CHARACTERIZATION OF OVERDOSE SURVIVORS AND THEIR OUTCOMES IN OPIOID AGONIST TREATMENT: FINDINGS FROM A PRAGMATIC, PAN-CANADIAN, RANDOMIZED CONTROL TRIAL

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Abstract

Background: Canada is currently facing an overdose epidemic primarily attributed to prescription and synthetic opioids. Previous work has revealed that individuals with a history of non-fatal overdose (NFO) are at a higher risk of mortality, but little is known about treatment outcomes among this population. The aim of this thesis was to characterize opioid agonist treatment (OAT) seeking individuals with prescription-type opioid use disorder (POUD) and a history of NFO, as well as their treatment outcomes.

Methods: Data were drawn from OPTIMA, a multi-site, 24-week, pragmatic, randomized control trial evaluating the relative effectiveness of buprenorphine/naloxone and methadone models of care for adults with POUD. Multivariable logistic regression was used to determine correlates of NFO and to explore treatment retention among participants with a history of NFO. Analysis of covariance (ANCOVA) was used to examine the mean difference in opioid use between treatment arms. Finally, descriptive statistics were produced to determine the prevalence of overdose during treatment and investigate patterns of opioid use before and after overdose.

Results: Among the 272 randomized participants, 159 (58%) had a lifetime history of NFO. Homelessness, receiving income assistance and positive urine drug screens (UDS) for fentanyl and methamphetamine were all independently associated with a history of NFO. Among participants with a history of NFO, retention was 17% for the buprenorphine/naloxone group and 18% for the methadone group and was not statistically different between the treatment arms ($p = 0.54$). Across the study period, there was an 11.9% adjusted mean difference in opioid-free UDS, favouring the buprenorphine/naloxone arm (95% CI= 3.5 to 20.3; $p=0.0057$). A total of 24 overdoses were reported during the study period (6 participants randomized to buprenorphine/naloxone; 12

randomized to methadone). All participants that initiated treatment continued to use opioids after overdose.

Conclusions: Findings from this research indicate that a considerable proportion of OAT-seeking individuals have a history of NFO. Low retention rates and high opioid use in treatment highlight the importance of an individualized, multidimensional approach to treatment for this population. Timely initiation of low-barrier treatment and interventions to address socio-structural barriers could potentially mitigate future overdose and improve treatment outcomes.

Lay summary

Since 2016, there have been over 26,000 deaths related to opioid use in Canada. The introduction of fentanyl into the drug supply has led to a rise in opioid-related harms including hospital admissions, non-fatal overdoses (NFO) and deaths. This thesis explored factors associated with a history of NFO and treatment outcomes among overdose survivors. We found that a high proportion of people seeking treatment had a history of overdose and that social and substance use related factors were associated with a lifetime history of overdose. These factors may be potential targets for the development of screening tools and other interventions to identify individuals at high risk of future overdose. Additionally, treatment outcomes were poor among this population supporting the need for new interventions to improve long-term retention in treatment, to reduce the ongoing use of illicit opioids, and prevent overdose during treatment.

Preface

This statement is to certify that the work presented in this thesis was conceived, written, and disseminated by Hannah Crepeault. With significant input from co-supervisors Drs. M. Eugenia Socias and Lianping Ti, and committee member Paxton Bach, Hannah Crepeault designed the studies and wrote the data analysis plan. All statistical analyses were performed by Hannah Crepeault and all manuscripts contained in this thesis were prepared, written and edited by Hannah Crepeault.

Data for the analyses were drawn from the OPTIMA trial (Optimizing patient centered-care: a pragmatic randomized control trial comparing models of care in the management of prescription opioid misuse). Dr. M. Eugenia Socias had access to the data and takes full responsibility for the accuracy of the results. This study was approved by the University of British Columbia and Providence Health Care Research Ethics Board and the ethics certificate number is H16-01887. OPTIMA was registered in clinicaltrials.gov (NCT03033732).

A version of Chapter 2 has been presented at the following conferences: Virtual Solutions for Substance Use Care Conference (Virtual, January 2022), Innovations in Addiction Medicine and Science Annual Conference (Hollywood, FL, April 2022), Department of Experimental Medicine & Experimental Medicine Research Expo (Vancouver, BC, May 2022) and the Canadian Association of Health Services and Policy Research Annual Conference (Virtual, June 2022). A version of Chapter 3 has been presented at the BC Centre on Substance Use Annual Conference (Virtual, May 2022).

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List of Abbreviations

AL – Alberta

ANCOVA – Analysis of covariance

AOR – Adjusted odds ratio

BC – British Columbia

BDI-II – Beck Depression Score Inventory, Version 2

BIPOC – Black, Indigenous, People of colour

CI – Confidence interval

CRISM – Canadian Research Initiative in Substance Misuse

DSM-5 - Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

EMS- Emergency Medical Services

IQR – Interquartile range

NFO – Non-fatal overdose

OAT – Opioid agonist treatment

ON – Ontario

OPTIMA- Optimizing patient centered-care: A pragmatic randomized control trial comparing models of care in the management of prescription opioid misuse

OR – Odds ratio

OUD – Opioid use disorder

POUD – Prescription opioid use disorder

QC - Quebec

SD – Standard deviation

US – United States

UDS – Urine drug screen

VIF – Variance inflation factor

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This thesis is dedicated to my dear friend Aryton James Zachary Walsh who was a light to all those around him and to all those who have lost someone to overdose.

Chapter 1: Background, rationale and research objectives

1.1 Background

1.1.1 The Canadian overdose epidemic

Historically, Canada has had one of the highest rates of opioid consumption worldwide,[1,2] contributing to over 26,000 opioid-related deaths in the last five years.[3] Since the 1990s, there have been three distinct waves which have each contributed to a rise in opioid-related mortality.[4,5,6] The first wave stems from a drastic increase in opioid prescribing rates across North America in the late-1990s.[1,7] Around this time, pharmaceutical companies advocated for the use of opioids to manage pain while spreading misinformation about their safety and addictive potential.[8] Many of these opioids were diverted to the unregulated drug supply, resulting in a significant increase in nonmedical prescription opioid use.[9] From 2004 to 2010, the number of daily doses of opioids consumed in Canada nearly doubled,[10] and by 2011, there was significant evidence indicating that opioid prescribing practices along with opioid misuse were contributing to a rise in opioid-related morbidity and mortality.[1,11,12]

By 2012, several interventions were implemented in response to the growing prescription opioid epidemic, including prescription monitoring systems,[13,14] targeting sources of overprescribing,[14] and the development and distribution of opioid prescription guidelines.[11,15] Studies conducted following the implementation of these interventions have shown that the number of opioids prescribed had decreased,[15,16,17] but the demand for opioids among the Canadian population did not simultaneously decline.[9] These prescribing restrictions coupled with a high supply demand contributed to the second wave of the overdose epidemic, characterized by

a resurgence of heroin use and a rapid increase in deaths related to heroin.[18,19] The third wave began in 2013, with the emergence of highly potent synthetic opioids in the unregulated drug supply, including fentanyl and its analogues.[1,20,]

Since fentanyl and its analogues were first detected in Canada's unregulated drug supply, they have contributed to a steady rise in overdose deaths.[21,22] In 2016, the number of opioid-related deaths involving fentanyl was 67% and has since risen to approximately 87% in 2021.[23] Fentanyl has not only contributed to a stark increase in deaths but also other related harms, including non-fatal overdoses (NFO), hospitalizations, increased risk of infectious disease and reduced quality of life.[24,25] This may be partly due to a growing prevalence of individuals knowingly using and actively seeking fentanyl as well as the adulteration of other substances (e.g., stimulants, benzodiazepines) with fentanyl.[26,27,28] Of note, this has been mainly reported in the Western provinces, particularly British Columbia (BC), which has been the epicentre of the opioid crisis for many years.[29]

More recently, a dramatic increase in overdose deaths involving both opioids and stimulants, particularly cocaine and methamphetamine, has been described as the fourth wave of the overdose epidemic.[22,30] Although stimulants have been prevalent in Canada's unregulated drug supply for many years, there has been a significant increase in methamphetamine use among people with an existing opioid use disorder.[31] In 2021, approximately 86% of stimulant deaths also involved an opioid, highlighting the polysubstance use nature of the current overdose epidemic.[32] In addition to overdose deaths, there has been a rise in HIV outbreaks and hospitalizations related to methamphetamine use in many Canadian regions.[22,28] The reasons for concurrent use of potent opioids and stimulants are poorly understood, however it is known that there are implications for

overdose prevention and response strategies as well as substance use disorder treatment outcomes.[33,34]

The burden associated with synthetic and prescription opioid misuse has prompted the development of several interventions targeting individuals at high risk of opioid-related harm. For example, the distribution of naloxone for opioid overdose reversal, supervised injection and overdose prevention sites, expansion of evidence-based pharmacotherapies, safe supply programs and drug checking services have been widely expanded across Canada to mitigate overdose risk.[30,35] For those who have developed opioid use disorder (OUD), the increased availability, accessibility and effectiveness of evidence-based treatments has been a primary focus for decreasing opioid-related morbidity and mortality.[36]

1.1.2 The management of prescription-type opioid use disorder with opioid agonist treatment

Opioid agonist treatments, including methadone and buprenorphine/naloxone, are the recommended options for managing OUD in Canada.[37] Methadone has been an effective treatment option since the 1960s, with extensive literature reporting on the beneficial outcomes of treatment with methadone.[38,39] Some of these benefits include reductions in non-medical opioid use,[40,41] mortality risk,[42,43] criminal behaviour,[44] as well as improvements in the overall quality of life,[40,43,45] and linkage to medical, mental health and social services.[44,46] Many studies have reported on retention rates in methadone treatment, which are highly variable across models of care and treatment populations, ranging from 31%-91% at 12 months.[47,48,49,50] Despite the many benefits of methadone, several characteristics may deter patients from engaging and being retained in methadone treatment. For example, methadone is a full agonist of the μ-opioid receptor, which increases the risk of respiratory depression, sedation and overdose.[48,51] A study by Sordo et al.,

examined the risk of mortality during methadone treatment and found that the risk of mortality is high during the first four weeks of treatment and after termination of treatment.[43] To mitigate the risk of overdose during treatment initiation, methadone must be titrated slowly, and it may take several months to reach a therapeutic dose.[48,52] For some patients, non-prescribed opioid use may persist to compensate for withdrawal symptoms, which can increase the likelihood of treatment discontinuation.[48] Additionally, patients are required to visit a clinic or pharmacy daily to ingest methadone, which may be unrealistic for those who are employed or whose daily activities may interfere with clinic hours.[53]

Buprenorphine/naloxone has similar treatment outcomes to methadone, including reductions in non-medical use of opioids, reductions in risk of mortality, high patient satisfaction and linkage to treatment for medical co-morbidities.[54,55,56] However, buprenorphine/naloxone has a superior safety profile compared to methadone as it is only a partial μ-opioid receptor agonist.[57] There is a ceiling effect on its activity, meaning there is little risk of respiratory depression and overdose at higher doses.[58] Another benefit of buprenorphine/naloxone is that there is no bioaccumulation which allows for a faster titration to an effective dose.[59] In addition to the increased safety profile, take-home dosing can be prescribed for stable patient populations which provides more flexibility for those who are unable to attend daily clinic visits. Studies have demonstrated that retention in buprenorphine/naloxone treatment are comparable to methadone at higher doses, which is why it is strongly recommended as the first-line treatment option in Canada.[38,60,53] Despite the many benefits of buprenorphine/naloxone, there are limitations to its use. For example, initiation of buprenorphine/naloxone can be challenging as the patient needs to avoid using other opioids for several hours (i.e. at least 24-48 hours) to avoid precipitated withdrawal.[61,62] This has been reported as significant barrier to uptake along with reluctance to

long-term maintenance.[61,58] To date, many studies comparing the effectiveness of methadone and buprenorphine have been conducted in populations that primarily use heroin, and few have been done in people who use prescription and synthetic opioids within a realistic model of care.[63] It is currently unclear whether findings from these trials are applicable to patient populations who use prescription and synthetic opioids.

