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Induction of Transdermal Buprenorphine (Butrans®) to Extended-Release Buprenorphine Subcutaneous Injection (Sublocade®) for Opioid Use Disorder: A Case Series & A Qualitative Study on the Experiences, Barriers, and Understanding of Opioid Agonist Treatment Among Youth with Opioid Use Disorder in Vancouver, British Columbia

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Hannah Schneiderman

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School of Medicine

Supervisors: Dr. Colm O'Tuathaigh, Dr. Niamh Coakley, Dr. Pouya Azar, Dr. Martha Ignaszewski, and Dr. George Budd

Head of School: Prof. Paula O'Leary

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ABSTRACT

The opioid crisis is a profound public health crisis, with devastating impacts on individuals, families, and communities in North America. Vancouver is one of the most affected regions in Canada. To combat the rising opioid overdose epidemic, opioid agonist treatment and harm reduction services have become more readily accessible, and patient centered. The most effective approach to decreasing the morbidity and mortality of people with opioid use disorder is opioid agonist treatment. Initiation of opioid agonist treatment, including buprenorphine and methadone, is a complex and crucial step in care for those beginning pharmacological treatment, as well as those transitioning between medications, as poor treatment retention is largely attributed to discomfort during the induction period due to precipitated withdrawal symptoms. A variety of techniques and protocols have been developed to combat treatment barriers, including rapid micro-induction using sublingual buprenorphine-naloxone; this method eliminates the need for an abstinence period prior to administration of the first dose of buprenorphine/naloxone, and lowers the risk of precipitated withdrawal symptoms. We conducted a case series, involving two patients, that demonstrates the efficacy and safety of a novel induction technique using transdermal buprenorphine (Butrans)®, to extended-release buprenorphine subcutaneous injection (Sublocade®) for the treatment of opioid use disorder, done over a 48-hour period. Both patients experienced minimal withdrawal symptoms throughout induction and no adverse effects. This technique, also called the IPPAS method, has similar advantages to that of rapid micro-induction, in addition to reduced nurse workload, steadier blood level concentrations of buprenorphine, and increased accuracy of dose administration. In addition, this technique is more outpatient friendly with less reliance on patients to time their own doses. There is a need for further research among larger patient populations to assess the safety and efficacy of this induction method using transdermal buprenorphine in different settings and patient demographics, including youth with OUD.

A population at increased risk of overdose, with lower rates of accessing pharmacological treatment, are youth (15-24 years old). Since 2018, over 1000 people between the age of 0 to 29 have died from illicit drug toxicity in Canada. Despite the effectiveness of opioid agonist treatment for opioid use disorder, only 2.4% of youth who use opioids receive pharmacological treatment compared to 26.3% of adults who use opioids. Another study found that less than 2% of youth who have suffered from a nonfatal opioid-related overdose received the recommended evidence-based pharmacotherapy. Understanding perceptions of OAT among this highly vulnerable young population is essential in combating barriers and harmful perceptions of treatment that lead to reduced treatment access. Few studies have investigated

these perceptions among youth. We conducted a qualitative study involving semi-structured interviews among twelve young people with opioid use disorder at Foundry Vancouver-Granville clinic in Vancouver, British Columbia. The findings of this study highlight the complexities involving individual experiences of initiation and retention of opioid agonist treatment, as well as the unique barriers of treatment that young people with opioid use disorder experience. The four major themes identified during thematic analysis include: preparedness to begin opioid agonist treatment, effects of opioid agonist treatment on personal relationships and social life, navigating the pharmacological treatment options, and the role of the healthcare worker. The data from this qualitative research study on the experiences of pharmacological treatment among youth with opioid use disorder can be used to inform future research efforts, clinical practice, and policy change to improve the treatment and social supports available for young people struggling with opioid misuse. Future research is essential to further develop our understanding of young people, and their experiences seeking and retaining opioid agonist treatment for opioid use disorder.

Keywords: Opioid agonist treatment, Opioid use disorder, Perceptions, Youth, Transdermal buprenorphine, Induction

PREFACE

The research presented in Chapter 3 was conducted with the Complex Pain and Addiction Services Team at Vancouver General Hospital in Vancouver, British Columbia. Written consent was obtained from both patients. Dr. Pouya Azar, James Wong, Dr. Martha Ignaszewski, and Hannah Schneiderman were responsible for data collection; Hannah Schneiderman was responsible for writing of the case series.

The research presented in Chapter 4 was conducted with the Complex Pain and Addiction Services Team and Foundry Vancouver-Granville Clinic Team in Vancouver, British Columbia. The study was approved by the Behavioural Research Ethics Board (BREB) of the University of British Columbia (H21-03769). Hannah Schneiderman, with input from the supervisory committee, designed the study. James Wong and Hannah Schneiderman were responsible for data collection. Hannah Schneiderman was responsible for data analysis. Hannah Schneiderman was responsible for writing of the thesis. There are no publications of the above research studies thus far.

DECLARATION

This is to certify that the work I am submitting is my own and has not been submitted for another degree, either at University College Cork or elsewhere. All external references and sources are clearly acknowledged and identified within the contents. I, Hannah Schneiderman, have read and understood the regulations of University College Cork concerning plagiarism and intellectual property.

Signature: 

Date: January 5th, 2022

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LIST OF ABBREVIATIONS

ARYS- at-risk youth study

ASAM- The American Society of Addiction Medicine

BC- British Columbia

BCCSU- The British Columbia Centre on Substance Use

BREB- Behavioral Research Ethics Committee

BUP-XR- long-acting buprenorphine subcutaneous injection

CDC- Centres for Disease Control and Prevention

COWS- clinical opiate withdrawal scale

CPAS- Complex Pain and Addiction Services

DA- dopamine

DSM-5- Diagnostic and Statistical Manual of Mental Disorders

DTES- downtown east side

FDA- U.S. Food and Drug Administration

GPCR- G protein-coupled receptor

HCV- hepatitis C virus

HDM- hydromorphone

HIV- human immunodeficiency virus

iOAT- injectable opioid agonist treatment

LC- locus coeruleus

MAT- medication-assisted treatment

MMT- methadone maintenance treatment

MOUD- medications for opioid use disorder

NA- noradrenaline

NAc- nucleus accumbens

NAOMI- North American Opiate Medication Initiative

NIMBY- Not-In-My-Back-Yard

NMDA- N-methyl-D-aspartate

NSDUH- National Survey on Drug Use and Health

OAT- opioid agonist treatment

OPS- overdose prevention sites

OUD- opioid use disorder

PPO- pre-printed orders

RAAM- rapid access to addiction medicine

RCT- randomized control trial

SALOME- Study to Assess Longer-term Opiate Medication Effectiveness

SAMSHA- The Substance Abuse and Mental Health Services Association

SIS- supervised injection sites

SL- sublingually

SROM- slow-release oral morphine

SUD- substance use disorder

TA- thematic analysis

TD- transdermal

THN- take-home naloxone

TOSCA- Toronto and Ottawa Supervised Consumption Assessment Study

VTA- ventral tegmental area

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DEDICATION

To those who have lost their lives to addiction and those who are suffering from addiction.

"Not every story has a happy ending…but the discoveries of science, the teachings of the heart, and the revelations of the soul all assure us that no human being is ever beyond redemption. The possibility of renewal exists so long as life exists. How to support that possibility in others and in ourselves is the ultimate question."

-Gabor Maté, In the Realm of Hungry Ghosts: Close Encounters with Addiction

CHAPTER 1: INTRODUCTION

OPIOIDS: INDICATIONS AND ADVERSE EFFECTS

For thousands of years, opioids have been used for the treatment of pain [1]. In fact, the earliest records of opium prescriptions were discovered in 8000-year-old hardened Sumerian clay-tablets [2] [3]. Ancient civilizations, including the Greeks, Romans, Arabs, Egyptians, and Chinese, used opium for its analgesic properties [1]. Opioids are referenced in the Bible and the Odyssey, and notable minds and leaders including Homer, Napoleon, Marcus Aurelius, and Hitler, were known for their opioid use [3].

Opium alkaloids, an organic compound with strong biological activities in man, are derived from the opium poppy seed and referred to as opium [1]. The term opiates describe naturally occurring alkaloids, including codeine and morphine [1]. The term opioid, however, is broader and describes all compounds that work at the opioid receptors [1]. Opioid receptors are found throughout the central nervous system and peripheral tissue [1]. In response to a noxious or painful stimulus, endogenous peptides (dynorphins, enkephalins, endorphins) normally stimulate these receptors [4]. The first endogenous opioid, enkephalin, was only discovered and characterized in 1975 [1]. There are three sub-types of opioid receptors: mu, kappa, and delta receptors [1].

