

**A PILOT STUDY ON RISK AND PROTECTIVE FACTORS FOR OPIOID OVERDOSE
AMONG PEOPLE WHO USE STREET FENTANYL DURING THE COVID-19
PANDEMIC**

by

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A pilot study on risk and protective factors for opioid overdose among people who use street fentanyl during the COVID-19 pandemic

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Abstract

North America is in the midst of an opioid overdose epidemic. British Columbia has been particularly impacted by the epidemic, as over 7,000 have died from illicit drug overdoses since the crisis was declared a public health emergency in 2016. These deaths have largely been fueled by the widespread prevalence of illicitly manufactured fentanyl. Moreover, the crisis has now been exacerbated by the COVID-19 pandemic, as several jurisdictions have experienced record numbers of overdose deaths in 2020. We undertook a narrative review to describe the risk and protective factors for opioid overdose examined in the current literature. While a range of factors have been studied, it remains unclear how factors previously identified in those using heroin, and how novel fentanyl-related factors are influencing the risk of overdose in those using fentanyl. We thereby conducted a cross-sectional pilot study to investigate the risk and protective factors for non-fatal opioid overdose among 36 participants using street fentanyl during the COVID-19 pandemic. We found that 86.1% reported the intentional use of fentanyl, and 47.2% reported having overdosed in the past six months. These findings add to the growing evidence base that more individuals are intentionally using fentanyl, rather than unintentionally using it. Gender, history of opioid overdose, and suicidal ideation were identified as risk factors for recent overdose. Route of administration, receiving opioid agonist treatment, and receiving safe supply were not significantly associated with overdose. This suggests that risk and protective factors previously identified in individuals who use heroin should be re-examined as their contributions to overdose risk may be different in individuals who use fentanyl. Novel factors related to fentanyl and the pandemic should be further investigated to examine their roles in overdose risk. Future studies in this urgently needed area of research will improve the identification of

individuals at risk of overdose, and inform the development of tailored interventions and policies to improve health outcomes in this vulnerable population.

Lay Summary

Over 20,000 Canadians have died from opioid overdoses since 2016. Illicitly manufactured fentanyl has been the main driver of overdose deaths in recent years. The opioid overdose crisis has now been worsened by the COVID-19 pandemic, as record numbers of overdoses were reported throughout Canada in 2020. This thesis explored the risk and protective factors for opioid overdose among individuals who used street fentanyl during the COVID-19 pandemic. From a pilot study, we found that the majority of participants used fentanyl intentionally, and that nearly half reported having overdosed in the past six months. These findings support the growing evidence that more individuals are knowingly using fentanyl. Gender, history of opioid overdose, and suicidal ideation were identified as risk factors for recent overdose. These are potential targets for the development and implementation of interventions to reduce the risks of overdose-related harms and mortality in this vulnerable population.

Preface

The work contained in this thesis was conducted at the Addictions and Concurrent Disorders Research Group at the University of British Columbia and at Vancouver General Hospital. This study was approved by the Behavioural Research Ethics Board of the University of British Columbia (H19-02231).

James Wong and Dr. Michael Krausz, with input from supervisory committee members (Dr. Christian G. Schütz and Dr. Kerry L. Jang), designed the study. James Wong and Jean Westenberg were responsible for data collection. James Wong was responsible for data analysis and writing of the thesis.

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List of Abbreviations

ACE – adverse childhood experiences

AHR – adjusted hazard ratio

AOR – adjusted odds ratio

BC – British Columbia

CERB – Canadian Emergency Response Benefit

CI – confidence interval

COVID-19 – coronavirus disease 2019

CPAS – Complex Pain and Addiction Service

HIV – human immunodeficiency virus

iOAT – injectable opioid agonist treatment

IQR – interquartile range

IRR – incidence rate ratio

OAT – opioid agonist treatment

OR – odds ratio

PO – prescription opioids

PTSD – post-traumatic stress disorder

PWID – people who inject drugs

PWUD – people who use drugs

PWUO – people who use opioids

OUD – opioid use disorder

SD – standard deviation

SEM – socioeconomic marginalization

SHR – sub-hazard ratio

SCS – supervised consumption services

SROM – slow-release oral morphine

SUD – substance use disorder

US – United States

VCH – Vancouver Coastal Health

VGH – Vancouver General Hospital

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Dedication

To all those who have lost their lives to the overdose crisis and all those who suffer from addiction.

Chapter 1: Introduction

1.1 The Opioid Overdose Crisis

The opioid overdose epidemic in North America is a significant public health crisis. In Canada, over 20,000 people have died from opioid overdose since 2016.¹ While the crisis in the 2000s and early 2010s was driven by non-medical prescription opioid (PO) and heroin use, the recent surge in overdose deaths is largely attributed to illicitly manufactured synthetic opioids, primarily fentanyl.² In the United States (US) from 2017 to 2018, PO and heroin deaths decreased by 13.5% and 4.1% respectively while synthetic opioid deaths increased by 10%.³⁻⁵ Synthetic opioids were also involved in 67% of all opioid deaths in the US in 2018.⁵ Furthermore, the COVID-19 pandemic has now exacerbated the ongoing overdose crisis as many jurisdictions have experienced record numbers of overdose deaths in 2020. In the US, over 81,000 overdose deaths occurred during the 12 months ending in May 2020, marking the highest number of overdose deaths recorded in a 12-month period.⁶ In Canada, 1,705 opioid overdose deaths occurred from July to September 2020, which was the highest quarterly count since 2016.¹ Of note, the province of British Columbia (BC) has been the epicentre of the epidemic in Canada. In 2020, 1,716 British Columbians died from illicit drug overdoses, marking the province's deadliest year for overdose deaths as nearly five people died per day in BC due to overdose.⁷ With overdose deaths continuing to rise, it is clear that the overdose epidemic is not abating.

Against the backdrop of the rising fatal opioid overdoses, people who use drugs (PWUD) are also experiencing increases in non-fatal opioid overdoses. Non-fatal overdose strongly predicts both subsequent non-fatal and fatal overdoses, and can lead to significant morbidity including cardiac and pulmonary problems, renal failure, and cognitive impairment from

hypoxia.⁸⁻¹¹ Understanding the risk and protective factors associated with opioid overdose is critical in informing the development of effective overdose prevention strategies and treatment approaches for opioid use disorder (OUD). The majority of previous studies on the correlates of non-fatal overdose have focused on overdoses involving PO and heroin, as little is known about the factors associated with non-fatal overdose among individuals using street fentanyl (also known as illicitly manufactured fentanyl or non-pharmaceutical fentanyl). As fentanyl-involved overdoses continue to increase, there is thus a dire need to understand the rapidly changing risk environment created by the proliferation of fentanyl in the illicit drug supply. With overdoses accelerating during the COVID-19 pandemic, it is also important to examine the links between the pandemic and increased overdose risk. It has been suggested that changed patterns of drug use due to disruptions in the illicit drug trade, impacts to services, and the psychosocial effects of the pandemic have led to the increase in overdoses, but few studies have investigated these factors.

1.2 Aims and Objectives

The overall aim of this thesis is to explore the risk and protective factors for opioid overdose in the midst of the dual public health emergencies of the overdose crisis and COVID-19 pandemic. Chapter 2 is a narrative review where we sought to summarize the current body of literature on the factors associated with overdose. Chapters 3 and 4 respectively describe the methodology and results of a cross-sectional pilot study of individuals using fentanyl in Vancouver, BC during the COVID-19 pandemic, where we aimed to determine the prevalence of non-fatal overdose and characterize its risk and protective factors. Lastly, in Chapter 5, we

discuss the findings of the pilot study, compare them with the existing literature, and outline future areas of research.

Chapter 2: Narrative Review

2.1 Overview

The risk of opioid overdose is influenced by a multitude of biological and behavioural factors, as well as social and structural factors. Much of the existing research has examined these factors in populations using PO and heroin. As the landscape of non-medical opioid use has increasingly shifted towards synthetic opioids, little is known about the factors associated with overdose among individuals who use fentanyl. This narrative review provides an overview of the risk and protective factors for opioid overdose – we highlight studies examining these factors in individuals using fentanyl, and discuss COVID-19-related factors potentially associated with overdose. The review is structured into the following domains: substance use factors, treatment and harm reduction factors, psychiatric factors, and social and structural factors.

2.2 Substance Use Factors

2.2.1 Type of Opioid

The type of opioid used by the individual is associated with the risk of overdose as different opioids have varying levels of potency and duration of action.^{12,13} Heroin carries a high risk of overdose as it is more potent than most PO such as codeine, hydrocodone, and oxycodone.¹⁴ Even more potent is fentanyl, which is 50-100 times more potent than morphine and 25-50 times more potent than heroin. Fentanyl is clinically used as an anesthetic and analgesic and was first developed in 1959. However, since the 1970s, fentanyl has been illicitly manufactured in laboratories, and sold by itself or mixed into other street substances.^{14,15} In a cross-sectional survey conducted among people who inject drugs (PWID) in BC, fentanyl was found to be more strongly associated with recent non-fatal overdose (OR = 4.30; 95% CI = 1.93-

9.58) than heroin injection (OR = 3.04; 95% CI = 1.59-5.80).¹⁶ As the illicit drug market has been increasingly adulterated with fentanyl over the past decade, the growing availability of potent fentanyl analogues, especially carfentanyl, is also particularly alarming.¹⁷ Carfentanyl, an opioid exclusively used for veterinary use with large animals, is associated with an extremely high risk of overdose, due to it being 100 times more potent than fentanyl. In a recent study which reviewed 1,035,923 overdose death records in the US from 1979 to 2019, the 2016-2017 surge and 2018 decline in overdose deaths was found to be associated with the sudden rise and fall of carfentanyl availability.¹⁸ All together, these findings indicate that people who use heroin are exposed to fluctuating variations in drug potency depending on the extent of contamination with fentanyl and fentanyl analogues, thereby increasing overdose risk.¹⁹ In BC where the overdose crisis has been largely driven by the increasing adulteration of synthetic opioids, recent drug checking studies have reported that 84.1% to 90.6% of samples expected to be heroin tested positive for fentanyl.^{20,21}

Additionally, the illicit drug market has reportedly become more unpredictable due to disrupted supply chains, border closures, and shut down of overseas drug labs brought by the COVID-19 pandemic.^{22,23} Using electronic medical record data of 14,669 patients from 67 opioid agonist treatment (OAT) clinics in Ontario, fentanyl use among patients increased by 108% from April to September 2020.²⁴ While the increased use may be in part due to pandemic-related stress and anxiety, the results may also be evidence of increased fentanyl presence in the illicit drug market, and that individuals are obtaining drugs from unfamiliar drug networks due to shortages in their usual supply.

