CANNABIS USE DURING AN OPIOID-RELATED PUBLIC HEALTH CRISIS: IMPLICATIONS FOR THERAPEUTIC ADVANCEMENTS AND HARM REDUCTION INITIATIVES

by

Stephanie Louise Lake

M.Sc., The University of British Columbia, 2015
B.HSc. (Hons), The University of Ottawa, 2011

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

in

THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES

(Population and Public Health)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

December 2020

The following individuals certify that they have read, and recommend to the Faculty of Graduate and Postdoctoral Studies for acceptance, the dissertation entitled:

Cannabis use during an opioid-related public health crisis: Implications for therapeutic advancements and harm reduction initiatives

submitted by Stephanie Louise Lake in partial fulfillment of the requirements for

the degree of Doctor of Philosophy

in Population and Public Health

Examining Committee:

Dr. M-J Milloy, Department of Medicine, UBC (Vancouver)
Co-supervisor

Dr. Jane Buxton, School of Population and Public Health, UBC (Vancouver)
Co-supervisor

Dr. Zach Walsh, Department of Psychology, UBC (Okanagan)
Supervisory Committee Member

Dr. Daniel Steele, School of Population and Public Health, UBC (Vancouver)
University Examiner

Dr. Margot Young, Allard School of Law, UBC (Vancouver)
University Examiner

Additional Supervisory Committee Members:

Dr. Thomas Kerr, Department of Medicine, UBC (Vancouver)
Supervisory Committee Member

Abstract

Background: While opioid-related morbidity and mortality have risen in jurisdictions across North America, recent reforms to cannabis policy have sparked scientific inquiry into cannabinoid-based interventions to prevent or mitigate opioid-related harm. After systematically reviewing the literature on cannabis use during medication-based treatment of opioid use disorder (Chapter 2), this dissertation sought to: explore the role of cannabis in the relationship between methadone maintenance treatment (MMT) dose and treatment outcomes (Ch.3); characterize motivations for cannabis use (Ch.4); examine the association between cannabis use and illicit opioid use in the context of chronic pain (Ch.5); and document the impact of cumulative cannabis use on mortality (Ch.6) among marginalized people who use illicit drugs (PWUD).

Methods: Data for Chapters 3-6 were derived from two community-based prospective cohort studies of PWUD in Vancouver, Canada. Regression analyses of longitudinal data were conducted, including generalized estimating equations (GEEs) and Cox frailty models for recurrent events (Ch.3); latent class analysis and GEEs (Ch.4); generalized linear mixed effects models (Ch.5); and time-varying Cox regression with weighted cumulative exposure measures modelled as restricted cubic splines (Ch.6).

Results: In Chapter 3, frequent cannabis use significantly reduced the magnitude of the association between lower MMT dose and frequent illicit opioid use (n=1389), but not treatment retention (n=611). In Chapter 4, four latent classes of cannabis-using PWUD were identified, and links with socio-structural and health-related factors were observed, including poorer physical and mental health among therapeutic cannabis-using classes. In Chapter 5, high-frequency cannabis use was significantly negatively associated with high-frequency illicit opioid use among 1152 PWUD living with chronic pain. In Chapter 6, time to all-cause mortality was not impacted by increasing cumulative exposure to cannabis among 2211 PWUD.

Conclusions: Certain motivations for cannabis use among PWUD are rooted in unmet healthcare needs and self-directed harm reduction. The findings of this dissertation signal the importance of

conducting experimental research into cannabis for the management of opioid withdrawal and craving and as an opioid-sparing agent in the treatment of pain. In a newly legal environment, cannabis-based harm reduction efforts should be integrated alongside the provision of broader social and structural supports.

Lay Summary

There is growing scientific and public interest in how cannabis (marijuana) could help prevent or reduce the use of opioids such as heroin, prescription painkillers, and fentanyl. Experimental research has provided early evidence that certain molecular components of cannabis (called cannabinoids) could help reduce the dose of opioids required for pain relief and could help alleviate symptoms of opioid withdrawal and craving. Given high rates of opioid-related harm among people who use drugs (PWUD) in Vancouver, this dissertation aimed to examine why and how cannabis is used within this population, and whether the use of cannabis is linked to: lower frequency of illicit opioid use in the context of pain and opioid use disorder (OUD); retention in treatment for OUD; and death. The findings provided some early 'real-world' evidence of a potential beneficial role of cannabis in the treatment of OUD and pain, requiring rigorous follow-up testing through experimental research.

Preface

Under the guidance of my committee, Dr. M-J Milloy, Dr. Jane Buxton, Dr. Thomas Kerr, and Dr. Zach Walsh, I was responsible for conceiving, designing, analyzing (with the exception of Chapter 4), and writing all work presented in this dissertation. All research involving original data (presented in Chapters 3-6) was approved by the University of British Columbia/Providence Health Care research ethics boards (H05-50233 and H05-50234). The principal investigators of the Vancouver Injection Drug Users Study (Dr. Thomas Kerr and Dr. Kanna Hayashi) and the AIDS Care Cohort to evaluate Exposure to Survival Services (Dr. M-J Milloy), from which data for Chapters 3-6 were derived, had access to all of the study data; as corresponding authors, they take full responsibility for the integrity of the results and the accuracy of the analyses. The co-authors of the manuscripts (published or under review) derived from this dissertation, including Dr. M-J Milloy, Dr. Jane Buxton, Dr. Thomas Kerr, Dr. Zach Walsh, Dr. Kanna Hayashi, Dr. Ekaterina Nosova, Dr. Eugenia Socías, Dr. Evan Wood, Dr. Mark Ware, Dr. Ziva Cooper, and Ms. Michelle St. Pierre contributed only as is commensurate with supervisory committee, collegial, or co-investigator responsibilities.

Chapter 1 is original, unpublished work. I conducted all background research and wrote the chapter with guidance and input from my committee.

A version of **Chapter 2** has been published: "Lake S and St. Pierre M. The relationship between cannabis use and patient outcomes in medication-based treatment of opioid use disorder: A systematic review. *Clinical Psychology Review.* 2020; 82:101939." As the original author of this work, I have retained the right to re-use it in this dissertation. With guidance from my committee, I designed and led this systematic review of the literature, including conducting the

search, screening articles, assessing study quality, and preparing the first and final drafts of the manuscript. As my secondary reviewer, Michelle St. Pierre helped guide the study design, independently screened articles and rated studies, and provided methodological and substantive input on the draft. My committee also provided valuable input on drafts of this manuscript.

Chapter 3 is currently being prepared for submission to a peer-reviewed journal. I designed and wrote this study with guidance and input from my committee. In consultation with Dr. Ekaterina Nosova and Dr. M-J Milloy, I prepared the data and conducted all statistical analyses in R using RStudio.

A version of **Chapter 4** has been published and is re-used here under Creative Commons Attribution (CC BY): "Lake S, Nosova E, Buxton J, Walsh Z, Socías E, Hayashi K, Kerr T, and Milloy, M-J. Characterizing motivations for cannabis use in a cohort of people who use illicit drugs: A latent class analysis. *PLoS One*. 2020; 15(5):e0233463." I co-designed this study with Dr. M-J Milloy and prepared the first and final draft of the manuscript. Statistical analyses were undertaken by Dr. Ekaterina Nosova in close consultation with me. Study co-authors provided valuable input on the manuscript.

A version of **Chapter 5** has been published and is re-used here under Creative Commons Attribution (CC BY): "Lake S, Walsh Z, Kerr T, Cooper ZD, Buxton J, Wood E, Ware, M, and Milloy, M-J. Frequency of cannabis and illicit opioid use among people who use drugs and report chronic pain: A longitudinal analysis. *PLoS Medicine.* 2019;16(11):e1002967." I designed and wrote this study with guidance and input from my committee. In consultation with Dr. Ekaterina Nosova and Dr. M-J Milloy, I prepared the data and conducted all statistical analyses in R using RStudio. I prepared the first and final draft of this manuscript.

Chapter 6 is currently being prepared for submission to a peer-reviewed journal. I designed and wrote this study with guidance and input from my committee and Dr. Brandon Marshall. In consultation with Dr. M-J Milloy and Dr. Brandon Marshall, I prepared the data and conducted all statistical analyses in R using RStudio.

Chapter 7 is original, unpublished work. I conducted all background research and wrote the chapter with guidance and input from my committee.

Table of Contents

List of Tables

List of Figures

List of Boxes

List of Abbreviations

2-AG	2-arachidonoyl glycerol
95% CI	95% Confidence interval
ACCESS	AIDS Care Cohort to evaluate Exposure to Survival Services
ACMPR	Access to cannabis for medical purposes regulations
AHR	Adjusted hazard ratio
AIC	Akaike information criterion
AIDS	Acquired Immunodeficiency Syndrome
(A)HR	(Adjusted) hazard ratio
(A)OR	(Adjusted) odds ratio
ART	Anti-retroviral therapy
ASI	Addiction severity index
ASSIST	Alcohol, Smoking, and Substance Involvement Screening Tool
BC	British Columbia
BCCDC	British Columbia Centre for Disease Control
BCE	Before the Common Era
BIC	Bayesian information criterion
BSI	Brief Symptom Inventory
CB1R	Cannabinoid Receptor 1
CB2R	Cannabinoid Receptor 2
CBD	Cannabidiol
CCAT	Comprehensive Cannabis Assessment Tool
CIDI	Composite International Diagnostic Interview
CNS	Central nervous system
COWS	Clinical Opiate Withdrawal Scale
CUD	Cannabis use disorder
CYP	Cytochrome P450
DALY	Disability-adjusted life-year
DTES	Downtown Eastside
ECS	Endogenous cannabinoid system, or “endocannabinoid” system
FDA	United States Food and Drug Administration
GEE	Generalized estimating equation
GLMM	Generalized linear mixed-effects model

HAM-D	Hamilton Rating Scale for Depression
HIV	Human Immunodeficiency Virus
ICD-10	International Classification of Diseases – 10th Edition
IQR	Interquartile range
LASSO	Least absolute shrinkage and selection operator
LCA	Latent class analysis
LRCUG	Lower Risk Cannabis Use Guidelines
MAP	Maudsley Addiction Profile
MeSH	Medical Subject Heading
MOUD	Medication-based treatment for opioid use disorder
MMT	Methadone maintenance treatment
NHLBI	National Heart, Lung, and Blood Institute
OAT	Opioid agonist treatment
OPS	Overdose prevention site, or overdose prevention service
OTI	Opioid Treatment Index
OUD	Opioid use disorder
PO	Pharmaceutical opioid, or prescription opioid
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PTSD	Post-traumatic stress disorder
PWUD	People who use (illicit) drugs
QIC	Quasi-information criterion
QOL-Bref	Quality of Life - Brief
RRR	Relative risk ratio
SCID-1	Structural Clinical Interview for DSM-IV Axis 1 Disorders
SOWS	Subjective Opiate Withdrawal Scale
THC	Delta-9-tetrahydrocannabinol
UDS	Urine drug screen
U.S.	United States
VANDU	Vancouver Area Network of Drug Users
VAS	Visual Analogue Scale
VIDUS	Vancouver Injection Drug Users Study
WHO	World Health Organization

Acknowledgements

This dissertation would not have been possible without my large support network of mentors and colleagues. I owe enduring gratitude to my supervisor, Dr. M-J Milloy, who firmly believed in me—even in the moments when I didn't believe in myself. His unwavering support allowed me to grow immensely as a scientist over the past five years. I am tremendously thankful for the mentorship I received from my co-supervisor, Dr. Jane Buxton, who has been with me since day one as a Master's student at UBC. I often find myself wondering 'What Would Jane Do' when approaching a topic. I think this speaks to her deep compassion for people who use drugs and unmatched wealth of clinical and practical harm reduction knowledge. I also want to express my sincerest gratitude to Dr. Thomas Kerr, who took a chance on me seven years ago and has never stopped encouraging me since. I truly would not be where I am today without his continuous support and generosity. Finally, I owe special thanks to Dr. Zach Walsh, whose clinical mental health expertise offered a new perspective on many parts of this dissertation. His thoughtful feedback and encouragement throughout this process has enriched the quality of my work immensely.

I humbly acknowledge that this work was undertaken on the unceded traditional territories of the Coast Salish People, including the traditional territories of the xʷməθkwəy̓əm (Musqueam), Skwxwú7mesh (Squamish), and Sə̓lílwətaʔ/Selilwitulh (Tsleil-Waututh) Nations. This research was possible thanks to the generous contributions of participants in the VIDUS and ACCESS studies. I would also like to acknowledge past and present interviewers, nurses, and administrative staff, who worked hard to maintain the smooth operation of these studies. I am extremely grateful

to Dr. Ekaterina Nosova, who generously offered statistical guidance on many aspects of this dissertation.

I'm lucky to have had the opportunity to learn from and work with a group of bright, inspiring, and encouraging colleagues both in and outside of Vancouver. My doctoral experience was greatly enriched through the time spent with colleagues at the British Columbia Centre on Substance Use (BCCSU), including Dr. Mary Clare Kennedy, Dr. Brittany Barker, Dr. Lianping Ti, Pauline Voon, Dr. Elena Argento, Dr. Tessa Cheng, Huiru Dong, Sanjana Mitra, Michelle Olding, Kate Jaffe, and Dr. Mohammad Karamouzian. I would also like to acknowledge other Canadian women training in cannabis science/policy who were a constant source of inspiration and knowledge over the course of this project—in particular, Michelle St. Pierre, Kira London-Nadeau, and Dr. Jenna Valleriani.

I was able to see this project through to completion thanks to the generous support from a UBC Four-Year Fellowship, a Canadian Institutes of Health Research Doctoral Award, a Pierre Elliott Trudeau Foundation Doctoral Scholarship, and the Evelyn Martin Memorial Fellowship. In addition, my training was generously supported through salary support from the BCCSU.

I am extremely lucky to have benefitted from the support of my family and friends throughout my time in graduate school. I am especially grateful to my parents, Terry and Lisa, for their unconditional love and encouragement, and to my sisters, Shannon and Gemma, for offering a sense of comfort I could not have found with anyone else. Finally, I am incredibly thankful to my partner, Daniel, whose love and support pushed me to keep going, even when I went dark-side. Thank you for encouraging me (or sometimes just putting up with me) from across the room while I analyzed, drafted, and edited a substantial amount of this dissertation at home during COVID-19.

Dedication

To my grandparents, Denise and Joe Harris

Chapter 1: Introduction

1.1 Opioids and related harms in the United States and Canada

Over the past two decades, rising rates of opioid-related morbidity and mortality have resulted in one of the most urgent public health crises facing Canada and the United States (U.S.). Opioids—drugs derived from the exudate of the opium poppy (i.e., opiates) or synthetically-manufactured to mimic the pharmacological properties of opiates (1)—act on cellular receptors in the body's central nervous system (CNS) to block the release of pain-signaling neurotransmitters (1). In addition to their analgesic properties, opioids also have an extensive history of non-medical use due to their ability to cause a pleasurable effect by increasing the production of dopamine in the brain (1, 2). Naturally-derived opioids, such as morphine, have long been used in medical practice for the management of acute and chronic pain (2, 3). Beginning in the mid-1990s, exposure to opioids increased sharply in Canada and the U.S. coinciding with aggressive marketing campaigns by pharmaceutical opioid manufacturers that encouraged the liberal prescribing of newly-formulated semi-synthetic opioids (e.g., OxyContin/oxycodone) for a wide range of purposes (4). Between 2006 and 2011, an estimated 30 million tablets and transdermal patches of high-dose opioids were dispensed from retail pharmacies in Canada every year (5).

One of the most notable adverse effects of chronic opioid use is the possible development of an opioid use disorder (OUD). Signs of OUD include, but are not limited to, physical dependence (e.g., withdrawal), the use of larger amounts over time, and persistent use despite physical, psychological, or social consequences (6). An estimated 5% of people who are prescribed opioids for pain and up to 30% who use illicit opioids for non-therapeutic purposes will meet diagnostic criteria for OUD (7, 8). The global burden of disease from alcohol and illicit drug use has doubled

since 1990, and roughly 42% of the increase is attributable to OUD (9). Today, the age-standardized prevalence of OUD is estimated to be 353 cases per 100,000 worldwide, and 1,168 cases per 100,000 across the U.S. and Canada (10).

Although increased provider awareness and policy interventions (e.g., prescription drug monitoring programs) have contributed to reduced diversion of prescription opioids (11), the opioid dispensation rate still remains high in Canada and the U.S. compared to other countries (12). There is also some evidence that these interventions may have created unintended negative consequences (13). For instance, patients have reported being forced to source opioids from unregulated illicit markets due to inadequate pain management as a result of policy interventions (e.g., limits on the length of prescriptions) to reduce opioid dispensations (14). Indeed, recent comparative research across U.S. jurisdictions shows that the adoption of a prescription drug monitoring program was associated with a subsequent 22% increase in poisoning deaths from heroin (15), adding to the findings of an earlier systematic review that identified six studies reporting increases in heroin-related overdoses following the adoption of a prescribing monitoring program (13).

Opioids are respiratory depressants and in the event of an overdose may cause respiratory failure, anoxic brain injury, or even death (16). In 2007, poisoning deaths (90% of which were drug overdoses) surpassed deaths from motor vehicle accidents to become the leading cause of unintentional injury-related death among people living in 20 states in the U.S.. Even before the rise of synthetic opioids (discussed in greater detail in Section 1.2, below), poisoning deaths had become the leading cause of accidental death in the U.S. (17) and among Canadians aged 25-64 (18). In regions with well-established heroin markets (e.g., Vancouver, Canada), the non-medical use of prescription opioids increased but likely played a smaller role in trajectories towards higher-

risk (i.e., unregulated) opioid use, as heroin already dominated the opioid market (19). The use of unregulated opioids such as heroin carries an even greater risk of overdose due to a complete lack of reliable information about the dosage, purity, and possible contaminants of the drug. Following the wave of pharmaceutical opioid deaths in Canada and the U.S., two subsequent waves of opioid-related overdose deaths were observed (20): beginning in 2010, there was an increase in heroin-related overdose deaths resulting, in part, from individuals progressing from pharmaceutical opioids to illicit opioids in many geographic regions (21); and beginning in 2013, there was an increase in overdose deaths associated with powerful illicitly-manufactured synthetic opioids, most notably fentanyl (22), which is described in greater detail in 1.2., below. Currently, an estimated 130 Americans (20) and another 12 Canadians die of an opioid-related overdose each day, while another 15 are hospitalized (23). Further, the use of opioids by Canadians was associated with an estimated $1.7 billion in losses from premature mortality or long-term disability in 2014 (24), and in 2017, for the first time in over 40 years, there was no increase in the estimated life expectancy at birth for Canadians as a result of the substantial increase in opioid-related deaths among young males (25). In particular, the 0.3-year reduction in life expectancy reported in the province of British Columbia was a major contributor to the delay in life expectancy growth observed nationally (25).

1.2 A provincial public health emergency from fentanyl-related deaths

1.2.1 The emergence of fentanyl in the province

Beginning in 2016, drug-related overdose deaths began to rise at an unprecedented rate across the province of British Columbia. That year, there were 914 apparent drug overdose deaths—approximately 80% more deaths than in 2015 (26). By April 2016, the provincial health

officer declared drug-related overdoses a provincial public health emergency (27). Today, the number of overdose deaths remains extremely high, with 981 apparent drug overdose deaths recorded in 2019 (a relative decrease from 2018, but still higher than before the public health emergency was declared (28)). Data from the provincial coroner shows that the majority (85%) of annual deaths during this time were related to fentanyl or its more potent analogues, such as carfentanil. (For context: fentanyl was detected in only 4% of the province's drug poisoning fatalities in 2012 (28)).

Fentanyl is a synthetic opioid analogue with a potency up to 100 times that of morphine (29). Although fentanyl is not a novel opioid (it has traditionally been used in the treatment of severe chronic pain (30)), as early as 2014, there were reports of illicitly-manufactured fentanyl being sold in powder (e.g., as "heroin") or tablet form (e.g., as "OxyContin") in the province (31). Powder fentanyl can be snorted, smoked, or injected. Due to its relatively high potency compared to other illicit opioids (e.g., heroin), even trace amounts of fentanyl may be sufficient to cause a potentially fatal overdose from respiratory arrest (31). Indeed, much of the early media coverage of the overdose crisis in the province focused on incidents of opioid overdose following accidental fentanyl exposure through the use of non-opioid drugs including cocaine, methamphetamine, and MDMA, or through the use of opioids that were thought to originate in the medical (i.e., regulated) system (32-34). While provincial data from public drug-checking services confirms that about 4-5% of these non-opioid drugs test positive for fentanyl, approximately 90% of drugs sold as heroin in certain regions of the province, including the Greater Vancouver Regional District, are estimated to be contaminated with fentanyl (35). At 37 deaths per 100,000 individuals in 2018, the highest annual overdose death rate in the province occurred in the regions covered by Vancouver Coastal Health Authority—most notably, Vancouver (36). The majority of the deaths in Vancouver have

been concentrated in the Downtown Eastside (DTES) neighbourhood (37)—home to a large population of people who use drugs (PWUD) among whom high-intensity poly-drug use involving the use of illicit opioids is common (38).

1.2.2 People who use drugs face additional challenges during the overdose crisis

PWUD experience high rates of morbidity and mortality and are a marginalized and vulnerable population with unique and complex health care needs. It is well established that the potential harms associated with illicit drug use are exacerbated by social and structural adversities, such as stigmatization, homelessness, and incarceration, which are disproportionately experienced by PWUD (39). These factors may also contribute to sub-optimal engagement with the healthcare system, illustrated by low initiation and retention in treatment for substance use disorders or infection with blood-borne pathogens including HIV and hepatitis C virus (HCV (40, 41)). The health of PWUD is further compromised by prevalent co-morbidities, including antecedent and current psychological trauma and chronic pain—a complex and often hard-to-treat health problem. For example, in a study of people who inject drugs in California, about half of respondents reported living with pain (42). It is common for PWUD to be denied a prescription for pain medication on suspicion of drug-seeking, often resulting in the self-management of pain through the use of unregulated opioids (43, 44)—an increasingly dangerous practice in the context of a contaminated unregulated drug supply (45). In addition, a substantial proportion of marginalized PWUD have survived exposure to trauma in early life or in adulthood (46-48). For example, a recent study of PWUD in Vancouver's DTES found that 39% of respondents met criteria for a provisional diagnosis of post-traumatic stress disorder (PTSD (49)). Survivors of trauma are at an increased risk of overdose, possibly through high-risk use of opioids and/or other substances as a self-medication strategy (49, 50). In addition to PTSD, other mental health conditions are common

among marginalized PWUD, including anxiety, depression, bipolar disorder, schizophrenia, and borderline personality disorder, for which opioids and other substances may be used to self-medicate (51-55).

1.2.3 Evidence-based responses to the overdose crisis

In response to the rapidly growing number of opioid overdoses across the province, several evidence-based harm reduction initiatives were introduced or expanded. First, in 2012, the British Columbia Centre for Disease Control (BCCDC) implemented a province-wide, publicly-funded take-home naloxone program. Naloxone is an opioid antagonist that can restore breathing in the event of an overdose due to its higher affinity for opioid receptors than fentanyl. BC's naloxone program ensures that people who are at risk of experiencing or witnessing an overdose are able to access naloxone (and receive training in overdose response) without a prescription and free of charge at participating community pharmacies and other sites (56). Within 20 months of its implementation the province, 85 overdoses were reversed using take-home naloxone kits (57). By 2017, over 56,000 kits were dispensed in one year, and more than 14,000 were used to reverse an overdose (58).

Second, the declaration of a provincial public health emergency led to a ministerial order that oversaw the rapid expansion of overdose prevention services (OPS) in the province. These are low-barrier observed consumption sites that can be set up relatively quickly and easily (e.g., via a tent, van, or in a single room occupancy hotel) in areas frequented by people at high risk of overdose (59). As of March 2018, in over 800,000 visits, 5,386 overdoses were reversed across the province's 25 overdose prevention sites; zero deaths were recorded (58).

Third, there was a substantial rise in the number of people on opioid agonist treatment (OAT, such as buprenorphine or methadone) for OUD. In 2017, after the declaration of the public

health emergency in B.C., the average monthly number of people receiving OAT in the province increased from 18,095 to 22,191 (60). This coincided with the release of provincial guidelines recommending buprenorphine and methadone as first- and second-line treatments for OUD, respectively, and injectable OAT (e.g., with hydromorphone or diacetylmorphine) if oral OAT is not successful (61). While actively engaged on OAT, patients are less likely to use illicit opioids (62), acquire a blood-borne pathogen (e.g., HIV (63) or HCV (64)), experience an overdose (62, 65), and be hospitalized (66). A recent study over 30,000 patients in the U.S. compared the effectiveness of six different OUD treatments and found that OAT was the only treatment pathway that reduced the risk of subsequent overdose or serious opioid-related acute care (67). Mathematical models have projected that an additional 3,030 individuals across the province would have died of overdose in just over 1.5 years had the three aforementioned harm reduction interventions not been implemented (60).

Despite the scaling up of evidence-based responses to the escalating overdose crisis, it has become increasingly clear, given the cumulating overdose death toll, that no intervention on its own is a panacea. This has led to calls for innovative strategies to contribute to a multi-faceted approach to tackling this complex public health challenge (14, 68). In more recent years, these calls have included an exploration of cannabinoid-based interventions to address the overdose crisis (69).

1.3 Cannabis, cannabinoids, and the endogenous cannabinoid system

1.3.1 Cannabis and cannabinoids

Cannabis—a general term for a wide variety of preparations derived from the *Cannabis sativa* plant—is one of the world's oldest domesticated plants. Its use in medicine, spiritual

ceremonies, and as a recreational substance dates back more than 5,000 years (70). Cannabis contains over 70 plant-based cannabinoid compounds (i.e., phytocannabinoids); the most notable ones being delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC, a lipid found in all cannabis, is the primary psychoactive component of cannabis (71). It exerts its effects by attaching to naturally-occurring cannabinoid receptors (detailed in Section 1.3.2., below). Its discovery by Gaoni and Mechoulam in the 1960s spurred major advancements in the biochemical, pharmacological, and clinical understanding of cannabis (72). CBD is a non-intoxicating phytocannabinoid with anxiolytic and anti-inflammatory properties (70)), discussed in greater detail below (Section 1.3.2.3).

1.3.2 The endogenous cannabinoid system

The endogenous cannabinoid system (ECS) is a complex neuro- and immuno-modulatory system involved in the regulation of homeostasis in the body (73, 74). The ECS is composed of cellular membrane receptors CB1R and CB2R, expressed throughout the body and concentrated in the CNS (CB1R) and the immune system (CB2R), and their cannabinoid ligands—namely 2-arachidonoyl glycerol (2-AG) and arachidonoyl ethanolamide (anandamide (73)). These endocannabinoid neurotransmitters lock into the endocannabinoid receptors to help regulate a number of neurophysiological processes involved in emotion and stress, sleep, memory, appetite, pain processing and response, and immune functioning (75-78). Certain phytocannabinoids (namely THC) share structural and pharmacological similarities with the body's endocannabinoids, thus phytocannabinoid exposure may result in modulation of CB1R and CB2R, however the resulting physiological effects may not necessarily be mimicked (78). Ongoing developments in the scientific understanding of the ECS and its implications for health and disease have opened the door to several avenues of inquiry into the potential therapeutic role of

cannabinoids and the ECS for a range of physical and mental health conditions and their symptoms, including pain, trauma, anxiety, and OUD.

1.3.2.1 Pain

Analgesia is one of cannabis' oldest therapeutic uses, estimated to have been employed in Indian folk medicine as far back as the third century BCE (79), and used as an analgesic in biomedicine since the early 1800s (80). Modern scientific research has discovered a key role of the ECS in pain perception and response (70). CB1R is present in peripheral nerve endings and abundant in regions of the brain and spinal cord responsible for processing pain stimuli, while both CB1R and CB2R are expressed in non-neuronal cells involved in inflammatory processes (78). Agonism of the endocannabinoid receptors is thought to induce analgesia by modulating the pain threshold and by preventing the release of pro-inflammatory factors (e.g., cytokines, chemokines) in non-nervous tissues (78). Importantly, despite that opioids are often a first-line of therapy for a range of chronic pain conditions, they seem to have limited effectiveness in managing neuropathic pain—pain caused by nerve damage, for example, in fibromyalgia, multiple sclerosis, cancer, diabetic neuropathy, and HIV-related neuropathy (81). Preclinical studies (82) and a number of clinical trials in humans have demonstrated that the administration of cannabinoid-based medicines (including smoked or vapourized dried herbal cannabis) results in short-term reductions of neuropathic pain (83-89) without causing serious short-term adverse events (90). A recently-published comprehensive evidence review of the therapeutic applications of cannabis by the U.S. National Academies of Sciences, Engineering, and Medicine concludes that there is substantial evidence to support cannabis as an effective treatment for chronic pain in adults (91).

The co-distribution of endocannabinoid receptors and opioid receptors in the dorsal horn of the spinal cord and key structures of the brain involved in antinociception (e.g., raphne nuclei

in the brainstem, central medial thalamic nuclei), and the resulting synergism of these two receptor systems (92, 93), provides biological plausibility for the potential application of cannabis in response to mounting opioid use and related harms. In practice, this synergism between the cannabinoid and opioid systems suggests that, rather than administrating a high dose of opioids, analgesia might be achieved with a non-analgesic dose of opioids if co-administered with a cannabinoid. While this phenomenon, known as an "opioid-sparing effect" is strongly supported in animal models, until recently, it had little reproducibility in human experimental research, possibly due to several overlapping study limitations (94). Since then, two small experimental studies (blinded, placebo-controlled, and within-subject) have tested the opioid sparing effect in healthy humans, again producing mixed results. Cooper and colleagues demonstrated that pain threshold and tolerance could be improved when a low dose of opioids was coupled with smoked cannabis in 18 healthy regular cannabis smokers (95), but Babalonis and colleagues found that dronabinol (an FDA- and Health Canada-approved pharmaceutically-prepared isomer of THC) did not enhance—and in some doses attenuated—opioid-induced analgesia in 10 healthy cannabis non-using volunteers (96).

1.3.2.2 Trauma, stress, and anxiety

With growing preclinical research supporting the role of endogenous cannabinoids in reducing fear, anxiety, and stress, researchers are turning to the ECS as a possible target of intervention for treating anxiety, trauma, and stress-related disorders (97). Studies of cannabis use for therapeutic purposes show a high number of individuals using cannabis to relieve symptoms of mental health conditions, including PTSD and anxiety (98, 99). This area of research may be relevant to the current overdose crisis given the substantial overlap between mental health

problems with substance use disorders, and the common practice of engaging in substance use to cope with under- or untreated mental illness (52).

CB1R is prevalently expressed in regions of the brain responsible for emotional and memory processes (e.g., emotional regulation, memory storage), including the amygdala, hippocampus, and prefrontal cortex (100). Trauma and stress can cause disruptions to these processes, and there is some evidence to suggest the administration of cannabinoids may help to mitigate stress-induced anxiety and fear response (76, 101). Again, much of this evidence comes from animal models, and has been more challenging to demonstrate in human studies. Although there are a few clinical trials underway in Canada (102) and the U.S. (103), no experimental studies have yet been published on the effectiveness of cannabinoid-based medicines in the treatment of PTSD. While patient reports tend to be positive (104), observational research has been mixed. Cross-sectional research tends to show worse symptom severity among cannabis-using patients (105, 106), but longitudinal studies have suggested an initial worse symptomology is improved over time for cannabis-using patients (107, 108). In an epidemiological investigation into the potential modifying effect of cannabis use on the association between PTSD and severe mental illness in the Canadian population, I produced evidence to suggest a possible beneficial effect (109).

Anxiety is one of the leading conditions for which medical cannabis is used, and patients have reported anxiolytic benefits of cannabis use in a number of survey-based studies (98, 110-113). Despite that self-medicating symptoms of anxiety with cannabis is common, the anxiogenic effects of THC (especially at high doses) are well-documented (114). CBD has shown promise as a novel treatment for anxiety disorders, based on the results of preclinical studies and a small number of experimental studies of acute anxiety in humans (115); however, there is a critical need

to conduct longer-term clinical research in this area, as the state of the evidence remains limited (91).

1.3.2.3 Opioid use disorder

The ECS is involved in enhancing the brain's reward signaling pathway via agonism of CB1R (116). The need to develop improved pharmacotherapies for substance use disorders has led to increased investigation of the ECS as a potential treatment target (117). Although this area of research is in its early stages, THC and CBD both offer some promise in addressing OUD symptoms through various biological pathways.

OUD is a chronic relapsing condition that can be challenging to treat due, in part, to the severe withdrawal symptoms associated with physical dependence, including nausea and vomiting, fluctuating temperature and chills, enhanced pain sensitivity, anxiety and stress, and irritability (6). Patients experiencing these unpleasant symptoms may relapse to opioid use as a means of alleviating their withdrawal. Cannabis' anti-emetic effect in humans is well-established and THC-based preparations, including dronabinol, have been used for over 30 years in the treatment of chemotherapy-induced nausea and vomiting (91). In animal models, agonism of CB1R alleviates somatic symptoms of withdrawal including vomiting, diarrhea, anorexia, and tremors (118). In a recent survey of 200 individuals in the U.S. who use both cannabis and opioids, 63% reported using cannabis in an attempt to treat symptoms of opioid withdrawal—most often anxiety (76%), tremors (54%), sleep problems (48%), bone/muscle aches (46%), and restlessness (45% (119)). To date, experimental evidence of benefit in humans is limited: two small experimental studies have tested the effect of dronabinol on opioid withdrawal in humans, producing mixed results. One study recorded significant reductions in opioid withdrawal severity relative to placebo during induction onto naltrexone (an opioid antagonist treatment for OUD

(120)); the other recorded reductions in certain subjective measures of opioid withdrawal for dronabinol (relative to placebo), but the effects were modest in comparison to the administration of oxycodone (121). However, concerns that THC may support relapse to opioids given its potential to enhance the rewarding effect of opioids via its agonism of CB1R (122, 123) have led to exploration of alternative cannabinoids to exploit in the treatment of OUD.

The phytocannabinoid CBD offers some promise in this area, as it has low affinity for CB1R, and is therefore not implicated in the reward pathway in the same way as THC (123). CBD appears to have a complex indirect mechanism of action that is less well understood, however its anxiolytic and anti-emetic properties have been well-documented in animal models (97, 124), and preclinical studies also demonstrate its potential to address opioid withdrawal and reduce relapse (125-127). Hurd and colleagues recently published the first human experimental study (randomized, blinded, placebo-controlled) to test CBD administration in the treatment of OUD, and reported significant improvements in acute and protracted heroin cue-induced craving and anxiety among a small sample of individuals with OUD (128).

1.4 Cannabis in Canada

1.4.1 Bill C-45: The Cannabis Act

In the lead-up to the 2015 Canadian federal election, citing high adolescent usage rates, strains on the justice system, and revenues for organized crime, Liberal Party leader Justin Trudeau announced the party's intent to legalize and regulate the production, sale, and use of cannabis for non-medical purposes (129). Soon after, the Liberal Party was elected into a majority government, and Bill C-45 (the *Cannabis Act*) was introduced in the House of Commons (130). The Bill formally came into effect on October 17, 2018 (131).

Bill C-45 sets out a number of key regulatory elements for cannabis production, distribution and sale, and possession. The law provides the federal government with oversight of the supply chain of retail cannabis—from cultivation by federally-licensed producers, to sale by provincially or territorially licensed distributors—requiring all products to meet quality standards. Adults (i.e., individuals aged 18 years and older, however this minimum can and has been increased at the provincial/territorial-level) can possess up to 30 grams of dried cannabis or equivalent in non-dried form, provided it has been obtained legally (i.e., grown for personal use or bought from a licensed seller). The passage of Bill C-45 also introduced more than 40 new criminal penalties for operating outside of the new law (132). For example, under the *Cannabis Act*, selling cannabis outside of the new legal system is prohibited and the penalty can range from a ticket to prison, depending on the amount.

1.4.2 Access to cannabis for medical purposes

Since 2001, Canada has had a legal framework in place for physician-authorized to access government-regulated medical cannabis for therapeutic purposes (133). The most recent iteration of this law before legalization was the *Access to Cannabis for Medical Purposes Regulations* (ACMPR (134)). Under the ACMPR, authorized patients could buy cannabis directly from a federally licensed producer of medical cannabis; become a registered grower of cannabis for personal use; or designate someone to grow cannabis on their behalf. Following legalization, access to cannabis for medical purposes continues to be provided to authorized patients under the *Cannabis Regulations* of the *Cannabis Act* (134). Statistics Canada survey data reveals a high degree of overlap between medical and non-medical use (135). Currently, there are over 350,000 patients in Canada who are authorized to use cannabis (136).

1.5 The potential beneficial role of cannabis use during the overdose crisis

Coincident with the public health crisis of unprecedented numbers of overdose deaths, Canada became the first major industrialized country to legalize and regulate non-medical cannabis. Jurisdictions across the U.S. have also experienced rising numbers of opioid-related deaths while liberalizing state-level medical and/or non-medical cannabis laws. In recent years, there has been an emergence of research exploring the potential influencing role of increasing cannabis access and use in the context of an overdose crisis. This research, described in greater detail below, includes exploration of the role of cannabis as an alternative to opioid analgesics in the management of pain, as a supporting medicine in the treatment of OUD, and as a more general harm reduction strategy in high-risk populations.

1.5.1 Population-level research

Over the past decade, an increasing number of US states, including Washington, Oregon, California, and Colorado, reformed their medical and non-medical cannabis laws, facilitating comparative analyses to evaluate the public health impacts of cannabis legalization. In 2014, Bachhuber and colleagues published the results of a ten-year comparative population-level analysis demonstrating that the passage of a state medical cannabis law was associated with 25% lower rate of annual opioid overdose deaths (137). Although the authors could not explore individual-level behaviours given the nature of the data, their finding spurred the hypothesis that increasing access to legal cannabis facilitates reductions in opioid analgesic use for pain management via an opioid-sparing or full substitution effect.

In the wake of Bachhuber and colleagues' findings, a growing number of studies have sought to confirm and further explore this cannabis substitution hypothesis using different datasets and/or other opioid-related outcomes, producing generally consistent findings that medical and/or

non-medical cannabis legalization is associated with reduced pharmaceutical opioid use, lower rates of treatment for OUD, and fewer opioid overdose deaths (138-146). However, Shover and colleagues recently re-assessed Bachhuber and colleagues' research question using updated data and found that, although the initial ten-year finding was replicated, the trend lost statistical significance in proceeding years before reversing direction in 2017 (147). These emergent findings cast some doubt on the cannabis substitution hypothesis in favour of the possibility that the connections between liberalized cannabis policies and improved opioid-related outcomes were spurious. An obvious major limitation of these population-based ecological analyses is their inability to reveal any underlying trends at the individual-level; this is a requirement for exploring the potential of cannabis as part of a larger strategy to mitigate opioid-related harm (148).

1.5.2 Cannabis and opioid use among pain patients

Research among people using cannabis therapeutically confirms that the use of cannabis to replace or reduce the use of opioids for pain management is already common practice (149-158). For example, about one-third of patients accessing cannabis from a BC-based licensed producer of cannabis in 2015 reported using cannabis as a treatment alternative to pharmaceutical opioids (155), and two-thirds of chronic pain patients using medical cannabis in California reported substituting cannabis for pharmaceutical opioids (152). Subjectively, patients report that cannabis is well-tolerated and effective relative to prescribed opioids; for example, in a sample of over 2,000 medical cannabis patients in California, more than 90% agreed or strongly agreed that cannabis was preferred over opioids to manage pain, and that side-effects from cannabis were more tolerable than those from opioids (152). A small study from New Mexico found that, relative to chronic non-cancer pain patients on pharmaceutical opioids not enrolled in the state's medical cannabis program, those who were enrolled in the medical cannabis program were more likely to

reduce daily prescription opioid dosages or cease prescription opioid use altogether (158). Cannabis patients also reported significant reductions in pain levels after enrollment and indicated improvements in quality of life without any significant adverse events (158). However, these studies have been relatively small, marked by selection bias, and few have compared changes in opioid use relative to a non-exposure group, making it difficult to discern how much (if any) improvement can be attributable to cannabis. Indeed, in larger studies comparing cannabis-using and non-using individuals with chronic pain, findings are less consistent. For example, in an observational cohort of 1514 patients prescribed opioid treatment for pain management, Campbell *et al.* did not find a reduction in pain severity or prescribed opioid use among patients who reported trying cannabis for pain management over the study period (159); whereas, in a secondary analysis of cross-sectional data from 790 HIV-positive people living with chronic pain, Sohler *et al*. found that cannabis-using participants were significantly less likely to be using pharmaceutical opioids compared to cannabis non-using participants (160).

1.5.3 Cannabis and opioid use among PWUD

Not surprisingly, the prevalence of cannabis use within populations of PWUD is much higher than in the general population. In my previous research exploring cannabis use and adherence to antiretroviral therapy among marginalized PWUD living with HIV in Vancouver, I noted past six-month cannabis use in approximately half of the study sample, and past six-month daily use in 20% (161). Despite the high prevalence of use, cannabis has historically received little attention in epidemiological research involving PWUD, likely due to its low risk of harm relative to other drug use practices, such as injecting illicit opioids or stimulants (162). However, more recently, a small number of studies examining cannabis' potential opioid-sparing effects have extended to PWUD, and particularly those engaging in higher risk opioid use and/or struggling

with OUD. For example, a cross-sectional study of people who inject drugs in California demonstrated that cannabis use was associated with reduced frequency of heroin injection (42), and qualitative research in the same setting describes a common trend of smoking cannabis to reduce anxiety and opioid cravings when transitioning from high-frequency to low-frequency or cessation of heroin injection (163). At least three recent qualitative studies (including one involving street-involved young PWUD in Vancouver (164)) document similar experiences with the use of cannabis in supporting transitions to lower-risk drug use or abstinence (163, 165).

A high prevalence of cannabis use has also been recorded across studies of patients entering or undergoing medication-based treatment of OUD (MOUD). For example, in a multicenter study of patients on methadone maintenance treatment (MMT) for OUD in treatment sites across Ontario, one-in-two patients were using cannabis (166). The experimental practice of prescribing cannabis to manage patients' symptoms of opiate withdrawal was documented by clinicians in the medical literature as early as 1891 (80), and conceptualizations of cannabis use as an *ad hoc* (i.e., self-directed or improvised, as necessary) opioid substitute to manage withdrawal have been noted in the clinical literature for at least four decades (167). There are currently polarized views within the medical community towards cannabis use during MOUD. For example, in many treatment settings, patients on MOUD are still routinely urine-tested for evidence of other drug use (168). Testing positive for THC may signal the need for treatment adaptations (e.g., an increase in the treatment dose), but in many cases (particularly across the U.S.), it could result in consequences to the patient (e.g., the loss of take-home doses (169)). In contrast, some clinicians in Canada have authorized the use of cannabis as an adjunct therapy during MOUD (170) and a growing number of US states, including New York, New Jersey, and Pennsylvania, have authorized the use of medical cannabis in the treatment of conditions for which opioids could be prescribed, including

OUD (171, 172). Despite this, it remains unclear what role cannabis plays in supporting or impeding treatment progress for patients maintained on MOUD. For example, Scavone and colleagues noted a significant negative correlation between frequency of cannabis use and severity of opioid withdrawal among 91 patients undergoing MMT (173), while Wasserman and colleagues found that cannabis use at treatment outset and during MMT was significantly associated with quicker relapse to heroin use (174).

1.6 Rationale

The quickly shifting cannabis policy landscape across Canada gives rise to a host of important research questions about the possible relationships between cannabis use more broadly (i.e., for medical and/or non-medical purposes), high-risk drug use, and health outcomes among populations with long-term experience using illicit opioids and other drugs. From a public health perspective, these questions are driven by the implication that cannabis could potentially be leveraged as a form of harm reduction (i.e., a strategy to reduce adverse consequences of drug use) among high-risk drug using populations. Scientific exploration into the potential therapeutic and harm reduction applications of cannabinoids has been encouraged by prominent policymakers, including BC's former Provincial Health Officer and Canada's former Minister of Health (both while serving in their policymaking capacities (175)). Although ecological studies provide a compelling hypothesis that access to cannabis facilitates reductions in opioid use and drug-related harms, there is an ongoing need to investigate these trends over time at the individual-level, including among PWUD. In particular, links between cannabis use and opioid use among PWUD with pain and/or undergoing treatment for OUD have yet to be longitudinally evaluated.

1.7 Study Methods

1.7.1 Study setting

Vancouver's DTES, a highly concentrated urban neighbourhood containing approximately 20,000 inhabitants within approximately two square kilometres (176), is widely known for its open illicit drug market (177); widespread criminalization and marginalization of residents (177); high rates of disease and disability (178-180); and extreme poverty, marked by densely packed low-income housing, shelters, and homelessness (176). PWUD who live or access services in Vancouver's DTES neighbourhood are an especially vulnerable population during the opioid overdose public health emergency, as many contend with a host of co-occurring social and structural adversities (e.g., stigma, criminalization, precarious employment and housing) in addition to physical and mental comorbidities.

Although a number of the neighbourhood's metrics generally correspond with low quality of life, the DTES community also exudes many qualities that foster resilience, connection, and support (181). For example, many would deem Vancouver's DTES the birthplace of modern drug-related harm reduction policy in Canada, thanks to the tireless advocacy of community members in response to localized public health crises including an injection-related HIV outbreak in the 1990s that co-occurred with mounting overdose deaths (182, 183). These community-led efforts ultimately prompted the opening of the first licit public supervised injection site (Insite) in the DTES in 2003 (184). Since then, programs borne from, or strongly influenced by, DTES-based grassroots activism (e.g., peer-led overdose prevention sites, injectable opioid agonist treatment, take-home naloxone) provide a blueprint for many of the current harm reduction responses to the overdose crisis seen nationwide and beyond (185).

The possession of small amounts of cannabis has been *de facto* decriminalized in the city since 2012—although, it is worth noting that drug arrest data suggests the lax enforcement of these laws has been inconsistently and inequitably applied, with Black and Indigenous individuals over-represented in arrests for cannabis possession (186). Against this backdrop, a more recent DTES-led harm reduction initiative has been the establishment of at least two different cannabis distribution programs. The Cannabis Substitution Project operates out of the offices of the Vancouver Area Network of Drug Users (VANDU), the neighbourhood's leading drug user-run advocacy organization. It began in 2017 as a once-weekly first-come-first-served program in which interested community members would line up for a pre-packaged preparation of cannabis products supplied by local illicit cannabis growers and distributors (187). The program now runs twice per week, serving approximately 200 people each day (188). The High Hopes Foundation, also founded in 2017, operates out of the offices of the Vancouver Overdose Prevention Society (OPS (189)). This program serves a smaller number of registered participants on an informal, per-needs basis (188). Similar to the Cannabis Substitution Project, the availability of products within this program is dependent on donations from illicit growers and/or producers (188). One aim of these programs is to support PWUD in the DTES to reduce, regulate, or stop their use of drugs through the use of cannabis; however the status of each program is precarious given the previous prohibited status of cannabis distribution more broadly and the newly illegal status of distributing cannabis outside of the legal framework (188). In addition to these cannabis distribution programs, the DTES (and Vancouver more generally) is home to several illegal retail cannabis stores. In the years preceding legalization, there was a proliferation of retail cannabis stores across Vancouver such that the city moved to regulate these stores rather than attempt to shut them down (190). Although many stores have since gone out of business or are now operating under the federal

regime (191), a few unregulated stores remain in the DTES, offering products at discount prices to economically-marginalized community members (188).

1.7.2 Study materials

This research draws on data from two ongoing prospective cohort studies of PWUD: The Vancouver Injection Drug Users Study (VIDUS) and the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS). Together, these cohorts include detailed measures from repeated interviews of over 2,000 Vancouver-based PWUD at risk of or living with HIV.

VIDUS was established in 1996 with the objective of understanding the social, structural, and behavioural determinants of HIV acquisition among people who inject drugs. Following the development of combination antiretroviral therapy (ART) for HIV infection in the mid-1990s arose the need to better understand barriers to ART among HIV-positive PWUD. In 2005, HIV-positive PWUD in VIDUS were transitioned to ACCESS, a separate but linked prospective cohort. All HIV-negative VIDUS participants remained in the VIDUS cohort, and (aside from HIV-specific measures), all interview questions were harmonized to allow for combined statistical analyses from 2005-onwards. All data for this research project was obtained from interviews beginning on or after December 1, 2005.

Participants for either study are recruited through diverse community-based strategies including self-referral and extensive street and community outreach from various settings in the DTES and other settings in which PWUD live or spend time (e.g., Downtown South (192)). Eligibility criteria for VIDUS include being at least 18 years of age at enrolment, residing in the Greater Vancouver area, and reporting injecting an illicit drug in the month prior to enrolment. Eligibility criteria for ACCESS includes being HIV-positive (as determined by a positive serologic test confirmed at a study visit or through a health care provider), at least 18 years of age, residing

in the Greater Vancouver area, and reporting using an illicit drug (other than or in addition to cannabis) in the month prior to enrolment.

In each cohort, participants complete an interviewer-administered baseline questionnaire at a DTES study site and are subsequently scheduled for a twice-annual (i.e., every six months) follow-up interview. Each study interview consists of two portions: the first is conducted by a trained interviewer and covers a range of demographic characteristics, drug use patterns, behavioural factors (e.g., syringe sharing, public injecting), use of harm reduction strategies (e.g., supervised injection site usage), and socio-structural exposures (e.g., incarceration). Measures of cannabis use more broadly (e.g., frequency of use) have been longstanding components of the cohort questionnaires; however, questions designed to elicit more specific information about cannabis use (e.g., reasons for use, modes of administration, preferred products) were added to the cohort questionnaires beginning in 2016. The second portion of the interview is conducted by a study nurse and covers HIV and other health-related issues. Participants also provide a blood sample for HIV testing (VIDUS) or monitoring (ACCESS). Study nurses refer participants to appropriate health services if requested or needed. Any VIDUS participant who becomes HIV-positive over the study period are transferred into ACCESS. All participants provide written informed consent prior to the first data collection, and receive a $40 honorarium upon completion of each interview. Both studies were approved by the UBC/Providence Healthcare Research Ethics Board.

1.8 Theoretical approach

The development of research questions for this project were informed by merging early hypothesis-generating evidence from preclinical, human experimental, patient observational, and

population-level observational studies (reviewed above). While there is strong neuro-psycho-pharmacological support for the hypothesis that cannabis could serve as an adjunct or alternative to opioids in the management of certain risk factors for overdose, PWUD also face inequities related to the criminalization and stigmatization of drugs and exacerbated by the social determinants of health, including gender (experiences of sexism, misogyny), race (experiences of racism, racial inequities), socioeconomic status, access to education and employment, and physical and social environments (193)—that create major barriers to engaging in harm reduction practices (194). Thus, if cannabis use has an underlying biological effect that contributes to reducing opioid use for certain applications (e.g., pain, managing OUD, sleep, etc.) among PWUD, it is important to consider how powerful social and structural forces within the broader Risk Environment might offset these benefits.

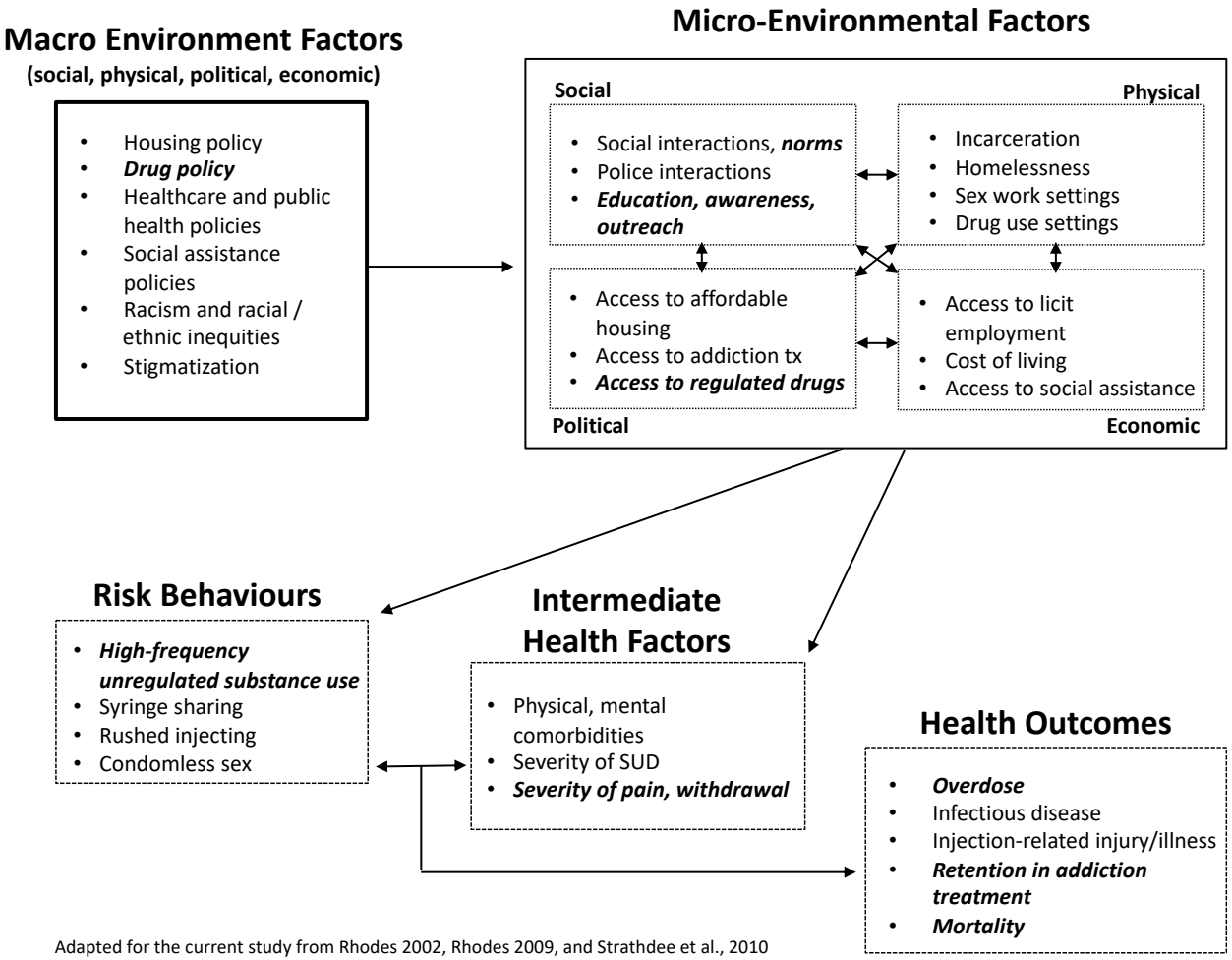
Rhodes and colleagues originally proposed the Risk Environment Framework to describe the social and structural production of HIV risk behaviours among PWUD (195). The framework recognizes a series of exposures on the micro- and macro-levels within the social, physical, economic, and political environments that interact with individual-level factors to influence the risk of drug-related harms (39, 195-197). This theory is in contrast with individualistic behavioural theories (e.g., the health belief model), which have been criticized for overlooking the influence of social determinants of health (195). Rhodes and colleagues' theoretical approach treats health behaviours (e.g., frequent use of opioids) and health outcomes (e.g., overdose, death) as the product of interacting individual-level factors (e.g., severity of pain, withdrawal) and factors within the social, physical, political, and economic environments (e.g., social supports, homelessness, incarceration), that are themselves influenced by macro-level environmental exposures (e.g., housing policy, regulation of psychoactive substances). The framework has since

been adapted from HIV to conceptualize risk of range of drug-related harms including overdose (198), exposure to violence (199, 200), and harm reduction and health service utilization (201, 202) among PWUD. As shown in Figure 1.1., for the purpose of this thesis, the Risk Environment Framework has been adapted from HIV risk to drug-related morbidity more generally. In particular, this research project was undertaken with specific consideration of the macro- and micro-level political and social environments regulating the status and availability of cannabis and other drugs. In Figure 1.1., factors within the modified Risk Environment Framework thought to be underpinned by a potential "substitution effect" of cannabis on other substances (in particular, opioids) are emphasized in bold, italics.

The "substitution effect"—a theory originating in behavioural economics—postulates that a shift in the access to or availability of one product creates shifts in usage patterns of another product when the products have overlapping applications (203). Recently, this theory has been used to inform economic research into the effect of medical and non-medical cannabis law reform on broad measures of opioid use and its harms (e.g., see Powell *et al*., 2018 (144); Lucas *et al*., 2013 (153)). Although federal legalization of cannabis occurred relatively recently, and evaluations of how legalization has shaped access to cannabis and resulting health outcomes among PWUD in the DTES are ongoing, the substitution effect underpins the substance-specific relationships considered in this research given cannabis' *de facto* decriminalized status, its normalization of use, and high availability within the community (reviewed above). In anticipation for major policy reforms throughout Canada and nearby jurisdictions in the U.S., attitudes towards cannabis and interest or awareness of its potential therapeutic applications have shifted in the general population (204, 205) and among PWUD in the DTES, as evidenced by the emergence of cannabis-based harm reduction programs to address the overdose crisis. These shifting patterns in

access to and knowledge of cannabis for harm reduction and therapeutic purposes may have spurred new trends in cannabis use among PWUD with implications for opioid use and relative outcomes (i.e., a sort of substitution effect even before any regulatory change).

Figure 1.1. Modified Risk Environment Framework



Adapted for the current study from Rhodes 2002, Rhodes 2009, and Strathdee et al., 2010

1.9 Study objectives

In light of a relatively narrow understanding of cannabis use patterns in the context of higher-risk polysubstance use, and given an emerging interest in establishing the therapeutic applications of cannabinoids, particularly in the context of substance use and dependence, the broad objectives of this thesis are: to explore how and why cannabis is used by marginalized PWUD; and to examine how the health of marginalized PWUD is influenced by the use of cannabis, particularly in the context of an unprecedented opioid-related overdose crisis.

This dissertation includes a systematic review of existing literature and four quantitative data-driven chapters that set out to investigate these two objectives on a finer level.

As discussed in Section 1.2.3., medication-based treatment for OUD has been established as one of the strongest interventions to protect against opioid overdose, and as discussed in Section 1.5.3., despite that cannabis use is prevalent among patients on OUD treatment, it is often viewed in a negative light by clinicians. However, the evidence of cannabis' impact during OUD treatment remains unclear. **Chapter 2** is a systematic review of the clinical and observational research on the relationship between cannabis use and a number of critical treatment outcomes including opioid use, treatment adherence, and treatment retention among patients undergoing medication-based treatment for OUD. The intent of this chapter is to synthesize and summarize the evidence in order to establish what is known and which questions should be further examined about the influence of cannabis among people undergoing treatment for OUD.

Chapter 3 was designed and developed based on the findings of the systematic review to explore the possible differential influence of cannabis use for patients who are at high and low risk of relapse during methadone maintenance treatment. Specifically, this chapter investigates frequent cannabis use as a potential modifying factor in the relationship between receiving a lower

methadone dose and: (1) engaging in frequent illicit opioid use during treatment (using generalized estimating equations), and (2) being retained in treatment (using a recurrent events Cox frailty model) among PWUD accessing methadone maintenance treatment for up to 13 years.

Chapter 4 provides an in-depth characterization of cannabis use in the VIDUS and ACCESS cohort studies. Using latent class analysis, this study identifies four classes of cannabis use according to self-reported motivations for use. Using generalized estimating equations, this study also identifies a range of social, structural, and health-related factors that are associated with periodic membership in these classes.

In light of high rates of chronic pain and marginalized PWUD, and the common practice of self-medicating with illicit opioids, **Chapter 5** follows a subgroup of PWUD living with chronic pain and employs generalized linear mixed effects models and descriptive statistics to understand whether engaging in frequent cannabis use is associated with a lower likelihood of frequent illicit opioid use.

As the dissertation's final quantitative exploration, **Chapter 6** uses a novel weighted cumulative average variable to estimate exposure to cannabis and other major substance classes (alcohol, opioids, stimulants) for up to 12 years, and employs a Cox model with time-varying covariates to examine time-to-all-cause mortality associated with increasing cumulative average exposure to each substance use class.