1.1.3 Patient populations with a history of non-fatal overdose

As the number of fatal opioid overdoses has increased in Canada, so has the number of non-fatal overdoses (NFO). It is estimated that for every fatal overdose, there are upwards of 20 NFOs.[64] In the first six months of 2021, there were over 30,000 Emergency Medical Services (EMS) responses for suspected opioid-related overdoses across the country, representing a 76% increase from 2019.[32] Most people who experience an overdose do survive,[65] however, there are numerous health-related complications that can follow an overdose event. These include physical consequences such as hypoxic-ischemic brain injury, physical injury, peripheral neuropathy, chest infections and renal problems, as well as mental consequences such as cognitive impairments, trauma and changes in behaviour.[66,67,68] These complications can lead to more frequent contact with health care services and an overall reduction in quality of life.[69]

It is well-known that overdose survivors are at an elevated risk of subsequent overdose and death, especially among those with repeated NFO events.[70,71,72,] Subsequent overdose is highest in the first year following overdose,[73] suggesting that timely initiation of treatment may mitigate this risk.[74] A recent study by Larochelle *et al*. demonstrated that engagement in methadone or buprenorphine following an overdose was associated with a reduced risk of all-cause and opioid-related mortality.[75] Engagement in treatment has also been associated with reduced incidence of subsequent overdose.[76] Findings from these studies suggest that identifying individuals with a

history of NFO and retaining them in OAT may reduce the number of opioid-related fatal and non-fatal overdoses and improve the quality of life for this population. Currently, little is known about how different treatment modalities impact retention and opioid use among people with a history of NFO. Understanding the treatment needs among this particularly high-risk population is essential for the improvement of current interventions.

In addition to improving treatment outcomes, understanding the risk and protective factors associated with a history of NFO is essential for the development of effective overdose prevention strategies. Currently the majority of the existing literature has examined a variety of biological, social, structural and substance use factors in populations that primarily use heroin.[77,78] As mentioned previously, the unregulated drug market has changed extensively in the last few years, resulting in more people using prescription and synthetic opioids, including fentanyl. Little is known about correlates of overdose among a population that has high rates of fentanyl and prescription opioid use and are seeking treatment. In light of these changes in drug use patterns, the need to examine correlates of non-fatal overdose is crucial to inform prevention and treatment interventions.

1.2 Rationale

People with a history of non-fatal overdose (NFO) are a vulnerable population with increased morbidity and mortality rates.[71,79] Factors associated with NFO have been studied extensively in people who use heroin and prescription opioids (e.g., oxycodone, morphine), but few studies have been done in Canadian treatment-seeking populations since the introduction of fentanyl and other potent synthetic opioids in the unregulated drug supply. A greater understanding of risk factors in the current treatment-seeking population is essential for developing prevention and intervention strategies to mitigate future risk of opioid-related harms, including overdose. Additionally, little is known about treatment outcomes, particularly retention in treatment, suppression of opioid use and rates of overdose during treatment among individuals with a history of NFO. The current study provides the opportunity to characterize overdose survivors during the fentanyl-era and determine outcomes in opioid agonist treatment at seven clinical sites in four Canadian provinces.

1.3 Objectives

This thesis aims to characterize treatment-seeking individuals with POUD and history of NFO and determine their outcomes in opioid agonist treatment. The three primary objectives of this thesis are:

1. **To investigate the demographic, social and structural factors associated with a history of NFO among people with prescription-type opioid use disorder.** Using multivariable logistic regression, Chapter 2 examines the correlates of NFO in a treatment-seeking population that primarily uses prescription-type opioids (licit or illicit, including fentanyl). Variables were selected *a-priori* and based on existing literature examining correlates of

NFO in diverse opioid-using populations in a variety of settings. This analysis provides critical information about correlates of NFO during the fentanyl era, and how they compare to existing research on risk and protective factors for overdose.

2. **To examine opioid agonist treatment outcomes among individuals with a history of NFO.** Chapter 3 explores retention in opioid agonist treatment and non-medical opioid use among those with a history of NFO. Using multivariable logistic regression, we determined the relative effectiveness of buprenorphine/naloxone versus methadone on retention in the assigned treatment or any OAT. Additionally, we investigated the mean difference in opioid-free urine drug screens between the two treatment groups to determine if buprenorphine/naloxone is as effective as methadone for reducing illicit opioid use.
3. **To describe the overdose events that took place during the study period among those with a history of NFO and examine opioid use before and after overdose.** Chapter 4 presents the demographic and substance use characteristics of individuals who experienced an overdose event during the study period. We also illustrated patterns of opioid use before and after the overdose event to determine if there were any reductions in opioid use following an overdose.

1.4 Overview of thesis

This thesis is divided into five chapters. Chapter 1 provides an overview of the opioid epidemic in Canada and the current treatment options available for the treatment of opioid use disorder. It also summarizes the existing literature on the harms associated with non-fatal overdose (NFO) and knowledge gaps regarding the characterization of overdose survivors and their outcomes in opioid agonist treatment. Chapter 2 focuses on identifying the prevalence and correlates of NFO in a treatment-seeking population with prescription-type opioid use disorder. Chapter 3 examines the relative effectiveness of buprenorphine/naloxone and methadone on retention in treatment and suppression of opioid use among participants with a history of NFO. Chapter 4 characterizes the participants with a history of NFO who overdosed during the study period and describes patterns of substance use before and after overdose. Lastly, Chapter 5 summarizes key findings from Chapters 2-4 and discusses study limitations and several directions for future research.

1.5 Conceptual Frameworks

Rhodes' Risk Environment Framework is among the most commonly used theoretical frameworks for understanding drug-related harms.[80] The Risk Environment Framework focuses on investigating how physical, social, economic and policy factors interact at the micro, meso and macro environmental levels to increase the risk of drug-related harm.[81] This framework highlights the dynamic relationship between an individual and their environment and expands the responsibility of risk beyond the individual to include social and political systems.[82] Previous studies have drawn from the Risk Environment Framework to examine individual, social and structural factors that may increase the risk of opioid overdose,[83,84,85] however many of these studies were conducted prior to the introduction of fentanyl in the unregulated drug supply. As the overdose risk environment has rapidly changed in recent years, we have adapted Rhodes' framework to examine individual and socio-structural-level correlates of NFO among individuals with POUD who are currently seeking treatment (Figure 1.1). For example, individual factors that may be correlated with a history of NFO include injection drug use and psychiatric comorbidities,[85,86] while socio-structural factors may include homelessness, receiving income assistance and history of incarceration.[87,88] This conceptual framework was used as a guide for variable selection in Chapter 2.

The cascade of care framework was created to measure engagement along the continuum of care for individuals with chronic diseases including human immunodeficiency virus (HIV),[89,90,91] hepatitis C virus (HCV),[92,93] and more recently, opioid use disorder (OUD).[94] The continuum of care comprises several stages; linkage to treatment, treatment initiation, retention in treatment and long-term recovery, where system-wide effectiveness can be measured.[95] Mugavero and colleagues proposed a socio-ecological framework that details individual, relationship,

community, health, care system and factors that impact engagement along the continuum of HIV clinical care.[96] Based on the existing literature identifying factors associated with retention in opioid agonist treatment (OAT),[97,98] we have adapted this framework to examine the individual, community, health care system and policy factors that may specifically impact retention in OAT among individuals with a history of NFO. (Figure 1.2) This conceptual framework was used as a guide for variable selection in Chapter 3.

Figure 1: Conceptual framework to examine correlates of non-fatal overdose among people with prescription-type opioid use disorder

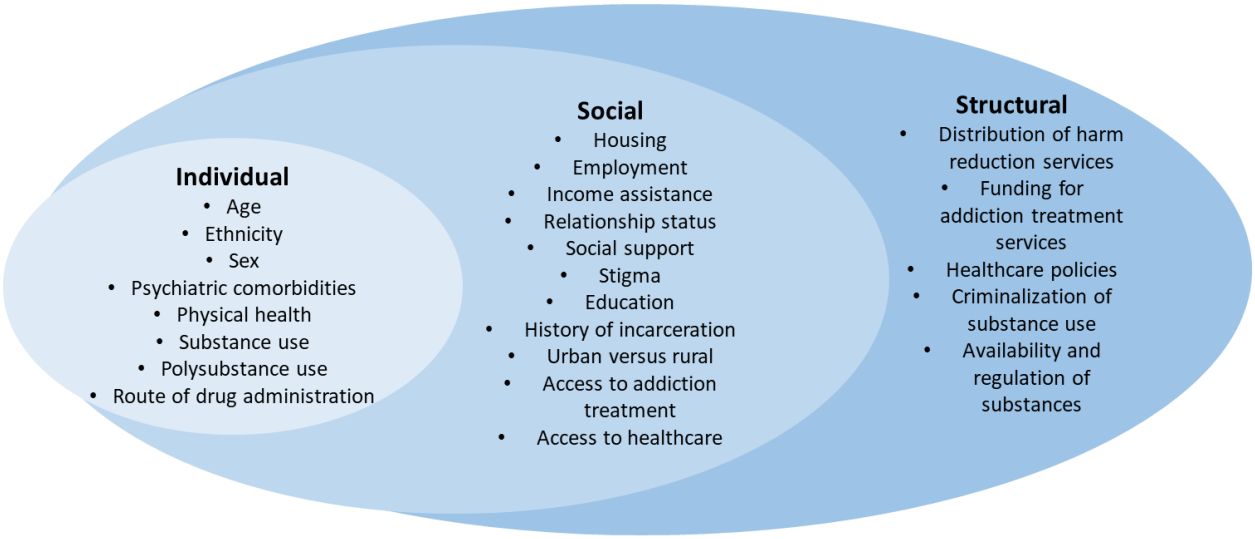
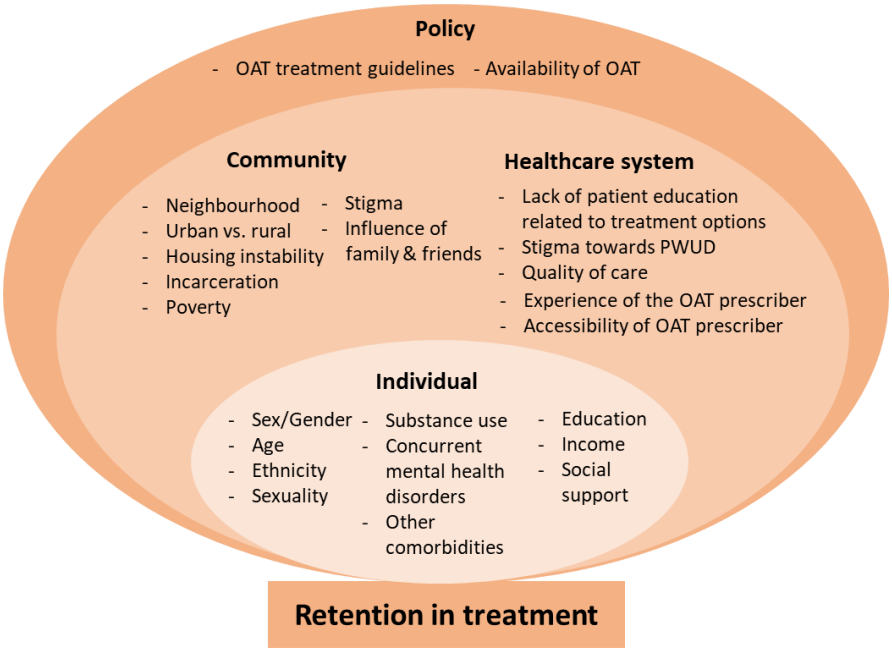


Figure 2: Conceptual framework of socio-ecological factors that impact retention in treatment among people with a history of non-fatal overdose



1.6 Study Design

This research was conducted using data from OPTIMA (Optimizing patient centered-care: A pragmatic randomized control trial comparing models of care in the management of prescription opioid misuse), the first clinical trial funded and conducted by the Canadian Research Initiative in Substance Misuse (CRISM). The OPTIMA trial was a multi-center, open-label, 2-arm, 24-week, randomized control trial. The primary objective was to examine the relative effectiveness of flexible take-home dosing buprenorphine/naloxone versus supervised consumption of methadone in suppressing opioid use in individuals with POUD including those that primarily use fentanyl.

Participants were recruited between October 2, 2017 and March 23, 2020 at seven clinical sites in four Canadian provinces including: The Rapid Access Addiction Clinic (Vancouver, BC); The Opioid Dependency Program Clinic (Edmonton, AL); The Opioid Dependency Program Clinic (Calgary, AL); The Centre for Addiction sand Mental Health (Toronto, ON); the Ontario Addiction Treatment Centre (Sudbury, ON); The Centre Hospitalier de l'Université de Montréal (Montréal, QC); and The Centre de Recherche et d'Aide pour Narcomane (Montréal, QC).

Eligibility for the trial included being between 18 and 64 years old, having a POUD diagnosis (defined by DSM-5 criteria), being non-pregnant, willing to be randomized to methadone or buprenorphine/naloxone, able to provide written and informed consent and able to communicate with research staff. Exclusion criteria are described in detail elsewhere.[99] Briefly, participants were excluded if they had any physical or mental health condition that inhibited informed consent, reported heroin as the most frequently used opioid in the last 30 days, were enrolled in OAT in the 30 days prior to initiation, were taking medications that interact with either of the study medications, had a previous adverse reaction to study medications or were pending

legal action that would interfere with study completion. Interested participants verbally consented to a pre-screening interview to determine their eligibility.