2.2.2 Polysubstance Use

Polysubstance (or polydrug) use, the consumption of multiple substances by an individual, is a well-established factor associated with opioid overdose risk. The use of a speedball, a mixture of heroin and cocaine which acts as a depressant and stimulant respectively, places an individual at heightened risk of overdose.²⁵ The individual may experience anxiety, high blood pressure, strong/irregular heartbeat from the stimulant while also experiencing drowsiness and suppression of breathing from the opioid. The risk for overdose increases as the effects of cocaine wear off more quickly than the effects of heroin; fatal slowing of the breathing can occur when the stimulant effects wear off and the full effects of the opioid are subsequently experienced. In a cross-sectional survey of 203 PWUD in Baltimore, Maryland, US, speedball injection was found to be more strongly associated with recent non-fatal overdose (AOR = 2.63, 95% CI = 1.23–5.64) than heroin injection by itself (AOR = 0.13, 95% CI = 0.03–0.49).²⁶ While the use of speedballs is intentional, it is important to note that street fentanyl is increasingly and without users' awareness being mixed into stimulants, resulting in a high risk of overdose and death among individuals who have little to no opioid tolerance.^{27,28} Results from US drug seizure data showed that the presence of fentanyl in cocaine and methamphetamine samples respectively tripled and increased 179% from 2015 to 2016.²⁹

The concurrent use of opioids and benzodiazepines also increases the risk of overdose and death as both types of substances sedate individuals and suppress breathing. Over the past two decades, benzodiazepine co-involvement in opioid overdose deaths has become increasingly common. In an epidemiological study drawing on data from 399,230 opioids overdose deaths in the US, benzodiazepine involvement in these deaths increased from 8.7% in 1999 to 21.0% in 2017.³⁰ For PWUD who are not intentionally using opioid and benzodiazepines together, their

synergistic effects still pose a threat to them due to the volatility and adulteration of the illicit drug market. Recent Canada-wide drug checking reports have reported that increasing numbers of drugs samples through to be opioids unexpectedly contain benzodiazepines and benzodiazepine analogues, particularly etizolam, flualprazolam, and flubromazolam.³¹ Moreover, novel adulterants such as xylazine (a central nervous system depressant related to clonidine) and synthetic cannabinoids have been detected in drug samples expected to be heroin/fentanyl.^{32,33} These findings are concerning as these substances do not respond to naloxone.

2.2.3 Route of Administration

Another well-studied factor associated with overdose risk is route of administration of the opioid. A high bioavailability, which is the fraction of the drug reaching the systemic circulation, generally indicates a high absorption rate and thus increased overdose risk.³⁴ Bioavailability is influenced by the route of administration, the dose of the drug taken, and the purity of the drug. Assuming that the dose and purity remain constant, the intravenous route (injecting into vein) carries the highest risk of overdose, followed by intramuscular (injecting into muscle), inhalation (smoking, chasing), intranasal (snorting), and lastly oral. As a result, the majority of interventions from health agencies and governments has focused on injection drug use, while overdoses and deaths attributed to other routes have received less attention and resources.³⁵ However, over the years, there have been a number of reports of individuals transitioning from injection to non-injection drug use in cities across the US and other countries like Amsterdam, Brazil, and Malaysia.³⁶ The prevalence of smoking is also apparent in BC – since 2017, smoking has been the most common mode of consumption identified in illicit drug overdose deaths.³⁷

From 2016 to 2019, injection decreased from 37% to 25% while smoking increased from 28% to 40%.

As the illicit drug supply becomes increasingly adulterated with fentanyl, fentanyl analogues, and other substances, it is possible that routes of administration which have been traditionally considered to be safer than injection may not in fact be that much safer. For instance, the risk of overdose from smoking carfentanyl may still be quite high as it is 100 times more potent than fentanyl.

2.2.4 History of Overdose

Having a history of overdose is known to be strongly associated with the risk of subsequent overdose. Several longitudinal cohort studies have demonstrated this association. In an Australian study which followed 413 heroin users for 11 years, those who had overdosed in the past 12 months were significantly more likely to have previously overdosed (OR = 10.37; 95% CI = 1.38-78.08).³⁸ Among a cohort of 1829 PWUD followed for 14 years in Vancouver, having a history of overdose was strongly associated with reporting an overdose in the past six months (AOR = 3.41; 95% CI = 2.83–4.12).³⁹

2.2.5 Substance Use Behaviours

It has been found that certain drug use behaviours increase the risk of opioid overdose. Using opioids in the absence of witnesses increases overdose risk as there are no individuals around to monitor one another, carry out resuscitation procedures, and contact emergency services.³⁴ In times of the COVID-19 pandemic, the primary way to reduce viral transmission has been limiting person to person contact. Jurisdictions around the world have implemented

lockdowns to increase physical isolation and slow down COVID-19 transmission; governments and public health officials have instructed the public to practice physical distancing and limit activities outside home. PWUD may thereby be conflicted on whether to use alone, which may decrease risk of COVID-19 exposure but increase overdose risk, or to use with others, which may increase risk of COVID-19 exposure but decrease overdose risk.

Even though fentanyl is the drug most involved in overdose deaths and it continues to proliferate in communities across North America, the links between overdose risk and fentanyl-related behaviours and attitudes remain under-studied.⁴⁰ Few studies have examined how PWUD have viewed and responded to the increase of fentanyl in the illicit drug supply. A recent study of 432 people who use opioids (PWUO) in New Jersey from 2018 to 2019 found that nearly all participants (95%) have heard of fentanyl, most (80%) believed that it was a dangerous drug, and 40% used fentanyl.⁴¹ In another study of 308 PWUO from three US cities in 2017, participants who preferred fentanyl to other opioids were more likely to have a history of overdose.⁴²

The COVID-19 pandemic may also encourage changes to higher-risk drug use behaviours increase the risk of overdose. For instance, PWUD may stockpile their drug of choice to avoid withdrawal, however, this could increase the likelihood of an overdose if the individual consumes a larger amount than usual.⁴³ If the supply from their usual dealer becomes limited, PWUD may turn to another dealer which could provide them with a different ‘batch,’ potentially increasing their chances of overdosing. Additionally, if their drug of choice becomes unavailable, PWUD may turn to other substances, which may result in an overdose due to unfamiliarity with the new substance.⁴⁴ As no studies have examined the associations between these COVID-19 driven behaviours and overdose risk, there is a need to explore this area in future research.

2.3 Treatment and Harm Reduction Factors

2.3.1 Opioid Agonist Treatment

OAT is currently the most effective treatment for OUD. It involves a range of PO medications to reduce illicit opioid use, decreasing craving and withdrawal symptoms, improve health and social functioning, and prevent overdose and death.⁴⁵ In Canada, the primary OAT medications are buprenorphine which is the recommended first-line treatment, methadone as the second-line option, and slow-release oral morphine (SROM) when the first two options have been deemed to be ineffective or contraindicated.⁴⁶

The protective effects of OAT against overdose have been well-demonstrated in the literature. In a longitudinal cohort study which followed 1,587 PWID in Vancouver for 8 years, participation in methadone treatment was found to have a strong protective effect against non-fatal overdose (AOR = 0.51; 95% CI = 0.44-0.59).⁴⁷ In another 10-year cohort study of 11,199 patients from substance use disorder (SUD) treatment facilities in Denmark, patients receiving buprenorphine had a lower risk of non-fatal overdose (SHR = 0.75; 95% CI = 0.62-0.91) than those in non-pharmacological treatment.⁴⁸

There has been a growing body of research suggesting that buprenorphine carries a greater safety profile than methadone in terms of overdose risk as it exhibits a ceiling effect on respiratory depression – the effects of buprenorphine plateau even when an individual takes more of the medication.^{49,50} An Australian study of 5646 OUD patients showed that buprenorphine was protective against overdose with 9.25 non-fatal overdose admissions for every fatal overdose, compared to 6.77 for methadone; buprenorphine also had significantly fewer non-fatal opioid overdose admissions than methadone ($p = 0.018$).⁵¹ Another study in the United Kingdom

involving over 19 million prescriptions over a 6-year period found that buprenorphine was six times safer than methadone regarding fatal overdose risk.⁵²

Despite the superior safety profile of buprenorphine over methadone, it may not be suitable for all patients due to contraindications, side effects, and patient experiences and preferences. For patients with more severe OUD, buprenorphine may be unsuccessful in reducing withdrawal symptoms and methadone may instead be preferred. Methadone generally has higher treatment retention than buprenorphine so it is recommended over buprenorphine/naloxone for patients who are at high risk of attrition. Given that patients may not benefit from these two mainstay treatments, there is an urgent need to expand OAT options in order to optimize treatment for all patients with OUD. SROM has been increasingly and successfully used in Canada as a third-line option and in several European countries.^{53,54} Emerging evidence suggests that SROM has similar efficacy to methadone in terms of street opioid suppression and retention, and also a superior safety profile compared to methadone; however, several systematic reviews have concluded that the clinical studies evaluating SROM had relatively small sample sizes.^{55–57}

Furthermore, injectable OAT (iOAT) with either diacetylmorphine (prescription heroin) or hydromorphone is available in Canada and some European countries for patients with severe OUD who are refractory to oral OAT. Clinical trials of diacetylmorphine have demonstrated reductions in street drug use, criminal activity, and involvement in sex work, as well as improving treatment retention and overall health and wellbeing for individuals who have not benefitted from other OAT options.^{58–60} Although there were significantly more overdose events reported in the diacetylmorphine group compared to the methadone and hydromorphone groups in these clinical trials, diacetylmorphine is an effective, safe treatment for patients with severe,

treatment-refractory OUD when monitored by a health care team. As iOAT is a logistically and resource-intensive option for patients and there are stringent government regulatory barriers impeding its expansion, these two medications unfortunately still remain a limited option in Canada.

As OAT medications were developed prior to the ubiquity of illicit, non-pharmaceutical fentanyl, its effectiveness is unclear among individuals using fentanyl. There have been no clinical trials and only observational studies evaluating OAT for this population.^{61,62} With buprenorphine, recent studies have reported that people using fentanyl have experienced more frequent instances of precipitated withdrawal and difficulty with the induction process compared to people using heroin.^{63,64} As fentanyl and its analogs are far more potent than heroin and have higher affinity for mu-opioid receptors, higher doses of buprenorphine may be needed for effective treatment.^{65,66} However, other studies have suggested that OAT has remained effective among fentanyl-using individuals. In a qualitative study among PWUO exposed to fentanyl-contaminated heroin, participants reported actively seeking out a buprenorphine/naloxone prescriber and found the medication to be effective for them.⁶⁷ A study which compared six-month buprenorphine retention rates between fentanyl-positive and heroin-positive patients did not find any significant differences in retention, but the fentanyl positive group did have a lower abstinence rate at the six-month follow-up.⁶⁸ In two studies examining the outcomes of methadone treatment in patients exposed to fentanyl, it was found that there were high abstinence rates during six-month and twelve-month follow-up periods and no deaths for those who remaining in treatment.^{69,70} Interestingly, a population-based cohort study of over 55,000 individuals on OAT from 1996 to 2018 in BC reported that the relative risk of all-cause mortality off OAT was higher after the introduction of fentanyl in the illicit drug supply.⁷¹ This suggests

that the protective effect of OAT on mortality increased as fentanyl became more prevalent in BC. As fentanyl-involved overdoses and deaths continue to rise, further research is urgently needed to investigate the effects of OAT among fentanyl-using individuals in order to optimize treatment success.