Chapter 2: The relationship between cannabis use and patient outcomes in medication-based treatment of opioid use disorder: A systematic review

2.1 Introduction

OUD is a leading contributor to the global burden of disease from illicit drug use, which has grown by more than 50% since 2000 (9). In jurisdictions across the U.S. and Canada, deaths from opioid-related overdose have skyrocketed as a result of the challenges associated with increased non-medical use of, and dependence on, prescription opioids (206) and the emergence of highly potent synthetic opioids (e.g., fentanyl) in the unregulated drug supply (22). Today, it is estimated that 353 in 100,000 people globally are living with an OUD, with high-income countries in North America experiencing a disproportionately high prevalence at 1,168 per 100,000 (10).

As OUD is a chronic disease with no cure, the current gold standard treatment for managing OUD is pharmacotherapy (i.e., MOUD), usually in combination with psychosocial support such as counseling (207). Three medication treatment modalities have been approved by the U.S. Food and Drug Administration (FDA): methadone (an opioid agonist), buprenorphine (a partial opioid agonist), and naltrexone (an opioid antagonist (207)). Under optimal treatment adherence and retention, MOUD supports: reductions in illicit opioid use (208), drug-related infectious disease (e.g., HIV, hepatitis C virus (209)), and overdose risk (210); retention in treatment for comorbidities (e.g., HIV (211)); and improvements in health-related quality of life (212). However, patients tend to exhibit lower treatment retention when engaged in concurrent use of other substances including amphetamines, benzodiazepines, and cocaine (213). In some opioid

treatment settings, testing positive for an illicit substance could result in termination of the treatment (168)

As reviewed in Section 1.5.3., above, the prevalence of cannabis use is high among patients seeking or receiving treatment for OUD (214). Some studies have documented continued or intensifying cannabis use following MOUD initiation (215-218), and particularly in the interim period prior to dose stabilization (i.e., maintenance (173, 219)). A number of early studies noted better clinical outcomes experienced by patients who engaged in cannabis use during methadone maintenance treatment (220-222), initially lending support to the hypothesis that cannabis substitutes for opioids (167). However, recent studies describing links between cannabis and worse (223) or unimproved (224) methadone outcomes have since challenged this hypothesis. Further, although buprenorphine is now recommended as a first-line therapy in Canada (225) and interest in naltrexone as an alternative to methadone is growing (226), the potential impact of cannabis use on markers of success in these other OUD treatment modalities has not been well established.

In light of the quickly shifting legal landscape of medical and non-medical cannabis across North America and various European settings, along with the ongoing public health emergency of opioid-related overdose deaths, there is an urgent need to better understand how cannabis use might impact OUD treatment outcomes. The aim of this study was to systematically search and review clinical and epidemiological literature to summarize the evidence on the impact of cannabis use on treatment outcomes for the three most common modalities of OUD pharmacotherapy—methadone, buprenorphine, and naltrexone.

2.2 Methods

This review was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) group statement (227), as summarized in Appendix A.1. The protocol for this review has been registered in Prospero (CRD42019125097).

2.2.1 Search strategy

The search strategy was designed by the primary author (SL) in consultation with the dissertation committee and a systematic review specialist. SL conducted the search.

The following scientific databases were searched from inception to February 1, 2019: *Medline, Embase, PsycInfo, Web of Science, CINAHL, and EBM Reviews*. Search terms for cannabis and opioid substitution treatment (and their synonyms) were combined using the appropriate Boolean operators. MeSH terms for cannabis and MOUD (e.g., "opioid substitution treatment", "methadone maintenance treatment") were included wherever possible (please see Appendix A.2 for a sample search strategy). In addition, *Google Scholar* was searched (from inception to March 15, 2019) with the terms "Cannabis" and "Opioids", and all records with both terms in the title and the first 200 records with both terms as keywords were retrieved. Finally, reference lists of prominent articles and conference abstracts were scanned to manually add potentially relevant articles that had been missed through the database searches. The search was restricted peer-reviewed articles published in the English language.

2.2.2 Eligibility criteria

As summarized in Table 2.1., studies that were considered relevant for this review were community-based epidemiological or clinic-based (observational or experimental) human research that quantitatively assessed the association between cannabis use and a clinical outcome among patients undergoing methadone, buprenorphine, or naltrexone treatment for OUD. The following

types of articles were excluded: qualitative research studies, case reports, case series, ecological studies, and descriptive studies. Studies were included if they assessed the use of naturalistic cannabis (as opposed to pharmaceutical cannabinoids such as dronabinol or nabilone, or cannabis isolates such as THC or CBD alone) at treatment outset and/or during treatment. As the majority of cannabis use among is expected to be naturalistic and clinically unauthorized, this justification was made to improve the comparability of findings across studies and increase generalizability of findings to most cannabis-using patients. Studies were excluded if they only assessed lifetime exposure to cannabis or did not operationalize cannabis exposure at the patient-level (for example, living in a state with a medical cannabis law would not be considered an eligible exposure). The primary outcome areas of interest were: 1) opioid craving, opioid withdrawal, and/or non-prescribed opioid use; 2) treatment adherence; and 3) treatment stabilization and/or retention. The following secondary measures were also recorded, wherever possible, from studies that reported at least one primary outcome: 1) health-related quality of life during treatment; and 2) other substance use during treatment.

Table 2.1. Relevant population, interventions, comparisons, outcomes, and study designs (PICOS) criteria for inclusion

Criteria	Definition
Population	Clinical- or community-based sample of patients undergoing methadone, buprenorphine, or naltrexone treatment for opioid use disorder
Interventions	Individual-level operationalization of naturalistic cannabis use
Comparisons	Non-use of cannabis, or less frequent use of cannabis (depending on how "intervention" is operationalized)
Outcomes	Primary outcome area 1: opioid craving, opioid withdrawal, and/or non-prescribed opioid use; Primary outcome area 2: treatment adherence; Primary outcome area 3: treatment stabilization and/or retention; Secondary outcome area 1: health-related quality of life during treatment; Secondary outcome area 2: other substance use during treatment
Study design	Studies reporting the results of a statistical test (e.g., Chi-square, ANOVA) or model (e.g., Cox proportional hazards regression) to determine the relationship cannabis use and at least one of the primary outcomes of interest. Acceptable types of research designs include: prospective or retrospective cohort studies, randomized controlled studies (including *post hoc* analyses), case-control studies, cross-sectional studies

2.2.3 Study screening

All records were imported from their respective databases into Endnote (Version X7, Clarivate Analytics) and duplicates were removed. The primary reviewer (SL) scanned all titles and eliminated records that clearly did not meet eligibility requirements (e.g., conference abstracts, articles published in a language other than English, commentaries). The remaining records were exported from Endnote into Covidence, a Cochrane-recommended online tool for streamlining the article screening and extraction process. In Covidence, the primary reviewer and a secondary reviewer (MSP) independently screened titles and abstracts for relevance. At this stage, articles were tagged as "Yes" (relevant), "No" (clearly not relevant") and "Maybe" (potentially relevant) based on information in the abstract. Only articles tagged with "Yes" or "Maybe" moved forward to the full-text screening stage. Any discordant coding by the reviewers resulting in conflict in the advancement of an article (i.e., "No/Maybe" or "No/Yes") was discussed until a consensus was reached. A conservative elimination approach was adopted at this stage, whereby articles for which

cannabis was possibly assessed but not mentioned in the abstract (e.g., studies examining predictors of treatment retention in which cannabis use was possibly measured but not reported in the abstract) were coded as "Maybe".

Full-text versions of all articles coded as "Yes/Yes", "Maybe/Yes", and "Maybe/Maybe" in the abstract screening stage were retrieved and independently assessed by the primary author and secondary reviewer. For each article eliminated at this stage, the main reason for exclusion was recorded. Any conflicts between reviewers were discussed until a consensus was reached.

2.2.4 Data extraction and quality assessment

For all articles meeting study eligibility, the primary author used a standardized form to capture detailed information on study methods, setting and population (including baseline group differences by cannabis use status if available), intervention/exposure, and outcomes of interest. Data from each relevant study was abstracted in Covidence and assessed for completeness and accuracy by the secondary reviewer.

The National Institutes of Health's National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Observational and Cross-sectional studies was used to assess study quality (228). This tool uses 14 criteria to assess each study's potential for selection bias, information bias, measurement bias, and confounding. For each criteria item, the rater assigns an answer of "Yes", "No", Not applicable", or "Cannot determine/Not recorded". As outlined by the NHLBI, these answers are not meant to translate into a final numeric score for overall quality, but are useful in guiding the rater to a final assessment of the study's quality as "Poor", "Fair", or "Good". As some studies did not explicitly set out to quantify an independent association between cannabis use and a treatment outcome, but rather analyzed a cannabis use measurement *post hoc* or as one of many patient characteristics, the quality rating assigned to each study may not

necessarily reflect that study's propensity for reducing bias in addressing its primary research objective. The primary reviewer rated all studies, and to ensure that ratings were fair and consistent, the secondary reviewer used the assessment tool to independently rate the quality of a random sample of 12 studies (32% of studies) and checked the primary author's scoring for the remaining studies. Any discrepancies in individual criteria assessments or overall quality ratings were discussed between reviewers until a consensus was reached. Although each study's quality rating was not directly based on numeric score, the proportion of eligible categories in which the raters marked "Yes" was calculated for each study after a quality rating was given. In general, this proportion was >75% for studies rated as good quality, 50-75% for studies rated as fair quality, and <50% for studies rated as poor quality.

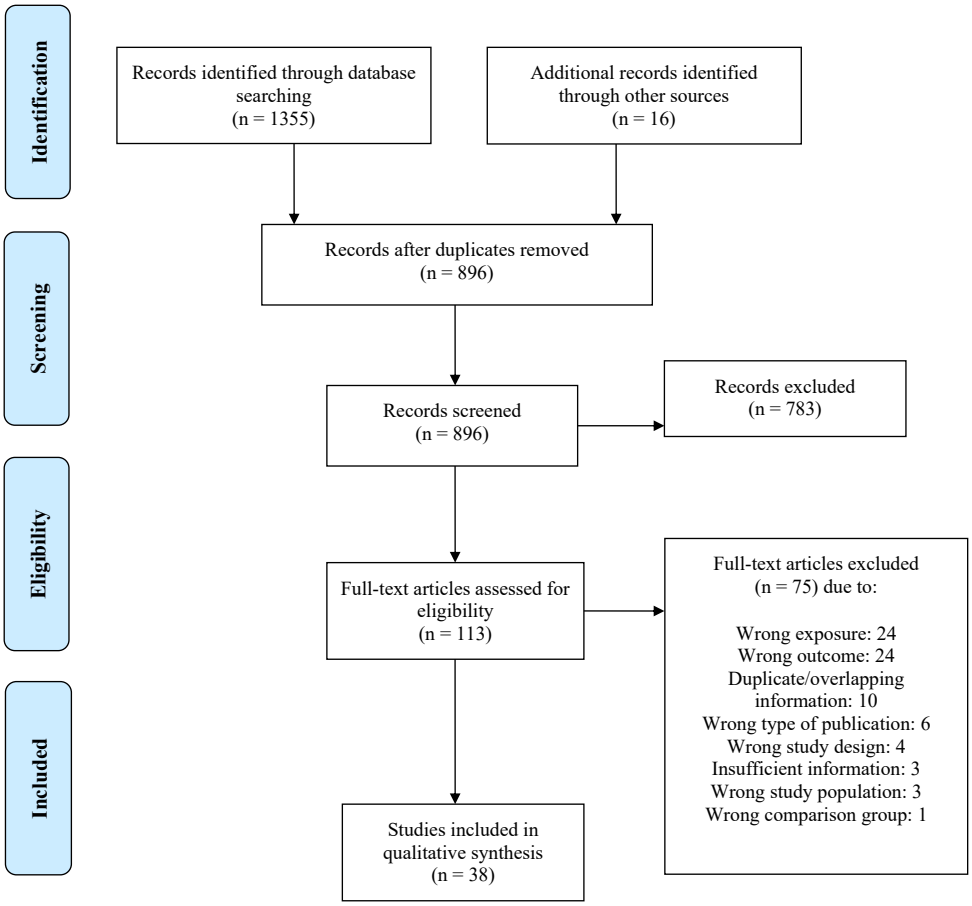
2.2.5 Data synthesis and analysis

Owing to the substantial heterogeneity in cannabis exposure assessments, outcome measures, treatment modalities, and treatment times observed, a meta-analysis was not conducted. Studies were grouped their assessed outcome and patient treatment modality (i.e., methadone, buprenorphine, naltrexone, mixed modalities) and conducted a qualitative assessment and narrative summary of findings. Study quality ratings were used to guide the narrative summary such that studies with ratings of good or fair quality were prioritized as example material to describe trends in findings. Wherever possible, adjusted estimates of the association between cannabis and an outcome (e.g., AOR, AHR) are reported. Bivariable estimates are reported in cases where cannabis was excluded from multivariable analyses or multivariable analyses were not performed.

2.3 Results

In total, 1371 (896 unique) records were screened for eligibility. Title and abstract screening resulted in the exclusion of 783 records. A full-text review of the remaining 113 articles resulted in a further 75 articles being excluded from consideration. A final 38 studies met the inclusion criteria. The PRISMA flowchart detailing the record screening and review process is shown in Figure 2.1.

Figure 2.1. PRISMA flow diagram



2.3.1 Summary of included studies

Among the 38 included studies, just over half (n = 20, 53%) were conducted in the U.S., followed by Canada (n = 4), France (n = 3), Sweden, Israel and India (n = 2 each), and England, Scotland, Ireland and Italy (n = 1 each). One study used a comparative sample of patients from the U.S. and Israel. The median year of publication was 2014 (range: 1996 – 2018), and the median sample size was 155 (range: 36 – 7717). Methadone was the most commonly studied treatment modality (n = 21, 55%), followed by buprenorphine (n = 7, 18%) and naltrexone (n = 6, 16%). An additional four studies (11%) included patients on different modalities (e.g., methadone and buprenorphine patients). Several of the included studies examined multiple treatment outcomes, with retention being the most commonly studied primary clinical outcome across all treatment modalities (n = 26, 68%).

Study designs included clinic- or community-based prospective cohort studies (n = 13, 34%), secondary analyses of clinical trials (n = 12, 32%), retrospective patient chart reviews (n = 9, 24%), and cross-sectional studies (n = 4, 11%). No clinical trial with the primary objective of investigating plant-based cannabis as an adjunct treatment to OUD pharmacotherapy was identified. The majority of studies (n = 22, 58%), including 38% of prospective cohort, 58% of clinical trials, 89% of retrospective chart reviews, and 50% of cross-sectional studies, were rated as having fair methodological quality in assessing the relationship between cannabis use and a treatment outcome. Eight (21%) studies had good methodological quality, and eight (21%) were rated as poor. While all four study designs contributed to the poorly rated studies (including 31% of prospective cohort, 8% of clinical trials, 11% of retrospective chart reviews, and 50% of cross-sectional studies), only studies with prospective cohort (31%) and clinical trial designs (33%) were

rated as having good quality. A detailed breakdown of the quality assessments for each study is provided in Appendix B.3.

2.3.2 Cannabis use measures

There was a great degree of heterogeneity across studies with regard to cannabis exposure assessment. Cannabis use was a primary focus in roughly one-third (n = 14) of the included studies (173, 216, 220, 221, 224, 229-237). These studies tended to record more detailed information about patterns of use (e.g., categorizing frequency of use, repeated measures throughout treatment) than studies in which cannabis was one of many potential predictors of a treatment outcome. Just over half of the studies (n = 21, 55%) used urine drug screens (UDS) to assess exposure to tetrahydrocannabinol (THC). The remaining studies (n = 17, 46%) ascertained self-reported measures of cannabis use with interviewer-administered questionnaires and scales. A minority of studies (n = 14, 37%) produced an adjusted estimate of the association between cannabis use and a treatment outcome; however, potentially important confounding factors, including co-occurring substance use patterns and treatment dose, were rarely accounted for.

Most studies provided prevalence estimates for cannabis use at treatment baseline and/or throughout the study period. Using information from these studies, the median prevalence of cannabis use at treatment baseline was 23% (range: 12-67%), and the median prevalence of frequent (i.e., near-daily or daily) cannabis use was 18.5% (range: 16-33%). The median recorded cumulative prevalence of cannabis use throughout treatment (of varying lengths) was 58% (range: 28-79%).

2.3.3 Opioid craving, withdrawal, and non-prescribed use

Studies measuring non-medical opioid use (or influencing factors such as opioid craving and withdrawal) during MOUD are summarized in Table 2.1. We identified 21 studies (including

13 methadone (173, 174, 216, 220, 221, 224, 233, 238-240)), four buprenorphine (229, 236, 237, 241), two naltrexone (235, 242), and two mixed modalities (243, 244)) that examined associations between cannabis use and opioid use during treatment. The results of these studies produced mixed evidence resulting in no consistent pattern of a positive or negative impact of cannabis use at treatment outset or during treatment. The majority of studies (n = 14, 67%, including nine methadone (173, 216, 221, 224, 232, 234, 238, 240, 245), all four buprenorphine (229, 236, 237, 241), and one naltrexone (235)) produced estimates that did not meet statistical significance. For example, Epstein and Preston analyzed secondary data from three methadone trials and did not find that individuals who used cannabis after achieving abstinence had a significantly higher risk of an opioid relapse (HR = 1.20, 95% CI: 0.69 – 2.09). Similarly, Hill *et al.* conducted a secondary analysis of data from a trial comparing a 12-week buprenorphine-naloxone treatment to a two-week buprenorphine-naloxone detoxification among young opioid dependent patients and did not detect significantly different odds of opioid use for those who screened positive for cannabis use at baseline (OR = 0.99, 95% CI: 0.96 – 1.01) or throughout treatment (OR = 1.56, 95% CI: 0.86 – 2.80 (237)).

A small number of studies (n = 4, 19%, including three methadone (174, 233, 239) and one mixed modalities (244)) noted possible negative impacts of cannabis use during treatment. For example, Wasserman *et al.* prospectively studied patients who had been stabilized on methadone for over three weeks and observed that self-reported cannabis use significantly increased the likelihood of subsequent relapse to heroin use (X^2=7.62, p<0.05 (174)). By contrast, three studies (14%, including one methadone (220), one naltrexone (242), and one mixed modalities (243)) found evidence of significantly lower prevalence or frequency of opioid use among cannabis using patients. However, these studies were mixed in documenting a possible dose-response relationship

between cannabis use and opioid use frequency. For example, in a cross-sectional study of 200 methadone patients, Best *et al.* noted an statistically significant inverse relationship between cannabis and heroin use frequency, with cannabis non-users reporting the highest number of heroin use days in the previous month (5.8 days on average) and daily cannabis users reporting the fewest (0.8 heroin use days on average; $F = 11.07$, $p < 0.001$ (220)). However, a secondary analysis of a naltrexone trial recorded significantly fewer opioid-positive urine drug screens among moderate cannabis users (15.0%), but not frequent users (71.4%), relative to non-users (60.0%; $F = 9.381$, $p < 0.001$ (242)) .

Of the five studies (including three methadone (173, 216, 234), one buprenorphine (229), and one naltrexone (120)) that measured opioid craving and/or withdrawal, three (60%, including two methadone (216, 234), and one buprenorphine (229)) did not find a statistically significant relationship between cannabis use and opioid craving or withdrawal. The remaining two studies noted a significant reduction in at least one measurement of opioid withdrawal among cannabis users. For example, Scavone *et al.* conducted a retrospective chart review of 91 methadone outpatients and found a statistically significant inverse relationship between cannabis use frequency (categorized into none, occasional, frequent) and severity of opioid withdrawal during treatment induction ($X^2 = 6.71$, $p = 0.035$ (173)); however, it should be noted that they did not observe a significant negative correlation between percentage of cannabis-positive and opioid-positive urine screens during this treatment stage ($r = 0.104$, $p = 0.332$). In a secondary analysis of a trial of dronabinol (a synthetic isomer of THC) as an adjunct treatment during a naltrexone induction, Bisaga *et al.* found that although weekly cannabis use during the outpatient phase was not significantly associated with differences in opioid craving or acute withdrawal severity, weekly cannabis users exhibited significantly lower severity of protracted withdrawal symptoms ($F = 4.43$,

$p = 0.037$)—a finding driven by lower insomnia and anxiety scores among weekly cannabis users (120).

Table 2.2. Summary of included studies: opioid craving, withdrawal, and non-prescribed use

Study	Study design	Quality	Study sample	Exposure	Outcome	Findings
1. Methadone						
Best *et al.*, 1999 (220); Scotland	Cross-sectional study	Fair	200 methadone patients on at a community drug clinic (mean age = 32 years, 30% women)	Past 30-day frequency (days) of cannabis use, self-reported at time of study, categorized as no use, occasional use, daily use	Past 30-day frequency (days) of heroin use, self-reported at time of study	The mean number of heroin use days was significantly higher for cannabis non-users (5.8) compared to occasional users (1.6) and daily users (0.8; F=11.07, p<0.001); the association remained significant in multivariable linear regression (β=-0.248, p<0.001)
Epstein and Preston, 2003 (224); USA	Secondary analysis of pooled data from three clinical trials	Good	408 methadone outpatients from 3 clinical trials (mean age = 39 years, 60% women)	Frequency of cannabis use, assessed by weekly UDS, categorized as 0%, 1-17%, 18-100%	(1) Frequency of opioid use, assessed with weekly UDS; (2) Relapse to opioid use after ≥3 weeks of abstinence, assessed with UDS	(1) Cannabis use frequency was not associated with opioid use during stabilization or maintenance phases (p>0.05); (2) Cannabis use during opioid abstinence did not predict relapse to opioid use (HR=1.20, 95% CI=0.69-2.09, p=0.52)
Epstein and Preston, 2015 (234); USA	Secondary analysis of a clinical trial	Fair	116 outpatients in a methadone taper phase of a clinical trial (mean age = 39 years, 47% women)	Any cannabis use, assessed with weekly UDS for 10 weeks	(1) Severity of opioid withdrawal, self-reported with 24-item symptom assessment questionnaire, assessed every 2 weeks; (2) Frequency of opioid use, assessed with weekly UDS	(1) Cannabis users had slightly higher withdrawal scores than non-users (least squares mean 28.29 *vs.* 26.06), but the difference was not significant (F=0.33, p=0.57); past-week cannabis use was not associated with lower next-week withdrawal score (F=0.001, p=0.98); (2) Cannabis users and non-users had similar mean percentage of opioid-positive UDS (54% *vs.* 52%; p-value not reported)

Study	Study design	Quality	Study sample	Exposure	Outcome	Findings
Levine *et al.*, 2015 (238); USA	Retrospective chart review	Fair	290 methadone outpatients from one clinic (mean age = 50 years, 40% women)	Any cannabis use, assessed with UDS at treatment baseline	Frequency of opioid use over 1 year, assessed with UDS	Cannabis use in the first month of treatment was not significantly associated with opioid use among men or women in the study (statistics not reported)
Lions *et al.*, 2014 (245); France	Secondary analysis of a clinical trial	Fair	158 patients initiating methadone in either primary care or a specialized centre (median age = 33 years, 15% women)	Past-month daily cannabis use, assessed with OTI at treatment baseline and 12 months	Past-month opioid use, assessed with OTI at 12 months	Baseline cannabis use was not associated with opioid use at 12 months (OR=1.46, 95% CI=0.61-3.53); daily cannabis use at 12 months was associated with opioid use at 12 months in bivariable (OR=2.81, 95% CI=1.22-6.48) but not multivariable analysis (statistics not reported)
Nava *et al.*, 2007 (216); Italy	Prospective cohort study	Poor	121 community-recruited patients beginning methadone treatment (mean age = 29 years, 13% women)	Heavy cannabis use, defined as past 6 month use and current use ≥7 times per week, self-reported at treatment baseline	(1) Heroin craving, assessed with VAS at months 1, 3, 12; (2) Heroin withdrawal, assessed with Wang Scale at months 1, 3, 12; (3) Frequency of opioid use over 1 year, assessed with weekly UDS	(1) Reduction in opioid cravings among cannabis users (Z=-5.24, p<0.001) and non-users (Z=-5.02, p<0.001), but no between-group differences (statistics not reported); (2) Reduction in withdrawal symptoms among cannabis users (Z=-7.58, p<0.001) and non-users (Z=-7.30, p<0.001), but no between-group differences (statistics not reported); (3) Reduction in opioid use among cannabis users (Z=-3.42, p<0.001) and non-users (Z=-3.18, p<0.001), but no between-group differences (statistics not reported)

Study	Study design	Quality	Study sample	Exposure	Outcome	Findings
Nirenberg *et al.*, 1996 (221); USA	Prospective cohort study	Poor	70 methadone outpatients at an urban veterans medical site (mean age = 39 years, 1% women)	Frequency of cannabis, assessed with weekly UDS for 45 weeks, categorized as none (0%), intermittent (1-33%), moderate (34-67%), and consistent (68-100%)	Frequency of opioid use, assessed with weekly UDS for 45 weeks	No significant difference observed in the mean percent of opioid-positive UDS between cannabis non-users (10.8%), intermittent users (22.0%), moderate users (19.4%) or consistent users (8.8%; F=1.13, p=0.34)
Proctor *et al*., 2016 (239); USA	Retrospective chart review	Fair	2410 methadone inpatients from 26 treatment sites across the USA (mean age = 35 years, 40% women)	Any cannabis use, assessed with UDS at intake (month 0) and months 3, 6, 9	Frequency of opioid use, assessed with UDS at months 3, 6, 9, and 12	Cannabis use at intake was not significantly associated with opioid use at any assessment (OR range=0.23-1.17, all p>0.05); cannabis use in month 3 (AOR=2.03, 95% CI=1.03-3.98) and 9 (AOR=5.19, 95% CI=1.26-21.47) was significantly associated with opioid use 3 months later; cannabis use at month 6 was not associated with opioid use 3 months later (AOR=0.31, 95% CI=0.09-1.14)
Saxon *et al.*, 1996 (222); USA	Secondary analysis of a clinical trial	Fair	337 patients beginning methadone at an urban treatment site (mean age = 38 years, 38% women)	Past 6-month frequency of cannabis use, self-reported using ASI at treatment intake, categorized on a scale from 0 (never) to 6 (≥4 times/day)	Frequency of opioid use, assessed with weekly UDS for up to 2 years	Baseline cannabis use frequency was not significantly associated with opioid use frequency during treatment (unadjusted β=0.05, p>0.05)

Study	Study design	Quality	Study sample	Exposure	Outcome	Findings
Scavone *et al.*, 2013 (173); USA	Retrospective chart review	Fair	91 methadone outpatients enrolled at one treatment site (mean age = 39 years, 40% women)	(1) Frequency of cannabis use, assessed with monthly UDS over 9 months, categorized as none, occasional (1-3 months), frequent (>3 months) or expressed as a percentage	(1) Opioid withdrawal severity, assessed with COWS during induction phase (subsample, n=40); (2) Frequency of opioid use during induction and stabilization phases, assessed with monthly UDS	(1) Severity of opioid withdrawal decreased with increasing cannabis use frequency category (X^2=6.71, p=0.035); (2) Percentage of THC-positive UDS did not correlate significantly with opioid-positive UDS during induction (r=0.104, p=0.332) or stabilization (r=0.038, p=0.734)
Somers and O'Connor, 2012 (240); Ireland	Retrospective chart review	Fair	117 patients starting methadone at one treatment site (mean age = 34 years, 36% women)	Any cannabis use, assessed with UDS, assessed at treatment baseline (month 0) and months 3, 9, 15	Opioid use, defined as ≥20% heroin-positive UDS during the 8-week period proceeding each exposure assessment	Cannabis use was not significantly associated with subsequent opioid use at any assessment point (OR range=0.78-1.45, all p<0.05)
Wasserman *et al.*, 1998 (174); USA	Prospective cohort study	Fair	74 patients stabilized on methadone treatment with ≥3 weeks of opioid abstinence (mean age = 43 years, 41% women)	Any cannabis use, self-reported and confirmed with UDS at baseline, 8 weeks, 6 months	Relapse to heroin use, assessed with UDS during weeks 2-8 and 6 months post-baseline	Baseline cannabis use was associated with heroin relapse in weeks 2-8 (Cox X^2=8.39, p<0.004) and 6 months later (Cox X^2=7.90, p<0.005); cannabis use was associated with relapse to heroin in the subsequent week (Cox X^2=7.62, p<0.006)
Weizman *et al.*, 2004 (232); Israel	Prospective cohort study	Fair	176 patients starting methadone treatment at one clinic (mean age = 38 years)	Cannabis “abuse”, assessed with SCID-1 on patients who screened positive for possible cannabis abuse (≥3 consecutive cannabis UDS over 12 months)	Heroin use, assessed with UDS at 12 months	Cannabis use was not significantly associated with heroin use 12 months after treatment initiation (statistics not reported)

Study	Study design	Quality	Study sample	Exposure	Outcome	Findings
Zielinski *et al.*, 2017 (233); Canada	Cross-sectional study	Fair	777 methadone patients recruited from 16 treatment sites across the province of Ontario (mean age = 38 years, 47% women)	1) Any past 30-day cannabis use, self-reported using MAP at time of study; (2) Past 30-day "heaviness" of cannabis use, self-reported using MAP at time of study (calculated as [n days used*typical dose in grams])	Any past 3-month opioid use, assessed with regular (approx. weekly) UDS	(1) Cannabis use was not significantly associated with illicit opioid use overall (AOR=1.16, 95% CI=0.77-1.75); cannabis use was significantly associated with opioid use among women (AOR=1.82, 95% CI=1.18-2.82) but not men (AOR=1.11, 95% CI=0.73-1.69); (2) Heaviness of cannabis use was not significantly associated with opioid use among men (AOR=1.01, 95% CI=1.00-1.01) or women (AOR=1.00, 95% CI=0.99-1.01)
2. Buprenorphine						
Abrahamsson *et al.*, 2016 (241); Sweden	Prospective cohort study	Fair	44 outpatients initiating interim buprenorphine-naloxone treatment phase (mean age = 35 years, 11% women)	Past 30-day frequency (days) of cannabis use, self-reported at treatment/study baseline	Any opioid use, assessed with UDS during interim treatment phase	Opioid-abstinent patients reported fewer mean days of cannabis use at baseline (5.9 *vs.* 8.6), but the difference was not significant (p>0.100)

Study	Study design	Quality	Study sample	Exposure	Outcome	Findings
Bagra *et al.*, 2018 (229); India	Cross-sectional study	Poor	100 outpatients on buprenorphine-naloxone for ≥3 months at a community drug treatment clinic (mean age = 44 years, 0% women)	Past 3-month cannabis use, self-reported using ASSIST at time of study	(1) Any past 3-month opioid craving, self-reported at time of study; (2) Past 3-month opioid withdrawal, self-reported at time of study; (3) Past 3-month opioid use, self-reported using ASSIST at time of study	(1) Cannabis users had higher prevalence of opioid craving (22.9% *vs.* 16.9%), but the difference was not significant (p=0.650); (2) Cannabis users had higher prevalence of acute (22.9% *vs.* 13.8%) and protracted (28.6% *vs.* 27.7%) opioid withdrawal symptoms, but the differences were not significant (p=0.748, p=1.00, respectively); (3) Cannabis users had higher prevalence of opioid use during treatment (17.1% *vs.* 13.8%), but the difference was not significant (p=0.660)
Budney *et al.*, 1998 (236); USA	Secondary analysis of pooled data from three clinical trials	Fair	79 patients undergoing a 7-22 week buprenorphine taper and behavioural therapy, derived from a larger (n=107) patient sample (mean age = 34 years, 37% women)	(1) Any cannabis use, self-reported (past 30-days) at treatment baseline, and assessed with thrice-weekly UDS (2) Frequency of cannabis use, assessed with thrice-weekly UDS	Weeks of continuous opioid abstinence, assessed with thrice-weekly UDS	(1) Weeks of continuous opioid abstinence was not significantly different between cannabis users and non-users (8.4 *vs.* 8.5 weeks, p>0.05); (2) Frequency of cannabis use did not correlate significantly with weeks of opioid abstinence (r=-0.07, p>0.05)

Study	Study design	Quality	Study sample	Exposure	Outcome	Findings
Hill *et al.*, 2013 (237); USA	Secondary analysis of a clinical trial	Good	152 young people initiating a 12-week treatment or 2-week detoxification with buprenorphine-naloxone (mean age = 19 years, 41% women)	(1) Past 30-day frequency (days) of cannabis use, self-reported at baseline, categorized as none (0), occasional (1-19), frequent (≥20); (2) Cannabis use during treatment, assessed with UDS at weeks 4, 8, 12	Opioid use, assessed with UDS at weeks 4, 8, 12	(1) Baseline cannabis use frequency was not associated with opioid use (OR=0.99, 95% CI=0.96-1.01); (2) Cannabis use during treatment was not associated with opioid use (OR=1.56, 95% CI=0.86-2.80)
3. Naltrexone						
Bisaga *et al.*, 2015 (120); USA	Secondary analysis of a clinical trial	Fair	60 patients initiating 8-week depot naltrexone trial with dronabinol (n = 40) or placebo (n = 20; mean age = 30 years, 17% women)	Weekly cannabis use, self-reported (and confirmed with UDS) at treatment baseline and weekly throughout trial	(1) Any opioid cravings, self-reported at baseline and weekly throughout 8-week trial; (2) Acute and protracted withdrawal symptoms, assessed with SOWS and HAM-D, respectively at baseline and weekly throughout trial	(1) Weekly cannabis use during outpatient treatment was not significantly associated with opioid craving (statistics not reported); (2) Weekly cannabis use at baseline was not significantly associated with acute withdrawal during inpatient phase (F<0.01, p=0.96); cannabis use during outpatient phase was not associated with acute withdrawal (statistics not reported), but was associated with lower severity of protracted withdrawal (F=4.43, p=0.037), driven by lower insomnia and anxiety scores

Study	Study design	Quality	Study sample	Exposure	Outcome	Findings
Church *et al.*, 2001 (242); USA	Secondary analysis of a clinical trial	Fair	47 community-recruited patients initiating naltrexone (mean age = 34 years, 23% women)	Frequency of cannabis use, assessed with twice-weekly UDS for 24 weeks, categorized as none (0%), intermittent (1-50%), daily (51-100%)	Frequency of opioid use, assessed with weekly UDS over 24 weeks	Intermittent cannabis users had significantly fewer opioid-positive UDS (15.0%) compared to daily cannabis users (71.4%) and non-users (60.0%; F=9.381, p<0.001)
Raby *et al.*, 2009 (235); USA	Secondary analysis of a clinical trial	Good	63 patients in a controlled trial of behavioural naltrexone therapy at one site (mean age = 36 years, 17% women)	Frequency of cannabis use, assessed with twice-weekly UDS for 6 months, categorized as none (0%), intermittent (1-79%), and consistent (≥80%)	Frequency of opioid use, assessed with twice-weekly UDS for 6 months	The mean proportion of treatment weeks with opioid-positive UDS did not differ significantly between cannabis non-users (0.37), intermittent users (0.25), and consistent users (0.39; F=0.80, p=0.46)
4. Mixed treatments						
Eastwood *et al.*, 2019 (243); England	Prospective cohort study	Good	7717 patients enrolled in methadone or buprenorphine treatment in England (mean age = 34 years, 27.9% women)	Cannabis use trajectory over 5 years, determined with latent trajectory analysis from self-reported measures obtained every 6 months, categorized as Class 1 ("continued low-level"), Class 2 ("low and decreasing"), Class 3 ("high and increasing")	Heroin use trajectory over 5 years, determined with latent trajectory analysis from self-reported measures obtained every 6 months	Members of the "decreasing" and "low-level" heroin use trajectories tended to belong to the "high and increasing" cannabis use group; e.g., relative to the "continued high-level" heroin group, "rapidly decreasing" heroin users were more likely to be "high and increasing" cannabis users (RRR=2.04, 95% CI=162-2.56); please refer to the original study and its supplementary files for all findings

Study	Study design	Quality	Study sample	Exposure	Outcome	Findings
Roux *et al.*, 2011 (244); France	Prospective cohort study	Poor	235 community-recruited PWUD with HIV enrolled in methadone or buprenorphine treatment (median age = 34 years, 31% women)	Daily cannabis use in the previous 6 months, self-reported every 6 months	Any non-medical use of opioids in the previous 6 months, self-reported every 6 months	Daily cannabis use was significantly associated with non-medical opioid use (AOR=1.32, 95% CI=1.08-1.60)

Note: 95% CI = 95% Confidence interval; (A)HR = (Adjusted) Hazard ratio; (A)OR = (Adjusted) Odds ratio; ASI = Addiction Severity Index; ASSIST = Alcohol, Smoking and Substance Involvement Screening Tool; COWS = Clinical Opiate Withdrawal Scale; HAM-D = Hamilton Rating Scale for Depression; MAP = Maudsley Addiction Profile; PWUD = People who use drugs; RRR = Relative risk ratio; SCID-1 = Structural Clinical Interview for DSM-IV Axis 1 Disorders; SOWS = Subjective Opiate Withdrawal Scale; UDS = Urine drug screen; VAS = Visual Analogue Scale

2.3.4 Treatment adherence

A total of six studies (including two methadone (173, 246), two buprenorphine (229, 247), and two naltrexone (235, 242)) measured cannabis use as a potential predictor of adherence to OUD pharmacotherapy and are summarized in Table 2.2. Cannabis was not significantly associated with treatment adherence in the methadone studies (173, 246) and one of two buprenorphine studies (229). The other buprenorphine study, which was rated as poor quality, found that patients who used cannabis were significantly less likely to adhere to their treatment, as denoted by pill count at a call-back interview ($\beta = 0.24$, one-sided $p = 0.02$ (247)). The remaining two studies were secondary analyses of naltrexone trials and both noted an inverted-U-shaped dose-response trend in which intermittent cannabis users exhibited significantly improved adherence relative to non-users or consistent users (235, 242).

Table 2.3. Summary of included studies: treatment adherence

Study	Study design	Quality	Study sample	Exposure	Outcome	Findings
1. Methadone						
Roux *et al.*, 2014 (246); France	Secondary analysis of a clinical trial	Fair	145 patients on methadone treatment in a multi-site open-label clinical trial (median age = 32 years, 15% women)	Daily cannabis use in the previous month, self-reported with OTI at baseline (month 0) and months 3, 6, 12	Adherence to methadone, self-reported using a questionnaire at baseline (month 0) and months 3, 6, 12	Baseline cannabis use was not significantly associated with adherence at 12 months (OR=1.19, 95% CI=0.47-2.98; cannabis use at 12 months was not significantly associated with adherence at 12 months (OR=1.92, 95% CI=0.76-4.78)
Scavone *et al.*, 2013 (173); USA	Retrospective chart review	Fair	91 methadone outpatients enrolled at one treatment site (mean age = 39 years, 40% women)	(1) Past 30-day cannabis use, self-reported at treatment intake; (2) Any cannabis use, assessed with monthly UDS for 9 months	Total number of daily dispensation absences in the first 9 months of treatment	(1) Baseline cannabis use did not predict treatment non-adherence (t=0.982, p=0.330); (2) Cannabis use in the methadone induction (pre-stabilization) phase was not associated with medication non-adherence (t=1.212, p=0.230)
2. Buprenorphine						
Bagra *et al.*, 2018 (229); India	Cross-sectional study	Poor	100 outpatients on buprenorphine for ≥3 months at a community drug treatment clinic (mean age = 44 years, 0% women)	Past 3-month cannabis use, self-reported using ASSIST at time of study	Mean number of days treatment was taken in the past 3 months at time of study	The mean number of compliant treatment days did not differ significantly between cannabis users and non-users (86.2 *vs.* 87.3, p=0.584)
Fareed *et al.*, 2014 (247); USA	Cross-sectional study	Poor	69 buprenorphine-naloxone outpatients from a veteran affairs medical center (mean age = 52 years, 6% women)	Any cannabis use, assessed with UDS at call-back interview	Treatment adherence at time of call-back, determined by correct pill count and UDS	Cannabis use was significantly associated with treatment non-compliance (β=0.24, one-sided p=0.02)

Study	Study design	Quality	Study sample	Exposure	Outcome	Findings
3. Naltrexone						
Church *et al.*, 2001 (242); USA	Secondary analysis of a clinical trial	Fair	47 community-recruited patients initiating naltrexone (mean age = 34 years, 23% women)	Frequency of cannabis use, assessed with twice-weekly UDS for 24 weeks, categorized as none (0%), intermittent (1-50%), daily (51-100%)	Proportion of all naltrexone doses taken in 24-week period, reported by patient's significant other	Intermittent cannabis use was significantly associated with improved treatment compliance (81.2% of doses taken) compared to frequent cannabis use (34.6%) and non-use (32.8%; F=8.454, p<0.001)
Raby *et al.*, 2009 (235); USA	Secondary analysis of a clinical trial	Good	63 patients in a controlled trial of behavioural naltrexone therapy at one site (mean age = 36 years, 17% women)	Frequency of cannabis use, assessed with twice-weekly UDS for 6 months, categorized as none (0%), intermittent (1-79%), and consistent (≥80%)	Treatment adherence, assessed with twice-weekly UDS over 6 months	Treatment adherence was significantly higher in intermittent cannabis users (0.86) than non-users (0.56) or consistent users (0.69, p=0.03)
Note: 95% CI = 95% Confidence interval; ASSIST = Alcohol, Smoking and Substance Involvement Screening Tool; OR = Odds ratio; OTI = Opioid Treatment Index; UDS = Urine drug screen						

2.3.5 Treatment retention

As shown in Table 2.3, a total of 26 studies (including 12 methadone (173, 216, 224, 230, 232, 248-252), five buprenorphine (236, 237, 241, 253, 254), six naltrexone (120, 235, 242, 255-257) and three mixed modalities (213, 231, 243)) were identified that examined a possible association between cannabis use and retention in treatment. Similar to the findings for opioid use, the majority of these studies (n = 16, 58%, including eight methadone (173, 216, 222, 224, 232, 248-250), four buprenorphine (236, 237, 241, 253), and four naltrexone (242, 255-257)) did not find that cannabis use was significantly associated with a patient's length of time in, or ability to stabilize on, treatment. For example, Peles *et al.* analyzed data from two prospective cohorts of methadone patients in Las Vegas, USA and Tel Aviv, Israel and found similar retention times after one year of treatment in Tel Aviv (3.4 *vs.* 3.7 years, respectively; $X^2 = 1.8$, $p = 0.20$) or Las Vegas (2.1 *vs.* 2.5 years, respectively; $X^2 = 0.8$, $p = 0.40$); although retention time was significantly shorter for patients who used cannabis at treatment baseline in Las Vegas (1.6 *vs.* 2.2 years, respectively, $X^2 = 4.2$, $p = 0.04$), the authors noted that the association lost significance after adjusting for several treatment covariates (250). Five studies (19%; including three methadone (230, 238, 252), one buprenorphine (254), and one mixed modalities (213)) suggested a possible negative impact of cannabis on treatment retention. For example, in their chart review of young opioid-dependent outpatients treated with buprenorphine-naloxone, Matson *et al.* noted that any cannabis use at a study visit significantly increased the likelihood of not returning for a subsequent treatment visit (HR = 1.73, 95% CI: 1.14 – 2.63 (254)). Similar to the distribution of findings for opioid use, a handful of studies (n = 5, 20%; including one methadone (251), two naltrexone (120, 235), and two mixed modalities (231, 243)) also noted significantly higher retention among cannabis users, yet there was again inconsistency between studies in the apparent dose-response effect. For

example, in the study by Socías *et al.* of community-recruited people who use drugs initiating opioid agonist (methadone or buprenorphine) treatment, the odds of remaining in retention six months later were significantly increased for daily cannabis users (AOR = 1.20, 95% CI: 1.02 – 1.43), but not occasional users (AOR = 1.00, 95% CI: 0.87 – 1.14), relative to non-users (231); whereas, Raby *et al.* noted that cannabis use on an intermittent (AHR = 0.23, 95% CI: 0.09 – 0.57), but not consistent (AHR = 1.42, 95% CI: 0.49 – 4.10), basis was significantly associated with longer time retained in naltrexone treatment (235). A similar trend was also noted in the study by Church *et al.*, in which intermittent cannabis users were retained for longer (92.7 days) than frequent (51.6 days) or non-users (48.0 days), but the association did not meet statistical significance ($p = 0.159$ (242)).

Table 2.4. Summary of included studies: treatment stabilization and retention

Study	Study design	Quality	Study sample	Exposure	Outcome	Findings
1. Methadone						
Epstein and Preston, 2003 (224); USA	Secondary analyses of pooled data from three clinical trials	Good	408 outpatients in clinical methadone treatment studies (mean age = 39 years, 60% women)	Frequency of cannabis use, assessed with weekly UDS, categorized as 0%, 1-17%, 18-100%	Time to treatment discontinuation, up to 25 weeks (2 studies) or 29 weeks (1 study)	Frequency of cannabis use during treatment was not associated with drop-out (range of *p*-values from survival analysis in 3 studies = 0.62-0.79)
Franklyn *et al.*, 2017 (230); Canada	Retrospective chart review	Fair	644 patients initiating methadone at 58 treatment sites in Ontario (median age = 33 years, 44% women)	(1) Any cannabis use at baseline, assessed with UDS; (2) Heavy cannabis use during treatment, assessed with UDS for 18 months, categorized as ≥75% *vs.* <75%	Time to treatment discontinuation, up to approx. 18 months	(1) Baseline cannabis use was significantly associated with drop-out (AHR=1.39, 95% CI=1.06-1.83); in sex-stratified analyses, baseline cannabis use was significantly associated with drop-out in women but not men (2) Heavy cannabis use was significantly associated with drop-out (AHR=1.48, 95% CI=1.13-1.93); in sex-stratified analyses, heavy use was significantly associated with drop-out among men but not women
Joe, 1998 (248); USA	Prospective cohort study	Fair	981 outpatients on methadone treatment at 11 sites (mean age = 37 years, 39% women)	Weekly cannabis use, self-reported at treatment/study intake	Retained in treatment for at least 360 days	Baseline weekly cannabis use was not significantly associated with treatment discontinuation (AOR=1.14, $p>0.05$)

Study	Study design	Quality	Study sample	Exposure	Outcome	Findings
Klimas *et al.*, 2018 (249); Canada	Prospective cohort study	Poor	823 community-recruited PWUD on methadone treatment and report alcohol use (median age = 42 years, 40% women)	Past 6-month daily cannabis use, self-reported every 6 months	Time to treatment discontinuation, estimated as the mid-point between last interview report of MMT to first interview report of no MMT	Daily cannabis use was not significantly associated with treatment discontinuation (HR=0.84, 95% CI=0.65-1.11, *p*=0.229)
Levine *et al.*, 2015 (238); USA	Retrospective chart review	Fair	290 methadone outpatients from one clinic (mean age = 50 years, 40% women)	Any cannabis use, assessed with UDS in the first month of treatment	Retained in treatment for at least 1 year	Cannabis abstinence in the first month of treatment was significantly associated with being retained on treatment 1 year later among men (AOR=5.00, 95% CI=1.61-14.29) and women (AOR=9.09, 95% CI=2.33-33.33)
Nava *et al.*, 2007 (216); Italy	Prospective cohort study	Poor	121 community-recruited patients beginning methadone treatment (mean age = 29 years, 13% women)	Heavy cannabis use, defined as past 6-month use and current use ≥7 times per week, self-reported at treatment baseline	Treatment discontinuation, assessed at 2 weeks, 3 months, 12 months post-intake	Cannabis use was associated with slightly higher treatment retention, but the difference was not significant (statistics not reported)

Study	Study design	Quality	Study sample	Exposure	Outcome	Findings
Peles *et al.*, 2008 (238); USA & Israel	Prospective cohort study	Good	794 methadone outpatients from treatment clinics in Tel-Aviv (n = 492, mean age = 37 years , 27% women) and Las Vegas (n = 302, mean age = 43 years, 37% women)	Any cannabis use, assessed with UDS at treatment baseline (month 1) and after one year (month 13)	Time (days) to treatment discontinuation, up to 5.8 years	Baseline cannabis use was associated with shorter treatment retention in Las Vegas (1.6 *vs.* 2.2 years; X^2=4.2, p=0.04) but not Tel-Aviv (3.4 *vs.* 3.3 years; X^2=0.2, p=0.80); in multivariable analysis, the association between cannabis use and treatment retention in the Las Vegas sample was no longer statistically significant (statistics not reported); (2) Cannabis use at 13 months was not associated with retention in Las Vegas (2.1 *vs.* 2.5 years; X^2=0.8, p=0.40) or Tel-Aviv (3.4 *vs.* 3.7 years; X^2=1.8, p=0.20)
Saxon *et al.*, 1996 (222); USA	Secondary analysis of a clinical trial	Fair	337 patients beginning methadone at an urban treatment site (mean age = 38 years, 38% women)	Frequency of cannabis use in the previous 6 months, self-reported using ASI at treatment baseline	Retained in treatment up to 18 months	Baseline cannabis use frequency was not associated with 18-month treatment retention (AHR=1.08, 95% CI=0.97-1.20)
Scavone *et al.*, 2013 (173); USA	Retrospective chart review	Fair	91 methadone outpatients enrolled at one treatment site mean age = 39 years, 40% women	Any cannabis use during treatment induction, assessed with monthly UDS	Retained in treatment up to 9 months	Cannabis use during induction phase was not significantly associated with early treatment drop-out (X^2=3.01, p=0.222)
Schiff *et al.*, 2007 (251); Israel	Retrospective chart review	Poor	2683 methadone patients from 8 treatment sites (mean age = 43 years, 12% women)	Any cannabis use, assessed with UDS for 13 months	Percentage of days in treatment (1-13 month period), categorized as 100% *vs.* 0%	Cannabis use during treatment was associated with increased likelihood of 100% retention (AOR=1.43, 95% CI=1.15-1.78)

Study	Study design	Quality	Study sample	Exposure	Outcome	Findings
Weizman *et al.*, 2004 (232); Israel	Prospective cohort study	Fair	176 patients starting methadone treatment at one clinic (mean age = 38 years)	Cannabis "abuse", assessed with SCID-1 on patients who screened positive for possible cannabis abuse (≥3 consecutive cannabis UDS over 12 months)	Number of days in treatment, up to 12 months	Cannabis use was not significantly associated with treatment retention in bivariable analysis (HR=0.84, 95% CI=0.65-1.09), or after adjusting for co-occurring substance use (statistics not reported)
White *et al.*, 2014 (252); USA	Retrospective chart review	Fair	604 methadone patients at a private, non-profit treatment site (mean age = 53 years, 49% women)	Any cannabis use, assessed with UDS during the 3-month study baseline period	Retained in treatment at the re-assessment period (14-16 months after study baseline)	Baseline cannabis use was associated with increased likelihood of treatment discontinuation (OR=3.3, 95% CI=1.6-6.8), but cannabis-only use was not associated with early discontinuation (OR=0.5, 95% CI=0.7-9.8)
2. Buprenorphine						
Abrahamsson *et al.*, 2016 (241); Sweden	Prospective cohort study	Fair	44 outpatients initiating interim buprenorphine-naloxone treatment phase (mean age = 35 years, 11% women)	Past 30-day frequency (days) of cannabis use, self-reported at treatment/study baseline	Successful transfer from intermediate to full-scale treatment	Patients who were successfully transferred to full-scale treatment had fewer mean days of cannabis use at baseline (5.2 *vs.* 10.4, p=0.059); in a multivariable model, cannabis use was no longer significantly associated with successful transfer (p=0.270)
Budney *et al.*, 1998 (236); USA	Secondary analysis of pooled data from three clinical trials	Fair	79 patients undergoing a 7-22 week buprenorphine taper and behavioural therapy, derived from a larger (n=107) patient sample (mean age = 34 years, 37% women)	(1) Any cannabis use, self-reported (past 30-days) at treatment baseline, and assessed with thrice-weekly UDS (2) Frequency of cannabis use, assessed with thrice-weekly UDS	Percentage of treatment weeks completed	(1) The percentage of weeks retained on treatment did not differ significantly between cannabis users and non-users (65% *vs.* 60%, p>0.05); (2) Frequency of cannabis use did not correlate significantly with weeks of treatment retention (r=-0.21, p>0.05)

Study	Study design	Quality	Study sample	Exposure	Outcome	Findings
Håkansson *et al.*, 2016 (253); Sweden	Prospective cohort study	Good	36 patients entering full-scale buprenorphine treatment following interim treatment (median age = 33 years, 11% women)	Past 30-day frequency (days) of cannabis use, self-reported using ASI at baseline and assessed with weekly UDS throughout interim and full-scale treatment	Retained in treatment 9 months after intake	Retention in treatment was not significantly associated with frequency of cannabis use at baseline (p=0.689) or during either interim (p=0.297) or full-scale treatment phase (p=0.965)
Hill *et al.*, 2013 (237); USA	Secondary analysis of clinical trial	Good	152 young people initiating a 12-week treatment or 2-week detoxification with buprenorphine-naloxone (mean age = 19 years, 41% women)	Past 30-day frequency (days) of cannabis use, self-reported at baseline, categorized as none (0), occasional (1-19), frequent (≥20)	Retained in treatment 12 weeks after intake	The proportion of patients retained on treatment did not differ significantly by frequency of baseline cannabis use (non-use: 52%, occasional use: 39%, frequent use: 44%, p=0.38)
Matson *et al.*, 2014 (254); USA	Retrospective chart review	Fair	103 youth buprenorphine-naloxone outpatients from one clinic (mean age = 19 years, 50% women)	Any cannabis use, assessed with UDS at treatment intake and periodically over 1 year	Treatment discontinuation, defined as not returning for a scheduled treatment visit	Cannabis use at the previous treatment visit was associated with a higher likelihood of treatment discontinuation at the next visit (HR=1.73, 95% CI=1.14-2.63)
3. Naltrexone						
Bisaga *et al.*, 2015 (120); USA	Secondary analysis of a clinical trial	Fair	60 patients initiating 8-week depot naltrexone trial with dronabinol (n = 40) or placebo (n = 20; mean age = 30 years, 17% women)	Weekly cannabis smoking, self-reported (and confirmed with UDS) at treatment baseline and weekly throughout trial	(1) Inpatient phase: Successful transfer to injectable naltrexone; (2) Outpatient phase: time to treatment/study drop-out	(1) No association between weekly cannabis use at baseline and successful transfer to outpatient phase (X^2=1.45, p=0.230); (2) Weekly cannabis use during treatment was associated with longer treatment retention (HR=4.83, 95% CI=1.09-21.36)

Study	Study design	Quality	Study sample	Exposure	Outcome	Findings
Chaudhry *et al.*, 2012 (255); USA	Retrospective chart review	Fair	142 patients on naltrexone at one treatment site (mean age = 26 years, 6% women)	Past-week frequency (days) of cannabis use, self-reported at outpatient assessment, categorized as none (0), occasional (1-5), and frequent (6-7)	Successful progression to treatment phase 3 (≥17 weeks of treatment)	Odds of treatment retention were lower for frequent (OR=0.46, 95% CI=0.19-1.11) and occasional cannabis users (OR=0.32, 95% CI=0.12-0.71), relative to non-users (any *vs.* none, p=0.04); cannabis use was not associated with retention in a multivariable model (statistics not reported)
Church *et al.*, 2001 (242); USA	Secondary analysis of a clinical trial	Fair	47 community-recruited patients initiating naltrexone (mean age = 34 years, 23% women)	Frequency of cannabis use, assessed with twice-weekly UDS, categorized as none (0%), intermittent (1-50%), daily (51-100%)	Retained in treatment up to 24 weeks	Intermittent cannabis users were retained on treatment for more days (92.7) than frequent users (51.6) or non-users (48.0), but the association was not statistically significant (F=1.932, p=0.159)
Dayal *et al*., 2016 (256); India	Prospective cohort study	Fair	140 opioid-dependent outpatients on naltrexone treatment at a tertiary care site (mean age = 32 years, 1% women)	Any cannabis use, self-reported at treatment baseline	Retained in treatment at 90 days, 180 days	Baseline cannabis users had significantly higher treatment retention at 90 days (X^2=6.86, p=0.009) but not at 180 days (X^2=2.69, p=0.100); in multivariable analysis, baseline cannabis use was not significantly associated with treatment discontinuation (90 days: AOR=0.46, 95% CI=0.19-2.21; 180 days: AOR=0.10, 95% CI=0.17-3.46
Jarvis *et al.*, 2018 (257); USA	Secondary analysis of a clinical trial	Poor	144 patients beginning a clinical trial for oral naltrexone (mean age = 43 years, 29% women)	Past 30-day frequency (days) of cannabis use, self-reported at study intake	Successful completion of outpatient oral naltrexone induction phase	Mean baseline cannabis use days did not differ significantly between those who successfully completed induction (4.6 days) and those who dropped out (3.6 days, p=0.485)

Study	Study design	Quality	Study sample	Exposure	Outcome	Findings
Raby *et al.*, 2009 (235); USA	Secondary analysis of a clinical trial	Good	63 patients in a controlled trial of behavioural naltrexone therapy at one site, (mean age = 36 years, 17% women)	Frequency of cannabis use, assessed with twice-weekly UDS for 6 months, categorized as none (0%), intermittent (1-79%), and consistent (≥80%)	Time (days) to treatment discontinuation, up to 182 days	Intermittent cannabis use was significantly associated with longer treatment retention relative to non-use (AHR=0.23, 95% CI: 0.09-0.57); consistent cannabis use was not significantly associated with longer retention (AHR=1.42, 95% CI=0.49-4.1)
4. Mixed treatments						
Eastwood *et al.*, 2019 (243); England	Prospective cohort study	Good	7717 patients enrolled in methadone or buprenorphine treatment in England (mean age = 34 years, 28% women)	Cannabis use trajectory over 5 years, determined with latent trajectory analysis from self-reported measures obtained every 6 months, categorized as Class 1 ("continued low-level"), Class 2 ("low and decreasing"), Class 3 ("high and increasing")	Successful completion and no presentation for further treatment within 6 months (summative measure based on opioid/cocaine abstinence, treatment completion, remission from OUD), assessed in year 6 and 7	Within the "decreasing then increasing" heroin use trajectory, cannabis trajectory 2 was negatively associated with treatment success (relative to group 1; AOR=0.50, 95% CI=0.28-0.92); within the "rapid decreasing heroin use" trajectory, cannabis trajectory 2 was positively associated with treatment success (relative to group 1; AOR=2.39, 95% CI=1.29-4.40); please refer to the original study and its supplementary files for all findings
Hser *et al.*, 2014 (213); USA	Secondary analysis of a clinical trial	Good	1267 patients from 9 opioid treatment programs across the country (mean age = 37 years, 32% women)	Cannabis use, assessed with weekly UDS over 24 weeks	Time-to treatment discontinuation, up to 24 weeks	Cannabis use was associated with treatment discontinuation in buprenorphine (HR=1.78, 95% CI=1.32-2.40) and methadone (HR=3.43, 95% CI=2.01-5.88) groups.

Study	Study design	Quality	Study sample	Exposure	Outcome	Findings
Socías *et al.*, 2018 (231); Canada	Prospective cohort study	Good	820 community-recruited people initiating methadone or buprenorphine-naloxone treatment (median age = 38, 42% women)	Frequency of past 6-month cannabis use, self-reported every 6 months, categorized as ≥daily, <daily, and none	Retained in treatment for an approximate 6-month period, defined as self-reported methadone or buprenorphine treatment in the current and immediately previous 6-month period	Daily cannabis use was associated with improved treatment retention relative to no use (AOR=1.20, 95% CI=1.02-1.43); occasional use was not significantly associated with treatment retention (AOR=1.00, 95% CI=0.87-1.14)

Note: 95% CI = 95% Confidence interval; (A)HR = (Adjusted) Hazard ratio; (A)OR = (Adjusted) Odds ratio; ASI = Addiction Severity Index; ASSIST = Alcohol, Smoking and Substance Involvement Screening Tool; OUD = Opioid use disorder; SCID-1 = Structural Clinical Interview for DSM-IV Axis 1 Disorders; UDS = Urine drug screen

2.3.6 Secondary outcomes

Each of the above studies was reviewed for their reporting of one or more secondary outcomes of interest including other substance use and measures of physical or psychological health. These findings are summarized in Table 2.4.