If eligible, the participant scheduled a screening interview, provided written informed consent, and completed screening assessments. Screening assessments included questionnaires related to demographics, OUD diagnosis, medical and psychiatric history, addiction severity, non-fatal overdose, and urine drug screen data. Once eligibility was confirmed, participants completed baseline assessments which could take place on the same day as screening or within a 28-day period. Baseline assessments included questionnaires about pain, severity of depression and anxiety, health service utilization, risk behaviours, substance craving and quality of life. Once all assessments were completed, participants were randomized to either daily witnessed ingestion of methadone or flexible take-home dosing of buprenorphine/naloxone models of care. The time from randomization to treatment initiation could last up to 14 days. If participants did not initiate treatment within this timeframe, they were considered a treatment initiation failure.

After treatment initiation, participants attended follow-up visits every two weeks for the 24-week intervention and were compensated up to $560 ($40/visit) for their time. Assessments completed every two weeks included urine drug screens (UDS),, self-reported treatment adherence and adverse events. The study followed local and international ethical guidelines and was approved by every clinical site's Research Ethics Committee. The trial was registered to clinicaltrials.gov (NCT03033732).

Chapter 2: Demographic and socio-structural factors associated with a history of non-fatal overdose among individuals with prescription-type opioid use disorder

2.1 Introduction

North America experienced a rapid rise in the availability of prescription opioids in the early 2000s, with Canada and the United States (U.S.) having the highest rates of prescription opioid use worldwide.[28] In response to increased morbidity and mortality associated with non-prescribed opioid use, several interventions were implemented to control and monitor opioid prescribing in Canada (e.g. the National Opioid Use Guideline Group recommendations).[100,101] However, these upstream interventions focusing on opioid prescribing and opioid-related harms have not curbed the overdose epidemic.[32] In recent years, there has been a shift with soaring overdose mortality now largely attributable to fentanyl and its analogues being the predominant opioid circulating in the unregulated drug supply.[11,27]

Along with an increase in fatal overdoses, there has been a proportional increase in non-fatal overdoses (NFOs) across Canada.[102] For example, in the first six months of 2021 alone, there were more than 17,400 Emergency Medical Services (EMS) responses to opioid-related overdoses in 9 Canadian provinces.[32] This number most likely underestimates the number of NFOs, as they can now be reversed in the community by non-medical personnel using naloxone[103] and many people who experience a NFO do not receive emergency medical attention.[104] The prevalence of NFO is a significant public health concern as numerous studies have demonstrated that those with a history of NFO are at a greater risk of future fatal and non-fatal overdose.[105,73,70]

Identifying factors associated with NFO provides an opportunity to implement preventative measures that could potentially reduce overdose rates and their associated harms. Many studies have previously determined biological,[106,107,108] social,[109] structural,[110,87,76] and substance use factors[111,112,110] associated with increased risk of NFO. However, the focus of many of these studies has been on factors associated with NFO among people who inject heroin or prescription opioids in one setting,[113,104] and it is unclear whether these factors influence NFO risk among treatment-seeking individuals who use prescription-type opioids and fentanyl analogues across multiple Canadian settings. Therefore, the objective of this study was to conduct an exploratory examination of factors associated with NFO among treatment-seeking individuals with prescription-type opioid use disorder (POUD), including unregulated fentanyl use, in four major Canadian provinces. Understanding these factors during a time of unparalleled overdose rates and a continuously evolving unregulated drug supply may help with the development of individualized and community interventions to reduce future overdose risk.

2.2 Methods

2.2.1 Study sample

The current study is a secondary analysis from the OPTIMA trial, a two-arm, pragmatic, open-label clinical trial evaluating the effectiveness of buprenorphine relative to methadone.[114] The study sample included all randomized participants with valid responses to questions assessing lifetime and recent (i.e., last six months) history of NFO, and valid baseline urine drug screens (UDS). Of 272 randomized participants, one participant was missing valid responses to the NFO questionnaire, and four were missing UDS data; these participants (1.5%) were removed from further analyses, resulting in a total analytic sample of 267 participants.

2.2.2 Variable selection

A range of social, demographic and substance use variables were included as potential explanatory variables based on previous research and *a priori* relationships described in the literature.[107,87,102,84,115,116,77] The variables included were: age (in years); biological sex (male vs. female); ethnicity [white vs. Black, Indigenous and people of colour (BIPOC)], marital status (married or common law vs. never married, separated, divorced, widowed or other); education (High school, technical school, college or university vs. none, elementary or middle school); received income assistance (yes vs. no); homelessness (yes vs. no); depression severity as assessed by the Beck Depression Inventory-II (BDI-II; range 0-63, with higher scores representing worse depression symptoms)[117]; suicidal ideation in the last 30 days (yes vs. no); consumed alcohol to intoxication in the last 30 days (yes vs. no); positive UDS for amphetamine/methamphetamine (yes vs. no); positive UDS for benzodiazepines (yes vs. no); positive UDS for cocaine (yes vs. no); positive UDS for cannabis (yes vs. no); positive UDS for fentanyl (yes vs. no); positive UDS for other opioids including non-prescribed buprenorphine and methadone, morphine, oxycodone, heroin or hydromorphone (yes vs. no); polysubstance use which was defined as a positive UDS for two or more substances (yes vs. no) and intravenous injection as the usual or most recent route of administration (yes vs. no). All these variables refer to screening or baseline assessments before randomization and the start of the assigned treatment.

2.2.3 Statistical analyses

First, we conducted descriptive statistics to characterize the study sample, stratified by self-reported history of NFO. Categorical variables were analyzed with the Pearson's χ^2 test (or the Fisher's exact test when one or more cells contained an expected value of 5 or less), and continuous variables with the Mann Whitney U test. Next, we used descriptive statistics to summarize the

circumstances of the most recent overdose, including the substances involved, and type of care received. Specifically, we analyzed the questions "What were the drugs you were using at the time of your last overdose", "Did someone call an ambulance or take you to a hospital?" and "Were you given naloxone?".

Next, we investigated the relationship between all explanatory variables and self-reported history of NFO using binary logistic regression and calculated unadjusted odds ratios and 95% confidence intervals. We then constructed an explanatory multivariable logistic regression model using an *a priori*-defined statistical approach, where all explanatory variables, excluding intravenous drug use, were simultaneously added into the model, regardless of significance in unadjusted analyses. Intravenous drug use was excluded from the final model because it was highly correlated with both positive urine drug screen for fentanyl ($p < 0.001$) and positive urine drug screen for methamphetamine ($p < 0.001$). Variance Inflation Factor (VIF) scores were calculated to determine the presence of multicollinearity for all logistic regression models.

Finally, we performed a sub-analysis to determine the relationship between all explanatory variables and self-reported NFO in the last six months. We used binary logistic regression and calculated unadjusted odds ratios and 95% confidence intervals. For the sub-analysis we only examined bivariate relationships as we did not have an adequate sample size to build a multivariable model. There was a total sample size of 84 participants, which was insufficient for the inclusion of all explanatory variables without overfitting the multivariable model. All statistical analyses were performed using R Studio version 1.4.1106. All *p*-values are two-sided.

2.3 Results

Of the 267 participants included in the analysis, 154 (58%) reported at least one NFO in their lifetime. Among these, 83 (55%, 31% of all participants) reported having a NFO in the last six months. Of those with a lifetime history of NFO, 124 (78%) reported multiple overdose events with a median number of 3 events [Quartile 1- Quartile 3 (Q1-Q3): 2-7].

Selected characteristics of the study sample are presented in Table 2.1. Around two-thirds were male (174; 65%) and self-identified as white (179; 67%). The median age was 38 years (Q1-Q3: 31-46). Current use of substances, including polysubstance use was common, with opioids being the most prevalent (55% had positive UDS for fentanyl and 84% for other opioids), followed by methamphetamine (51%). Socio-economic marginalization and mental health comorbidities were also prevalent as indicated by high rates of homelessness (37%) and receipt of income assistance (45%), as well as high BDI-II scores (median 25, Q1-Q3 1-3: 17- 34; with scores greater than 19 indicating moderate depression).

When asked about the circumstances of their last overdose, the majority of participants reported using opioids (87%), with few reporting alcohol (6%), benzodiazepine (8%) or stimulant (15%) use. Participants were able to choose all that apply, so these percentages sum to over 100%. Furthermore, 104 (68%) participants were administered naloxone and 92 (60%) were either taken to the hospital or an ambulance was called in response to the overdose.

The results of bivariable and multivariable analyses of factors associated with history of NFO are presented in Table 2.2. Several factors were positively associated ($p < 0.05$) with a history of NFO in the bivariable analysis including: self-identifying as white (odds ratio [OR] = 2.44; 95% confidence interval [CI] = 1.42 - 4.27); having received income assistance (OR = 1.97; 95% CI =

1.20 – 3.27); homelessness (OR = 3.52; 95% CI = 2.05 – 6.20); suicidal ideation in the last 30 days (OR = 2.30; 95% CI = 1.15 – 4.84); positive urine drug screen for methamphetamine (OR = 5.84; 95% CI = 3.45 – 10.10); positive urine drug screen for fentanyl (OR = 5.30; 95% CI = 3.15 – 9.08), polysubstance use (OR = 4.49; 95% CI = 2.19 – 9.82) and intravenous drug use (OR = 4.72; 95% CI = 2.82 – 8.04). At least high school level education (OR = 0.60; 95% CI = 0.36 - 0.99) was negatively associated with a history of NFO.

In the multivariable model, having received income assistance in the last month (adjusted odds ratio [AOR] = 2.17, 95% CI = 1.18 – 4.09), being homeless (AOR = 2.40, 95% CI = 1.25 – 4.56); having a positive urine drug screen for methamphetamine (AOR = 2.59, 95% CI = 1.17 – 5.80); and having a positive urine drug screen for fentanyl (AOR = 2.31, 95% CI = 1.01 – 5.30) remained significantly associated ($p < 0.05$) with a lifetime history of NFO (Figure 2.1). Tests to determine if the data met the assumption of collinearity indicated that multicollinearity was not a concern (VIF < 3). Our sub-analysis evaluating unadjusted correlates of recent NFO (i.e., NFO in the last six months), yielded similar results to the main analysis, and are presented in Table 2.3.

2.4 Discussion

This study examined the prevalence and factors associated with NFO among treatment-seeking individuals with a POUD diagnosis, including those who primarily use fentanyl and fentanyl analogues. A history of NFO was highly prevalent, with over half of the study sample reporting at least one overdose in their lifetime and over a third of participants reporting at least one event in the previous six months. Factors independently associated with a lifetime history of NFO included being homeless, having received income assistance in the last month, and having a positive UDS for methamphetamine and fentanyl at screening.

Prevalence rates of history of NFO observed in our study are considerably higher than those reported in a recent systematic review focusing on people who inject drugs[104] and other previous studies that focus on individuals who use prescription opioids prior to the fentanyl era.[118] Possible explanations for this discrepancy include differences in study population, timing of the study, risk of overdose and definition of NFO. First, our definition of people with POUD also included those using licit or illicit fentanyl, a highly potent opioid and known risk factor for overdose.[119] Second, NFO has been previously described as a potential motivator to seek substance use treatment based on cognitive motivation theories.[120] As we examined a treatment-seeking population, we may be enriching our population with those that have a recent history of NFO. Third, ambulance data are often used to measure prevalence of overdose, but many people who experience NFO do not receive medical attention given the availability of naloxone, fear of police presence and stigma when receiving healthcare in an acute care setting.[121,122] Our study used self-reported measures of NFO which may more accurately reflect people's experience with overdose.

It is concerning that over a third of participants did not receive care from emergency services or at the hospital following overdose. Recent evidence indicates that individuals who are not transported to the hospital following care from emergency services for overdose are at an increased risk of subsequent NFO.[123] This may be due to naloxone's short half-life and the risk of opioid toxicity following naloxone administration when potent opioids are consumed. Transport to hospital allows for the opportunity to monitor individuals to ensure they are no longer at risk of subsequent overdose. Transport to hospital after overdose may also increase access to essential services such as OAT, social services or naloxone programs as well as linkage to care for physical and psychological comorbidities. Future studies should empirically explore whether transport to

hospital reduces the risk of subsequent overdose and improves linkage to additional services among individuals with a lifetime history of NFO.