With the overdose crisis now being compounded by the COVID-19 pandemic, concerns have been raised that it has become more difficult for PWUD to access OAT which in turn may increase their risk of overdose during these dual crises.⁷² Qualitative studies of PWUD from across Canada found patients reporting difficulty accessing OAT due to reduction in operation hours at OAT clinics and therefore the inability to receive the medications for multiple days; some expressed frustration with having to discontinue and/or start the induction process multiple times which affected their opioid tolerance levels.^{73–75} Additionally, a US study of 1,148 patients with SUDs found that 67% of individuals who overdosed during the pandemic reported disruptions in their SUD treatment.⁷⁶ They also found that individuals experiencing these treatment disruptions had four times the odds of having overdosed. In response, there has been a growing number of approaches and policy changes implemented to improve treatment access during the COVID-19 pandemic, such as prescribing OAT through telemedicine and the temporary removal of legal and regulatory barriers to OAT.^{77,78} As it is critical that PWUD receive OAT without interruption during the pandemic, further studies should aim to improve the availability and accessibility of this life-saving treatment.

2.3.2 Naloxone

Along with OAT, evidence-based harm reduction programs and services should be offered to all patients with OUD.⁷⁹ Harm reduction is an approach which aims to minimize the

negative health and social consequences of substance use. It has been shown to significantly reduce substance-related harms, including transmission of HIV and Hepatitis C, and overdose deaths.⁸⁰ One primary harm reduction intervention is the use of naloxone, an opioid antagonist medication which prevents death during an opioid overdose.³⁴ Community-based provision of naloxone through take-home naloxone programs have been implemented throughout the world, and several systematic reviews have shown their effectiveness in reducing overdose mortality among PWUD.^{81,82} However, when tending overdoses involving fentanyl and other highly potent opioids, recent studies have reported that higher initial and cumulative doses of naloxone are needed to reverse them.^{83,84}

2.3.3 Supervised Consumption Services

Supervised consumption services (SCS), another type of harm reduction intervention, are facilities where PWUD are provided sterile injecting equipment to inject pre-obtained substances under the supervision of staff trained to respond to overdoses.⁸⁵ Additionally, SCS often provide education of safer drug use practices and referrals to health and social services. As the primary function of SCS is to prevent mortality, few studies have examined whether SCS use has an effect on non-fatal overdose risk. On the one end, it is thought that SCS use reduces overdose risk as PWUD do not need to rush injections and are provided safer drug use education.⁸⁶ On the other end, it has been hypothesized that PWUD may offset their reduced fatal overdose risk by partaking in riskier behaviours such as consuming larger or higher potency doses.⁸⁷ The current literature, while limited to only two studies, does suggest that more frequent SCS use does not increase non-fatal overdose risk.^{88,89} Nevertheless, non-fatal overdoses were common among

clients in these studies, which underscore the need to prevent non-fatal overdose and related morbidity in this population.

2.3.4 Drug Checking Services

Drug checking services are harm reduction interventions allowing PWUD to determine the contents of the substances they bring in so they can avoid consuming unknown and potentially dangerous adulterants.⁹⁰ While these initiatives first emerged in the party drug scene of Europe in the 1990s, they have grown in popularity in the fentanyl era as a strategy to reduce overdose morbidity and mortality in Canada. A recent study examining 1,411 drug checks at Insite, Canada's first SCS, from 2016-2017 found that 36% of participants planned to reduce their drug use and 11% planned to dispose of their drug.²¹ Among all participants, intended dose reduction was significantly associated with a lower odd of overdose (OR = 0.41; 95% CI = 0.18-0.89). Although there have been no published studies directly examining the association between drug checking service use and overdose, recent studies found that willingness to use fentanyl test strips is high among PWUD regardless of whether they have overdosed or not.^{91,92} Future research could examine if positive drug checking results lead to reductions in overdose risk behaviours.

2.3.5 Harm Reduction Services Disrupted by the COVID-19 Pandemic

Harm reduction programs and services have been disrupted by the COVID-19 pandemic through reductions in services and or shutdowns. In a qualitative study conducted with PWUD throughout Canada, more than half of participants who used these services identified negative changes in service delivery during the pandemic.⁷³ They reported reduced physical capacity, long

wait times, and limited harm reduction supplies at SCS. Some reported that SCS were completely closed, which impacted their ability to reduce overdose risk. A US study of 1148 patients with SUDs found that individuals unable to access naloxone and syringes were more likely to have overdosed during the pandemic (OR = 7.88; OR = 10.1).⁷⁶ Additionally, an International Society of Addiction Medicine survey conducted among 177 addiction medicine professionals across 77 countries reported that harm reduction services were reduced in 41% of the countries.⁹³ Further research is needed to investigate the pathways in which COVID-19-related disruptions in harm reduction services have impacted overdose risk.

2.3.6 Safe Supply

In March 2020, a unique province-sanctioned ‘safe supply’ program in BC was implemented in response to the dual public health emergencies of the overdose crisis and COVID-19 pandemic⁹⁴. The tenet of safe supply is that the regulated provision of legal pharmaceutical-grade ‘safe supply’ medications as alternatives to street fentanyl will help to decrease overdose risk and support physical distancing, reducing the risk of COVID-19 transmission⁹⁵. Safe supply is different from OAT as therapeutic doses of OAT medications do not elicit mind/body altering properties that street drugs and safe supply medications have. For individuals with OUD, hydromorphone and sustained-release oral morphine tablets are the current safe supply medications offered.

Currently, the evidence base for safe supply is limited. Since 2019, a safe supply pilot program has been operating at a Vancouver SCS since 2019, where hydromorphone tablets are provided to PWUD and they are able to administer these tablets under nurse supervision.^{96,97}

There have been two publications on this program – one discussed the barriers and facilitators of

the program's implementation while the other was a qualitative study of 42 clients where outcomes of reduced drug use, decreased overdose risk, and improved health and well-being were reported.^{96,97} While the preliminary evidence of safe supply is promising, there have been anecdotal reports from physicians concerned with the diversion of safe supply medications and its subsequent harms (e.g. worsening and development of SUD among PWUD and opioid naïve individuals), and also reports of physicians reluctant to prescribe these medications.^{98–100}

While the safe supply program in BC has been rolled out for over a year, there has been no published literature examining its impacts. A BC-wide project evaluating the program through mixed-methods approaches and analysis of surveillance and administrative data is underway.^{101,102} Given the potential benefits and of harms of safe supply, evaluation of the program and its outcomes is urgently needed.

2.4 Psychiatric Factors

2.4.1 Mental Health Symptoms and Disorders

Individuals with OUD have high rates of co-occurring mental illness. A study using nationally representative 2015-2017 survey data of 170,3000 adults with OUD in the US found that 64.3% (95% CI: 60.4%–67.9%) of these individuals had a past-year mental illness.¹⁰³ A recent analysis by the Public Health Agency of Canada, which examined 10,082 OUD hospitalizations across the country (excluding Quebec) from 2018-2019, reported similar rates of mental illness, as 56% of the OUD hospitalizations had a co-diagnosis of a mental disorder.¹⁰⁴ Additionally, it has been found that psychiatric comorbidities can contribute to increased risk of mortality and poorer health-related quality of life among individuals with OUD.^{105,106} As psychiatric illnesses can exacerbate OUD and also worsen treatment outcomes, it is

recommended that individuals with concurrent mental health and SUDs receive treatment for both disorders simultaneously, however, very few are able to access the treatments for both.^{107–109} While a range of mental illnesses have been found to be common among PWUO, mood and anxiety disorders appear to be the most prevalent.^{104,110}

Psychiatric symptoms and disorders can also increase the risk of opioid overdose. In a study of 368 PWUO in Boston, those with severe depression were more likely to have reported a recent overdose (OR = 2.46; 95% CI = 1.24–4.89), as were those with post-traumatic stress disorder (PTSD) (OR = 2.27; 95% CI = 1.37–5.60), and those with psychosis (OR = 2.39; 95% CI = 1.10–5.15).¹¹¹ Similarly, in a recent study of 432 PWUO in New Jersey from 2018-2019, those with a history of PTSD were more likely to have recently overdosed (AOR = 3.84; 95% CI = 1.41–10.46).⁴¹ A meta-analysis on the association between depression and non-fatal overdoses among people using illicit drugs found that those with depression were 50% more likely to have a history of overdose compared to those without depression.¹¹² It has been hypothesized that individuals with psychiatric disorders use substances to relieve emotional suffering in order to ease or self-medicate the symptoms of their disorders.¹¹³ Although mental health disorders often co-occur in individuals with OUD, a high proportion of these individuals do not receive the proper care, and relatively little research has been devoted to these concurrent conditions in the wake of the opioid overdose crisis.¹¹⁴ It is thus crucial to better facilitate access to integrated, tailored interventions for this population as addressing concurrent mental health and substance use disorders can reduce overdose risk, improve morbidity and mortality outcomes.

2.4.2 Suicidal Behaviours

Opioid-using individuals commonly experience both suicide attempts and unintentional overdoses, as 20 to 30% of individuals with OUD report a history of both suicide attempt and unintentional overdose.^{115,116} Additionally, suicidal behaviour (ideation, attempts and completed suicide) and opioid overdose share multiple common risk factors including polysubstance use, injection drug use, and depression.^{117,118} A major challenge has been the difficulty in differentiating unintentional (accidental) and intentional (suicide) overdoses. Traditionally, research examining heroin-using individuals have reported that only around 10% overdose intentionally.^{115,116} However, these studies assessed the intention of overdose events dichotomously, that is either intentional or unintentional. There has been growing evidence indicating that suicide intentionality is instead dimensional, with suicidal motivations falling along a continuum of severity throughout time.¹¹⁹ When asking participants of their frequency and intensity of ratings of desire to die using a continuous scale, Connery et al¹¹⁸ reported that nearly 60% of 54 individuals with OUD expressed some desire to take their lives before their most recent overdose. This suggests that suicidal behaviours in the OUD population are far more prevalent than previously thought.