Ten studies (including six methadone (173, 220-222, 224, 232), three buprenorphine (229, 236, 237), and one naltrexone (235)) examined the relationship between cannabis use and other substance use during treatment. Two studies (one methadone (220) and one naltrexone (229)) noted significantly increased alcohol use among cannabis-using patients. Seven studies (including five methadone (220-222, 224, 232), two buprenorphine (236, 237), and one naltrexone (235)) measured differences in cocaine (or crack) use between cannabis using and non-using patients, and produced mixed findings. Two of these studies (including one methadone (232) and one naltrexone (235)) detected significantly increased cocaine use among cannabis-using patients, while Saxon *et al.* and Best *et al.* recorded significant prospective and cross-sectional inverse associations, respectively, between frequency of cannabis and frequency of crack/cocaine use among methadone patients (220, 222). The remaining four studies did not find that frequency of cannabis use correlated with cocaine use during treatment. Another six studies (including four methadone (173, 220, 221, 232), one buprenorphine (236), and one naltrexone (235)) examined benzodiazepine use during treatment. Similarly, these studies were inconsistent in their findings, with three methadone studies finding benzodiazepine use to increase significantly with cannabis use frequency (173, 220, 232), and the remaining three studies not detecting significant differences in benzodiazepine use according to cannabis use status.

Five studies (including three methadone (220, 224, 233) and two buprenorphine (229, 236)) employed some measurement of physical, psychological, and/or general health in relation to

cannabis use. Two cross-sectional methadone studies observed significantly poorer health indicators among cannabis-using patients: Best *et al.* found that frequent cannabis users had significantly lower general health, which was driven by poorer appetite among frequent users (220), and Zielinski *et al.* noted significantly poorer psychological functioning among cannabis users (233). Otherwise, cannabis use status was not significantly related to measures of psychological health (224, 229, 236), and other indicators of physical health or functioning (229, 233).

Table 2.5. Summary of included studies: secondary outcomes (quality of life and other substance use)

Study	Study design	Study sample	Exposure	Outcome	Findings
1. Methadone					
Best *et al.*, 1999 (220); Scotland	Cross-sectional study	200 methadone patients on at a community drug clinic (mean age = 32 years, 30% women)	Past 30-day frequency (days) of cannabis use, self-reported at time of study, categorized as no use, occasional use, daily use	(1) Frequency of past 30-day alcohol use, self-reported using MAP at time of study; (2) Frequency of past 30-day crack cocaine use, self-reported using MAP at time of study; (3) Frequency of past 30-day illicit benzodiazepine use, self-reported using MAP at time of study; (4) Psychiatric wellbeing score, assessed with BSI at time of study; (5) General health score, assessed with MAP at time of study	(1) Cannabis non-users reported significantly more alcohol use days (9.6) than daily users (4.3; F=5.24, p<0.01); the association remained significant in a multivariable model (β=-0.148, p=0.029); (2) Cannabis non-users reported significantly more crack use days (1.7) than daily users (0.1; F=4.67, p<0.05); not tested in multivariable model; (3) Daily cannabis users reported significantly more benzodiazepine use days (8.2) than occasional (5.2) and non-users (4.0; F=2.95, p=0.05); not tested in multivariable model; (4) Daily cannabis users scored significantly higher (19.0) than non-users (14.3) and occasional users (14.3) for severity of psychiatric problems (anxiety and depression; F=6.44, p<0.01); in a multivariable model, anxiety and depression scores were not significantly associated with frequency of cannabis use (β=0.099, p=0.224 and β=0.080, p=0.331, respectively) (5) Daily users exhibited poorer general health (score = 50.8) than occasional (44.4) or non-users (47.7, p<0.0.5); in a multivariable model, total health score was not significantly associated with frequency of cannabis use (β=-0.102, p=0.267)

Study	Study design	Study sample	Exposure	Outcome	Findings
Epstein and Preston, 2003 (224); USA	Secondary analysis of pooled data from three clinical trials	408 methadone outpatients from 3 clinical trials (mean age = 39 years, 60% women)	Frequency of cannabis use, assessed by weekly UDS, categorized as 0%, 1-17%, 18-100%	(1) Use of primary illicit drug (cocaine in 2 studies; opioids in 1 study) during intervention (contingency management) phase, assessed with weekly UDS; (2) Resume use of primary drug after intervention phase, assessed with weekly UDS; (3) Psychosocial functioning, assessed with ASI at post-treatment follow-ups (3, 6, 12 months)	(1) Cannabis use frequency was not significantly associated with continued primary drug use during stabilization (statistics not reported); (2) Cannabis use frequency was not significantly associated with primary drug use during the maintenance phase (statistics not reported); (3) Cannabis use frequency was not significantly associated with differences in psychosocial functioning (statistics not reported)
Hill *et al.*, 2013 (237); USA	Secondary analysis of clinical trial	152 young people initiating a 12-week treatment or 2-week detoxification with buprenorphine-naloxone (mean age = 19 years, 41% women)	Past 30-day frequency (days) of cannabis use, self-reported at baseline, categorized as none (0), occasional (1-19), frequent (≥20)	Cocaine use, assessed with UDS at 4, 8, and 12 weeks	Cannabis use was positively associated with baseline cocaine use ($p<0.04$), but not associated with cocaine use during treatment (statistics not reported)
Nirenberg *et al.*, 1996 (221); USA	Prospective cohort study	70 methadone outpatients at an urban veterans medical site (mean age = 39 years, 1% women)	Frequency of cannabis use over 45 weeks, assessed with weekly UDS, categorized as none (0%), intermittent (1-33%), moderate (34-67%), and consistent (68-100%)	(1) Frequency of cocaine use over 45 weeks, assessed with weekly UDS; (2) Frequency of benzodiazepine use over 45 weeks, assessed with weekly UDS	(1) Frequency of cocaine did not differ by cannabis use frequency ($F=1.17$, $p=0.33$); (2) Frequency of benzodiazepine use did not differ by cannabis use frequency ($F=2.10$, $p=0.11$)

Study	Study design	Study sample	Exposure	Outcome	Findings
Saxon *et al.*, 1996 (222); USA	Secondary analysis of a randomized controlled trial	337 patients beginning methadone at an urban treatment site (mean age = 38 years, 38% women)	Past 6-month frequency of cannabis use, self-reported using ASI at treatment intake, categorized on a scale from 0 (never) to 6 (≥4 times/day)	(1) Frequency of any illicit drug use, assessed with weekly UDS for up to 2 years; (2) Frequency of cocaine use, assessed with weekly UDS for up to 2 years	(1) Frequency of cannabis use was not significantly associated with frequency of any illicit drug use (unadjusted β=0.06, p>0.05); (2) Baseline cannabis use frequency was significantly and negatively associated with frequency of cocaine use (adjusted β=-0.11, p<0.05)
Scavone *et al.*, 2013 (173); USA	Retrospective chart review	91 methadone outpatients enrolled at one treatment site (mean age = 39 years, 39% women)	Frequency of cannabis use over 9 months, assessed with monthly UDS	Frequency of illicit benzodiazepine use over 9 months, assessed with monthly UDS	Frequency of cannabis use was positively correlated with frequency of illicit benzodiazepine use during treatment (r=0.374, p<0.01)
Weizman *et al.*, 2004 (232); Israel	Prospective cohort study	176 patients starting methadone treatment at one clinic (mean age = 38 years)	Cannabis "abuse", assessed with SCID-1 on patients who screened positive for possible cannabis abuse (≥3 consecutive cannabis UDS over 12 months)	(1) Benzodiazepine use, assessed with UDS at 12 months; (2) Amphetamine use, assessed with UDS at 12 months; (3) Cocaine use, assessed with UDS at 12 months; (4) Total number of illicit drugs used, assessed with UDS at 12 months	(1) Benzodiazepine use was more frequent among patients who "abused" cannabis (F=18.48, p<0.001); (2) Amphetamine use was more frequent among patients who "abused" cannabis (F=9.29, p=0.003); (3) Cocaine use was more frequent among patients who "abused" cannabis (F=4.06, p=0.045); (4) The mean number of distinct classes of drugs used at month 3 was significantly higher among patients who abused cannabis (1.6 *vs.* 0.79; t=5.63, p<0.001)
Zielinski *et al.*, 2017 (233); Canada	Cross-sectional study	777 patients on methadone at treatment sites across the province (mean age = 38, 47% women)	Past 30-day cannabis use, self-reported using MAP at time of study	(1) Psychological functioning, assessed with MAP (0-40 points) at time of study; (2) Physical functioning, assessed with MAP (0-40 points) at time of study	(1) Cannabis users had slightly worse psychological functioning (MAP score: 14.27 *vs.* 12.90, p=0.040); (2) Cannabis users had slightly worse physical functioning, but the difference was not significant (16.02 *vs.* 15.06, p=0.085)
2. Buprenorphine					

Study	Study design	Study sample	Exposure	Outcome	Findings
Bagra *et al.*, 2018 (229); India	Cross-sectional study	100 outpatients on buprenorphine for ≥3 months at a community drug treatment clinic (mean age = 44 years, 0% women)	Past 3-month cannabis use, self-reported using ASSIST at time of study	(1) Past 3-month alcohol use, self-reported using ASSIST at time of study; (2) Quality of life, assessed with WHOQOL-Bref at time of study	(1) Cannabis users had a higher prevalence of alcohol use (57.1% *vs.* 24.6%, p=0.001); (2) Mean scores for physical, psychological, social, and environmental quality of life did not differ significantly between cannabis users and non-users (all p<0.05)
Budney *et al.*, 1998 (236); USA	Secondary analysis of pooled data from three clinical trials	79 patients undergoing a 7-22 week buprenorphine taper and behavioural therapy, derived from a larger (n=107) patient sample (mean age = 34 years, 37% women)	Any cannabis use, self-reported (past 30-days) at treatment baseline, and assessed with thrice-weekly UDS	(1) Frequency of cocaine use, assessed with thrice-weekly UDS; (2) Frequency of benzodiazepine use, assessed with thrice-weekly UDS; (3) Psychosocial functioning, assessed with at treatment baseline and 12-month follow-up	(1) The percentage of cocaine-positive UDS did not differ significantly between cannabis users and non-users (13% *vs.* 14%, p<0.05); (2) The percentage of benzodiazepine-positive UDS did not differ significantly between cannabis users and non-users (32% *vs.* 40%, p<0.05); (3) No pre-post changes between cannabis users and non-users in any ASI subscales (e.g., mean psychiatric score change=-0.01 for cannabis users and 0.04 for non-users, p<0.05)
3. Naltrexone					
Raby *et al.*, 2009 (235); USA	Secondary analysis of a randomized controlled trial	63 patients in a controlled trial of behavioural naltrexone therapy at one site (mean age = 36 years, 17% women)	Frequency of cannabis use, assessed with twice-weekly UDS for 6 months, categorized as none (0%), intermittent (1-79%), and consistent (≥80%)	(1) Frequency of cocaine use over 6 months, assessed with twice-weekly UDS; (2) Frequency of benzodiazepine use over 6 months, assessed with twice-weekly UDS	1) Proportion of cocaine-positive UDS increased with cannabis use frequency (non-users=0.07, intermittent users=0.25, consistent users=0.39, p<0.009); (2) Proportion of benzodiazepine-positive UDS did not differ significantly between cannabis non-users (0.37), intermittent users (0.25), or consistent users (0.39, p>0.05)

Note: ASI = Addiction Severity Index; ASSIST = Alcohol, Smoking and Substance Involvement Screening Tool; BSI = Brief Symptom Inventory; HAM-D = Hamilton Rating Scale for Depression; MAP = Maudsley Addiction Profile; SOWS = Subjective Opioid Withdrawal Scale; WHOQOL-Bref = World Health Organization - Quality of Life - Brief version

2.4 Discussion

This review systematically searched the peer-reviewed scientific literature and synthesized findings of 38 observational and experimental studies documenting the relationship between cannabis use and treatment outcomes among patients undergoing methadone-, buprenorphine-, or naltrexone-based treatment of OUD. By widening the scope of research to all three Health Canada/FDA-approved pharmacotherapies and exploring additional potentially important cannabis-related outcomes including opioid craving, withdrawal, medication adherence, and quality of life, this work builds on McBrien and colleagues' review of cannabis use during methadone maintenance treatment (258). Some notable differences between treatment modalities were observed. Similar to McBrien and colleagues, this review describes a high degree of heterogeneity across methadone studies: the majority of studies did not document a significant (positive or negative) impact of cannabis on a treatment outcome, while some studies produced contradictory findings of positive (e.g., (220, 251)) or negative (e.g., (174, 238)) associations. Among studies restricted to buprenorphine-treated patients only, no evidence was found to suggest a beneficial effect of cannabis, and a small number of studies were indicative of significantly lower buprenorphine adherence and retention among cannabis users (213, 247, 254). By contrast, no evidence was obtained to suggest that cannabis use was significantly associated with more opioid use, reduced treatment adherence, or shorter treatment retention among patients taking naltrexone, and some of the reviewed naltrexone studies produced findings suggestive of improved outcomes in all three primary outcome areas (120, 235).

There is growing evidence to support a pharmacological rationale for the use of cannabis to address opioid craving and withdrawal (173). For example, preclinical experiments have demonstrated that exogenous agonists of the endogenous cannabinoid receptors (e.g., THC) lowers

the severity of protracted withdrawal symptoms (259, 260). Recent experimental research demonstrates that repeated administration of the phytocannabinoid CBD reduces cue-induced anxiety and craving and exerts protracted effects one week later among opioid-dependent patients with short-term abstinence (128). Notably, there was no evidence across treatment modalities to suggest that cannabis use increases cravings for opioids or worsens the severity of withdrawal symptoms, and there was some evidence of improvements in these outcomes for cannabis-using patients transitioning onto naltrexone (120) and methadone treatment (173). The remaining three methadone studies that measured opioid withdrawal did not observe an association between cannabis and withdrawal severity. One possibility, as noted by Hill *et al.* is that cannabis helps to mitigate post-acute withdrawal symptoms arising from treatment with an opioid antagonist, rather than an agonist, which would explain the generally more positive results seen for naltrexone adherence and retention among cannabis-using patients (237). This interpretation would leave open the possibility that patients treated with an agonist could also experience symptom mitigation from cannabis if their treatment is not effectively suppressing withdrawal. Although additional research is needed, Epstein and Preston began to probe this withdrawal management hypothesis by taking repeated measures of cannabis use and withdrawal symptoms during a methadone dose taper. They noted that, although cannabis use increased slightly (and not significantly) in the week following higher withdrawal, cannabis use did not precede significant reductions in withdrawal scores in the subsequent week, suggesting that cannabis was not effective in curbing withdrawal (234).

Treatment dose is one of the strongest predictors of longer-term patient success on MOUD (213, 222, 261, 262). It is plausible that patients receiving sub-optimal treatment doses are more likely to self-medicate with cannabis. Studies that fail to measure or account for dose adequacy

may mask a potential positive influence of cannabis on treatment outcomes. A small number of included studies (n = 7) compared treatment dose between cannabis using and non-using patients, and three (43%) noted significantly lower medication doses among patients who were using cannabis during treatment (229, 230, 233), while four (57%) did not find group differences (173, 216, 220, 232). Future research should test the hypothesis that the effect of low treatment dose on patient outcomes including opioid use varies by cannabis use status.

Some studies measured varying levels of exposure to cannabis (e.g., frequency or amount used), but a clear dose-response pattern could not be discerned, owing to discrepant findings across these studies. Differences between patient samples may partially explain these discrepant findings. One possibility is that high frequency cannabis use corresponds to intentional therapeutic applications in certain patient populations (e.g., community-based samples) while corresponding to higher-risk drug use and dependence or structural marginalization such as homelessness, poverty, and criminalization in others (e.g., clinic-based samples). For example, Socías and colleagues observed higher six-month retention among daily cannabis users in their community-recruited study of highly marginalized people initiating methadone or buprenorphine/naloxone in Vancouver, Canada, a setting with liberal access to cannabis (231). In contrast, daily use of cannabis may correlate more readily to poorer patient outcomes (particularly treatment adherence and retention) considering practices in certain clinical settings (particularly across the U.S.) that respond to evidence of ongoing illicit substance use, including cannabis use, with punitive policies such as denial of take-home doses and even involuntary patient discharge (263). In turn, such policies could have a disproportionately negative impact on adherence or retention for cannabis users. Indeed, at least eight of the reviewed studies (including five from the U.S. (222, 236, 238, 252, 254), two from Sweden (241, 253), and one from Israel (232)) explicitly stated that some

patient privileges (e.g., take-home doses, dose increases, remaining in the program) were contingent on drug-free urine screens. The current review demonstrates that the implications for cannabis use concurrent with MOUD are likely to vary across individuals; as such, cannabis use during MOUD should be considered on an individual-basis. Clinicians working with individuals on MOUD who are interested in cannabis as an adjunctive therapy may benefit from taking a patient-centered approach and clarifying why and how the patient feels cannabis use may assist in their treatment progress. This is a departure from the long-held approach of abstinence-only recovery programs. Future research should consider individual differences such as cannabis use history, motivations for use, personality factors, and mood to determine for who and when cannabis use is indicated or contraindicated in the treatment of OUD.

While this review fulfills a critical need to collect, synthesize, and compare findings pertaining to cannabis use during MOUD, it was met with a number of limitations. First, the search was restricted to peer-reviewed articles published in English, and it is possible that potentially important clinical findings published in another language were missed. A meta-analysis was not conducted, as the reviewers concluded that any numerical result would be rendered clinically meaningless due to the heterogeneity across studies in variable measurement, treatment times, and modalities. For example, within each outcome area of interest, there was a lack of consistency in outcome measurement (e.g., past 30-day self-reported frequency of heroin use *vs.* current detection of various opioids in urine), which may have also played a role in discrepant findings across studies. As noted, this review did not report on the efficacy of pharmaceutically manufactured cannabinoid medications (e.g. dronabinol) as adjunctive medication MOUD. The primary findings of the study by Bisaga *et al.,* in which patients randomized to dronabinol during a naltrexone induction experienced significantly lower severity of withdrawal compared to patients randomized

to placebo (120), was excluded on this basis; however, a secondary finding of this study pertaining to cannabis use during the trial was retained in the review.

This review is also limited by certain methodological shortcomings of the included research. Many studies were limited by small sample sizes, short observation periods, and over-representation of certain patients (particularly white males). As noted, the included studies exhibited a high degree of heterogeneity with respect to the measurement of cannabis use, with some studies measuring cannabis use in much greater detail (e.g., repeated frequency measures throughout treatment) than others (e.g., any use at treatment baseline). There are several factors contributing to this lack of measurement consistency. First, a universally accepted and scientifically supported standardized unit to measure cannabis (or cannabinoid content, e.g., THC) exposure has yet to be established and implemented across studies (although some have been proposed (264)). Second, the majority of studies were not explicitly focused on the influence of cannabis use on treatment outcomes; as a result, crude measurements of any cannabis use (either self-reported or positive urine screens) at treatment baseline or over the treatment period were often used. These measures may fail to capture a biological effect if one does exist, as the time between the actual exposure and the outcome is likely to vary widely between patients in a given study. In addition, studies lacking an explicit cannabis-related objective rarely accounted for potentially important confounding or mediating factors (e.g., social and economic adversities, medication dose, treatment satisfaction, co-occurring substance use patterns, opioid withdrawal and craving). However, given the generally non-significant cannabis-related findings of these broader studies, coupled with the mixed results of the 14 studies with cannabis as a primary focus, the overall consensus of this review is unlikely to be biased by selective reporting or unpublished null data. While several of the review's findings emerged from randomized controlled trials,

cannabis was not the randomized intervention in any of these studies. Given high rates of cannabis use during MOUD, clinical trials involving plant-based cannabinoids (*vs.* placebo) are a critical next step towards understanding the therapeutic applications of cannabis in real-world OUD treatment settings. Finally, no studies collected detailed data on the type of cannabis used or method used to consume it.

2.5 Conclusions

In this review summarizing the relationship between cannabis use and a number of treatment outcomes among patients engaged in MOUD, there was a lack of consistent evidence to support either of the opposing claims that co-use of cannabis is detrimental or beneficial to treatment success, as the majority of studies did not record a statistically significantly association between cannabis use and treatment outcomes. For each outcome of interest, a small number of studies produced evidence to suggest a beneficial or impeding role of concurrent cannabis use. The exception was withdrawal, for which no evidence was found to suggest a worse outcome for cannabis users. However, many of the reviewed studies were not designed to measure an independent effect of cannabis and are thus subject to bias. Given prevalent co-use of cannabis by people in MOUD, there is a clear need for rigorous experimental research to establish the feasibility and effectiveness of supplementing OUD pharmacotherapy with cannabis—particularly in the early stages of treatment when withdrawal may be more severe. The current state of evidence would also be strengthened by more observational studies designed with cannabis use as a primary exposure of interest. The majority of studies did not find treatment outcomes to differ by cannabis use. Given high rates of cannabis use documented among patients, medication-based treatment programs should reconsider punitive policies that treat cannabis use as a non-compliant patient

behaviour, as the evidence reviewed here would suggest that such policies may pose a higher threat to treatment success than cannabis use itself. Clinicians who work with individuals using cannabis concurrently during MOUD should take a patient-centered approach to ensure that cannabis use plays a supportive, rather than interruptive, role in their treatment progress.

Chapter 3: Exploring the role of cannabis in the relationship between methadone treatment dose and patient outcomes: A longitudinal analysis

3.1 Introduction

In many jurisdictions across Canada and the U.S., drug overdose continues to be a leading cause of premature death (22, 265). Opioid-related deaths in the U.S. have increased by an estimated 345% over 15 years, representing 5.2 years of life lost per 1000 population (266). In the province of British Columbia (BC), Canada, where overdose deaths were declared a province-wide public health emergency in 2016 (27), the vast majority (>80%) of fatal drug overdoses involve fentanyl—a highly potent synthetic opioid that has overtaken the illicit drug market across the province (28).

For people living with opioid use disorder (OUD), pharmacological management with an opioid agonist, such as methadone or buprenorphine/naloxone, is the most effective medication-based intervention against opioid overdose (67, 267). A recent study estimated that the provision of these opioid agonist therapies in the province of BC prevented approximately 600 deaths in under two years (60). Retention in evidence-based treatment is critical to preventing non-prescribed (i.e., illicit) opioid use (208) and subsequent overdose (210). Studies from diverse treatment settings demonstrate that higher methadone doses are strongly positively correlated with retention in treatment (222, 261, 268-273) and negatively correlated with continued use of illicit opioids (239, 274-276). This would suggest that patients receiving adequate treatment doses are less likely to discontinue treatment in favour of illicit opioid use to manage opioid withdrawal (277). However, many patients continue to receive inadequate dosages for optimal management

of OUD. For instance, roughly one in five methadone patients in the U.S. are prescribed doses below the minimum recommended standard of 60 mg/day (278).

Continued use of substances (e.g., alcohol, opioids, cocaine, methamphetamine, benzodiazepines) while on medication-based treatment of OUD is often linked to worse clinical outcomes (213, 273, 279). Concurrent cannabis during OUD treatment is common, with prevalence of co-use typically approximately 50% in clinical studies of patients receiving methadone maintenance treatment (MMT (166, 174, 224, 240, 280)). As discussed in Chapter 2, in many treatment programs for OUD across the U.S. and Canada, evidence of cannabis use (e.g., through detection of THC in urine) may result in treatment restrictions, such as denial of take-home doses and, in extreme cases, involuntary termination of treatment (168). In contrast, on the heels of earlier ecological reports of reduced population rates of pharmaceutical opioid use and overdose in states with legal access to medical cannabis (e.g., (144, 281, 282), many states are now authorizing the use of medical cannabis in the treatment of OUD (171, 172). However, studies have produced inconsistent evidence of the impact of cannabis use during medication-based treatment for OUD, including MMT, as demonstrated through the systematic review in Chapter 2.

In evaluating treatment outcomes, few studies have considered the potentially important relationship between treatment dose and cannabis use. There is a mounting rationale for examining the potential beneficial role of cannabis in mitigating the association between drivers of opioid withdrawal and/or craving and clinical outcomes during opioid agonist treatment (283). Grinspoon details the experimental practice of treating opioid withdrawal with cannabis beginning in the late 1800s, and points to two small human experiments that favourably reported on opioid substitution with cannabis-based medicines in the 1940s (80). Recent qualitative studies describe the *ad hoc* strategy among some people who use illicit opioids of using cannabis to address opioid cravings

and withdrawal during periods of transitioning away from high-intensity opioid use (163, 165). Cannabis is often used therapeutically to manage sleep and pain-related symptoms of disease (e.g., neuropathic pain, multiple sclerosis) or negative side-effects from pharmacological management of chronic disease (e.g., nausea, vomiting, and appetite suppression from cancer, HIV treatment (98, 284)). Many of these common therapeutic indications of cannabis are also symptomatic of opioid withdrawal (e.g., nausea and vomiting, insomnia, enhanced pain sensitivity (6)). Some observational studies have noted significantly lower treatment doses among cannabis-using patients on medication-based treatment of OUD including MMT and buprenorphine-naloxone (229, 230, 233), possibly reflecting a strategy to supplement inadequate treatment doses with cannabis (173). Recently, two small experimental studies among human subjects have presented evidence of improvements in severity of opioid withdrawal with the administration of THC (120) and suppression of opioid cravings with the administration of CBD (128).

Using over twelve years of data from two community-recruited cohorts of individuals who use illicit drugs (PWUD) in Vancouver, Canada, this study sought to explore the relationship between frequent cannabis use and indicators of treatment success among people engaged in MMT—specifically, whether cannabis acts as an effect measure modifier in widely established relationships between receiving a lower methadone dose and 1) using illicit opioids during treatment, and 2) discontinuing treatment. If cannabis supports reductions in opioid withdrawal and/or craving associated with low MMT dosages, the strength of these associations is hypothesized to be reduced during periods of frequent cannabis use.

3.2 Methods

Data for this study were derived from VIDUS and ACCESS studies, as described in Section 1.7.2. Two separate analyses were conducted to examine the outcomes of illicit opioid use and MMT retention, described in detail below.

3.2.1 Analysis 1: Illicit opioid use

3.2.1.1 Study sample

From December 1, 2005 to November 30, 2018, participants were asked about their current and past six-month enrolment in MMT for OUD at baseline and each six-month follow-up interview. To analyze the outcome of opioid use during treatment, the sample was restricted to periods in which the participant reported current enrolment in MMT at the time of their interview (Figure 3.1).

3.2.1.2 Measures

3.2.1.2.1 Outcome measure

At each of their biannual study interviews, participants were asked if they had used heroin or pharmaceutical opioids illicitly (i.e., diverted, counterfeit, or not-as-prescribed use) by injection or non-injection (i.e., smoking, snorting, oral administration) during the previous six months. Participants were provided a list of pharmaceutical opioids with corresponding pictures for ease of identification. If they indicated any past six-month use of either heroin or pharmaceutical opioids, they were asked to estimate the average frequency of use during that time (none, about once/month, about 2-3 times/month, about once/week, 2-3 times/week, and about once/day). Illicit opioid use was dichotomized into ≥ daily and < daily use to examine high intensity opioid use as an indicator of OUD severity and correlate of treatment discontinuation (285). Participants who

endorsed using heroin or pharmaceutical opioids daily or more on average in the past six months were coded as '1' for the outcome (i.e., daily illicit opioid use) for that follow-up period.

3.2.1.2.2 Exposure measures

The main exposures of interest daily methadone dose (as the primary independent variable) and cannabis use (as the hypothesized effect measure modifier).

All participants who endorsed past six-month MMT were asked to report their current daily dose in mL. In February 2014, the province changed the formulation of methadone provided under the provincial drug plan from a 1mg/mL pharmacy-compounded formulation to a 10 mg/mL commercially-available formulation (i.e., Methadose (286)). Thus, all doses reported after February 2014 were multiplied by 10 to standardize the variable to 1mg/mL. Likely misclassification errors were corrected through a manual inspection of the dosage data, particularly around the time of the formulation change. The median treatment dose of all study observations (90 mg/d) was used to distinguish lower (<90 mg/d) from higher (≥90 mg/d) doses. This cut-point is also supported by previous evidence in this setting and others showing longer attenuation of heroin effects and improved treatment outcomes at high doses, defined as ≥100 mg/d (211, 273, 277).

At each interview period, participants were asked if they had used cannabis in the previous six months and, if so, they were asked to estimate the average frequency of use during that time (using the same categorizations as opioid use frequency, i.e., none, about once/month, about 2-3 times/month, about once/week, 2-3 times/week, and about once/day). As it was hypothesized that high-frequency use of cannabis would be required to observe an effect (if one exists), cannabis use frequency was dichotomized into ≥ daily and < daily use.

3.2.1.2.3 Secondary variables

Efforts were made to account for the potential confounding influence of several secondary variables known or *a priori* hypothesized to impact MMT-related outcomes and which may be linked with MMT dose or cannabis use. The following variables were considered for these analyses: (1) sociodemographic factors, including sex (male *vs.* female), current age (per year older), racial identity (white vs. non-white), legal employment (yes *vs.* no), homelessness (defined as living on the street with no fixed address, consistent with previous work (40), yes *vs.* no), and incarceration (yes *vs.* no); (2) substance use and health-related factors, including HIV serostatus (positive *vs.* negative), ≥ daily alcohol use (yes *vs.* no), and ≥ daily stimulant (crystal methamphetamine or crack/powder cocaine) use (yes *vs.* no); and (3) treatment-related factors, including calendar year of treatment (≥2014 *vs.* <2014, corresponding to changes in the methadone formulation, which had widespread unintended impacts on opioid relapse (286)), percent time spent on MMT (measured as the cumulative percent of all interview periods, up to and including the current period, in which the participant was enrolled in MMT [categorized as >75% *vs.* ≤75%], and engagement in other substance use treatment (e.g., counselling, residential treatment). Aside from HIV status, which is confirmed through serology, all variables are self-reported. With the exception of sex and racial identity, all variables are time-varying and refer to the previous six month period at each study interview.

3.2.1.3 Statistical analysis

First, baseline socio-demographic and health-related characteristics were examined for all participants who reported current MMT enrolment at least once over the study period. These observations were stratified by cannabis use status and group differences were tested using

Pearson's Chi-Square test (categorical variables) or Wilcoxon rank-sum test (numeric variables). Here, the baseline observation was defined as the first interview period in which current MMT enrolment was reported.

Next, to examine the relationship between each independent variable and the outcome (daily illicit opioid use), bivariable and multivariable generalized estimating equations (GEE) with an exchangeable correlation structure to account for possible correlation from repeated measures within individuals over time were constructed. First, the crude bivariable relationships to the outcome for lower MMT dose and cannabis use were examined separately. Then, effect measure modification was explored by including a product term between dose and cannabis. Following this, all hypothesized confounders outlined above were added to the model to estimate the adjusted association between methadone dose and daily illicit opioid use within each strata of cannabis. The significance of effect measure modification was checked using the likelihood ratio test.

3.2.2 Analysis 2: Treatment retention

3.2.2.1 Study sample

To analyze the outcome of treatment retention, the sample was restricted to participants who initiated (or re-initiated) MMT during the study period (December 1, 2005 to November 30, 2018), defined as reporting past six-month MMT after at least one interview of reporting no past six-month MMT. Participants who reported being on MMT at study recruitment (baseline) were not eligible for analysis until they re-initiated a subsequent treatment episode during the study period (Figure 3.1).

3.2.2.2 Measures

3.2.2.2.1 Outcome measure

The outcome of interest was time-to treatment discontinuation. Time-zero was defined as the date of initiating or re-initiating MMT and was estimated at the beginning of the first six-month period in which the participant endorsed past six-month MMT enrolment. Using time-updated self-reported information about past six-month and current MMT enrolment at each interview, the estimated discontinuation time was coded as follows: (1) If a participant endorsed current and past six-month enrolment, they were considered retained on treatment for that six-month period; (2) if a participant did not endorse current MMT enrolment but did endorse past six-month enrolment, they were estimated to have discontinued treatment at the mid-point between the beginning of that six-month interview period and the current interview date (3); if a participant did not endorse current or past six-month MMT enrolment, they were estimated to have discontinued treatment at the mid-point between their previous interview date and the beginning of that six-month period. If they did not miss any interviews between these two six-month periods and a mid-point could not be calculated, the discontinuation date was estimated to be one week after the start of the current interview period. After treatment discontinuation, all follow-up data from that participant was censored until (if) they re-initiated another treatment episode during the study.

Participants who were still enrolled in MMT at the end of the study period were right-censored. Participants were considered lost to regular follow-up if the time between two consecutive interviews exceeded 24 months. In this case, they were censored at the time of their last contact before being lost to regular follow-up and were considered re-eligible for analysis once

they returned for a follow-up interview. If MMT enrolment was reported during this interview, it was considered a new treatment episode.

3.2.2.2.2 Exposure measures

As described under 3.2.1.2.2, the primary independent variable of interest was daily methadone dose (<90 mg/d *vs.* ≥90 mg/d), and the hypothesized effect measure modifier was cannabis use (≥daily *vs.* <daily). For participants who were estimated to have discontinued MMT at a date preceding their interview, the dose reported at the time of their previous interview during that treatment episode was used (participants who discontinued a new treatment episode before six months did not have a prior dosage measurement for that episode and were handled separately—see statistical analysis protocol described under 3.2.2.3).

3.2.2.2.3 Secondary variables

With the exception of percent time spent on treatment (which is accounted for in the outcome of time retained in treatment), the hypothesized confounders are those described under 3.2.1.2.2. Two additional treatment-related factors were also considered for the retention analysis: engagement in MMT at study recruitment (yes *vs.* no) and treatment episode number (corresponding to each additional continuous period of treatment from initiation to discontinuation/censorship [categorized into episodes 1, 2, ≥3]. Of note, high-frequency opioid use (the outcome in Analysis 1) was conceptualized as an intermediate factor in the relationship between MMT dose and retention and was not statistically treated as a confounder.

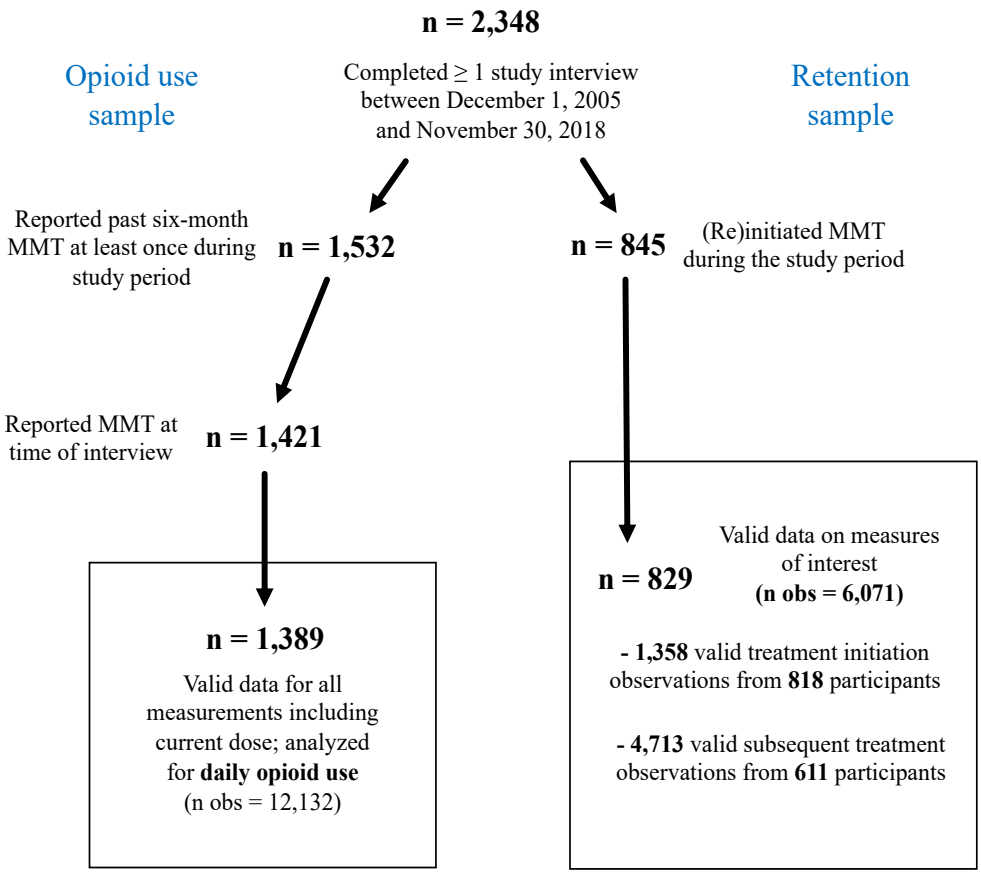
3.2.2.3 Statistical analysis

Socio-demographic and health-related characteristics at the beginning of the first treatment episode (i.e., treatment baseline) were examined for all participants who initiated a treatment episode during the study. These observations were stratified by cannabis use status and group

differences were tested using Pearson's Chi-Square test (categorical variables) or Wilcoxon rank-sum test (numeric variables).

Unfortunately, information on MMT dose was only asked of participants who endorsed current MMT enrolment at the time of their interview. Thus, the primary explanatory variable could not be analyzed for participants who discontinued MMT within the first six months of initiating a new treatment episode. As the first few months after treatment initiation represent a high-risk period in which patients may experience difficulty stabilizing on treatment due to withdrawal and craving, the dataset was split into observations to be analyzed separately for the potential relationship between cannabis use and short-term retention, and the cannabis-modified relationship between dose and long-term treatment retention. The analytic sub-sample for short-term retention comprised of each participant's first observation from every new treatment episode (a period lasting $\leq$ six months). The analytic sub-sample for long-term treatment retention comprised of each participant's remaining observations (if applicable) from each treatment episode (i.e., a period lasting $\geq$ six months; Figure 3.1).

Figure 3.1. Flowchart illustrating the composition of the analytic samples



Given low variability in the measurable number of days until discontinuation or censorship within the first six months of treatment resulting from the study's biannual interview protocol, short-term retention was modelled as a binary outcome (i.e., retained ≤six months; yes *vs.* no). To prevent underestimating ≤six-month discontinuation in cases where participants could not be scheduled for a subsequent interview at exactly six months, short-term retention was defined as ≤200 days to allow for an approximate three-week buffer period. Separate GEE models were built

to examine the relationship between high-frequency cannabis use and discontinuing treatment within six months of initiation, adjusting for the hypothesized confounders above.

Then, to model the relationship between MMT dose (and its potential modification by high-frequency cannabis use) and time-to-treatment discontinuation after six months, bivariable and multivariable Cox gamma-frailty models were built, including a product term to allow the effect of treatment dose to vary by cannabis use status. This model was chosen given that participants could have recurring discontinuation events across multiple treatment episodes. The frailty term represents an unobservable random variable corresponding to each individual's deviation from the baseline hazard function and accounts for the potential correlation of recurrent treatment episode lengths within individuals. This modelling approach has been applied to previous observational research of MMT retention over long study periods (270, 287). First, similar to the effect measure modification approach used in Analysis 1, the crude bivariable relationships to the outcome for lower MMT dose and cannabis use were examined separately. Then, effect measure modification was explored by including a product term between dose and cannabis. Following this, all hypothesized confounders outlined above were added to the model to estimate the adjusted association between methadone dose and time-to-treatment discontinuation within each strata of cannabis. The likelihood ratio test was used to check for significance of effect measure modification.

A sensitivity analysis was conducted to ensure that the inclusion of participants who transitioned to buprenorphine/naloxone (Suboxone; the second most common medication-based treatment for OUD in this study setting) did not obscure the findings due to fundamental differences with participants whose treatment discontinuation reflected a lack of engagement with

OUD treatment. Here, participants who discontinued MMT but endorsed buprenorphine/naloxone enrolment during the same six-month period were censored rather than coded as having experienced the outcome.

All analyses were conducted in R (Version 3.6.3, R Foundation for Statistical Computing, Vienna, Austria) using RStudio (Version 1.2.5033). All *p*-values are two-sided.

3.3 Results

3.3.1 Analysis 1: Illicit opioid use

Between December 1, 2005 and November 30, 2018, a total of 2348 participants were recruited and completed at least one study interview. Of them, 1532 (65.2%) endorsed past six-month MMT, and 1421 (92.8%) endorsed current MMT at least once. In total, 1389 (97.7%) current MMT patients completed all measures of interest including current MMT dose and were included in the first analysis of high-frequency illicit opioid use during treatment (Figure 3.1). These individuals contributed a median of 7 interviews (Interquartile Range [IQR]: 3 – 14) each, totaling 12132 observations over 6066 person-years of follow-up. Baseline characteristics of this sample, stratified by cannabis use status, are summarized in Table 3.1. As shown, 281 (20.2%) participants endorsed high-frequency cannabis use at baseline; this group was slightly younger (median age 40.1 *vs.* 41.7 years, p=0.010) and was represented by significantly more males than the occasional/non-user group (67.3% *vs.* 56.9%, p=0.002). High-frequency (i.e., ≥ daily) opioid use in the last six months was reported by 439 (31.6%) respondents at baseline, and a total of 770 (55.4%) respondents reported high-frequency opioid use during MMT at least once over the study period.

Table 3.1. Baseline characteristics of 1,389 PWUD who reported current MMT during at least one study interview between December 1, 2005 and November 30, 2018

Characteristic	Overall n = 1389	≥ Daily cannabis use[1]		*p*-value
		Yes n = 281; 20.2%	No n = 1108; 79.8%	
Sociodemographic factors				
Sex				
Male	819 (59.0)	189 (67.3)	630 (56.9)	0.002
Female	570 (41.0)	92 (32.7)	478 (43.1)	
Age				
Median (IQR)	41.4 (34.6 – 47.9)	40.1 (33.7 – 46.7)	41.7 (34.9 – 48.4)	0.010
Racial identity				
White	848 (61.1)	178 (63.3)	670 (60.5)	0.415
Non-white	541 (38.9)	103 (36.7)	438 (39.5)	
Employment[1]				
Yes	255 (18.4)	58 (20.6)	197 (17.8)	0.308
No	1134 (81.6)	223 (79.4)	911 (82.2)	
Homelessness[1]				
Yes	435 (31.3)	80 (28.5)	355 (32.0)	0.280
No	954 (68.7)	201 (71.5)	753 (68.0)	
Incarceration[1]				
Yes	199 (14.3)	42 (14.9)	157 (14.2)	0.813
No	1190 (85.7)	239 (85.1)	951 (85.8)	
Substance use, health, treatment factors				
Daily alcohol use[1]				
Yes	59 (4.2)	12 (4.3)	47 (4.2)	1.000
No	1330 (95.8)	269 (95.7)	1061 (95.8)	
Daily stimulant use[1]				
Yes	642 (46.2)	122 (43.4)	520 (46.9)	0.323
No	747 (53.8)	159 (56.6)	588 (53.1)	
Daily opioid use[1]				
Yes	439 (31.6)	83 (29.5)	356 (32.1)	0.445
No	950 (68.4)	198 (70.5)	752 (67.9)	
HIV serostatus				
HIV-positive	529 (38.1)	107 (38.1)	422 (38.1)	1.000
HIV-negative	860 (61.9)	174 (61.9)	686 (61.9)	
Other addiction treatment[1]				
Yes	269 (19.4)	54 (19.2)	215 (19.4)	1.00
No	1120 (80.6)	227 (80.8)	893 (80.6)	

Characteristic	Overall n = 1389	≥ Daily cannabis use[1]		*p*-value
		Yes n = 281; 20.2%	No n = 1108; 79.8%	
Daily MMT dose[2]				
Lower (< 90 mg)	765 (55.1)	149 (53.0)	616 (55.6)	0.479
Higher (≥ 90 mg)	624 (44.9)	132 (47.0)	492 (44.4)	

Note: [1]Refers to exposures in the previous six months; [2]Daily MMT dose was reported at the time of interview; IQR = Interquartile range

Table 3.2 depicts the bivariable and multivariable relationships with high-frequency opioid use for the primary and secondary independent variables. As shown, at the bivariable level, lower daily MMT dose (i.e., < 90 mg) was significantly associated with high-frequency illicit opioid use (Odds Ratio [OR] = 1.72, 95% CI [Confidence Interval]: 1.53 – 1.93, $p<0.001$), and high-frequency cannabis use was not significantly associated with this outcome (OR = 1.03, 95% CI: 0.89 – 1.20, $p=0.660$). The addition of a product term for cannabis and MMT dose yielded a significant interaction ($X^2=10.5$, $p=0.001$) such that during periods of no/less frequent cannabis use, being on a lower MMT dose increased the odds of daily illicit opioid use by 86% (OR = 1.86, 95% CI: 1.64 – 2.11, $p<0.001$), yet during periods of high-frequency cannabis use, the increased odds of daily illicit opioid use were 29% (OR = 1.29, 95% CI: 0.99 – 1.56; $p=0.057$). The interaction between dose and cannabis use remained significant ($X^2=6.72$, $p=0.010$) after adjusting for a number of socio-demographic, substance use, and treatment-related factors (Adjusted OR [AOR] for <90 mg dose during periods of low/no cannabis use = 1.86, 95% CI: 1.61 – 2.16, $p<0.001$; AOR for <90 mg dose during periods of high-frequency cannabis use = 1.30, 95% CI: 1.01 – 1.67, $p=0.039$). The interaction can also be interpreted within each cannabis/dose combination (reference: < daily cannabis, higher dose), as displayed visually in Figure 3.2. Other factors that were significantly positively associated with high-frequency illicit opioid use in

multivariable analysis included homelessness, incarceration, daily stimulant use, and receiving MMT in 2014 or later (i.e., during the overdose crisis and after the methadone formulation change). Older age, living with HIV, and having more MMT experience (i.e., being on MMT for >75% of all study interviews) were all significantly and negatively associated with high-frequency illicit opioid use during treatment (all $p<0.05$; Table 3.2).

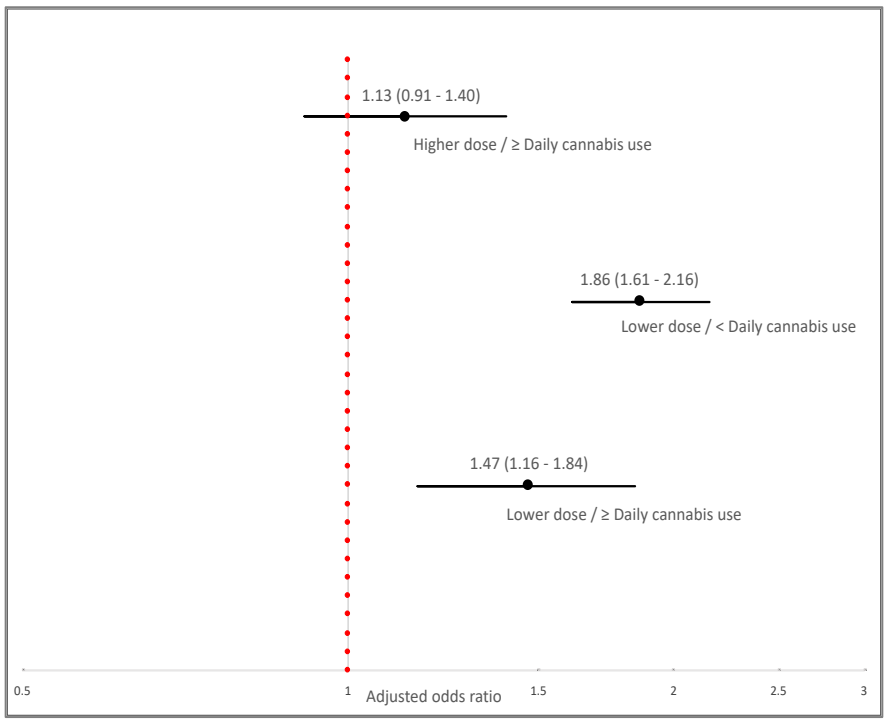
Table 3.2. Bivariable and multivariable relationships between independent variables and daily opioid use among 1389 PWUD on MMT between December 1, 2005 and November 30, 2018

Variable	Daily illicit opioid use[1]			
	Odds Ratio (95% CI)	***p*-value**	**Adjusted Odds Ratio (95% CI)**	***p*-value**
Treatment dose[2] (primary independent variable), pooled estimate				
Daily MMT dose (<90 mg/d *vs.* ≥90 mg/d)	1.72 (1.53 – 1.93)	<0.001	--	--
Cannabis use[1] (hypothesized effect measure modifier), pooled estimate				
Daily cannabis use (Yes *vs.* no)	1.03 (0.89 – 1.20)	0.660	--	--
Treatment dose estimate[2], stratified by cannabis use[1,3]				
(Daily cannabis use = no): MMT dose (<90 mg/d *vs.* ≥90 mg/d)	1.86 (1.64 – 2.11)	<0.001	1.86 (1.61 – 2.16)	<0.001
(Daily cannabis use = yes): MMT dose (<90 mg/d *vs.* ≥90 mg/d)	1.24 (0.99 – 1.56)	0.057	1.30 (1.01 – 1.67)	0.039
Socio-demographic factors				
Sex (Male *vs.* female)	0.90 (0.76 – 1.08)	0.258	1.19 (0.99 – 1.43)	0.066
Age (Per year increase)	0.96 (0.96 – 0.97)	<0.001	0.96 (0.95 – 0.96)	<0.001
Racial identity (White *vs.* non-white)	0.83 (0.70 – 0.99)	0.034	0.95 (0.80 – 1.14)	0.591
Employed[1] (Yes *vs.* no)	0.89 (0.80 – 1.00)	0.044	0.90 (0.79 – 1.02)	0.106
Homeless[1] (Yes *vs.* no)	1.96 (1.72 – 2.23)	<0.001	1.68 (1.47 – 1.94)	<0.001
Incarcerated[1] (Yes *vs.* no)	1.57 (1.33 – 1.85)	<0.001	1.24 (1.04 – 1.49)	0.020

Variable	Daily illicit opioid use[1]			
	Odds Ratio (95% CI)	***p*-value**	**Adjusted Odds Ratio (95% CI)**	***p*-value**
Substance use and health factors				
Daily alcohol use[1] (Yes *vs.* no)	1.11 (0.92 – 1.34)	0.285	1.04 (0.83 – 1.29)	0.754
Daily stimulant use[1] (Yes *vs.* no)	2.14 (1.91 – 2.39)	<0.001	2.35 (2.07 – 2.68)	<0.001
HIV serostatus (Positive *vs.* negative)	0.65 (0.55 – 0.78)	<0.001	0.75 (0.63 – 0.90)	0.002
Treatment-related factors				
Calendar year (≥2014 *vs.* <2014)	1.48 (1.34 – 1.64)	<0.001	2.40 (2.11 – 2.73)	<0.001
Percent time on MMT (>75% *vs.* ≤75%)	0.66 (0.57 – 0.76)	<0.001	0.71 (0.60 – 0.83)	<0.001
Other addiction treatment[1] (Yes *vs.* no)	0.97 (0.86 – 1.10)	0.636	0.88 (0.76 – 1.00)	0.054

Note: [1]Refers to the six-month period preceding interview; [2]Daily MMT dose was reported at the time of the interview; [3]Measure of effect measure modification by cannabis use: Unadjusted: $X^2 = 10.5$, $p = 0.001$; Adjusted: $X^2=6.72$, $p=0.010$; 95% CI = 95% Confidence interval

Figure 3.2. Adjusted odds of daily illicit opioid use within strata of treatment dose and cannabis use (relative to higher dose / < daily cannabis use) among 1389 PWUD on MMT in Vancouver, Canada, December 1, 2005 – November 30, 2018



Note: Estimates adjusted for sex, age, racial identity, employment, homelessness, incarceration, daily alcohol use, daily stimulant use, HIV serostatus, calendar year of treatment, percent time on treatment, MMT enrolment at study recruitment, and enrolment in other addiction treatment; AOR is shown on the log scale.

3.3.2 Analysis 2: Treatment retention

In total, 845 participants (34.0% of initial sample) initiated an MMT episode over the study period, of whom 829 (98.1%) had complete data on measures of interest and were eligible for the retention analyses (Figure 3.1). These individuals contributed 6,071 observations to the retention analyses, representing 1,390 distinct MMT episodes across 3,356 person-years. Participants spent a median of 37.9 cumulative months (IQR: 11.8 – 48.6) in treatment. The majority of MMT initiates (n = 477; 57.5%) experienced only one treatment episode, while the remaining participants re-enrolled in MMT for subsequent treatment episodes, with the majority of them (n = 212; 60.4%)

re-enrolling in MMT only once more; the maximum number of treatment episodes observed was 7, reported by one participant. Overall, 530 (63.9%) MMT enrollees discontinued treatment a total of 872 times over 3,356 person-years for a crude treatment discontinuation incidence rate of 26.0 per 100 person-years (95% CI: 24.3 – 27.7).

As described in Figure 3.1, 818 (98.7%) MMT (re)initiates had complete data in the first interview after initiating an MMT episode and were analyzed for short-term retention. High-frequency cannabis use was reported by 17.0% (n=139) of these patients at the start of their first treatment episode (Table 3.3). High-frequency cannabis users were more likely to be male (69.8% *vs.* 56.3%, p=0.004) and legally employed (27.3% *vs.* 17.7%, p=0.012). No other differences at treatment initiation were recorded (Table 3.3). In total, 240 (29.3%) individuals discontinued treatment at or before six months in at least one of their treatment episodes. As shown in Table 3.4, there was not a significant relationship observed between high-frequency cannabis use and retention in treatment at six months (OR = 1.02, 95% CI: 0.71 – 1.47; AOR = 0.98, 95% CI: 0.66 – 1.45; both p>0.05).

Table 3.3. Baseline characteristics of 818 PWUD who initiated an MMT episode between December 1, 2005 and November 30, 2018

Characteristic	**Overall** n = 818	**Daily cannabis use**[1]		***p*-value**
		Yes n = 139; 17.0%	**No** n = 679; 83.0%	
Sociodemographic factors				
Sex				
Male	479 (58.6)	97 (69.8)	382 (56.3)	0.004
Female	339 (41.4)	42 (30.2)	297 (43.7)	
Age				
Median (IQR)	42.4 (35.0 – 49.2)	43.4 (35.7 – 48.4)	42.2 (34.9 – 49.5)	1.000
Racial identity				
White	464 (56.8)	82 (59.0)	383 (56.4)	0.641
Non-white	353 (43.2)	57 (41.0)	296 (43.6)	

Characteristic	Overall n = 818	Daily cannabis use[1]		*p*-value
		Yes n = 139; 17.0%	No n = 679; 83.0%	
Employment[1]				
Yes	158 (19.3)	38 (27.3)	120 (17.7)	0.012
No	660 (80.7)	101 (72.7)	559 (82.3)	
Homelessness[1]				
Yes	274 (33.5)	41 (29.5)	233 (34.3)	0.318
No	544 (66.5)	98 (70.5)	446 (65.7)	
Incarceration[1]				
Yes	90 (11.0)	16 (11.5)	90 (13.3)	0.675
No	712 (89.0)	123 (88.5)	589 (86.7)	
Substance use, health, treatment factors				
Daily alcohol use[1]				
Yes	36 (4.4)	8 (5.8)	28 (4.1)	0.530
No	782 (95.6)	131 (94.2)	651 (95.9)	
Daily stimulant use[1]				
Yes	346 (42.3)	60 (43.2)	286 (42.1)	0.894
No	472 (57.7)	79 (56.8)	393 (57.9)	
Daily opioid use[1]				
Yes	329 (40.1)	52 (38.5)	277 (41.6)	0.571
No	472 (59.9)	83 (61.5)	389 (58.4)	
HIV status				
HIV-positive	273 (33.4)	50 (36.0)	223 (32.8)	0.539
HIV-negative	545 (66.6)	89 (64.0)	456 (67.2)	
Other addiction treatment[1]				
Yes	172 (21.0)	33 (23.7)	139 (20.5)	0.455
No	646 (79.0)	106 (76.3)	540 (79.5)	
MMT dose[2,3]				
Lower (< 90 mg/d)	436 (64.1)	75 (64.1)	361 (64.1)	1.000
Higher (≥ 90 mg/d)	244 (35.9)	42 (35.9)	202 (35.9)	

Note: [1]Refers to exposures in the previous six months; [2]Daily MMT dose was reported at the time of interview; [3]Cells for MMT dose do not add up to 818 as participants who discontinued treatment before their interview were ineligible for this question; IQR = Interquartile range

Table 3.4. Bivariable and multivariable associations between all independent variables and ≤six-month retention among 818 PWUD initiating an MMT episode between December 1, 2005 and November 30, 2018

Variable	MMT discontinuation at six months			
	Odds Ratio (95% CI)	***p*-value**	**Adjusted Odds Ratio (95% CI)**	***p*-value**
Primary independent variable				
Daily cannabis use[1] (Yes *vs.* no)	1.02 (0.71 – 1.47)	0.908	0.98 (0.66 – 1.45)	0.920
Socio-demographic factors				
Sex (Male *vs.* female)	1.15 (0.87 – 1.52)	0.318	1.28 (0.94 – 1.75)	0.120
Age (Per year increase)	0.98 (0.97 – 1.00)	0.035	0.98 (0.97 – 1.00)	0.056
Racial identity (White *vs.* non-white)	0.78 (0.60 – 1.03)	0.082	0.82 (0.61 – 1.10)	0.180
Employed[1] (Yes *vs.* no)	1.23 (0.90 – 1.68)	0.189	1.17 (0.83 – 1.64)	0.359
Homeless[1] (Yes *vs.* no)	1.32 (0.99 – 1.76)	0.056	1.17 (0.86 – 1.58)	0.313
Incarcerated[1] (Yes *vs.* no)	1.47 (1.01 – 2.12)	0.042	1.23 (0.84 – 1.82)	0.290
Substance use and health factors				
Daily alcohol use[1] (Yes *vs.* no)	1.55 (0.93 – 2.59)	0.091	1.42 (0.84 – 2.41)	0.187
Daily stimulant use[1] (Yes *vs.* no)	0.95 (0.72 – 1.25)	0.697	1.00 (0.74 – 1.35)	0.994
Daily opioid use[1,2] (Yes *vs.* no)	2.61 (2.00 – 3.42)	<0.001	--	--
HIV serostatus (Positive *vs.* negative)	0.71 (0.53 – 0.97)	0.029	0.74 (0.53 – 1.01)	0.060
Treatment-related factors				
Calendar year (≥2014 *vs.* <2014)	2.11 (1.61 – 2.75)	<0.001	2.59 (1.92 – 3.49)	<0.001
Other addiction treatment[1] (Yes *vs.* no)	1.27 (0.92 – 1.74)	0.212	1.23 (0.89 – 1.69)	0.243
Treatment episode number (2 *vs.* 1)	0.98 (0.72 – 1.32)	0.871	0.98 (0.72 – 1.32)	0.184
(≥3 *vs.* 1)	1.00 (0.68 – 1.48)	0.982	0.62 (0.39 – 0.97)	0.035
MMT at study recruitment (Yes *vs.* no)	0.59 (0.43 – 0.81)	0.001	0.57 (0.41 – 0.80)	0.001

Note: [1]Refers to the six-month period preceding interview; [2]Opioid use is conceptualized as an intermediate factor in the relationship between low MMT dose and treatment discontinuation; 95% CI = 95% Confidence interval

A further 611 (73.7%) treatment (re)initiates remained in MMT for longer than six months and were included in the long-term retention analysis (Figure 3.1). Of them, 337 (55.2%) discontinued treatment at least once for a total of 457 discontinuation events. Table 3.5 shows the results of the bivariable and multivariable Cox frailty models. Before considering a potential interaction with cannabis, lower MMT dose was significantly associated with treatment discontinuation (Hazard Ratio [HR] = 2.05, 95% CI: 1.66 – 2.53, $p<0.001$), while daily cannabis use was not significantly associated with discontinuation (HR = 0.91, 95% CI: 0.71 – 1.18, $p=0.496$). The unadjusted hazard of discontinuation for <90 mg/d relative to ≥90 mg/d was similar between the strata of cannabis use (HR = 2.10, 95% CI: 1.66 – 2.65, $p<0.001$ during no/low-frequency cannabis use; HR = 1.85, 95% CI: 1.13 – 3.03, $p=0.014$ during high-frequency cannabis use), consistent with a lack of effect measure modification, as confirmed through a likelihood ratio test ($X^2=2.67$, $p=0.300$). This finding of a lack of effect measure modification held after considering the influence of several hypothesized confounders ($X^2=0.05$, $p=0.830$). The adjusted relative hazard of treatment discontinuation for each cannabis-dose treatment group (reference: < daily cannabis, high dose) is depicted in Figure 3.3. In the adjusted Cox frailty model, significant associations were observed between additional socio-demographic, substance use, and treatment-related factors and shorter time-to treatment discontinuation, including non-white racial identity, homelessness, incarceration, later (≥2014) year of treatment, and second treatment attempt during the study (all $p<0.05$; Table 3.5).