In our sample, nearly half of those with a history of NFO reported currently being homeless and similar to findings from other studies,[112,124,125] homelessness was found to be positively associated with a history of NFO. It is well known that people who do not have stable housing often do not receive sufficient healthcare and represent a large proportion of individuals with substance use disorders, mental health disorders, physical health problems and past trauma.[126,127] Furthermore, socioeconomic marginalization, including housing insecurity, has been shown to increase chronic stress due to health inequality, social exclusion, and stigmatization.[87] The stigmatization of both homelessness and substance use may result in potentially dangerous behaviours such as public injection or using alone which can heighten the risk of overdose.[128] Our findings support previous recommendations that clinicians should be aware that homelessness may be associated with an increased risk of future overdose.[128] They also indicate that many people seeking treatment are unstably housed which provides a unique opportunity for clinicians to link patients to social support services while in treatment. Connecting individuals with low-barrier housing interventions such as Housing First,[129] coupled with harm reduction services may be a critical first step in creating stability for this high risk population.

Many studies have evaluated how other elements of socioeconomic marginalization, like poverty and social assistance programs, contribute to health crisis events like overdose.[130,131,132] Both in the U.S. and Canada, income assistance programs, which consist of a synchronized payment on the same day each month, have been implemented to reduce the harmful effects of extreme poverty.[133,134] Previous research shows a relationship between synchronized income assistance payments and substance use-related harms including increased consumption of

substances, higher rates of fatal and NFOs, increased hospitalizations, increased demands on first responders, and reduced engagement in substance use treatment.[135,130,136,137] In the present study, approximately half of participants with a history of NFO had received income assistance in the 30 days prior to treatment initiation and similar to previous findings, income assistance was positively associated with having a history of NFO. Modifications to both social and structural interventions have been proposed to help mitigate the risk of drug-related harm after synchronized disbursement including alternative timing of disbursement, socio-economic education programs and labor market regulation.[135,138,139] For example, a recent randomized control trial suggested that alternative timing and frequency of income assistance payments reduced overall drug consumption immediately following government payment days; however, there was an increase in exposure to violence.[139] Taken together, these findings highlight the need to further explore and evaluate alternative disbursement schedules and upstream interventions that facilitate employment and income generation to determine the impact on substance use related harm, including overdose.

Our findings also showed that people currently using methamphetamine and fentanyl were more likely to have a history of NFO. We found that of those with a history of NFO, 68% had a positive UDS for methamphetamine, 70% were positive for fentanyl and 63% were positive for both at screening, indicating that a large proportion of individuals with a history of NFO continue to use substances, including concomitant use of opioids and stimulants. These findings are somewhat expected as the co-use of opioids and stimulants, particularly methamphetamine, has become more frequently observed across Canada and the U.S.[140] Moreover, the use of fentanyl, methamphetamine as well as polysubstance use are all well-known predictors of fatal and non-fatal overdose.[15,141,142] The finding that POUD with a history of overdose continue to use fentanyl and methamphetamine suggests an ongoing risk for future overdose, highlighting a need for

interventions that address this risk while people seek treatment. Currently, OAT are among the most effective interventions for reducing risk of morbidity and mortality for those with opioid use disorder however access and retention in treatment remains low.[143,144] Furthermore, evidence-based pharmacological treatment options for people with stimulant use disorder are limited and the outcomes of those that exist are inconsistent.[141] Behavioral interventions, such as contingency management, have been studied extensively in the context of substance use and have shown promise in reducing illicit opioid and psychostimulant use.[145] Future studies should investigate contingency management not only in the context of abstinence of substance use but in relation to overdose-related morbidity and mortality.

This study has several limitations. First, the data used for this analysis was cross-sectional in nature so temporal relationships between risk factors and overdose could not be determined. Some of the lifetime events or behaviours that were considered in this study may have taken place after the NFO, which does not allow for causal inferences. Second, the study only included treatment seeking individuals with POUD at seven Canadian sites across four provinces and participants were recruited through contact with staff at these sites. While a multisite design increases generalizability of our findings, they may not be applicable to those who fall outside these jurisdictions, specifically other individuals who are out of care who may be particularly at high risk of overdose. Third, history of NFO and all other data, except urine drug testing, were self-reported which may have introduced biases, including social desirability and recall bias. There is also the potential for misallocation bias as we did not explicitly define the term overdose when participants were interviewed.

Despite these limitations, the present study adds to our understanding of NFO among the treatment-seeking population with POUD in Canada. Specifically, we found that a lifetime history

of NFO was common, particularly among socially marginalized persons and those using fentanyl and methamphetamine. Prospective evaluation of overdose risk factors should be explored in the current climate of the Canadian overdose crisis to identify risk and protective factors of future fatal and non-fatal overdoses.

Table 1: Selected baseline characteristics of 267 treatment-seeking individuals with prescription-type opioid use disorder, stratified by history of non-fatal overdose

Characteristic	Total (%) (*n* = 267)	History of NFO		*p* - value
		Yes; n (%) (*n* = 154)	No; n (%) (*n* = 113)	
Sociodemographic				
Age, median (q1 – q3)†	38 (31 – 46)	38 (32 – 46)	37 (30 – 46)	0.866
Male sex	174 (65.2)	96 (62.3)	78 (69.0)	0.316
White ethnicity	179 (67.0)	91 (59.1)	88 (77.9)	0.002
Married, common law or engaged	29 (10.7)	22 (13.8)	7 (6.2)	0.473
At least secondary school	165 (61.8)	103 (66.9)	62 (54.9)	0.062
Received income assistance	120 (44.9)	80 (51.9)	40 (35.4)	0.010
Homelessness	99 (37.1)	75 (48.7)	24 (21.2)	<0.001
Incarceration in the last 30 days*	13 (4.90)	11 (7.20)	2 (1.8)	0.085
Mental Health				
Beck depression inventory-II, median (q1 – q3)	25 (17.0 – 34.0)	26 (18.0 – 36.0)	22 (15.8 – 30.2)	0.023
Suicidal ideation	45 (16.9)	33 (21.4)	12 (10.6)	0.030
Substance Use				
Consumed alcohol to intoxication	44 (16.5)	22 (14.3)	22 (19.5)	0.337
Intravenous route of administration	142 (53.2)	106 (68.8)	36 (31.9)	<0.001
Positive urine drug screening (UDS)				
Amphetamine/methamphetamine	137 (51.3)	106 (68.8)	31 (27.4)	<0.001
Benzodiazepines	38 (14.2)	23 (14.3)	16 (14.2)	1.000
Cocaine	75 (28.1)	44 (28.6)	31 (27.4)	0.947
Tetrahydrocannabinol	119 (44.6)	71 (46.1)	48 (42.5)	0.642
Other opioids (excluding fentanyl)‡	223 (83.5)	129 (83.8)	94 (83.2)	1.000
Fentanyl	148 (55.4)	111 (72.1)	37 (32.7)	<0.001
Polysubstance use•	227 (85.0)	143 (92.9)	84 (74.3)	<.0.001

† Notes: (q1 – q3) = upper and lower quartiles
* Notes: Fisher's exact test was used
‡ Notes: Other opioids = (buprenorphine, morphine, oxycodone, methadone, heroin, hydromorphone, tramadol)
• Notes: Polysubstance use = 2 or more positive urine drug screens

Table 2: Univariable and multivariable analyses of factors associated with a history of non-fatal overdose among 267 treatment-seeking individuals with prescription-type opioid use disorder

Characteristic	Odds Ratio (OR)	
	Unadjusted OR (95% CI)†	Adjusted OR (95% CI)
Sociodemographic		
Age	0.99 (0.97 – 1.02)	1.02 (0.99 – 1.06)
Male sex	1.35 (0.81 – 2.27)	1.32 (0.67 – 2.60)
White ethnicity	2.44 (1.42 – 4.27)	1.60 (0.82 – 3.15)
Married, common law or engaged	0.57 (0.12 – 2.11)	0.57 (0.19 – 1.60)
At least secondary school	0.60 (0.36 – 0.99)	0.58 (0.31 – 1.07)
Received income assistance	1.97 (1.20 – 3.27)	2.17 (1.18 – 4.09)
Homelessness	3.52 (2.05 – 6.20)	2.40 (1.25 – 4.68)
Incarceration in the last 30 days	4.26 (1.11 – 27.90)	1.06 (0.23 – 7.61)
Mental Health		
Beck depression inventory-II score	1.02 (1.00 – 1.05)	1.00 (0.98 – 1.03)
Suicidal ideation	2.30 (1.15 – 4.84)	1.88 (0.77 – 4.85)
Substance Use		
Consumed alcohol to intoxication	0.69 (0.36 – 1.32)	1.53 (0.68 – 3.50)
Positive urine drug screening (UDS)		
Amphetamine/methamphetamine	5.84 (3.45 – 10.10)	2.59 (1.17 – 5.80)
Benzodiazepines	1.01 (0.51 – 2.05)	1.55 (0.64 – 3.86)
Cocaine	1.06 (0.62 – 1.83)	0.72 (0.36 – 1.45)
Tetrahydrocannabinol	1.16 (0.71 – 1.89)	1.16 (0.60 – 2.25)
Other opioids (excluding fentanyl)‡	1.04 (0.54 – 2.00)	1.15 (0.48 – 2.68)
Fentanyl	5.30 (3.15 – 9.08)	2.31 (1.01 – 5.30)
Polysubstance UDS•	4.49 (2.19 – 9.82)	1.66 (0.58 – 4.93)

‡ Notes: Other opioids = (buprenorphine, morphine, oxycodone, methadone, heroin, hydromorphone, tramadol)
• Polysubstance use = 2 or more positive urine drug screens
† CI = Confidence interval

Table 3: Individual and socio-structural factors associated with non-fatal overdose in the last six months among treatment-seeking individuals with prescription-type opioid use disorder

Characteristic	History of recent NFO		Unadjusted OR (95% CI)	p-value
	Yes; n (%) (*n* = 83)	No; n (%) (*n* = 184)		
Sociodemographic				
Age, median (q1 – q3)†	37 (31 – 43)	39 (31 – 48)	0.97 (0.95 – 1.00)	0.036
Male sex	53 (63.9)	121 (65.8)	0.92 (0.54 – 1.59)	0.762
White ethnicity	49 (59.0)	130 (70.7)	0.60 (0.35 – 1.03)	0.063
Married, common law or engaged	10 (12.)	14 (7.6)	1.66 (0.69 – 3.89)	0.244
At least secondary school	60 (72.3)	105 (57.1)	0.51 (0,29 – 0.88)	0.019
Received income assistance	38 (45.8)	109 (59.2)	1.72 (1.02 – 2.91)	0.042
Homelessness	44 (53.0)	55 (29.9)	2.65 (1.55 – 4.54)	<0.001
Incarceration in the last 30 days*	7 (8.4)	6 (3.3)	2.70 (0.87 – 8.65)	0.083
Mental Health				
Beck depression inventory-II, median (q1 – q3)	30.0 (19 – 40)	22 (16 – 30.8)	1.04 (1.02 – 1.06)	<0.001
Suicidal ideation	24 (28.9)	21 (11.4)	3.16 (1.64 – 6.14)	0.001
Substance Use				
Consumed alcohol to intoxication	11 (13.3)	33 (17.9)	0.70 (0.32 – 1.42)	0.342
Intravenous route of administration	64 (77.1)	78 (42.4)	4.58 (2.58 – 8.43)	<0.001
Positive urine drug screening (UDS)				
Amphetamine/methamphetamine	64 (77.1)	73 (39.7)	5.12 (2.88 – 9.45)	<0.001
Benzodiazepines	7 (8.4)	31 (16.8)	0.45 (0.18 – 1.02)	0.074
Cocaine	22 (26.5)	53 (28.8)	0.89 (0.49 – 1.58)	0.485
Tetrahydrocannabinol	35 (42.2)	84 (45.7)	0.87 (0.51 – 1.46)	0.691
Other opioids (excluding fentanyl)‡	64 (77.1)	159 (86.4)	0.53 (0.27 – 1.04)	0.060
Fentanyl	65 (78.3)	83 (45.1)	4.39 (2.46 – 8.17)	<0.001
Polysubstance use	78 (94.0)	149 (81.0)	3.66 (1.50 – 11.0)	0.009

* Notes: Fisher's exact test was used
† Notes: (q1 – q3) = upper and lower quartiles
‡ Notes: Other opioids = (buprenorphine, morphine, oxycodone, methadone, heroin, hydromorphone)
• Notes: Polysubstance use = 2 or more positive urine drug screens

Chapter 3: Retention in supervised methadone vs. take-home dosing buprenorphine/naloxone treatment among individuals with a history of non-fatal overdose

3.1 Introduction

Across the United States and Canada, the overdose crisis continues to escalate, transitioning from primarily driven by diverted prescription opioids to illicitly manufactured synthetic opioids (i.e., fentanyl).[22,49] For example, in Canada, just 4% of deaths were attributed to fentanyl in 2012, which has since increased to nearly 86% in 2021.[146] In addition to an increase in morbidity and mortality associated with fentanyl use,[147] anecdotal evidence suggests that people who use illicit fentanyl may experience more difficulties initiating and remaining in treatment, introducing a new challenge for treating patients with opioid use disorder.[148]

Currently, the standard of care for opioid use disorder in both Canada and the U.S are opioid agonist treatments (OATs) such as buprenorphine/naloxone and methadone.[38,149] Despite numerous studies indicating that both of these treatment options reduce the risk of all-cause and overdose-related mortality,[43] reduce unregulated opioid use,[38] and improve quality of life,[150] it is estimated that only one in five patients with OUD access treatment and the majority are not retained in treatment beyond 12 months.[151] Many social and structural barriers impact access and retention in OAT.[150,152,153] Some of these barriers include strict program requirements (e.g., daily visits to pharmacy, fixed pharmacy hours),[154] limited access to treatment (e.g., unable to access a trained clinician that prescribes OAT, non-continuity of care following incarceration, simpler to access substances from the unregulated drug supply),[154,155] social determinants of health (e.g.,

poverty, unemployment, homelessness, mental and physical health conditions) and attitudinal barriers resulting from stigma related to substance use.[122,156]

Particularly for those with a history of non-fatal overdose (NFO), it is crucial for people with OUD to access and engage in OAT, as they are at a high risk of an array of adverse health outcomes, including subsequent overdose and mortality.[29,71] Previous studies indicate that between 7% and 17% of individuals who survive an overdose experience another within one year, and a high proportion of these are fatal.[71,157] Overdose survivors are also at a higher risk of other health-related complications such as hypoxic brain injury, heart complications, seizures, nerve damage and changes in cognitive and physical functioning, requiring increased health care utilization.[66] Evidence suggests that individuals enrolled in OAT have a lower risk of non-fatal overdose compared to those not in treatment,[76,75] highlighting the value of engaging those with a history of NFO in OAT to prevent future harm.