Despite the prevalence of suicidal behaviours among opioid-using individuals, there have been few studies assessing the associations between these behaviours and overdose. Richer et al¹²⁰ found that street youth who endorsed suicidal ideation were nearly twice as likely to have experienced an unintentional non-fatal overdose than those without suicidal ideation (AOR = 1.88; 95% CI = 1.23–2.54). Hakansson et al¹²¹ reported that a history of suicide was a risk factor for non-fatal overdose (AOR = 1.92; 95% CI 1.40-2.63), however, the study did not delineate the overdose intent. The studies assessed the suicidal behaviours dichotomously, so if they were

instead assessed dimensionally, it is possible that stronger associations would have been observed. Overall, our understanding of the complex links between overdose and suicide remains limited; there is an urgent need to further investigate these associations in order to improve the prevention of both overdose and suicide.

2.4.3 Social Isolation during the COVID-19 Pandemic

The effects of social isolation related to the COVID-19 pandemic could disproportionately impact the mental health of individuals with OUD who have high rates of mental health problems and psychological trauma.¹²² Social isolation is known to negatively affect mental health and exacerbate symptoms of mental health disorders.¹²³ A recent Canada-wide qualitative study found that physical distancing and social isolation worsened the mental health and wellbeing of PWUD, and they experienced increased feelings of fear and anxiety due to the pandemic.¹²⁴ In an Austrian study, Yazdi et al¹²⁵ found that from a sample of 127 patients with alcohol use disorder, 53.5% of individuals experienced negative emotions (e.g. depression, fear, anxiety) due to the pandemic, and these individuals were more likely to relapse than those who did not experience these emotions. Further studies could investigate whether mental health problems caused and exacerbated by the pandemic increase the risk of overdose among PWUD.

2.5 Social and Structural Factors

2.5.1 Gender

In addition to the biological and behavioural correlates aforementioned, opioid overdose risk is influenced by social and structural factors. Demographic characteristics, such as gender and ethnicity, have been found to be associated with opioid overdose risk, as studies have

demonstrated an increased risk of overdose among men, white individuals, and indigenous individuals.¹²⁶

More men than women have been dying from opioid overdoses – from 2016 to 2019, men accounted for 70-74% and 67-69% of overdose deaths in Canada and the US respectively.^{1,127} Some studies have also demonstrated male gender to be a risk factor for opioid overdose. Havens et al¹²⁸ found male gender was associated with an increased likelihood of lifetime non-fatal overdose (IRR = 1.72; 95% CI = 1.06-2.81) among 400 individuals using heroin or PO to get high. Similarly, among 432 individuals using heroin/fentanyl, Kline et al⁴¹ reported those who had recently overdosed, compared to those who had never overdosed, were more likely to be male (AOR = 4.04; 95% CI = 1.48-11.05). In a prospective study of nearly 3,000 participants with SUDs (primarily crack/cocaine, opioids) in the US, men were more likely to have experienced a recent non-fatal overdose than women (AOR = 1.91; 95% CI = 1.13-3.22).¹²⁹

Additionally, some studies have examined the reasons for differences in overdose risk between men and women. Some research has found that compared to women, men are more likely to inject and use larger amounts of street opioids, which can contribute to heightened overdose risk.¹³⁰ Moreover, previous studies have shown how masculinity norms, such as reluctance to seek medical help, impulsivity, risk-taking, toughness, and stoicism, can impact the health and wellbeing of men.¹³¹⁻¹³³ It has been suggested that such norms play a role in increased street opioid use and overdose risk among men, but research in this area is limited. A recent qualitative study in Ireland reported that street drug use among men was associated with machoism, which helped with their socialization and sense of belonging in their social circles.¹³⁴

Aside from the sociocultural factors contributing to overdose risk, factors related to biological sex may also play a role. Estrogens and androgens differentially affect how men and

women perceive and modulate pain.^{135,136} As pain is a risk factor for overdose, sex differences in pain may lead to differences in overdose risk between men and women.¹³⁷ Moreover, positron emission tomography imaging studies have demonstrated sex differences in opioid receptors in humans. In a study with healthy human participants, mu-opioid receptor binding was found to be higher in several brain regions in females compared to men.¹³⁸ These findings suggest that the efficacy of drugs targeting opioid receptors differ between men and women, and warrant further investigation.

Given the gaps in understanding the relationship between sex, gender, and overdose, there is a critical need for further studies on the biological sex differences and gendered social and structural conditions that affect overdose risk so evidence-based, interventions can be catered for both men and women.

2.5.2 Ethnicity

Regrading ethnicity, it was found that the highest rates of opioid deaths in US metropolitan areas occurred among white people, but death rates were seen to have significantly increased among nearly all ethnic groups in recent years, particularly among black people.¹³⁹ In Canada, there appears to be limited population-level data on the ethnicity make-up of individuals who have died from overdose¹. However, there has been special attention paid to First Nations populations as they traditionally have high rates of problematic substance use compared to other ethnicities. In both BC and Alberta, indigenous people are five times more likely to experience an opioid overdose than non-indigenous people, and three times more likely to die from an opioid overdose.^{140,141} In BC, it has also been recently reported that overdose deaths among South Asians have been rapidly increasing.¹⁴² Future research should continue to examine the

links between ethnicity and overdose, and culturally tailored treatment and care is much needed to target the needs of all ethnic groups experiencing high rates of overdose.

2.5.3 Education, Employment, and Housing

Educational attainment, employment status, housing status have also been found to be associated with the risk for overdose. A recent systematic review which included studies published between 2000 and 2018 examined the role of socioeconomic marginalization (SEM) on opioid overdose.¹⁴³ Six of the eight studies found that higher levels of educational attainment were associated with lower rates of overdose. The relationships between employment status and overdose, and also between housing status and overdose, appeared to be less clear, as some studies did not find conclusive evidence to support these associations. In studies which did find significant associations, higher levels of unemployment, homelessness, and lower housing prices were associated with higher overdose rates.

In the Vancouver Coastal Health (VCH) region of BC, nearly half (47%) of illicit drug overdose deaths between 2018 and 2021 occurred in ‘other residences’ which include social/supportive housing, single room occupancy hotels, shelters, and hotels.¹⁴⁴ Factors relating to SEM are believed to elevate overdose risk as the chronic stress stemming from social exclusion and inequality promotes stress responses, worsening overall health.¹⁴⁵ The review which also examined other factors including income and health insurance concluded that there were strong associations in the hypothesized direction, that is increased SEM was associated with increased overdose risk. However, it also revealed that the evidence base is overall lacking as many studies had limited validity.

The findings from these studies on SES indicate that it is important to further explore the deep social and structural roots of the overdose crisis, which have been overshadowed by the focus on risk factors solely related to substances.¹⁴⁶ Initiatives aiming to decrease SEM among individuals at risk of overdose are much needed to address the overdose epidemic.

2.5.4 Correctional Facility Release

It is well-established that individuals recently released from a correctional facility are at a high risk of overdose. This is because reduced opioid tolerance due to reductions in use during incarceration and subsequent relapse to opioid use increase the risk of overdose when transitioning to the community.¹⁴⁷ In fact, opioid overdose mortality is the leading cause of deaths among individuals released from a correctional facility.¹⁴⁸ Several epidemiological studies and reviews have demonstrated the high risk of both non-fatal and fatal opioid overdose among former inmates.^{148–151} A 12-year cohort study in Ontario reported that formally incarcerated individuals were 20 more times likely to die from overdose than the general population.¹⁴⁹ A meta-analysis showed the overdose death was 27 times more likely for those formally incarcerated.¹⁵⁰ In order to mitigate post-release overdose following release, it is imperative to provide overdose prevention interventions, such as OAT, tailored to the needs of this vulnerable group upon their transition into the community.

2.5.5 Socioeconomic Impact of the COVID-19 Pandemic

While the social and economic impacts of the COVID-19 pandemic have affected everyone, they are especially damaging for marginalized populations like those living with OUD. The pandemic has worsened socioeconomic vulnerabilities such as unemployment and unstable

housing which are known to be risk factors for overdose. Thus, social and economic stressors stemming from the pandemic could increase overdose risk.¹⁵² Moreover, many individuals including those with OUD have received income assistance payments provided by governments to financially support individuals during the pandemic.^{153,154} As of September 2020, nearly 9 million Canadians have received the Canada Emergency Response Benefit (CERB).¹⁵⁵ Many of the income assistance payments distributed during the pandemic have been given out in a synchronous fashion (e.g. every week), however, there has been extensive research demonstrating the high prevalence of drug-related harms, including overdose, coinciding with synchronous income assistance among PWUD.¹⁵⁶ Anecdotal reports from outreach workers have stated that CERB has contributed to an increase in fatal overdoses during the pandemic¹⁵³. Future research should examine the associations between COVID-19-related synchronous income assistance payments and overdose risk, so policies are developed to mitigate any unintended harms.

2.6 Conclusion

Current research has identified a wide range of risk and protective factors for overdose related to biology, behaviour, treatment, harm reduction, and socioeconomic status. Over the years, the increasing prevalence of fentanyl in the illicit drug market has led to a significant change in the overdose risk environment for PWUD. From our review, we found that it remains unclear how factors previously identified in those using heroin (e.g. route of administration, OAT) are influencing overdose risk in those using fentanyl, and how novel fentanyl-related factors (e.g. fentanyl test strips, safe supply) are affecting overdose risk. Moreover, a number of commentaries and expert opinions have discussed potential COVID-19-related factors associated

with overdoses (e.g. changes to the illicit drug supply, disruptions to treatment services), but there is currently limited primary data linking the pandemic to the increase in overdoses.

Altogether, the findings from our review indicate there is an urgent need for future studies to identify and characterize the risk and protective factors for overdose, especially in those using fentanyl and vulnerable to the effects of the pandemic.

Chapter 3: Methods

3.1 Study Aim

The primary aim of this cross-sectional pilot study was to investigate the risk and protective factors for non-fatal opioid overdose among individuals using street fentanyl during the COVID-19 pandemic. We sought to 1) examine the prevalence of overdose, 2) determine the associations between previously identified factors and overdose, and 3) determine the associations between novel fentanyl-related, COVID-19-related factors and overdose.

3.2 Study Setting, Recruitment, and Data Collection

This study was conducted in Vancouver, BC. Since the crisis was declared a public health emergency in 2016, Vancouver has had the highest rate of overdose deaths of any BC township.¹⁵⁷ Illicitly manufactured fentanyl has become extremely common in the street drug supply in BC – recent drug checking studies have found that 84.1% to 90.6% of ‘heroin’ samples in BC testing positive for fentanyl.^{20,21} During the pandemic, overdose mortality in BC has escalated to record highs as 2020 marked a record year for overdose deaths in BC.¹⁵⁷ The high prevalence of street fentanyl and recent unprecedented spike in overdose deaths make BC a particularly appropriate setting to examine the risk and protective factors for fentanyl-related overdose during the COVID-19 pandemic.