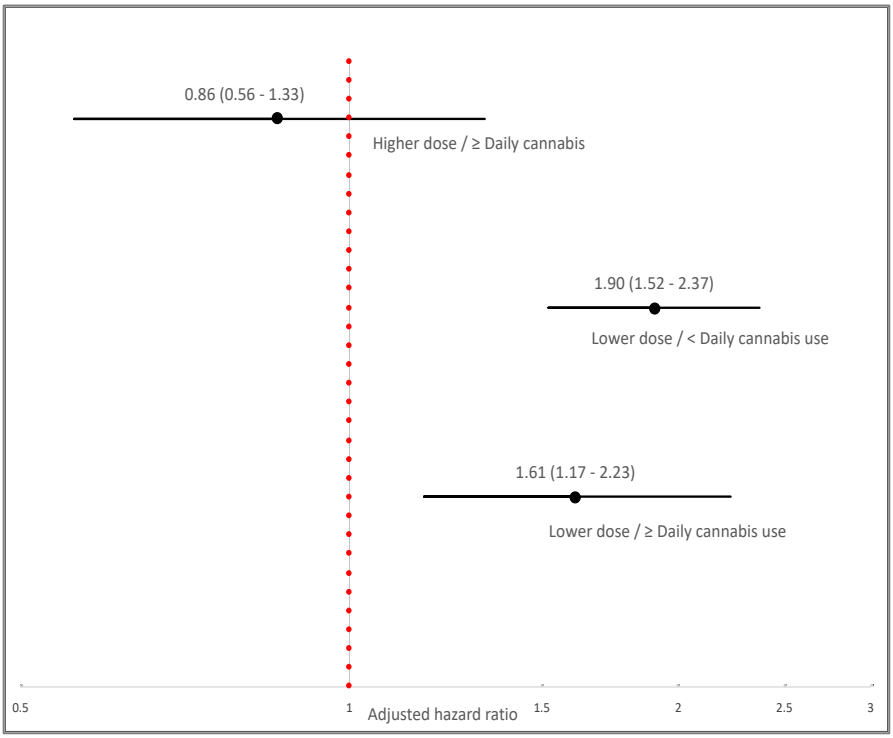
Table 3.5. Bivariable and multivariable associations between all independent variables and ≥six-month retention in MMT among 611 PWUD on MMT between December 1, 2005 and November 30, 2018

Variable	Time-to-MMT discontinuation (>6 months)			
	Hazard Ratio (95% CI)	***p*-value**	**Adjusted Hazard Ratio (95% CI)**	***p*-value**
Treatment dose[2] (primary independent variable), pooled estimate				
MMT dose (<90 mg/d *vs.* ≥90 mg/d)	2.05 (1.66 – 2.53)	<0.001	--	--
Cannabis use[1] (hypothesized effect measure modifier), pooled estimate				
Daily cannabis use (Yes *vs.* no)	0.91 (0.71 – 1.18)	0.496	--	--
Treatment dose estimate[2], stratified by cannabis use[1,3]				
(Daily cannabis use = no): MMT dose (<90 mg/d *vs.* ≥90 mg/d)	2.10 (1.66 – 2.65)	<0.001	1.90 (1.52 – 2.37)	<0.001
(Daily cannabis use = yes): MMT dose (<90 mg/d *vs.* ≥90 mg/d)	1.85 (1.13 – 3.03)	0.014	1.87 (1.16 – 3.01)	0.010
Socio-demographic factors				
Sex (Male *vs.* female)	1.14 (0.92 – 1.41)	0.220	1.22 (1.00 – 1.49)	0.055
Age (Per year increase)	0.98 (0.97 – 1.00)	0.007	0.99 (0.98 – 1.00)	0.079
Racial identity (White *vs.* non-white)	0.74 (0.60 – 0.91)	0.004	0.77 (0.64 – 0.94)	0.010
Employed[1] (Yes *vs.* no)	1.05 (0.83 – 1.34)	0.702	1.02 (0.80 – 1.29)	0.897
Homeless[1] (Yes *vs.* no)	1.83 (1.44 – 2.32)	<0.001	1.44 (1.13 – 1.83)	0.003
Incarcerated[1] (Yes *vs.* no)	2.07 (1.49 – 2.89)	<0.001	1.54 (1.11 – 2.14)	0.011
Substance use and health factors				
Daily alcohol use[1] (Yes *vs.* no)	1.21 (0.85 –1.73)	0.283	1.11 (0.80 – 1.55)	0.535
Daily stimulant use[1] (Yes *vs.* no)	1.23 (1.00 –1.52)	0.050	1.20 (0.98 – 1.47)	0.083
Daily opioid use[1,4] (Yes *vs.* no)	2.48 (2.03 – 3.03)	<0.001	--	--
HIV status (Positive *vs.* negative)	0.87 (0.70 – 1.09)	0.218	0.94 (0.77 – 1.15)	0.560
Treatment-related factors				
Calendar year (≥2014 *vs.* <2014)	1.25 (1.02 – 1.52)	0.029	1.27 (1.03 – 1.57)	0.027
Other addiction treatment[1] (Yes *vs.* no)	1.39 (1.09 – 1.76)	0.007	1.26 (1.00 – 1.59)	0.052

Variable	Time-to-MMT discontinuation (>6 months)			
	Hazard Ratio (95% CI)	***p*-value**	**Adjusted Hazard Ratio (95% CI)**	***p*-value**
Treatment episode number (2 *vs.* 1)	1.33 (1.08 – 1.65)	0.008	1.28 (1.03 – 1.60)	0.030
(≥3 *vs.* 1)	1.50 (1.13 – 1.98)	0.005	1.30 (0.96 – 1.76)	0.090
MMT at study recruitment (Yes *vs.* no)	0.77 (0.61 – 0.96)	0.018	0.84 (0.68 – 1.03)	0.085

Note: [1]Refers to the six-month period preceding interview; [2]Daily MMT dose was reported at the time of the interview; [3]Measure of effect measure modification by cannabis use: Unadjusted: X^2=2.19, p=0.300; Adjusted: X^2=0.05, p=0.830; [4]Opioid use is conceptualized as an intermediate factor in the relationship between low MMT dose and treatment discontinuation; 95% CI = 95% Confidence interval

Figure 3.3. Adjusted hazard of treatment discontinuation within strata of treatment dose and cannabis use (relative to higher dose / < daily cannabis use) among 611 MMT initiates in Vancouver, Canada, December 1, 2005 – November 30, 2018



Note: Estimates adjusted for sex, age, racial identity, employment, homelessness, incarceration, daily alcohol use, daily stimulant use, HIV serostatus, calendar year of treatment, treatment episode, and MMT enrolment at study recruitment; AHR is shown on the log scale.

In a sensitivity analysis censoring individuals at the time of buprenorphine/naloxone initiation, the main finding of a lack of effect measure modification between cannabis and dose on time-to treatment discontinuation did not change; however, the association with later year of treatment was no longer evident (p=0.159), suggesting that the earlier association with calendar year of treatment was partially explained by increased transitions to buprenorphine/naloxone in years corresponding with the methadone formulation change.

3.4 Discussion

While there has been growing and widespread interest in the possible therapeutic applications of cannabinoids, including in the management of OUD (283), this study sought to explore whether cannabis use may play a modifying role in the established relationship between lower methadone treatment dose and two critical patient-level outcomes: illicit opioid use and treatment retention. This study involving marginalized PWUD on MMT provided some evidence to suggest that the relationship between lower methadone dose and high-frequency illicit opioid use is lower during periods of high-frequency cannabis use, but this finding does not appear to translate into better retention in treatment.

In general, previous clinical studies involving patients on MMT have not produced findings that characterize cannabis as a preventative measure against opioid use during treatment. An early cross-sectional study by Best and colleagues in Scotland noted significant negative correlations between number of days of cannabis use and heroin use in the past month, with daily cannabis users recording 0.8 heroin use days on average compared to 1.6 and 5.8 days for occasional and non-users, respectively (220). Since then, the majority of studies reporting on cannabis use among

MMT patients have not found evidence of a significant relationship (positive or negative) with non-medical opioid use (173, 216, 221, 222, 224, 232, 234, 238-240, 245). Two notable limitations across many of these studies threaten the potential to detect a true relationship (positive or negative) between cannabis use and opioid use during treatment: the measurement of cannabis use at treatment initiation only (216, 222, 238, 245), and the use of any (rather than frequent) as the minimal threshold for cannabis use (234, 238-240). Furthermore, the majority of these studies conceptualize cannabis as an independent variable (often one of many), rather than a behaviour with the potential to modify the influence of another major risk factor for illicit opioid use. In addressing this gap, the current study produced evidence in support of the hypothesis that the relationship between MMT dose (which is known to negatively correlate with opioid withdrawal and craving) and high-frequency illicit opioid use differs based on the concurrent use of cannabis—specifically, the strength of the association is elevated during periods of no or infrequent concurrent cannabis use.

The present finding may be indicative of the effective use of cannabis as a self-management strategy to address opioid craving or alleviate negative symptoms associated with withdrawal, in particular anxiety, nausea/vomiting, and insomnia (119). However, potential drug-drug interactions between cannabinoids and methadone also warrant consideration. For example, *N*-demethylation of methadone is completed by cytochrome P450 (CYP) enzymes including CYP3A4 and CYP2C19 and CYP2C9 (288); cannabinoids are thought to be metabolized by, and may also act as inhibitors of, these CYP enzymes. Inhibition of CYP enzymes involved in methadone metabolism could result in higher methadone serum concentrations (289) with possible implications for mitigating opioid withdrawal and craving. In particular, CBD appears to be a

potent inhibitor of CYP34A (290, 291), although, it should be noted that the clinical relevance of this relationship remains unclear and CBD levels in the cannabis used by this population were not reported by participants (and likely not known to them as the majority of data collection preceded legalization). This hypothesis will require in-depth pharmacological exploration, especially as the understanding of cannabinoid pharmacokinetics is incomplete and actively evolving. Although (to my knowledge), no other studies have employed the same methodology to examine the present research question, the findings of the current study can be contrasted with a small number of other non-experimental studies that have explored this hypothesis in other ways. Scavone *et al.* conducted a retrospective chart review of 91 OUD patients initiating MMT, comparing changes in opioid withdrawal severity over time by cannabis use frequency, and found decreasing withdrawal severity with increasing frequency of cannabis use (173). However, their finding did not translate to lower frequency of illicit opioid use among their patients during either induction or stabilization phases (173). Epstein and Preston reported that past-week cannabis use was not associated with reduced withdrawal severity in the preceding week, and there was no significant interaction between cannabis use and treatment dose on the severity of withdrawal (234). Thus, the possibility remains that those engaging in high-frequency cannabis use during MMT in the current setting differ by a latent factor from those engaging in less frequent or no cannabis use, which created a spurious interaction with dose in its relationship with opioid use. However, this study attempted to measure and account for these potential differences through considering the influence of a number of other socio-demographic factors, substance use patterns, and treatment conditions, and it is notable that few significant differences according to frequency of cannabis use were observed at baseline.

Despite the evidence to suggest that cannabis and methadone dose interact to produce cannabis-dependent relationships between lower dose and illicit opioid use among marginalized PWUD on MMT, a similar trend was not observed for treatment retention. First, the odds of treatment retention within the first six months were examined for those initiating MMT during the study period (given that current treatment dose could not be measured or imputed for participants who discontinued treatment within the approximate six-month period). Here, high-frequency cannabis use was not found to significantly increase or decrease the odds of short-term treatment retention in unadjusted or adjusted models. This finding for short-term retention is similar to those reported previously in other settings (173, 224, 232). Of note, however, this finding was inconsistent with one previously observed in the current study population, whereby high-frequency (but not occasional) cannabis use was associated with increased odds of retention in opioid agonist treatment (MMT or buprenorphine-naloxone) six months later (231). As the study authors confirmed a similar finding after restricting their sample to MMT patients only (292), this difference may have resulted from the current study's examination of six-month discontinuation only at the first study observation after treatment initiation. Then, the influence of high-frequency cannabis use as a potential effect measure modifier in the relationship between lower MMT dose and the time-to treatment discontinuation was modelled, taking into consideration multiple treatment episodes per person, but no evidence of effect measure modification was found. This is despite the finding that high-frequency cannabis use interacts with a lower MMT dose to reduce the risk of high-frequency illicit opioid use, and in turn, high-frequency opioid use is a particularly strong risk factor for treatment discontinuation (as exemplified by the bivariable results of Tables 3.4 and 3.5).

Aside from the main focus on cannabis interactions, the current analysis revealed some notable secondary findings. Several of this study's findings were consistent with those of Nosyk and colleagues, who were the first to adapt the approach of using a Cox frailty model to analyze retention for multiple MMT episodes per patient (270); most notably, the likelihood of treatment retention increased with age and treatment dose, and decreased with increasing treatment episodes and calendar year. Additionally, several significant social- and structural-level risk factors for treatment discontinuation were observed, including non-white racial identity, homelessness, and incarceration. These indicators of social and structural marginalization have been repeatedly shown to strongly and negatively impact OUD treatment access, adherence and retention in this setting and others (293-296). It is therefore possible that, even if the finding of an interaction between cannabis and dose on illicit opioid use reflects a biological effect, these individual-level improvements in symptoms cannot overcome the structural barriers within the broader social, physical, political, and economic environments that help shape treatment access, adherence, and retention for marginalized PWUD in this setting (39). As visually summarized in Figures 3.2. and 3.3., a clear and consistent finding of both analyses was that higher MMT doses are associated with improved treatment outcomes including reduced frequency of illicit opioid use and longer retention, regardless of cannabis use status. Clinicians should be aware that patients receiving lower doses (up to 90 mg/d) may engage in continued illicit opioid use as a result of insufficient suppression of withdrawal and opioid effects. In particular, high-frequency use of cannabis may act as a signifier of insufficient management of withdrawal or opioid effects at the current treatment dose. In such cases, working with the patient on a plan to increase the treatment dose (or transition to another form of medication-based treatment) may be warranted.

The ability to exploit up to 13 years' worth of multiple MMT episodes per participant from over 800 PWUD in a community setting with widespread low-barrier access to MMT is a major strength of this research. However, the observational nature of this study presents a number of limitations that should be considered when interpreting these findings. First, it is not possible to randomly select PWUD from the community and, despite a diverse strategy for community recruitment, thus it cannot be guaranteed that the cohorts are generalizable to the entire population of PWUD. Second, the six-month data collection structure prevented the ability to record important details regarding any changes to methadone dose and exact timing of enrolment/discontinuation within each six-month period. Although attempts were made to limit observations outside of MMT engagement (e.g., by only including current MMT patients in the first analytic sample), the temporality of events within each six-month period cannot be discerned. In particular, it is possible for exposure data to continue or commence after treatment discontinuation for participants who were estimated to discontinue treatment mid-way through the previous six-month period (rather than at the start of the subsequent six-month period, in which case, exposure observations reported in that period were not analyzed). Fortunately, this situation only occurred in a small number (345, 5.7%) of study observations. Aside from HIV serostatus, all information is obtained via self-report; although self-report of MMT dose, substance use, and associated risk behaviours among PWUD are generally valid and reliable (297, 298). Finally, the study questionnaire did not elicit information about certain dimensions of cannabis use that could better illuminate the findings. These dimensions include cannabis composition (e.g., THC *vs.* CBD) and potency, modes of administration (e.g., smoking, oral ingestion, etc.), typical quantity used, and number of uses per day for the daily users.

The limitations of this study raise important issues that should be addressed in future research looking to investigate a therapeutic role of cannabinoids in the treatment of OUD. First, as new scientific discoveries emerge involving the endogenous cannabinoid system and its interaction with various cannabinoids and other bioactive components of cannabis preparations (e.g., terpenoids), it will be important to determine which (if any) cannabis-based products, doses, and modes of administration are optimal to administer as adjunct treatments to OUD pharmacotherapy. THC seems potentially important given its anti-emetic properties (see evidence reviewed in Chapter 1). However, THC is intoxicating and is implicated in neurological reward pathways, which raises concerns about the development of dependence and other harms (122). Cannabis with higher CBD content (e.g., equal amounts of THC and CBD) or isolated CBD is a potentially useful alternative. After demonstrating that CBD can be safely administered alongside strong opioids (299), Hurd and colleagues reported the results of a small experimental study in which oral CBD or a placebo was randomized for treatment of opioid craving in 42 drug-abstinent, heroin-dependent patients (128). CBD was found to reduce heroin cue-induced cravings and anxiety, and these effects persisted one week after CBD administration (128). However, these participants were not undergoing concurrent methadone treatment and the possible drug-drug interactions between CBD and methadone will require close examination, as discussed above. Considering the discussion of CBD's potential underlying role in the observed findings, information about the use of CBD-prominent cannabis cultivars would be especially pertinent to the current study. Under a legal framework, Canadian research can begin to address this gap, but only if patients are using regulated products. There are no experimental studies to date that have evaluated the long-term application of cannabis (or a cannabinoid) as an adjunct treatment in the

long-term management of OUD; this will be a critical knowledge gap to address given that many people living with OUD will be engaged on MMT for life. Finally, cannabis was legal for non-medical use during only the final six weeks of this 13-year study period. It would be interesting to re-examine these relationships in the era of legalized non-medical cannabis, given that patients are regularly tested for and expected to refrain from other substance use (including cannabis). While patients are unlikely to be involuntarily discharged from treatment as a consequence of cannabis use in this setting, they may feel more comfortable and supported in discussing cannabis as a complementary treatment for OUD with their healthcare provider under a legal framework, and it is possible that the findings of this study would differ under those conditions.

3.5 Conclusion

Through demonstrating that the association between a lower methadone dose and frequent illicit opioid use is reduced during periods of high-frequency cannabis use, this study provides some evidence that cannabis may be a helpful *ad hoc* strategy for some individuals in the management of opioid withdrawal and craving during MMT. However, cannabis does not appear to reduce the risk of treatment discontinuation at lower methadone doses. There are a number of potential underlying reasons for this discrepancy in outcomes—notably, the potential therapeutic result of using cannabis to address withdrawal is likely to be negligible against certain exogenous social and structural factors (e.g., homelessness, incarceration) that contribute to suboptimal treatment conditions (of which low dose is only one indicator). This study provides preliminary evidence from a real-word setting to highlight critical areas of future experimental investigation into the possible adjunctive administration of cannabis for medication-based management of OUD.

Chapter 4: Characterizing motivations for cannabis use in a cohort of people who use illicit drugs: A latent class analysis

4.1 Introduction

Cannabis is the most common illicit (i.e., internationally scheduled) drug consumed worldwide (300). The preponderance of health and social research on cannabis tends to conceptualize its usage as non-medical (i.e., recreational) and often problematic in nature (301, 302). However, coinciding with policy reforms across the U.S. and Canada, there has been a recent shift in the public perception of cannabis (303), bringing a growing interest in the range of its possible therapeutic applications. In Canada, more than 350,000 individuals possess a medical authorization to use cannabis for a range of conditions including chronic pain, insomnia, arthritis, and post-traumatic stress disorder (304, 305).

Cannabis has long been incorporated into poly-substance use among marginalized people who use illicit drugs (PWUD). For example, approximately half of PWUD living with HIV in Vancouver, Canada report past six-month cannabis use (161), compared to a past-year prevalence of nearly 15% in the general population (306). Yet, aside from HIV acquisition and disease progression (161, 307-310), the complex nature of cannabis use within the context of regular polysubstance use has received little attention as a primary topic of interest in epidemiological research involving marginalized PWUD. Emerging qualitative research has broached the idea that cannabis may serve a range of therapeutic purposes in these populations. PWUD describe purposefully engaging in cannabis use as a form of harm reduction (e.g., to manage opioid cravings or prevent escalation to higher-intensity opioid use (163, 165, 311)). These accounts are further supported by emerging experimental research demonstrating a potential role of cannabinoids in

reducing opioid craving and withdrawal (128). In light of the ongoing opioid overdose crisis throughout Canada and the U.S. in which marginalized PWUD have borne the brunt of morbidity and mortality, the evolving understanding of cannabis' therapeutic potential raises important questions about whether—and, if so, how—cannabinoid-based interventions could be implemented and individually-tailored as a form of harm reduction (69).

Latent class analysis (LCA) is a statistical method that uses a combination of observed characteristics to identify discrete unobserved (i.e., latent) classes within a heterogeneous sample (312). In recent years, a growing number of studies involving PWUD have employed LCA methodology to characterize poly-substance use and behavioural risk profiles (313-321). Findings from these studies have highlighted important classifications of risk for overdose (318, 321), HIV and hepatitis C virus transmission (315, 317, 319, 320), injection-related infection and injury (313), sexual risk behaviours and sexually transmitted disease infection (314-316), and comorbid mental health concerns (319). While some studies have employed LCA methodology to understand motivations for cannabis use (322, 323), this research has tended to focus on young adult and student populations, conceptualizes cannabis use as inherently problematic, and leaves potential therapeutic motivations unexplored. For instance, a recent study of cannabis-using Americans aged 19-20 developed latent classes through examining motivations related to experimenting, getting high, relaxing, socializing, escaping problems/coping, peer pressure, dependence, and modifying the effects of other drugs in order to understand which classes were associated with problematic cannabis use 15 years later (323).

The objectives of the current study were to: 1) explore the range of therapeutic and non-therapeutic reasons for cannabis use among marginalized PWUD in Vancouver, Canada, during a community-wide opioid overdose crisis; 2) use LCA to assign membership to discrete groups of cannabis users based on reasons for use; and 3) estimate the relationships between class membership and a range of demographic, socio-structural, substance use, and other health-related factors.

4.2 Methods

Data for this study were derived from VIDUS and ACCESS studies, as described in Section 1.7.2.

4.2.1 Study sample

For the purposes of this study, the follow-up period was restricted to June 1, 2016 to November 30, 2018, as new cannabis measures—including information on reasons for use and sources of access—were added to the questionnaire in June 2016.

4.2.2 Latent class model

4.2.2.1 Measures

All participants who self-reported any cannabis use in the previous six-month period were asked a follow-up question on the reason(s) why they used it. Participants were asked to endorse their reason(s) for cannabis use from a list of pre-determined categories (detailed in Box 4.1) which emerged from a literature review and piloting process. Specifically, the categories were developed by cohort investigators and select study co-authors through knowledge of non-medical and medical uses of cannabis, with special attention to health issues that disproportionately affect PWUD (e.g., HIV and treatment side-effects, opioid withdrawal and craving, acute and chronic pain). The

categories were distributed to study staff (including interviewers and research nurses with several years of experience working with the study population), peer research associates, community medical cannabis advocates, and healthcare providers, who provided additional input. There was also an option for participants to specify another reason under "Other" if it was missing from the option list. These string responses were scrutinized after each biannual interview round to identify any missing or emergent categories. Aside from "Other", each of the categories was treated as a binary variable (yes *vs.* no).

Box 4.1 Categories for cannabis use reasons

(1) To relieve pain, including multiple sclerosis (MS), arthritis, etc.
(2) To help with sleep
(3) To help with HIV medications and AIDS symptoms
(4) To treat nausea or loss of appetite
(5) To substitute for other substances including heroin, crack, meth, or alcohol
(6) To relieve stress
(7) To treat a mental health concern other than addiction
(9) For spiritual purposes
(10) For creativity
(11) To get high, recreation, socialize
(12) To come down off of other drugs
(13) To treat withdrawal

4.2.2.2 Statistical analysis

First, with the research supervisor, a consensus-based approach was used to re-categorize all string responses under "Other" reasons for cannabis use into a pre-determined option wherever possible. A function heat map was generated to visualize clustering of individuals by reason(s) for cannabis use, and to inspect the number of responses for each variable. The variable "Help with HIV medications and AIDS symptoms" was removed at this stage due to low cell count; the two categories "Spiritual purposes" and "Creativity" were combined into a single variable for "Spirituality/Creativity"; and the two categories "To come down off of other drugs" and "To treat withdrawal" were combined into a single variable for "Manage addiction".

Then, an LCA was conducted, using the 13 reasons for use to build empirically discrete groups based on the cannabis-using profiles of the cohort at each interview period. The R package *poLCA* was used to estimate the number of latent classes in the sample and the likelihood of each participant's class membership. This software employs expectation-maximization and Newton-Raphson algorithms to find maximum likelihood estimates of the model parameters (324). The classes were developed from observations at each interview period, meaning that individuals who contributed multiple observations to the data could belong to one class at one time and another class at another time over the study period. Different class models (2-, 3-, 4-, 5, and 6-class models) were tested using a combination of exploratory methods and *a priori* theoretical guidelines. Bayesian information criterion (BIC), Akaike information criterion (AIC), Pearson's Chi-square goodness of fit (χ^2), and likelihood ratio (G^2) statistics were examined for model fit. To avoid problems with generalizability that may arise from creating groups that are either very similar but extremely small or very large but extremely heterogeneous, a pre-specification was made that latent classes should represent no less than 5% and no more than 50% of sample observations. The number of times to estimate the model using different starting probability values was set to 20.

4.2.3 Latent class regression

4.2.3.1 Measures

Several socio-demographic, behavioural, and health-related factors hypothesized to vary by class membership were considered in these analyses. Unless otherwise specified, all variables are self-reported and refer to experiences in the six-month period prior to each study interview. Socio-demographic covariates included: age; sex; racial identity (white *vs.* non-white); DTES residency; education level (≥high school *vs.* <high school); and legal employment. Socio-structural

variables included: homelessness and incarceration. Substance use variables included: alcohol use; cocaine use; heroin injection (of note, during this study period, a high proportion of drugs sold as heroin in the community contained fentanyl (35), thus "heroin" injection refers to the injection of heroin as well as drugs sold as heroin); illicit prescription opioid use (i.e., non-medical use of prescribed, diverted, or counterfeit pharmaceutical opioids); crack use; cannabis use; and crystal methamphetamine use (all categorized as ≥ daily *vs.* < daily, to be consistent with previous analyses). Health-related variables included: hepatitis C serostatus at time of interview; HIV serostatus at time of interview; lifetime mental illness diagnosis; non-fatal overdose; pain severity in the past week (assessed with the Brief Pain Inventory, dichotomized into moderate-severe [mean score 4.5-10]) *vs.* none-mild [mean score 0-4.4]); depression, anxiety (each assessed with PROMIS short-form, dichotomized into moderate/severe [T-score ≥60] *vs.* none/mild [T-score ≤59.9]); self-perceived general health rating (good-excellent *vs.* poor-fair); and addiction treatment enrolment.

For descriptive purposes, the following sources for obtaining cannabis (defined in Box 4.2) were also examined: dealer, friend, private, compassion club, retail dispensary, a licensed medical cannabis producer, or a legal store (added in the final interview period [June 1, 2018 – November 30, 2018], coinciding with legalization [October 17, 2018]).

Box 4.2. Categories for cannabis sources

(1) Dealer
(2) Friend/family
(3) Private grower (participant grows it themselves or pays a grower)
(4) Compassion club (a local cooperative providing low-cost cannabis for medical purposes to patients in financial need)
(5) Dispensary DTES (a retail store located in the DTES neighbourhood selling products that are not produced or sold through legal medical or non-medical cannabis systems)
(6) Dispensary outside DTES (same as above, but located outside of the DTES neighbhourhood)
(7) Licensed medical cannabis producer (legal producers of medical cannabis selling to medically-authorized patients)
(8) Legal retail store (legally regulated store for non-medical cannabis; added in the final interview period [June 1, 2018 – November 30, 2018], coinciding with legalization [October 17, 2018])

4.2.3.2 Statistical analysis

First, binary outcome variables were created for each class (i.e., Class 1 *vs.* Other; Class 2 *vs.* Other, and so on). As the data could contain ≥1 observations from each participant, generalized estimating equations (GEE) were used to explore bivariable relationships between each variable above and class membership. This method estimates standard errors for each parameter using an exchangeable correlation structure to account for repeated measures within individuals (325). Then, multivariable GEE models were built to predict membership in each class. These models included all covariates (aside from cannabis sources) that were associated with the outcome at $p<0.10$ in bivariable analyses. An iterative backward variable selection approach was used in which the covariate with the highest *p*-value was removed first, and changes to model quasi-information criterion (QIC) were examined. The final models were determined once QIC reached its lowest point. An OR of < 1 indicates a negative association with the outcome (i.e., reduced odds of class membership for the exposure in question); whereas an OR of >1 indicates a positive association with the outcome (i.e., increased odds of class membership for the exposure in question).

All analyses were conducted in R (Version 3.5.0, R Foundation for Statistical Computing, Vienna, Austria). All *p*-values are two-sided.

4.3 Results

4.3.1 Sample characteristics

Between June 1, 2016 and November 30, 2018, 1447 PWUD completed 5400 interviews (median number of interviews per participant = 3). Of these individuals, 897 (62.0%) reported using cannabis during 2686 (49.7%) study visits and were included in this study. Table 4.1 summarizes the socio-demographic characteristics of this sample at baseline. As shown, the median age of participants in this study was 47.7 years (Interquartile Range [IQR] = 38.4 – 54.6), one-third (33.3%) were women, and just under half (44.8%) were white. Over the study period, the median prevalence of past six-month ≥daily cannabis use ranged from 41.1% to 50.3% (median: 47.6%), whereas ≥ weekly use ranged from 23.2% to 29.9% (median: 27.7%) and < weekly use ranged from 21.1% to 27.1% (median: 23.9%).

Table 4.1 Baseline sociodemographic characteristics of 897 PWUD who reported cannabis use between June 1, 2016 and November 30, 2018

Characteristic	N	%
Age		
Median, IQR	47.7	38.4 – 54.6
Sex		
Male	598	66.7
Female	299	33.3
Racial identity		
White	402	44.8
Non-white	493	55.0
Education		
≥ High school	423	47.2
< High school	453	50.5
Legal employment[1]		
Yes	269	30.0
No	627	70.0
Homelessness[1]		
Yes	190	21.2
No	705	78.6
DTES residency[1]		
Yes	540	60.2
No	357	39.8
Incarceration[1]		
Yes	45	5.0
No	850	94.8

Note: [1]Refers to exposures or experiences in the previous six months; IQR = Interquartile range

4.3.2 Selection of latent class model

Fit indices (AIC, BIC, χ^2, G^2) and class sizes were compared between all five tested latent class models. The 2- and 3-class models were ruled out on the basis of poor model fit (Appendix B.1). A 6-class model was ruled out as two classes represented very small (<5%) portions of the data (Appendix B.2). The 5-class model also had one class with fewer than 5% of observation. As the 4- and 5-class model yielded similar fit statistics, the 4-class model was selected for superior interpretability.

4.3.3 Latent classes

The representation of cannabis use motivations overall and across the emergent latent classes is summarized in Table 4.2. Of the 653 (72.8%) participants who completed more than one interview over the study period, 157 (24.0%) remained in the same class at each follow-up period. Of the remaining 496 participants who shifted classes during the study period, 353 (71.2%) occupied two classes at different points over the study period and 130 (26.2%) moved between three classes. A smaller number (n = 13, 2.6%) of respondents were categorized into each of the four classes at different times over the study period.

4.3.3.1 Class 1: "Recreational" class

Class 1, representing the second largest group (n observations = 848; 31.6%), was characterized as using cannabis predominantly for non-therapeutic (i.e., recreational) purposes such as intoxication, socialization, life enjoyment, etc. All member of this class indicated using cannabis for intoxication, and there was almost no therapeutic use of cannabis in this class aside from coping with stress, which was apparent in 13.4% of observations.

4.3.3.2 Class 2: "Non-pain therapeutic" class

Class 2 represented the largest latent group (n observations = 1007; 37.5%) and was distinct from other classes in the therapeutic use of cannabis for a number of conditions other than the management of pain. Specifically, a member of this class would have a substantial probability of using cannabis to treat insomnia (50%), nausea/loss of appetite (45%), and/or to manage stress (45%). As is the case with all classes, using cannabis for intoxication was also common (29% of observations).

4.3.3.3 Class 3: "Pain" class

Class 3 (n observations = 588; 21.9%) was characterized as using cannabis predominantly to manage pain, as all members in this group used cannabis for pain relief. Although, there was some additional use of cannabis for other non-pain therapeutic reasons (including nausea/loss of appetite [26.9%], insomnia [21.9%], and stress [16.8%]), and recreational reasons (including intoxication [25.5%]), these therapeutic and recreational motives were under-represented compared to the below Class 4, in which pain tended to be addressed in conjunction with another health issue.

4.3.3.4 Class 4: "Pain +" class

Class 4, the smallest group (n observations = 243; 9.0%), was distinct from other classes in that cannabis was serving at least one other therapeutic purpose (e.g., sleep [97.9%], nausea/loss of appetite [76.5%], stress [65.4%]) in addition to pain management (100%). Members of this class also engaged in recreational cannabis use more than the other two therapeutic classes (49.8%), and there was also a higher representation of less conventional potentially therapeutic applications of cannabis compared to other classes. For example, some members classified into this group were also using cannabis to substitute for another substance including alcohol or opioids (26.3%), to manage a mental illness (21.4%), for spiritual purposes (12.4%), or to treat addiction or manage withdrawal (9.5%).

Table 4.2. Representation of cannabis use motivations overall and within latent classes among 897 PWUD who reported cannabis use between June 1, 2016 and November 30, 2018

	Overall n = 2686; 100%	**Class 1:** n = 848; 31.6%	**Class 2:** n = 1007; 37.5%	**Class 3:** n = 588; 21.9%	**Class 4:** n = 243; 9.0%
Cannabis use reasons		**Proportion of observations**			
Intoxication	0.53	**1.00**	0.29	0.26	**0.50**
Pain relief	0.31	<0.01	<0.01	**1.00**	**1.00**
Mental health	0.08	0.02	0.10	0.06	0.21
Insomnia	0.32	0.00	**0.50**	0.22	**0.98**
Substitution	0.12	0.05	0.15	0.12	0.26
Nausea	0.29	0.00	0.45	0.27	**0.65**
Creativity / Spirituality	0.06	0.07	0.07	<0.01	0.12
Stress	0.32	0.13	0.45	0.17	**0.77**
Manage addiction	0.04	<0.01	0.06	0.02	0.09
Characterization	NA	Recreational	Non-pain therapeutic	Pain	Pain +

Note: Class-specific proportions ≥0.50 are shown in bold.

4.3.4 Sources of cannabis across classes

Illicit dispensaries in the DTES neighbourhood were the most common source of cannabis overall, reported in over 50% of interview periods. Many individuals also reported acquiring cannabis from a friend/family member (34.9% of observations) or a dispensary outside of the DTES (16.3% of observations). Less common sources were dealers, a compassion club, private growers, and licensed producers. As shown in Fig 4.1., dispensaries (mostly those located in the DTES neighbourhood) were the "most important" source of cannabis for the majority of members from classes 2 (60.6%), 3 (61.9%), and 4 (69.5%), while friends/family were the most commonly reported primary source of cannabis in class 1 (46.7%). Bivariable analyses confirmed these class differences in cannabis access patterns (Table 4.3). Additionally, membership in class 3 ("Pain") was positively associated with obtaining cannabis from a compassion club. There were very few reports of accessing cannabis through the authorized medical cannabis system (n = 12; 0.45%),

and only 2 participants (from Classes 3 and 4; 0.07%) accessed legal non-medical cannabis after legalization.

Figure 4.1. Primary source of cannabis reported overall and by class membership, June 1, 2016 – November 30, 2018 (n = 897, observations = 2686)

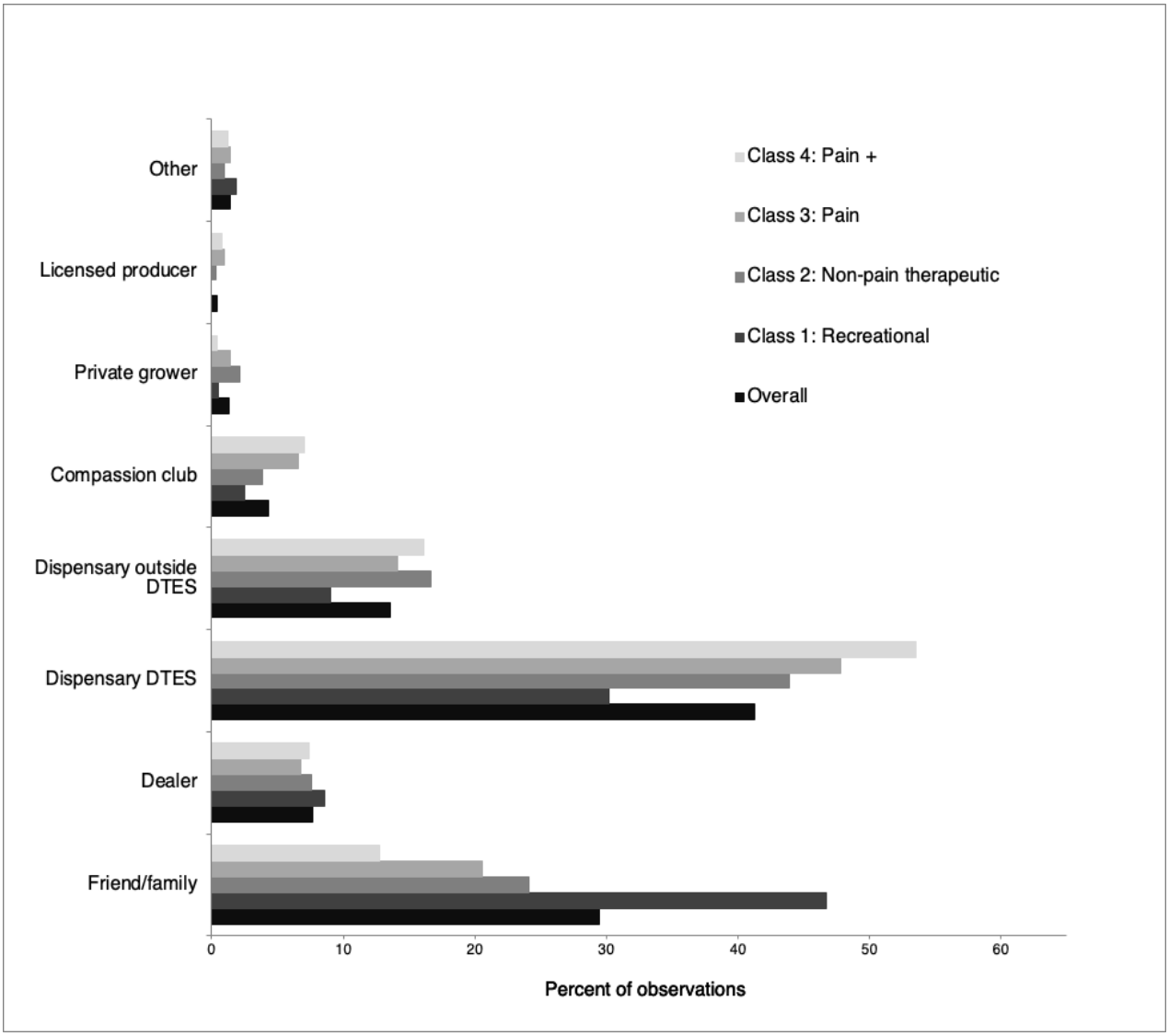


Table 4.3. Bivariable associations between cannabis sources and cannabis use classes (n = 897; observations = 2686)

Cannabis source	**Class 1:** "Recreational"		**Class 2:** "Non-pain therapeutic"		**Class 3:** "Pain"		**Class 4:** "Pain +"	
	Odds Ratio (95% CI)	***p*-value**	**Odds Ratio (95% CI)**	***p*-value**	**Odds Ratio (95% CI)**	***p*-value**	**Odds Ratio (95% CI)**	***p*-value**
Friend or private grower	**1.97 (1.64 – 2.36)**	**<0.001**	**0.74 (0.62 – 0.89)**	**0.001**	**0.72 (0.58 – 0.87)**	**0.001**	**0.59 (0.43 – 0.81)**	**0.001**
Dispensary	**0.40 (0.33 – 0.48)**	**<0.001**	**1.54 (1.29 – 1.82)**	**<0.001**	**1.45 (1.17 – 1.80)**	**0.001**	**2.03 (1.46 – 2.83)**	**<0.001**
Dealer	0.99 (0.78 – 1.26)	0.917	1.03 (0.81 – 1.31)	0.814	0.91 (0.67 – 1.23)	0.527	1.08 (0.71 – 1.65)	0.724
Compassion club	**0.74 (0.55 – 0.99)**	**0.044**	0.83 (0.59 – 1.16)	0.268	**1.48 (1.02 – 2.14)**	**0.039**	1.54 (0.92 – 2.55)	0.098
Medical cannabis licensed producer	(NA)	(NA)	0.65 (0.21 – 1.99)	0.455	2.26 (0.70 – 7.27)	0.172	3.33 (0.83 – 13.41)	0.091

Note: 95% CI = 95% Confidence interval; NA = 0 cells counts for medical cannabis licensed producer in Class 1; Bold indicates statistical significance at $p<0.05$

4.3.5 Latent class analysis using GEE

Class 1 ("Recreational") was significantly associated with a host of socio-demographic factors at the bivariable-level, including being male, living in the DTES, and experiencing recent homelessness and/or incarceration. The odds of daily alcohol use were significantly increased in this class, while the odds of daily prescription opioid and daily cannabis use were significantly lower than other classes. Members of this class had lower odds of reporting common co-morbidities experienced among PWUD. Specifically, they were less likely to be living with HIV, to have a mental illness diagnosis, or to live with moderate-severe levels of pain. They were also significantly more likely to report good-to-excellent self-perceived health (Table 4.4). In a multivariable model, the associations with DTES residency, homelessness, incarceration, daily prescription opioid use, and self-perceived health were removed from consideration or lost significance (Table 4.5).

As shown in Table 4.4, membership in class 2 ("Non-pain therapeutic") was significantly and positively associated with using cannabis daily and living with HIV, and negatively associated with moderate-severe pain and being enrolled in addiction treatment in bivariable analysis. In a multivariable model, all associations remained significant except daily cannabis use (Table 4.5).

At the bivariable-level (Table 4.4), members of class 3 ("Pain") were slightly older than members of other classes, and less likely to be male or experiencing homelessness. Membership in this class was also positively associated with daily cannabis use and daily prescription opioid use. In terms of health-related factors, this group had significantly increased odds of a lifetime mental illness diagnosis and experiencing moderate-severe pain, and significantly lower odds of good-excellent self-perceived quality of health; however, they also had significantly lower odds of experiencing a recent non-fatal overdose. In a multivariable model, age, homelessness, and daily

prescription opioid use were removed from consideration, and an additional negative association with daily heroin injection emerged (p=0.039; Table 4.5).

Membership in class 4 ("Pain +") was not significantly associated with any socio-demographic characteristics. At the bivariable-level, members of this class had significantly increased odds of daily cocaine and cannabis use. They also had significantly increased odds of experiencing moderate-severe levels of anxiety. These associations remained significant in a multivariable model, along with an emergent negative association with daily alcohol use (Table 4.5). Despite the high prevalence of cannabis use for pain management, the odds of moderate-severe pain were not significantly increased for this class relative to the others (bivariable p=0.125).

Table 4.4. Bivariable generalized estimating equations of factors associated with membership in each latent class (n = 897; observations = 2686)

Characteristic	**Class 1:** "Recreational"		**Class 2:** "Non-pain therapeutic"		**Class 3:** "Pain"		**Class 4:** "Pain +"	
	Odds Ratio (95% CI)	***p*-value**	**Odds Ratio (95% CI)**	***p*-value**	**Odds Ratio (95% CI)**	***p*-value**	**Odds Ratio (95% CI)**	***p*-value**
Socio-demographic factors								
Age	0.99 (0.98 – 1.00)	0.086	1.00 (0.99 – 1.01)	0.777	**1.01 (1.00 – 1.02)**	**0.038**	1.00 (0.98 – 1.01)	0.719
Male	**1.36 (1.08 – 1.71)**	**0.010**	1.08 (0.88 – 1.33)	0.471	**0.62 (0.48 – 0.80)**	**<0.001**	0.95 (0.69 – 1.29)	0.726
White	0.88 (0.71 – 1.09)	0.229	1.07 (0.88 – 1.31)	0.487	0.96 (0.75 – 1.23)	0.763	1.23 (0.91 – 1.66)	0.179
≥ High school education	1.22 (0.98 – 1.51)	0.076	0.84 (0.69 – 1.03)	0.089	1.01 (0.79 – 1.29)	0.928	0.92 (0.68 – 1.24)	0.582
Legal employment	1.04 (0.88 – 1.24)	0.624	0.93 (0.78 – 1.11)	0.423	0.99 (0.81 – 1.22)	0.943	1.03 (0.76 – 1.40)	0.858
DTES residency[1]	**1.22 (1.00 – 1.48)**	**0.049**	0.89 (0.74 – 1.06)	0.197	0.87 (0.69 – 1.09)	0.225	1.21 (0.89 – 1.64)	0.219
Homelessness[1]	**1.26 (1.01 – 1.59)**	**0.042**	0.94 (0.74 – 1.18)	0.588	**0.74 (0.56 – 0.99)**	**0.044**	1.13 (0.77 – 1.67)	0.531
Incarceration[1]	**1.53 (1.03 – 2.27)**	**0.033**	0.69 (0.45 – 1.06)	0.093	0.69 (0.44 – 1.09)	0.114	1.42 (0.80 – 2.52)	0.225
Substance use factors								
Daily alcohol use[1]	**1.59 (1.23 – 2.06)**	**<0.001**	0.87 (0.66 – 1.16)	0.348	0.78 (0.55 – 1.10)	0.156	0.62 (0.37 – 1.05)	0.075
Daily cocaine use[1]	1.18 (0.77 – 1.80)	0.444	0.84 (0.57 – 1.23)	0.365	0.57 (0.30 – 1.08)	0.084	**1.92 (1.13 – 3.26)**	**0.016**
Daily heroin injection[1]	1.20 (0.95 – 1.51)	0.126	0.94 (0.75 – 1.18)	0.600	0.78 (0.60 – 1.02)	0.074	1.11 (0.78 – 1.59)	0.556
Daily PO use[1]	**0.67 (0.47 – 0.97)**	**0.032**	0.89 (0.59 – 1.34)	0.576	**1.72 (1.07 – 2.77)**	**0.024**	1.21 (0.58 – 2.55)	0.609
Daily crack use[1]	1.01 (0.73 – 1.42)	0.931	1.05 (0.77 – 1.44)	0.765	0.85 (0.58 – 1.24)	0.397	1.09 (0.66 – 1.81)	0.741
Daily cannabis use[1]	**0.35 (0.29 – 0.42)**	**<0.001**	**1.20 (1.01 – 1.43)**	**0.039**	**1.54 (1.25 – 1.89)**	**<0.001**	**4.61 (3.30 – 6.44)**	**<0.001**

Characteristic	**Class 1:** "Recreational"		**Class 2:** "Non-pain therapeutic"		**Class 3:** "Pain"		**Class 4:** "Pain +"	
	Odds Ratio (95% CI)	***p*-value**	**Odds Ratio (95% CI)**	***p*-value**	**Odds Ratio (95% CI)**	***p*-value**	**Odds Ratio (95% CI)**	***p*-value**
Daily crystal meth use[1]	0.87 (0.69 – 1.11)	0.262	1.07 (0.85 – 1.35)	0.553	1.02 (0.78 – 1.33)	0.895	1.05 (0.70 – 1.57)	0.826
Health-related factors								
HCV-positive	1.02 (0.78 – 1.33)	0.895	0.94 (0.74 – 1.21)	0.647	1.21 (0.88 – 1.67)	0.249	0.81 (0.55 – 1.20)	0.295
HIV-positive	**0.58 (0.47 – 0.73)**	**<0.001**	**1.59 (1.31 – 1.94)**	**<0.001**	1.11 (0.86 – 1.42)	0.429	0.92 (0.67 – 1.25)	0.579
Mental illness diagnosis	**0.64 (0.51 – 0.79)**	**<0.001**	1.05 (0.86 – 1.29)	0.634	**1.59 (1.21 – 2.09)**	**0.001**	1.16 (0.84 – 1.61)	0.355
Non-fatal overdose[1]	1.09 (0.86 – 1.39)	0.462	1.19 (0.95 – 1.50)	0.125	**0.71 (0.54 – 0.94)**	**0.015**	0.77 (0.50 – 1.19)	0.245
Moderate-severe pain[2]	**0.57 (0.48 – 0.68)**	**<0.001**	**0.69 (0.59 – 0.82)**	**<0.001**	**2.95 (2.41 – 3.60)**	**<0.001**	1.26 (0.94 – 1.69)	0.125
Moderate-severe depression[2]	1.05 (0.82 – 1.34)	0.713	0.83 (0.66 – 1.05)	0.127	1.05 (0.80 – 1.39)	0.707	1.38 (0.96 – 2.00)	0.084
Moderate-severe anxiety[2]	0.83 (0.67 – 1.03)	0.096	0.99 (0.80 – 1.23)	0.930	0.94 (0.74 – 1.21)	0.648	**1.75 (1.25 – 2.44)**	**0.001**
Good-excellent perceived health	**1.31 (1.10 – 1.56)**	**0.002**	1.05 (0.87 – 1.25)	0.632	**0.70 (0.57 – 0.86)**	**0.001**	0.94 (0.70 – 1.26)	0.674
Addiction treatment[1]	1.07 (0.90 – 1.28)	0.440	**0.78 (0.65 – 0.93)**	**0.006**	1.18 (0.94 – 1.48)	0.145	1.27 (0.93 – 1.73)	0.136

Note: [1]Past six months; [2]Past week; 95% CI = 95% Confidence Interval; HCV = Hepatitis C virus; IQR = Interquartile Range; PO = Pharmaceutical opioid; Bold indicates statistical significance at $p<0.05$

Table 4.5. Multivariable generalized estimating equations of factors independently associated with membership in each latent class (n = 897; observations = 2686)

Characteristic	**Class 1:** "Recreational"		**Class 2:** "Non-pain therapeutic"		**Class 3:** "Pain"		**Class 4:** "Pain +"	
	Odds Ratio (95% CI)	***p*-value**	**Odds Ratio (95% CI)**	***p*-value**	**Odds Ratio (95% CI)**	***p*-value**	**Odds Ratio (95% CI)**	***p*-value**
Socio-demographic factors								
Age	0.99 (0.98 – 1.00)	0.156	--	--	--	--	--	--
Male sex	**1.62 (1.23 – 2.13)**	**0.001**	--	--	**0.65 (0.51 – 0.84)**	**0.001**	--	--
≥ High school education	--	--	0.86 (0.71 – 1.05)	0.147	--	--	--	--
Homelessness[1]	1.34 (0.97 – 1.83)	0.074	--	--	--	--	--	--
Incarceration[1]	--	--	0.71 (0.46 – 1.10)	0.127	--	--	--	--
Substance use factors								
Daily alcohol use[1]	**1.77 (1.26 – 2.48)**	**0.001**	--	--	--	--	**0.44 (0.23 – 0.82)**	**0.010**
Daily cocaine use[1]	--	--	--	--	--	--	**2.07 (1.11 – 3.85)**	**0.021**
Daily heroin injection[1]	--	--	--	--	**0.74 (0.55 – 0.98)**	**0.039**	--	--
Daily cannabis use[1]	**0.27 (0.21 – 0.34)**	**<0.001**	1.15 (0.96 – 1.38)	0.124	**1.58 (1.28 – 1.97)**	**<0.001**	**5.39 (3.68 – 7.91)**	**<0.001**
Health-related factors								
HIV-positive	**0.59 (0.45 – 0.77)**	**<0.001**	**1.57 (1.28 – 1.92)**	**<0.001**	--	--	--	--
Mental illness diagnosis	**0.72 (0.56 – 0.93)**	**0.013**	--	--	**1.39 (1.07 – 1.82)**	**0.015**	--	--
Non-fatal overdose[1]	--	--	--	--	**0.66 (0.49 – 0.89)**	**0.007**	--	--
Moderate-severe pain[2]	**0.52 (0.41 – 0.67)**	**<0.001**	**0.70 (0.58 – 0.83)**	**<0.001**	**2.76 (2.24 – 3.40)**	**<0.001**	--	--

Characteristic	Class 1: "Recreational"		Class 2: "Non-pain therapeutic"		Class 3: "Pain"		Class 4: "Pain +"	
	Odds Ratio (95% CI)	***p*-value**	**Odds Ratio (95% CI)**	***p*-value**	**Odds Ratio (95% CI)**	***p*-value**	**Odds Ratio (95% CI)**	***p*-value**
Moderate-severe anxiety[2]	0.79 (0.61 – 1.02)	0.073	--	--	--	--	**1.93 (1.37 – 2.72)**	**<0.001**
Good-excellent perceived health	1.21 (0.96 – 1.52)	0.106	--	--	0.81 (0.65 – 1.00)	0.051	--	--
Addiction treatment[1]	--	--	**0.83 (0.69 – 1.00)**	**0.049**	--	--	--	--

Note: [1]Past six months; [2]Past week; 95% CI = 95% Confidence interval; IQR = Interquartile Range; Bold indicates statistical significance at $p<0.05$; -- indicates variable was not included in the final multivariable model

4.4 Discussion

LCA was used to categorize 897 PWUD who use cannabis into groups defined by their motivations for cannabis use. Three classes encompassing over two-thirds (n = 1838; 68.4%) of the sample observations were characterized—in full or in part—by some type of therapeutic cannabis use (class 2: "Non-pain therapeutic"; class 3: "Pain"; class 4: "Pain +"), and all four classes included individuals who also used cannabis for intoxication (class-specific prevalence: 25-100%), demonstrating substantial overlap in therapeutic and non-therapeutic use. This finding is consistent with recent survey data from medical cannabis and general population samples in Canada (135) and the U.S. showing a high prevalence of engaging in both medical and recreational cannabis use, especially in jurisdictions where non-medical cannabis is also legal (326, 327).

Bivariable and multivariable analyses of class membership revealed several notable differences. First, daily cannabis use was significantly and positively associated with all three of the classes that endorsed therapeutic cannabis use (class 2: "Non-pain therapeutic"; class 3: "Pain"; class 4: "Pain +"), and negatively associated with the class characterized by non-medical cannabis use (class 1: "Recreational"). Coupled with the increased odds of accessing cannabis through a more consistent and reliable source such as a dispensary (class 2: "Non-pain therapeutic"; class 3: "Pain"; class 4: "Pain +"), compassion club (class 3: "Pain"), or the licensed medical cannabis system (class 4: "Pain +"), and not through informal/illicit sources (e.g., friend/family, private grower, or dealer), this trend suggests an intentional incorporation of cannabis into a daily routine among therapeutic users. Although daily use is often considered a component of problematic cannabis use (e.g., using the WHO ASSIST (328)), medical users tend to exhibit lower scores on cannabis use problems components of such screening/diagnostic tools, despite a higher likelihood

of daily use (329, 330). In contrast to the therapeutic groups, the current data suggests that cannabis use within the non-therapeutic class may reflect opportunistic cannabis use as part of a broader pattern of poly-substance use.

Second, despite increased odds of experiencing social and structural vulnerabilities (e.g., homelessness, incarceration) in class 1 ("Recreational"), several positive health outcomes (e.g., better self-perceived general health, less pain, less anxiety, lack of diagnosed mental illness, HIV-negative) were associated with membership in the class, while members of classes 2-4, characterized by therapeutic motivations for use, tended to exhibit poorer indicators of health. These patterns are likely indicative of frequent cannabis use to address poor health rather than poor health resulting from frequent cannabis use, as has been described previously (331, 332). These findings suggest that daily cannabis use among PWUD may signify an unmet healthcare need, such as under- or unmanaged chronic pain or mental illness. These correlations also point to the need to conduct clinical studies to better understand the independent effects of cannabis use on health and well-being, especially among marginalized PWUD.

The study setting and many other communities across Canada and the U.S. are experiencing an opioid overdose crisis rooted, in part, in inadequately or inappropriately-managed chronic pain (44, 333) and sparked by widespread exposure to an unregulated illicit opioid supply contaminated with potent opioid analogues (334). It is notable that members of class 3 ("Pain") had significantly lower odds of reporting a recent non-fatal overdose and daily heroin injection relative to the other classes. Previous analyses of state-level data from the U.S. have described reduced rates of opioid overdose linked to cannabis legalization (144, 281, 282), thought to emerge from individuals replacing opioids with cannabis for pain relief (150, 152, 155), but a more recent study presents updated population-level data to dispute this hypothesis (147), highlighting a clear

need for individual-level research. This study is the first, to my knowledge, to observe a lower likelihood of accidental overdose among high-risk PWUD using cannabis for pain. Although it is possible that cannabis is being used to reduce or offset the use of (drugs sold as) heroin to manage pain within this class, of note is the positive bivariable association with daily pharmaceutical opioid use (Table 4.4). It is possible that the negative association with overdose observed here could be partially explained by the use of regulated pharmaceutical opioids over unregulated and increasingly toxic opioids to manage pain (334, 335). Indeed, a recent cross-sectional analysis of urine drug screens collected from members of three Vancouver-based cohorts of PWUD (including the two examined here) shows that those who screened positive for THC had significantly lower odds of fentanyl exposure (336). The self-reported pharmaceutical opioid measure, however, represents all non-medical pharmaceutical opioid use—including diverted or not-as-prescribed use of pharmaceutically regulated opioids as well as unregulated counterfeit pills. This finding may also reflect an opioid-sparing effect of cannabis, whereby opioids may not be replaced, but the dosage or frequency of opioid required for analgesia is reduced with the use of cannabis (94). Cooper *et al.* recently tested this phenomenon in a blinded, placebo-controlled experimental study among 18 healthy adults, demonstrating significantly reduced pain responses from a sub-therapeutic dose (2.5 mg) of oxycodone when co-administered with smoked cannabis (5.6% THC (95)). Future research is needed to investigate exposure to opioids—including heroin, fentanyl, and other opioid analgesics—among PWUD with pain, including longitudinal studies to test the opioid-sparing hypothesis.

Finally, although class 4 ("Pain +") contained a higher proportion of observations in which cannabis was used as a strategy to reduce other high-risk substance use and manage symptoms of addiction, significantly different odds of daily use of opioids, crack, or methamphetamine were

not observed in this group. It was noted, however, that daily alcohol use was less apparent in this class. Previous research involving frequent users of crack-cocaine in this population demonstrates the intentional use of cannabis as a strategy to reduce frequency of crack use (337). Interestingly, engaging in daily use of cocaine was positively associated with membership in the "Pain+" class, possibly reflecting the strategy of using cannabis to "come down" from or stabilize the effects of cocaine (338, 339), including to facilitate sleep (339). Although there was a high proportion of observations in which cannabis was reportedly used for insomnia (98%), the lack of association with high frequency use of other stimulants in this class suggests further investigation is needed.

Notably, very few reports were observed from individuals accessing cannabis through legal routes—either the medical cannabis system (existing, in various forms, since 2001) or the new market for legal non-medical cannabis established in October 2018. The low levels of legal medical cannabis use might be a product of barriers to access that have been previous reported in other populations, including high prices, lack of consistent product supply and difficulties acquiring authorizations from physicians (340). As the current study period only included the first six weeks following non-medical cannabis legalization, it is too early to draw any conclusions from the lack of reports of accessing that market; it should be noted that only online legal sales were available during the study period. Illegal retail dispensaries were the most common source of cannabis and more likely to be accessed during membership in a therapeutic class, highlighting some possible negative consequences vulnerable PWUD may face as a result of restrictive approaches to cannabis legalization. Specifically, a financial barrier to the legal market is likely to arise when these illegal dispensaries are forced to closed—an intention the federal, provincial and municipal authorities have affirmed in planning implementation of the regulatory system for legal cannabis (341, 342). Future research should monitor the possible unintended health and social

impacts of eliminating these low-barrier sources of cannabis, including uptake of illicit opioids for pain relief.