Today, opioids are most often used for acute pain treatment, such as pre-operative sedation, trauma, surgical or diagnostic procedures, and acute medical problems [5]. Opioids can also be used in the treatment of moderate to severe pain that is inadequately treated or unresponsive to nonopioid analgesic treatments [5]. The goal in prescribing opioids for pain treatment is to optimize effectiveness in analgesia and quality of life, and to minimize nontherapeutic adverse effects [5]. To ensure safe and effective opioid use, medication regimens must be patient-centered and individualized. Due to the opioid crisis and rising concerns of opioid use disorder (OUD) development, many patients are at risk of undertreatment of pain; ethnic group disparities in pain control are of particular concern [6]. Inequities in pain assessment and management among minority populations, most documented among Black Americans, is largely caused by healthcare bias and systemic racism [6] [7].

Common adverse effects of opioids include gastrointestinal side effects (nausea, vomiting, constipation), central nervous system effects (dizziness, sedation, euphoria, dysphoria, restlessness, confusion), genitourinary effects (urinary retention), cholinergic effects (bradycardia, xerostomia), weight gain, diaphoresis, pruritis, urticaria, and cough suppression [1]. These effects are most often inseparable from

their desired effect; therefore, an important goal of chronic opioid therapy is to maintain a balance of benefits relative to risks [8]. An important and potentially life-threatening adverse effect of opioids is respiratory depression [1]. Risk of respiratory depression increases when opioids are used in conjunction with sedatives, such as benzodiazepines or alcohol, and in patients with pulmonary compromise [9,10]. Physical dependence is possibly the most common side effect of chronic opioid use [1]. Dependence results in withdrawal symptoms when opioids are abruptly discontinued or when an opioid antagonist is given; characteristic withdrawal symptoms include, nausea, vomiting, diarrhea, abdominal pain, fever, hypertension, tachycardia, tachypnea, restlessness, rhinorrhea, lacrimation, sneezing, yawning, sweating, tremor, myalgias, and piloerection [1,11].

Overall, the use of opioids has been a standard of care in patients with acute pain and moderate to severe pain who are unresponsive to nonopioid treatments [5]. In recent decades, the medical use of strong opioids has been re-evaluated due to rising concerns of opioid-related deaths and opioid misuse [12].

NEUROBIOLOGY OF OPIOID USE DISORDER

PHARMACOLOGY OF OPIOIDS

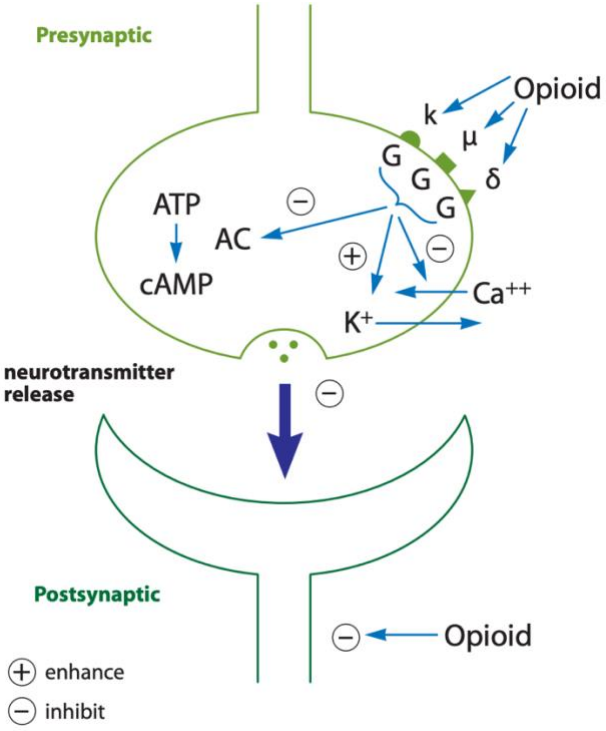
The risk of developing opioid addiction is a complex interaction between environmental, biological, and genetic factors [13]. To understand the development of tolerance, dependence, withdrawal, and opioid addiction, I will begin by outlining the pharmacology of opioids. Opioids act on an inhibitory class of G protein-coupled receptors (GPCR), including mu (μ), kappa (κ), and delta receptors (δ) [4 14]. These receptors are named after their prototype agonists: morphine, ketocyclazocine, and delta-alanine-delta-leucine-enkephalin, respectively [1]. Overall, mu and delta receptors mediate the analgesic and addictive properties, whereas kappa receptors have limited clinical analgesic properties due to undesirable effects including anxiety, hallucinations, and dysphoria [14]. The analgesic effects at mu, delta, and kappa opioid receptors by endogenous peptides, opioid agonists, and opioid antagonists, are further outlined in Table 1 below.

TABLE 1: ANALGESIC EFFECTS OF OPIOID RECEPTORS [1]

	Mu (μ)	**Delta (δ)**	**Kappa (κ)**
	• Mu 1 – Analgesia • Mu 2 – Sedation, vomiting, respiratory depression, pruritus, euphoria, anorexia, urinary retention, physical dependence	• Analgesia, spinal analgesia	• Analgesia, sedation, dyspnea, psychomimetic effects, miosis, respiratory depression, euphoria, dysphoria, dyspnea
Endogenous Peptides			
Enkephalins	Agonist	Agonist	
β-Endorphin	Agonist	Agonist	
Dynorphin A	Agonist		Agonist
Agonists			
Morphine	Agonist		Weak agonist
Codeine	Weak agonist	Weak agonist	
Fentanyl	Agonist		
Meperidine	Agonist	Agonist	
Methadone	Agonist		
Antagonists			
Naloxone	Antagonist	Weak Antagonist	Antagonist
Naltrexone	Antagonist	Weak Antagonist	Antagonist

Opioid receptors are located on the presynaptic terminals of the nociceptive C fibres and A delta fibers, and "when activated by an opioid agonist, will indirectly inhibit these voltage-dependent calcium channels, decreasing cAMP levels and blocking the release of pain neurotransmitters such as glutamate, substance P and calcitonin gene-related peptide from the nociceptive fibres, resulting in analgesia" [1]. The opioid receptors' location and mechanism of action is outlined in **Figure 1** below.

FIGURE 1: OPIOID RECEPTORS LOCATION [1]



Opioids and endogenous peptides activate presynaptic receptors on GABA neurons which inhibit the release of GABA in the ventral tegmental area (VTA) [1]. GABA, or gamma-aminobutyric acid, is the most common inhibitory neurotransmitter in the central nervous system; "the VTA is comprised of a group of neurons located around the midline of the midbrain floor and contains mainly neurons that produce" dopamine [15]. Dopamine (DA) is a neurotransmitter present in brain regions that regulate emotion, feelings of pleasure, movement, and motivation [16]. The inhibition of "GABA allows dopaminergic neurons to fire more vigorously, and the extra dopamine in the nucleus accumbens (NAc) is intensely pleasurable" [1]. The VTA is the anatomical site critical to the development of behavioural reward following repetitive drug use [15].

Opioids "may antagonize N-methyl-D-aspartate (NMDA) receptors, activating the descending serotonin and noradrenaline pain pathways from the brain stem" [1]. Activation or stimulation of the NMDA receptors can lead to neuropathic pain and the development of tolerance [1].

TOLERANCE, PHYSICAL DEPENDENCE, AND WITHDRAWAL

Opioid tolerance is defined as the diminishment of opioid effects caused by repeated exposure to the substance [11]; essentially, drug effects including analgesia and reward require higher doses to achieve similar effects. Acute desensitization of mu receptors is the initial step in the development of tolerance to opioids [17]. Long-term adaptive changes at the cellular, synaptic, and network levels also lead to opioid tolerance [18].

Physical dependence results from long-term use of opioids, and withdrawal symptoms occur when opioids are abruptly discontinued or when an opioid antagonist is given [1]. Withdrawal symptoms, or the signs of physical dependence, are less intense when the opioid is discontinued gradually [19]. The locus coeruleus (LC) is a region of the brain contributing to opioid dependence and the production of opioid withdrawal symptoms, located in the brainstem [16 20]. Neurons in the LC produce noradrenaline (NA), which is distributed throughout the brain [16]. NA stimulates breathing, blood pressure, wakefulness, among other vital functions. When opioid molecules attach onto mu opioid receptors in the LC, the production of NA is supressed [16]. Suppression of NA production by the LC results in slowed respiration, low blood pressure, and drowsiness [16]. These effects are seen in opioid intoxication [16]. With increased exposure to opioids, the LC neurons increase their level of activity and produce more NA [16]. When opioids are not present to suppress the enhanced production of NA in the LC, extremely unpleasant withdrawal symptoms occur including anxiety and diarrhea [16].