Many studies have evaluated the relative effectiveness of buprenorphine/naloxone versus methadone for retaining patients in treatment both in observational and clinical trial settings.[49,158,38] However, the majority of these studies have been conducted among individuals who primarily use heroin and have followed strict dosing regimens. It is unclear whether the results from these studies translate to those who use prescription-type and synthetic opioids (including fentanyl) under real-world treatment conditions, where methadone and buprenorphine/naloxone have different programmatic requirements. In addition, there is minimal research comparing r retention rates and illicit opioid use rates among those enrolled in buprenorphine/naloxone versus methadone treatment with a lifetime and recent history of NFO.[159,83] Based on the findings presented in Chapter 2, social-structural factors (i.e., homelessness, receiving income assistance) are associated with NFO, indicating that those with a history of NFO may experience greater social

marginalization and have different patterns of substance use compared to the general population of people with OUD.. Therefore, the objective of the current study was to determine the relative effectiveness of flexible take-home dosing of sublingual buprenorphine/naloxone compared to standardized supervised methadone models of care on OAT retention and reducing opioid use among individuals with POUD and a history of NFO in four major Canadian provinces.

3.2 Methods

3.2.1 Study sample

The present study is a secondary analysis of the OPTIMA trial, previously described in Chapter 1. The sample was restricted to all randomized participants that reported a lifetime history of NFO at the screening visit. Data regarding history of NFO was missing for one participant and four were missing urine drug screen data resulting in a total analytic sample of 154 participants with a lifetime history of NFO. In a sub-analysis, we further restricted the sample to randomized participants with a recent history of NFO (i.e. last six months). This resulted in an analytic sample of 83 participants with a recent history of NFO.

3.2.2 Outcome measures

The primary outcome measure was retention in the assigned treatment, defined as having an active prescription for the assigned OAT at week 24 and having a positive urine sample result for the assigned OAT (i.e., buprenorphine or EDPP) at week 24. Opioid use, measured by the proportion of opioid-free UDS (excluding the assigned study medication) during the 24 weeks, was a secondary outcome. UDS data were collected every two weeks after treatment initiation for a maximum of 12 samples per participant for the whole study period. We tested for the presence of the following opioids: morphine, oxycodone, fentanyl, tramadol, 6-monoacetylmorphine and

hydromorphone, methadone and buprenorphine/naloxone using a Rapid Response Multi-Drug Once Step Screen Test Panel and single test strips. Missing UDS data were considered opioid positive in the primary analysis.

3.2.3 Exposures

The primary exposure was the assigned treatment, either methadone provided via initial daily witnessed ingestion or buprenorphine/naloxone maintenance therapy provided via flexible take-home dose regimens. Based on existing literature describing factors that impact both treatment and retention,[40,160] a number of confounding variables were considered for inclusion in bivariable analyses assessing retention in treatment. The variables included were age (in years); biological sex (male vs. female); ethnicity (white vs. Black, Indigenous and People of color [BIPOC]); homelessness (yes vs. no); receiving income assistance in the last month (yes vs. no); clinical site (Ontario and Quebec [East Coast]) vs. Alberta and British Columbia [West Coast]); lifetime heroin use (yes vs. no); positive urine drug screen (UDS) for opioids including morphine, oxycodone, heroin, hydromorphone or fentanyl, unprescribed methadone or buprenorphine (yes vs. no); positive UDS for stimulants (yes vs. no). All variables refer to screening or baseline assessments prior to randomization and treatment initiation.

3.2.4 Statistical analyses

First, group differences between participants randomized to buprenorphine or methadone were assessed using Pearson's χ^2 test (or Fisher's exact test for small cell counts) for categorical variables and Mann Whitney U test for continuous variables. Next, we used descriptive statistics to determine the median number of days spent in treatment and the number of individuals that dropped out of treatment in the first 30 days. Descriptive statistics were produced for 120

participants (78%), for whom study completion data was available. We then investigated the effect of buprenorphine/naloxone treatment on retention relative to methadone using multivariable logistic regression. Multivariable logistic regression models were adjusted for the stratification variables, lifetime heroin use and clinical site, as all variables examined in bivariable analysis were not statistically significantly different between treatment groups ($p>0.05$). We conducted a sub-analysis, using the same approach as described above restricted to participants with a recent NFO.

Finally, we calculated the unadjusted and adjusted mean difference in opioid-free UDS between the buprenorphine/naloxone and methadone groups and its 95% confidence interval (0.05, two-sided) using an Analysis of Covariance (ANCOVA), adjusting for stratification variables clinical site, and lifetime heroin use. Shapiro-wilk and Brown-Forsythe tests were used to verify the assumptions of normality and variance homogeneity and Tukey's honest significant test was used to adjust for multiple comparisons. All statistical analyses were performed using R Studio version 1.4.1106. All *p*-values are two-sided.

3.2.5 Sensitivity analysis

First, we performed sensitivity analyses on the primary retention outcome using an alternative definition: having a prescription and positive UDS for any OAT including methadone, buprenorphine/naloxone, long-acting morphine or any other opioids used as treatment. In the secondary analysis, we analyzed the mean difference in opioid use (i.e., secondary outcome) using two alternative approaches: 1) excluding all missing UDS data, 2) only including data for participants that were retained in the assigned treatment at 24 weeks.

3.3 Results

3.3.1 Sample characteristics

A total of 154 (57% of 272 randomized participants) reported at least one NFO in their lifetime and had valid baseline UDS results and were therefore included in this analysis. Of these, 76 (49%) were randomized to methadone and 78 (51%) to buprenorphine/naloxone. Baseline characteristics of the entire sample, stratified by treatment arm are presented in Table 3.1. At baseline, the median age was 38 (interquartile range [IQR]: 32 – 46), 58 participants (38%) were female and 91 (59%) self-identified as white. Nearly half were homeless (49%) and received income assistance in the last month (52%). The majority of participants were enrolled in sites located in British Columbia or Alberta [West coast (71%)] and were positive for opioids (96%) and stimulants at baseline (79%). There were no significant differences between the two treatment groups at baseline for all variables examined. The median number of days spent in treatment was 162 days (IQR= 22.5 – 168) with 32 (27%) participants dropping out in the first 30 days after treatment initiation (of these, 53% were in the buprenorphine/naloxone and 47% in the methadone arm).

3.3.2 Treatment retention

Table 3.2 displays results of the bivariable and multivariable logistic regression analyses of the effect of type of assigned OAT on retention in treatment at 24 weeks among participants with a lifetime history of NFO. Retention in the assigned treatment was 17.7% for the buprenorphine/naloxone group and 18.4% for the methadone group (adjusted odds ratio [AOR] = 0.54, 95% CI: 0.17 – 1.54). When retention in any OAT was examined, these rates were 27.8% for

the buprenorphine/naloxone group and 19.7% for the methadone group (AOR = 1.22, 95% CI: 0.51 – 2.96).

Table 3.3 presents results of our sub-analysis restricted to the 83 participants with a recent NFO event. Retention in the assigned treatment was 7.1% for the buprenorphine/naloxone group compared to 23.8% in the methadone group (AOR = 0.13, 95% CI = 0.01 - 0.64). When retention in any OAT was examined, retention was 21.4% for the buprenorphine/naloxone group and 23.8% for the methadone group (AOR = 0.71, 95% CI: 0.21 – 2.30).

3.3.3 Opioid-free urine drug screen

Figure 3.1 displays the proportion of opioid-negative UDS during the study period, stratified by treatment arm. Among participants with a history of NFO, the buprenorphine/naloxone arm had a statistically significantly higher proportion of opioid-free UDS compared to methadone across all analyses (Table 3.4). For the total sample (n=154), including missing UDS data that were considered positive, the mean proportion of opioid negative UDS (±SD) was 19.3 (±32.2)% in the buprenorphine/naloxone group and 7.4 (±20.0)% in the methadone group (adjusted mean difference = 11.9%, 95% CI = 3.5 to 20.3, p = 0.0057). When missing UDS data were excluded, the mean proportion of opioid negative UDS were 36.2 (±41)% in the buprenorphine/naloxone group and 14.8 (28.7)% in the methadone group (adjusted mean difference = 21.4%, 95% CI = 12.4 to 30.4, p = <0.001). Finally, when we restricted the sample to participants who were retained in the assigned treatment (n=29), the mean proportion of opioid negative UDS were 73.8 (±20.1)% in the buprenorphine/naloxone arm and 30.0 (±43.8)% in the methadone arm (adjusted mean difference = 43.8, 95% CI =26.3 – 61.3, p = <0.001).

3.4 Discussion

The present study aimed to explore retention in OAT and opioid use among people with POUD and a history of NFO initiating supervised methadone or flexible take-home dosing buprenorphine/naloxone as part of a pan-Canadian pragmatic trial. The results indicate that levels of retention in the assigned or any treatment were overall low but we failed to find a statistically significant difference between the buprenorphine/naloxone and methadone groups. However, the proportion of opioid-free urine drug screens was significantly higher among participants in the buprenorphine/naloxone group compared to methadone group. When we restricted the sample to those with a history of NFO in the last 6 months, retention in the assigned treatment was higher in the methadone group.

Rates of retention observed in the present analysis are considerably lower than those that have been previously reported in other settings with differing populations [158,161,162] and compared to all participants enrolled in the OPTIMA trial,[163] with approximately one third of participants dropping out of treatment within the first 30 days. Low retention is a significant concern as the risk of mortality increases with the cessation of OAT treatment, and the protective effects of OAT do not continue after an individual drops out of treatment.[41,43] There are many possible explanations for why retention rates are lower in our study sample. First, we restricted the population to those with a lifetime and recent history of NFO. Recent studies indicate that a history of NFO is a significant predictor of treatment dropout at 90 and 120 days.[164,165] Second, the majority of those with a history of NFO tested positive for both opioids and stimulants during baseline assessments. It is possible that the concurrent use of stimulants may impact success in OAT treatment, which has been observed in previous studies.[166] Third, our study sample included

a large proportion of individuals who primarily use fentanyl. For participants who use fentanyl, anecdotal evidence suggests it may be more difficult to initiate OAT because of severe withdrawal symptoms or precipitated withdrawal during treatment initiation.[167] Participants may have had difficulty transitioning from fentanyl use to OAT, leading to poor retention rates. Many previous trials examining rates of retention included participants who use heroin or other, less potent prescription opioids which may be contributing to the differences seen in the present study.[63,39] Finally, the trial followed a pragmatic design, which reflects real life conditions and does not exclude those with significant comorbidities like existing randomized trials. It is also noteworthy that while we controlled for a number of confounding factors, there may be unmeasured confounding factors that may be impacting participant retention in treatment. These findings indicate that there is a need for additional interventions to prevent early dropout, especially among those with a history of NFO. A variety of adherence interventions have been studied in the context of treatment retention including cognitive behavioural therapy, contingency management, counselling, motivational interviewing and a variety of other psychosocial interventions.[41,179] Future studies that integrate rewards-based interventions with OAT should include populations that reflect those accessing care in real-world clinical settings, including those with a history of NFO, to determine how they impact treatment retention.