Recruitment for the study was originally anticipated to begin in the fall of 2019 at two housing facilities managed by Coast Mental Health, a BC non-profit organization which provides housing, support services, employment, and education services to approximately 5,500 tenants and clients, many of whom live with mental illness and substance use disorders.¹⁵⁸ The two housing facilities are St. Helen’s Hotel, a single room occupancy hotel, and Pacific Coast

Apartments, a supportive housing unit. These two facilities have approximately 200 tenants in total, with high reported numbers of opioid overdose events. Unfortunately, due to insufficient resources and capacity of Coast Mental Health in the fall of 2019, the high rates of clients dying from overdoses, and the subsequent COVID-19 pandemic in March 2020, recruitment had to be put on hold until further notice.

Through an ongoing collaboration with the Department of Psychiatry at Vancouver General Hospital (VGH), our research team instead conducted the study at the hospital through the Complex Pain and Addiction Service (CPAS). CPAS is an inpatient consultation service at VGH which integrates the assessment and treatment of pain, substance use, and mental health disorders of admitted patients regardless of their medical condition. It is comprised of physicians from multiple disciplines including Family Medicine, Internal Medicine, Emergency Medicine, Pain Medicine, and Psychiatry. Patients on inpatient units at VGH are referred to CPAS physicians by their primary admitting medical or surgical team.

To be eligible for the study, patients had to be 19 years or older, have a current diagnosis of OUD, were COVID-19 negative, and were not showing any symptoms of COVID-19. CPAS physicians identified eligible participants. Once an eligible patient was identified, the physicians asked the patient for permission to be contacted by the research team which consisted of two graduate research assistants. If the patient gave permission to be contacted, a research assistant approached the patient, explained the study, obtained oral consent, and answered study questions they may have had.

Once consent was given, participants completed an interviewer-administered questionnaire which elicited information on overdose history, socio-demographics, substance use patterns, treatment history, harm reduction utilization, mental health, and physical health. Details

about the survey questions are elaborated on in 3.3 Survey Instrument. The data was collected through tablet computers on a web-based survey platform developed by InputHealth, a Canadian software company developing patient-centered health data management. All participants were provided with a \$10 CAD honourarium.

Recruitment at VGH was anticipated to begin in early March 2020, but due to the COVID-19 pandemic, a research curtailment order for all non-essential research was put in place at VCH facilities. On-site human subject research at VGH was able to resume in June 2020, and research resumption request for our study was approved in September 2020. Participants were recruited from October 2020 to February 2021. COVID-19 safety standards set by VCH Infection Prevention and Control, Public Health, the Provincial Medical Officer, and the BC Centre for Disease Control were followed for all study procedures. This study was approved by the Behavioural Research Ethics Board of the University of British Columbia (H19-02231).

3.3 Survey Instrument

The survey instrument questions on overdose risk and protective factors were developed through an iterative process based on reviewing the literature on opioid overdose (Chapter 2: Narrative Review) and gathering expert opinion from six clinician-scientists/clinicians involved in the care of PWUD in BC. The instrument includes questions on opioid overdose history, socio-demographics, substance use patterns, treatment history, harm reduction utilization, mental health, and physical health.

The time frame of all survey questions referred to events or behaviours in the previous six months before the participant's admittance to the hospital, unless specified otherwise. For example, the survey question on OAT was "Before your admittance to the hospital, were you

receiving opioid agonist treatment in the past 6 months?” Face and content validity were established by incorporating feedback from the six clinician-scientists/clinicians and a psychometrician.

To assess history of opioid overdose, participants were asked “How many times have you experienced an opioid overdose in your life?” They were then asked, “How many times have you experienced an opioid overdose in 2020 and 2021?” and asked to specify which month they had overdosed. If the participant had overdosed in the past six months, they were asked whether they were hospitalized for any of them, why they think they overdosed, and whether they did anything to prevent futures ones from occurring. Our outcome variable for the study was non-fatal opioid overdose in the past six months (yes/no). The survey also assessed socio-demographic characteristics including age, gender, ethnicity, educational attainment, employment status, housing status, and correctional facility release.

For questions on substance use, participants were asked whether they used PO (medical use and non-medical use) and/or street opioids (defined as heroin, down, and fentanyl), and if so, what type of opioids they were (e.g. codeine, oxycodone, heroin, fentanyl), days used in an average month, average amount on a using day, whether they used them alone by themselves, main route of administration, and whether they used the opioids together other substances (e.g. stimulants, cannabis). Participants were also asked whether they used street fentanyl intentionally and/or unintentionally, whether and why they liked/disliked it. To assess the potential impact the COVID-19 pandemic has had on the illicit drug supply, participants were asked whether the pandemic made it difficult to get their opioid of choice (yes/no), and if so, what their opioid of choice was and what the difficulty was due to (open-ended question).

For questions on treatment history, participants were asked whether they were receiving OAT, and if so, what medication (buprenorphine/naloxone tablets, buprenorphine extended-release injection, methadone, slow-release morphine, injectable hydromorphone, and injectable diacetylmorphine), and how satisfied they were with the medication (five-point Likert scale). Participants were also asked whether the COVID-19 pandemic made it difficult to access OAT medication (yes/no), and whether they received any psychosocial treatment for their OUD.

Regarding questions on harm reduction utilization, participants were asked “Have you carried Naloxone/Narcan with you?” (yes/no) and “Have you used any of the following harm reduction supplies/services?” The answer choices to the latter question were harm reduction supplies other than Naloxone/Narcan (e.g. syringes, stericups, cookers), getting your drugs tested, and SCS; participants could tell us the type of supply/service if none of these aforementioned answer choices fit their response. Participants were then asked whether the COVID-19 pandemic made it difficult to access any harm reduction supplies/services (yes/no), and if so, which ones were difficult to access. Participants were also asked whether they were receiving any safe supply medications, and if so, what type of medication, whether they used it, whether they have overdosed from it, whether it was difficult to obtain it, whether they have diverted it to obtain street drugs, and what it helped with (reducing withdrawal, craving, risk of overdose, exposure to illicit drug supply, exposure to COVID-19; no benefits; other benefits: please specify).

Mental illness history was ascertained with “Have you ever been diagnosed with a mental illness by a health profession?” This was followed by “Please specify the mental illness(es).” and for each illness, “Over the past six months, have you been treated for it with medication and/or psychotherapy by a health professional?” Self-harm, suicidal ideation, and suicide attempts were

gathered by asking the following: “Have you intentionally participated in any self-harm behaviours?” “Have you thought about killing yourself” “Have you ever tried killing yourself?” “Was this attempt in the past six months?” Early trauma experiences were assessed by the Adverse Childhood Experiences (ACE) questionnaire, which consists of ten items on child maltreatment and household challenges.¹⁵⁹

HIV and Hepatitis C were gathered by asking “Have you ever tested positive for HIV/Hepatitis C?” Chronic pain was ascertained with “Have you experienced chronic pain, that is pain that lasts three months or longer?” This was followed by, “Please rate the pain on a typical day (numeric scale of 1 – 10).” and “Please indicate where you most often experience this pain (head and neck, chest and abdomen, back, hands and/or feet, arms, legs, other: please specify).”

3.4 Data Analysis

Descriptive statistics, including frequencies, percentages, means, and medians, were calculated, and thematic analysis was used to analyse the responses for open-ended questions. All statistical analyses were conducted on IBM SPSS Statistics Version 27. Statistical significance was set at the level of $p < 0.05$.

A multivariable logistic regression model was built to determine the factors associated with non-fatal opioid overdose in the recent six months, which was as the binary outcome variable (yes/no). As a result of recruitment challenges due to the pandemic (research assistants not permitted to access COVID-19 triage units with eligible patients, COVID-19 outbreaks on the units where patients were recruited, patients leaving against medical advice), only 48 participants were recruited.

For our analysis, we examined participants who reported using street opioids (defined as heroin, down, and fentanyl) in the past six months, as the majority of opioid-related deaths in North America have been attributed to street opioids.^{1,3-5} As there were five participants who reported only using PO in the past six months and seven participants with more than 50% of missing data, the final sample size for our analysis was 36 cases.

Six binary candidate explanatory variables were selected based on findings from the narrative review and consultations with the clinician-scientists/clinicians: gender (male/female), history of opioid overdose (yes/no), suicidal ideation (yes/no), route of administration (injection/smoking), receiving OAT (yes/no), and receiving safe supply (yes/no). These factors were chosen from each of the substance use, treatment and harm reduction, psychiatric, and social and structural domains described in the narrative review, and have been found to be associated with opioid overdose in prior research.^{38,39,47,48,120,121,128,129,160,161} One of the 36 cases was missing data for the suicidal ideation variable, so 35 cases were used for the regression analysis. All six candidate explanatory variables were simultaneously entered into the regression analysis.

Chapter 4: Results

4.1 Socio-Demographic Characteristics

A total of 36 participants were included in the present study. All were inpatients with a current diagnosis of OUD, and reported using street fentanyl (knowingly and/or suspected) in the previous six months. The mean age was 41.17 years (SD: 10.44 years), with 20 males and 16 females. Half (n = 18) of the participants were white, 12 (33.33%) were indigenous, and the other six participants (16.67%) were Black/Hispanic/Multi-Race. Other socio-demographic characteristics are shown in Table 4.1.

Table 4.1 Socio-Demographic Characteristics

	Frequency	Percentage
Age	Mean: 41.17 years (SD: 10.44 years)	
Gender		
Male	20	55.56%
Female	16	44.44%
Ethnicity		
White	18	50%
Indigenous	12	33.33%
Black	1	2.78%
Hispanic	1	2.78%
Multi-Race	4	11.11%
Released from correctional facility^a		
Yes	2	5.56%
No	34	94.44%
Education		
Elementary/middle school (up to Grade 9)	5	13.89%
Some high school (Grade 10, 11)	5	13.89%
High school certificate (completed Grade 12)	10	27.78%
Post-secondary (e.g. technical school, trade school, college, university)	16	44.44%
Employment status^a		
Student	1	3.03%
Employed for wages	6	18.18%
Self-employed	2	6.06%
Out of work and looking for work	6	18.18%
Out of work but not currently looking for work	8	24.24%

	Frequency	Percentage
Employment status^a		
Unable to work	10	30.30%
Housing status^a		
Stable housing (owning or renting house/apartment)	13	36.11%
Non-stable housing (hotel, single room occupancy hotel, temporary stay at someone else's house/apartment, etc.)	11	30.56%
Shelter	4	11.11%
On the street (indoor public place, bus or train station, abandoned building, etc.)	5	13.89%
Institution (detox, nursing home, jail or prison, hospital, treatment or recovery residence, etc.)	1	2.78%
Stable and non-stable housing	1	2.78%
Shelter and on the street	1	2.78%
Satisfaction with housing status^a		
Very satisfied	3	8.57%
Satisfied	9	25.71%
Neutral	2	5.71%
Dissatisfied	9	25.71%
Very dissatisfied	12	34.29%
Had significant intimate partner(s)^a		
Yes	12	33.33%
No	24	66.67%
Relationship with intimate partner(s)^a (n = 12)		
Very bad	3	25%
Bad	0	0%
Neutral	1	8.33%
Good	2	16.67%
Very good	5	41.67%
Have any children		
Yes	21	58.33%
No	14	38.89%
Had pet(s) living with them^a		
Yes	12	33.33%
No	24	66.67%

^aRefers to previous six months

Missing values account for frequencies and percentages which do not add up to 100%

4.2 Non-Fatal Opioid Overdose History

The vast majority, 75% (n = 27), reported a history of non-fatal opioid overdose. The 27 participants experienced a median of 6.50 lifetime overdoses (IQR: 11) – 12 participants reported

one to five overdoses, seven participants reported six to ten overdoses, and eight participants reported more than ten overdoses. Nearly half of the participants, 47.22% (n = 17), experienced an opioid overdose in the previous six months.