The mesolimbic reward system, containing the ventral tegmental area, is another brain region that contributes to the production of opioid withdrawal symptoms [16]. Opioid tolerance causes reduction of DA released by the VTA into the NAc [16]. This reduction of DA into the NAc can result in reduced feelings of pleasure from normally rewarding activities, including eating and sex [16].

ADDICTION: OPIOID USE DISORDER

Addiction has been defined as a chronic, neurobiological disease [11]. Genetic, psychosocial, and environment factors contribute to the development of addiction [11]. The term addiction has been stigmatized in society, and therefore the terms opioid use disorder or substance use disorder are widely preferred and used.

The allostatic brain changes due to opioid use is what continues many OUD behaviours like relapse and drug-seeking [21]; allostasis is a stress-specific term that refers to the biological mechanism that protects the body from both internal and external stresses, by maintaining internal homeostasis [22]. In this case, the

external stress is opioid consumption. This, however, is not the only factor contributing to the development of addiction. Current literature acknowledges that craving is in a complex interplay with reward and motivation, stress and negative affect, and learning, memory, and executive functioning [21]. "Wanting" is the preoccupation of craving and desire to take more drugs, while "liking" is defined as pleasurable experience associated with a drug [21]. Genetic factors can explain a substantial degree of familial aggregation of substance use disorder [23]. A study investigating familial transmission of substance use disorder found an 8-fold increased risk of drug disorders among the relatives of probands with substance use disorders including opioids, cocaine, cannabis, and alcohol [23].

The Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) is used to determine a diagnosis of opioid use disorder. OUD is defined in the DSM-5 as a problematic pattern of opioid use leading to clinically significant impairment or distress [24]. Additional screening tools designed for youth specifically include GAIN-SS and CRAFFT; these tools assess for substance use disorders, as well as co-occurring mental health disorders [25]. Table 2 below outlines the DSM-5 criteria for opioid use disorder, including both psychosocial and environment factors.

TABLE 2: DSM-5 CRITERIA FOR OPIOID USE DISORDER [24]

DSM-5 Criteria for Opioid Use Disorder		
1	Opioids are often taken in larger amounts or over a longer period than was intended	The presence of at least 2 of these symptoms indicates an Opioid Use Disorder (OUD) The severity of the OUD is defined as: MILD: The presence of 2 to 3 symptoms MODERATE: The presence of 4 to 5 symptoms SEVERE: The presence of 6 or more symptoms
2	There is a persistent desire or unsuccessful efforts to cut down or control opioid use	
3	A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects	
4	Craving or a strong desire to use opioids	
5	Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home	
6	Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids	
7	Important social, occupational, or recreational activities are given up or reduced because of opioid use	
8	Recurrent opioid use in situations in which it is physically hazardous	
9	Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by opioids.	
10	Tolerance,* as defined by either of the following: a) Need for markedly increased amounts of opioids to achieve intoxication or desired effect b) Markedly diminished effect with continued use of the same amount of opioid	
11	Withdrawal,* as manifested by either of the following: a) Characteristic opioid withdrawal syndrome b) Same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms	

* Patients who are prescribed opioid medications for analgesia may exhibit these two criteria (withdrawal and tolerance), but would not necessarily be considered to have a substance use disorder.

In summary, the definition of "addiction" has been the subject of much debate over recent decades. Unfortunately, stigmatization and misinformation of addiction within the healthcare system and society causes devastating effects on individuals living with opioid use disorder [26].

THE OPIOID CRISIS IN NORTH AMERICA

The opioid crisis is a profound public health crisis, with devastating impacts on individuals, families, and communities in North America [27,28]. The opioid overdose crisis can be outlined by three distinct waves, with an emerging fourth wave of growing concern [29]. The first wave began in the early 1990's with increased prescribing of opioids including methadone, oxycodone, and hydrocodone [30]. The second wave began in 2010 with increases in overdose deaths involving heroin, as heroin overdose doubled in the U.S. from 2010 to 2012 [31]. The increase in overdose deaths involving synthetic opioids, particularly fentanyl, marked the beginning of the third wave of the opioid epidemic in 2013 [32]. The market for fentanyl is continuously changing; fentanyl can now be found in combination with heroin and cocaine [33]. Data suggests that a fourth wave has begun, characterized as a stimulant/opioid epidemic with mental illness co-morbidities being more evident [29]. From 2017-2018, 63% of opioid deaths tested positive for benzodiazepine, cocaine, or methamphetamine [10]. In 2016, the Centres for Disease Control and Prevention (CDC) found that over 50% of opioid overdose deaths involved fentanyl, and over 50% of deaths that tested positive for fentanyl or fentanyl analogues (carfentanil, furanylfentanyl, acetylfentanyl) also tested positive for additional illicit drugs [34]. The current rise in stimulant-related deaths is heavily intertwined with the opioid epidemic [33].

In Canada, the opioid crisis is growing rapidly, driven by both prescription and illegal opioid use [28]. The regions within Canada most affected are Western Canada (British Columbia (BC), Alberta) and the Northern Territories (Northwest Territories, Yukon) [28]. The 2021 BC Coroner's Service found that illicit drug toxicity ranks second only to cancer in terms of years of life lost [35]. In the US, the opioid overdose crisis is equally devastating. Opioid-related overdose deaths in the US has risen significantly over the last decade, with 21,088 deaths in 2010, to 47,802 deaths in 2018, and reaching 68,630 deaths in 2020 [36]. 9.5 million people aged 12 or older, or 3.4% of the population, misused opioids in 2020, according to the National Survey on Drug Use and Health (NSDUH) [37]. To combat the rising opioid overdose epidemic, opioid agonist treatment (OAT) and harm reduction services have become more readily accessible, and patient centered.

AIMS AND OBJECTIVES OF THESIS

Chapter 2 is a narrative review where I sought to summarize the current body of literature on the socio-demographic factors, psychiatric history, and substance use behaviour that influences opioid misuse and overdose, treatment and management of OUD, and barriers and perceptions of OAT. Chapter 2 will highlight the gaps in existing literature and understanding that provided a basis for formulation of the overall aims of this thesis.

The overall aim of Chapter 3 is to present two cases in which inpatients with opioid use disorder were successfully induced onto Sublocade®, a long-acting buprenorphine subcutaneous injection (BUP-XR), using transdermal (TD) buprenorphine, Butrans®. This chapter will describe the unique benefits of this novel induction method.

The aim of Chapter 4 is to identify and describe the perceptions, understanding, and barriers of OAT among youth with OUD through a qualitative study. This chapter will describe the methodology and results of this study, as well as compare results with existing literature, and outline future areas of research.

CHAPTER 2: NARRATIVE REVIEW

OVERVIEW

A pillar of the public health response to the opioid crisis in North America is opioid agonist treatment. OAT, such as buprenorphine or methadone, are proven to be effective in reducing illicit opioid use among those with opioid use disorder [38,39]. In addition, OAT can improve physical and psychological health, and social functioning, in a diverse range of settings and population demographics [40]. Most importantly, retention in OAT is associated with substantial decreases in morbidity and mortality among people with OUD [41,42]. To achieve optimal effectiveness of OAT, the approach to treatment must be patient-oriented and individualized. This functions to reduce barriers, support facilitators, and tackle stigmatization influencing initiation and retention of OAT.