We failed to find any statistically significant difference in retention in the assigned treatment among those with a lifetime history of NFO. There is limited research investigating retention rates for a population with POUD and a history of NFO, but studies conducted in individuals with OUD also indicate that buprenorphine/naloxone is non-inferior to methadone for retaining participants in treatment.[49,63] However, analyses from the entire population of individuals enrolled in OPTIMA (regardless of their history of NFO) indicate that participants randomized to

buprenorphine/naloxone had reduced odds of being retained in the assigned treatment compared to those on methadone.[168] This suggests that factors other than the OAT medication (i.e. social, structural factors) may impact retention, including a history of NFO. It may also suggest that people with a history of NFO have different characteristics than the general population of individuals with POUD which should be considered by clinicians when developing a treatment plan for patients.

The fact that we failed to find a significant difference between arms regarding retention in any OAT are similar to those among the whole OPTIMA sample,[168] and confirm the potential benefits of stepped care strategies initially described by a study by Kakko and colleagues among people using heroin.[169] Specifically in that randomized trial, people who initiated buprenorphine/naloxone were allowed to switch to methadone if unsuccessful with buprenorphine, with findings indicating that both approaches (stepped care vs methadone) resulted in similar treatment retention rates. Altogether, our findings along with buprenorphine's superior profile support the inclusion of buprenorphine/naloxone as first-line treatment option in the Canadian guidelines for people with a history of NFO, as long as the opportunity to transition to methadone (or other OAT) is available for those who are unsatisfied with their treatment.

We found that those with a recent history of NFO and randomized to methadone had higher retention rates than those randomized to buprenorphine. Methadone may be superior for this particularly vulnerable population because of daily supervision rather than take-home dosing. Furthermore, methadone is a full agonist treatment, which may be more effective for the high proportion of individuals in this cohort who primarily use potent opioids like fentanyl. While we found a statistically significant difference between the two groups, this analysis was exploratory in nature and likely underpowered. Furthermore, these results should be interpreted cautiously as

there were high attrition rates, and only a small proportion of participants were retained in both methadone and buprenorphine/naloxone groups which may limit generalizability to other populations.

Another important finding from this analysis is that participants randomized to buprenorphine had a statistically higher proportion of opioid-negative UDS over the 24 weeks than those randomized to methadone. These findings were consistent across all sensitivity analyses. This is supported by previous studies in OUD populations demonstrating that buprenorphine/naloxone is superior in reducing opioid use.[158,59] This may be explained by buprenorphine having a shorter induction time than methadone and that patients can reach a therapeutic dosage with buprenorphine more quickly, relying less on illicit opioids to curb withdrawal symptoms. Methadone is metabolized slower than buprenorphine, and it can take several weeks for the patient to reach their optimal dose,[170] which may result in higher rates of illicit opioid use. Another possible explanation is that buprenorphine/naloxone has a high affinity but lower activation of the μ-opioid receptor, which can cause precipitated withdrawal in individuals who do not abstain from using other opioids. In comparison, methadone is a full agonist, resulting in greater activation of the μ-opioid receptor and does not cause precipitated withdrawal if an individual continues to use other opioids. These results further support the use of buprenorphine/naloxone as the first-line treatment option for those with a history of NFO. Nonetheless, many participants continued to use illicit opioids throughout the trial in both treatment groups. Current interventions may not be sufficient to reduce opioid use in those with a history of NFO and consideration of higher dosing regimens or alternative pharmacotherapies like injectable OAT, and slow-release oral morphine may be warranted for better treatment outcomes.[171,172] For individuals who continue to use opioids, evidence-informed harm reduction

strategies such as supervised consumption sites,[173] drug checking services,[174,175] distribution of naloxone,[176] and safe supply[177] are essential to prevent opioid-related morbidity and morality.

A number of limitations should be noted when interpreting findings from the current study. First, participant history of NFO was self-reported which may have been impacted by recall bias, social desirability or underreporting. Second, all missing or unavailable UDS data were classified as positive for the opioid positive UDS outcome which may have resulted in an over-estimation of the proportion of opioid positive UDS. However, sensitivity analyses revealed that even when missing UDS data were excluded the results were consistent. Third, the study was restricted to participants with a history of NFO at seven Canadian sites, therefore findings may not be generalizable to those that fall outside these jurisdictions. Fourth, due to a small sample size we were only able to consider a small number of variables that could potentially impact treatment retention among those with a history of NFO which may have resulted in unmeasured confounding. However, the confounders that were included in the analysis were well balanced between treatment groups.

To summarize, this secondary analysis of a clinical trial for the treatment of POUD demonstrated that while overall retention rates in the assigned or any treatment were alarmingly low among those with a history of NFO, retention rates did not differ between those randomized to buprenorphine/naloxone and methadone. Opioid use remained high in both treatment groups, but those randomized to buprenorphine/naloxone had a higher proportion of opioid-free UDS than those in the methadone group. These findings indicate that buprenorphine/naloxone is non-inferior to methadone, supporting its recommendation as a first-line treatment option in Canadian therapeutic guidelines. They also highlight the need for additional interventions that target treatment retention, particularly in the early stages of treatment. These interventions may include

increasing the accessibility of alternative pharmacotherapies for those that are unsuccessful in methadone and buprenorphine treatment, concurrent psychosocial interventions with OAT, and creating screening tools to identify those at high risk of treatment dropout.

Table 4: Baseline characteristics of participants with a history of non-fatal overdose, stratified by assigned treatment arm

	Total, n (%) (n = 154)	Opioid agonist treatment, n (%)		*p* - value
		Methadone (*n* = 76)	Buprenorphine (*n* = 78)	
Age, median (IQR)†	38 (32-46)	38 (31-44)	37.5 (32-47)	0.859
Sex				
Male	96 (62.3)	47 (61.8)	49 (62.8)	1.000
Female	58 (37.7)	29 (38.2)	29 (37.2)	
Ethnicity				
White	91 (59.1)	44 (57.9)	47 (60.3)	0.893
BIPOC*	63 (40.9)	32 (42.1)	31 (39.7)	
Homelessness				0.875
No	79 (51.3)	38 (50.0)	41 (52.6)	
Yes	75 (48.7)	38 (50.0)	37 (47.4)	
Income assistance				
No	74 (48.1)	40 (52.6)	34 (43.6)	0.336
Yes	80 (51.9)	36 (47.4)	44 (56.4)	
Clinical site†				
East Coast	45 (29.2)	19 (25.0)	26 (33.3)	0.337
West Coast	109 (70.8)	57 (75.0)	52 (66.7)	
Lifetime heroin use				
Absence	33 (21.4)	17 (22.4)	16 (20.5)	0.933
Presence	121 (78.6)	59 (77.6)	62 (79.5)	
Positive UDS for opioids				
No	6 (3.9)	2 (2.6)	4 (5.1)	0.701
Yes	148 (96.1)	74 (97.4)	74 (94.9)	
Positive UDS for stimulants‡				
No	32 (20.8)	61 (80.3)	17 (21.8)	0.908
Yes	122 (79.2)	15 (19.7)	61 (78.2)	
Recent history of NFO				
No	71 (46.1)	34 (44.7)	37 (47.4)	0.862
Yes	84 (54.2)	42 (55.3)	41 (52.6)	

*BIPOC: Black, Indigenous and People of Colour

† West coast: British Columbia and Alberta, East Coast: Quebec and Ontario

‡ Positive UDS for stimulants includes: methamphetamine/amphetamines and cocaine

† IQR: interquartile range

Table 5: Logistic regression analyses for the association between methadone versus buprenorphine/naloxone and retention in treatment among participants with a lifetime history of non-fatal overdose and prescription-type opioid use disorder

	Retention in treatment (n=154)		Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)
	No, n (%)	Yes, n (%)		
Retention in assigned treatment				
Methadone	62 (81.6)	14 (18.4)	Ref	Ref
Buprenorphine/Naloxone	65 (82.3)	14 (17.7)	0.95 (0.42–2.18)	0.54 (0.17-1.54)
Retention in any treatment				
Methadone	61 (80.3)	15 (19.7)	Ref	Ref
Buprenorphine/Naloxone	57 (72.2)	22 (27.8)	1.57 (0.75-3.37)	1.22 (0.51-2.96)

*Odds ratio is adjusted for lifetime heroin use and clinical site. CI, confidence interval

Table 6: Logistic regression analyses for the association between methadone versus buprenorphine/naloxone and retention in treatment among participants with a recent history of non-fatal overdose and prescription-type opioid use disorder

	Retention in treatment (n=83)		Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)
	No, n (%)	Yes, n (%)		
Retention in assigned treatment				
Methadone	32 (76.2)	10 (23.8)	Ref	Ref
Buprenorphine/Naloxone	39 (92.9)	3 (7.1)	0.25 (0.05–0.88)	0.13 (0.01-0.64)
Retention in any treatment				
Methadone	32 (76.2)	10 (23.8)	Ref	Ref
Buprenorphine/Naloxone	33 (78.6)	9 (21.4)	0.87 (0.31-2.44)	0.71 (0.21-2.30)

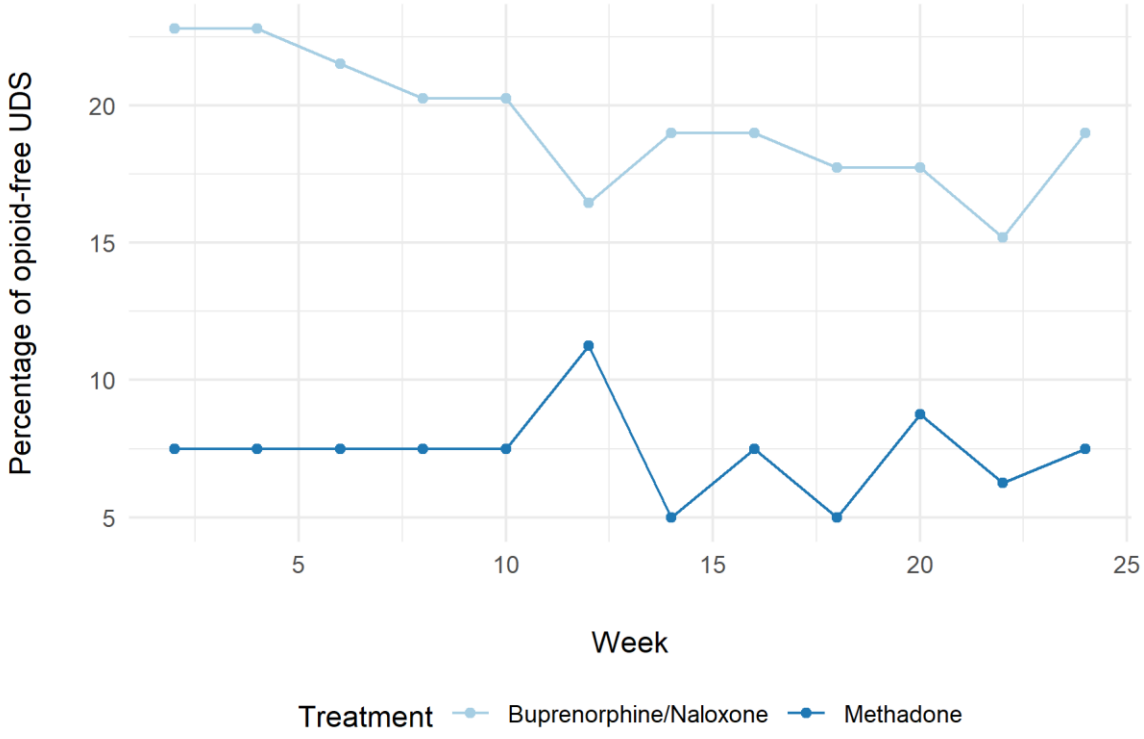
*Odds ratio is adjusted for lifetime heroin use and clinical site. CI, confidence interval

Table 7: Mean difference in the proportion of opioid-free urine drug screens in the buprenorphine/naloxone and methadone treatment arms among participants with a history of non-fatal overdose and prescription-type opioid use disorder

Analyses	% Negative UDS for opioids				Adjusted mean difference[1]	95% CI
	Buprenorphine/naloxone		Methadone			
	mean	SD	mean	SD		
Total	19.3	32.2	7.4	20	11.9	3.5 - 20.3
Based on available UDS	36.2	41	14.8	28.7	21.4	12.4 – 30.4
With participants retained on assigned OAT	73.8	20.1	30	33.7	43.8	26.3 - 61.3

[1]OR is adjusted for clinical sites and lifetime heroin use. CI, confidence interval; UDS, urine drug screen; OAT, opioid agonist treatment; SD, standard deviation

Figure 3: Percentage of opioid-free urine drug screens for participants receiving buprenorphine/naloxone or methadone across the 24-week intervention period, including missing urine drug screens as positive for opioids



Chapter 4: Overdose events during opioid agonist treatment among individuals with a history of non-fatal overdose: A case series

4.1 Introduction

Canada is in the midst of a public health emergency as hospitalizations, overdoses and deaths attributed to opioid use continue to rise across the country.[182,183] In the first six months of 2021, there were over 5000 deaths attributed to opioid use with the majority occurring in the provinces of British Columbia, Alberta, and Ontario[32,184] Engaging individuals with opioid use disorder (OUD) in evidence-based treatments has been a primary strategy to reduce opioid-related harms. Currently, opioid agonist treatments (OAT), including methadone and buprenorphine/naloxone, are the standard of care in Canada.[172] Both of these treatments have proven to be effective in decreasing non-medical opioid use, reducing transmission of blood-borne infections, reducing risk of overdose and mortality, and improving mental and physical health when patients are retained in treatment.[151] Particularly for those who have a history of non-fatal overdose, treatment with methadone or buprenorphine has shown to reduce mortality by 59% and 38%, respectively, highlighting the importance of engaging this high risk population in treatment.[75]

Despite the many benefits of OAT, findings from previous research suggest that there are periods of increased risk of overdose and death during and after treatment.[43] Particularly among patients enrolled in methadone, they are at the highest risk of overdose and mortality during the first four weeks of treatment and immediately following withdrawal from treatment.[185,43,186] Treatment type (e.g., methadone) is a known risk factor for overdose during treatment initiation,[43,76] but other demographic, socio-structural and substance use characteristics that may

impact overdose risk during treatment have not been thoroughly described, specifically among those with a lifetime history of NFO.

