Name(if applicable)	Version(if applicable)	Date

Annual approval

*Annual approval implies that the most recent **HREB approved** versions of the protocol, Investigator Brochures, advertisements, letters of initial contact or questionnaires, and recruitment methods, etc. are approved.*

Consent and Assent Form(s):

CERTIFICATION

The University of Manitoba (UM) Health Research Board (HREB) has reviewed the annual study status report for the research study/project named on this ***Certificate of Annual Approval*** as per the category of review listed above and was found to be acceptable on ethical grounds for research involving human participants. Annual approval was granted by the Chair or Acting Chair, UM HREB, per the response to the conditions of approval outlined during the initial review (full board or delegated) of the annual study status report.

HREB ATTESTATION

The University of Manitoba (UM) Health Research Board (HREB) is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulations of Manitoba. In respect to clinical trials, the HREB complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations of Canada and carries out its functions in a manner consistent with Good Clinical Practices.

QUALITY ASSURANCE
The University of Manitoba Research Quality Management Office may request to review research documentation from this research study/project to demonstrate compliance with this approved protocol and the University of Manitoba Policy on the Ethics of Research Involving Humans.

CONDITIONS OF APPROVAL:

1. The study is acceptable on scientific and ethical grounds for the ethics of human use only. ***For logistics of performing the study, approval must be sought from the relevant institution(s).***
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to the research study/project, and for ensuring that the authorized research is carried out according to governing law.
4. **This approval is valid until the expiry date noted on this certificate of annual approval. A Bannatyne Campus Annual Study Status Report** must be submitted to the REB within 15-30 days of this expiry date.
5. Any changes of the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be reported to the HREB for consideration in advance of implementation of such changes on the **Bannatyne Campus Research Amendment Form.**
6. Adverse events and unanticipated problems must be reported to the REB as per Bannatyne Campus Research Boards Standard Operating procedures.
7. The UM HREB must be notified regarding discontinuation or study/project closure on the **Bannatyne Campus Final Study Status Report**.

Sincerely,

[redacted]

Chair, Health Research Ethics Board
Bannatyne Campus

UNIVERSITY OF MANITOBA | Research Ethics and Compliance

Research Ethics - Bannatyne
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HEALTH RESEARCH ETHICS BOARD (HREB)

CERTIFICATE OF ANNUAL APPROVAL

PRINCIPAL INVESTIGATOR:	INSTITUTION/DEPARTMENT:	ETHICS #:
Wajd Alkabbani	U of M/Pharmacy	HS18824 (H2015:271)
HREB MEETING DATE (If applicable):	**APPROVAL DATE:** August 27, 2018	**EXPIRY DATE:** **September 1, 2019**
STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (If applicable): Dr. Christine Leong		

PROTOCOL NUMBER:	PROJECT OR PROTOCOL TITLE:
NA	Trend in Prescription Synthetic Cannabinoid Medication and Health Outcomes in Manitoba (2004-2015)
SPONSORING AGENCIES AND/OR COORDINATING GROUPS: NA	

Submission Date of Investigator Documents:	HREB Receipt Date of Documents:
August 1, 2018	August 2, 2018

REVIEW CATEGORY OF ANNUAL REVIEW: **Full Board Review** ☐ **Delegated Review** ☒

THE FOLLOWING AMENDMENT(S) and DOCUMENTS ARE APPROVED FOR USE:

Document Name(if applicable)	Version(if applicable)	Date

Annual approval

*Annual approval implies that the most recent **HREB approved** versions of the protocol, Investigator Brochures, advertisements, letters of initial contact or questionnaires, and recruitment methods, etc. are approved.*

Consent and Assent Form(s):

CERTIFICATION

The University of Manitoba (UM) Health Research Board (HREB) has reviewed the annual study status report for the research study/project named on this ***Certificate of Annual Approval*** as per the category of review listed above and was found to be acceptable on ethical grounds for research involving human participants. Annual approval was granted by the Chair or Acting Chair, UM HREB, per the response to the conditions of approval outlined during the initial review (full board or delegated) of the annual study status report.

HREB ATTESTATION

The University of Manitoba (UM) Health Research Board (HREB) is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulations of Manitoba. In respect to clinical trials, the HREB complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations of Canada and carries out its functions in a manner consistent with Good Clinical Practices.

QUALITY ASSURANCE

The University of Manitoba Research Quality Management Office may request to review research documentation from this research study/project to demonstrate compliance with this approved protocol and the University of Manitoba Policy on the Ethics of Research Involving Humans.

CONDITIONS OF APPROVAL:

1. The study is acceptable on scientific and ethical grounds for the ethics of human use only. ***For logistics of performing the study, approval must be sought from the relevant institution(s).***
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to the research study/project, and for ensuring that the authorized research is carried out according to governing law.
4. **This approval is valid until the expiry date noted on this certificate of annual approval. A Bannatyne Campus Annual Study Status Report** must be submitted to the REB within 15-30 days of this expiry date.
5. Any changes of the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be reported to the HREB for consideration in advance of implementation of such changes on the **Bannatyne Campus Research Amendment Form.**
6. Adverse events and unanticipated problems must be reported to the REB as per Bannatyne Campus Research Boards Standard Operating procedures.
7. The UM HREB must be notified regarding discontinuation or study/project closure on the **Bannatyne Campus Final Study Status Report**.