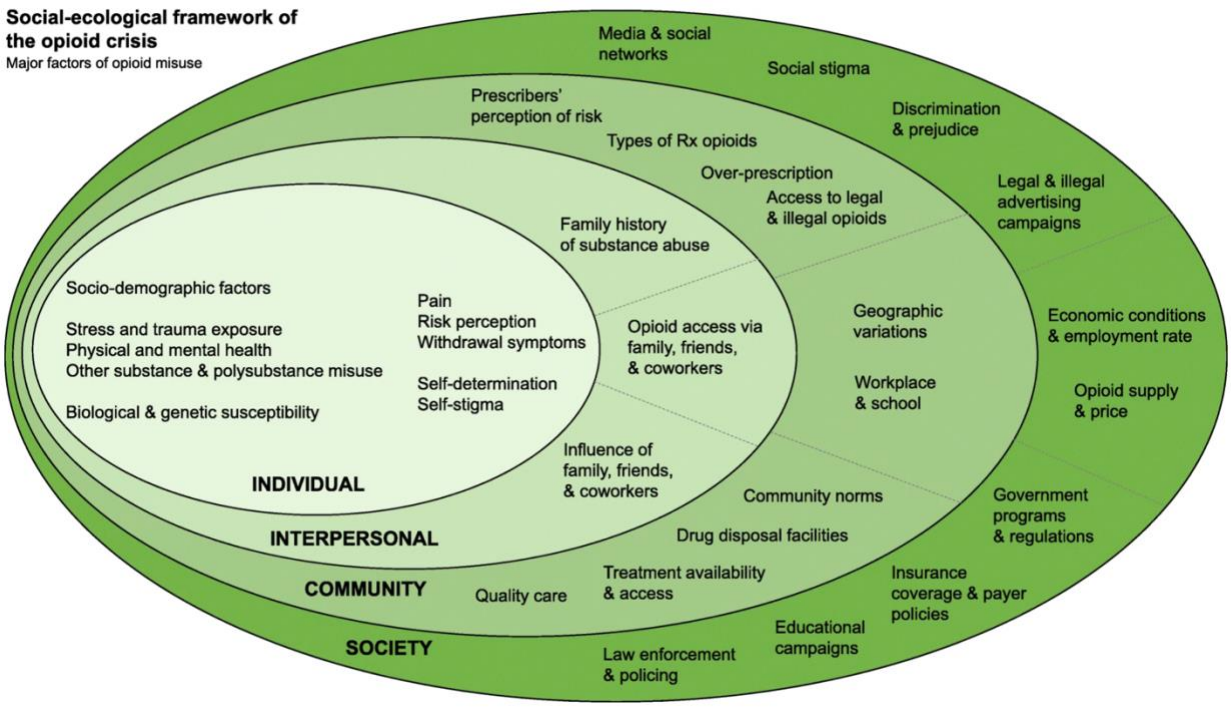
A population at increased risk of overdose, with lower rates of accessing pharmacological treatment, are youth. Since 2018, over 1000 people have died from illicit drug toxicity in Canada, ages 0 to 29 [43] . Youth, ages 15 to 24, represent the highest proportion of intentional, opioid poisoning hospitalization in Canada [44]. In 2021, the BC Centre for Disease Control found that illicit drug toxicity was the leading cause of death for those aged 19 to 39 years, accounting for 45% of all deaths [45]. The most effective approach to decreasing the morbidity and mortality of people with opioid use disorder is OAT [42,46]. Despite the effectiveness of OAT, less than 2% of youth who have suffered from a nonfatal opioid-related overdose received the recommended evidence-based pharmacotherapy [42,46]. Understanding perceptions of OAT among this highly vulnerable young population is essential in combating barriers and harmful perceptions of treatment that lead to reduced treatment access. Few studies have investigated these perceptions among youth.

This narrative review provides an overview of the epidemiology of adults and youth with OUD, highlighting the risk and protective factors for the development of OUD and opioid-related overdose. These factors contextualize the experiences of OAT among people living with OUD. Next, I will provide an overview of the treatment and management of opioid use disorder for youth and adults, including OAT and harm reduction practices. Finally, I will summarize the current literature that analyzes barriers, perceptions, and experiences of OAT among youth and adults, while highlighting areas for further research.

FACTORS INFLUENCING OPIOID MISUSE AND OVERDOSE

Opioid misuse and overdose are influenced by socio-demographic factors such as age, gender, ethnicity, education level, employment status, and housing status [47]. In addition, psychiatric history and substance use behaviours such as polysubstance use, type of opioid used, and route of administration, can influence opioid misuse and risk of overdose [48] [49]. Risk of opioid misuse and overdose is complex and multifactorial, and understanding these factors is essential for clinical practice and policy change [50]. In addition, these risk factors oscillate during transition periods such as induction of pharmacological treatment, discharge from treatment or hospital, and upon release from incarceration [50]. A study examining the socio-ecological framework of the opioid crisis found a multitude of risk factors for opioid misuse on four main levels: society, community, interpersonal, and individual [47]. Figure 2 below demonstrates the intricacies of risk factors for opioid misuse [47].

FIGURE 2: SOCIO-ECOLOGICAL FRAMEWORK OF THE OPIOID CRISIS [47]



SOCIO-DEMOGRAPHIC FACTORS

According to The Substance Abuse and Mental Health Services Association (SAMSHA) the following socio-demographic factors are associated with increased risk of opioid overdose in the U.S.: male, low income, lack of permanent housing, low education level, not married, LGBT identity, and drug injection [51]. In a Canadian context, similar risk factors are seen. A study examining determinants of overdose incidents

in five Canadian cities found that 97% of subjects were living on the street and 25% experienced a non-fatal overdose within the past 6 months [52]. Other determinants found included male and white ethnic background [52].

Age and gender are significant risk factors for opioid misuse. Drug toxicity deaths in BC from 2011-2021 have remained high among men, while female rates of death began trending upward in 2021 [43]. Across Canada, approximately 74% of deaths occur among males [28]. From 1999 to 2017, the death rate of synthetic opioid overdose among women aged 30-64 in the United States rose by 1,643% [53]. In 2020, 43 was the median age of those who died from illicit drug toxicity in BC [35]. According to the BC Centre for Disease Control, illicit drug toxicity was the leading cause of death for those aged 19 to 39 years, and the second-leading cause of death among those aged 40 to 59 years, accounting for 20% of all deaths [45]. A U.S. longitudinal cross-sectional study found similar age and gender risk factors; from 1999-2019, nearly 80,000 persons aged 55 or older died due to opioid overdose; rates varied substantially by sex, race, and ethnicity over time [54]. Nearly 80% were 55-64 years old, and 59% were men [54].

Ethnicity is an important risk factor to consider when integrating culturally appropriate care and creating change through a racial equity lens [55]. First Nation populations are among those at greatest risk in Canada; BC and Alberta reports found that Indigenous people were three times more likely to die from an opioid related overdose than their Non-First Nations counterparts [56,57]. First Nation women died at nearly 10 times the rate of other female BC residents [58]. Ethnic disparities are also seen in the U.S., as Black and Native American populations are at significantly increased risk of overdose compared with white people [59].

Income, employment, and housing status are additional overdose and opioid misuse risk factors [47]. A U.S. population-based study examining the epidemiology of emergency department visits for opioid overdose found that lower household income was associated with frequent emergency department visits [60]. Another U.S. study found that disability, unemployment, and unmarried status were associated with OUD [61]. A systematic review on socioeconomic marginalization and opioid-related overdose found that criminal justice system involvement, lower income, unemployment, social support, homelessness, and lower education status were risk factors for overdose [62]. Overall, these socio-demographic factors are important to address when creating a personalized management plan for OUD [63].

PSYCHIATRIC FACTORS

Co-occurring substance use and psychiatric disorders are common among adults with OUD and increase the risk of morbidity and mortality among these individuals; in addition, these co-occurring diagnoses were found to worsen psychosocial functioning and substance use outcomes [64] . Data from the NSDUH from 2015-2017 found that 64.3% of adults with OUD suffered from mental illness in the past year [48]. In Canada, 43% of individuals with opioid-related hospitalizations were found to have a psychiatric co-diagnosis [65]. Individuals pharmacologically treated for OUD with buprenorphine-naloxone or methadone were found to have higher rates of psychiatric disorders [66].

A Canadian study examining the sensitivity and specificity of self-reported psychiatric diagnoses among 683 participants with OUD found that 24% reported having a psychiatric disorder, and only 64% of participants met criteria for a psychiatric diagnosis [67]. Meanwhile, 75% of the individuals who did not report a psychiatric co-morbidity did meet criteria for a diagnosis [67].

Some risk factors for co-occurring OUD and severe mental illness include male gender, younger age, never been married, use of marijuana before age 18, and ease of obtaining certain drugs [68]. Gender difference in psychiatric co-morbidities among populations with both opioid and sedative use disorders have been identified; post-traumatic stress disorder and antisocial personality disorder were associated with both women and men with opioid and sedative use disorders, while depressive disorder and schizotypal personality disorders were associated with women only [69].

Due to the increased morbidity and mortality of co-occurring psychiatric and substance use disorders, psychiatric assessment of individuals with OUD is important in providing personalized and effective medical care [70]. Further research on the implications of psychiatric co-morbidities on populations with OUD on OAT can be used to improve pharmacological management of both psychiatric and substance use disorders [71].

SUBSTANCE USE BEHAVIOURS

Substance use behaviours are important risk factors influencing opioid misuse and overdose; these behaviours include polysubstance use, the type of opioid used, and the route of administration.