Additionally, little is known about whether patterns of opioid use change after an overdose event while patients are enrolled in OAT. The existing literature primarily examines rates of opioid prescribing following an overdose event and show that the number of opioids dispensed to patients following overdose does not significantly decrease.[187] However, for patients who are already enrolled in OAT, overdose may be a motivator for increased engagement in treatment and reduced illicit opioid use. This case series describes the overdose events that took place during a pragmatic, randomized control trial among participants with a history of non-fatal overdose. The purpose of this study was to characterize participants that overdosed during treatment and examine patterns of opioid use before and after overdose.

4.2 Methods

4.2.1 Setting and sample

The sample for the present study included all randomized participants of the OPTIMA trial who reported a history of non-fatal overdose at screening and an overdose event during the study period. All overdoses were documented by qualified research staff within 24 hours of their occurrence or the site's knowledge of the event, using the severe adverse event form. A retrospective case series was completed on a total of 18 participants.

4.2.2 Case descriptions

Participant data was extracted from screening and baseline assessments as well as the severe adverse event reporting form to create the case description for each participant. The

variables collected were: age, sex (male vs. female), ethnicity, study site, recent history of non-fatal overdose (yes vs. no), history of medications for opioid use disorder (yes vs. no), urine drug screen results at screening, assigned treatment arm (buprenorphine/naloxone vs. methadone), medication dose at the time of overdose, retention in any OAT (yes vs. no), urine drug test results at study visit prior to overdose, naloxone administration for overdose (yes vs. no) and relatedness to the study medication.

4.2.3 Opioid-free UDS before and after overdose

Urine drug screen (UDS) data, collected every 2 weeks after treatment initiation, was used to determine patterns of opioid use before and after overdose. We tested for the presence of the following opioids: morphine, oxycodone, fentanyl, tramadol, 6-monoacetylmorphine and hydromorphone, unprescribed methadone and buprenorphine/naloxone using a Rapid Response Multi-Drug Once Step Screen Test Panel and single test strips. At each study visit, UDS were considered positive if there was a presence of any opioid other than the assigned study medication.

4.2.4 Statistical analysis

Among participants with a history of NFO, descriptive statistics were calculated for baseline characteristics and variables related to the overdose event. All statistics were summarized as frequencies (%). Incidence rates in person-years were calculated for individuals with and without a history of NFO. A figure was produced to visualize the date of overdose and prevalence of opioid use before and after overdose.

4.3 Results

During the study period, the incidence rates of overdose were 50.6 cases per 100 person-years among individuals with a history NFO versus 5.4 cases per 100 person-years among participants without a history of NFO. The sociodemographic and substance use profiles of the 18 unique participants who overdosed during the study are presented in Table 4.1. Two thirds of overdose cases were among male participants (12; 66%) and over half among participants of Indigenous ancestry (55.5%) with unstable living situations (61%). The median age at the time of the overdose event was 35 years of age (q1-q3: 29-42). The most common substances used by participants at baseline were methamphetamine (89% had positive UDS), followed by fentanyl (83%) and other opioids (56%). A prior overdose within six months of enrolment was also common with two-thirds (67%) of participants reporting at least one.

A total of 24 non-fatal overdose events from the 18 unique participants were reported during the study period with three participants reporting more than one OD (median = 1). The majority (88%) of overdoses were unrelated to the study medication which was determined by the study physician at the time of reporting the overdose. Naloxone administration was reported for 20 (87%) overdose events. The most common self-reported substance used at the time of overdose was fentanyl (41%) or another type of opioid (29%) and most overdoses took place at the participant's home (50%). Study sites in Alberta had the highest number of overdoses (78%) with few in British Columbia (17%) and Quebec (5%). At the study visit prior to overdose, the majority of participants had a positive UDS for fentanyl (78%) and methamphetamine (89%).

Figure 4.1 illustrates the timing of the overdose event and patterns of opioid use before and after an overdose event in two-week intervals. Of those who overdosed during the trial, 12 (67%)

were initially randomized to methadone and 6 (33%) to buprenorphine/naloxone A total of 7 participants switched study medications during the study period, 4 (66%) who were randomized to buprenorphine and 3 (25%) who were randomized to methadone. Among those randomized to buprenorphine/naloxone, a total of 10 overdoses were reported over the 24-week study period. Three overdoses took place within the first four weeks of treatment initiation with the majority occurring after the 12th week in treatment. In the methadone group, a total of 14 overdoses were reported. Four overdoses took place prior to treatment initiation, and four took place immediately after treatment initiation. The remainder occurred after the 12th week in treatment. Excluding participants who failed treatment initiation, all participants had at least one positive UDS for opioids after the overdose event. The majority (94%) of participants were positive (or considered positive for those missing UDS data) for opioids at every study visit following overdose.

4.4 Discussion

To our knowledge, this study is among the first to examine opioid use patterns before and after overdose within multiple Canadian treatment settings. Of the 18 participants with a history of NFO that overdosed during the 24-week trial, two thirds were randomized to the methadone arm. The majority of overdoses were considered unrelated to the study medication and nearly half took place between randomization and the first follow-up visit, with four participants failing treatment initiation. The most common substances used at screening and the visit prior to overdose were fentanyl and methamphetamine, and participants continued to use opioids throughout treatment, even after overdose.

There was a higher incidence of overdose during treatment among participants with a history of NFO compared to those without a history of NFO. These results are somewhat

unsurprising as it is well documented that individuals with a history of NFO are at a higher risk of subsequent fatal and non-fatal overdose.[73,157] Despite these results being descriptive, they do indicate that a history of NFO could be a potential risk marker for overdose during treatment and should be considered by clinicians when patients are initiating treatment. As this study was exploratory and was restricted to a very small sample size, no conclusions or causal inferences can be drawn about other factors associated with NFO during treatment among those with a history of NFO. However, certain demographic and substance use factors were common among the participants included in this study and should be highlighted as an area for future research. Some of these factors included self-identifying as male, reporting unstable living situations, having less than high school education, having positive UDS for methamphetamine and fentanyl at baseline, having a history of treatment with OAT and experiencing a NFO in the 6 months prior to enrollment in treatment. One previous study has looked at factors associated with overdose during treatment for opioid use disorder and found that having a positive UDS for opioids at baseline, having a history of OAT treatment were positively associated with overdose during treatment. .[164] Future studies should investigate these factors and how they relate to overdose in a larger cohort and specifically among those with a previous history of overdose. This could potentially aid in the development of a screening tool to identify individuals at high risk of overdose during treatment.

Although these results are descriptive in nature, they support the existing literature that the risk of overdose is high during the first four weeks of OAT, especially for people enrolled in methadone. In our sample, we found that of the 12 participants randomized to methadone, eight overdosed within four weeks of treatment randomization. This may be explained by the increased risk of respiratory depression and sedation with methadone compared to buprenorphine/naloxone, when initial doses of methadone are too high or there is concomitant use of other opioids.[45,38] The

majority of study physicians reported that the overdose events were unrelated to the study medication, indicating that the overdose events were most likely the result of continued opioid use. As people with a history of NFO are at a greater risk of subsequent overdose, buprenorphine/naloxone may be the preferred first-line treatment option because there is a significantly lower risk of respiratory depression, even at higher doses.[56] Future studies should empirically compare the relative safety profiles for methadone and buprenorphine/naloxone for people with a history of NFO as well as other health-related outcomes (e.g., all-cause and overdose related mortality, improvements in quality of life).

Another surprising yet concerning finding is that all participants continued to use opioids while in treatment, despite experiencing an overdose. One possible explanation for the continued use of opioids is that the majority of participants were positive for fentanyl at baseline and at the study visit prior to overdose, suggesting that there is a high prevalence of fentanyl use within this study sample. Recent reports have shown that due to the high potency of fentanyl, buprenorphine/naloxone initiation can be more complicated, with longer periods of precipitated withdrawal.[62] Symptoms of severe withdrawal may explain why two thirds of participants that were initially randomized to buprenorphine/naloxone switched to methadone during the study period and why we observed a high rate of continued opioid use during the 24-week intervention. For those randomized to methadone, it can take several weeks for patients to reach a therapeutic dose,[188] which may result in the use of illicit opioids to curb withdrawal symptoms. Additionally, a recent study by Mackay *et al.*, showed that individuals who are exposed to fentanyl are more likely to be dissatisfied with their OAT which is a known predictor for continued illicit substance use. Finally, there is the possibility that participants did not take the assigned study medications, resulting in overall poor treatment adherence and suppression of illicit opioid use.

Findings from this study highlight the need to further examine the role of fentanyl in the treatment of OUD and how this impacts treatment initiation, treatment adherence and risk of overdose during treatment among individuals with a history of NFO. Innovative treatment strategies may be also warranted to improve treatment outcomes among this population. For example, administering low doses of buprenorphine/naloxone (i.e. microdosing) may help facilitate the treatment initiation process and reduce rates of early treatment dropout.[189] Another potential strategy is the co-prescription of slow-release oral morphine (SROM) with methadone. This could be particularly beneficial during treatment initiation when doses of methadone are subtherapeutic and withdrawal symptoms are not relieved by methadone alone.[190] However this remains an experimental approach and there are potential risks associated with the combination of multiple long-acting medications.

There are several limitations that should be considered when interpreting these findings. First, the sample size was limited and was comprised of individuals recruited from seven Canadian sites which decreases the generalizability of the results to other populations and jurisdictions. Second, all data except urine drug screens were self-reported which may have introduced recall and social desirability bias. Third, we were underpowered to quantitatively examine any statistical differences in opioid use before and after overdose. All results from this study are exploratory and should be examined further in larger-scale studies.

In conclusion, this case series examined 18 participants with a history of non-fatal overdose that experienced an overdose while enrolled in supervised methadone or take-home dosing buprenorphine/naloxone models of care. Among those in the methadone arm, overdose in the first four weeks of treatment was common and four participants did not initiate treatment after overdose. Among both treatment arms, illicit opioid use was highly prevalent before and after

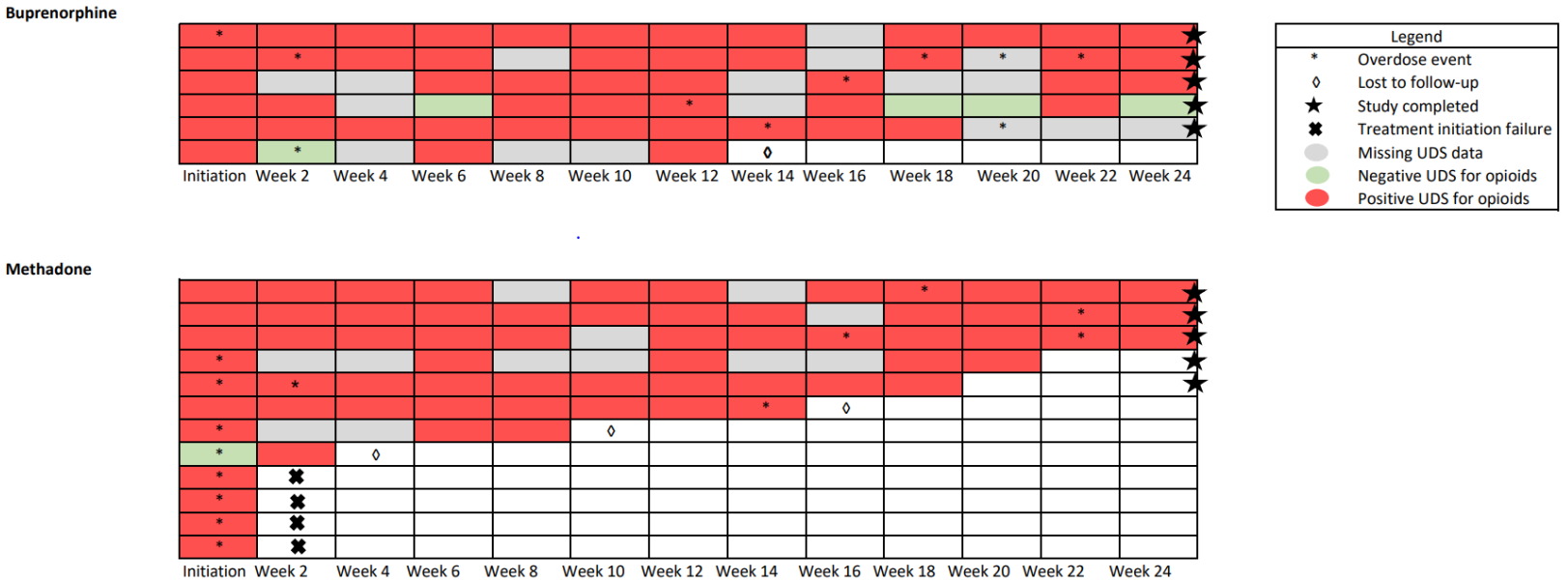
overdose. These findings underscore the need for further research into non-fatal overdose during opioid agonist treatment to determine possible areas for intervention.