The findings of this study should be interpreted in the context of several limitations. First, generalizability to the local PWUD population and to other groups of PWUD may not be warranted, and special attention should be paid to the older age (i.e., potential survivorship bias) and high representation of HIV-positive respondents through the amalgamation of ACCESS data. All data other than HIV and hepatitis C serostatus are based on self-report. However, the likelihood of responding according to social norms is minimized as self-report of illicit drug use is already an eligibility requirement to be interviewed for these studies. Furthermore, previous research supports that PWUD provide accurate and reliable accounts of their recent drug use history (297). Third, important details regarding cannabis consumed among participants, including cultivar ("strain"), cannabinoid concentrations, typical amount used, and mode(s) used to consume it, were not collected at the time of study. Specifically, as respondents were using cannabis ahead of legalization or engaging in illicit cannabis use in the short period of study following legalization, it was not possible to capture details about the composition of unregulated cannabis. This study also did not screen for cannabis use disorder or possible cannabis-related harms during the study period. These details would provide additional context to the therapeutic and non-therapeutic cannabis use profiles among PWUD and should be examined in future research. Fourth, reasons for cannabis use outside of those defined in the study questionnaire required re-categorization during data analysis in order to be considered for the latent class analysis. While most string responses mapped readily to a pre-determined category (e.g., "cut back on cigarettes" = Substitution), others were less clear (e.g., "menopause", "helps me function") and are subject to misclassification error. However, these responses accounted for <3% of all observations and are

unlikely to have meaningfully impacted the findings. Fifth, this analysis is based on the results of repeated surveys; although this study accounted for within-person observations over time, temporality within six-month interview periods could not be discerned and causality cannot be inferred from this analysis. Finally, although the final six weeks of the approximately 130-week study period occurred after Canada legalized non-medical cannabis, this regulatory change is unlikely to have substantially influenced the study findings. Personal possession and use of cannabis has long been decriminalized in Vancouver; no retail outlets selling legal cannabis existed in Vancouver during the study period.

4.5 Conclusion

In this study of PWUD contending with numerous social and structural vulnerabilities and experiencing high rates of drug-related harms, motivations for cannabis use were observed to occur on a spectrum from specific therapeutic (e.g., pain management) to broader non-medical use, with a high degree of overlap in between. These findings suggest that an individual's intentions around cannabis use may be closely linked to social and environmental adversities, co-occurring substance use, and states of physical and mental health. Certain indicators of poor physical and mental health were more likely among classes defined by at least some therapeutic use, suggesting that engaging in cannabis use for therapeutic purposes might signify an otherwise unmet healthcare need. Health care professionals working with marginalized PWUD should invite open conversations about cannabis use and intentions with patient to determine how medical cannabis might fit into a comprehensive treatment plan, or if a more suitable treatment is available—particularly in the context of health conditions tightly linked to long-term use of illicit drugs (e.g., pain, nausea/loss of appetite, insomnia, HIV symptoms). Although Canada has recently legalized non-medical

cannabis, almost no reports of PWUD accessing cannabis via legal non-medical or medical cannabis systems were observed. This finding highlights possible barriers to access among a population who may benefit from regulated products and who risk being further criminalized for their participation in the unregulated cannabis market.

Chapter 5: Frequency of cannabis and illicit opioid use among people who use drugs and report chronic pain: A longitudinal observational analysis

5.1 Introduction

Opioid-related morbidity and mortality continues to rise across Canada and the U.S. (22, 265). In many regions, including Vancouver, Canada—where drug overdoses were declared a public health emergency in 2016—the emergence of synthetic opioids (e.g., fentanyl) in illicit drug markets has sparked the unprecedented surge in death (343). The overdose crisis is also the culmination of shifting opioid usage trends (i.e., from initiating opioids via heroin to initiating with pharmaceutical opioids (344)) that can be traced back, in part, to the over-prescription of pharmaceutical opioids for chronic non-cancer pain (345).

Despite this trend of liberal opioid prescribing, certain marginalized populations experiencing high rates of pain, including PWUD, are lacking access to adequate pain management through the health care system (44, 346). Under- or untreated pain in this population can promote higher-risk substance use, as patients may seek illicit (i.e., unregulated heroin, counterfeit/diverted pharmaceutical opioids) opioids to manage pain (44, 346). In Vancouver, this practice poses a particularly high risk of accidental overdose, as almost 90% of drugs sold as heroin are estimated to be contaminated with synthetic opioids, such as fentanyl (347). Another less examined pain self-management strategy among PWUD is the use of cannabis (348). Unlike illicit opioids or illicit stimulants, the cannabis supply (unregulated or regulated) has not been contaminated with fentanyl, and cannabis is not known to pose a direct risk of fatal overdose (349). As a result, cannabis has been embraced by some, including emerging community-based harm reduction

initiatives in Vancouver, as a possible substitute for opioids in the non-medical management of pain and opioid withdrawal (189). Further, clinical evidence supports the use of cannabis or cannabinoid-based medications for the treatment of certain types of chronic non-cancer pain (e.g., neuropathic pain (91)).

As more jurisdictions across North America introduce legal frameworks for medical or non-medical cannabis, ecological studies have provided evidence to suggest that states providing access to legal cannabis experience population-level reductions in opioid use (139, 140, 142, 143, 350), opioid dependence (144, 282), and fatal overdose (144, 146, 281). However, these state-level trends do not necessarily represent changes within individuals (351), highlighting a critical need to conduct individual-level research to better understand whether cannabis use is associated with reduced use of opioids and risk of opioid-related harms, particularly among individuals with pain. Of particular interest is a possible opioid-sparing effect of cannabis, whereby a smaller dose of opioids provides equivalent analgesia to a larger dose when paired with cannabis. Although this effect has been identified in pre-clinical studies (94), much of the current research in humans is limited to patient reports of reductions in the use of prescription drugs (including opioids) as a result of cannabis use (150, 152-156, 158, 352-355). However, a recent study among patients on long-term prescription opioid therapy produced evidence to counter the narrative that cannabis use leads to meaningful reductions in opioid prescriptions or dose (159). These divergent findings confirm an ongoing need to understand this complex issue. To date, there is a lack of research from real-world settings exploring the opioid-sparing potential of cannabis among high-risk individuals who may be engaging in frequent illicit opioid use to manage pain. This study therefore sought to examine whether frequency of cannabis use was related to frequency of illicit opioid use among

PWUD who report living with chronic pain in Vancouver, Canada, the setting of an ongoing opioid overdose crisis.

5.2 Methods

Data for this study were derived from VIDUS and ACCESS studies, as described in Section 1.7.2.

5.2.1 Study sample

To examine the use of illicit opioids and cannabis for the possible self-management of pain among PWUD, the sample was restricted to individuals experiencing major or persistent pain. Beginning at follow-up period 17 (i.e., June 2014), the following question was added to the study questionnaire: "In the last six months, have you had any major or persistent pain (other than minor headaches, sprains, etc.)?" All study observations were included from each participant with pain beginning at the first follow-up interview in which they reported pain. For example, a participant who responded "no" to the pain question at follow-up 17 and "yes" at follow-up 18 would be included beginning at follow-up period 18.

5.2.2 Measures

5.2.2.1 Outcome measure

The outcome of interest was frequent use of illicit opioids, defined as reporting non-medical use of heroin or pharmaceutical opioids (diverted, counterfeit, or not-as-prescribed use) by injection or non-injection (i.e., smoking, snorting, oral administration) at least once daily on

average in the previous six months. This outcome was captured as described in Chapter 3, Section 3.2.2.1.

5.2.2.2 Primary independent variable

The main independent variable was cannabis use, captured through the question "In the last six months, have you used marijuana (either medical or non-medical) for any reasons (e.g., to treat a medical condition or for a non-medical reason, like getting high)?" Those who responded "yes" were also asked to estimate their average past six-month frequency of use according to the frequency categories described above. Frequency was further categorized as "daily" (i.e., ≥1/day), "occasional" (i.e., <1/month, 1-3/month, 1/week, 2-3/week), and "none" (no cannabis use; reference category).

5.2.2.3 Secondary variables

Several socio-demographic, substance use, and health-related factors with the potential to confound the association between cannabis use and illicit opioid use were also taken into consideration. Secondary socio-demographic variables included in this analysis were: sex (male *vs*. female); racial identity (white *vs*. other); age (in years); employment (yes *vs*. no); incarceration (yes *vs*. no); homelessness (yes *vs*. no); and residence in the DTES neighbourhood (yes *vs*. no). We considered the following substance use patterns: ≥ daily crack or cocaine use (yes *vs*. no); ≥ daily methamphetamine use (yes *vs*. no); and ≥ daily alcohol consumption (yes *vs*. no). Health-related factors that were hypothesized to bias the association between cannabis and opioids were: enrolment in opioid agonist treatment (i.e., methadone or buprenorphine/naloxone; yes *vs*. no); HIV serostatus (HIV-positive *vs*. HIV-negative); prescription for pain (including prescription opioids; yes *vs*. no); and average past-week pain level (mild-moderate, severe *vs*. none). The pain

variable was self-reported using a pain scale ranging from 0 (no pain) to 10 (worse possible pain). A rating of 3 was used as the cut-point for mild-moderate pain and 7 was used as the cut-point for moderate-severe pain. Although there is no universal standard for pain categorization, these cut-points are common and have been validated in other pain populations (356). Due to low cell count for mild pain (scores 1-3), this variable was collapsed with moderate pain (scores 4-6) to create the mild-moderate category. With the exception of sex and racial identity, all variables are time-updated and refer to behaviours and exposures in the six-month period preceding the interview. All variables except HIV status were derived through self-report.

5.2.3 Statistical analysis

First, differences in characteristics at baseline were explored according to daily cannabis use status (*vs.* occasional/none) using Chi-square tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. Then, bivariable associations between each independent variable and the outcome were estimated using generalized linear mixed-effects models (GLMM) with a logit-link function to account for repeated measures within individuals over time. Next, a multivariable GLMM was built to estimate the adjusted association between frequency of cannabis use and illicit opioid use. The least absolute shrinkage and selection operator (LASSO) approach was used to determine which variables to include in the multivariable model. This method uses a tuning parameter to penalize the model based on the absolute value of the magnitude of coefficients (i.e., L1 regularization), shrinking some coefficients down to 0 (i.e., indicating their removal from the multivariable GLMM). Four-fold cross-validation was used to determine the optimal value of the tuning parameter. GLMMs were estimated using complete cases (98.6-100% of observations for bivariable estimates; 99.0% of observations for multivariable estimates).

In the most recent interview period (June 1, 2017 to November 30, 2017), participants who reported any cannabis use in the previous six-month period were eligible for the follow-up question: "Why did you use it?" Respondents could select multiple options from a list of answers or offer an alternative reason under "Other". This data was analyzed descriptively and comparisons between ≥ daily and < daily cannabis users were analyzed using Chi-square or Fisher's test for small cell counts.

All analyses were conducted in R (version 3.5.0, R Foundation for Statistical Computing, Vienna, Austria) using RStudio (Version 1.1.456). All *p*-values are two-sided.

5.3 Results

Between June 1, 2014 and November 30, 2017, 1489 participants completed ≥1 study visit, of whom 1476 (99.1%) had complete data for all measures of interest and were considered potentially eligible for these analyses**.** In total, 1152 (78.0%) reported recent major or persistent pain during at least one six-month interview period and were included in this analysis. All observations from these individuals were considered from the first report of chronic pain, yielding 5350 study observations, equal to 2676.5 person-years of observation. There were 424 (36.8%) female participants in the analytic sample, and the median age at the earliest interview was 49.3 years (interquartile range [IQR]: 42.3 – 54.9).

Over the study period, a total of 410 (35.6%) respondents reported daily and 557 (48.4%) reported occasional cannabis use at least once in the previous six months; 455 (39.5%) reported daily illicit opioid use in the previous six months at least once. At baseline (i.e., the first interview in which chronic pain was reported), 583 (50.6%) participants were using cannabis either

occasionally (n = 322; 28.0%) or daily (n = 261; 22.7%), and 269 (23.4%) were using illicit opioids daily. At baseline, 693 (60.2%) participants self-reported a lifetime chronic pain diagnosis including bone, mechanical, or compressive pain (n = 347, 50.1%), inflammatory pain (n = 338, 48.8%), neuropathic pain (n = 129, 18.6%), muscle pain (n = 54, 7.8%), headaches/migraines (n = 41, 5.9%), and other pain (n = 53, 7.6%).

Table 5.1 provides a summary of baseline characteristics of the sample stratified by daily cannabis use status (yes *vs.* no). Daily cannabis use at baseline was significantly more common among men (72.8% *vs.* 60.4%, $p<0.001$) and significantly less common among those who used illicit opioids daily (15.3% *vs.* 25.7%, $p<0.001$).

Table 5.1. Baseline characteristics of 1152 PWUD with chronic pain, stratified by daily cannabis use

Characteristic	**≥ Daily cannabis use[1] (n, %)**		***p*-value**
	Yes = 261 (22.7)	**No = 891 (77.3)**	
Age			
Median (IQR)	49.0 (42.0– 54.5)	49.6 (42.4 – 48.5)	0.391
Sex			
Male	190 (72.8)	538 (60.4)	<0.001
Female	71 (27.2)	353 (39.6)	
Racial identity			
White	140 (53.6)	491 (55.1)	0.728
Non-white	121 (46.4)	400 (44.9)	
Employment[1]			
Yes	74 (28.4)	206 (23.1)	0.099
No	187 (71.6)	685 (76.9)	
Incarceration[1]			
Yes	15 (5.8)	49 (5.5)	0.985
No	244 (94.2)	840 (94.5)	
Homelessness[1]			
Yes	31 (11.9)	148 (16.3)	0.066
No	229 (88.1)	742 (83.4)	

Characteristic	≥ Daily cannabis use[1] (n, %)		*p*-value
	Yes = 261 (22.7)	No = 891 (77.3)	
Opioid agonist treatment[1]			
Yes	129 (49.4)	470 (53.3)	0.304
No	132 (50.6)	412 (46.7)	
Daily crack / cocaine use[1]			
Yes	43 (16.5)	142 (16.0)	0.916
No	218 (83.5)	748 (84.0)	
Daily Methamphetamine use[1]			
Yes	22 (8.4)	102 (11.5)	0.202
No	239 (91.6)	788 (88.6)	
Daily Alcohol use[1]			
Yes	28 (10.9)	83 (9.4)	0.467
No	229 (89.1)	803 (90.6)	
Daily illicit opioid use[1]			
Yes	40 (15.3)	229 (25.7)	<0.001
No	221 (84.7)	662 (74.3)	
HIV serostatus			
Positive	112 (42.9)	408 (45.8)	0.452
Negative	149 (57.1)	483 (54.2)	
Prescription for pain[1]			
Yes	139 (54.1)	413 (47.3)	0.064
No	118 (45.9)	461 (52.7)	
Average pain level[2]			
Severe	101 (38.5)	330 (37.0)	0.525
Mild-Moderate	139 (53.4)	474 (53.2)	0.618
None	19 (7.3)	77 (8.7)	

Note: [1]Refers to exposures/behaviours in the previous six months; [2]Past-week; IQR = Interquartile range; Cells for each variable might not add up to the column total, as participants can refuse to answer questions

In bivariable longitudinal analyses (Table 5.2), daily cannabis use was significantly and negatively associated with daily illicit opioid use (OR = 0.60; 95% CI: 0.40 – 0.90, p=0.013). Other factors that were negatively associated with daily illicit opioid use in crude analyses were: age (OR = 0.90 per year older; 95% CI: 0.88 – 0.92, p<0.001); employment (OR = 0.73, 95% CI: 0.54 – 0.99, p=0.044); HIV sero-positivity (OR = 0.41, 95% CI: 0.26 – 0.65, p<0.001); and having a prescription for pain medication (OR = 0.67, 95% CI: 0.51 – 0.88, p=0.004). Significant positive associations with daily illicit opioid use were detected for DTES residency (OR = 2.71; 95% CI:

1.99 – 3.69, p<0.001); homelessness (OR = 2.95; 95% CI: 2.06 – 4.20, p<0.001); incarceration (OR = 2.00, 95% CI: 1.16 – 3.46, p=0.013); daily crack or cocaine use (OR = 2.77, 95% CI: 1.94 – 3.96, p<0.001); daily methamphetamine use (OR = 6.63, 95% CI: 4.31 – 10.19, p<0.001); and pain level (OR = 1.33, 95% CI: 1.00 – 1.76, p=0.046 for mild-moderate pain; OR = 1.75, 95% CI: 1.28 – 2.38, p<0.001 for severe pain). As shown in Table 5.2, after adjustment for confounders, the odds of concomitant daily opioid use were significantly reduced, relative to non-users, during periods of daily cannabis use (Adjusted Odds Ratio [AOR] = 0.50, 95% CI: 0.33 – 0.74; p<0.001), but not during periods of occasional use (AOR = 0.94, 95% CI: 0.69 – 1.27; p=0.682).

Table 5.2. Unadjusted and adjusted generalized linear mixed effects models of factors associated with ≥ daily illicit opioid use among 1152 PWUD with chronic pain in Vancouver, Canada

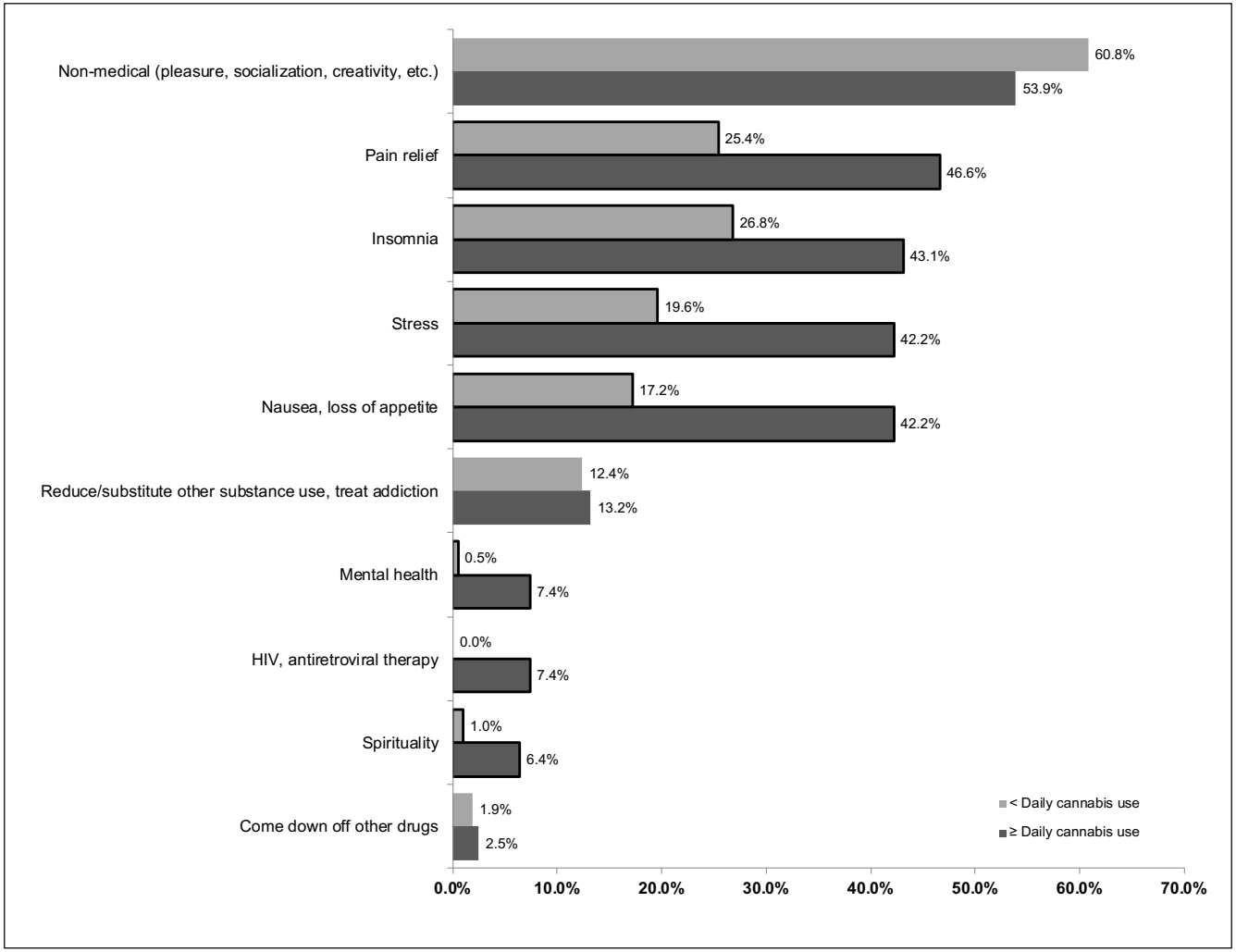
Characteristic	Odds Ratio (95% CI)			
	Unadjusted	*p*-value	Adjusted	*p*-value
Cannabis use[1]				
Occasional *vs.* None	1.04 (0.77 – 1.40)	0.818	0.94 (0.69 – 1.27)	0.682
≥ Daily *vs.* none	0.60 (0.40 – 0.90)	0.013	0.50 (0.33 – 0.74)	<0.001
Sex				
Male *vs.* Female	0.65 (0.41 – 1.03)	0.067	—	—
Age				
Per year older	0.90 (0.88 – 0.92)	<0.001	0.92 (0.90 – 0.94)	<0.001
Racial identity				
White *vs.* Non-white	0.98 (0.62 – 1.54)	0.920	--	--
Follow-up period				
Per 6-month interview interval	0.99 (0.94 – 1.05)	0.767	--	--
Downtown Eastside residency[1]				
Yes *vs.* No	2.71 (1.99 – 3.69)	<0.001	2.12 (1.54 – 2.90)	<0.001
Homelessness[1]				
Yes *vs.* No	2.95 (2.07 – 4.21)	<0.001	1.91 (1.33 – 2.73)	<0.001
Incarceration[1]				
Yes *vs.* No	2.00 (1.16 – 3.46)	0.013	1.27 (0.73 – 2.22)	0.393
Employment[1]				
Yes *vs.* No	0.73 (0.54 – 0.99)	0.044	0.79 (0.58 – 1.07)	0.134
Opioid agonist treatment[1]				
Yes *vs.* No	0.90 (0.66 – 1.22)	0.495	--	--

Characteristic	Odds Ratio (95% CI)			
	Unadjusted	*p*-value	Adjusted	*p*-value
Daily alcohol consumption[1]				
Yes *vs.* No	0.91 (0.57 – 1.44)	0.673	--	--
Daily crack/cocaine use[1]				
Yes *vs.* No	2.77 (1.94 – 3.96)	<0.001	2.74 (1.93 – 3.90)	<0.001
Daily methamphetamine use[1]				
Yes *vs.* No	6.63 (4.31 – 10.19)	<0.001	4.60 (3.02 – 7.02)	<0.001
HIV serostatus				
Positive *vs.* Negative	0.41 (0.26 – 0.65)	<0.001	0.48 (0.32 – 0.74)	<0.001
Pain prescription[1]				
Yes *vs.* No	0.67 (0.51 – 0.88)	0.004	0.86 (0.65 – 1.13)	0.274
Average pain level[2]				
Mild-Moderate *vs.* None	1.33 (1.00 – 1.75)	0.046	--	--
Severe *vs.* None	1.75 (1.29 – 2.37)	<0.001	--	--

Note: [1]Refers to exposures/behaviours in the previous six months; [2]Past-week; -- indicates variable was not included in the final multivariable model; 95% CI = 95% Confidence interval

Of the 414 daily and occasional cannabis users who were interviewed from June 1, 2017 to November 30, 2017, the most commonly reported motivations for use were for recreation (i.e., to get high, socialize; n = 237, 57.2%), to manage pain (n = 148, 35.7%), to aid with sleep (n = 144, 34.8%), to manage stress (n = 127, 30.7%), to treat nausea or loss of appetite (n = 123, 29.7%), and to reduce the use of other substances/treat addiction or withdrawal (n = 53, 12.8%). Self-reporting pain, insomnia, stress, nausea, mental health, HIV, and spirituality as reasons for use were all significantly more common for daily cannabis users relative to occasional users ($p<0.05$; Figure 5.1).

Figure 5.1. Self-reported reasons for cannabis use among daily (n = 204) and occasional (n = 210) cannabis-using PWUD with chronic pain, June 1, 2017 – November 30, 2017.



Note: Borders indicate Chi-square or Fisher's $p<0.05$; Fisher's test used for mental health and HIV comparisons.

5.4 Discussion

In this longitudinal study examining trends in past six-month frequency of cannabis and illicit opioid use, the odds of daily illicit opioid use were estimated to be reduced by about half among those who reported daily cannabis use. However, no significant association between occasional cannabis use and high-frequency opioid use was observed, suggesting that there may be an intentional therapeutic element associated with high-frequency cannabis use. This is supported by cross-sectional data from the sample in which certain intentions for cannabis were observed to differ according to cannabis use frequency. Specifically, daily users reported therapeutic motivations for cannabis use (including to address pain, stress, nausea, mental health, and symptoms of HIV or antiretroviral therapy, or to improve sleep) significantly more than occasional users, and non-medical motivations—although common among all users—were not more likely to be reported by daily users. Together, these findings suggest that PWUD experiencing pain might be using cannabis as an *ad hoc* strategy to reduce the frequency of opioid use.

In a recent study, Olfson and colleagues analyzed longitudinal data from a large U.S. national health survey and found that cannabis use increases, rather than decreases, the risk of future non-medical prescription opioid use in the general population (357). Their study provided important evidence to challenge the hypothesis that increasing access to cannabis facilitates reductions in opioid use. When compared to the findings of Olfson *et al.*, the current study reveals a contrasting relationship between cannabis use and frequency of opioid use, possibly due to inherent differences in the sampled populations and their motivations for using cannabis. Within the current study population, poly-substance use is the norm; HIV and related comorbidities are

common; and pain management through prescribed opioids is often denied, increasing the likelihood of non-medical opioid use for a medical condition (44, 348). Furthermore, the current study is largely focused on this relationship in the context of pain (i.e., by examining individuals with self-reported pain and accounting for intensity of pain). The current study findings align more closely with those of a recent study conducted among HIV-positive patients living with chronic pain, in which the authors found that patients who reported past-month cannabis use were significantly less likely to be taking prescribed opioids (160). While this finding could have resulted from prescription denial associated with the use of cannabis (or any illicit drug), daily cannabis users in the current study were actually *more* likely to have been prescribed a pain medication at baseline, and adjusting for this factor in a longitudinal multivariable model did not negate the significant negative association with frequent illicit opioid use.

The idea of cannabis as an adjunct or substitute to opioids in the management of chronic pain has recently earned more serious consideration among some clinicians and scientists. A growing number of studies involving patients who use cannabis to manage pain demonstrate reductions in the use of prescription analgesics alongside favourable pain management outcomes (150, 152-156, 352-355). For example, Boehnke *et al.* found that chronic pain patients reported a 64% mean reduction in the use of prescription opioids after initiating cannabis, alongside a 45% mean increase in self-reported quality of life (150). Degenhardt *et al.* found that, in a cohort of Australian patients on prescribed opioids for chronic pain, those using cannabis for pain relief (6% of patients at baseline) reported better analgesia from adjunctive cannabis (70% average pain reduction) than opioid use alone (50% average reduction (355)). However, more recent high-quality research has presented findings to question this narrative. For example, in the four-year follow-up analysis of the above Australian cohort of pain patients, no significant temporal

associations were observed between cannabis (occasional or frequent) and a number of outcomes including prescribed opioid dose, pain severity, opioid discontinuation, and pain interference (159). Thus, several other explanations for the current study results, aside from an opioid-sparing effect, are worthy of consideration.

Individuals with chronic pain regardless of their opioid use status were selected for inclusion in this study to avoid exclusion of individuals who may have already ceased illicit opioid use at baseline, as these individuals may reflect an important subsample of those already engaged in cannabis substitution. On the other hand, there may be important characteristics, unrelated to pain, among regular cannabis users in this study that predispose them to engage in less frequent or no illicit opioid use at the outset. Efforts were made to measure and control for these factors, but the possibility of a spurious connection cannot be ruled out. For example, individuals in this cohort who are consuming cannabis daily for therapeutic purposes may simply possess greater self-efficacy to manage health problems and control their opioid use (358). However, it is notable that this study's finding is in line with a previous study demonstrating that cannabis use correlates with lower frequency of illicit opioid use among a sample of people who inject drugs in California, all of whom used illicit opioids (42). The current study builds on this work by addressing chronic pain, obtaining detailed information on motivations for cannabis use, and examining longitudinal patterns.

Previous research involving medical cannabis patients demonstrates positive correlations between severity of pain and frequency of cannabis use (359, 360). In the current study, relative to occasional users, a significantly higher proportion of daily users endorsed cannabis use to address pain as well as other therapeutic purposes that may influence pain and pain interference. After pain, insomnia and stress were the second and third most commonly reported motivations

for therapeutic cannabis use (43% and 42%, respectively) among daily cannabis users. Inability to fall or stay asleep are common symptoms of pain-causing conditions (361), and experiencing these symptoms increases the likelihood of opioid misuse among chronic pain patients (362). The relationship between sleep deprivation and pain is thought to be bidirectional (361, 363), suggesting that improved sleep management may improve pain outcomes. Similarly, psychological stress (particularly in developmental years) is a well-established predictor of chronic pain (364) and is likely to also result from chronic pain. Thus, another possible explanation is that cannabis substitutes for certain higher-risk substance use practices in addressing these pain-associated issues without necessarily addressing the pain itself.

Notably, the current study findings are consistent with emerging knowledge of the form and function of the human endocannabinoid and opioid receptor systems. The endogenous cannabinoid system (ECS), consisting of cannabinoid receptors (CB1R and CB2R) and modulators (the endocannabinoids anandamide and 2-AG), is involved in key pain processing pathways (365). The co-localization of endocannabinoid and μ-opioid receptors in brain and spinal regions involved in antinociception (93), and the modification of one system's nociceptive response via modulation of the other (366, 367) has raised the possibility that the phytocannabinoid THC might interact synergistically with opioids to improve pain management. A recent systematic review and meta-analysis found strong evidence of an opioid-sparing effect for cannabis in animal pain models, but little evidence from nine studies in humans (94). However, the authors of the meta-analysis identified several important limitations potentially preventing these studies from detecting an effect, including low sample sizes, single doses, sub-therapeutic opioid doses, and lack of placebo (94). Since then, Cooper and colleagues published the results of a double-blind, placebo-controlled, within-subject study among humans in which they found that pain threshold and

tolerance were improved significantly when a non-analgesic dose of an opioid was co-administered with a non-analgesic dose of cannabis (95). Suggestive of a synergistic effect, these findings provided evidence for cannabis' potential to lower the opioid dose need to achieve pain relief (95).

Finally, there is pre-clinical and pilot clinical research to suggest that cannabinoids, particularly CBD, may play a role in reducing heroin cue-induced anxiety and cravings (128) and symptoms of withdrawal (123). Although preliminary, this research supports the idea that cannabis may also be used in stabilizing individuals undergoing opioid withdrawal; as an adjunct to prescribed opioids to manage opioid use disorder (OUD); or as a harm reduction strategy. Although this evidence extends beyond chronic pain patients, it warrants consideration here given the shared history of illicit substance use amongst the study sample. It is not clear what role harm reduction or treatment motivations may have played in the current study since daily and occasional users did not differ significantly in reporting cannabis use as a strategy to reduce or treat other substance use. The phenomenon of using cannabis as a tool to reduce frequency of opioid injection has been highlighted through qualitative work in this setting (164) and others (163, 165), but further research is needed to determine whether this trend is widespread enough to produce an observable effect. Clinical trials that can randomize participants to a cannabis intervention will be critical to establishing the effectiveness of cannabis for both pain management and as an adjunctive therapy for the management of OUD. This would begin to shed light on whether the current finding could be interpreted as causal, what the underlying mechanisms might be, and how to optimize cannabis-based interventions in clinical or community settings.

There are several important limitations to this study that should be taken into consideration. First, the cohorts are not random samples of PWUD, limiting the ability to generalize these findings to the entire community or to other settings. The older median age of the sample should especially be taken into consideration when interpreting these findings against those from other settings. Second, as discussed above, the possibility of residual confounding cannot be ruled out. Third, aside from HIV serostatus, this study relied on self-report for all variables, including substance use patterns. Previous work shows PWUD self-report to be reliable and valid against biochemical verification (297), and there is no reason to suspect that responses about the outcome would differ by cannabis use status, especially since this study was nested within a much larger cohort study on general substance use and health patterns within the community. Major or persistent pain, which qualified respondents for inclusion in this study, was also self-reported. The definition for chronic pain used for this study is likely to be more sensitive than other assessments of chronic pain (e.g., clinical diagnoses or assessments that capture length of time with pain). Although more than half (60%) of the sample reported ever having been diagnosed with a pain condition, it is possible that some of the included respondents would not have met criteria for a formal chronic pain diagnosis. A strength of this study is the ability to longitudinally assess the research question through the analysis of time-updated data, but it should be noted that these time-varying measures refer to exposures/behaviours in the previous six months, and it was not possible decipher temporality within these six-month intervals. For example, daily cannabis use and/or daily opioid use could have occurred closer to the start, end, sporadically, or consistently throughout these six-month periods. For this reason and others discussed above, the relationships observed here should be interpreted as correlations and not as confirmation that cannabis use reduces opioid use in this population. Finally, important dimensions of cannabis use (described in

limitations of Chapters 2 and 3) were not captured through the questionnaire. In particular, this study would have further benefitted from an examination of the outcome by number of times used per day and THC and CBD concentrations of cannabis consumed. Future research will need to address these gaps to provide a more detailed picture of the *ad hoc* use of cannabis for pain and other health concerns among PWUD.

5.5 Conclusions

In conclusion, this study provides preliminary observational evidence to suggest that high-frequency use of cannabis may be serving as an adjunct to or substitute for illicit opioid use among PWUD with chronic pain in a setting with high opioid-related morbidity and mortality. The findings of this study have implications for health care and harm reduction service providers. In chronic pain patients with complex socio-structural and substance use backgrounds, patients may be using cannabis as a means of treating health problems or reducing substance-related harm. In the context of the current opioid crisis and the recent roll-out of a national regulatory framework for cannabis in Canada, frequent use of cannabis among PWUD with pain may play an important role in preventing or substituting high-frequency illicit opioid use. PWUD describe a wide range of motivations for cannabis use, some of which may have stronger implications in the treatment of pain and OUD. Patient-physician discussions of these motivations may aid in the development of a treatment plan that minimizes the likelihood of high-risk pain management strategies, yet there remains a clear need for further training and guidance specific to medical cannabis use for pain management (368).

Chapter 6: Cumulative exposure to cannabis and other substances and all-cause mortality among people who use illicit drugs: A longitudinal analysis

6.1 Introduction

People who use illicit drugs (PWUD) experience elevated morbidity and mortality. Globally, over the past three decades, the burden of disease attributed to the use of alcohol and illicit drugs has increased along with the prevalence of substance use disorders (10). High-income countries in North America (i.e., the U.S. and Canada) experience the highest age-standardized drug-related burden of disease in the world (1,380 disability-adjusted life-years [DALYs] per 100,000 people), driven primarily by substance use disorders, cancers, HIV, and cirrhosis from chronic injection-related hepatitis C virus infection (10). A review of 67 cohort studies from 25 countries estimates that people who use injection drugs die at almost 15 times the rate of the general population—particularly from causes related to HIV and drug overdose (369).

The U.S. and Canada also experience the highest burden of disease attributable to cannabis use and dependence, at 57.1 DALYs per 100,000 people (301). Along with several jurisdictions across the U.S. (e.g., Colorado, California, Oregon, Washington), Canada has adopted a legal framework for the non-medical use of cannabis in an effort to regulate its production, sale, and use. There is limited longitudinal research to adequately inform whether cannabis use increases the risk of all-cause mortality in the general population (370). By applying a comparative risk assessment to Canadian epidemiological data, Fischer and colleagues estimated up to 267 cannabis-attributable motor vehicle accidents and up to 280 cannabis-attributable lung cancer deaths in Canada in 2010 (371). However, the overall consensus of epidemiological research on these longer-term harms is equivocal, with recent meta-analyses suggesting the risks associated

with cannabis use are lower than previously thought (e.g., for cannabis-related motor vehicle injuries and deaths (372, 373)) or not significantly elevated (e.g., for lung cancer (374)). While the mortality risks associated with other commonly used illicit drugs, including heroin and cocaine, are widely documented in previous epidemiological research involving PWUD (375, 376), studies evaluating cannabis use among these populations are lacking.

In regions across Canada and the U.S., the health of PWUD has been marked by evolving drug-related public health crises. In Vancouver, Canada, injection-related HIV infections and drug overdoses in the mid-1990s increased the risk of death among marginalized PWUD (192). Currently, a new generation of PWUD, along with those who survived the previous HIV- and overdose-related public health crises, are facing an opioid overdose crisis driven by the emergence of illicitly-manufactured fentanyl in the local drug market. Of the 1,537 suspected drug toxicity deaths recorded in the province of British Columbia in 2018, 87% were attributable—at least in part—to the use of fentanyl or a fentanyl analogue (e.g., carfentanil (28)).

Although the bulk of epidemiological research involving the health of PWUD has not prioritized the measurement and analysis of cannabis use as a possibly influential substance use exposure, emerging research suggests that cannabis is an important part of poly-substance use among many PWUD. In Chapter 4, it was demonstrated that PWUD report using cannabis for many different but often overlapping purposes, including recreation and relaxation, sleep, pain, symptoms of HIV and side-effects of antiretroviral therapy, symptoms of drug withdrawal, and mental health. Recently, community-led cannabis distribution programs have been implemented in low-income areas in Vancouver and other cities in the province in an effort to provide free or affordable cannabis to PWUD for therapeutic or harm reduction purposes (e.g., reduce the use of other substances, stabilize the effects of stimulants (188)).

Given these quickly developing interests in cannabis-based harm reduction initiatives during an era of legalized cannabis, it is important to understand how cannabis might affect long-term morbidity and mortality among PWUD. In addition, given the shift from an AIDS-related mortality crisis over a decade ago to the current overdose crisis, there is a need to re-analyze the risk of death associated with the use of other common substances over time. Modelling drug dose as a weighted sum of past and current doses is increasingly used in epidemiological studies when repeated measures are available and the impact of drug exposure on the outcome is hypothesized to change as a function of cumulative exposure and recency of exposure (377, 378). To date, no studies involving PWUD have employed this method to understand how historical and current patterns of substance use influence the risk of death. The objective of this study is to longitudinally assess how cumulative and current exposure to cannabis and other substances over time (expressed as a weighted cumulative average) influences the risk of death in a cohort of highly marginalized PWUD in Vancouver, Canada.

6.2 Methods

Data for this study were derived from VIDUS and ACCESS studies, as described in Section 1.7.2.

6.2.1 Study sample

All participants who recruited into VIDUS or ACCESS and completed ≥ 1 study interview between December 1, 2005 and November 30, 2017 were eligible for this analysis.

6.2.2 Measures

6.2.2.1 Outcome measure

The outcome of interest for this study was death from any cause. Dates and causes of death were obtained for participants during the study period using a confidential data linkage with the British Columbia Vital Statistics Agency. The Vital Statistics database classifies causes of death according to the International Classification of Diseases, 10th edition (ICD-10). Interview and death dates were used to calculate time-to-death or censorship. As each interview period covers experiences occurring over the previous six-month period, time 0 was defined as six months before the baseline interview date. Participants who were not identified as deceased during the study period were right-censored on the date of their last interview. Consistent with previous mortality analyses (379, 380), study participants who were identified as deceased >24 months after their last study interview were censored at the time of their last interview so as to avoid potential bias arising from relying on outdated and possibly inaccurate exposure data in relation to death for these individuals. Causes of death were classified according to the following six categorizations: (1) HIV-related; (2) overdose; (3) liver-related; (4) other (i.e., non-HIV, non-liver) non-accidental; (5) other (i.e., non-overdose) accidental; and (6) unknown (deaths for which the cause had not yet been determined at the time of data collection).

6.2.2.2 Weighted cumulative average exposure variables

The main exposures of interest for this analysis were frequency patterns of cannabis and other substance use over the study period. At baseline and each follow-up period, participants were asked about their use of cannabis, alcohol (including drinking alcohol, e.g., beer, spirits and non-drinking alcohol, e.g., mouthwash, hand sanitizer), heroin, pharmaceutical opioids (non-prescribed use), methamphetamine, cocaine, and crack in the previous six-month period. For each substance,

participants who endorsed any past six-month use were asked to estimate the average frequency of use during the previous six months: (1) less than once per month; (2) a few times per month; (3) once per week; (4) a few times per week; and (5) at least once per day. For each substance, these classifications were used to calculate the approximate proportion of days used in the past six-month period, from 0.00 (corresponding to no use) to 1.00 (corresponding to once per day; Appendix C.1). At this stage, the following substances were pooled together to create classes: heroin and pharmaceutical opioids (class: opioids); methamphetamine, cocaine, and crack (class: stimulants).

Using an approach similar to Bundy *et al.* (381), a weighted cumulative average exposure to each substance class was calculated from information reported in the current and all previous interviews, whereby the current proportion of substance use days was weighted by 0.5 and the cumulative average proportion from all previous interviews was weighted by 0.5 (Box 6.1). The weighted cumulative average exposure, expressed as a proportion from 0 to 1, accounts for each participant's substance use frequency history while placing more emphasis on frequency reported in the current follow-up period (381, 382). For example, if a participant endorsed daily cannabis use (1.00) at follow-up 4, <weekly use (0.15) at follow-up 3, >weekly use (0.58) at follow-up 2, and daily use (1.00) at follow-up 1, their weighted cumulative average exposure to cannabis use at follow-up 4 would be 0.79 [(1.00*0.5)+(((1.00+0.58+0.15)/3)*0.5)], whereas their unweighted cumulative exposure would have been 0.68 [(1.00 + 1.00 + 0.58 + 0.15)/4]. For each participant's first study interview, the measure for current frequency of use was used, as there was no previous frequency data to weight. These weighted cumulative averages were used to categorize participants into the following frequency categories: (1) No/low cumulative use, corresponding to a weighted cumulative average exposure of <0.15 (reference group); (2) Moderate cumulative use,

corresponding to a weighted cumulative average exposure of ≥0.15 to <0.75; (3) High cumulative use, corresponding to a weighted cumulative average exposure of ≥0.75. These categories were informed by *a priori* conceptualized clinical relevance and guided by the underlying distribution of the data (as demonstrated in Appendix C.1 for each participant's first observation). The continuous values of these variables were also preserved to examine their potential non-linear relationships with mortality.

Box 6.1. Formula for estimating the weighted cumulative average exposure

$$\boldsymbol{WCAE_i = w_f f_i + \frac{1-w_f}{i} \sum_{j=0}^{i-1} f_j}$$, where:

$\boldsymbol{WCAE_i}$ is the weighted cumulative average exposure at the ith interview,

$\boldsymbol{f_i}$ is the frequency of use (expressed as a proportion) at the ith interview, and

$\boldsymbol{w_f}$ is the weight assigned to the frequency of use at the ith interview.

6.2.2.3 Secondary variables

Several additional variables known or *a priori* hypothesized to influence the relationship between various substance use patterns and mortality were considered in the analysis. These included: age (per year older); sex (male *vs.* female); racial identity (white *vs.* non-white); legal employment (yes *vs.* no); homelessness (yes *vs.* no); incarceration (yes *vs.* no); any injection drug use (yes *vs.* no); enrolment in opioid agonist treatment (OAT; i.e., methadone or buprenorphine/naloxone) opioid use disorder (yes *vs.* no); and HIV serostatus (positive *vs.* negative). With the exception of sex and racial identity, all variables are time-updated and refer to current (age, year of follow-up, serostatus) or previous six-month (employment, homelessness, incarceration, injection drug use, opioid agonist treatment) exposures.

6.2.3 Statistical analysis

First, sample characteristics were examined at baseline. Chi-square tests (and Wilcoxon rank-sum test for age) were used to examine differences between those who did and did not use cannabis at baseline. Descriptive statistics were used to summarize the distribution of weighted cumulative average exposure to each class of drugs by respondents who used those drugs during the study period.

Second, a crude incidence density of mortality was calculated and the classification of deaths over the study period, and across time periods corresponding with the lead-up to and coinciding with the current overdose crisis, were descriptively summarized.

Then, the association between each independent variable and time-to-all-cause mortality was modelled using extended Cox models with time-varying covariates. As drug overdose deaths began increasing substantially in the province mid-way through the study period, a time (calendar year) interaction was checked for all cumulative weighted average substance use variables before building the adjusted model. Similarly, time interactions were checked (and reported if significant) for injection drug use, HIV status, and opioid agonist treatment throughout the study period. All variables of interest (and time-substance interaction terms, if significant) were added to a multivariable Cox model to examine adjusted associations with all-cause mortality.

To further examine the potential non-linear relationship between cumulative substance use exposures and all-cause mortality, a *post hoc* analysis was conducted in which the weighted cumulative average exposure variables were fit as restricted cubic splines to a multivariable Cox model. The number and placement of knots for each variable were determined by comparing the AIC. As a sensitivity analysis to test the robustness of the weighted cumulative average exposure variables, additional *post hoc* analyses were conducted with historical and current exposure

weights set to (1) 0.75 and 0.25, respectively (i.e., back-weighted), and (2) 0.25 and 0.75, respectively (i.e., front-weighted), and with no weights applied to the variables.

All analyses were conducted in R (Version 3.6.3, R Foundation for Statistical Computing, Vienna, Austria) using RStudio (Version 1.2.5033). All *p*-values are two-sided.

6.3 Results

Between December 1, 2005 and November 30, 2017, 2260 individuals were enrolled in this study, of whom 2211 (97.8%) had complete data for all variables of interest and were included in the analytic sample. These individuals were followed for a median of 92.6 months (interquartile range [IQR]: 35.8 – 134.1). As displayed in Table 6.1, the median age of the participants at baseline was 41.2 (IQR: 34.1 – 47.5) years, slightly more than one-third of participants (35.1%) were female, and approximately one half (57.1%) were white. Cannabis use in the previous six months was reported by 1220 (55.2%) of participants at baseline, 43.0% of whom (n = 525) endorsed at least daily use. Separating the sample by cannabis use at baseline revealed a slightly but significantly younger median age (41.0 *vs.* 41.5 years), a higher proportion of males (71.8% *vs.* 56.4%), lower levels of enrolment in opioid agonist treatment (39.3% *vs.* 44.9%), more pharmaceutical opioid use (33.6% *vs.* 26.8%), cocaine use (51.6% *vs.* 42.2%), crack use (79.8% *vs.* 67.9%), methamphetamine use (35.1% *vs.* 22.5%), and alcohol use (60.4% *vs.* 41.1%) in the cannabis use group (all $p<0.05$).

Table 6.1. Baseline characteristics of 2211 people who use illicit drugs enrolled in the VIDUS or ACCESS cohorts in Vancouver, Canada, stratified by cannabis use at first study visit

Characteristic	Overall n = 2211 (100)	Cannabis use[1]		*p*-value
		Yes n = 1220 (55.2)	No n = 991 (44.8)	
Age Median (IQR)	41.2 (34.1 – 47.5)	41.0 (33.6 – 47.4)	41.5 (34.8 – 47.8)	0.029
Sex				
Male	1435 (64.9)	876 (71.8)	561 (56.4)	<0.001
Female	776 (35.1)	344 (28.2)	435 (43.6)	
Racial identity				
White	1263 (57.1)	710 (58.2)	553 (55.8)	0.276
Non-white	948 (42.9)	510 (41.8)	438 (44.2)	
Employment[1]				
Yes	518 (23.4)	304 (24.9)	214 (21.6)	0.074
No	1693 (76.6)	916 (75.1)	777 (78.4)	
Homelessness[1]				
Yes	811 (36.7)	464 (38.0)	347 (35.0)	0.156
No	1400 (63.3)	756 (62.0)	644 (65.0)	
Incarceration[1]				
Yes	363 (16.4)	209 (17.1)	154 (15.5)	0.343
No	1848 (83.6)	1011 (82.9)	837 (84.5)	
HIV serostatus				
Positive	902 (40.7)	499 (40.9)	403 (40.7)	0.945
Negative	1309 (59.2)	721 (59.1)	588 (59.3)	
Opioid agonist treatment[1]				
Yes	925 (41.8)	480 (39.3)	445 (44.9)	0.009
No	1286 (58.0)	740 (60.7)	546 (55.1)	
Injection drug use[1]				
Yes	1912 (86.5)	1067 (87.5)	845 (85.3)	0.151
No	299 (13.5)	153 (12.5)	146 (14.7)	
Heroin use[1]				
Yes	1317 (59.6)	731 (59.9)	586 (59.1)	0.741
No	894 (40.4)	489 (40.1)	405 (40.9)	
PO use[1]				
Yes	676 (30.6)	410 (33.6)	266 (26.8)	<0.001
No	1535 (69.4)	810 (66.4)	725 (73.2)	
Cocaine use[1]				
Yes	1048 (47.4)	630 (51.6)	418 (42.2)	<0.001
No	1163 (52.6)	590 (48.4)	573 (57.8)	
Crack use[1]				
Yes	1647 (74.5)	974 (79.8)	673 (67.9)	<0.001
No	564 (25.5)	246 (20.2)	318 (32.1)	

Characteristic	Overall n = 2211 (100)	Cannabis use[1]		*p*-value
		Yes n = 1220 (55.2)	No n = 991 (44.8)	
Methamphetamine use[1]				
Yes	651 (29.5)	428 (35.1)	223 (22.5)	<0.001
No	1560 (70.5)	792 (64.9)	768 (77.5)	
Alcohol use[1]				
Yes	1144 (51.7)	737 (60.4)	407 (41.1)	<0.001
No	1067 (48.2)	483 (39.6)	584 (58.9)	

Note: [1]Refers to the six-month period preceding interview; 95% CI = 95% Confidence interval; IQR = Interquartile range; VIDUS = Vancouver Injection Drug Users Study; ACCESS = AIDS Care Cohort to evaluate Exposure to Survival Services; PO = Pharmaceutical opioids

Stimulants were the most commonly used substance class, with 2097 participants (94.8%) using cocaine, crack, or crystal methamphetamine at least once during the study. Another 1824 (82.5%) used illicit opioids at least once. The prevalence of alcohol and cannabis use was slightly lower at 78.9% (n = 1745) and 75.7% (n = 1674), respectively. Table 6.2 provides summary statistics of weighted cumulative exposure to each substance class among users of each class overall and during periods of active use throughout the study. As shown, stimulants were used at the highest frequency, with a 0.51 median (IQR: 0.20 – 0.87) cumulative average exposure among those who used stimulants at least once during the study, and 0.64 (IQR: 0.36 – 0.94) during periods of active use. This relatively small discrepancy between medians suggests that stimulant use was reported during most follow-up periods for these respondents. Cannabis and opioids were also used relatively frequently during periods of active use, with weighted cumulative exposure medians of 0.58 (IQR: 0.17 – 0.90) and 0.56 (IQR: 0.17 – 0.87), respectively. The weighted cumulative frequency of alcohol use was low in comparison (0.08 among users, and 0.15 during periods of any use).

Table 6.2. Distribution of substance use frequency[1] over the 12-year study period (2005-2017), by users of each substance, overall, and during periods of active use

Type of substance used	N (%)	Median	IQR
Illicit opioids, all study periods	1824 (82.5)	0.21	0.05 – 0.63
Illicit opioids, periods of active use		0.56	0.17 – 0.87
Stimulants, all study periods	2097 (94.8)	0.51	0.20 – 0.87
Stimulants, periods of active use		0.64	0.36 – 0.94
Alcohol, all study periods	1745 (78.9)	0.08	0.02 – 0.27
Alcohol, periods of active use		0.15	0.07 – 0.50
Cannabis, all study periods	1674 (75.7)	0.26	0.04 – 0.76
Cannabis, periods of active use		0.58	0.17 – 0.90

Note: [1]Weighted cumulative average frequency, expressed as a proportion of days used; IQR = Interquartile Range

In total, 362 individuals died over the study period; 34 of these deaths (9.4% of deaths; 1.5% of the sample) occurred during a period of loss to regular follow-up (i.e., >24 months without an interview). The remaining 328 participants, representing 14.8% of the sample, died over 15,485.5 person-years of follow-up for a crude mortality incidence density of 2.12 (IQR: 2.01 – 2.91) deaths per 100 person-years. Causes of death among the 328 participants who died during follow-up are summarized in Table 6.3. The first death in the study period occurred in January of 2006, thus the table is separated into three three-year periods (i.e., 2006-2009; 2010-2013; 2014-2017). The first period corresponds to a period preceding the overdose crisis, the middle period corresponds with the years leading up to the overdose crisis in which overdoses were increasing at relatively steady rates, and the final period corresponds with the current overdose crisis. The proportion of deaths was evenly distributed across study periods, with about one-third of deaths occurring in each period. The crude mortality rate was highest between 2006 and 2009, at 2.38 deaths per 100 person-years (95% CI: 1.93 – 2.82). The majority of deaths (n = 229; 69.8%) occurred among individuals who were living with HIV, and 13.7% of deaths overall (19.7% among those with HIV) were caused by HIV. The proportion of HIV-related deaths was highest during 2006-2010 (23.4%) and subsequently declined in later years (10.9% in 2010-2013; 6.5% in 2014-2017); however, it is worth noting that the number of deaths currently classified as ‘Unknown’ at

the time of study was substantially higher in the latter two periods, and some of these deaths may subsequently be classified as HIV-related. Most deaths (n = 121; 36.9%) were related to other non-accidental causes, including cancers (33.1%), lung diseases (17.4%), bacterial, viral, or fungal infections (17.4%), cardiovascular diseases or stroke (15.7%), causes related to mental illness and substance use disorders (9.1%), and kidney disease (4.1%). Overdoses accounted for 14.9% of deaths overall. The highest number of overdose deaths were recorded in the first time period (2006-2009); however, the proportion of overdose deaths are very likely to be underestimated in the latter periods (particularly between 2015-2017) as a result of their temporary classification as "Unknown" until a cause of death can be confirmed by a coroner. Sixteen (4.8%) participants died from non-cancer liver diseases, and all but one of these deaths occurred in the latter two periods. Other accidental causes, including fatal injuries from suicide (n = 5), assault (n = 3), and motor vehicle accidents (n = 2) accounted for a smaller proportion (3.4%) of deaths.

Table 6.3. Mortality rate and causes of death for 328 people who use illicit drugs in Vancouver, Canada who died between January 1, 2006 and November 30, 2017

	Overall	**2006 – 2009**	**2010 – 2013**	**2014 – 2017**
Crude mortality rate[1]	2.12	2.38	2.02	2.00
(95% CI)	(1.89 – 2.35)	(1.93 – 2.82)	(1.64 – 2.40)	(1.62 – 2.37)
Cause of death	328 (100.0)	111 (33.8)	110 (33.5)	107 (32.6)
HIV-related	45 (13.7)	26 (23.4)	12 (10.9)	7 (6.5)
Overdose	49 (14.9)	25 (22.5)	12 (10.9)	12 (11.2)
Liver-related	16 (4.8)	1 (0.9)	8 (7.3)	7 (6.5)
Other accidental	12 (3.7)	7 (6.3)	4 (3.6)	1 (0.9)
Other non-accidental	121 (36.9)	41 (41.0)	40 (37.7)	33 (31.4)
Unknown[2]	85 (25.9)	6 (5.4)	33 (30.0)	46 (43.0)

Note: [1]Per 100 person-years; [2]These deaths were classified as unknown at the time of data acquisition, but are subject to reclassification pending further coroner investigation; 95% CI = 95% Confidence interval

The results of bivariable and multivariable Cox regression are shown in Table 6.4. In bivariable analyses, relative to low or no cumulative exposure levels, a high cumulative exposure

to alcohol was associated with a significantly higher risk of mortality (hazard ratio [HR] = 1.76, 95% CI: 1.18 – 2.64), while high cumulative exposure to illicit opioids (HR = 0.63, 95% CI: 0.44 – 0.92) and moderate cumulative exposure to cannabis (HR = 0.74, 95% CI: 0.56 – 0.98) were associated with a significantly lower risk of mortality ($p<0.05$). The risk of mortality was not found to depend on calendar time for any of the cumulative substance use exposures.

In multivariable analyses (Table 6.4), after adjusting for HIV infection and other predictors of mortality, high levels of cumulative exposure to alcohol remained significantly and strongly associated with mortality (adjusted hazard ratio [AHR] = 1.84, 95% CI: 1.22 – 2.76), but the associations between high cumulative illicit opioid use and moderate cumulative cannabis use were rendered non-significant (AHR = 0.77, 95% CI: 0.51 – 1.16; AHR: 0.76, 95% CI: 0.57 – 1.00, respectively). Other factors that were significantly associated with increased risk of all-cause mortality in the multivariable analysis were age (AHR = 1.03, 95% CI: 1.01 – 1.02 for each additional year of age), HIV-positivity (AHR = 5.58 in 2005 – 2009; 2.48 in 2010 – 2013; 3.88 in 2014 – 2017; all $p<0.001$), and recent injection drug use (AHR = 1.40, 95% CI: 1.07 – 1.85). Additional factors found to be significantly associated with a decreased risk of all-cause mortality were recent employment (AHR = 0.44, 95% CI: 0.31 – 0.63) and enrolment in opioid agonist treatment from 2014 onwards (AHR = 0.34, 95% CI: 0.32 – 0.65).