As seen in the fourth wave of the opioid crisis, polysubstance abuse is driving opioid-related overdose deaths [29]. In Canada, 46% of hospitalizations for OUD were found to have a co-occurring substance related diagnosis, including alcohol, cocaine, stimulants, sedatives, hallucinogens, or

cannabinoids [65]. Risk factors for non-fatal opioid overdose include daily use of heroin, benzodiazepines, cocaine or methamphetamine, binge drug use, public injecting, and previous non-fatal overdose [72].

The risk of overdose is also influenced by route of administration. In general, a high bioavailability equates to a high rate of absorption and increased risk of overdose [49]. Bioavailability is the proportion of the drug that reaches the systemic bloodstream; this is determined by the type of metabolism the drug undergoes, the dose taken, and the purity of the drug [49]. The risk of overdose in descending order is intravenous, intramuscular, inhalation, intranasal, and oral [49]. In addition to increased overdose risk, injection drug users are at increased risk of contracting human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infections [73].

Finally, the types of opioids used can significantly influence risk of overdose. Illicitly manufactured fentanyl is driving the increased mortality seen in the last decade [74,75], as "fentanyl is approximately 50 times more potent than heroin and 100 times more potent than morphine" [76]. A U.S. cross-sectional survey found that a quarter of participants who used drugs reported a preference for fentanyl compared to other opioids [75]. Fentanyl adulteration is found in heroin, counterfeit opioid tablets, as well as stimulants such as cocaine [75,77].

EPIDEMIOLOGY OF YOUNG PEOPLE WITH OPIOID USE DISORDER

The World Health Organization (WHO) and United Nations defines 'youth' as people aged 15-24 years old; WHO defines 'adolescents' as individuals between 10-19 years old and 'young people' as people between 10-24 years old [78]. OUD and opioid-related overdose have become increasingly prevalent among young populations; Illicit drug toxicity deaths in British Columbia among people 0-18 years old have increased by 7-fold, with 4 deaths in 2011 to 29 deaths in 2021 [43]. In the U.S., 286,000 people or 0.9% of adolescents aged 18 to 25 were found to have an opioid use disorder in the past year, and 80,000 people or 0.3% of adolescents, aged 12 to 17 [79].

A systematic review on the risk factors for drug overdose among young people found that polysubstance use, psychiatric comorbidities, unstable housing, and witnessing a drug overdose death were significant predictors of overdose death in young people, specifically [80]. A study analyzing data from the NSDUH in the U.S. found that 6% of adolescents between 12-17 years old reported nonmedical prescription opioid use, and 8% reported a major depressive episode in the past year [81]. Among adolescents who used

nonmedical prescription opioids, 15% reported past year opioid dependence, and 20% reported a major depressive episode [81].

Children exposed to substance use disorders (SUD) are at higher risk of developing a SUD themselves, and approximately 8.7 million, or 1 in 8 children in the US aged 17 or younger live in a household with at least one parent who has a SUD [82,83]. The impact of opioid-use on families and children is severely under-researched, yet a major contributor to the global burden of adult drug misuse, especially in minority ethnic and indigenous groups [84]. Only 4% of information in addiction textbooks, and an estimated 2% of federally funded addiction research in the US, focuses on family or child issues related to substance misuse [85,86].

In British Columbia, efforts are being made to research more into at-risk youth with opioid use disorder, as there is currently a lack of research internationally. The At-Risk Youth Study (ARYS) follows over 900 youth, exploring the individual, social, economic, and environment factors that influence the health and well-being of street-involved youth in Vancouver [87]. In addition, the Improving Treatment Together Project aims to improve the experiences and outcomes of substance use services in the local community for young people who use opioids in Vancouver [88].

TREATMENT AND MANAGEMENT OF OPIOID USE DISORDER

The evolution of the treatment and management of opioid use disorder over recent decades can be attributed to increased research efforts, activism and advocacy among communities, and policy change [89]. This section will discuss the safety and efficacy of available pharmacological treatments such as withdrawal management, opioid agonist therapies including buprenorphine and methadone, specialist-led alternative approaches including slow-release oral morphine and injectable hydromorphone, and safe supply medications including sustained-release oral morphine tablets and hydromorphone. I will outline important harm-reduction practices that have been proven to reduce the morbidity and mortality of OUD, in addition to youth specific treatment and management. First, I will discuss the continuum of care, a framework used for the treatment of opioid use disorder.

THE TREATMENT CONTINUUM

The continuum of care for the treatment of opioid use disorder describes a range of services, including screening, assessment, brief interventions, rapid access clinics and community outreach,

withdrawal management, pharmacological interventions, psychosocial interventions, ongoing care, and harm reduction services [90]. The continuum of care is customizable for specific needs and goals and allows for individualistic care of OUD [90]. Table 3 below was developed by the Canadian Centre on Substance Use and Addiction.

TABLE 3: THE CONTINUUM OF CARE [90]

Continuum of Care								
Harm Reduction								
Screening	Assess-ment	Brief Interven-tions	Rapid Access Clinics	Community Outreach	Withdrawal Manage-ment	Pharmaco-logical Interven-tions	Psychosocial Interven-tions	Recovery, Sustaining Wellness & Ongoing Care

Screening and Assessment for opioid use disorder commonly overlap in practice [90]. Screening is used to identify individuals at risk for experiencing harms from opioids [91]. Factors such as polysubstance use, mental health, and physical health concerns should be addressed during screening [92]. Early recognition of physical dependence on opioids is essential [93]. This often involves primary care-based screening questions on drug use [94]. Assessment, however, functions to identify OUD, determine severity of OUD, and intensity of treatment to be considered for the individual [91]. In addition, appropriate laboratory tests should be completed including liver function tests, Hepatitis B and C tests, HIV tests, and urine or oral fluid drug screening [91]. Among those at highest risk of contracting HIV and HCV infections are injection drug users [73]. As displayed in Table 2, the DSM-5 criterion is commonly used to establish a diagnosis of OUD [24].

Brief interventions refer to motivational interviewing regarding the harms of opioid and polysubstance use. The Screening, Brief Intervention, and Referral to Treatment (SBIRT) framework is commonly used in any clinical setting [95]. Education for healthcare workers in all settings, including the emergency department, is important for provider knowledge and understanding of available social, behavioural, and pharmacological treatments, as well as OUD [96,97]. SBIRT is an evidence-based approach to identify and deliver early intervention and treatment to individuals struggling with substance use disorders [95]. The focus of SBIRT is to increase insight regarding substance use and motivate the patient to implement behavioural change; a non-judgemental approach is essential [95]. Brief educational video interventions and telephone-delivered interventions have also shown effectiveness in reducing opioid overdose and positive attitudes towards medications for OUD [98,99].Mindfullness-based interventions promote non-judgemental

awareness of substance use and can be another beneficial tool for patients with significant trauma history, with the potential to reduce substance use [100].

Rapid access clinics play a vital role in providing timely, low barrier access to medical treatment and addiction specialists; referral to rapid access clinics typically takes a few days [90]. The Rapid Access to Addiction Medicine (RAAM) Clinic in Toronto, Ontario found that patients referred by their primary care physicians or the emergency department demonstrated higher rates of opioid abstinence compared to those who did not access RAAM; in addition, 65% of patients with OUD were prescribed buprenorphine at RAAM, which lowers opioid overdose risk [101]. Rapid intervention is effective in reducing emergency department visits and wait times; a randomized control trial (RCT) comparing delayed versus rapid intervention found that providing immediate access to addiction services results in reduced emergency department visits in 6 months [101,102].

Community outreach is broad in practice; examples include education, harm reduction resources, and service referrals provided in a community setting among individuals who use drugs [90,103]. Harm reduction services will be discussed in further detail below. Some best practices for community outreach include gaining the trust of people who use drugs, conducting outreach at times of greatest risk such as evening or early morning, and providing sufficient training and supports for outreach workers [103].