4.2.1 Circumstances of Recent Non-Fatal Opioid Overdose

Of the 17 participants who overdosed in the past 6 months, seven were hospitalized. When asked why they think they overdosed, the two most common reasons given were using more than intended (n = 6) and the drugs being too strong (n = 5). When asked whether they did anything to prevent future overdoses from happening, four said they did not do anything, three said they used harm reduction services/supplies, and three said they used smaller doses.

4.3 Substance Use

All 36 participants reported using street opioids (defined as fentanyl/heroin/down) in the past six months. 86.1% (n = 31) stated they used street fentanyl intentionally during this period. The remaining 13.9% (n = 5) said they used street fentanyl unintentionally. This meant that all 36 participants had used street fentanyl (regardless of their intention) in the past six months. Given that all participants reported using fentanyl and that recent drug checking studies have shown that the vast majority of ‘heroin’ in BC contains fentanyl, we refer to the street opioids participants used as fentanyl^{20,162,163}.

Both injection and smoking were common methods to use street fentanyl. Nearly half, 47.2% (n = 17), stated injection was their main route of administration, while slightly more than half, 52.8% (n = 19) stated smoking was their main route. Slightly more than half, 52.8% (n = 19), reported using stimulants (e.g. crystal meth, cocaine) together with fentanyl in the previous

six months. Most participants, 72.2% (n = 26) stated that the COVID-19 pandemic did not make it difficult to obtain fentanyl. Among the 10 who reported that the pandemic affected their ability to get fentanyl, nine said it was due to the cost, eight said it was due to the availability, and 6 said they were concerned with contracting COVID-19. Other substance use patterns and behaviors are shown in Table 4.2.

Table 4.2 Substance Use Patterns and Behaviours

	Frequency	Percentage
Type of street opioid used^a		
Heroin	2	5.56%
Fentanyl	13	36.11%
Down (Slang Term for Street Opioids)	8	22.22%
Heroin and Down	5	13.89%
Fentanyl and Down	5	13.89%
Heroin, Fentanyl, and Down	3	8.33%
Days used fentanyl in an average month^a		
Daily	27	75%
Not daily	8	22.22%
Average amount of fentanyl on a using day^a	Mean: 0.94 grams (SD: 0.79 grams)	
Used fentanyl alone^a		
Yes	23	63.89%
No	13	36.11%
Used fentanyl intentionally^a		
Yes	31	86.11%
No	5	13.89%
Used fentanyl unintentionally^a		
Yes	21	60%
No	14	40%
Used prescription opioids (for non-OAT and non-safe supply purposes) with a doctor's prescription^a		
Yes	12	33.33%
No	24	66.67%
Used prescription opioids without a doctor's prescription or in larger doses than prescribed^a		
Yes	7	19.44%
No	29	80.56%

	Frequency	Percentage
Injected fentanyl into artery^a		
Yes	12	33.33%
No	24	66.67%
Reused needles^a		
Yes	18	50.0%
No	18	50.0%
Shared needles^a		
Yes	5	13.89%
No	31	86.11%
Witnessed someone overdosing on opioids^a		
Yes	8	22.22%
No	28	77.78%
Assessed own risk of experiencing opioid overdose^a		
Very low risk	17	47.22%
Low risk	4	11.11%
Medium risk	4	11.11%
High risk	4	11.11%
Very high risk	6	16.67%

^aRefers to previous six months

Missing values account for frequencies and percentages which do not add up to 100%

4.3.1 Attitudes and Perspectives towards Fentanyl

When asked whether they liked anything about fentanyl, half of the participants (n = 18) replied with yes. The common reason (n = 9) was that fentanyl helped with pain relief, but it was unclear whether this was referring to physical and/or psychological pain. Eight participants said they liked the strength of fentanyl, while three said it helped them deal with their emotions/feelings/trauma. The vast majority, 74.1% (n = 25), reported that there was something they disliked about fentanyl. The most common aspect participants disliked about fentanyl was its strength. Five participants also stated its effects were too short, while three said it made them dope sick. When asked whether they were worried about a friend or someone they care about overdosing on fentanyl in the past six months, slightly more than half, 52.8% (n = 19) were worried, 8.3% (n = 3) were neutral, and 27.8% (n = 10) were not worried.

4.4 Treatment History and Harm Reduction Utilization

Around half, 55.6% (n = 20), were on OAT in the past six months. Methadone (n = 13) was the common medication, followed by buprenorphine/naloxone (n = 6) and slow-release oral morphine (n = 5). Patient satisfaction with OAT varied – seven were satisfied, six were neutral, and six were dissatisfied. A quarter (n = 5) of the 20 participants on OAT stated that COVID-19 made it difficult to access medications. The majority, 83.3% (n = 30), reported receiving no psychosocial treatment for their OUD.

The use of harm reduction services and supplies in the previous six months was high. More than three-quarters, 77.8% (n = 28), carried naloxone, while more than half, 66.7% (n = 24) reported using harm reduction supplies (other than naloxone, e.g. syringes, stericups/cookers). Half (n = 18) used supervised consumption sites, while drug checking (41.7%, n = 15) was a bit less common. More than a quarter, 30.6% (n = 11), reported that COVID-19 made it difficult to access harm reduction supplies and services. A few specifically stated that there were long line-ups to supervised consumption sites.

Most, 61.1% (n = 22), were not prescribed safe supply medications over the past 6 months. Among those prescribed these medications, nine were prescribed only oral hydromorphone, two were prescribed only sustained-release oral morphine, and three were prescribed both oral hydromorphone and sustained-release oral morphine. Further details on safe supply are described in Table 4.3.

Table 4.3 Safe Supply

	Frequency	Percentage
Type of safe supply medication prescribed^a		
Oral hydromorphone	9	25%
Sustained-release oral morphine	2	5.56%
Oral hydromorphone and Sustained-release oral morphine	3	8.33%
None	22	61.11%
Used prescribed oral hydromorphone^a		
Yes	10	27.78%
No	25	69.44%
Used prescribed sustained-release oral morphine^a		
Yes	5	13.89%
No	31	86.11%
Diverted oral hydromorphone^a (n = 12)		
Yes	4	33.33%
No	6	50.00%
Diverted sustained-release oral morphine^a (n = 5)		
Yes	0	0%
No	5	100%
Benefits of oral hydromorphone^a (n = 12)		
Reduce withdrawal, craving	1	8.33%
Reduce exposure to illicit drug supply, COVID-19	1	8.33%
Reduce withdrawal, exposure to illicit drug supply, COVID-19	1	8.33%
Reduce withdrawal, craving, exposure to illicit drug supply, COVID-19	1	8.33%
Reduce withdrawal, risk of overdose, exposure to illicit drug supply, COVID-19	1	8.33%
Reduce craving, exposure to illicit drug supply, COVID-19	1	8.33%
Reduce withdrawal, craving, risk of overdose, exposure to illicit drug supply, COVID-19	2	16.67%
No benefits	3	25%
Benefits of sustained-release oral morphine^a (n = 5)		
Reduce risk of overdose, exposure to illicit drug supply, exposure to COVID-19	1	20%
Reduce withdrawal, craving, risk of overdose, exposure to illicit drug supply, exposure to COVID-19	3	60%
No benefits	1	20%
Difficulty obtaining oral hydromorphone from physician/nurse practitioner^a (n = 12)		
Yes	4	33.33%
No	7	58.33%

	Frequency	Percentage
Difficulty obtaining sustained-release oral morphine from physician/nurse practitioner^a (n = 5)		
Yes	2	40%
No	3	60%

^aRefers to previous six months

Missing values account for frequencies and percentages which do not add up to 100%

4.5 Mental Health Characteristics

The lifetime prevalence of mental illness was high as 63.9% (n = 23) reported they have been diagnosed with a mental illness by a health professional. Depression (44.4%, n = 16), was the most common, followed by anxiety disorders (36.11%, n = 13). Other mental illnesses self-reported by participants were: bipolar disorder (n = 2), post-traumatic stress disorder (n = 5), borderline personality disorder (n = 2), and attention deficit disorder (n = 1). Only around a third (n = 7) of those reporting a lifetime diagnosis of mental illness received treatment in the previous 6 months.

Self-harm behaviours in the previous 6 months were reported by 22.9% (n = 8) of the participants. Suicidal ideation in the previous 6 months was a bit more common, 37.1% (n = 13). Nearly half, 47.2% (n = 17), stated they have attempted suicide, while 19.4% (n = 7) stated they have attempted suicide in the past 6 months. Other mental health characteristics are shown in Table 4.4.

Table 4.4 Mental Health Characteristics

	Frequency	Percentage
Experienced a stressful life event that has disrupted life in a major way^a		
Yes	30	83.33%
No	6	16.67%
Regularly involved in meaningful activities^a		
Yes	19	52.78%
No	17	47.22%
Contact with^a		
Family members	9	25.0%
Friends	3	8.33%
Both family members and friends	18	50.0%
None	6	16.67%
Set goals for yourself in near future^a		
Yes	26	74.29%
No	9	25.71%

^aRefers to previous six months

4.6 Adverse Childhood Experiences

The average score on the 10-item scale was 5.43 (SD = 2.87). Individual ACE items are shown in Table 4.5.