Sincerely,

[redacted]

Bannatyne Campus

Manitoba
Health, Seniors and Active Living
Health Information Privacy Committee
4043-300 Carlton Street, Winnipeg, Manitoba, Canada R3B 3M9
T 204-786-7204 **F** 204-945-1911
www.manitoba.ca

November 3, 2016

Wajd Alkabbani
[redacted]

HIPC No. 2015/2016 – 22
File number to be quoted on correspondence

Dear Wajd,

Re: Trend in Prescription Synthetic Cannabinoid Medication and Health Outcomes in Manitoba (2004-2015)

The Health Information Privacy Committee has considered and ***approved*** your request for access to data for the purposes of the above named project.

Any significant changes to the proposed study design should be reported to the Chair/HIPC for consideration in advance of their implementation. Also, please be reminded that any manuscripts and presentation materials resulting from this study must be submitted to Manitoba Health, Seniors and Active Living for review. Specifically, manuscripts must be submitted *at least **30** calendar days* prior to the intended publication and presentation materials must be submitted *at least **10** calendar days* prior to the presentation.

Researcher Agreement will need to be completed before work on this project can commence. This will be initiated by **MCHP**. If you have any questions or concerns, please do not hesitate to contact Saila Parveen, Committee Coordinator at (204)786-7204.

Yours truly,

[redacted]c.
Chair, Health Information Privacy Committee

c.c.[redacted]

[redacted]

From: [redacted]
Monday, October 31, 2016 11:22 AM
To: [redacted] Director - Vital Statistics (CCA)
Subject: Re: MCHP Data Access Request (Alkabbani)
Attachments: Response - conditionally approved-4.pdf; HREBcbd.pdf; CBRx_HIPC_Submission_Revised.doc; Retrospective_Charts_or_Records_Review_Submision_Form_June_10__2014_CBRx....doc; cannabinoids HERB approval 2017.pdf; HIPC_Amendment_Approval.pdf; HREB_Amendment_Approval.pdf; HREB_Amendment_Submission.pdf; Revised_project_synopsis.doc; VS_Data_Access_Request.pdf

Hi Farzana,

The Vital Statistics Agency ***conditionally approves*** the data access request by Wajd Alkabbani entitled, *Trend in Prescription Cannabinoid Medication and Health Outcomes in Manitoba (2004-2016) [HIPC Number: 2015/2016 – 22].*

The Vital Statistics Agency's approval is conditional on final and full HIPC approval (IE: all conditions in the conditional HIPC approval are met).

Warm regards,

[redacted]
Assistant Director
Vital Statistics Agency / Bureau de l'état civil
Department of Justice / Ministère de la justice
[redacted]

From: [redacted]
Sent: October-31-16 11:01 AM
To: [redacted]
Cc: [redacted]
Subject: RE: MCHP Data Access Request (Alkabbani)

UNIVERSITY OF MANITOBA | Rady Faculty of Health Sciences

Max Rady College of Medicine
Manitoba Centre for Health Policy
Community Health Sciences
408-727 McDermot Avenue
Winnipeg, Manitoba
Canada, R3E 3P5
[redacted]

January 11, 2017

Wajd Alkabbani
Faculty of Graduate Studies
[redacted]

Dear Wajd:

Re: Project Entitled, Trend in Prescription Cannabinoid Medication and Health Outcomes in Manitoba (2004-2015)
MCHP #: 2017-001

Enclosed is a copy for your records of the fully executed Researcher Agreement, representing approval to proceed with the above research project at the Manitoba Centre for Health Policy (MCHP) using Manitoba Health, Seniors and Active Living data. It is important that the requirements outlined in this agreement be shared with all members of your project team, specifically Section 5 obligations respecting use and disclosure and Section 6 regarding reports, monitoring and enforcement. It is also important that all correspondence with MCHP relating to this project reference the MCHP project number.

We look forward to facilitating access to the Population Health Research Data Repository for your project. To [redacted]l (Manager, Program and Analysis System) at [redacted] Senior grants Accountant, at MCHP will be contacting you regar ng nvo c ng or your pro ect.

If any changes are made to the original approved study protocol, they must be submitted to the Health Research Ethics Board for approval and the data providers. A copy of the submissions and approvals must also be sent to MCHP. Please remember due to process changes with both the Health Research Ethics Board and MCHP in Janauary 2016, it is the PI's responsibility to provide MCHP an electronic copy of your Health Research Ethics Board Annual Approval Certificate. To prevent project access delays please send the approval to the MCHP Repository Access Unit via [redacted] within the month of expiration.

We would be glad to assist you in meeting ongoing project requirements for maintaining access to the data, as outlined at our website: http://umanitoba.ca/medicine/units/mchp/resources/access_re_ortin_.html Should you have any questions, please do not hesitate to contact the Repository Access Unit [redacted]

Sincerely,

[redacted]

Associate Director, Data Access and Use
Manitoba Centre for Health Policy
[redacted]