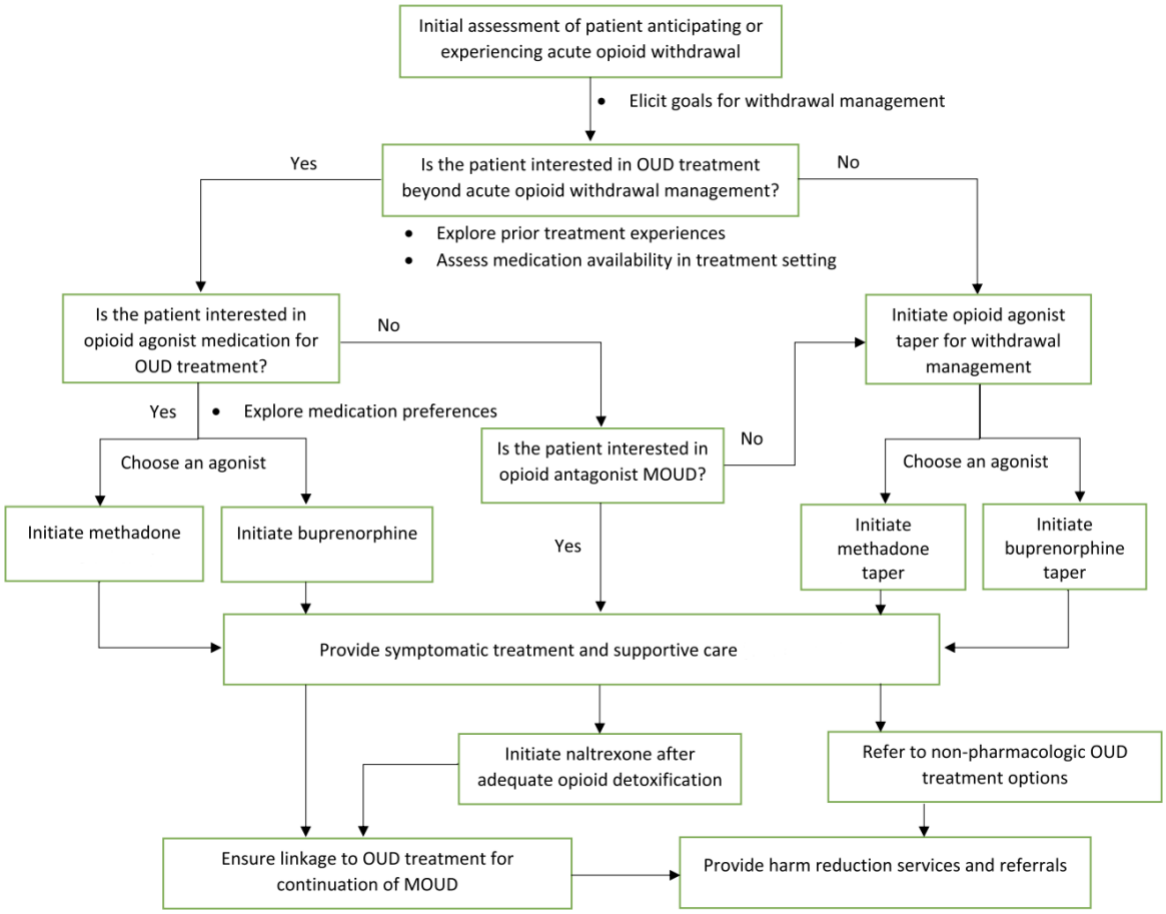
Withdrawal management is preferably accompanied with long-term addiction care, including OAT, intensive outpatient treatment and/or residential treatment, and is not considered an effective or safe independent treatment for OUD [90]. The primary goals of opioid withdrawal management are to engage patients in initiating OAT and harm reduction, and relieve acute suffering of opioid withdrawal [104]:

Alpha$_2$-adrenergic agonists and supportive medications for specific symptoms provide the basis of non-opioid withdrawal treatment [93]; clonidine and lofexidine are commonly used alpha$_2$-adrenergic receptor agonists [105]. Alpha$_2$-adrenergic agonists have been found more effective at reducing the severity of opioid withdrawal symptoms than placebo and can be used for withdrawal management [106,107]. Supportive medications target specific withdrawal symptoms such as insomnia, musculoskeletal pain, and nausea [104].

Opioid withdrawal can also be managed through opioid agonist tapers such as methadone taper or buprenorphine/naloxone taper [107]. Patients are encouraged to continue the MOUD treatment, however, if OAT is not continued, medically managed withdrawal with slow agonist tapers can take several days to weeks [104]. Figure 3 depicts a withdrawal management approach [104]. This figure also shows the option to

initiate onto naltrexone, an opioid antagonist, after adequate opioid detoxification [104]. Naltrexone can be considered for individuals seeking to abstain from opioids [108].

FIGURE 3: APPROACH TO OPIOID WITHDRAWAL MANAGEMENT [104]



Pharmacological interventions will be discussed further below. Psychosocial interventions can be done at an individual, family, or community level and is often provided alongside pharmacological therapy; examples of psychosocial intervention include cognitive behavioural therapy, behavioural couples therapy, or family therapy [90]. A study looking at the role of psychosocial factors on relapse in opioid dependence found higher self-efficacy was significantly associated with lesser odds of relapse, suggesting that an individualized treatment plan, aiming to improve psychosocial variables, can reduce relapse rates and improve effectiveness of pharmacological management of OUD [109]. In contrast, a systematic review comparing agonist maintenance treatments with psychosocial services versus agonist maintenance treatments alone found that "adding any psychosocial support to standard maintenance treatments does not add additional benefits" [110]. While some literature shows no benefit to the psychosocial treatment of

OUD, clinical practice guidelines recommend psychosocial treatments to be routinely offered, in addition to pharmacotherapies [111]. Recovery, sustaining wellness, and ongoing care, as per the continuum of care, recognizes that recovery is an individualized and personal experience; therefore, a combination of the above services can be utilized in recovery.

Overall, the continuum of care is a flexible and well-recognized framework for the recognition, management, and treatment of substance use disorders. To provide the most effective care, it is essential to address treatment challenges that arise and adapt the continuum of care appropriately; challenges may include racial and ethnic disparities, the COVID-19 pandemic, and stigmatization [112]. Ethnic disparities require a significant need for cultural adaptation of OAT and culturally grounded interventions [113]. Continual analysis of the effectiveness of the elements of the continuum of care is important to identify gaps in care, inform policy decisions, and improve health outcomes for individuals suffering from OUD [114].

OPIOID AGONIST THERAPIES

The term opioid agonist treatment, or OAT, is widely used throughout Canada. Terms such as medications for opioid use disorder (MOUD) or opioid maintenance treatment can also be used to describe OAT. Currently, there are three medications approved by the U.S. Food and Drug Administration (FDA) for treating opioid use disorder; these include the full opioid agonist methadone, the partial opioid agonist buprenorphine, and the opioid antagonist, extended-release naltrexone [115]. Naltrexone is an opioid receptor antagonist which blocks the euphoric effects of opioids [107]. In Canada, buprenorphine is the recommended first-line treatment for OUD, methadone is the second-line treatment option, and slow-release oral morphine (SROM) is given when buprenorphine and methadone are ineffective [107].

In 1964, researchers began to address the major public health problem of heroin use and developed an effective pharmacotherapy called methadone-maintenance treatment (MMT) [116]. Methadone is a synthetic opioid agonist that fully activates the mu-opioid receptors in the brain and is administered in liquid formulation [115]. It is long-acting, meaning that its effects last for an extended period of time [115]. In 2002, the FDA approved of buprenorphine for office-based treatment of opioid use disorder, making it the first accessible opioid medication in the U.S. in general doctors' offices [117]. Buprenorphine is a partial μ-opioid receptor agonist that strongly binds to the opioid receptors [118]. Buprenorphine is available in a variety of formulations, including sublingual (SL) tablets, skin patches, and extended-release parenteral formulations such as implant or injection [119].

Sublingual tablets containing buprenorphine alone are available, brand name Subutex® [119]. Suboxone® is comprised of a combination of buprenorphine/naloxone in a 4:1 ratio, given sublingually, and is the most common OAT given in Canada [120]. Generic buprenorphine-naloxone tablets are also now available [119]. Sublocade® is an extended-release, subcutaneous injectable formulation of buprenorphine, used for the management of moderate to severe OUD [121]. Sublocade is administered monthly, at a minimum of every 26 days, via abdominal subcutaneous injection [121]. On April 30th, 2020, Sublocade was made available in British Columbia [121]. Patients are commonly induced and stabilized on 8-24mg of SL buprenorphine/naloxone for a minimum of 7 days prior to their first dose of Sublocade [121]; novel induction methods will be discussed in greater detail in Chapter 3. Patients are commonly prescribed a starting dose of 300mg/month for 2 months, followed by maintenance doses of 100mg/month [121]. A maintenance dose of 300mg/month can be prescribed at the discretion of the treating prescriber [121]. On Nov 30th, 2017, the FDA approved Sublocade for use in the United States [122]. In May of 2016, the FDA approved the first extended-release buprenorphine implant, called Probuphine®, which has a 6-month duration [123]. Buprenorphine is also available as a transdermal patch, brand name Butrans® [124].

Each medication containing buprenorphine has unique advantages and disadvantages. A qualitative study conducted in the United Kingdom comparing implants and depot injections for treating opioid dependence found that participants identified "both benefits and concerns, and variable needs and preferences with respect to each delivery system" [122]. This study found that participants routinely reported an importance to know whether the medication contained an antagonist drug; the perception of long-acting OAT containing an antagonist drug was dependant on the participants motivation to achieve abstinence, due to the concern that antagonists would reduce effects of street opioids [122].