Table 4.5 Adverse Childhood Experiences

	Frequency	Percentage
Parent or another adult in the household often swore, insulted, put down, or humiliated you		
Yes	21	63.64%
No	12	36.36%
Parent or another adult in the household pushed, grabbed, slapped, or threw something at you		
Yes	20	60.61%
No	13	39.39%
Adult or person at least 5 years older ever touched or fondled or had you touch their body in a sexual way		
Yes	11	33.33%
No	22	66.67%
Often felt that no one in your family loved you or thought you were special		
Yes	24	72.73%
No	9	27.27%

	Frequency	Percentage
Often felt that you didn't have enough to eat, had to wear dirty clothes, and had no one to protect you		
Yes	13	39.39%
No	20	60.61%
Parents ever separated or divorced		
Yes	25	73.53%
No	9	26.47%
Mother or stepmother was often pushed, grabbed, slapped, or had thrown something at her		
Yes	14	41.18%
No	20	58.82%
Lived with anyone who was a problem drinker or alcoholic or who used street drugs		
Yes	25	73.53%
No	9	26.47%
Household member was depressed or mentally ill or attempted suicide		
Yes	16	47.06%
No	18	52.94%
Household member went to prison		
Yes	12	36.36%
No	21	63.64%

4.7 Physical Health Characteristics

The prevalence of HIV was low, 8.3% (n = 3), while around half, 47.2% (n = 17), stated they have tested positive for Hepatitis C. Slightly more than half, 55.6% (n = 20), experienced chronic pain in the past six months. Among these participants, their median score on the numeric rating scale was 9.0 (IQR: 3.0).

4.8 Multivariable Regression Model

A multivariable logistic regression model was built to ascertain the effects of gender, history of opioid overdose, suicidal ideation, main route of administration of fentanyl, receiving OAT, and receiving safe supply on the likelihood that participants experienced a non-fatal opioid

overdose in the previous six months. The logistic regression model was statistically significant, $\chi^2(6) = 23.46$, $p < .05$. The model explained 65.3% (Nagelkerke R^2) of the variance in non-fatal opioid overdose and correctly classified 77.1% of cases. Sensitivity was 81.3%, specificity was 73.7%, positive predictive value was 72.2%, and negative predictive value was 82.4%. Of the six predictor variables, three were statistically significant: gender, history of opioid overdose, and suicidal ideation. Males had 27.94 times higher odds to experience a recent opioid overdose. Individuals with had a history of opioid overdose had 103.19 times higher odds to experience a recent opioid overdose, and individuals reporting suicidal ideation had 32.08 times higher odds to experience a recent opioid overdose. Table 4.6 summarizes the results of the multivariable logistic regression.

Table 4.6 Multivariable Logistic Regression Model for Experiencing a Recent Non-Fatal Opioid Overdose among Individuals who use Street Fentanyl (n = 35)

	Unstandardized Beta	Standard Error	Wald	Degree of Freedom	p	Adjusted Odds Ratio (AOR)	95% CI
Gender (Male vs. Female)	3.33	1.55	4.64	1	0.03	27.94	1.35 - 578.06
History of Opioid OD (Yes vs. No)	4.64	2.19	4.49	1	0.03	103.19	1.42 - 7514.02
Suicidal Ideation^a (Yes vs. No)	3.47	1.66	4.37	1	0.04	32.08	1.24 - 827.45
Route of Administration^a (Injection vs. Smoking)	-1.98	1.23	2.61	1	0.11	0.14	0.01 - 1.53
Received OAT^a (Yes vs. No)	-1.90	1.20	2.45	1	0.12	0.15	0.01 - 1.59
Received Safe Supply^a (Yes vs. No)	-0.69	1.17	0.34	1	0.56	0.50	0.05 - 5.01

^aRefers to previous six months

Chapter 5: Discussion

5.1 Overview

In our pilot study, we examined the prevalence and risk, protective factors of opioid overdose among individuals using street fentanyl during the COVID-19 pandemic. We found a high prevalence of recent non-fatal opioid overdose, with nearly half (47.2%) reporting having overdosed in the previous six months. Gender, history of opioid overdose, and suicidal ideation were identified as risk factors for recent non-fatal opioid overdose. Route of administration, receiving OAT, and receiving safe supply were not statistically significantly associated with overdose.

5.2 Prevalence of Recent Non-Fatal Opioid Overdose

The overdose prevalence in our pilot study exceeds that of recent studies conducted among PUWD in BC and US settings with high fentanyl prevalence before the pandemic. In a cross-sectional study of 316 street-recruited PWUO in Maryland, US, 35.1% of participants overdosed in the past year.¹⁶⁴ In another cross-sectional study of 425 PWID in West Virginia, US, 42.6% overdosed in the past six months.¹⁶⁵ A study in Vancouver examined illicit drug overdose prevalence among 999 PWUD from December 2016 to May 2017, and found that 16.9% had overdosed in the previous six months.¹⁶⁶ Another study of 303 clients of BC harm reduction facilities from May to August 2018 reported that 26.7% experienced an overdose in the previous six months.¹⁶⁷

While these studies had slight differences in study designs and samples (e.g. illicit drug overdose, PWUD) than ours (e.g. opioid overdose, people using street opioids), it is nevertheless concerning to see that such a high percentage of our participants having recently overdosed. This

finding may be reflective of the synergetic effects of the COVID-19 pandemic, increasing toxicity of BC's illicit drug supply, and changing user preferences towards fentanyl. With the majority of our participants (86.1%) reporting the intentional use of street fentanyl, this provides support that a growing number of PWUD are purposely seeking out fentanyl and preferring it over other opioids.^{42,167} In addition, fentanyl has become increasingly pervasive in BC – fentanyl was detected in 29% of illicit drug deaths in 2015 and in 85-86% of deaths from 2018-2020.¹⁶⁸ During the pandemic from April 2020 to January 2021, deaths with extreme fentanyl concentrations (>50ug/L) increased by 64% compared to the 15-month period leading up to the pandemic. 2020 was also a record year for overdose calls to BC Emergency Health Services.^{169,170} Expert opinions and commentaries have noted that potential reasons for the increases in overdoses are more individuals using drugs alone due to social isolation, difficulty accessing care, and changes in drug supply due to border closures and travel restrictions – further studies are needed to closely investigate the pathways linking the COVID-19 pandemic to the increasing overdoses.¹⁷¹

5.3 Risk and Protective Factors for Recent Non-Fatal Opioid Overdose

The rapid proliferation of fentanyl in the illicit drug market has undoubtedly created considerable changes in the overdose risk environment for those who use street opioids due to the high potency of fentanyl. However, little is known how the risk, protective factors previously identified in those using heroin are influencing the risk of overdose in those using fentanyl. It is also not known how novel factors related to fentanyl use and the pandemic are affecting overdose risk among fentanyl-using individuals.

From our pilot study, we found that certain factors studied in the pre-fentanyl-era literature (male gender, history of overdose, and suicidal ideation) have persisted as risk factors for fentanyl-related overdose, while other previously identified factors (route of administration and OAT) were not significantly associated with fentanyl-related overdose. Safe supply, an innovation introduced in response to the toxic drug supply and COVID-19 pandemic, was also found to be not significantly associated with overdose. In the following sections, we will be discussing these factors in the context of previous research and the dual public health emergencies.

5.3.1 Gender

Male gender was significantly and positively associated with recent non-fatal opioid overdose (Table 4.6, AOR = 27.94, 95% CI = 1.35–578.06, $p = 0.03$). This finding is line with other studies which have found a higher risk of overdose among male PWUO compared to female PWUO.^{10,128,129,172,173} Additionally, with the majority (76.4%) of recent overdoses occurring among our male participants, this finding appears to reflect that men in BC have been disproportionately affected by the overdose crisis, especially during the pandemic. Since March 2020, the illicit drug death rate in BC has dramatically increased among men, while the death rate among women has remained relatively constant from before to now during the pandemic.¹⁵⁷ From January to September 2020, most (77%) opioid-related deaths in Canada occurred among men.¹

While opioid overdoses have historically been more common among men, there is evidence suggesting that the gender gap in overdose deaths has widened further during the current fentanyl crisis in North America. In a study examining opioid overdose deaths in

Delaware, a US state which has experienced an increase in fentanyl-involved overdose deaths in the past decade (fentanyl detected in 15.7% of opioid overdose deaths in 2013, increased to 76.2% in 2017), the male-to-female death rate increased from 1.9 in 2013 to 2.6 in 2017.¹⁷⁴ Similarly in BC, the male-to-female illicit drug death rate has increased from 3.2 in 2013 to 4.5 in 2017 (fentanyl detected in 15% of illicit drug deaths in 2013, increased to 82% in 2017).^{157,168} Future studies should investigate the underlying factors driving this demographic shift in opioid overdoses.

Despite the high prevalence of overdoses in men, research examining the gender differences in opioid overdoses has been limited. Some studies and commentaries have reported that increased likelihood of injection drug use in male PWUD, masculinity norms, such as impulsivity and unwillingness to seek medical help, could lead to heightened overdose risk among men.^{130–134} A better understanding of the relationship between male gender and overdose, and male-specific interventions are urgently needed to prevent more men from dying of overdose.

5.3.2 History of Opioid Overdose

History of opioid overdose was significantly and positively associated with recent non-fatal opioid overdose (Table 4.6, AOR = 103.19, 95% CI = 1.42–7514.02, $p = 0.03$). This finding is consistent with the existing literature as numerous studies have demonstrated increased risks of both subsequent non-fatal and fatal overdoses after an overdose.^{175–179} These studies examined the association between non-fatal overdose and subsequent overdose among individuals using heroin and other street drugs, but to our knowledge, there have been no studies examining this association among those using fentanyl. Our study is therefore the first to demonstrate that

overdose history is a strong risk factor for subsequent overdose in fentanyl-using individuals. This is not an unexpected finding given that OUD is a chronic, relapsing disorder.¹⁸⁰ However, what is not known is whether relapse rates differ between those using heroin and those using fentanyl. If rates differ, the association between non-fatal overdose and subsequent overdose could differ between these individuals.

A study, which followed 2317 PWID for a median of 61 months, found that an increasing number of non-fatal overdoses was associated with a greater risk of subsequent fatal overdose, indicating a dose-response relationship.¹⁷⁵ If such a relationship holds true in our sample, it would be concerning as there were a high number of overdoses (median: 6.50, IQR: 11) in those who overdosed. To conclude, our findings underscore the importance of screening individuals for a history of overdose in order to identify those with a high risk of continued overdose. These individuals should be engaged with overdose prevention strategies to reduce the risks of subsequent overdose-related harms and mortality.

5.3.3 Suicidal Ideation

Suicidal ideation was significantly and positively associated with recent non-fatal opioid overdose (Table 4.6, AOR = 32.08, 95% CI = 1.24–827.45, $p = 0.04$). This finding corroborates the results of previous studies showing that suicidal ideation increases the risk of overdose risk.^{120,121} Hakansson et al¹²¹ found that suicidal ideation increased the odds of non-fatal overdose (OR = 1.82; 95% CI = 1.43–2.32) in a sample of 1113 opioid-using Swedish criminal justice clients. In a longitudinal study of 858 street youth, Richer et al¹²⁰ found that those with suicidal ideation were nearly twice as likely to have experienced a non-fatal overdose (AOR = 1.88; 95% CI = 1.23–2.54).