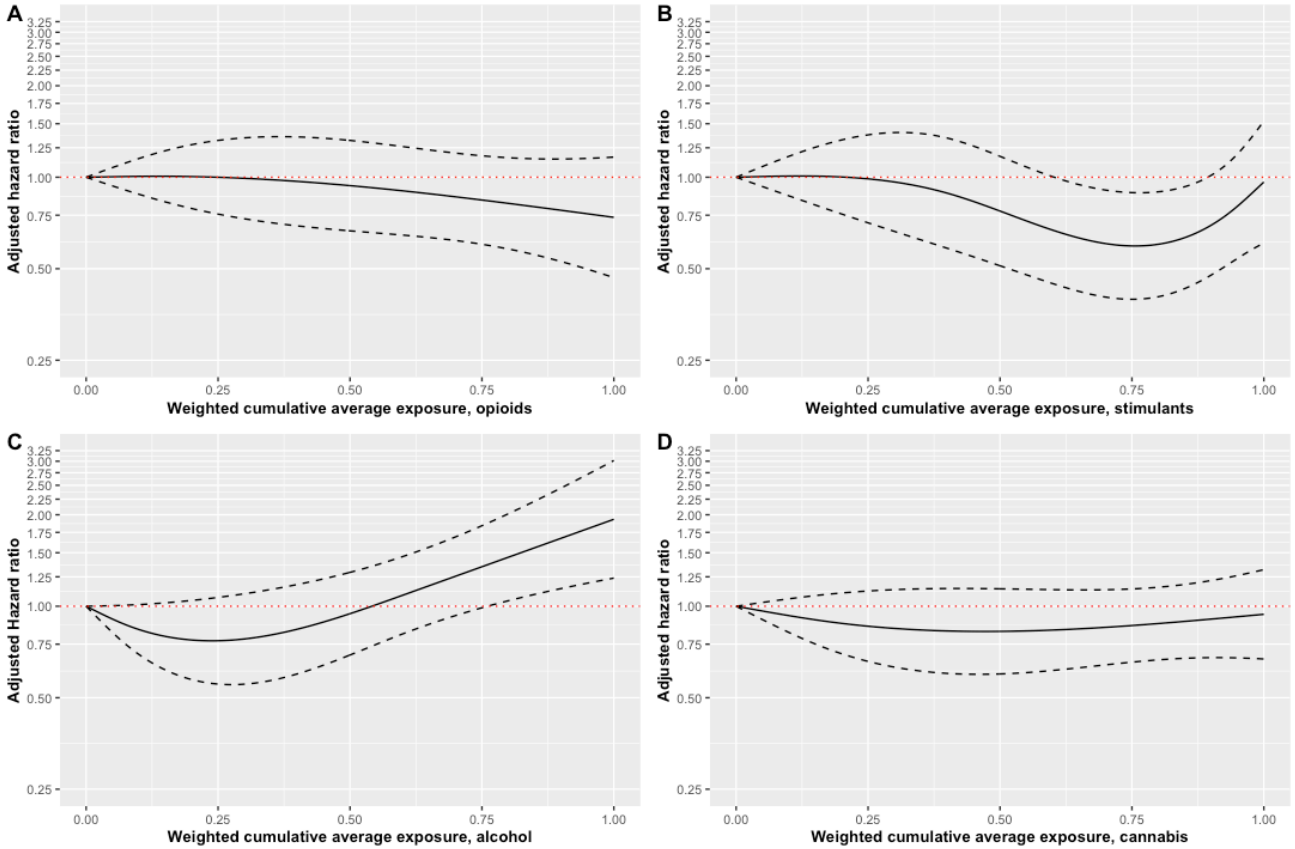
Table 6.4. Bivariable and multivariable associations with all-cause mortality among 2211 PWUD in Vancouver, Canada between December 1, 2005 and November 30, 2017

Variable	All-cause mortality			
	Hazard Ratio (95% CI)	*p*-value	Adjusted Hazard Ratio (95% CI)	*p*-value
Socio-demographic factors				
Sex				
Male *vs.* female	1.11 (0.88 – 1.41)	0.376	1.09 (0.85 – 1.40)	0.488
Age				
Per year increase	1.03 (1.02 – 1.05)	<0.001	1.03 (1.01 – 1.04)	<0.001
Racial identity				
White *vs.* non-white	0.94 (0.75 – 1.17)	0.567	1.00 (0.79 – 1.26)	0.972
Employed[1]				
Yes *vs.* no	0.40 (0.28 – 0.57)	<0.001	0.44 (0.31 – 0.63)	<0.001
Homeless[1]				
Yes *vs.* no	0.98 (0.73 – 1.31)	0.883	1.21 (0.90 – 1.64)	0.210
Incarcerated[1]				
Yes *vs.* no	0.86 (0.56 – 1.35)	0.519	0.98 (0.62 – 1.56)	0.943
Injection drug use[1]				
Yes *vs.* no	1.12 (0.89 – 1.40)	0.346	1.40 (1.07 – 1.85)	0.015
OAT, year (*vs.* no OAT)[1]				
OAT (2005 – 2009)	1.69 (1.17 – 2.45)	0.005	1.48 (0.95 – 2.31)	0.082
OAT (2010 – 2013)	0.69 (0.49 – 0.98)	0.036	0.94 (0.64 – 1.38)	0.746
OAT (2014 – 2017)	0.49 (0.34 – 0.70)	<0.001	0.45 (0.32 – 0.65)	<0.001
HIV positive, year (*vs.* HIV-)				
HIV+ (2005 – 2009)	7.14 (4.73 – 10.79)	<0.001	5.58 (3.55 – 8.77)	<0.001
HIV+ (2010 – 2013)	2.55 (1.78 – 3.65)	<0.001	2.48 (1.72 – 3.58)	<0.001
HIV+ (2014 – 2017)	3.50 (2.67 – 4.60)	<0.001	3.88 (2.92 – 5.15)	<0.001
Substance Use				
Illicit opioid use[2]				
Moderate *vs.* none/low	0.79 (0.61 – 1.02)	0.075	0.92 (0.69 – 1.22)	0.557
High *vs.* none/low	0.63 (0.44 – 0.92)	0.015	0.77 (0.51 – 1.16)	0.211
Stimulant use[2]				
Moderate *vs.* none/low	0.91 (0.70 – 1.19)	0.501	0.82 (0.62 – 1.10)	0.183
High *vs.* none/low	0.85 (0.62 – 1.15)	0.295	0.77 (0.54 – 1.09)	0.144
Alcohol use[2]				
Moderate *vs.* none/low	0.78 (0.57 – 1.05)	0.100	0.89 (0.66 – 1.21)	0.466
High *vs.* none/low	1.76 (1.18 – 2.64)	0.006	1.84 (1.22 – 2.76)	0.004
Cannabis use[2]				
Moderate *vs.* none/low	0.74 (0.56 – 0.98)	0.033	0.76 (0.57 – 1.00)	0.054
High *vs.* none/low	0.91 (0.67 – 1.23)	0.520	0.89 (0.65 – 1.21)	0.455

Note: [1]Refers to the six-month period preceding interview; [2]Substance use variables are time-updated and refer to current (0.5 weight) and cumulative previous (0.5 weight) frequency of use; 95% CI = 95% Confidence interval

Figure 6.1 depicts the substance use variables modelled continuously as restricted cubic splines to allow for non-linear relationships with all-cause mortality. For opioids (Figure 6.1A) and stimulants (Figure 6.1B), the risk of death crosses below the reference point (AHR=1.00) weighted cumulative average exposures of 0.25-0.30. For opioids, the 95% CI of the AHR is distributed on either side of 1.00 for all values of exposure, demonstrating a lack of statistical significance throughout. These findings were robust to differential weighting (Appendix C.2). For stimulants, the negative association reverses back at an exposure of approximately 0.75 to converge towards the reference point. Weighted cumulative average stimulant exposures between 0.60 and 0.85 are shown to be negatively associated with mortality with 95% confidence. Similar trends are observed in the front- and back-weighted splines (Appendix C.3). Alcohol takes on a J-shaped relationship with all-cause mortality, in which an initial reduction in the risk estimate reverses quickly (at exposures of approximately 0.15), crosses back over the reference point at an exposure of 0.55 and continues to climb, reaching significance at exposures of 0.75 and higher (Figure 6.1C). The estimated risk of death for increasing cumulative alcohol exposure appears sensitive to alternative weighting such that placing more weight on previous alcohol use increases the magnitude of association with mortality (e.g., AHR = 2.25 at maximum exposures) with significance reached at lower levels (beginning at exposure levels of 0.65; Appendix C.4). The relationship between cannabis and all-cause mortality (Figure 6.1D) is shallowly U-shaped, with the risk decreasing slightly as cumulative exposures increase up to 0.40, before reversing direction and converging back towards the reference point. At no point is the AHR estimated below 1.00 with 95% confidence, consistent with a lack of statistical significance. Similar trends are observed for the front- and back-weighted variables (Appendix C.5).

Figure 6.1. The non-linear relationship between weighted cumulative average exposure to each substance class and all-cause mortality, modelled continuously using restricted cubic splines.



Note 1: Panel A = opioids, panel B = stimulants, panel C = alcohol, panel D = cannabis. **Note 2:** Estimates are adjusted for age, sex, race, employment, incarceration, homelessness, opioid agonist treatment, injection drug use, and HIV status. **Note 3:** Restricted cubic splines for opioids, cannabis, and alcohol have three knots; stimulants has four knots. **Note 4:** Solid line indicates the adjusted hazard of death at a given weighted cumulative average proportion of substance use (reference is 0); dashed lines indicate 95% confidence intervals around this estimate; estimates are plotted on the log scale.

6.4 Discussion

In this analysis of all-cause mortality over a 12-year study period among over 2000 PWUD, the cumulative average exposure to four major substance classes, including cannabis, were quantified and analyzed as potential predictors of death. The findings of this study demonstrate that, before controlling for additional factors including HIV status, enrolment in opioid agonist treatment, and injection drug use, moderate cumulative exposure to cannabis and high cumulative exposure to opioids are associated with reduced risk of death, while high cumulative exposure to alcohol is associated with increased risk of death. However, after controlling for these other strong predictors of mortality, only high cumulative exposure to alcohol over the study period increased the risk of mortality in this cohort of highly marginalized individuals engaging in poly-substance use.

This analysis was designed with a specific objective of measuring cannabis as a potential exposure of interest. While the risk of death associated with other commonly used substances including stimulants, opioids, and alcohol among marginalized PWUD have been studied across a number of settings (383-388), cannabis is rarely considered in such analyses. A literature search revealed two studies of similar populations against which to compare the current findings. Fuster and colleagues modelled time-to-death associated with cannabis use upon admission to detoxification services in a cohort of cocaine, opiate, or alcohol-dependent patients in Spain (389). Gjersing and Bretteville-Jensen evaluated time-to-death among polysubstance users in various Norwegian cities according to a number of substance use patterns at study baseline, including *any* and *frequent* cannabis use (390). Although the current study used a different approach by estimating the impact of a time-updated weighted cumulative average exposure to cannabis over

the study period, it shares a similar conclusion to both studies: cannabis use does not appear to increase the risk of death among those engaging in riskier forms of substance use. As even extremely high THC doses are not thought to cause fatal toxicity in humans (349), the lack of positive association with mortality is an expected finding.

However, beyond simply not increasing the risk of mortality, there was rationale to believe that the risk of death may actually be reduced with increasing cumulative exposure to cannabis given previous observations of improved indicators of risk associated with high-frequency cannabis use among PWUD in this setting. For example, in Chapter 5, it was shown that daily cannabis use was associated with significantly lower odds of daily illicit opioid use among PWUD with persistent pain in this cohort , and Reddon *et al.* examined substance use data from a similarly structured cohort of young (aged 14-26) PWUD in Vancouver and reported that daily cannabis use was associated with significantly slower transition to injection drug use (391). There has also been a growing interest in using cannabis as a harm reduction strategy in the local setting, as evidenced by uptake of cannabis distribution programs in the DTES neighbourhood (188). While previous research in this setting would suggest some possible therapeutic and harm reduction benefits associated with cannabis, these findings have been limited to periods of high frequency cannabis use (231, 337, 392). In contrast, more occasional use may be indicative of opportunistic supplementation of cannabis into poly-substance use patterns, as was explored through the latent class analysis in Chapter 4. This hypothesis was reinforced by the baseline characteristics of participants in the current study, in which recent pharmaceutical opioid, crack, cocaine, methamphetamine, and alcohol use was significantly higher among recent cannabis users (the majority of whom were using occasionally). Although a lower risk of death at the bivariable-level was recorded among those cumulatively exposed to moderate levels of cannabis, this estimate is

unlikely to reflect a true relationship with cannabis use given the lack of a dose-response effect. The association also fell just short of statistical significance (p=0.054) after controlling for co-occurring socio-demographic, substance use, and clinical exposures. Chapter 4 used data from the recent cannabis-using members of this cohort to identify four latent classes of cannabis users based on their motivations for use; of note, those engaging in cannabis use primarily for recreational purposes used cannabis less frequently and exhibited indicators of improved physical and mental health, while those self-medicating with cannabis were more likely to use cannabis daily and generally exhibited poorer health. It is hypothesized that the reduced risk of death initially observed during periods of moderate cannabis use was driven by younger age and fewer comorbidities among occasional cannabis users before controlling for other factors that correlate with poorer health (e.g., age, injection drug use, HIV infection). The *post hoc* analysis revealed an additional finding that was masked in the primary multivariable analysis: exposure to stimulants at weighted cumulative averages between 0.60 and 0.85 was significantly negatively associated with all-cause mortality. This finding might reflect a reduced ability or desire to engage in high-frequency stimulant use during periods of severe morbidity before death, which would create the illusion that higher frequency stimulant use reduces the risk of mortality. Although, had this been the case, a stronger negative association for the front-weighted variable in sensitivity analysis would likely have emerged. As these findings were robust to alternative weighting of the variable, additional exploration will be required to understand potential underlying explanations.

High exposure to alcohol was the only cumulative substance use pattern found to be significantly associated with death over the study period. Several epidemiological studies across a diversity of settings have examined the risk of mortality associated with high frequency alcohol drinking among PWUD and produced mixed findings. For instance, a previous study using time-

updated data from the current cohort study found that recent binge alcohol use—defined as using a higher amount than usual—was independently associated with mortality (388), and two measures of hazardous alcohol drinking were found to predict mortality over a three-year study period among PWUD with HIV in St. Petersburg, Russia (393). In contrast, in a two-year study of Vietnamese men who inject drugs, increasing past 30-day alcohol use days at each interview period did not significantly increase the risk of death (394), and mortality risk over five years was not significantly increased by baseline or time-updated measurements of heavy drinking (measured through a modified version of the AUDIT survey instrument) in a cohort of people who inject drugs in Melbourne, Australia (395). The current finding suggests that *cumulative* exposure alcohol may be an important contributing factor to all-cause mortality among PWUD, with historical patterns of alcohol use as particularly relevant predictors—a finding that was further strengthened by back-weighting the variable in sensitivity analysis. Alcohol is associated in a dose-dependent fashion with a wide range of acute and chronic potentially life-threatening harms, including accidents and injuries, and development of cancers, heart disease, diabetes, and liver problems (396), and these harms tend to be magnified by socioeconomic inequalities (397, 398). It is worth noting that the alcohol use frequency measurement included exposure to non-beverage forms of alcohol (e.g., rubbing alcohol, mouthwash). These forms of alcohol are highly concentrated and may further exacerbate acute (e.g., unintentional injury) and chronic (e.g., liver, kidney damage) health problems (399, 400). Indeed, a simple descriptive examination revealed that 20% of those who consumed non-beverage alcohol in the study died during follow-up, compared to 13% of those who consumed only licit forms of alcohol. Given harm reduction services are primarily designed for the use of drugs by smoking or injection, PWUD who drink alcohol regularly, including non-beverage forms of alcohol, may face additional risks that are not

being met by harm reduction services. This finding emphasizes the need to further fund and expand community-based alcohol harm reduction initiatives (e.g., managed alcohol programs, drop-in centres that allow on-site drinking (401, 402)) for PWUD who engage in high-risk drinking.

It is notable that, despite that the current sample was not restricted to PWUD who used opioids (about 20% had never used opioids during the study period), a significant inverse association between OAT enrolment and mortality was apparent in the latter period of the study (2014 – 2017), coinciding with the emergence of fentanyl and the eventual declaration of a provincial public health emergency in 2016 (343). This finding suggests a strong protective effect of OAT against the toxic unregulated drug supply. It also aligns with a recent study by Pearce *et al.,* who analyzed risk of mortality for all patients accessing OAT in the province from 2010 to 2018 and found that the relative risk of all-cause mortality associated with being off treatment increased from 110% to 160% after the emergence of fentanyl and 240% after the public health emergency declaration (403).

A major strength of the current study was the ability to examine up to 12 years of time-updated data from over 2000 PWUD linked to a comprehensive source of mortality data. This study is distinct in that it characterized substance use by cumulative exposure during the study, rather than by a single measurement at baseline or time-updated measurements of use in a period immediately preceding death or censorship. In the former scenario, the possibility of detecting a true relationship between the exposure and outcome deteriorates as time passes; and in the latter scenario, there is the potential for a true relationship to be obscured by abrupt changes in substance use patterns associated with severe morbidity immediately preceding death (e.g., ceasing high frequency drug use in the time period closely preceding death due to severe morbidity, hospitalization, etc.). Efforts were made to mitigate each of these methodological challenges

through calculating weighted cumulative average substance use exposures that account for historical usage patterns while still prioritizing more recent exposures (382). However, the current study also has a number of limitations to be taken into consideration. First, despite extensive outreach associated with study recruitment procedures, VIDUS and ACCESS are not random samples of PWUD in Vancouver and these findings may not necessarily generalize to the population of PWUD in Vancouver or other settings. In particular, the oversampling of PWUD living with HIV and the older median age of this study sample should be taken into consideration. For example, a sample of younger PWUD from this or a similar setting would likely have different substance use trends (e.g., a higher baseline prevalence of methamphetamine use (404)) and a different distribution of mortality causes (e.g., a lower proportion of deaths related to other non-accidental causes and a higher proportion of deaths related to overdoses and other accidental causes (385), possibly resulting higher mortality rate during the period of time corresponding with the overdose crisis). Second, aside from HIV serostatus and mortality, this study relied on self-reported measures for all exposures. Although self-reported substance use and other measures in such studies are shown to be reasonably valid and reliable (297), they are nonetheless subject to issues of recall and reporting according to perceived social desires. Finally, this study was restricted to the cause of death information available from the BC Vital Statistics Database at the time of analysis. Many of the deaths currently classified as "Unknown", particularly in recent years, will later be updated to a specific cause. It is probable that a large percentage of these unknown deaths will later be categorized as overdose deaths, but it is currently not possible to analyze them as such.

6.5 Conclusion

Interest in the use of cannabis as a harm reduction strategy among marginalized PWUD has grown substantially in recent years. An analysis of data from over 2000 PWUD in Vancouver from 2005 to 2017 did not reveal a significant (positive or negative) association between cumulative exposure to cannabis and all-cause mortality. However, a high cumulative exposure to alcohol greatly increased the risk of death in this population, highlighting the need for alcohol-specific harm reduction education and programming to be integrated with opioid- and stimulant-specific harm reduction interventions. Future research should continue to monitor shifts in cannabis use patterns, particularly in this new era of cannabis distribution and cannabis legalization in Canada.

Chapter 7: Conclusion

7.1 Summary of study rationale and research objectives

While rates of opioid-associated overdose morbidity and mortality have recently risen to unprecedented levels across Canada, the non-medical use of cannabis has become increasingly normalized within social and political spheres, culminating in its legalization by the federal government in 2018. In the province of British Columbia, the overdose crisis has been concentrated among marginalized PWUD in Vancouver's DTES who also face a number of social and structural adversities, including precarious access to stable housing and employment and the ongoing stigmatization and criminalization of illicit drug use. Owing to its relative innocuousness compared to other drugs such as heroin, methamphetamine or crack cocaine, the use of cannabis among PWUD has historically been assumed to be prevalent but not considered worth examining in much detail. Yet, against a rapidly developing scientific understanding of the endogenous cannabinoid system (ECS) and its role in several neuro-biological pathways that interact with the opioid system, population-level research has produced compelling evidence for the study of cannabis use among those at high risk of opioid overdose. While studies have examined interrelationships between cannabis use and opioid use among medical cannabis and chronic pain patients, PWUD suffer at disproportionate rates from opioid dependence and overdose but have been largely overlooked as a population of interest in this previous research.

After an extensive review of the literature, this dissertation sought to compile several years' worth of data from two cohorts of marginalized PWUD in Vancouver to understand cannabis use patterns and motivations for use in this population, and to investigate relationships between

cannabis use and health outcomes that are closely linked with the current opioid crisis and hypothesized to be modifiable by cannabis use if an underlying biological effect were to exist.

7.2 Summary of research findings and unique contributions

7.2.1 Cannabis use during medication-based treatment of opioid use disorder

Management of OUD through pharmacotherapy is one of the strongest clinical interventions to prevent opioid overdose (60, 65, 67, 267). Cannabis is commonly used extra-medically by patients undergoing treatment for OUD (166, 232), including for the possible self-management of opioid craving and withdrawal (119), yet there is no clear consensus among clinicians and researchers about the impact of cannabis use on treatment outcomes. While some programs regularly monitor for co-use of drugs (including cannabis) and may take punitive action (e.g., denial of take-home doses or termination of prescriptions) if presented with evidence of patient cannabis use (168), other programs view cannabis use as relatively benign and some clinicians who specialize in addiction treatment even provide authorization for the medical use of cannabis while on MOUD (170). Accordingly, the work for this dissertation began with a systematic review of peer-reviewed epidemiological studies to better understand how cannabis use during MOUD impacts critical patient outcomes including continued opioid use, opioid craving and withdrawal, treatment adherence, and treatment retention. I build on the work of a previous systematic review of cannabis during MMT (258) by widening the scope of research to the three most common pharmacotherapies for management of OUD (i.e., methadone, buprenorphine, and naltrexone) and by including additional key outcomes hypothesized to be influenced by cannabis—notably, opioid craving and withdrawal.

In total, I reviewed and summarized the findings of 38 studies documenting the relationship between cannabis use and treatment outcomes for patients on methadone, buprenorphine, or naltrexone treatment for OUD. These studies produced inconsistent evidence of any relationship between cannabis use and treatment outcomes: no significant association was observed in the majority of studies, while a smaller number of studies produced evidence suggestive of possible detrimental and beneficial effects of cannabis use during MOUD. I also noted several common limitations to the included studies and compared findings across treatment outcomes, modalities, patient populations, and methodological approaches to guide priorities for future research. Overall, the findings of Chapter 2 suggest that concurrent cannabis use is unlikely to independently undermine treatment progress for patients on MOUD, and a patient-centered approach to cannabis might best support these patients in meeting their treatment goals.

7.2.2 Exploration of cannabis use as an effect measure modifier between lower methadone doses and MMT treatment outcomes

In the process of conducting the review for Chapter 2, I noted that lower pharmacotherapy doses were strongly and consistently associated with worse patient outcomes, including increased or continued illicit opioid use during treatment and treatment discontinuation (213, 222, 261, 262). I also observed that some studies recorded lower treatment doses among cannabis-using patients (229, 230, 233), raising the possibility that cannabis use might lower the dose needed for effective treatment for OUD. In light of emerging research to suggest a potential therapeutic role of cannabinoids in the treatment of opioid withdrawal and suppression of opioid cravings (120, 125-128) and an apparent *ad hoc* patient strategy of using cannabis to mitigate certain withdrawal symptoms (e.g., nausea (119)), a clear and feasible next step for observational research was to conceptualize and test cannabis as a potential effect measure modifier between treatment dose (as

a risk factor for opioid craving and withdrawal) and treatment outcomes. I sought to address this knowledge gap through two analyses of PWUD on MMT presented in Chapter 3. First, using a GEE-based longitudinal model, I analyzed the cannabis-dependent associations between lower (<90 mg/d) treatment dose and high-frequency illicit opioid use among 1389 PWUD who were enrolled on MMT at least once during a 13-year period. I observed a statistically significant interaction between high-frequency cannabis use and lower treatment dose such that the increased odds of daily illicit opioid use for patients on lower treatment doses were reduced from 86% during periods of no/low cannabis use to 30% during periods of regular cannabis use. Then, using observations from 611 patients who initiated MMT over the study period, I constructed Cox gamma-frailty models to test for cannabis-dependent associations between lower treatment dose and MMT discontinuation. I did not find that high-frequency cannabis use significantly modified the dose-dependent risk of treatment discontinuation in these patients. In addition, I noted several social and structural exposures within the broader risk environment (39)—including experiencing homelessness and incarceration—that presented challenges to long-term treatment retention. As the first study (to my knowledge) to model cannabis use as a potential effect measure modifier in the association between MMT dose and treatment outcomes, this study demonstrates that the relationship between cannabis use and treatment outcomes may be more complex than previously conceptualized in observational analyses, and provides preliminary evidence to inform the planning of experimental trials to evaluate cannabinoids as adjunct treatments in MOUD.

7.2.3 Characterizing cannabis use among marginalized PWUD

Given a lack of detailed understanding of cannabis use patterns among PWUD, Chapter 4 presents the findings of a latent class analysis of observations from 897 cannabis-using PWUD based on their self-reported reasons for use. Four classes were identified through this approach,

including: PWUD using cannabis primarily for non-therapeutic reasons; PWUD using cannabis primarily for a therapeutic reason other than pain (including insomnia and nausea/loss of appetite); PWUD using cannabis primarily to manage pain; and PWUD using cannabis for pain and at least another therapeutic (including insomnia, nausea/loss of appetite, stress) and/or non-therapeutic reason. A series of GEE-based models were applied to estimate the odds of class membership for a range of demographic, social, structural, drug-related, and health-related factors. Several notable class-specific trends emerged, including more frequent use of cannabis and indications of poorer physical and mental health among therapeutic classes, and more social and structural marginalization (e.g., homelessness, incarceration [bivariable-level only]) in the predominantly non-therapeutic class. Those using heroin regularly and those experiencing a recent non-fatal overdose were significantly less likely to be characterized in the pain relief cannabis use class, raising the possibility that some individuals may be using cannabis to reduce or substitute the use of heroin to manage pain. This is the first study, to my knowledge, documenting the spectrum of cannabis use motivations—from strictly therapeutic to strictly recreational—among PWUD. The LCA approach allowed for a characterization of users that would not have been evident using crude data, and contributes to a growing literature base of epidemiological studies employing LCA methods to better understand poly-substance use patterns and risk profiles among marginalized PWUD (313-321).

7.2.4 Frequency of cannabis and illicit opioid use among PWUD with pain

While a growing number of studies involving medical cannabis patients demonstrate significant reductions in the use of opioids in favour of cannabis for the treatment of certain types of pain (149-158), little was known about whether cannabis use is associated with reduced frequency of illicit opioid use (e.g., heroin, fentanyl) among PWUD engaging in poly-substance

use. Chapter 5 explored the relationship between high frequency cannabis use and high frequency illicit opioid use among 1152 PWUD who reported pain at least once over a three-and-a-half year period using generalized linear mixed-effects models. After controlling for a number of hypothesized confounders, I found that, compared to those who did not use cannabis, the odds of engaging in high frequency illicit opioid use were significantly lower (by 50%) for daily cannabis users, but not significantly lower for occasional users. I also examined self-reported reasons for use among recent daily and occasional cannabis users, and noted that certain therapeutic reasons (including pain, insomnia, stress, mental health, and HIV infection) were reported significantly more often among the daily users. By employing a longitudinal design, restricting the sample to PWUD with pain, and recording intentions behind cannabis use, this chapter addressed specific knowledge gaps identified by Kral *et al.* after they noted a significant and negative cross-sectional association between frequency of cannabis use and frequency of opioid use among people who inject drugs in California (42).

7.2.5 Cumulative exposure to cannabis and all-cause mortality

In Chapter 6, I used Cox models with time-varying covariates to estimate the risk of all-cause mortality by a cumulative measure of exposure to cannabis and other substance classes (alcohol, opioids, stimulants) for up to twelve years among 2211 PWUD contributing 15,485 person-years of follow-up. As has been demonstrated previously, the burden of death in this population was high, with 328 (15%) recorded deaths during the study, the majority of which occurred in the ACCESS (i.e., HIV-positive) cohort and were classified as non-accidental causes other than HIV and liver damage. Although at the bivariable-level, those with a moderate cumulative exposure to cannabis were at a reduced risk of mortality, the association did not continue to decrease with increasing cumulative cannabis exposure, as would be expected if a

causal association existed. Furthermore, after adjusting for a number of hypothesized confounders, alcohol was the single substance found to significantly increase the risk of mortality in a dose-dependent fashion in this population, demonstrating the prevalent harms of alcohol, even in a population with long-term experience using drugs often deemed to carry higher risks. Although this is not the first study to examine associations between certain substance use patterns and all-cause mortality among PWUD, few previous studies had included a consideration of cannabis use alongside other substances. Further, rather than examining baseline or repeated cross-sectional frequencies of use, this study posits that all-cause mortality may be more accurately modelled through a weighted cumulative exposure level (i.e., an individual's history of substance use coupled with their current use (377, 382)). I created these weighted cumulative substance use variables based on a similar mathematical approach undertaken in a mortality analysis of patients with chronic kidney disease (381); to my knowledge, it is the first study to adapt this method in a population of PWUD.

7.3 Policy, clinical, and practical recommendations

Coincident with ongoing cannabis policy reforms throughout Canada and parts of the U.S., there has been a renewed interest in researching the potential harms and therapeutic benefits of cannabinoids, as evidenced by increased funding and recent calls for cannabis-specific research from the main health funding agencies in Canada (405) and the U.S. (406). Given the recency with which the Canadian government legalized non-medical cannabis, the findings of this research are presented at a critical point in time.

7.3.1 Pain, other unmet healthcare needs, and integration of medical cannabis into care

A common theme that emerged throughout this research was the use of cannabis by PWUD to manage otherwise unmet healthcare needs. Research involving medical cannabis patients in Canada and the U.S. points to chronic pain as the most common therapeutic motivation for medical cannabis use across populations (407). This trend was also apparent among marginalized PWUD included in these analyses. For example, one-third of cannabis-using PWUD (and almost one-half of daily users) with pain reported cannabis use to self-manage pain in their most recent interview (Chapter 5), and pain relief was reported as the motivation behind 100% of observations constituting latent classes 3 ("Pain") and 4 ("Pain+") in Chapter 4. These findings are also in line with previous research among medical cannabis patients showing that severity of pain correlates with cannabis usage frequency (359, 360). With increasing clinician and policymaker concerns about misuse and diversion of opioid analgesics in recent years (408), PWUD in this setting have reported their pain going under- and untreated as a result of being denied a prescription to treat their pain-causing condition (44, 409). The negative association between frequent cannabis use and frequent illicit opioid use among marginalized PWUD with pain observed in Chapter 5 prompts a hypothesis that high-frequency cannabis use reduces the need to self-medicate pain with opioids sourced from outside of the medical system. However, rigorous follow-up research (including qualitative interviews and experimental data) will be needed to test this hypothesis against other possible explanations (e.g., differences in risk and health profiles that are not explained by cannabis use status and were not adequately captured).

Beyond pain, the findings of this dissertation also demonstrate the use of cannabis to self-manage several other healthcare needs. As shown in Chapter 4, high-frequency use of cannabis and certain indicators of poorer physical (e.g., HIV infection, increased pain severity, poorer self-

perceived health) and mental health (e.g., lifetime diagnosis of mental illness, increased anxiety symptoms) increased the odds of membership in a latent class defined by therapeutic motivations for cannabis use. In Chapter 5's sub-analysis of 414 cannabis-using PWUD with pain, more than 40% of those engaging in daily cannabis use were doing so to help with sleep, reduce stress, and/or treat nausea/vomiting or loss of appetite. Clinicians and other healthcare professionals who treat marginalized PWUD should be aware that cannabis use occurs on a spectrum among marginalized PWUD, from primarily non-medical purposes to primarily therapeutic purposes with substantial overlap in between these applications. As shown in Chapter 4, although cannabis use for non-medical purposes (e.g., intoxication, relaxation) was reported in over half of interviews among cannabis-using PWUD, cannabis use for at least one therapeutic purpose including pain relief, insomnia, stress, or nausea/appetite stimulation was prevalent in about a third of interviews, and cannabis use for harm reduction purposes including to substitute for other substances and to manage withdrawal symptoms was also reported by a smaller number of participants.

Obtaining information about patient motivations behind cannabis use in a non-stigmatizing and non-judgmental way may guide healthcare professionals to adjust treatment plans accordingly (e.g., switch patient onto a pain medication, increase methadone treatment dose, or authorize the use of medical cannabis if appropriate). Currently, however, despite high demand across healthcare professions, formal scientific education and training in cannabis and the ECS is lacking in Canada (410-412). Structural changes will be required to better support healthcare professionals in minimizing harms and maximizing benefits for their cannabis-using patients. First, medicine, nursing, and pharmacy curricula should be updated to include education around the ECS and cannabis, including chemical composition and differences across chemovars; interactions with the opioid system; metabolic pathways and implications for drug-drug interactions; current therapeutic

exploitations; acute and chronic adverse effects; and population health impacts. Second, although practice standards (i.e., minimum professional and ethical standards of conduct) for medical cannabis prescribing have been established (e.g., in British Columbia, by the College of Physicians and Surgeons of British Columbia (413)) and a simplified cannabinoid prescribing guideline for primary care providers was recently released by the College of Family Physicians of Canada (414), the use of pharmaceutical cannabinoids (e.g., nabilone) is recommended over medical cannabis in cases where cannabis may offer relief (e.g., spasticity in multiple sclerosis, chemotherapy-induced nausea and vomiting). As such, clinicians may still lack important practical knowledge (e.g., safe dosing and titration; drug effects, metabolism, and adverse events across chemovars/routes of administration) to advise patients interested in (or already) self-medicating with plant-based cannabis. To this end, at least one evidence-informed document has been published (415), but such guidelines have not have been endorsed or adopted by a professional body (e.g., the College of Physicians and Surgeons of British Columbia). The recent legalization of cannabis in Canada provides a critical window of opportunity to address these needs.

7.3.2 Access to cannabis for marginalized PWUD

At the provincial/territorial and municipal levels, policy modifications are still being made in response to ongoing monitoring and evaluation; for example, the province of Québec raised the minimum legal age of cannabis consumption from 18 to 21 years earlier in 2020 (416). In terms of this study's population of interest, an ongoing concern among municipal and provincial policymakers is the establishment and enforcement of the new system to sell legal cannabis in the DTES. Despite that a medical cannabis system has been established in Canada for almost two decades, very few cannabis-using PWUD accessed cannabis from this regulated system (Chapter 4). In the data used for this dissertation, there were only two reports of accessing cannabis from a

federally-regulated non-medical cannabis source in the six weeks following the legalization of non-medical cannabis (Chapter 4). In recent qualitative interviews, clients of free cannabis distribution programs in the DTES reported that financial barriers blocked access to the legal cannabis market. This is a concern within the community and presents a substantial barrier to adhering to the new laws set out in Bill C-45 (188).

In 2015, during the City of Vancouver's efforts to regulate illicit cannabis dispensaries, a zoning bylaw was created to prevent the establishment of cannabis retail outlets throughout much of the DTES (417). In anticipation of federal non-medical cannabis legalization in October 2018, these zoning regulations were amended to enable operation of legal non-medical cannabis retail stores under the city's previously established regulatory system, thereby continuing to block operation in the DTES (418). However, in June 2019, after hearing scientific testimony from community researchers (including findings presented in Chapters 4 and 5 of this dissertation) and first-hand accounts from harm reduction workers and PWUD, Vancouver City Council voted unanimously on a motion to amend the bylaw to allow retail cannabis in the DTES (conditional on consultation with the BC Liquor Control and Licensing Branch and DTES community organizations including VANDU (419)).

Unfortunately, Bill C-45 leaves little room for modifications that cater to the needs of vulnerable and economically-marginalized individuals who rely on cannabis for therapeutic purposes. For example, illicit dispensaries in the DTES have been known to weigh out low-cost dried cannabis to match the amount that a community member is able to pay (e.g., $5 for an approximate gram of dried cannabis (188)), whereas federally-legal products are only sold in prepackaged quantities ranging from $7 to $18 per gram (420). Thus, in the era of cannabis legalization, PWUD are presented with a new threat of criminalization, as—even with the eventual

establishment of legal cannabis sales in the DTES—they are unlikely to have the financial resources to participate in the legal market. Given the substantial proportion of marginalized PWUD who use cannabis with therapeutic intentions (Chapter 4), and preliminary findings suggestive of a beneficial effect (Chapters 3, Chapter 5), there is an ongoing need to support community-based initiatives that provide cannabis products at low or no cost to PWUD. Ideally, the products supplied to these initiatives would be legal and regulated; but at the very least, they should be quality-tested with cannabinoid composition and dosages clearly labelled.

7.3.3 Cannabis-based harm reduction strategies within the broader risk environment

Throughout this dissertation, even when cannabis use coincided with reductions in high-risk substance use practices—for example, reduced illicit opioid use in the context of concurrent pain (Chapter 5) and lower treatment dose during MMT (Chapter 3)—it was also apparent that substantial improvements in long-term health and wellbeing may be rarely gained through cannabis alone (Chapter 3, Chapter 6). Social and structural-level exposures within the risk environment (39) were repeatedly shown to strongly influence the risk of opioid-related harm and all-cause mortality in this population. For instance, in Chapter 3, although PWUD on lower doses of MMT had reduced odds of using illicit opioids daily when co-using cannabis, this possible underlying mitigating role of cannabis to suppress opioid withdrawal and/or craving did not appear to translate to meaningful longer-term engagement in treatment. Experiencing homelessness and/or incarceration were both found to increase the risk of earlier treatment discontinuation. In Chapter 6, although cumulative exposure to most substances (with the exception of alcohol) were not found to increase the risk of mortality, certain structural factors, including access to employment and engagement with opioid agonist treatment (methadone or buprenorphine/naloxone), contributed to reducing the risk of death. While community-run

cannabis distribution programs have been established in the DTES (as described in Chapter 1, Section 1.7.1.), the findings of this dissertation support the need to integrate social and structural supports with any cannabis-based harm reduction initiative to ensure the potential harms are minimized and the potential benefits maximized. The appropriate resources should be in place such that PWUD accessing cannabis-based harm reduction can be connected with employment, housing, legal, and clinical supports as needed. For example, PWUD accessing cannabis to aid with opioid withdrawal or craving may benefit from connections to appropriate MOUD treatment programs or the new safer supply initiatives (421), while PWUD accessing cannabis to aid with sleep while living outside may benefit from connections to housing support.

7.4 Study strengths and limitations

7.4.1 Strengths

This research benefitted from a number of methodological strengths that allowed for the adoption of novel approaches to address existing knowledge gaps and evolving research questions.

Depending on the research question, I was able to draw on between two-and-a-half (Chapter 4) to 13 (Chapter 3) years' worth of time-updated data to examine longitudinal trends in cannabis use and specific health outcomes. Repeated measurements allowed for closer temporal proximity between exposures and outcomes. For example, as noted in Chapters 2 and 3, several previous studies evaluating cannabis use in relation to MOUD outcomes relied on an extrapolative measurement of cannabis use at treatment outset (216, 222, 238, 241, 245, 248, 252, 256, 257), which would be unlikely to reveal a potential biological association with a subsequent treatment-related outcome after a substantial amount of time passes. The analysis presented in Chapter 3 addressed this shortcoming by including time-updated measurements of past six-month cannabis

use frequency. Similarly, in Chapter 6, repeated substance use frequency measures gathered at six-month intervals allowed for the development of a variable to estimate the weighted cumulative average exposure variables to evaluate how the combination of current and historical substance use was linked to the risk of death. However, this six-month interval data also has some limitations discussed in greater detail below.

Second, a major strength of this research comes from the setting in which it was conducted. Although experimental research is needed to confirm the feasibility and effectiveness of cannabinoid-based interventions to address a number of health problems prevalent among PWUD, it is useful to have a preliminary understanding of how some of these relationships are developing in a real-world setting (148). Despite having very little data from this population after cannabis legalization (and, in some chapters, none), the city's previous *de facto* decriminalized approach to cannabis and the proliferation of a retail cannabis industry makes Vancouver the closest possible approximation to a legal cannabis landscape in Canada in the era of prohibition. Furthermore, given the urgency of the current public health emergency of opioid overdose, a strength of this study was a relatively short (approximately one year) lag period between data collection and analysis. This allowed for preliminary findings of my dissertation to inform the city's ongoing response to the crisis (as discussed in Section 7.3, above) and the design of imminent clinical trials.

Finally, for the purpose of this dissertation, I led the development of additional measures of cannabis use, including all/primary reasons for use and sources of cannabis, which were incorporated into the study instrument in 2016. The addition of these questions provided data to differentiate patterns of therapeutic/non-therapeutic cannabis use, and facilitated a better understanding of possible underlying relationships between cannabis use, opioid use, and other health outcomes. The generation of this data also helped drive priorities for future research

involving this population (discussed in Section 7.5, below), and its relevance to the field was recently confirmed in an expert commentary that specifically called for cannabis-related public health research to be guided by an understanding of the complex underlying intentions behind cannabis use (422).

7.4.2 Limitations

In addition to the strengths noted above, there are also a number of limitations that require careful consideration when interpreting the findings of this research. As the sample criteria, variable definitions, and statistical approaches may vary between the individual studies of this dissertation, certain study-specific limitations are detailed above in their respective chapters. As Chapters 3-6 relied on data collected from VIDUS and ACCESS, they are subject to some common limitations that are noted in each chapter and discussed in greater detail below.

VIDUS and ACCESS are long-running community-recruited open prospective cohorts. Members were not recruited via random sampling nor are they necessarily representative of the population of PWUD in Vancouver. This limitation is common among studies involving members of criminalized and hard-to-reach populations, as no registry exists to randomly sample study participants from the community on the basis of their substance use. Despite that efforts were made to increase the representativeness of the sample, including the use of diverse sample recruitment methods (e.g., recruiting in collaboration with community organizations and street outreach in the DTES and other neighbourhoods with higher concentrations of PWUD (192)), the findings of this study cannot be generalized to the broader population of PWUD in Vancouver nor to PWUD in other settings. In particular, the older median age, the oversampling of PWUD living with HIV (via pooled analyses with ACCESS), and the unique characteristics of the DTES (e.g., high concentration of PWUD, prevalent poly-substance use, open drug selling and use, relatively

progressive and concentrated harm reduction programming and clinical services) should be taken into consideration when comparing these findings against those from other samples and settings.

With the exception of HIV status (a documented independent variable in Chapters 3-6) and all-cause mortality (Chapter 6), the analyses of this dissertation relied on self-reported measures. Self-report of behaviours and exposures in the previous six months, including the disclosure of illegal activities, is subject to bias from recall inaccuracies and responding according to perceived social norms/desires. However, as previously shown, self-report by PWUD can be considered generally reliable even at long recall periods and valid against biochemical verification (297). In addition, even in cases of accurate response and complete recall, self-reporting the use of unregulated drugs may not reflect a true representation of the drugs that were consumed, given that the composition and purity of unregulated drugs cannot be confirmed. However, any recall and response discrepancies are likely to be non-differential as this dissertation is nested within two much larger research projects and neither interviewers nor participants were aware of the specific objectives of these individual analyses. In addition, interviewers are trained to minimize the potential of response bias through developing rapport over repeated study visits, reassuring participant anonymity and data confidentiality, and reserving more sensitive questions (e.g., those covering behaviours that are stigmatized or illegal) for the latter part of the interview.

As these are observational studies, the exposure of interest (methadone dose and cannabis use in Chapter 3, cannabis use in Chapters 5 and 6) is not randomly assigned. In each study, careful consideration of variables that likely correlate with cannabis use and predict of the outcome were included to minimize bias from confounding. However, the possibility of unmeasured (i.e., residual) confounding cannot be ruled out. Additional questions were added to the study questionnaire in recent years that allowed for more nuanced exploration of research questions (e.g.,

the addition of a pain scale in 2014; the addition of cannabis use reasons in 2016). However, certain analyses required the maximum possible number of study observations (e.g., Cox model to analyze time-to MMT discontinuation in Chapter 3, Cox model to analyze time-to death in Chapter 6) and were thus limited to measures that could be consistently collected from 2005 to 2018, possibly increasing the vulnerability to residual confounding. It is possible that PWUD engaging in frequent cannabis use may be inherently different than other PWUD in ways that were not captured in our surveys (see, for example, discussion in Section 5.4.). Next steps for addressing this important limitation are discussed in Section 7.5., below.

With the exception of Chapter 6, in which a confirmed death date was ascertained through linkage with the provincial vital statistics registry, another limitation of these six-month recall periods is the inability to time-stamp the occurrence of exposure and outcome within each six-month period, if not occurring consistently throughout. I discuss the specifics of this limitation as it relates to the data in question separately in Chapters 3-5.

Finally, throughout the study period, data was not collected on the type of cannabis used, mode of administration used to consume it, cannabinoid content (e.g., ratio of THC to CBD) or dose (e.g., mg THC) of products used. With an increasing understanding of the complexity of the ECS and its interactions with components of cannabis, detailing this information will help clarify the potential therapeutic applications and harmful aspects of cannabis use for different treatment conditions. The broad categorization of cannabis may have therefore masked important differences in exposure-outcome relationships between users. However, due to cannabis being a prohibited substance until October 2018, this limitation is common to all observational cannabis research conducted before legalization. Cannabis' newly legal status in Canada brings an opportunity to paint a more nuanced characterization of cannabis' therapeutic and adverse effects.

7.5 Recommendations for future research

Although findings of this dissertation have addressed certain knowledge gaps identified in the literature (as described in Chapters 1 and 2), they also highlight additional research questions involving cannabis use among PWUD that were beyond the scope of the current research project.

First, as a collection of observational studies, this dissertation does not purport to describe a causal association between cannabis and any substance use or health-related outcome. Instead, it provides a preliminary signal of possible relationships to be explored further through experimental research. As experimental work begins to investigate the hypothesized opioid sparing effect of cannabinoids in humans (94), the target population of this research should extend beyond healthy volunteers and those prescribed opioids for pain to also include people who are using illicit opioids to manage pain. After summarizing the inconsistent state of research around cannabis use during MOUD in Chapter 2, and expanding on the current state of the research around cannabis and MMT treatment dose in Chapter 3, a critical next step in this area of research will be an experimental trial to closely monitor clinical outcomes (including objective and subjective measurements of opioid withdrawal and craving) associated with randomized exposure to cannabis (or placebo) as an adjunct therapy to MOUD. As clinical assessments of opioid withdrawal were not available for participants on MMT, methadone dose was chosen as a primary independent variable in Chapter 3 given its close relationship to opioid use during treatment, possibly via suppression of withdrawal and opioid craving (423). Last year, I helped secure funding to implement enhanced cannabis data collection measures to the cohort surveys, and I have adapted the Subjective Opioid Withdrawal Scale (SOWS) to be piloted in the cohorts. This will provide

important preliminary data to help clarify the potential underlying role of withdrawal in the relationship between methadone dose, cannabis use, and opioid use observed in Chapter 3.

An important component of this future experimental research will be determining the treatment agent, given a number of trade-offs in scientific rationale, patient risk, and study quality between cannabinoid-based treatment agents, dosages, and modes of administration. For instance, dried flower remains the most frequently used form of cannabis among medical users (353, 424), thus selecting dried cannabis may increase external validity in a clinical trial, but smoking as the method of consumption carries additional risks to respiratory health (425), and inhalation as a route of administration may present challenges to ensuring dosage consistency across participants (e.g., due to variation in lung capacity). Vapourizing dried cannabis (i.e., inhaling vapour created using a device that heats the flower without burning it) presents fewer acute (e.g., carbon monoxide exposure (426)) and chronic health risks (e.g., bronchitis (427)) to the user, and vapourizing as a mode of administration is equally favoured to smoking among medical users (353, 424, 428). Vapourized cannabis has been successfully administered in previous double-blind randomized controlled trials of cannabis for neuropathic pain (87, 88); however vapourizers for dried cannabis are expensive and challenging to use for some patients (429), reducing the likelihood of adoption in a real-world setting—particularly for marginalized patients. Oral administration of cannabis (e.g., via sublingual oil, gel capsules) does not expose patients to the risks of smoking and can be administered in a more controlled and consistent dose, making it a preferred mode of administration for optimizing patient health and internal validity; however, oil-based products may produce varied effects between patients/timing of administration as they are metabolized in the liver (unlike smoked/vapourized cannabis, which is absorbed from the lungs into the bloodstream (430)). Furthermore, as oral preparations are less popular than dried flower (135, 428), they could

have the unintended consequence of promoting secondary cannabis smoking/vapourizing during the study. In terms of specific components of cannabis, CBD has shown promise in preventing heroin cravings and anxiety during abstinence (125-128); yet, THC's anti-emetic effects may be an integral part of self-medication with cannabis during MOUD (118, 124). Biochemical and pharmacological exploration of cannabis' interaction with the ECS has given rise to a theorized entourage effect (431), which suggests that whole-plant cannabis (i.e., all the bioactive molecules produced by the cannabis plant) might serve as a more suitable treatment candidate than any cannabinoid alone (e.g., CBD, THC, or pharmaceutical formulations of THC such as dronabinol). In developing larger trials to investigate a therapeutic role of cannabis for pain and OUD, pilot trials will be needed to determine optimal cannabis chemovars (colloquially referred to as "strains" (432)), as each is likely to produce different effects based on its own unique composition of cannabinoids (most notably THC and CBD) and terpenoids (components that are responsible for the aroma and flavour of the plant and have a synergistic relationship with cannabinoids (433)). Considering the newly legal status of non-medical cannabis in Canada, collecting patient data on desired and perceived effects of recently used cannabis products (and their modes of consumption) might be a feasible and useful preliminary step to designing this pilot research. Currently, however, unless products used by PWUD originate from the legal market (see discussion under Section 7.3.2., above), this information may not be available to the user (or may not be valid). Here, collaborations across academic disciplines (e.g., epidemiology, pharmacology, and plant science) and community organizations of PWUD may facilitate the development of creative solutions to begin bridging this informational gap (e.g., by testing and identifying the chemical composition of cannabis products frequently sold/donated to and used by PWUD in the DTES).

Despite that cannabis is widely considered to be relatively low-risk in comparison to other commonly used regulated substances (e.g., alcohol) and unregulated substances (e.g., illicit opioids (162)), it is still a psychoactive drug that carries certain health risks, including: the potential exacerbation of underlying mental health issues; increased risk of injury during acute intoxication (e.g., motor vehicle accident), and meeting diagnostic criteria for cannabis use disorder (CUD (371, 434)). While this dissertation sought to examine cannabis' potential therapeutic and harm reduction applications among marginalized PWUD, future research should consider the possible adverse impacts of cannabis use in this population. In particular, the prevalence of CUD among PWUD has yet to be documented as no psychometric assessment tools to measure for problematic cannabis use have been adapted to PWUD. Behaviours viewed as problematic and indicative of CUD in more general samples may not have the same implications for individuals with several years of poly-substance use experience. Thus, psychometric assessment tools for CUD will need to be modified and piloted for validation among PWUD. Currently, a supplemental questionnaire for cannabis-using participants in VIDUS and ACCESS is being implemented with the objective of developing, validating, and implementing the Composite Cannabis Assessment Tool (CCAT) among marginalized PWUD (435). The CCAT is a comprehensive tool that assesses for problematic, therapeutic, and recreational aspects of cannabis use (436), making it an optimal tool to adapt to PWUD.

Furthermore, marginalized PWUD contend with high rates of comorbid mental illness—often undiagnosed and/or untreated—and may engage in substance use as a self-medication strategy (51-55). Although emerging research provides compelling evidence to target the ECS in pharmacological treatment of anxiety (97) and PTSD (437), a large literature base consistently demonstrates correlations between cannabis use (particularly high frequency use beginning in

developmental years) and the development or worsening of mental illness—including increased bipolar symptoms in those with bipolar disorder; increased thoughts of suicide; the development of social anxiety disorder; and the development of schizophrenia or other psychoses (91)—among the general population. Yet, due to the complex and overlapping pathways driving co-morbidity between substance use disorders and mental health disorders, it remains unclear to what extent (if any) cannabis is a causal factor in triggering or exacerbating mental illness (91). Still, given that cannabis is used by some individuals to self-medicate symptoms of mental illness, as exemplified in about 8% of recent interviews among cannabis-using PWUD (Chapter 4), more research among this population is needed to further elucidate the role of cannabis among those with comorbid and mental illness (e.g., whether more severe symptoms are experienced during periods of frequent cannabis use; whether reporting cannabis use to manage mental health problems is associated with improvements in symptoms). Any experimental clinical research involving cannabinoid-based interventions among PWUD should take a cautious approach to minimize the risk of adverse mental health effects. This could be done through selecting treatment products and dosages that are line with the lower risk cannabis use guidelines (LRCUG), such as products with low-moderate THC concentrations, an equal ratio of CBD to THC, non-smoking modes of administration (438); excluding those with specific pre-existing mental health disorders (e.g., schizophrenia, bipolar disorder, major depression); and closely monitoring participants for the development or worsening of symptoms of mental distress. The LRCUG were developed for the general population of new and current cannabis users; it remains unclear whether these guidelines would resonate with marginalized PWUD who likely have limited access to alternative lower-risk cannabis products suggested by the LRCUG. Thus, study protocols that follow the LRCUG should also assess perception and acceptability of these guidelines among study participants.

Finally, given the ongoing establishment of community-run cannabis distribution programs throughout the province, there is a need to formally evaluate these programs to ensure that their potential benefits are not outweighed by possible risks. Simple descriptive quantitative research would provide a better understanding of who is using these programs and why, and whether the programs are achieving their objectives of supporting PWUD to manage health conditions or reduce drug-related harm (i.e., by controlling, reducing, or stopping use of other substances). A scientific evaluation of these programs would also generate helpful guidelines to improve service delivery and support client wellbeing (e.g., recommendations about the supplied cannabis products, cannabis health educational dissemination, and program integration with other social and health services). Recent qualitative interviews conducted with clients at both DTES cannabis distribution sites demonstrates that the current community- and peer-run model is favoured over a medicalized model for its low-barrier access (188); therefore, any future research-based recommendations should consider ways to support the health of PWUD without compromising their access to these programs.

7.6 Conclusion

Through a systematic review (Chapter 2) and a collection of longitudinal observational studies (Chapters 3-6), this dissertation sought to characterize the use of cannabis among PWUD, with a special focus on investigating the therapeutic and harm reduction applications of cannabis in the context of mounting opioid-related morbidity and mortality across the province. A wide range of non-medical and medical motivations for cannabis use were observed among marginalized PWUD, with pain, stress, and insomnia being the top therapeutic motivations for use. Important health-related differences according to cannabis use patterns and motivations provided

evidence to suggest frequent cannabis use could signify an unmet healthcare need among PWUD. The use of cannabis among PWUD undergoing MMT was common, and there was some evidence that cannabis may help address opioid craving and withdrawal during periods of lower treatment dose. However, the increased risk of treatment discontinuation for patients on lower doses was not modified by cannabis use, suggesting that long-term treatment progress is not improved with cannabis. Together with the findings of a systematic review examining the relationship between cannabis use and treatment outcomes for patients on FDA/Health Canada-approved OUD pharmacotherapy (methadone, buprenorphine, naltrexone), it was concluded that cannabis use during treatment is unlikely to impede patient progress but should be clinically monitored to ensure optimal patient health. There was a high prevalence of pain among marginalized PWUD and the use of cannabis to manage pain was common, especially among those using cannabis on a daily basis. Daily, but not occasional, use of cannabis was associated with significantly lower odds of daily illicit opioid use among PWUD with pain, providing some preliminary evidence from a real-world setting to suggest an opioid-sparing effect of cannabinoids (94) in this population; however, further clinical experimental research is warranted. Cumulative exposure to cannabis in this population was not significantly associated with all-cause mortality, including in the years coinciding with the overdose crisis.

With growing scientific and public inquiry into cannabinoid-based interventions to address opioid-related morbidity and mortality (69), the findings of this dissertation helped distill these interests down to two specific therapeutic applications to be rigorously tested in clinical settings: 1) the management of pain (particularly as a potential opioid-sparing agent); and 2) the management of opioid withdrawal and craving in the treatment of OUD. While some promising signals of cannabis' therapeutic potential were uncovered, this dissertation also produced

consistent data to reaffirm that social and structural marginalization act as powerful barriers to improving the health and wellbeing of PWUD. In a newly legal environment, cannabis should be viewed as one tool to exploit in a multi-faceted response to drug-related harms among PWUD, but it cannot be a solution on its own; may not translate well to other groups who are at risk of opioid-related harm (e.g., cannabis-naïve pain patients); and should be considered alongside the provision of broader social and structural supports.

References

1. Trescot A, Datta S, Lee M, Hansen H. Opioid pharmacology. Pain Physician. 2008;11:S133-S53.

2. Corbett AD, Henderson G, McKnight AT, Paterson SJ. 75 years of opioid research: the exciting but vain quest for the Holy Grail. Br J Pharmacol. 2006;147(S1):S153-S62.

3. Stefano GB, Pilonis N, Ptacek R, Kream RM. Reciprocal evolution of opiate science from medical and cultural perspectives. Med Sci Monit. 2017;23:2890-6.

4. Van Zee A. The promotion and marketing of oxycontin: Commercial triumph, public health tragedy. Am J Public Health. 2009;99(2):221-7.

5. Gomes T, Mamdani MM, Paterson JM, Dhalla IA, Juurlink DN. Trends in high-dose opioid prescribing in Canada. Can Fam Physician. 2014;60(9):826-32.

6. Pergolizzi JV, Jr., Raffa RB, Rosenblatt MH. Opioid withdrawal symptoms, a consequence of chronic opioid use and opioid use disorder: Current understanding and approaches to management. J Clin Pharm Ther. 2020;Epub ahead of print.

7. Higgins C, Smith BH, Matthews K. Incidence of iatrogenic opioid dependence or abuse in patients with pain who were exposed to opioid analgesic therapy: A systematic review and meta-analysis. Br J Anaesth. 2018;120(6):1335-44.

8. Santiago Rivera OJ, Havens JR, Parker MA, Anthony JC. Risk of heroin dependence in newly incident heroin users. JAMA Psychiatry. 2018;75(8):863-4.

9. Degenhardt L, Whiteford HA, Ferrari AJ, Baxter AJ, Charlson FJ, Hall WD, et al. Global burden of disease attributable to illicit drug use and dependence: Findings from the Global Burden of Disease Study 2010. Lancet. 2013;382:1564-74.

10. Degenhardt L, Charlson F, Ferrari A, Santomauro D, Erskine H, Mantilla-Herrara A, et al. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. Lancet Psychiatry. 2018;5(12):987-1012.

11. Surratt HL, O'Grady C, Kurtz SP, Stivers Y, Cicero TJ, Dart RC, et al. Reductions in prescription opioid diversion following recent legislative interventions in Florida. Pharmacoepidemiol Drug Saf. 2014;23(3):314-20.

12. Ladha KS, Neuman MD, Broms G, Bethell J, Bateman BT, Wijeysundera DN, et al. Opioid prescribing after surgery in the United States, Canada, and Sweden. JAMA Netw Open. 2019;2(9):e1910734.

13. Fink DS, Schleimer JP, Sarvet A, Grover KK, Delcher C, Castillo-Carniglia A, et al. Association Between Prescription Drug Monitoring Programs and Nonfatal and Fatal Drug Overdoses: A Systematic Review. Ann Intern Med. 2018;168(11):783-90.

14. Taha S, Maloney-Hall B, Buxton J. Lessons learned from the opioid crisis across the pillars of the Canadian drugs and substances strategy. Subst Abuse Treat Prev Policy. 2019;14(1):32.

15. Martins SS, Ponicki W, Smith N, Rivera-Aguirre A, Davis CS, Fink DS, et al. Prescription drug monitoring programs operational characteristics and fatal heroin poisoning. Int J Drug Policy. 2019;74:174-80.

16. Algera MH, Kamp J, van der Schrier R, van Velzen M, Niesters M, Aarts L, et al. Opioid-induced respiratory depression in humans: a review of pharmacokinetic-pharmacodynamic modelling of reversal. Br J Anaesth. 2019;122(6):e168-e79.

17. Causes of injury death: Highlighting unintentional injury. Centers for Disease Control and Prevention; 2018 [cited 2020 April 29]. Available from: https://www.cdc.gov/injury/wisqars/LeadingCauses.html.

18. Yao X, Skinner R, McFaull S, Thompson W. At-a-glance - 2015 injury deaths in Canada. Health Promot Chronic Dis Prev Can. 2019;39(6-7):225-31.

19. Lake S, Milloy MJ, Dong H, Hayashi K, Wood E, Kerr T, et al. Initiation into prescription opioid injection and associated trends in heroin use among people who use illicit drugs. Drug Alcohol Depend. 2016;169:73-9.

20. Understanding the epidemic. US Centers for Disease Control and Prevention; 2018 [cited 2020 March 18]. Available from: https://www.cdc.gov/drugoverdose/epidemic/index.html.

21. Rudd RA, Aleshire N, Zibbell JE, Gladden M. Increases in drug and opioid overdose deaths - United States, 2000-2014. Morb Mortal Wkly Rep. 2016;64(50):1378-82.

22. Scholl L, Seth P, Kariisa M, Wilson N, Baldwin G. Drug and opioid-involved overdose deaths - United States, 2013-2017. Morb Mortal Wkly Rep. 2018;67(51/52):1419-26.

23. Special Advisory Committee on the Epidemic of Opioid Overdoses. Opioid-related harms in Canada. Public Health Agency of Canada; 2020 [cited 2020 March 17]. Available from: https://health-infobase.canada.ca/substance-related-harms/opioids.

24. Canadian Substance Use Costs and Harms Scientific Working Group. Canadian substance use costs and harms [Internet]. Ottawa: Canadian Institute for Substance Use Research and Canadian Centre on Substance Use and Addiction; 2018. Available from: https://www.ccsa.ca/sites/default/files/2019-04/CSUCH-Canadian-Substance-Use-Costs-Harms-Report-2018-en.pdf.

25. Statistics Canada. Changes in life expectancy by selected causes of death, 2017 [Internet]. 2019 May 30. Available from: https://www150.statcan.gc.ca/n1/en/daily-quotidien/190530/dq190530d-eng.pdf?st=R--Qr3Py.

26. British Columbia Coroners Service. Illicit overdose deaths in BC: January 1, 2007 - December 31, 2016 [Internet]. 2017 January 18. Available from: http://www2.gov.bc.ca/assets/gov/public-safety-and-emergency-services/death-investigation/statistical/illicit-drug.pdf.

27. British Columbia Coroners Service. Illicit drug overdose deaths in BC: Findings of coroners' investigations [Internet]. 2018 September 27. Available from: https://www2.gov.bc.ca/assets/gov/birth-adoption-death-marriage-and-divorce/deaths/coroners-service/statistical/illicitdrugoverdosedeathsinbc-findingsofcoronersinvestigations-final.pdf.