There are advantages and disadvantages when comparing methadone and buprenorphine-naloxone for the treatment of OUD. In a study comparing overdose mortality associated with methadone and buprenorphine opioid agonist therapies for opioid dependence, the risk of overdose was lower for buprenorphine than methadone [125]. Buprenorphine-naloxone has a lower risk of overdose due to the ceiling effect and partial agonist effect of buprenorphine [25]. While methadone is associated with better retention in treatment than buprenorphine, buprenorphine has been found to be associated with lower rates of continued use of illicit opioids [126]. Therefore, methadone may be considered in patients with low treatment retention [126]. A systematic review comparing buprenorphine versus methadone maintenance found that buprenorphine is less effective than methadone is retaining people in treatment when flexible dose regimens or a fixed and low dose regimen (2-6 mg per day) is prescribed [127]. At fixed doses,

buprenorphine (above 7 mg per day) and methadone (40 mg or more per day) are equally effective in suppression of illicit opioid use and retaining people in treatment [127]. A systematic review concluded that the most effective range for methadone is 60 to 100 mg/day [128]. The same study found that lower doses of methadone were less effective in reducing opioid and cocaine use [128]. Due to the reduced risk of injection and diversion of buprenorphine-naloxone, a more flexible dosing schedule with take-home and daily witnessed doses is available, compared to methadone; methadone generally requires daily witnessed ingestion [25].

Initiation of opioid agonist treatment is a complex and crucial step in care for those beginning OAT, as well as those transitioning between medications, as poor treatment retention is largely attributed to discomfort during the induction period due to precipitated withdrawal symptoms [129]. The induction phase onto methadone and buprenorphine are periods of increased mortality risk, however, retention on these medications is associated with significant reduction in the risk of all cause and overdose mortality [130]. Initiation techniques will be explored in greater detail in Chapter 3. Qualitative studies exploring the experiences and barriers of adults with OUD on OAT will be explored in Chapter 4.

SPECIALIST-LED ALTERNATIVE APPROACHES

Specialist-led alternative approaches to opioid agonist treatment include prescription diacetylmorphine, injectable hydromorphone, and slow-release oral morphine (SROM). In 2009, North America's first heroin- assisted treatment study (NAOMI) was conducted in Vancouver, British Columbia [131]. The study compared diacetylmorphine, the active ingredient of heroin, versus methadone [131]. The study concluded that diacetylmorphine was more effective than oral morphine in "retention in addiction treatment or drug-free status and reduction in illicit-drug use or illegal activity" [131]. Among 115 patients who were randomly assigned to receive diacetylmorphine injections, 10 patients overdosed, and 6 patients experiences seizures [131]. Because of the high risk of overdose and seizure, the study concluded that diacetylmorphine maintenance therapy should only be prescribed in settings where medical intervention is available [131].

In 2016, the results were published for the Study to Assess Longer-term Opiate Medication Effectiveness (SALOME), a clinical trial that compared diacetylmorphine and injectable hydromorphone (HDM) [132]. The study provided evidence that injectable hydromorphone is noninferior to diacetylmorphine for treatment of long-term opioid dependence [132].

A randomized cross-over study comparing the efficacy of slow-release oral morphine (SROM), or Kadian®, and methadone as maintenance medication for OUD found SROM to be as effective as methadone [133]. Analysis of the results from this study found significantly better outcomes for SROM as compared to methadone including overall severity of mental symptoms and treatment satisfaction [134]. There was no significant different in drug or alcohol use between groups [134]. Heroin craving scores were significantly lower with SROM compared to methadone, while cocaine craving was not affected [135]. Compared to SROM, methadone produced significantly longer QT-c intervals [136]. Drug induced long QT syndrome serves as a surrogate marker on ECG for risk of developing ventricular arrythmias, and occurs with a wide range of medications, including methadone and morphine [137]. Overall, specialist-led alternatives, including SROM and injectable hydromorphone, are not considered routine interventions for OUD, however, can be considered in consultation with addiction specialists as a third-line treatment [138].

SAFE SUPPLY MEDICATIONS

In contrast to OAT, an evidence-based approach for the treatment of OUD, involving medications such as methadone, buprenorphine, or slow-release oral morphine, safe supply medications refer to non-treatment-based distribution of safer opioids, including hydromorphone and sustained-release oral morphine tablets, and is a newer harm reduction approach [139] [140]. According to the Canadian Association of People Who Use Drugs, safe supply is based on "a moral foundation that the individual choosing to use drugs has the right to do so and people who use drugs should not be treated as morally deficient, be criminalized, or deemed mentally ill for their drug use" [141].

'Safe supply' opioid programs were first introduced in British Columbia in March of 2020, to combat the significant rise of opioid overdoses following the COVID-19 pandemic stay-at-home orders [142]; the closure of treatment centres and harm reduction services have contributed to the rise of overdose deaths [139]. In the U.S., there was a 17.59% increase in opioid overdoses following the commencement of stay-at-home orders [143]. The British Columbia Centre on Substance Use's (BCCSU) Risk Mitigation Guidelines allows for the prescribing of a safe supply of pharmaceutical-grade alternatives to illicit opioids, including hydromorphone [144]. Safe supply has become a trending and controversial topic, and research is still limited; concerns include increased availability of opioids, diversion, and a reduced interest in OAT with the availability of safe supply medications [145]. Safe supply has been shown to reduce people's use of illicit opioids from a toxic drug supply, thereby reducing overdose risk [146].

As discussed above, adaptability and flexibility in response to challenges are essential for the effectiveness of the continuum of care. A scoping review found six innovative strategies in which services available to people with OUD were adapted during the COVID-19 pandemic: home delivery of services, extended take-home medications, uptake of long-acting medications, outreach, and makeshift services, expanded telemedicine services, and safe supply of opioids [147]. A qualitative evidence synthesis of opioid agonist therapy during major disruptions including hurricanes, earthquakes, and terrorist attacks, aiming to inform health system response to the COVID-19 pandemic, found that OAT systems lacked flexibility to adapt, leading to vulnerability of people who use drugs and healthcare providers [148]. Overall, safe supply is an innovative strategy to address the opioid crisis by reducing illicit fentanyl and fentanyl-adulterated opioid use, requiring more research and support from physicians and public health leaders [149].

HARM REDUCTION PRACTICES

Harm reduction practices should be implemented across the continuum of care, to minimize negative opioid use outcomes and prevent opioid-related overdose [90]. Harm reduction measures include, but are not limited to [25,90]:

- Access to Take-Home Naloxone (THN) kits, and education on recognizing and responding to overdose
- Supervised Injection Sites (SIS) and Overdose Prevention Sites (OPS)
- Access to and education on safer use of sterile syringes, needles, and other supplies
- Safe Supply Medications

In 1960, naloxone was synthesized as the first competitive opioid receptor antagonist, reversing the effects of opioid overdose [150 49]. Naloxone has a strong affinity for mu opioid receptors and has minimal adverse effects when administered in the absence of opioids [150]. In the subsequent decades, THN kits became increasingly accessible. In 1971, naloxone received regulatory approvals from the US FDA [49]. In 2016, Health Canada made emergency-use naloxone deregulated in BC, which allowed patients to purchase naloxone without a prescription [151]. Available naloxone formulations include intramuscular, intravenous, and subcutaneous injections [49]. The NARCAN™ Nasal Spray is the only nasal spray version of naloxone approved in Canada and is thought to be easier to administer in certain emergency situations [152]. In 2016, the Canadian Minister of Health signed an interim order that allowed importation of NARCAN® Nasal Spray into Canada while Health Canada completed an expedited review of the product to grant market approval [152,153]. Overall, individuals being treated for an opioid use disorder and those who are frequently around

someone at risk are recommended to possess a take-home naloxone kit [154]. In addition, these individuals should be trained in the use of naloxone in overdose, as well as how to recognize and respond to overdose [155] [156].

Access to supervised injection sites, also known as safe consumption sites, is an essential harm reduction practice. SIS provide a safe and hygienic environment for people to use pre-obtained drugs in the presence of health-care professionals [157]. InSite is the first sanctioned supervised drug injection site in North American, located in the Downtown East Side (DTES) of Vancouver [158]. A population-based study found a 35% reduction in overdose mortality after the opening of InSite within 500 metres of the SIS [159]. A systematic review on SIS showed no increased drug injecting, drug trafficking or crime in surrounding environments of SIS [160]. Since the opening of InSite in 2003, efforts were made to open additional SIS in Montreal, Toronto, Ottawa, and Victoria [161]. Following major efforts including the Toronto and Ottawa Supervised Consumption Assessment Study (TOSCA) conducted in 2012, thirty-eight supervised consumption sites have opened in Ontario, Quebec, Saskatchewan, Alberta, and British Columbia [162].