Table 8: Characteristics of participants who reported a non-fatal overdose during the 24-week intervention period

Characteristic	Total
Sex	Male (67%)
Age, years	35 (median)
Ethnicity	Caucasian (39%)
Stability of living situation	Very unstable (61%)
Highest level of education completed	High school (39%)
Study site	AB (78%)
Recent NFO (i.e. last 6 months)	Yes (67%)
Previous opioid agonist treatment	Yes (67%)
Positive urine drug test results at screening	Positive for Meth (89%) and Fyl (83%)
Treatment arm	MET (67%), BUP (33%)
Treatment initiation failure (yes vs. no)	Yes (22%)
Retention in any OAT	Yes (17%)
Substance use prior to overdose	Fyl (78%), Meth (89%)
Naloxone administered at overdose	Yes (83%)
Relatedness to study medication	unrelated (88%)

AB, Alberta; BUP, buprenorphine; MET, Methadone; meth, methamphetamine; Fyl, fentanyl; OAT, opioid agonist treatment

Figure 4: Urine drug screen data testing for the presence of opioids in participants who overdosed during the study period



Chapter 5: Summary of findings & future directions

5.1 Summary of findings

The purpose of this thesis was to characterize treatment-seeking individuals with POUD and a history of NFO as well as their outcomes in opioid agonist treatment (OAT). Previous research has identified people with a history of NFO as a particularly high-risk population. Therefore, it is critical to understand factors that may increase risk of future overdose and optimize treatment outcomes as they may differ from the general population of people with OUD. Data from the OPTIMA trial, a pan-Canadian, pragmatic randomized control trial, were used for the three data-driven analyses presented in this thesis. This research identified socio-demographic and substance use variables associated with a history of NFO (Chapter 2) and that treatment outcomes, both retention and suppression and opioid use, were overall low among those receiving buprenorphine/naloxone or methadone (Chapter 3). We also found that among participants who overdosed during the study period, illicit opioid use was common before and after overdose and that overdose within the first four weeks of randomization was prevalent among those receiving methadone (Chapter 4). Findings from this study support the importance of a multifactorial approach to treatment of POUD, especially for those with a history of NFO. Section 5.4 discusses in detail potential avenues for future research.

5.1.1 Prevalence and correlates of non-fatal overdose among treatment-seeking individuals with prescription-opioid use disorder

Understanding the factors associated with a history of overdose is crucial for the development of effective overdose prevention strategies and treatment interventions for people with POUD. Chapter 2 examined the prevalence and correlates of non-fatal overdose among

people seeking treatment with POUD. Based on previous research, we examined a variety of individual, social, structural and substance use variables as potential correlates of non-fatal overdose. We found that the prevalence of overdose was relatively high compared to the existing literature, with over half of participants reporting at least one overdose in their lifetime, and approximately a third reporting an overdose in the last six months. The majority of participants reported using opioids at the time of last overdose and approximately 70% of individuals were administered naloxone, underscoring naloxone's importance in the current overdose epidemic. Several factors were independently associated with a lifetime history of NFO, including homelessness, receiving incomes assistance, and positive UDS for methamphetamine and fentanyl at screening. Results from this analysis suggest that there are several areas that can be targeted for intervention among individuals with a history of NFO. For example, upscaling of low-barrier housing (i.e. Housing First), increased access to formal employment for marginalized people who use drugs and harm reduction services (i.e. drug checking, supervised consumption sites) for people who continue to use substances, including opioids and stimulants.

5.1.2 Opioid agonist treatment outcomes among individuals with a history of non-fatal overdose

In Canada, buprenorphine/naloxone and methadone are the recommended treatment options for people with opioid use disorder. Many studies have examined the relative effectiveness of buprenorphine/naloxone and methadone, but little is known about treatment outcomes among people with a history of NFO within a real-world clinical setting. Chapter 3 compared rates of OAT retention and opioid use between those randomized to buprenorphine/naloxone and methadone with a lifetime and recent history of NFO. We found that among those with a lifetime history of NFO, retention rates were similar between participants randomized to

buprenorphine/naloxone and methadone. However, retention rates were very low among both treatment arms, even when participants who switched medications were included in the analysis. We also found that a high proportion of participants withdrew from treatment within the first 30 days. This is concerning because there is an increased risk of overdose and mortality following the cessation of treatment, pointing to the need for improved adherence interventions. In addition, Chapter 3 showed that among those with a history of NFO, those randomized to buprenorphine/naloxone had a higher proportion of opioid-free UDS compared to methadone. These findings coupled with buprenorphine's increased safety profile, support its use as the first-line treatment option in Canada however there is a dire need to develop strategies that increase treatment retention.

5.1.3 Overdose events during opioid agonist treatment among individuals with a history of non-fatal overdose – a case series

Lastly, we sought to determine whether an overdose during OAT would alter rates of illicit opioid use. In Chapter 4 we investigated the overdoses that took place during the study period among participants with a history of NFO, as well as trends in opioid use before and after overdose. A total of 24 overdose events were reported among 18 participants, of which twelve were randomized to methadone and six were randomized to buprenorphine/naloxone. The majority of overdoses were unrelated to the study medication, and the use of other substances, primarily fentanyl, were reported at the time of overdose. This analysis also revealed that there were no significant changes in opioid use following the overdose event.

5.2 Implications

The findings from this thesis suggest that treatment-seeking individuals with a history of non-fatal overdose (NFO) are a unique population that differ in many ways from the general population of people with opioid use disorder (OUD). They indicate that a history of NFO should be taken into consideration by clinicians when individuals are starting OAT. Based on findings from Chapter 2, there are several factors that are associated with a history of NFO and without intervention, these factors may contribute to an increased likelihood of future overdose. In treatment-seeking populations, screening for a history of NFO and determining the factors and behaviours that may have contributed to the past overdose (i.e., fentanyl use, homelessness) may be helpful in determining an individualized and holistic treatment approach that addresses these factors and connect patients with the services they need. This may include overdose prevention interventions such as the provision of take-home naloxone kits, linkage to social services such as housing and employment services or referral to treatment for concurrent substance use disorders like stimulant use disorder. Addressing these factors may also help with improving outcomes in OAT such as retention and suppression of illicit opioid use. In Chapters 3 and 4, we explored treatment outcomes for those with a history of NFO and found that while retention was similar in treatment arms, buprenorphine/naloxone was superior to methadone in reducing illicit opioid use and there were fewer overdoses during treatment initiation among those randomized to buprenorphine/naloxone. This supports the use of buprenorphine/naloxone as a first-line treatment option in Canada, especially among those with a history of NFO, though preferences should always be considered within this context to ensure patient-centred care.

5.3 Strengths and limitations

The data used for the analyses in this thesis were drawn from OPTIMA, a pragmatic, multi-centre, 2-arm, open-label, randomized control trial involving adults with POUD. Access to the data produced from the first randomized control trial in Canada to compare the relative benefits of buprenorphine/naloxone and methadone within a realistic model of care is a considerable strength of this study. Additionally, the pragmatic design of this trial is a major strength as findings from this research reflect what would be seen in real-world clinical populations. As opposed to double-blind efficacy trials, this study design incorporates patient characteristics and diversity which increases external validity and applicability to clinical settings. Another strength of this study is that there was multisite enrollment within four Canadian provinces which also increases the diversity of participants and generalizability of the results.

This research also has a number of limitations that span across chapters and should be considered when interpreting the findings within this thesis. First, we identified individuals with a lifetime and recent history of NFO using self-reported questionnaire data. All variables except urine drug screen data were collected via self-report which may have introduced social desirability and recall bias. Second, we did not explicitly define the term "overdose" while interviewing participants which may have increased the risk of misallocation bias and underestimation of the number of people with a history of NFO. Third, we did not collect information on the timeline of when participants overdosed beyond the last six months. Fourth, participants were excluded from the trial if heroin had been their opioid of choice in the 30 days prior to enrolment, which should be considered when generalizing the results to other patient populations with opioid use disorder. Fourth, due to small sample size we could only consider a subset of variables to include in multivariate analyses in both Chapters 2 and 3. Additionally, only a small proportion of

participants overdosed during the study period, making the generalizability of results from Chapter 4 limited. Other specific strengths and limitations are included within each corresponding chapter.

5.4 Future directions

The present study has provided some preliminary insight into the characteristics of treatment-seeking individuals with POUD with a history of NFO and their outcomes in treatment. Chapter 2 identified several factors associated with a history of NFO, including those related to substance use, specifically fentanyl and methamphetamine use. Through this research, it has been made evident that many people who seek treatment for opioid use disorder concurrently use methamphetamine or other stimulants. To date, the focus of many randomized trials has been interventions for patient populations with either stimulant use disorder or opioid use disorder when many patients use them simultaneously. Recent studies have revealed that untreated stimulant disorder can complicate treatment for OUD and is associated with increases in hospitalizations and overdose deaths.[191,192] As the co-use of opioids and stimulants among treatment seeking individuals has risen dramatically in the last several years,[193] it is imperative to evaluate interventions that improve outcomes for both opioid and stimulant use disorders simultaneously. Currently, there are no pharmacotherapies for the treatment of stimulant use disorder, however psychosocial interventions have shown promise in reducing stimulant use. Implementation of psychosocial therapies to treat stimulant use disorder in conjunction with OAT should be evaluated to determine if this improves treatment outcomes, especially for people with a history of NFO.

In Chapter 3, we found that among participants with a history of NFO, retention rates in both methadone and buprenorphine/naloxone were quite low across all analyses. Using the conceptual framework by Holzman and colleagues as a guide, potential barriers and facilitators of retention in OUD populations could be investigated further.[194] Examining factors, such as individual, social, structural and substance use that impact treatment retention is a crucial first step for developing interventions to improve retention rates among people with a history of NFO.

Additionally, there is extensive research regarding strategies to improve retention in antiretroviral therapy that could be applied to populations in OAT. Evaluation of these adherence strategies alongside OAT is another promising avenue for future research.

Based on findings in Chapter 4, another avenue for future research is to examine factors associated with overdose during OAT. As mentioned previously, a large body of research is dedicated to examining factors associated with a history of overdose, but little is known about risk and protective factors for overdose during treatment. Future studies could examine administrative health records including hospital records, addiction and mental health treatment records, emergency medical services records and coroner reports to identify a broad range of factors that are associated with overdose during treatment within a much larger population.

5.5 Conclusions

This thesis sought to characterize treatment-seeking individuals with a history of NFO and evaluate their outcomes in OAT using data from a pragmatic, randomized control trial. The three data-driven analyses included in this thesis revealed that many treatment seeking individuals have a lifetime history of NFO and that treatment retention and opioid-free UDS in both buprenorphine/naloxone and methadone treatment are low among this population. They also highlighted that opioid use persists even after overdose during treatment. Findings from this research underscore the importance of connecting the silos that exist in addiction care. For people with a history of overdose, addressing factors at the individual, social and structural level that impact retention and adherence in treatment are essential to reduce the risk of future overdose and death. Ultimately, the Canadian overdose epidemic will continue to escalate without the implementation of low-barrier, evidence-based, individualized treatment options for people with prescription-type opioid use disorder and a history of non-fatal overdose.

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