28. British Columbia Coroners Service. Fentanyl-detected illicit drug toxicity deaths January 1, 2012 to December 31, 2019 [Internet]. BC Ministry of Public Safety and Solicitor General; 2019 December 5. Available from: https://www2.gov.bc.ca/assets/gov/birth-adoption-death-marriage-and-divorce/deaths/coroners-service/statistical/illicit-drug.pdf.

29. Paix A, Coleman A, Lees J, Grigson J, Brooksbank M, Thorne D, et al. Subcutaneous fentanyl and sufentanil infusion substitution for morphine intolerance in cancer pain management. Pain. 1995;63(2):263-9.

30. Wang DD, Ma TT, Zhu HD, Peng CB. Transdermal fentanyl for cancer pain: Trial sequential analysis of 3406 patients from 35 randomized controlled trials. J Cancer Res Ther. 2018;14(Supplement):S14-s21.

31. Jafari S, Buxton JA, Joe R. Rising fentanyl-related overdose deaths in British Columbia. Can J Addict. 2015;6(1):4-6.

32. Fisher G. Cocaine laced with fentanyl a growing concern: 9 overdoses in 20 minutes in Delta. CBC News [Internet]. 2016 September 1 [cited 2017 August 24]; Available from: http://www.cbc.ca/news/canada/british-columbia/delta-police-nine-overdose-warning-1.3744776.

33. Teen dead from suspected fentanyl overdose 'had a bright future'. CBC News [Internet]. 2015 August 4 [cited 2020 April 13]; Available from: https://www.cbc.ca/news/canada/british-columbia/jack-bodie-teen-who-died-from-suspected-fentanyl-overdose-had-a-bright-future-1.3178556.

34. Fentanyl suspected in death of North Vancouver man, say RCMP. CBC News [Internet]. 2015 August 3 [cited 2020 April 13]; Available from: https://www.cbc.ca/news/canada/british-columbia/fentanyl-suspected-in-death-of-north-vancouver-man-say-rcmp-1.3178250.

35. Tupper KW, McCrae K, Garber I, Lysyshyn M, Wood E. Initial results of a drug checking pilot program to detect fentanyl adulteration in a Canadian setting. Drug Alcohol Depend. 2018;190:242-5.

36. British Columbia Coroners Service. Illicit drug overdose deaths in BC: January 1, 2008 - November 30, 2018 [Internet]. 2018 December 27. Available from: https://www2.gov.bc.ca/assets/gov/birth-adoption-death-marriage-and-divorce/deaths/coroners-service/statistical/illicit-drug.pdf.

37. Response to the opioid overdose crisis in Vancouver Coastal Health [Internet]. 2018. Available from: http://www.vch.ca/Documents/CMHO-report.pdf.

38. Drug Situation in Vancouver [Internet]. British Columbia Centre for Excellence in HIV/AIDS; 2013. Available from: http://www.cfenet.ubc.ca/sites/default/files/uploads/news/releases/war_on_drugs_failing_to_limit_drug_use.pdf.

39. Rhodes T. Risk environments and drug harms: A social science for harm reduction approach. Int J Drug Policy. 2009;20(3):193-201.

40. Milloy MJ, Kerr T, Bangsberg DR, Buxton J, Parashar S, Guillemi S, et al. Homelessness as a structural barrier to effective antiretroviral therapy among HIV-seropositive illicit drug users in a Canadian setting. AIDS Patient Care STDs. 2012;26(1):60-7.

41. Milloy MJ, Kerr T, Zhang R, Tyndall M, Montaner J, Wood E. Inability to access addiction treatment and risk of HIV infection among injection drug users recruited from a supervised injection facility. J Public Health (Oxf). 2010;32(3):342-9.

42. Kral AH, Wenger L, Novak SP, Chu D, Corsi KF, Coffa D, et al. Is cannabis use associated with less opioid use among people who inject drugs? Drug Alcohol Depend. 2015;153:236-41.

43. Ti L, Voon P, Dobrer S, Montaner J, Wood E, Kerr T. Denial of pain medication by health care providers predicts in-hospital illicit drug use among individuals who use illicit drugs. Pain Res Manag. 2015;20(2):84-8.

44. Voon P, Callon C, Nguyen P, Dobrer S, Montaner JSG, Wood E, et al. Denial of prescription analgesia among people who inject drugs in a Canadian setting. Drug Alcohol Rev. 2015;34(2):221-8.

45. Dassieu L, Kabore JL, Choiniere M, Arruda N, Roy E. Chronic pain management among people who use drugs: A health policy challenge in the context of the opioid crisis. Int J Drug Policy. 2019;71:150-6.

46. Medrano M, Zule W, Hatch JP, Desmond D. Prevalence of childhood trauma in a community sample of substance-abusing women. Am J Drug Alcohol Abuse. 1999;25(3):449-62.

47. Wang Z, Du J, Sun H, Wu H, Xiao Z, Zhao M. Patterns of childhood trauma and psychological distress among injecting heroin users in China. PLoS One. 2010;5(12):e15882.

48. Walton G, Co SJ, Milloy MJ, Qi J, Kerr T, Wood E. High prevalence of childhood emotional, physical and sexual trauma among a Canadian cohort of HIV-seropositive illicit drug users. AIDS Care. 2011;23(6):714-21.

49. Lee WK, Hayashi K, DeBeck K, Milloy MJS, Grant C, Wood E, et al. Association between posttraumatic stress disorder and nonfatal drug overdose. Psychol Trauma. 2019.

50. Lake S, Hayashi K, Milloy MJ, Wood E, Dong H, Montaner J, et al. Associations between childhood trauma and non-fatal overdose among people who inject drugs. Addict Behav. 2015;43:83-8.

51. Pabayo R, Alcantara C, Kawachi I, Wood E, Kerr T. The role of depression and social support in non-fatal drug overdose among a cohort of injection drug users in a Canadian setting. Drug Alcohol Depend. 2013;132(3):603-9.

52. Bolton JM, Robinson J, Sareen J. Self-medication of mood disorders with alcohol and drugs in the National Epidemiologic Survey on Alcohol and Related Conditions. J Affect Disord. 2009;115(3):367-75.

53. Maremmani AG, Bacciardi S, Gehring ND, Cambioli L, Schütz C, Akiskal HS, et al. The impact of mood symptomatology on pattern of substance use among homeless. J Affect Disord. 2015;176:164-70.

54. Maremmani AG, Bacciardi S, Gehring ND, Cambioli L, Schütz C, Jang K, et al. Substance use among homeless individuals with schizophrenia and bipolar disorder. J Nerv Ment Dis. 2017;205(3):173-7.

55. Mackesy-Amiti ME, Donenberg GR, Ouellet LJ. Prevalence of psychiatric disorders among young injection drug users. Drug Alcohol Depend. 2012;124(1-2):70-8.

56. Find a site. Toward the Heart: BCCDC Harm Reduction Services; 2020 [cited 2020 May 19]. Available from: https://towardtheheart.com/site-finder.

57. Banjo O, Tzemis D, Al-Qutub D, Amlani A, Kesselring S, Buxton JA. A quantitative and qualitative evaluation of the British Columbia Take Home Naloxone program. CMAJ Open. 2014;2(3):E153-61.

58. Lysyshyn M, Buxton J. Harm reduction innovation during an overdose emergency. UBC Med J. 2018;10(1):4.

59. Wallace B, Pagan F, Pauly BB. The implementation of overdose prevention sites as a novel and nimble response during an illegal drug overdose public health emergency. Int J Drug Policy. 2019;66:64-72.

60. Irvine MA, Kuo M, Buxton JA, Balshaw R, Otterstatter M, Macdougall L, et al. Modelling the combined impact of interventions in averting deaths during a synthetic-opioid overdose epidemic. Addiction. 2019;114(9):1602-13.

61. British Columbia Ministry of Health, British Columbia Centre on Substance Use. Guidance for injectable opioid agonist treatment for opioid use disorder [Internet]. 2018. Available from: https://www.bccsu.ca/wp-content/uploads/2017/10/BC-iOAT-Guidelines-10.2017.pdf.

62. Bozinoff N, DeBeck K, Milloy MJ, Nosova E, Fairbairn N, Wood E, et al. Utilization of opioid agonist therapy among incarcerated persons with opioid use disorder in Vancouver, Canada. Drug Alcohol Depend. 2018;193:42-7.

63. Ahamad K, Hayashi K, Nguyen P, Dobrer S, Kerr T, Schutz CG, et al. Effect of low-threshold methadone maintenance therapy for people who inject drugs on HIV incidence in Vancouver, BC, Canada: an observational cohort study. Lancet HIV. 2015;2(10):e445-50.

64. Nolan S, Dias Lima V, Fairbairn N, Kerr T, Montaner J, Grebely J, et al. The impact of methadone maintenance therapy on hepatitis C incidence among illicit drug users. Addiction. 2014;109(12):2053-9.

65. Pierce M, Bird SM, Hickman M, Marsden J, Dunn G, Jones A, et al. Impact of treatment for opioid dependence on fatal drug-related poisoning: A national cohort study in England. Addiction. 2016;111(2):298-308.

66. Russolillo A, Moniruzzaman A, Somers JM. Association of methadone treatment with substance-related hospital admissions among a population in Canada with a history of criminal convictions. JAMA Netw Open. 2019;2(3):e190595.

67. Wakeman SE, Larochelle MR, Ameli O, Chaisson CE, McPheeters JT, Crown WH, et al. Comparative effectiveness of different treatment pathways for opioid use disorder. JAMA Netw Open. 2020;3(2):e1920622.

68. Tyndall M. Perspectives on the drug overdose crisis in BC. BC Med J. 2017;59(2):89.

69. Lucas P. Rationale for cannabis-based interventions in the opioid overdose crisis. Harm Reduct J. 2017;14(1):58.

70. Pertwee RG. Cannabinoid pharmacology: The first 66 years. Br J Pharmacol. 2006;147 Suppl 1(Suppl 1):S163-S71.

71. Pacher P, Batkai S, Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. Pharmacol Rev. 2006;58(3):389-462.

72. Gaoni Y, Mechoulam R. Isolation, structure, and partial synthesis of an active constituent of hashish. Journal of the American Chemical Society. 1964;86(8):1646-7.

73. Hillard CJ. The endocannabinoid signaling system in the CNS: A primer. In: Parsons L, Hill M, editors. International Review of Neurobiology. 125: Academic Press; 2015. p. 1-47.

74. Acharya N, Penukonda S, Shcheglova T, Hagymasi AT, Basu S, Srivastava PK. Endocannabinoid system acts as a regulator of immune homeostasis in the gut. PNAS. 2017;114(19):5005-10.

75. Hillard CJ, Beatka M, Sarvaideo J. Endocannabinoid Signaling and the Hypothalamic-Pituitary-Adrenal Axis. Compr Physiol. 2017;7(1):1-15.

76. Passie T, Emrich HM, Karst M, Brandt SD, Halpern JH. Mitigation of post-traumatic stress symptoms by Cannabis resin: A review of the clinical and neurobiological evidence. Drug Test Anal. 2012;4(7-8):649-59.

77. Pandey R, Mousawy K, Nagarkatti M, Nagarkatti P. Endocannabinoids and immune regulation. Pharmacol Res. 2009;60(2):85-92.

78. Manzanares J, Julian M, Carrascosa A. Role of the cannabinoid system in pain control and therapeutic implications for the management of acute and chronic pain episodes. Curr Neuropharmacol. 2006;4(3):239-57.

79. Dwarakanath SC. The use of opium and cannabis in the traditional systems of medicine in India. Bull Narc. 1965;1:15-9.

80. Grinspoon L. Marihuana Reconsidered. Cambridge, MA: Harvard University Press; 1971.

81. McNicol ED, Midbari A, Eisenberg E. Opioids for neuropathic pain. Cochrane Database Syst Rev. 2013(8):CD006146.

82. Donvito G, Nass SR, Wilkerson JL, Curry ZA, Schurman LD, Kinsey SG, et al. The endogenous cannabinoid system: a budding source of targets for treating inflammatory and neuropathic pain. Neuropsychopharmacology. 2017;43(1):52-79.

83. Iskedjian M, Bereza B, Gordon A, Piwko C, Einarson TR. Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain. Curr Med Res Opin. 2007;23(1):17-24.

84. Wilsey B, Marcotte T, Tsodikov A, Millman J, Bentley H, Gouaux B, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. J Pain. 2008;9(6):506-21.

85. Ellis RJ, Toperoff W, Vaida F, van den Brande G, Gonzales J, Gouaux B, et al. Smoked medicinal cannabis for neuropathic pain in HIV: A randomized, crossover clinical trial. Neuropsychopharmacology. 2009;34(3):672-80.

86. Ware MA, Wang T, Shapiro S, Robinson A, Ducruet T, Huynh T, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ. 2010;182(14):E694-701.

87. Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H. Low-dose vaporized cannabis significantly improves neuropathic pain. J Pain. 2013;14(2):136-48.

88. Wilsey B, Marcotte TD, Deutsch R, Zhao H, Prasad H, Phan A. An exploratory human laboratory experiment evaluating vaporized cannabis in the treatment of neuropathic pain from spinal cord injury and disease. J Pain. 2016;17(9):982-1000.

89. Andreae MH, Carter GM, Shaparin N, Suslov K, Ellis RJ, Ware MA, et al. Inhaled cannabis for chronic neuropathic pain: A meta-analysis of individual patient data. J Pain. 2015;16(12):1221-32.

90. Wang T, Collet JP, Shapiro S, Ware MA. Adverse effects of medical cannabinoids: a systematic review. CMAJ. 2008;178(13):1669-78.

91. Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda; Board on Population and Public Health Practice; Health and Division of Medicine, National Academies of Sciences, Engineering, and Medicine. The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research [Internet]. Washington, D.C.: The National Academies Press; 2017. Available from: http://nationalacademies.org/hmd/reports/2017/health-effects-of-cannabis-and-cannabinoids.aspx.

92. Cichewicz DL. Synergistic interactions between cannabinoid and opioid analgesics. Life Sci. 2004;74(11):1317-24.

93. Welch SP. Interaction of the cannabinoid and opioid systems in the modulation of nociception. Int Rev Psychiatry. 2009;21(2):143-51.

94. Nielsen S, Sabioni P, Trigo JM, Ware MA, Betz-Stablein BD, Murnion B, et al. Opioid-sparing effect of cannabinoids: A systematic review and meta-analysis. Neuropsychopharmacology. 2017;42(9):1752-65.

95. Cooper ZD, Bedi G, Ramesh D, Balter R, Comer SD, Haney M. Impact of co-administration of oxycodone and smoked cannabis on analgesia and abuse liability. Neuropsychopharmacology. 2018;43(10):2046-55.

96. Babalonis S, Lofwall MR, Sloan PA, Nuzzo PA, Fanucchi LC, Walsh SL. Cannabinoid modulation of opioid analgesia and subjective drug effects in healthy humans. Psychopharmacology (Berl). 2019;236(11):3341-52.

97. Patel S, Hill MN, Cheer JF, Wotjak CT, Holmes A. The endocannabinoid system as a target for novel anxiolytic drugs. Neurosci Biobehav Rev. 2017;76(Pt A):56-66.

98. Walsh Z, Callaway R, Belle-Isle L, Capler R, Kay R, Lucas P, et al. Cannabis for therapeutic purposes: patient characteristics, access, and reasons for use. Int J Drug Policy. 2013;24(6):511-6.

99. Kosiba JD, Maisto SA, Ditre JW. Patient-reported use of medical cannabis for pain, anxiety, and depression symptoms: Systematic review and meta-analysis. Soc Sci Med. 2019;233:181-92.

100. Trezza V, Campolongo P. The endocannabinoid system as a possible target to treat both the cognitive and emotional features of post-traumatic stress disorder (PTSD). Front Behav Neurosci. 2013;7:100.

101. Zer-Aviv MT, Segev A, Akirav I. Cannabinoids and post-traumatic stress disorder: Clinical and preclinical evidence for treatment and prevention. Behav Pharmacol. 2016;27(7):561-9.

102. Evaluating safety and efficacy of cannabis in participants with chronic posttraumatic stress disorder (NCT02517424). ClinicalTrials.gov; [cited 2018 January 30]. Available from: https://clinicaltrials.gov/ct2/show/results/NCT02517424.

103. O'Neil ME, Nugent SM, Morasco BJ, Freeman M, Low A, Kondo K, et al. Benefits and harms of plant-based cannabis for posttraumatic stress disorder: A systematic review. Ann Intern Med. 2017;167(5):332-40.

104. Bonn-Miller M, Rousseau GS. Marijuana use and PTSD among veterans. In: Gonzales JJ, McGee MP, Kemp R, editors. Veteran Care and Services: Essays and Case Studies on Practices, Innovations and Challenges: McFarland; 2020.

105. Earleywine M, Bolles JR. Marijuana, expectancies, and post-traumatic stress symptoms: A preliminary investigation. J Psychoactive Drugs. 2014;46(3):171-7.

106. Gentes EL, Schry AR, Hicks TA, Clancy CP, Collie CF, Kirby AC, et al. Prevalence and correlates of cannabis use in an outpatient VA posttraumatic stress disorder clinic. Psychol Addict Behav. 2016;30(3):415-21.

107. Greer GR, Grob CS, Halberstadt AL. PTSD symptom reports of patients evaluated for the New Mexico Medical Cannabis Program. J Psychoactive Drugs. 2014;46(1):73-7.

108. Ruglass LM, Shevorykin A, Radoncic V, Smith KM, Smith PH, Galatzer-Levy IR, et al. Impact of cannabis use on treatment outcomes among adults receiving cognitive-behavioral treatment for PTSD and substance use disorders. J Clin Med. 2017;6(2):E14.

109. Lake S, Kerr T, Buxton J, Walsh Z, Marshall B, Wood E, et al. Does cannabis use modify the effect of post-traumatic stress disorder on severe depression and suicidal ideation? Evidence from a population-based cross-sectional study of Canadians. J Psychopharmacol. 2020;34(2):181-8.

110. Bonn-Miller MO, Boden MT, Bucossi MM, Babson KA. Self-reported cannabis use characteristics, patterns and helpfulness among medical cannabis users. Am J Drug Alcohol Abuse. 2014;40(1):23-30.

111. Woolridge E, Barton S, Samuel J, Osorio J, Dougherty A, Holdcroft A. Cannabis use in HIV for pain and other medical symptoms. J Pain Symptom Manage. 2005;29(4):358-67.

112. Reinarman C, Nunberg H, Lanthier F, Heddleston T. Who Are medical marijuana patients? Population characteristics from nine California assessment clinics. J Psychoactive Drugs. 2011;43(2):128-35.

113. Ogborne AC, Smart RG, Weber T, Birchmore-Timney C. Who is using cannabis as a medicine and why: An exploratory study. J Psychoactive Drugs. 2000;32(4):435-43.

114. Sharpe L, Sinclair J, Kramer A, de Manincor M, Sarris J. Cannabis, a cause for anxiety? A critical appraisal of the anxiogenic and anxiolytic properties. J Transl Med. 2020;18(1):374.

115. Wright M, Di Ciano P, Brands B. Use of cannabidiol for the treatment of anxiety: A short synthesis of pre-clinical and clinical evidence. Cannabis Cannabinoid Res. 2020;5(3):191-6.

116. Parsons LH, Hurd YL. Endocannabinoid signalling in reward and addiction. Nature Reviews Neuroscience. 2015;16(10):579-94.

117. Sloan ME, Gowin JL, Ramchandani VA, Hurd YL, Le Foll B. The endocannabinoid system as a target for addiction treatment: Trials and tribulations. Neuropharmacology. 2017;124:73-83.

118. Wills KL, Parker LA. Effect of pharmacological modulation of the endocannabinoid system on opiate withdrawal: A review of the preclinical animal literature. Front Pharmacol. 2016;7:187.

119. Bergeria CL, Huhn AS, Dunn KE. The impact of naturalistic cannabis use on self-reported opioid withdrawal. J Subst Abuse Treat. 2020;113:108005.

120. Bisaga A, Sullivan MA, Glass A, Mishlen K, Pavlicova M, Haney M, et al. The effects of dronabinol during detoxification and the initiation of treatment with extended release naltrexone. Drug Alcohol Depend. 2015;154:38-45.

121. Lofwall MR, Babalonis S, Nuzzo PA, Elayi SC, Walsh SL. Opioid withdrawal suppression efficacy of oral dronabinol in opioid dependent humans. Drug Alcohol Depend. 2016;164:143-50.

122. Wiese B, Wilson-Poe AR. Emerging evidence for cannabis' role in opioid use disorder. Cannabis Cannabinoid Res. 2018;3(1):179-89.

123. Hurd Y. Cannabidiol: Swinging the marijuana pendulum from 'weed' to medication to treat the opioid epidemic. Trends Neurosci. 2017;40(3):124-7.

124. Parker LA, Rock EM, Limebeer CL. Regulation of nausea and vomiting by cannabinoids. Br J Pharmacol. 2011;163(7):1411-22.

125. Ren Y, Whittard J, Higuera-Matas A, Morris CV, Hurd YL. Cannabidiol, a nonpsychotropic component of cannabis, inhibits cue-induced heroin seeking and normalizes discrete mesolimbic neuronal disturbances. J Neurosci. 2009;29(47):14764-9.

126. de Carvalho CR, Takahashi RN. Cannabidiol disrupts the reconsolidation of contextual drug-associated memories in Wistar rats. Addict Biol. 2017;22(3):742-51.

127. Markos JR, Harris HM, Gul W, ElSohly MA, Sufka KJ. Effects of cannabidiol on morphine conditioned place preference in mice. Planta Med. 2018;84(4):221-4.

128. Hurd YL, Spriggs S, Alishayev J, Winkel G, Gurgov K, Kudrich C, et al. Cannabidiol for the reduction of cue-induced craving and anxiety in drug-abstinent individuals with heroin use disorder: a double-blind randomized placebo-controlled trial. Am J Psychiatry. 2019;176(11):911-22.

129. Marijuana. Liberal Party of Canada; 2015 [cited 2016 July 5]. Available from: https://www.liberal.ca/realchange/marijuana/.

130. Bill C-45: An Act respecting cannabis and to amend the Controlled Drugs and Substances Act, the Criminal Code and other Acts, 42nd Parliament, 1 Sess. (2017).

131. Cannabis legalization and regulation. Government of Canada Department of Justice; 2018 [cited 2020 April 13]. Available from: https://www.justice.gc.ca/eng/cj-jp/cannabis/.

132. Jordan H. How legalizing pot could bring more arrests. Policy Options [Internet]. 2017 July 11 [cited 2017 September 7]. Available from: http://policyoptions.irpp.org/magazines/july-2017/how-legalizing-pot-could-bring-more-arrests/.

133. Understanding the new Access to Cannabis for Medical Purposes Regulations. Health Canada; 2016 [cited 2020 April 13]. Available from: https://www.canada.ca/en/health-canada/services/publications/drugs-health-products/understanding-new-access-to-cannabis-for-medical-purposes-regulations.html.

134. Cannabis for medical purposes under the Cannabis Act: information and improvements. Government of Canada; 2020 [cited 2020 May 17]. Available from: https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/medical-use-cannabis.html#_Access_to_cannabis.

135. National Cannabis Survey, second quarter 2019. Statistics Canada; 2019 [cited 2019 November 22]. Available from: https://www150.statcan.gc.ca/n1/daily-quotidien/190815/dq190815a-eng.htm.

136. Data on cannabis for medical purposes. Government of Canada; 2020 [cited 2020 April 6]. Available from: https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/research-data/medical-purpose.html.

137. Bachhuber MA, Arnsten JH, Cunningham CO, Sohler N. Does medical cannabis use increase or decrease the use of opioid analgesics and other prescription drugs? J Addict Med. 2018;12(4):259-61.

138. Bradford AC, Bradford WD. Medical marijuana laws reduce prescription medication use in Medicare Part D. Health Aff. 2016;35(7):1230-6.

139. Bradford AC, Bradford WD. Medical marijuana laws may be associated with a decline in the number of prescriptions for Medicaid enrollees. Health Aff. 2017;36(5):945-51.

140. Bradford AC, Bradford WD, Abraham A, Bagwell Adams G. Association between US state medical cannabis laws and opioid prescribing in the Medicare Part D population. JAMA Intern Med. 2018;178(5):667-72.

141. Kim JH, Santaella J, Cerda M, Martins SS. Medical marijuana laws and annual opioid analgesic sales in the United States. Drug Alcohol Depend. 2015;156:e111.

142. Liang D, Bao Y, Wallace M, Grant I, Shi Y. Medical cannabis legalization and opioid prescriptions: evidence on US Medicaid enrollees during 1993-2014. Addiction. 2018;113(11):2060-70.

143. Shi Y, Liang D, Bao Y, An R, Wallace MS, Grant I. Recreational marijuana legalization and prescription opioids received by Medicaid enrollees. Drug Alcohol Depend. 2019;194:13-9.

144. Powell D, Pacula RL, Jacobson M. Do medical marijuana laws reduce addictions and deaths related to pain killers? J Health Econ. 2018;58:29-42.

145. Wen H, Hockenberry JM, Cummings JR. The effect of medical marijuana laws on adolescent and adult use of marijuana, alcohol, and other substances. J Health Econ. 2015;42:64-80.

146. Livingston MD, Barnett TE, Delcher C, Wagenaar AC. Recreational cannabis legalization and opioid-related deaths in Colorado, 2000–2015. Am J Public Health. 2017;107(11):1827-9.

147. Shover CL, Davis CS, Gordon SC, Humphreys K. Association between medical cannabis laws and opioid overdose mortality has reversed over time. PNAS. 2019;116:12624-6.

148. Lake S, Milloy MJ. Access to medical cannabis is expanding across North America regardless of the opioid crisis-why not study if it could help? Addiction. 2018;113(8):1550-1.

149. Haroutounian S, Ratz Y, Ginosar Y, Furmanov K, Saifi F, Meidan R, et al. The effect of medicinal cannabis on pain and quality of life outcomes in chronic pain: a prospective open-label study. Clin J Pain. 2016;32(12):1036-43.

150. Boehnke KF, Litinas E, Clauw DJ. Medical cannabis use is associated with decreased opiate medication use in a retrospective cross-sectional survey of patients with chronic pain. J Pain. 2016;17(6):739-44.

151. Boehnke KF, Scott JR, Litinas E, Sisley S, Williams DA, Clauw DJ. Pills to pot: Observational analyses of cannabis substitution among medical cannabis users with chronic pain. J Pain. 2019;20(7):830-41.

152. Reiman A, Welty M, Solomon P. Cannabis as a substitute for opioid-based pain medication: Patient self-report. Cannabis Cannabinoid Res. 2017;2(1):160-6.

153. Lucas P, Reiman A, Earleywine M, McGowan SK, Oleson M, Coward MP, et al. Cannabis as a substitute for alcohol and other drugs: A dispensary-based survey of substitution effect in Canadian medical cannabis patients. Addiction Res Theory. 2013;21(5):435-42.

154. Lucas P, Walsh Z, Crosby K, Callaway R, Belle-Isle L, Kay R, et al. Substituting cannabis for prescription drugs, alcohol and other substances among medical cannabis patients: The impact of contextual factors. Drug Alcohol Rev. 2015;35(3):326-33.

155. Lucas P, Walsh Z. Medical cannabis access, use, and substitution for prescription opioids and other substances: A survey of authorized medical cannabis patients. Int J Drug Policy. 2017;42(Supplement C):30-5.

156. Corroon JM, Jr., Mischley LK, Sexton M. Cannabis as a substitute for prescription drugs - a cross-sectional study. J Pain Res. 2017;10:989-98.

157. Cooke AC, Knight KR, Miaskowski C. Patients' and clinicians' perspectives of co-use of cannabis and opioids for chronic non-cancer pain management in primary care. Int J Drug Policy. 2019;63:23-8.

158. Vigil JM, Stith SS, Adams IM, Reeve AP. Associations between medical cannabis and prescription opioid use in chronic pain patients: A preliminary cohort study. PLoS One. 2017;12(11):e0187795.

159. Campbell G, Hall WD, Peacock A, Lintzeris N, Bruno R, Larance B, et al. Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: findings from a 4-year prospective cohort study. Lancet Public Health. 2018;3(7):e341-e50.

160. Sohler NL, Starrels JL, Khalid L, Bachhuber MA, Arnsten JH, Nahvi S, et al. Cannabis use is associated with lower odds of prescription opioid analgesic use among HIV-infected individuals with chronic pain. Subst Use Misuse. 2018;53(10):1602-7.

161. Lake S, Kerr T, Capler R, Shoveller J, Montaner J, Milloy M-JM. High-intensity cannabis use and HIV clinical outcomes among HIV-positive people who use illicit drugs in Vancouver, Canada. Int J Drug Policy. 2017;42:63-70.

162. Nutt DJ, King LA, Phillips LD. Drug harms in the UK: A multicriteria decision analysis. Lancet. 2010;376(9752):1558-65.

163. Wenger LD, Lopez AM, Comfort M, Kral AH. The phenomenon of low-frequency heroin injection among street-based urban poor: drug user strategies and contexts of use. Int J Drug Policy. 2014;25(3):471-9.

164. Paul B, Thulien M, Knight R, Milloy MJ, Howard B, Nelson S, et al. "Something that actually works": Cannabis use among young people in the context of street entrenchment. PLoS One. 2020;15(7):e0236243.

165. Boeri M, Pereira E, Minkova A, Marcato K, Martinez E, Woodall D. Green hope: perspectives on cannabis from people who use opioids. Sociol Inq. 2020.

166. Zielinski L, Bhatt M, Sanger N, Plater C, Worster A, Varenbut M, et al. Association between cannabis use and methadone maintenance treatment outcomes: an investigation into sex differences. Biol Sex Differ. 2017;8(1):8.

167. Ellner M. Marijuana use by heroin abusers as a factor in program retention. J Consult Clin Psychol. 1977;45(4):709-10.

168. McElrath K. Medication-assisted treatment for opioid addiction in the United States: Critique and commentary. Subst Use Misuse. 2018;53(2):334-43.

169. Knopf A. Why are methadone patients still being punished for marijuana use? Filter [Internet]. 2019 March 31 [cited 2020 April 27]. Available from: https://filtermag.org/why-are-methadone-patients-still-being-punished-for-marijuana-use/.

170. Miller J. Ottawa doctor pioneers use of cannabis to help opioid addicts. Ottawa Citizen [Internet]. 2017 April 17 [cited 2017 November 23]; Available from: http://ottawacitizen.com/news/local-news/can-cannabis-help-addicts-reduce-or-stop-using-opioids.

171. New York State Department of Health announces opioid replacement now a qualifying condition for medical marijuana. New York State; 2018 [cited 2020 July 12]. Available from: https://www.health.ny.gov/press/releases/2018/2018-07-12_opioid_replacement.htm.

172. New Jersey to allow medical marijuana for opioid addiction treatment. Practical Pain Management; 2020 [cited 2020 December 1]. Available from: https://www.practicalpainmanagement.com/treatments/pharmacological/new-jersey-allow-medical-marijuana-opioid-addiction-treatment.

173. Scavone JL, Sterling RC, Weinstein SP, Van Bockstaele EJ. Impact of cannabis use during stabilization on methadone maintenance treatment. Am J Addict. 2013;22(4):344-51.

174. Wasserman DA, Weinstein MG, Havassy BE, Hall SM. Factors associated with lapses to heroin use during methadone maintenance. Drug Alcohol Depend. 1998;52(3):183-92.

175. The Canadian Press. Legalizing cannabis could offer promise for slashing opioid use, experts say. CBC News [Internet]. 2017 June 15 [cited 2017 November 23]; Available from: http://www.cbc.ca/news/health/cannabis-opioids-pain-treatment-1.4160769.

176. Wong T, Yan A. 2019 Downtown Eastside local area profile [Internet]. Simon Fraser University; 2019. Available from: https://www.sfu.ca/continuing-studies/about/program-units/city-program/blog/posts/2019-downtown-eastside-local-area-profile.html.

177. Wood E, Spittal PM, Small W, Kerr T, Li K, Hogg RS, et al. Displacement of Canada's largest public illicit drug market in response to a police crackdown. CMAJ. 2004;170(10):1551-6.

178. Maas B, Fairbairn N, Kerr T, Li K, Montaner JS, Wood E. Neighborhood and HIV infection among IDU: place of residence independently predicts HIV infection among a cohort of injection drug users. Health Place. 2007;13(2):432-9.

179. Maberley DA, Hollands H, Chang A, Adilman S, Chakraborti B, Kliever G. The prevalence of low vision and blindness in a Canadian inner city. Eye. 2007;21(4):528-33.

180. Somers JM, Moniruzzaman A, Rezansoff SN. Migration to the Downtown Eastside neighbourhood of Vancouver and changes in service use in a cohort of mentally ill homeless adults: a 10-year retrospective study. BMJ Open. 2016;6(1):e009043.

181. Ivsins A, Vancouver Area Network Of Drug Users, Benoit C, Kobayashi K, Boyd S. From risky places to safe spaces: Re-assembling spaces and places in Vancouver's Downtown Eastside. Health Place. 2019;59:102164.

182. Tyndall MW, Currie S, Spittal P, Li K, Wood E, O'Shaughnessy MV, et al. Intensive injection cocaine use as the primary risk factor in the Vancouver HIV-1 epidemic. AIDS. 2003;17(6):887-93.

183. Wood E, Tyndall M, Spittal P, Li C, Anis A, Hogg R, et al. Impact of supply-side policies for control of illicit drugs in the face of the AIDS and overdose epidemics: investigation of a massive heroin seizure. CMAJ: Canadian Medical Association Journal. 2003;168(2):165-69.

184. Small D, Palepu A, Tyndall MW. The establishment of North America's first state sanctioned supervised injection facility: A case study in culture change. Int J Drug Policy. 2006;17(2):73-82.

185. Young S, Fairbairn N. Expanding supervised injection facilities across Canada: lessons from the Vancouver experience. Can J Public Health. 2018;109(2):227-30.

186. Browne R. Black and Indigenous people are overrepresented in Canada's weed arrests. VICE [Internet]. 2018 April 18 [cited 2018 April 24]; Available from: https://news.vice.com/en_ca/article/d35eyq/black-and-indigenous-people-are-overrepresented-in-canadas-weed-arrests.

187. Lakić S. Cannabis Substitution Project claims its free 'care packages' help opioid users kick. Vancouver Courier [Internet]. 2018 March 22 [cited 2018 December 3]; Available from: https://www.vancourier.com/news/cannabis-substitution-project-claims-its-free-care-packages-help-opioid-users-kick-1.23209946.

188. Valleriani J, Haines-Saah R, Capler R, Bluthenthal R, Socias ME, Milloy MJ, et al. The emergence of innovative cannabis distribution projects in the downtown eastside of Vancouver, Canada. Int J Drug Policy. 2020;79:102737.

189. Fumano D. Pop-up Vancouver pot dispensary an 'outside the box' approach to opioid crisis. Vancouver Sun [Internet]. 2017 August 29 [cited 2017 November 30]; Available from: https://vancouversun.com/news/local-news/pop-up-vancouver-pot-dispensary-an-outside-the-box-approach-to-opioid-crisis/.

190. Johnson L. Marijuana dispensary regulations approved in Vancouver. [Internet]. 2015[cited 2020 April 4]; Available from: https://www.cbc.ca/news/canada/british-columbia/marijuana-dispensary-regulations-approved-in-vancouver-1.3126111.

191. Penner D. Rebellious Vancouver cannabis retailers fall into compliance with court order. The Vancouver Sun [Internet]. 2019 June 6 [cited 2020 April 4]; Available from: https://vancouversun.com/news/local-news/rebellious-vancouver-cannabis-retailers-fall-into-compliance-with-court-order/.

192. Tyndall MW, Craib KJP, Currie S, Li K, O'Shaughnessy MV, Schechter MT. Impact of HIV infection on mortality in a cohort of injection drug users. JAIDS. 2001;28(4):351-7.

193. Social Determinants of Health. Public Health Agency of Canada; 2016 [cited 2016 December 2]. Available from: http://cbpp-pcpe.phac-aspc.gc.ca/public-health-topics/social-determinants-of-health/.

194. Galea S, Vlahov D. Social determinants and the health of drug users: socioeconomic status, homelessness, and incarceration. Public Health Rep. 2002;117(Suppl 1):S135-S45.

195. Rhodes T. The 'risk environment': A framework for understanding and reducing drug-related harm. Int J Drug Policy. 2002;13:85-94.

196. Rhodes T, Singer M, Bourgois P, Friedman SR, Strathdee SA. The social structural production of HIV risk among injecting drug users. Soc Sci Med. 2005;61(5):1026-44.

197. Strathdee SA, Hallett TB, Bobrova N, Rhodes T, Booth R, Abdool R, et al. HIV and risk environment for injecting drug users: the past, present, and future. Lancet. 2010;376(9737):268-84.

198. Kerr T, Small W, Moore D, Wood E. A micro-environmental intervention to reduce the harms associated with drug-related overdose: evidence from the evaluation of Vancouver's safer injection facility. Int J Drug Policy. 2007;18(1):37-45.

199. Fairbairn N, Small W, Shannon K, Wood E, Kerr T. Seeking refuge from violence in street-based drug scenes: women's experiences in North America's first supervised injection facility. Soc Sci Med. 2008;67(5):817-23.

200. Kennedy MC, Hayashi K, Milloy MJ, Boyd J, Wood E, Kerr T. Supervised injection facility use and exposure to violence among a cohort of people who inject drugs: A gender-based analysis. Int J Drug Policy. 2020;78:102692.

201. McNeil R, Small W, Wood E, Kerr T. Hospitals as a 'risk environment': an ethno-epidemiological study of voluntary and involuntary discharge from hospital against medical advice among people who inject drugs. Soc Sci Med. 2014;105:59-66.

202. Foreman-Mackey A, Bayoumi AM, Miskovic M, Kolla G, Strike C. 'It's our safe sanctuary': Experiences of using an unsanctioned overdose prevention site in Toronto, Ontario. Int J Drug Policy. 2019;73:135-40.

203. Hursh SR, Galuska CM, Winger G, Woods JH. The economics of drug abuse: a quantitative assessment of drug demand. Mol Interv. 2005;5(1):20-8.

204. Resko S, Ellis J, Early TJ, Szechy KA, Rodriguez B, Agius E. Understanding public attitudes toward cannabis legalization: Qualitative findings from a statewide survey. Subst Use Misuse. 2019;54(8):1247-59.

205. Cunningham JA. Beliefs about cannabis at the time of legalization in Canada: Results from a general population survey. Harm Reduct J. 2020;17(1):2.

206. Paulozzi LJ, Ryan GW. Opioid analgesics and rates of fatal drug poisoning in the United States. Am J Prev Med. 2006;31(6):506-11.

207. Sofuoglu M, DeVito EE, Carroll KM. Pharmacological and Behavioral Treatment of Opioid Use Disorder. Psychiatric Research and Clinical Practice. 2019;1(1):4-15.

208. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database Syst Rev. 2009;3:Cd002209.

209. Platt L, Minozzi S, Reed J, Vickerman P, Hagan H, French C, et al. Needle syringe programmes and opioid substitution therapy for preventing hepatitis C transmission in people who inject drugs. Cochrane Database Syst Rev. 2017;9:Cd012021.

210. Sordo L, Barrio G, Bravo MJ, Indave BI, Degenhardt L, Wiessing L, et al. Mortality risk during and after opioid substitution treatment: Systematic review and meta-analysis of cohort studies. BMJ. 2017;357:j1550.

211. Lappalainen L, Nolan S, Dobrer S, Puscas C, Montaner J, Ahamad K, et al. Dose-response relationship between methadone dose and adherence to antiretroviral therapy among HIV-positive people who use illicit opioids. Addiction. 2015;110(8):1330-9.

212. Feelemyer JP, D. DJC, Arasteh K, Phillips BW, Hagan H. Changes in quality of life (WHOQOL-BREF) and addiction severity index (ASI) among participants in opioid substitution treatment (OST) in low and middle income countries: An international systematic review. Drug Alcohol Depend. 2014;134:251-8.

213. Hser YI, Saxon AJ, Huang D, Hasson A, Thomas C, Hillhouse M, et al. Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. Addiction. 2014;109(1):79-87.

214. Bawor M, Dennis BB, Varenbut M, Daiter J, Marsh DC, Plater C, et al. Sex differences in substance use, health, and social functioning among opioid users receiving methadone treatment: A multicenter cohort study. Biol Sex Differ. 2015;6:21.

215. Schifano F, Martinotti G, Cunniff A, Reissner V, Scherbaum N, Ghodse H. Impact of an 18-month, NHS-based, treatment exposure for heroin dependence: Results from the London Area Treat 2000 Study. Am J Addict. 2012;21(3):268-73.

216. Nava F, Manzato E, Lucchini A. Chronic cannabis use does not affect the normalization of hypothalamic-pituitary-adrenal (HPA) axis induced by methadone in heroin addicts. Prog Neuropsychopharmacol Biol Psychiatry. 2007;31(5):1089-94.

217. Best D, Harris J, Gossop M, Farrell M, Finch E, Noble A, et al. Use of non-prescribed methadone and other illicit drugs during methadone maintenance treatment. Drug Alcohol Rev. 2000;19(1):9-16.

218. Scheibe A, Shelly S, Gerardy T, von Homeyer Z, Schneider A, Padayachee K, et al. Six-month retention and changes in quality of life and substance use from a low-threshold methadone maintenance therapy programme in Durban, South Africa. Addict Sci Clin Pract. 2020;15(1):13.

219. Makarenko I, Pykalo I, Springer SA, Mazhnaya A, Marcus R, Filippovich S, et al. Treating opioid dependence with extended-release naltrexone (XR-NTX) in Ukraine: Feasibility and three-month outcomes. J Subst Abuse Treat. 2019;104:34-41.

220. Best D, Gossop M, Greenwood J, Marsden J, Lehmann P, Strang J. Cannabis use in relation to illicit drug use and health problems among opiate misusers in treatment. Drug Alcohol Rev. 1999;18(1):31-8.

221. Nirenberg TD, Liepman MR, Cellucci T, Swift RM, Sirota AD. Cannabis versus other illicit drug use among methadone maintenance patients. Psychol Addict Behav. 1996;10(4):222-7.

222. Saxon AJ, Wells EA, Fleming C, Jackson TR, Calsyn DA. Pre-treatment characteristics, program philosophy and level of ancillary services as predictors of methadone maintenance treatment outcome. Addiction. 1996;91(8):1197-209.

223. Fairbank JA, Dunteman GH, Condelli WS. Do methadone patients substitute other drugs for heroin? Predicting substance use at 1-year follow-up. Am J Drug Alcohol Abuse. 1993;19(4):465-74.

224. Epstein DH, Preston KL. Does cannabis use predict poor outcome for heroin-dependent patients on maintenance treatment? Past findings and more evidence against. Addiction. 2003;98(3):269-79.

225. Bruneau J, Ahamad K, Goyer ME, Poulin G, Selby P, Fischer B, et al. Management of opioid use disorders: a national clinical practice guideline. CMAJ. 2018;190(9):E247-E57.

226. Ahamad K, Milloy MJ, Nguyen P, Uhlmann S, Johnson C, Korthuis TP, et al. Factors associated with willingness to take extended release naltrexone among injection drug users. Addict Sci Clin Pract. 2015;10:12.

227. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Ann Intern Med. 2009;151(4):264-9.

228. Study quality assessment tools. NIH National Heart, Lung, and Blood Institute (NHLBI); n.d. [cited 2019 September 10]. Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.

229. Bagra I, Krishnan V, Rao R, Agrawal A. Does cannabis use influence opioid outcomes and quality of life among buprenorphine maintained patients? A cross-sectional, comparative study. J Addict Med. 2018;12(4):315-20.

230. Franklyn AM, Eibl JK, Gauthier GJ, Marsh DC. The impact of cannabis use on patients enrolled in opioid agonist therapy in Ontario, Canada. PLoS One. 2017;12(11):e0187633.

231. Socías ME, Wood E, Lake S, Nolan S, Fairbairn N, Hayashi K, et al. High-intensity cannabis use is associated with retention in opioid agonist treatment: A longitudinal analysis. Addiction. 2018;113(12):2250-58.

232. Weizman T, Gelkopf M, Melamed Y, Adelson M, Bleich A. Cannabis abuse is not a risk factor for treatment outcome in methadone maintenance treatment: A 1-year prospective study in an Israeli clinic. Aust N Z J Psychiatry. 2004;38(1-2):42-6.

233. Zielinski L, Bhatt M, Sanger N, Plater C, Worster A, Varenbut M, et al. Association between cannabis use and methadone maintenance treatment outcomes: an investigation into sex differences. Biol Sex Differ. 2017;8.

234. Epstein DH, Preston KL. No evidence for reduction of opioid-withdrawal symptoms by cannabis smoking during a methadone dose taper. Am J Addict. 2015;24(4):323-8.

235. Raby WN, Carpenter KM, Rothenberg J, Brooks AC, Jiang H, Sullivan M, et al. Intermittent marijuana use is associated with improved retention in naltrexone treatment for opiate-dependence. Am J Addict. 2009;18(4):301-8.

236. Budney AJ, Bickel WK, Amass L. Marijuana use and treatment outcome among opioid-dependent patients. Addiction. 1998;93(4):493-503.

237. Hill KP, Bennett HE, Griffin ML, Connery HS, Fitzmaurice GM, Subramaniam G, et al. Association of cannabis use with opioid outcomes among opioid-dependent youth. Drug Alcohol Depend. 2013;132(1–2):342-5.

238. Levine AR, Lundahl LH, Ledgerwood DM, Lisieski M, Rhodes GL, Greenwald MK. Gender-specific predictors of retention and opioid abstinence during methadone maintenance treatment. J Subst Abuse Treat. 2015;54:37-43.

239. Proctor SL, Copeland AL, Kopak AM, Hoffmann NG, Herschman PL, Polukhina N. Outcome predictors for patients receiving methadone maintenance treatment: Findings from a retrospective multi-site study. J Subst Use. 2016;21(6):601-13.

240. Somers CJ, O'Connor J. Retrospective study of outcomes, for patients admitted to a drug treatment centre board. Irish Med J. 2012;105(9):295-8.

241. Abrahamsson T, Widinghoff C, Lilliebladh A, Gedeon C, Nilvall K, Hakansson A. Interim buprenorphine treatment in opiate dependence: A pilot effectiveness study. Subst Abus. 2016;37(1):104-9.

242. Church SH, Rothenberg JL, Sullivan MA, Bornstein G, Nunes EV. Concurrent substance use and outcome in combined behavioral and naltrexone therapy for opiate dependence. Am J Drug Alcohol Abuse. 2001;27(3):441-52.

243. Eastwood B, Strang J, Marsden J. Change in alcohol and other drug use during five years of continuous opioid substitution treatment. Drug Alcohol Depend. 2019;194:438-46.

244. Roux P, Carrieri PM, Cohen J, Ravaux I, Spire B, Gossop M, et al. Non-medical use of opioids among HIV-infected opioid dependent individuals on opioid maintenance treatment: The need for a more comprehensive approach. Harm Reduct J. 2011;8.

245. Lions C, Carrieri MP, Michel L, Mora M, Marcellin F, Morel A, et al. Predictors of non-prescribed opioid use after one year of methadone treatment: An attributable-risk approach (ANRS-Methaville trial). Drug Alcohol Depend. 2014;135:1-8.

246. Roux P, Lions C, Michel L, Cohen J, Mora M, Marcellin F, et al. Predictors of non-adherence to methadone maintenance treatment in opioiddependent individuals: Implications for clinicians. Curr Pharm Des. 2014;20(25):4097-105.

247. Fareed A, Eilender P, Ketchen B, Buchanan-Cummings AM, Scheinberg K, Crampton K, et al. Factors affecting noncompliance with buprenorphine maintenance treatment. J Addict Med. 2014;8(5):345-50.

248. Joe GW. Effects of readiness for drug abuse treatment on client retention and assessment of process. Addiction. 1998;93(8):1177-90.

249. Klimas J, Nosova E, Socias E, Nolan S, Brar R, Hayashi K, et al. Factors associated with discontinuation of methadone maintenance therapy (MMT) among persons who use alcohol in Vancouver, Canada. Drug Alcohol Depend. 2018;186:182-6.

250. Peles E, Linzy S, Kreek MJ, Adelson M. One-year and cumulative retention as predictors of success in methadone maintenance treatment: A comparison of two clinics in the United States and Israel. J Addict Dis. 2008;27(4):11-25.

251. Schiff M, Levit S, Moreno RC. Retention and illicit drug use among methadone patients in Israel: a gender comparison. Addict Behav. 2007;32(10):2108-19.

252. White WL, Campbell MD, Spencerc RD, Hoffman HA, Crissman B, DuPont RL. Patterns of abstinence or continued drug use among methadone maintenance patients and their relation to treatment retention. J Psychoactive Drugs. 2014;46(2):114-22.

253. Håkansson A, Widinghoff C, Abrahamsson T, Gedeon C. Correlates of nine-month retention following interim buprenorphine-naloxone treatment in opioid dependence: A pilot study. J Addict. 2016;2016:8.

254. Matson SC, Hobson G, Abdel-Rasoul M, Bonny AE. A retrospective study of retention of opioid-dependent adolescents and young adults in an outpatient buprenorphine/naloxone clinic. J Addict Med. 2014;8(3):176-82.

255. Chaudhry ZA, Sultan J, Alam F. Predictors for retention in treatment with a UK community-based naltrexone programme for opioid dependence. Psychiatrist. 2012;36(6):218-24.

256. Dayal P, Balhara YPS, Mishra AK. An open label naturalistic study of predictors of retention and compliance to naltrexone maintenance treatment among patients with opioid dependence. J Subst Use. 2016;21(3):309-16.

257. Jarvis BP, Holtyn AF, Berry MS, Subramaniam S, Umbricht A, Fingerhood M, et al. Predictors of induction onto extended-release naltrexone among unemployed heroin-dependent adults. J Subst Abuse Treat. 2018;85:38-44.

258. McBrien H, Luo C, Sanger N, Zielinski L, Bhatt M, Zhu XM, et al. Cannabis use during methadone maintenance treatment for opioid use disorder: a systematic review and meta-analysis. CMAJ Open. 2019;7(4):E665-E73.

259. Yamaguchi T, Hagiwara Y, Tanaka H, Sugiura T, Waku K, Shoyama Y, et al. Endogenous cannabinoid, 2-arachidonoylglycerol, attenuates naloxone-precipitated withdrawal signs in morphine-dependent mice. Brain Res. 2001;909(1):121-6.

260. Vela G, Ruiz-gayo M, Fuentes JA. Anandamide decreases naloxone-precipitated withdrawal signs in mice chronically treated with morphine. Neuropharmacology. 1995;34(6):665-8.

261. Villafranca SW, McKellar JD, Trafton JA, Humphreys K. Predictors of retention in methadone programs: A signal detection analysis. Drug Alcohol Depend. 2006;83(3):218-24.

262. Peles E, Schreiber S, Adelson M. Factors predicting retention in treatment: 10-year experience of a methadone maintenance treatment (MMT) clinic in Israel. Drug Alcohol Depend. 2006;82(3):211-7.

263. Drug testing: A white paper of the American Society of Addiction Medicine [Internet]. American Society of Addiction Medicine (ASAM); 2013. Available from: https://www.asam.org/Quality-Science/publications/magazine/read/article/2013/12/16/asam-releases-white-paper-on-drug-testing.

264. Freeman TP, Lorenzetti V. 'Standard THC units': a proposal to standardize dose across all cannabis products and methods of administration. Addiction. 2020;115(7):1207-16.

265. Special Advisory Committee on the Epidemic of Opioid Overdoses. National report: Apparent opioid-related deaths in Canada (January 2016 to March 2018) [Internet]. Ottawa: Public Health Agency of Canada; 2018. Available from: https://www.canada.ca/en/public-health/services/publications/healthy-living/national-report-apparent-opioid-related-deaths-released-september-2018.html#consid.

266. Gomes T, Tadrous M, Mamdani MM, Paterson JM, Juurlink DN. The burden of opioid-related mortality in the United States. JAMA Netw Open. 2018;1(2):e180217.

267. Krawczyk N, Mojtabai R, Stuart EA, Fingerhood M, Agus D, Lyons BC, et al. Opioid agonist treatment and fatal overdose risk in a state-wide US population receiving opioid use disorder services. Addiction. 2020.

268. Strain EC, Stitzer ML, Liebson IA, Bigelow GE. Dose-response effects of methadone in the treatment of opioid dependence. Ann Intern Med. 1993;119(1):23-7.

269. Kelly SM, O'Grady KE, Mitchell SG, Brown BS, Schwartz RP. Predictors of methadone treatment retention from a multi-site study: a survival analysis. Drug Alcohol Depend. 2011;117(2-3):170-5.

270. Nosyk B, MacNab YC, Sun H, Fischer B, Marsh DC, Schechter MT, et al. Proportional hazards frailty models for recurrent methadone maintenance treatment. Am J Epidemiol. 2009;170(6):783-92.

271. Mullen L, Barry J, Long J, Keenan E, Mulholland D, Grogan L, et al. A national study of the retention of Irish opiate users in methadone substitution treatment. Am J Drug Alcohol Abuse. 2012;38(6):551-8.

272. Wickersham JA, Zahari MM, Azar MM, Kamarulzaman A, Altice FL. Methadone dose at the time of release from prison significantly influences retention in treatment: implications from a pilot study of HIV-infected prisoners transitioning to the community in Malaysia. Drug Alcohol Depend. 2013;132(1-2):378-82.

273. Peles E, Schreiber S, Sason A, Adelson M. Similarities and changes between 15- and 24-year survival and retention rates of patients in a large medical-affiliated methadone maintenance treatment (MMT) center. Drug Alcohol Depend. 2018;185:112-9.

274. Strain EC, Stitzer ML, Liebson IA, Bigelow GE. Methadone dose and treatment outcome. Drug Alcohol Depend. 1993;33(2):105-17.

275. Swensen G, Ilett KF, Dusci LJ, Hackett LP, Ong RTT, Quigley AJ, et al. Patterns of drug use by participants in the Western Australian methadone program, 1984-1991. Med J Australia. 1993;159(6):373-6.

276. Hser Y-I, Saxon AJ, Huang D, Hasson A, Thomas C, Hillhouse M, et al. Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. Addiction. 2014;109(1):79-87.

277. Donny EC, Walsh SL, Bigelow GE, Eissenberg T, Stitzer ML. High-dose methadone produces superior opioid blockade and comparable withdrawal suppression to lower doses in opioid-dependent humans. Psychopharmacology (Berl). 2002;161(2):202-12.

278. D'Aunno T, Pollack HA, Frimpong JA, Wutchiett D. Evidence-based treatment for opioid disorders: a 23-year national study of methadone dose levels. J Subst Abuse Treat. 2014;47(4):245-50.

279. Sullivan LE, Moore BA, O'Connor PG, Barry DT, Chawarski MC, Schottenfeld RS, et al. The association between cocaine use and treatment outcomes in patients receiving office-based buprenorphine/naloxone for the treatment of opioid dependence. Am J Addict. 2010;19(1):53-8.

280. Weizman T, Gelkopf M, Melamed Y, Adelson M, Bleich A. Cannabis abuse is not a risk factor for treatment outcome in methadone maintenance treatment: a 1-year prospective study in an Israeli clinic. Aust N Z J Psychiatry. 2004;38(1-2):42-6.

281. Bachhuber MA, Saloner B, Cunningham CO, Barry CL. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. JAMA Intern Med. 2014;174(10):1668-73.

282. Shi Y. Medical marijuana policies and hospitalizations related to marijuana and opioid pain reliever. Drug Alcohol Depend. 2017;173:144-50.

283. Scavone JL, Sterling RC, Van Bockstaele EJ. Cannabinoid and opioid interactions: implications for opiate dependence and withdrawal. Neuroscience. 2013;248:637-54.

284. Ware MA, Adams H, Guy GW. The medicinal use of cannabis in the UK: results of a nationwide survey. International Journal of Clinical Practice. 2005;59(3):291-5.

285. Hser YI, Huang D, Saxon AJ, Woody G, Moskowitz AL, Matthews AG, et al. Distinctive trajectories of opioid use over an extended follow-up of patients in a multisite trial on buprenorphine+naloxone and methadone. J Addict Med. 2017;11(1):63-9.

286. Socías ME, Wood E, McNeil R, Kerr T, Dong H, Shoveller J, et al. Unintended impacts of regulatory changes to British Columbia Methadone Maintenance Program on addiction and HIV-related outcomes: An interrupted time series analysis. Int J Drug Policy. 2017;45:1-8.

287. Cousins G, Boland F, Barry J, Lyons S, Keenan E, O'Driscoll D, et al. J-shaped relationship between supervised methadone consumption and retention in methadone maintenance treatment (MMT) in primary care: National cohort study. Drug Alcohol Depend. 2017;173:126-31.

288. Volpe DA, Xu Y, Sahajwalla CG, Younis IR, Patel V. Methadone metabolism and drug-drug interactions: In vitro and in vivo literature review. J Pharm Sci. 2018;107(12):2983-91.

289. Chalabianloo F, Westin AA, Skogvoll E, Bramness JG, Spigset O. Methadone serum concentrations and influencing factors: A naturalistic observational study. Psychopharmacology (Berl). 2019;236(11):3159-67.

290. Qian Y, Gurley BJ, Markowitz JS. The potential for pharmacokinetic interactions between cannabis products and conventional medications. J Clin Psychopharmacol. 2019;39(5):462-71.

291. Foster BC, Abramovici H, Harris CS. Cannabis and cannabinoids: Kinetics and interactions. Am J Med. 2019;132(11):1266-70.

292. Socias ME, Nosova E, Lake S, Hayashi K, Kerr T, Milloy M-J. A call for experimental research on the risks and benefits of cannabis in the context of treatment for opioid use disorder. CMAJ Open; 2019 [cited 2020 July 16]. Available from: http://cmajopen.ca/content/7/4/E665.short/reply#cmajo_el_1922.

293. Lo A, Kerr T, Hayashi K, Milloy MJ, Nosova E, Liu Y, et al. Factors associated with methadone maintenance therapy discontinuation among people who inject drugs. J Subst Abuse Treat. 2018;94:41-6.

294. Lundgren LM, Sullivan LM, Maina AW, Schilling RF. Client factors associated with length of stay in methadone treatment among heroin users who inject drugs: quantitative analysis of state-level substance abuse treatment utilization data. J Addict Med. 2007;1(1):26-32.

295. Hayashi K, Ti L, Ayutthaya PPN, Suwannawong P, Kaplan K, Small W, et al. Barriers to retention in methadone maintenance therapy among people who inject drugs in Bangkok, Thailand: a mixed-methods study. Harm Reduct J. 2017;14(1):63.

296. Wood E, Li K, Palepu A, Marsh DC, Schechter MT, Hogg RS, et al. Sociodemographic disparities in access to addiction treatment among a cohort of Vancouver injection drug users. Subst Use Misuse. 2005;40(8):1153-67.

297. Darke S. Self-report among injecting drug users: A review. Drug Alcohol Depend. 1998;51(3):253-63.

298. Langendam MW, van Haastrecht HJ, van Ameijden EJ. The validity of drug users' self-reports in a non-treatment setting: prevalence and predictors of incorrect reporting methadone treatment modalities. Int J Epidemiol. 1999;28(3):514-20.

299. Manini AF, Yiannoulos G, Bergamaschi MM, Hernandez S, Olmedo R, Barnes AJ, et al. Safety and pharmacokinetics of oral cannabidiol when administered concomitantly with intravenous fentanyl in humans. J Addict Med. 2015;9(3):204-10.

300. World Drug Report 2019. United Nations; 2019 [cited 2020 January 22]. Available from: https://wdr.unodc.org/wdr2019/en/index.html.

301. Degenhardt L, Ferrari AJ, Calabria B, Hall WD, Norman RE, McGrath J, et al. The global epidemiology and contribution of cannabis use and dependence to the global burden of disease: results from the GBD 2010 study. PLoS One. 2013;8(10):e76635.

302. Lev-Ran S, Imtiaz S, Taylor BJ, Shield KD, Rehm J, Le Foll B. Gender differences in health-related quality of life among cannabis users: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Drug Alcohol Depend. 2012;123(1-3):190-200.