It should be noted that suicidal ideation was common in our study, with 37.1% of participants reporting suicidal ideation in the past six months. Previous studies have estimated the lifetime prevalence of suicidal ideation to be around 50% in individuals who use heroin.^{182,183} There also has been growing evidence suggesting that suicidal ideation may underlie many overdose events.¹⁸⁴ Bohnert et al¹⁸⁵ found that suicidal intent was involved in 39% of non-fatal overdoses involving opioids or sedatives among patients in the ED. Connery et al¹¹⁸ reported even higher rates, reporting that 59% of 54 individuals who used heroin/fentanyl had expressed some desire to die before their most recent overdose. Given our findings and the limited literature in this research area, further studies are needed to more closely examine the relationship between suicidal ideation and overdose. Opioid-using individuals with suicidal ideation need to be identified, so they can be provided with effective, integrated suicide and overdose prevention interventions.

Furthermore, participants in our study were asked whether they experienced suicidal ideation in the past six months, which was a period of time during the COVID-19 pandemic. It is possible that the suicidal ideation may have, in part, stemmed from the pandemic, but we did not ask participants about this. A nationally representative survey of Canadian adults found that 6.4% of participants had suicidal ideation as a result of the pandemic, and another Canadian study found that in those with previous psychiatric history, suicidal ideation significantly increased during the pandemic compared to pre-pandemic estimates.^{187,188} However, to date, there has been no literature which has specifically assessed pandemic-related suicidal ideation among PWUD. Future research could examine whether suicidal ideation due to the pandemic could lead to increased overdose risk.

5.3.4 Route of Administration

Route of administration was not significantly associated with recent non-fatal opioid overdose (Table 4.6, AOR = 0.14, 95% CI = 0.01–1.53, $p = 0.11$). This non-significant result may be due to the small sample size of our pilot study.

In the current literature, a number of studies have demonstrated an association between route of administration and overdose, finding injection drug use to convey the highest risk of overdose due to rapid entry into the bloodstream.¹⁶⁰ For instance, in a Spanish study of 2,064 individuals who used heroin daily, the odds of overdosing was 4.1 times greater for those who injected heroin compared to those who smoked heroin.¹⁶⁰ In another study of 2,766 PWUD (primarily heroin, amphetamine use), the adjusted hazard for all-cause mortality was lower for smokers than injectors (AHR = 0.52, 95% CI = 0.28–0.97).¹⁸⁹

While such studies have shown a relationship between overdose and the route of administration of heroin and other street drugs, there have been no studies comparing the risk of overdose between different routes of administration of street fentanyl and analogues. Given the higher potency of fentanyl than heroin and unpredictability of the illicit drug supply, the risk of overdose may still be quite high with consumption routes which have been traditionally deemed to be safer than injection, such as smoking and snorting.^{34,166} In a case series, individuals who smoked fentanyl patches described the effects of smoking fentanyl similar to and as strong as injecting heroin.¹⁹⁰ Additionally, smoking is the most common of consumption involved in BC's illicit drug overdose deaths, suggesting that there is a high risk of overdose even smoking.³⁷ These findings, along with our non-significant results, underscore the need for future studies to examine how the different consumption routes of fentanyl affect the overdose risks of PWUD.

5.3.5 Opioid Agonist Treatment

OAT was not significantly associated with recent non-fatal opioid overdose (Table 4.6, AOR = 0.15, 95% CI = 0.01–1.59, $p = 0.12$). Similar to the other non-significant results, this result may be due to low statistical power arising from the small sample size.

Our finding is in contrast to the current literature as there have been decades of research demonstrating the effectiveness of OAT in decreasing overdose and mortality among those who use heroin and non-prescribed opioids.^{191,192} However, few studies have evaluated the outcomes of OAT among those who use fentanyl. Anecdotal, unpublished reports have discussed the increased likelihood of precipitated withdrawal during buprenorphine induction among fentanyl-using individuals, which may lead to poor retention and increased risk of overdose.^{63–66} Other studies have shown that OAT has remained effective among PWUD exposed to fentanyl, reporting similar retention rates between fentanyl-positive and heroin-positive patients, and high abstinence rates for those retained on OAT.^{68–70}

We only found one study examining the association between overdose and OAT among individuals who use fentanyl. In a sample of 432 PWUD, 40% of whom reported ever knowingly used fentanyl, any past or current methadone treatment was protective against overdose (AOR = 0.32, 95% CI = 0.11–0.96), but buprenorphine treatment was not associated with overdose risk.⁴¹ The researchers of this study postulated that their findings are due to the lower retention rates for buprenorphine relative to methadone.⁴¹

Compared to this study, the sample of our pilot was comprised of all fentanyl-using individuals, and we looked at whether participants were receiving any OAT in the past six months. Due to small cell sizes, we were unable to assess how different forms of OAT (methadone, buprenorphine/naloxone, slow-release oral morphine) affected overdose risk in our

regression model. Additionally, retention in OAT was not captured in our study – among the participants receiving OAT in the six-month period, some may have consistently taken the medication while others may have not. Retention in OAT has been shown to be associated with reductions in overdose and improvements in health outcomes and extensively in the literature.^{193,194} The various nuanced aspects of OAT, such as medication type and retention, should be assessed in future studies, in order to better understand the outcomes of OAT among those using fentanyl.

5.3.6 Safe Supply

Safe supply was not significantly associated with recent non-fatal opioid overdose (Table 4.6, AOR = 0.50, 95% CI = 0.05–5.01, $p = 0.56$). Despite the non-significant result, our pilot study is among the first to examine the outcomes of the government-sanctioned safe supply program in BC. The program was established in March 2020 in response to the dual public health emergencies of the opioid overdose epidemic and COVID-19 pandemic.⁹⁴ It is thought that safe supply medications reduce overdose risk because they provide PWUD a more consistent and safer supply of opioids than the potent and unpredictable street supply of fentanyl. Currently, there has been no published literature on the impacts of the program. However, there is some preliminary evidence supporting safe supply. In a qualitative study of 42 PWUD receiving hydromorphone tablets through a pilot safe supply program in Vancouver which has operated since January 2019, clients reported reduced illicit drug use, decreased overdose risk, and improved health and wellbeing.¹⁶¹

In commentaries and anecdotal reports, concerns regarding safe supply have been raised by physicians in BC and also in Ontario, where safe supply prescribing is practiced within pilot

programs – PWUD may not use the medications and divert them to procure fentanyl, as the medications are not potent enough to meet their opioid requirements.^{98,99} In our study, we interestingly found more than a third (Table 4.3, 36.3%) of those receiving safe supply reported diverting medications, however, more than half (Table 4.3, 54.5%) stated the medications were beneficial in relieving symptoms of their OUD. Given the currently limited evidence base for safe supply and its potential benefits and harms, studies are urgently needed to evaluate the outcomes of BC’s program.

5.4 Limitations

As a result of research restrictions imposed by the COVID-19 pandemic, the sample size of our pilot study was small. Our findings should thus be interpreted as preliminary. Also due to the limited sample size, we were able to include only a few explanatory variables in our regression model to assess their potential associations with recent non-fatal opioid overdose. The variables not included in our model were reported descriptively in Chapter 4: Results.

Since the data was collected cross-sectionally, the temporal relationships between risk factors and overdose could not be determined. Additionally, as data was self-reported, our findings are subjected to recall bias. Lastly, as our study was only comprised of inpatients at one acute care hospital in Vancouver, their overall health may have been poorer than other individuals with OUD, which may have increased their likelihood of experiencing a recent opioid overdose. So, our findings may not be generalizable to other individuals at risk of opioid overdose, including those who have other substances as their drug of choice (e.g. stimulant-users unknowingly taking fentanyl), and those in other settings (e.g. outpatient clinic, rural areas).

5.5 Future Directions

To strengthen our preliminary findings, we will be continuing with recruitment and data collection at VGH. We are also planning to expand the study to three other sites: the Anne Vogel Clinic (a community outpatient clinic in Richmond, BC providing care to patients with OUD), the Burnaby Centre for Mental health and Addiction (an inpatient tertiary care facility for adults with severe, concurrent mental health and substance use disorders), and an OAT clinic in Squamish, BC. This will enable us to generate more generalizable findings and make comparisons of overdose prevalence and the risk, protective factors for overdose between the different samples. Of note, as much of the research and policies on the overdose crisis in Canada have focused on large urban settings, our research in Squamish will shed light on the unique circumstances and needs of PWUD in smaller rural settings.¹⁹⁵

Future studies could utilize longitudinal designs to attempt determining the causal relationships between the risk, protective factors and overdose, allowing us to better understand the impacts of street fentanyl and the COVID-19 pandemic on overdose risk. Moreover, as we excluded patients who were COVID-19 symptomatic and/or positive, future studies could investigate whether PWUD with a COVID-19 diagnosis are at increased risk of overdose given that chronic lung diseases increase fatal opioid overdose risk among PWUD.¹⁹⁶

5.6 Conclusion

To our knowledge, this is the first study to investigate the risk and protective factors for opioid overdose among individuals using street fentanyl during the COVID-19 pandemic.

With all participants having recently used fentanyl and the majority reporting the intentional use of fentanyl, these findings indicate that patterns of use among PWUD have

rapidly shifted towards fentanyl. The dynamics of fentanyl use have been suggested to involve both supply-led factors (e.g. lower costs for dealers) and demand-led factors (e.g. preference for fentanyl over other drugs) – studies are needed to determine how the pandemic has disrupted drug markets, and how attitudes and behaviours around fentanyl have changed among PWUD.¹⁹⁷ Such research will generate evidence to guide clinicians who work with the increasing number of individuals using fentanyl.

Our findings on the risk factors for overdose have important clinical implications in preventing further overdoses in this high-risk population. Clinicians should screen for suicidal ideation and overdose history, and provide effective suicidal and overdose prevention interventions. As PWUD may underestimate their risk for overdose, frontline workers and clinicians should engage with PWUD to increase awareness and facilitate their management of overdose risk factors.¹⁹⁸

Furthermore, our findings suggest that risk and protective factors previously identified in individuals who use heroin should be re-examined as their contributions to overdose risk may be different in individuals who use fentanyl. Novel factors related to fentanyl and the COVID-19 pandemic, should be further investigated to examine their roles in overdose risk. This urgently needed area of research will enable clinicians to better identify individuals at risk of overdose, and inform the development of tailored interventions and policies to improve health outcomes in this vulnerable population.

Confronting the opioid overdose crisis will thus require comprehensive, evidence-based approaches which are resistant against the rise of fentanyl and the impacts of the COVID-19 pandemic, and address the multifaceted array of biological, psychosocial, and structural factors associated with opioid overdose.

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