303. Subbaraman MS, Kerr WC. Support for marijuana legalization in the US state of Washington has continued to increase through 2016. Drug Alcohol Depend. 2017;175:205-9.

304. Lucas P, Baron EP, Jikomes N. Medical cannabis patterns of use and substitution for opioids & other pharmaceutical drugs, alcohol, tobacco, and illicit substances; results from a cross-sectional survey of authorized patients. Harm Reduct J. 2019;16(1):9.

305. Data on cannabis for medical purposes. Government of Canada; 2019 [cited 2019 August 7]. Available from: https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/research-data/medical-purpose.html.

306. Canadian Tobacco, Alcohol and Drugs Survey (CTADS): Summary of results for 2017. Government of Canada; 2019 [updated 2019 January 4; cited 2019 June 17]. Available from: https://www.canada.ca/en/health-canada/services/canadian-tobacco-alcohol-drugs-survey/2017-summary.html#n3.

307. Peretti-Watel P, Spire B, Lert F, Obadia Y. Drug use patterns and adherence to treatment among HIV-positive patients: evidence from a large sample of French outpatients (ANRS-EN12-VESPA 2003). Drug Alcohol Depend. 2006;82 Suppl 1:S71-9.

308. Walley AY, Krupitsky EM, Cheng DM, Raj A, Edwards EM, Bridden C, et al. Implications of cannabis use and heavy alcohol use on HIV drug risk behaviors in Russian heroin users. AIDS Behav. 2008;12(4):662-9.

309. Slawson G, Milloy MJ, Balneaves L, Simo A, Guillemi S, Hogg R, et al. High-intensity cannabis use and adherence to antiretroviral therapy among people who use illicit drugs in a Canadian setting. AIDS Behav. 2014:1-8.

310. Vidot DC, Manuzak JA, Klatt NR, Pallikkuth S, Roach M, Dilworth SE, et al. Hazardous cannabis use and monocyte activation among methamphetamine users with treated HIV infection. JAIDS. 2019;81(3):361-4.

311. Boyd J, Fast D, Hobbins M, McNeil R, Small W. Social-structural factors influencing periods of injection cessation among marginalized youth who inject drugs in Vancouver, Canada: an ethno-epidemiological study. Harm Reduct J. 2017;14(1):31.

312. Hagenaars JA, McCutcheon A. Applied latent class analysis. Cambridge: Cambridge University Press; 2002.

313. Betts KS, Chan G, McIlwraith F, Dietze P, Whittaker E, Burns L, et al. Differences in polysubstance use patterns and drug-related outcomes between people who inject drugs receiving and not receiving opioid substitution therapies. Addiction. 2016;111(7):1214-23.

314. Mackesy-Amiti ME, Boodram B, Handanagic S, Paz-Bailey G, Prachand NG, Broz D. Latent classes of sexual risk behavior and engagement in outreach, intervention and prevention services among women who inject drugs across 20 US cities. JAIDS. 2018;79(3):305-14.

315. Meacham MC, Roesch SC, Strathdee SA, Lindsay S, Gonzalez-Zuniga P, Gaines TL. Latent classes of polydrug and polyroute use and associations with human immunodeficiency virus risk behaviours and overdose among people who inject drugs in Tijuana, Baja California, Mexico. Drug Alcohol Rev. 2017;37(1):128-36.

316. Melendez-Torres GJ, Bourne A, Hickson F, Reid D, Weatherburn P. Correlates and subgroups of injecting drug use in UK gay and bisexual men: Findings from the 2014 Gay Men's Sex Survey. Drug Alcohol Depend. 2018;187:292-5.

317. Monga N, Rehm J, Fischer B, Brissette S, Bruneau J, El-Guebaly N, et al. Using latent class analysis (LCA) to analyze patterns of drug use in a population of illegal opioid users. Drug Alcohol Depend. 2007;88(1):1-8.

318. Schneider KE, Park JN, Allen ST, Weir BW, Sherman SG. Patterns of polysubstance use and overdose among people who inject drugs in Baltimore, Maryland: A latent class analysis. Drug Alcohol Depend. 2019;201:71-7.

319. Kuramoto SJ, Bohnert AS, Latkin CA. Understanding subtypes of inner-city drug users with a latent class approach. Drug Alcohol Depend. 2011;118(2-3):237-43.

320. Harrell PT, Mancha BE, Petras H, Trenz RC, Latimer WW. Latent classes of heroin and cocaine users predict unique HIV/HCV risk factors. Drug Alcohol Depend. 2012;122(3):220-7.

321. Gicquelais RE, Genberg BL, Astemborski J, Celentano DD, Kirk GD, Mehta SH. Association of injection practices and overdose with drug use typologies: A latent class analysis among people who inject drugs in Baltimore, 2017. AIDS Educ Prev. 2019;31(4):344-62.

322. Krauss MJ, Rajbhandari B, Sowles SJ, Spitznagel EL, Cavazos-Rehg P. A latent class analysis of poly-marijuana use among young adults. Addict Behav. 2017;75:159-65.

323. Patrick ME, Bray BC, Berglund PA. Reasons for marijuana use among young adults and long-term associations with marijuana use and problems. J Stud Alcohol Drugs. 2016;77(6):881-8.

324. Linzer DA, Lewis JB. poLCA: An R package for polytomous variable latent class analysis. J Stat Softw. 2011;42(10).

325. Lee JH, Herzog TA, Meade CD, Webb MS, Brandon TH. The use of GEE for analyzing longitudinal binomial data: a primer using data from a tobacco intervention. Addict Behav. 2007;32(1):187-93.

326. Morean ME, Lederman IR. Prevalence and correlates of medical cannabis patients' use of cannabis for recreational purposes. Addict Behav. 2019;93:233-9.

327. Schauer GL, King BA, Bunnell RE, Promoff G, McAfee TA. Toking, vaping, and eating for health or fun: Marijuana use patterns in adults, U.S., 2014. Am J Prev Med. 2016;50(1):1-8.

328. Humeniuk R, Ali R. Validation of the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) and Pilot Brief Intervention. 2006 [cited 2019 August 7]. Available from: https://www.who.int/substance_abuse/activities/assist_technicalreport_phase2_final.pdf.

329. Richmond MK, Pampel FC, Rivera LS, Broderick KB, Reimann B, Fischer L. Frequency and risk of marijuana use among substance-using health care patients in Colorado with and without access to state legalized medical marijuana. J Psychoactive Drugs. 2015;47(1):1-9.

330. Sznitman SR. Do recreational cannabis users, unlicensed and licensed medical cannabis users form distinct groups? Int J Drug Policy. 2017;42:15-21.

331. Bohnert KM, Bonar EE, Arnedt JT, Conroy DA, Walton MA, Ilgen MA. Utility of the comprehensive marijuana motives questionnaire among medical cannabis patients. Addict Behav. 2018;76:139-44.

332. Lum HD, Arora K, Croker JA, Qualls SH, Schuchman M, Bobitt J, et al. Patterns of marijuana use and health impact: A survey among older Coloradans. Gerontol Geriatr Med. 2019;5:2333721419843707.

333. Dassieu L, Kabore JL, Choiniere M, Arruda N, Roy E. Chronic pain management among people who use drugs: A health policy challenge in the context of the opioid crisis. Int J Drug Policy. 2019.

334. Miller CL, Kerr T, Strathdee SA, Li K, Wood E. Factors associated with premature mortality among young injection drug users in Vancouver. Harm Reduct J. 2007;4:1.

335. Lake S, Hayashi K, Buxton J, Milloy MJ, Dong H, Montaner J, et al. The effect of prescription opioid injection on the risk of non-fatal overdose among people who inject drugs. Drug Alcohol Depend. 2015;156:297-303.

336. Hayashi K, Milloy MJ, Lysyshyn M, DeBeck K, Nosova E, Wood E, et al. Substance use patterns associated with recent exposure to fentanyl among people who inject drugs in Vancouver, Canada: A cross-sectional urine toxicology screening study. Drug Alcohol Depend. 2018;183:1-6.

337. Socías ME, Kerr T, Wood E, Dong H, Lake S, Hayashi K, et al. Intentional cannabis use to reduce crack cocaine use in a Canadian setting: A longitudinal analysis. Addict Behav. 2017;72:138-43.

338. Lau N, Sales P, Averill S, Murphy F, Sato S-O, Murphy S. A safer alternative: Cannabis substitution as harm reduction. Drug Alcohol Rev. 2015;34(6):654-9.

339. Goncalves JR, Nappo SA. Factors that lead to the use of crack cocaine in combination with marijuana in Brazil: a qualitative study. BMC Public Health. 2015;15:706.

340. Belle-Isle L, Walsh Z, Callaway R, Lucas P, Capler R, Kay R, et al. Barriers to access for Canadians who use cannabis for therapeutic purposes. Int J Drug Policy. 2014;25(4):691-9.

341. The Canadian Press. 9 illegal pot dispensaries in Vancouver must close after court decision, city says. CBC News [Internet]. 2019 May 31 [cited 2019 August 7]; Available from: https://www.cbc.ca/news/canada/british-columbia/pot-dispensary-closures-1.5158468.

342. Leblanc D, Hager M. Federal government targets black – and grey – markets with legal cannabis. The Globe and Mail [Internet]. 2018 January 2 [cited Available from: https://www.theglobeandmail.com/news/politics/federal-government-targets-black-and-grey-markets-with-legal-cannabis/article37471020/.

343. British Columbia Coroners Service. Fentanyl-detected illicit drug overdose deaths: January 1, 2012 to March 31, 2018. Government of British Columbia; 2018 [cited 2018 December 3]. Available from: https://www2.gov.bc.ca/assets/gov/public-safety-and-emergency-services/death-investigation/statistical/fentanyl-detected-overdose.pdf.

344. Cicero TJ, Ellis MS, Surratt HL, Kurtz SP. The changing face of heroin use in the United States: A retrospective analysis of the past 50 years. JAMA Psychiatry. 2014;71(7):821-6.

345. Kolodny A, Courtwright DT, Hwang CS, Kreiner P, Eadie JL, Clark TW, et al. The prescription opioid and heroin crisis: A public health approach to an epidemic of addiction. Annu Rev Public Health. 2015;36:559-74.

346. Dahlman D, Kral AH, Wenger L, Hakansson A, Novak SP. Physical pain is common and associated with nonmedical prescription opioid use among people who inject drugs. Subst Abuse Treat Prev Policy. 2017;12(1):29.

347. Drug Checking in British Columbia - March 2019. BC Centre on Substance Use; 2019 [cited 2019 April 9]. Available from: http://www.bccsu.ca/wp-content/uploads/2019/04/2019-03-BC-Drug-Checking-Report-Mar2019.pdf.

348. Voon P, Callon C, Nguyen P, Dobrer S, Montaner J, Wood E, et al. Self-management of pain among people who inject drugs in Vancouver. Pain Manag. 2014;4(1):27-35.

349. WHO Expert Committee on Drug Dependence Pre-Review: Delta-9-tetrahydrocannabinol [Internet]. World Health Organization; 2018. Available from: https://www.who.int/medicines/access/controlled-substances/Section3-thc-Toxicology.pdf?ua=1.

350. Kim JH, Santaella-Tenorio J, Mauro CM, Cerda M, Keyes KM, Hasin D, et al. State medical marijuana laws and the prevalence of opioids detected among fatally injured drivers. Am J Public Health. 2016;106:2032-37.

351. Finney JW, Humphreys K, Harris AS. What ecologic analyses cannot tell us about medical marijuana legalization and opioid pain medication mortality. JAMA Intern Med. 2015;175(4):655-6.

352. Reiman A. Cannabis as a substitute for alcohol and other drugs. Harm Reduct J. 2009;6:35.

353. Baron EP, Lucas P, Eades J, Hogue O. Patterns of medicinal cannabis use, strain analysis, and substitution effect among patients with migraine, headache, arthritis, and chronic pain in a medicinal cannabis cohort. J Headache Pain. 2018;19(1):37.

354. Piper BJ, Beals ML, Abess AT, Nichols SD, Martin MW, Cobb CM, et al. Chronic pain patients' perspectives of medical cannabis. Pain. 2017;158(7):1373-9.

355. Degenhardt L, Lintzeris N, Campbell G, Bruno R, Cohen M, Farrell M, et al. Experience of adjunctive cannabis use for chronic non-cancer pain: findings from the Pain and Opioids IN Treatment (POINT) study. Drug Alcohol Depend. 2015;147:144-50.

356. Woo A, Lechner B, Fu T, Wong CS, Chiu N, Lam H, et al. Cut points for mild, moderate, and severe pain among cancer and non-cancer patients: a literature review. Ann Palliat Med. 2015;4(4):176-83.

357. Olfson M, Wall MM, Liu SM, Blanco C. Cannabis use and risk of prescription opioid use disorder in the United States. Am J Psychiatry. 2018;175(1):47-53.

358. Bigand T, Wilson M, Riedy S, Lewis J. Cannabis use is related to self-efficacy but not sleep or pain symptoms: A survey of adults prescribed opioids for pain or opioid use disorders. J Pain. 2018;19 (3 Supplement 1):S28.

359. Cooke A, Chavez L, Freisthler B. The relationships between chronic pain and changes in health with cannabis consumption patterns. Int J Drug Policy. 2020;76:102657.

360. Boehnke KF, Scott JR, Litinas E, Sisley S, Williams DA, Clauw DJ. High-frequency medical cannabis use is associated with worse pain among individuals with chronic pain. J Pain. 2019.

361. Smith MT, Haythornthwaite JA. How do sleep disturbance and chronic pain inter-relate? Insights from the longitudinal and cognitive-behavioral clinical trials literature. Sleep Med Rev. 2004;8(2):119-32.

362. Hah JM, Sturgeon JA, Zocca J, Sharifzadeh Y, Mackey SC. Factors associated with prescription opioid misuse in a cross-sectional cohort of patients with chronic non-cancer pain. J Pain Res. 2017;10:979-87.

363. Kundermann B, Krieg J-C, Schreiber W, Lautenbacher S. The effects of sleep deprivation on pain. Pain Res Manage. 2004;9(1):25-32.

364. Burke NN, Finn DP, McGuire BE, Roche M. Psychological stress in early life as a predisposing factor for the development of chronic pain: Clinical and preclinical evidence and neurobiological mechanisms. J Neurosci Res. 2017;95(6):1257-70.

365. Woodhams SG, Sagar DR, Burston JJ, Chapman V. The role of the endocannabinoid system in pain. In: Schaible H-G, editor. Handb Exp Pharmacol. 227. Heidelberg: Springer; 2015. p. 119-43.

366. Smith PB, Welch SP, Martin BR. Interactions between delta 9-tetrahydrocannabinol and kappa opioids in mice. J Pharmacol Exp Ther. 1994;268(3):1381-7.

367. Mason DJ, Jr., Lowe J, Welch SP. Cannabinoid modulation of dynorphin A: correlation to cannabinoid-induced antinociception. Eur J Pharmacol. 1999;378(3):237-48.

368. Philpot LM, Ebbert JO, Hurt RT. A survey of the attitudes, beliefs and knowledge about medical cannabis among primary care providers. BMC Fam Pract. 2019;20(1):17.

369. Mathers BM, Degenhardt L, Bucello C, Lemon J, Wiessing L, Hickman M. Mortality among people who inject drugs: a systematic review and meta-analysis. Bull World Health Organ. 2013;91(2):102-23.

370. Calabria B, Degenhardt L, Hall W, Lynskey M. Does cannabis use increase the risk of death? Systematic review of epidemiological evidence on adverse effects of cannabis use. Drug Alcohol Rev. 2010;29(3):318-30.

371. Fischer B, Imtiaz S, Rudzinski K, Rehm J. Crude estimates of cannabis-attributable mortality and morbidity in Canada-implications for public health focused intervention priorities. J Public Health. 2016;38(1):183-8.

372. Rogeberg O, Elvik R. The effects of cannabis intoxication on motor vehicle collision revisited and revised. Addiction. 2016;111(8):1348-59.

373. Rogeberg O, Elvik R, White M. Correction to: 'The effects of cannabis intoxication on motor vehicle collision revisited and revised' (2016). Addiction. 2018;113(5):967-9.

374. Zhang LR, Morgenstern H, Greenland S, Chang S-C, Lazarus P, Teare MD, et al. Cannabis smoking and lung cancer risk: Pooled analysis in the International Lung Cancer Consortium. Int J Cancer. 2015;136(4):894-903.

375. Degenhardt L, Singleton J, Calabria B, McLaren J, Kerr T, Mehta S, et al. Mortality among cocaine users: A systematic review of cohort studies. Drug Alcohol Depend. 2011;113(2–3):88-95.

376. Degenhardt L, Bucello C, Mathers B, Briegleb C, Ali H, Hickman M, et al. Mortality among regular or dependent users of heroin and other opioids: A systematic review and meta-analysis of cohort studies. Addiction. 2011;106(1):32-51.

377. Abrahamowicz M, Bartlett G, Tamblyn R, du Berger R. Modeling cumulative dose and exposure duration provided insights regarding the associations between benzodiazepines and injuries. J Clin Epidemiol. 2006;59(4):393-403.

378. Sylvestre MP, Abrahamowicz M, Čapek R, Tamblyn R. Assessing the cumulative effects of exposure to selected benzodiazepines on the risk of fall-related injuries in the elderly. Int Psychogeriatr. 2012;24(4):577-86.

379. Lappalainen L, Hayashi K, Dong H, Milloy MJ, Kerr T, Wood E. Ongoing impact of HIV infection on mortality among people who inject drugs despite free antiretroviral therapy. Addiction. 2015;110(1):111-9.

380. Hayashi K, Dong H, Marshall BD, Milloy MJ, Montaner JS, Wood E, et al. Sex-based differences in rates, causes, and predictors of death among injection drug users in Vancouver, Canada. Am J Epidemiol. 2016;183(6):544-52.

381. Bundy JD, Bazzano LA, Xie D, Cohan J, Dolata J, Fink JC, et al. Self-reported tobacco, alcohol, and illicit drug use and progression of chronic kidney disease. Clin J Am Soc Nephrol. 2018;13(7):993-1001.

382. Hu FB, Stampfer MJ, Rimm E, Ascherio A, Rosner BA, Spiegelman D, et al. Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. Am J Epidemiol. 1999;149(6):531-40.

383. Saitz R, Gaeta J, Cheng DM, Richardson JM, Larson MJ, Samet JH. Risk of mortality during four years after substance detoxification in urban adults. J Urban Health. 2007;84(2):272-82.

384. Walley AY, Cheng DM, Libman H, Nunes D, Horsburgh CR, Jr., Saitz R, et al. Recent drug use, homelessness and increased short-term mortality in HIV-infected persons with alcohol problems. AIDS. 2008;22(3):415-20.

385. Evans JL, Tsui JI, Hahn JA, Davidson PJ, Lum PJ, Page K. Mortality among young injection drug users in San Francisco: a 10-year follow-up of the UFO study. Am J Epidemiol. 2012;175(4):302-8.

386. Merrall EL, Bird SM, Hutchinson SJ. Mortality of those who attended drug services in Scotland 1996-2006: record-linkage study. Int J Drug Policy. 2012;23(1):24-32.

387. Hayden A, Hayashi K, Dong H, Milloy MJ, Kerr T, Montaner JS, et al. The impact of drug use patterns on mortality among polysubstance users in a Canadian setting: a prospective cohort study. BMC Public Health. 2014;14:1153.

388. Johnson C, Dong H, Ahamad K, Hayashi K, Milloy MJ, Kerr T, et al. Impact of binge alcohol on mortality among people who inject drugs. Addict Behav Rep. 2015;2:28-32.

389. Fuster D, Sanvisens A, Bolao F, Zuluaga P, Rivas I, Farre M, et al. Cannabis as secondary drug is not associated with a greater risk of death in patients with opiate, cocaine, or alcohol dependence. J Addict Med. 2016.

390. Gjersing L, Bretteville-Jensen AL. Patterns of substance use and mortality risk in a cohort of 'hard-to-reach' polysubstance users. Addiction. 2018;113(4):729-39.

391. Reddon H, DeBeck K, Socias ME, Dong H, Wood E, Montaner J, et al. Cannabis use is associated with lower rates of initiation of injection drug use among street-involved youth: A longitudinal analysis. Drug Alcohol Rev. 2018;37(3):421-8.

392. Reddon H, DeBeck K, Socias ME, Lake S, Dong H, Karamouzian M, et al. Frequent cannabis use and cessation of injection of opioids, Vancouver, Canada, 2005-2018. Am J Public Health. 2020;110(10):1553-60.

393. Fairbairn NS, Walley AY, Cheng DM, Quinn E, Bridden C, Chaisson C, et al. Mortality in HIV-infected alcohol and drug users in St. Petersburg, Russia. PLoS One. 2016;11(11):e0166539.

394. Quan VM, Minh NL, Ha TV, Ngoc NP, Vu PT, Celentano DD, et al. Mortality and HIV transmission among male Vietnamese injection drug users. Addiction. 2011;106(3):583-9.

395. Nambiar D, Agius PA, Stoové M, Hickman M, Dietze P. Mortality in the Melbourne injecting drug user cohort study (MIX). Harm Reduct J. 2015;12:55.

396. Rehm J, Baliunas D, Borges GL, Graham K, Irving H, Kehoe T, et al. The relation between different dimensions of alcohol consumption and burden of disease: an overview. Addiction. 2010;105(5):817-43.

397. Probst C, Roerecke M, Behrendt S, Rehm J. Socioeconomic differences in alcohol-attributable mortality compared with all-cause mortality: A systematic review and meta-analysis. Int J Epidemiol. 2014;43(4):1314-27.

398. Katikireddi SV, Whitley E, Lewsey J, Gray L, Leyland AH. Socioeconomic status as an effect modifier of alcohol consumption and harm: analysis of linked cohort data. Lancet Public Health. 2017;2(6):e267-e76.

399. Lachenmeier DW, Rehm J, Gmel G. Surrogate alcohol: what do we know and where do we go? Alcohol Clin Exp Res. 2007;31(10):1613-24.

400. Crabtree A, Latham N, Morgan R, Pauly B, Bungay V, Buxton JA. Perceived harms and harm reduction strategies among people who drink non-beverage alcohol: Community-based qualitative research in Vancouver, Canada. Int J Drug Policy. 2018;59:85-93.

401. Stockwell T, Pauly BB, Chow C, Erickson RA, Krysowaty B, Roemer A, et al. Does managing the consumption of people with severe alcohol dependence reduce harm? A comparison of participants in six Canadian managed alcohol programs with locally recruited controls. Drug Alcohol Rev. 2018;37 Suppl 1:S159-s66.

402. Grazioli VS, Collins SE, Paroz S, Graap C, Daeppen J-B. Six-month outcomes among socially marginalized alcohol and drug users attending a drop-in center allowing alcohol consumption. Int J Drug Policy. 2017;41:65-73.

403. Pearce LA, Min JE, Piske M, Zhou H, Homayra F, Slaunwhite A, et al. Opioid agonist treatment and risk of mortality during opioid overdose public health emergency: population based retrospective cohort study. BMJ. 2020;368:m772.

404. Uhlmann S, DeBeck K, Simo A, Kerr T, Montaner JS, Wood E. Health and social harms associated with crystal methamphetamine use among street-involved youth in a Canadian setting. Am J Addict. 2014;23(4):393-8.

405. Weiss S. CIHR's cannabis initiative: Meeting the urgent need for more knowledge. Canadian Institutes of Health Research; 2018 [cited 2020 May 14]. Available from: https://cihr-irsc.gc.ca/e/51083.html.

406. Notice of special interest (NOSI): Public health research on cannabis. National Institutes of Health (NIH); 2019 [cited 2020 May 14]. Available from: https://grants.nih.gov/grants/guide/notice-files/NOT-DA-19-065.html?utm_source=dlvr.it&utm_medium=twitter.

407. Park JY, Wu LT. Prevalence, reasons, perceived effects, and correlates of medical marijuana use: A review. Drug Alcohol Depend. 2017;177:1-13.

408. Gwira Baumblatt JA, Wiedeman C, Dunn JR, Schaffner W, Paulozzi LJ, Jones TF. High-risk use by patients prescribed opioids for pain and its role in overdose deaths. JAMA Intern Med. 2014;174(5):796-801.

409. Voon P, Greer AM, Amlani A, Newman C, Burmeister C, Buxton JA. Pain as a risk factor for substance use: a qualitative study of people who use drugs in British Columbia, Canada. Harm Reduct J. 2018;15(1):35.

410. Balneaves LG, Alraja A, Ziemianski D, McCuaig F, Ware M. A national needs assessment of Canadian nurse practitioners regarding cannabis for therapeutic purposes. Cannabis Cannabinoid Res. 2018;3(1):66-73.

411. Ziemianski D, Capler R, Tekanoff R, Lacasse A, Luconi F, Ware MA. Cannabis in medicine: a national educational needs assessment among Canadian physicians. BMC Med Educ. 2015;15:52.

412. St Pierre M, Matthews L, Walsh Z. Cannabis education needs assessment among Canadian physicians-in-training. Complement Ther Med. 2020;49:102328.

413. Practice Standard: Cannabis for Medical Purposes [Internet]. College of Physicians and Surgeons of British Columbia; 2016 November 14. Available from: https://www.cpsbc.ca/files/pdf/PSG-Cannabis-for-Medical-Purposes.pdf.

414. Allan GM, Ramji J, Perry D, Ton J, Beahm NP, Crisp N, et al. Simplified guideline for prescribing medical cannabinoids in primary care. Can Fam Physician. 2018;64(2):111-20.

415. MacCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. Eur J Intern Med. 2018;49:12-9.

416. Legal age to buy cannabis in Quebec is now 21, the highest in Canada. CBC News [Internet]. 2020 January 1 [cited 2020 May 16]; Available from: https://www.cbc.ca/news/canada/montreal/legal-age-cannabis-edibles-1.5399211.

417. Motion: Cannabis as an alternative to opiates and more dangerous drugs on the Downtown Eastside [Internet]. Vancouver City Council; 2019 June 26. Available from: https://council.vancouver.ca/20190626/documents/cfsc3.pdf.

418. Amendments to zoning and development by-law and license by-law to align with the Cannabis Control and Licensing Act [Internet]. City of Vancouver 2018 May 29. Available from: https://council.vancouver.ca/20180605/documents/p5.pdf.

419. Courtenay P. Vancouver's city countil votes to end cannabis prohibition in the Downtown Eastside. Canncentral [Internet]. 2019 June 27 [cited 2020 May 13]; Available from: https://www.canncentral.com/vancouvers-city-council-votes-to-end-cannabis-prohibition-in-the-downtown-eastside.

420. Flower. BC Cannabis Stores; 2020 [cited 2020 May 13]. Available from: https://www.bccannabisstores.com/collections/flower.

421. Uguen-Csenge E. B.C. releases plan to provide safe supply of drugs during COVID-19 pandemic. CBC News [Internet]. 2020 March 26 [cited 2020 May 16]; Available from: https://www.cbc.ca/news/canada/british-columbia/safe-supply-drug-plan-covid-1.5511973.

422. Cooper ZD, Adinoff B. Necessity of addressing motivations for cannabis use to guide research. Am J Drug Alcohol Abuse. 2019;45(6):547-50.

423. Heikman PK, Muhonen LH, Ojanperä IA. Polydrug abuse among opioid maintenance treatment patients is related to inadequate dose of maintenance treatment medicine. BMC Psychiatry. 2017;17.

424. Boehnke KF, Scott JR, Litinas E, Sisley S, Clauw DJ, Goesling J, et al. Cannabis use preferences and decision-making among a cross-sectional cohort of medical cannabis patients with chronic pain. J Pain. 2019;20(11):1362-72.

425. Tetrault JM, Crothers K, Moore BA, Mehra R, Concato J, Fiellin DA. Effects of marijuana smoking on pulmonary function and respiratory complications: a systematic review. Arch Intern Med. 2007;167(3):221-8.

426. Abrams DI, Vizoso HP, Shade SB, Jay C, Kelly ME, Benowitz NL. Vaporization as a smokeless cannabis delivery system: a pilot study. Clin Pharmacol Ther. 2007;82(5):572-8.

427. Tashkin DP. How beneficial is vaping cannabis to respiratory health compared to smoking? Addiction. 2015;110(11):1706-7.

428. Shiplo S, Asbridge M, Leatherdale ST, Hammond D. Medical cannabis use in Canada: vapourization and modes of delivery. Harm Reduct J. 2016;13(1):30.

429. Aston ER, Scott B, Farris SG. A qualitative analysis of cannabis vaporization among medical users. Exp Clin Psychopharmacol. 2019;27(4):301-8.

430. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. Clin Pharmacokinet. 2003;42(4):327-60.

431. Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. Br J Pharmacol. 2011;163(7):1344-64.

432. Russo EB. The case for the entourage effect and conventional breeding of clinical cannabis: No “strain," no gain. Front Plant Sci. 2018;9:1969.

433. Russo EB, Marcu J. Cannabis pharmacology: The usual suspects and a few promising leads. Adv Pharmacol. 2017;80:67-134.

434. Imtiaz S, Shield KD, Roerecke M, Cheng J, Popova S, Kurdyak P, et al. The burden of disease attributable to cannabis use in Canada in 2012. Addiction. 2016;111(4):653-62.

435. Funding decisions database: Investigating cannabis as harm reduction during a community-wide overdose crisis. Canadian Institutes of Health Research; 2019 [cited 2020 May 19]. Available from: https://webapps.cihr-irsc.gc.ca/decisions/p/project_details.html?applId=392348&lang=en.

436. Thiessen MS, Walsh Z, Crosby K, Carroll C. Preliminary results for a pilot measure: Composite Cannabis Assessment Scale. Poster presented at the 77th Annual Canadian Psychological Association Convention; Victoria, Canada2016.

437. Berardi A, Schelling G, Campolongo P. The endocannabinoid system and post traumatic stress disorder (PTSD): From preclinical findings to innovative therapeutic approaches in clinical settings. Pharmacol Res. 2016;111:668-78.

438. Fischer B, Russell C, Sabioni P, van den Brink W, Le Foll B, Hall W, et al. Lower-risk cannabis use guidelines: a comprehensive update of evidence and recommendations. Am J Public Health. 2017;107(8):e1-e12.

Appendices

Appendix A Supplemental documents for Chapter 2

A.1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Chapter 2, Title, page 30
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	N/A (no abstract in dissertation chapter version)
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Section 2.1., Introduction, pages 30-31
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Section 2.2.2., Eligibility criteria, page 32 and Table 2.1, page 34
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Section 2.2., Methods, page 32
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Section 2.2.2., Eligibility criteria, pages 32-33
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Section 2.2.1., Search strategy, page 32
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix A.2., page 242
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Section 2.2.3., Study screening, pages 34-35
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any	Section 2.2.4., Data extraction and quality

		processes for obtaining and confirming data from investigators.	assessment, pages 41-42
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Table 2.1., page 40
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Section 2.2.4., Data extraction and quality assessment, pages 35-36
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Table 2.1., page 34 and Section 2.2.5., Data synthesis and analysis, page 36
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Section 2.2.5., Data synthesis and analysis, page 36
Risk of bias across studies		Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA (no meta-analysis) but will discuss possible scenarios (see 22)
Risk of bias across studies		Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 2.1., page 37
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Tables 2.2.-2.4., pages 43-70
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Section 2.3.1., Summary of included studies, page 38, Tables 2.2.-2.4., pages 43-70, Appendix A.3., page 243-244
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Tables 2.2.-2.4., pages 43-70
Synthesis of results	21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	Section 2.3.3.-2.3.6. and Tables 2.2.-2.4., pages 40-70
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	No formal assessment (see 15), but discussed in Section 2.4., Discussion, page 73
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA

DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Section 2.4., Discussion, pages 71-72
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Section 2.4., Discussion, pages 74-76
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Section 2.5., Conclusions, pages 76-77
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A for dissertation version

A.2 Sample search strategy (OVID Medline)

1. (medic* adj2 assist* adj2 therap*).ti,ab.
2. (opioid* adj2 agonist* adj2 therap*).ti,ab.
3. (opioid* adj2 substitut* adj2 treat*).ti,ab.
4. (opioid* adj2 substitut* adj2 therap*).ti,ab.
5. (opiate* adj2 substitut* adj2 treat*).ti,ab
6. (opiate* adj2 substitut* adj2 therap*).ti,ab
7. (opiate* adj2 agonist* adj2 therap*).ti,ab
8. (opiate* adj2 agonist* adj2 treat*).ti,ab
9. (opioid* adj2 antagonist* adj2 therap*).ti,ab
10. exp Opiate Substitution Treatment/
11. tetrahydrocannabinol.ti,ab
12. cannabidiol.ti,ab
13. THC.ti,ab
14. CBD.ti,ab
15. pot.ti,ab
16. weed.ti,ab
17. hash*.ti,ab
18. (opiate* adj2 antagonist* adj2 therap*).ti,ab
19. (opiate* adj2 antagonist* adj2 treat*).ti,ab
20. (medic* adj2 assist* adj2 treat*).ti,ab
21. (opioid* adj2 agonist* adj2 treat*).ti,ab
22. (opioid* adj2 antagonist* adj2 treat*).ti,ab
23. (opioid* adj2 replace* adj2 therap*).ti,ab
24. (opioid* adj2 replace* adj2 treat*).ti,ab
25. (opiate* adj2 replace* adj2 therap*).ti,ab
26. (opiate* adj2 replace* adj2 treat*).ti,ab
27. (methado* adj2 maint*).ti,ab
28. exp *“cannabis use”/ or exp *cannabis smoking/
29. exp *medical cannabis/
30. (cannabinoid* not synthetic cannabinoid*).ti,ab
31. exp *methadone treatment/
32. exp *buprenorphine plus naloxone/
33. *naltrexone/
34. marihuana.ti,ab
35. (cannabis not synthetic cannabis).ti,ab
36. (marijuana not synthetic marijuana).ti,ab
37. exp cannabis/
38. *cannabinoid/ or *cannabinol/ or *tetrahydrocannabinol/
39. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 28 or 29 or 30 or 34 or 35 or 36 or 37 or 38
40. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 31 or 32 or 33
41. 39 and 40
42. limit 41 to (human and English language)

A.3 Quality assessment details of 38 studies systematically reviewed in Chapter 2

Study	Criteria														Summary
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Abrahamsson et al., 2016	Y	Y	CD, NR	Y	N	Y	Y (o) N (r)	Y	Y	N	Y	CD, NR	N (o) NA (r)	N	Fair
Bagra et al., 2018	Y	Y	Y	Y	N	N	N	N	Y	N	Y	CD, NR	NA	N	Poor
Best et al., 1999	Y	Y	Y	Y	N	N	N	Y	Y	N	Y	N	NA	N	Fair
Bisaga et al., 2015	Y	Y	N	Y	Y	Y	Y (o, a) N (r)	N	Y	Y	Y	Y	N (o, a) NA (r)	N	Fair
Budney et al., 1998	Y	Y	CD, NR	Y	N	N (o) Y (r)	Y (o) N (r)	Y	Y	Y	Y	CD, NR	N (o) NA (r)	N	Fair
Chaudhry et al., 2012	Y	Y	Y	N	N	Y	N	Y	Y	N	Y	CD, NR	NA	N	Fair
Church et al., 2001	Y	Y	CD, NR	Y	N	N (o, a) Y (r)	Y (o) N (a, r)	Y	Y	Y	Y	CD, NR	CD, NR (o, a) NA (r)	N	Fair
Dayal et al., 2016	Y	Y	Y	Y	N	Y	Y	N	N	N	Y	CD, NR	NA	Y	Fair
Eastwood et al., 2019	Y	Y	CD, NR	Y	N	Y	Y	Y	Y	Y	Y	CD	Y	Y	Good
Epstein and Preston, 2003	Y	Y	CD, NR	N	Y	N (o) Y (r)	Y	Y	Y	Y	Y	CD, NR	Y (o) N (r)	Y	Good
Epstein and Preston, 2015	Y	Y	N	N	Y	Y	Y	N	Y	Y	Y	CD, NR	CD, NR	Y	Fair
Fareed et al., 2014	Y	Y	N	Y	N	N	N	N	Y	N	Y	N	CD, NR	N	Poor
Franklyn et al., 2017	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	CD, NR	NA	N	Fair
Håkansson et al., 2016	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	CD, NR	NA	N	Good

Study	Criteria														Summary
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Hill et al., 2013	Y	Y	Y	Y	Y	Y	Y (o) / N (r)	Y	Y	Y	Y	CD, NR	Y (o) / NA (r)	N	Good
Hser et al., 2014	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	CD, NR	NA	Y	Good
Jarvis et al., 2018	Y	Y	CD, NR	Y	N	Y	N	Y	N	N	N	CD, NR	NA	N	Poor
Joe 1998	Y	Y	Y	Y	N	Y	Y	N	N	N	Y	CD, NR	NA	Y	Fair
Klimas et al., 2018	Y	Y	Y	N	N	N	Y	N	Y	Y	Y	N	CD, NR	N	Poor
Levine et al., 2015	Y	Y	Y	Y	N	Y	Y	N	N	N	Y	CD, NR	NA	N	Fair
Lions et al., 2014	Y	Y	CD, NR	Y	N	Y	Y	N	Y	Y	Y	N	Y	N	Fair
Matson et al., 2014	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	CD, NR	N (o, a) / NA (r)	N	Fair
Nava et al., 2007	Y	Y	CD, NR	Y	N	Y	Y	N	N	N	Y	CD, NR	N (o), / NA (r)	N	Poor
Niremberg et al., 1996	Y	Y	CD, NR	N	N	N	N	Y	Y	Y	Y	CD, NR	CD, NR	N	Poor
Peles et al., 2008	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	NA	N	Good
Proctor et al., 2016	Y	Y	N	Y	N	Y	Y	N	N	Y	Y	CD, NR	CD, NR	Y	Fair
Raby et al., 2014	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	CD, NR	NA	Y	Good
Roux et al., 2011	Y	Y	CD, NR	Y	N	N	Y	N	N	Y	Y	N	CD, NR	N	Poor
Roux et al., 2014	Y	Y	CD, NR	Y	N	Y	Y	N	Y	Y	Y	N	N	N	Fair
Saxon et al., 1996	Y	Y	CD, NR	Y	N	Y	Y	Y	Y	N	Y	CD, NR	N (o) / NA (r)	Y	Fair
	Y	Y	Y	Y	N	N (o)	Y	Y	Y	Y	Y	CD, NR	NA	N	Fair

Study	Criteria														Summary
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	
Scavone et al., 2013						Y (r)									
Schiff et al., 2007	Y	Y	Y	N	N	Y	N	N	N	Y	N	CD, NR	NA	N	Poor
Socias et al., 2018	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	N	NA	Y	Good
Somers and O'Connor, 2012	Y	Y	CD, NR	Y	N	Y	Y	N	N	Y	Y	CD, NR	N	N	Fair
Wasserman et al., 1998	Y	Y	N	Y	N	Y	Y	N	Y	Y	Y	CD, NR	Y	N	Fair
Weizman et al., 2004	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	CD, NR	N (o) NA (r)	N	Fair
White et al., 2014	Y	Y	Y	Y	N	Y	Y	N	Y	N	N	CD, NR	NA	N	Fair
Zielinksi et al., 2017	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	CD, NR	NA	N	Fair

Criteria: 1) Research question/objective clearly stated; **2)** Study population clearly defined; **3)** ≥50% participation rate for eligible persons; **4)** Participants recruited from same/similar population (including time period) and inclusion/exclusion criteria clearly pre-specified; **5)** Sample size justification or power description provided; **6)** Exposure of interest measured prior to outcome measurement; **7)** Sufficient timeframe to observe a true relationship; **8)** differing levels of exposure variable measured (i.e., not a dichotomous examination); **9)** Exposure measurement clearly defined, valid, reliable, implemented consistently across all study participants; **10)** Exposures were assessed more than once over time; **11)** Outcome(s) measurement clearly defined, valid, reliable, implemented consistently across all study participants; **12)** Outcome assessors were blinded to the exposure status of participants; **13)** ≤ 20% loss to follow-up (note: this criteria marked as "NA" for cross-sectional studies and for prospective studies that evaluate treatment retention as the outcome); **14)** Key potential confounding variables were measured and accounted for in analysis between exposure and outcome. **Y** = Yes; **N** = No; **CD** = Cannot determine; **NR** = Not reported; **NA** = Not applicable; **o** = opioid use; **a** = adherence; **r** = retention

Appendix B Supplemental documents for Chapter 4

B.1 Fit statistics for latent class models fit to 2686 observations from 897 PWUD

Number of classes	AIC	BIC	χ^2	G^2
2	21578.24	21690.26	18346.24	913.85
3	21468.68	21639.66	12419.91	784.29
4	21382.55	21612.48	1786.88	678.16
5	21308.49	**21597.39**	903.14	584.1
6	**21262.08**	21609.93	**877.21**	**517.69**

Note: Bold = Ideal class model based on fit statistic; Shaded = Class model selected; AIC = Akaike information criterion; BIC = Bayesian information criterion; χ^2 = Pearson's chi-square goodness of fit; G^2 = Likelihood ratio / deviance statistic

B.2 Number (%) of observations in each class of various latent class models fit to 2686 observations from 897 PWUD

Number of classes	Class 1	Class 2	Class 3	Class 4	Class 5	Class 6
2	845 (31.5)	**1841 (68.5)**	-	-	-	-
3	179 (6.7)	909 (33.8)	1598 (59.5)	-	-	-
4	1007 (37.5)	588 (21.9)	848 (31.6)	243 (9.0)	-	-
5	**124 (4.6)**	961 (35.8)	350 (13.0)	874 (32.5)	377 (14.0)	-
6	1031 (38.4)	**117 (4.4)**	780 (29.0)	**130 (4.8)**	284 (10.6)	344 (12.8)

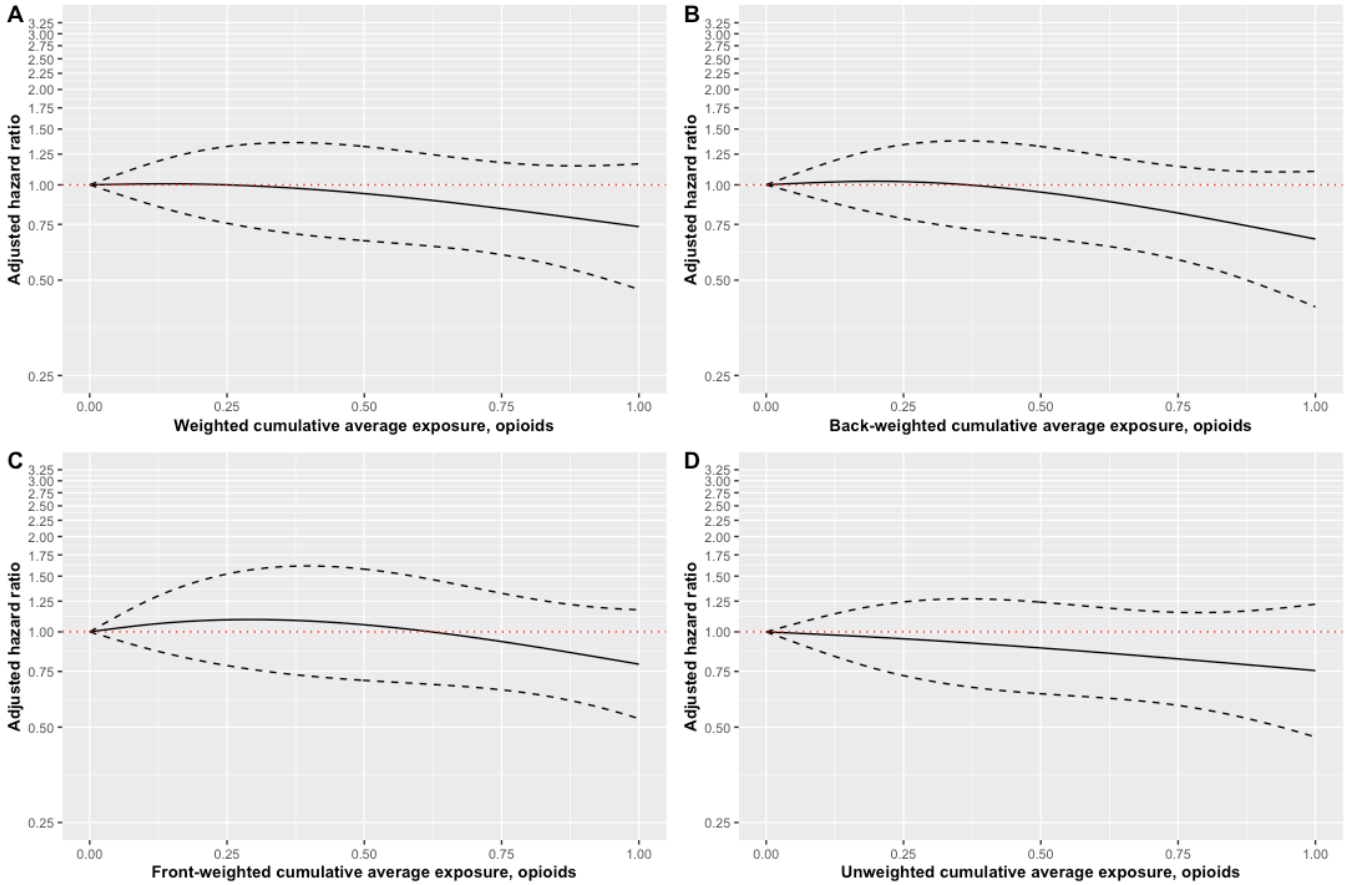
Note: Bold = Class is considered to have low interpretability based on number of observations; Shaded = Class model selected

Appendix C Supplemental documents for Chapter 6

C.1 Guide for estimating the number and proportion of use days from questionnaire data

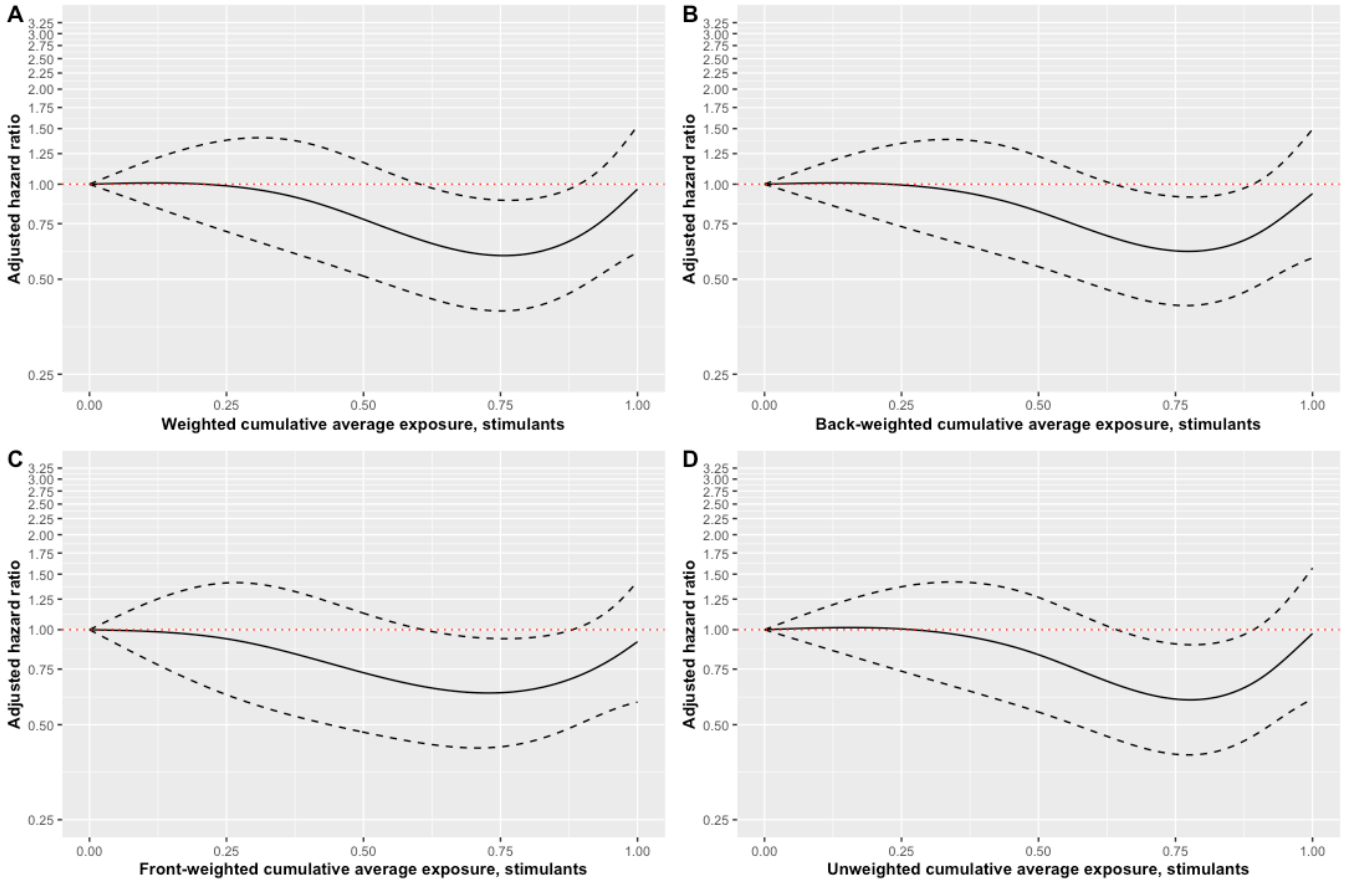
Frequency category	Approximate number of days in the previous six months	Approximate proportion of days used in the previous six months
0: Not used	0	0.00
1: Less than once per month	4	0.02
2: A few times per month	18	0.10
3: About once per week	27	0.15
4: A few times per week	106	0.58
5: About once per day	183	1.00

C.2 Spline regression comparing the non-linear relationship between average cumulative opioid exposure and all-cause mortality for differently weighted variables



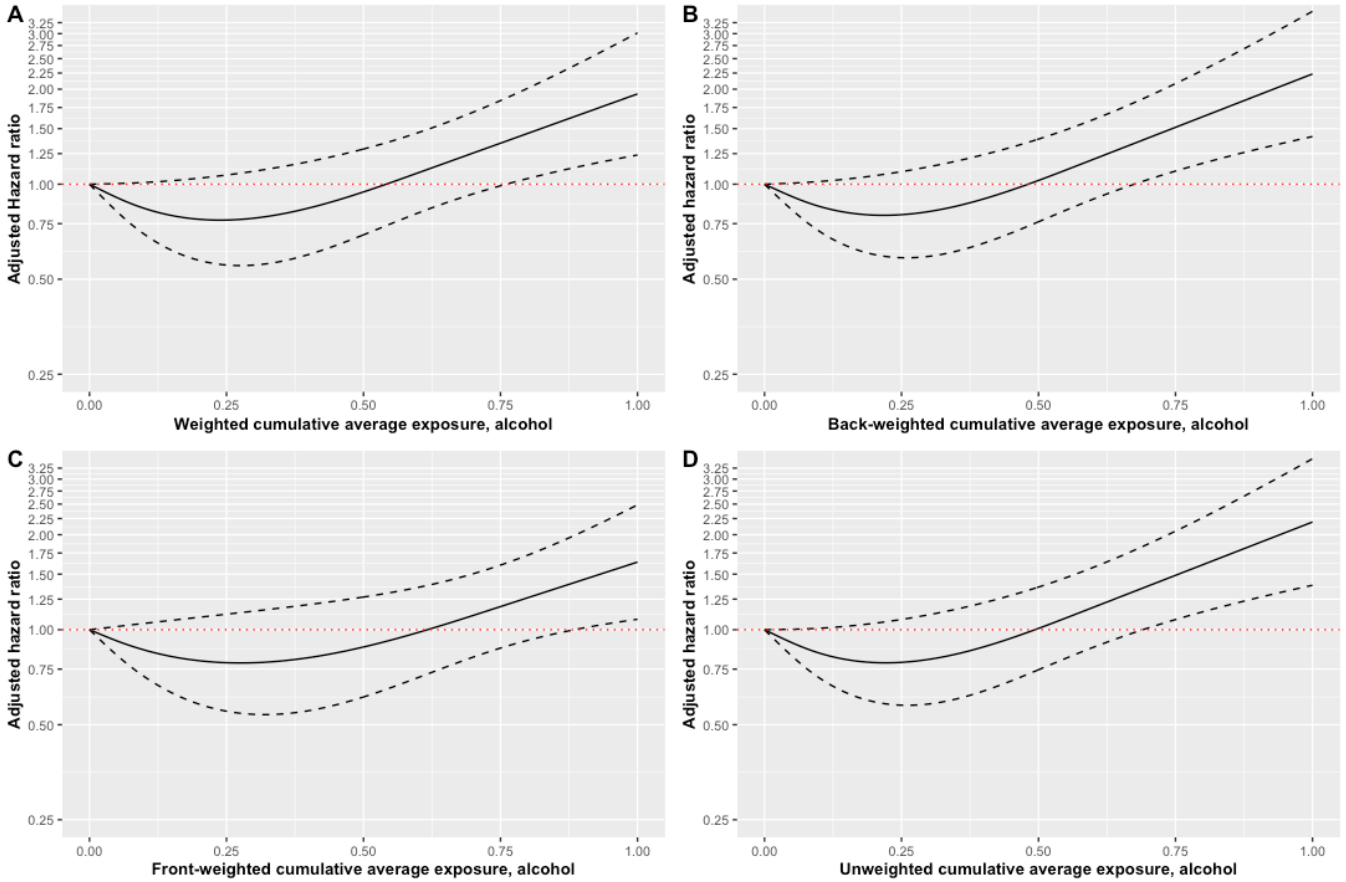
Note 1: Panel A = current use*0.5, previous use*0.5, panel B = current use*0.25, previous use*0.75, panel C = Current use*0.75, previous use*0.25, panel D = unweighted (average of previous and current frequency); **Note 2:** Estimates are adjusted for age, sex, race, employment, incarceration, homelessness, opioid agonist treatment, injection drug use, and HIV status. **Note 3:** Restricted cubic splines for opioids, cannabis, and alcohol have three knots; stimulants has four knots. **Note 4:** Solid line indicates the adjusted hazard of death at a given weighted cumulative average proportion of substance use (reference is 0); dashed lines indicate 95% confidence intervals around this estimate; estimates are plotted on the log scale.

C.3 Spline regression comparing the non-linear relationship between average cumulative stimulant exposure and all-cause mortality for differently weighted variables



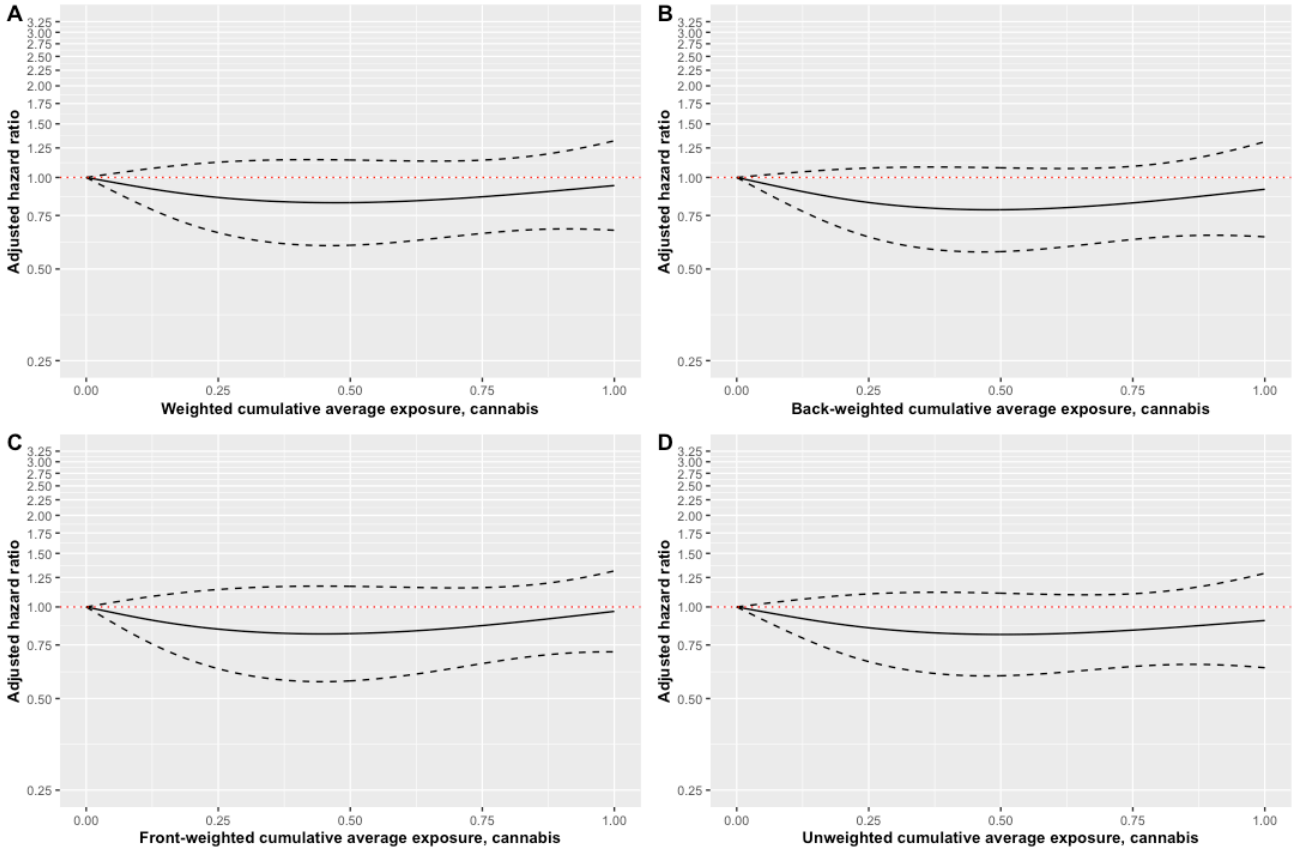
Note 1: Panel A = current use*0.5, previous use*0.5, panel B = current use*0.25, previous use*0.75, panel C = Current use*0.75, previous use*0.25, panel D = unweighted (average of previous and current frequency); **Note 2:** Estimates are adjusted for age, sex, race, employment, incarceration, homelessness, opioid agonist treatment, injection drug use, and HIV statu. **Note 3:** Restricted cubic splines for opioids, cannabis, and alcohol have three knots; stimulants has four knots. **Note 4:** Solid line indicates the adjusted hazard of death at a given weighted cumulative average proportion of substance use (reference is 0); dashed lines indicate 95% confidence intervals around this estimate; estimates are plotted on the log scale.

C.4 Spline regression comparing the non-linear relationship between average cumulative alcohol exposure and all-cause mortality for differently weighted variables



Note 1: Panel A = current use*0.5, previous use*0.5, panel B = current use*0.25, previous use*0.75, panel C = Current use*0.75, previous use*0.25, panel D = unweighted (average of previous and current frequency); **Note 2:** Estimates are adjusted for age, sex, race, employment, incarceration, homelessness, opioid agonist treatment, injection drug use, and HIV statu. **Note 3:** Restricted cubic splines for opioids, cannabis, and alcohol have three knots; stimulants has four knots. **Note 4:** Solid line indicates the adjusted hazard of death at a given weighted cumulative average proportion of substance use (reference is 0); dashed lines indicate 95% confidence intervals around this estimate; estimates are plotted on the log scale.

C.5 Spline regression comparing the non-linear relationship between average cumulative cannabis exposure and all-cause mortality for differently weighted variables



Note 1: Panel A = current use*0.5, previous use*0.5, panel B = current use*0.25, previous use*0.75, panel C = Current use*0.75, previous use*0.25, panel D = unweighted (average of previous and current frequency); **Note 2:** Estimates are adjusted for age, sex, race, employment, incarceration, homelessness, opioid agonist treatment, injection drug use, and HIV status. **Note 3:** Restricted cubic splines for opioids, cannabis, and alcohol have three knots; stimulants has four knots. **Note 4:** Solid line indicates the adjusted hazard of death at a given weighted cumulative average proportion of substance use (reference is 0); dashed lines indicate 95% confidence intervals around this estimate; estimates are plotted on the log scale.