Overdose prevention sites (OPS) began to open due to the difficulty of opening SIS [163]; OPS combines the "benefits of state-sanctioned injection services with community-driven implementation" [164]. Overall, SIS engages high-risk drug users, reduces overdose fatalities, and reduces high-risk behaviours that lead to HIV and hepatitis C infection including syringe sharing [157]. While the literature supports the effectiveness of SIS as a harm reduction service, limitations and challenges associated with SIS include legislative barriers, negative public perceptions, and police service support [157,165–169].

TREATMENT AND MANAGEMENT FOR YOUTH WITH OPIOID USE DISORDER

There is a much smaller body of research and available data on the efficacy of opioid agonist treatment in youth compared to adult populations [170,171]. While there is limited research on the use of opioid agonist treatments, such as buprenorphine and methadone, among young people specifically, several clinical studies have shown OAT to be an effective pharmacological treatment among this vulnerable, at-risk population.

Guidelines on the treatment of OUD among youth suggest the full range of available treatments, as described in the continuum of care, including assessment, interventions, pharmacological treatment, and harm reduction services; the first line pharmacological treatment in Canada for youth with moderate to severe OUD is buprenorphine-naloxone [90,172]. In the U.S., common medications used for youth with OUD

include extended-release naltrexone and buprenorphine [173]. The greater safety profile of buprenorphine, compared to full agonists such as slow-release oral morphine and methadone, is a large contributing factor in its favourability among young people [174]. A significant reduction in withdrawal symptoms, HIV-risk behaviours, treatment retention, and reduced drug use is seen among youth on buprenorphine [175,176]. Long-term buprenorphine-naloxone treatment is shown to be more effective in preventing relapse among youth than treatment of a shorter duration [177]. In addition to its clinical effectiveness, buprenorphine-naloxone treatment is more cost effective relative to brief detoxification for the outpatient treatment of youth with OUD [178].

While psychosocial treatment interventions and supports should be routinely offered to youth, it is recognized that timely recipient of OAT is more effective in treatment retention in care among youth than behavioural health services alone [172 179]. Unfortunately, only 29.4% of youth receive behavioural health services following an opioid-related overdose, compared to 43.3% of adults [180].

Despite the effectiveness of OAT for the treatment of OUD, a recent U.S. study found that only 2.4% of youth who use opioids receive pharmacological treatment compared to 26.3% of adults who use opioids [181]. While clinical studies support the effectiveness of OAT among youth, there are limited qualitative studies on youth's experiences of opioid agonist treatment contributing to the drastically lower proportion of youth compared to adults who receive OAT [182]. Exploration of this is essential for the development of patient-centered treatment with positive outcomes for young people; this will be discussed in further detail in Chapter 4.

CONCLUSION

The safety and effectiveness of OAT among adult populations is a well-researched field; efforts are being made to improve treatment methods by making pharmacological treatment more patient-centered by reducing barriers. Chapter 3 will outline a novel induction method that reduces barriers of accessing OAT by eliminating abstinence from opioids prior to induction and reducing precipitated withdrawal symptoms and healthcare staff workload. Chapter 4 will delve into the barriers, perceptions, and experiences of OAT among youth with OUD, an at-risk and under-researched patient population. To better meet the needs of this population and improve treatment, investigating the experiences of OAT among youth is essential.

CHAPTER 3: INDUCTION OF TRANSDERMAL BUPRENORPHINE (BUTRANS®) TO EXTENDED-RELEASE BUPRENORPHINE SUBCUTANEOUS INJECTION (SUBLOCADE®) FOR OPIOID USE DISORDER: A CASE SERIES

INTRODUCTION

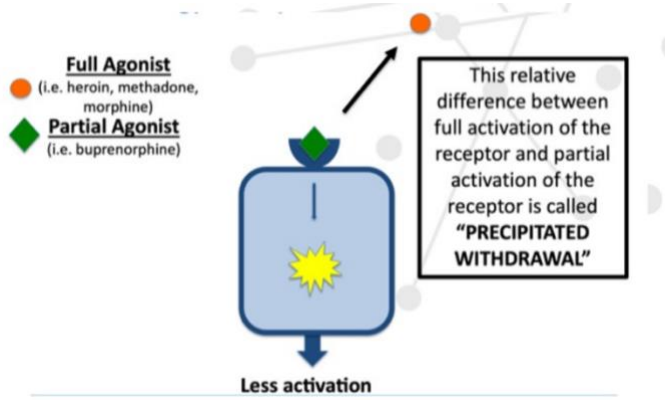
In this chapter, we will discuss two cases of successful induction of transdermal buprenorphine (Butrans®) to extended-release buprenorphine subcutaneous injection (Sublocade®) for the treatment of opioid use disorder. We will begin by discussing the pharmacological properties and alternative formulations of buprenorphine, the recommended first-line OAT for OUD in Canada [92,183]. We will then outline methods of induction for buprenorphine. These include but are not limited to standard induction and micro-induction or low-dose induction of sublingual buprenorphine-naloxone (Suboxone ®), in addition to a novel low-dose induction method using transdermal buprenorphine (Butrans®).

Buprenorphine is a partial μ-opioid receptor agonist [120]. The partial agonism of buprenorphine causes a 'ceiling' effect, reducing risk of respiratory depression and overdose [120]. As the dose increases, it does not result in further respiratory depression, making it a safer OAT option [120]. Buprenorphine has a rapid onset of 30-60 minutes, and a long dose dependent duration of action [184]. The plasma concentration peaks at approximately 1-4 hours [184]. A low dose of buprenorphine (2-4mg) has a 4–12-hour duration of action, and a moderate dose (4-8mg) has a 24-hour duration of action [184]. Over 8mg per day of buprenorphine has a 36–72-hour duration of action [184]. Buprenorphine has a strong binding affinity to the μ-opioid receptors compared to opioids such as methadone, heroin, or morphine, which have lower binding affinities to the μ-opioid receptor [25,120]. Buprenorphine can therefore displace other opioids that have relative weaker binding affinity at the receptors, causing precipitated withdrawal, in which the patient will experience markedly worse withdrawal symptoms [120]. This occurs when buprenorphine is introduced to opioid-dependent patients who have recently administered full opioid agonists [120]. Buprenorphine slowly dissociates from μ-opioid receptors, relieving withdrawal and craving symptoms for approximately 24 hours [120].

Precipitated withdrawal occurs when a full opioid agonist (i.e., heroin, methadone, morphine) is displaced by a partial opioid agonist (i.e., buprenorphine) [120]. Due to buprenorphine's high affinity for opioid receptors, buprenorphine will displace any full opioid agonist that is already bound to the opioid receptor

[120]. If buprenorphine is administered too early during standard induction, while full agonists still occupy the opioid receptor, precipitated withdrawal will occur [120].

FIGURE 4: PRECIPITATED WITHDRAWAL DIAGRAM [263]



The high binding affinity of buprenorphine, a partial opioid agonist, will displace molecules with a lower binding affinity (e.g., full opioid agonists including heroin, methadone, or morphine), causing precipitated withdrawal.

It is important to note that the safety of buprenorphine in terms of overdose risk is irrelevant when combined with other CNS depressants such as benzodiazepines, alcohol and xylazine [120]. The combined effect of opioids with central nervous system depressants has been shown to substantially increase the risk of life-threatening overdose [185–187].

Buprenorphine is available in a variety of formulations, including sublingual tablets, skin patches, and extended-release parenteral formulations such as implants or injections [119]. The current first line treatment for opioid use disorder in Canada is a combination production of buprenorphine/naloxone (Suboxone®) [188] [189] [118]. Naloxone is an opioid antagonist [120]. Suboxone is comprised of a combination of buprenorphine/naloxone in a 4:1 ratio and is given sublingually [120]. Buprenorphine/naloxone is available as 2mg/0.5mg or 8mg/2mg sublingual tablets; to achieve a target dose, tablets can be halved and/or combined [25]. Naloxone is an opioid antagonist that does not exert any effects when Suboxone is taken SL; this is due to limited sublingual absorption and almost complete first-pass metabolism of naloxone [120]. Therefore, Suboxone taken sublingually does not have any opioid antagonistic effects. However, when Suboxone is administered parenterally (intravenous, intramuscular, subcutaneous injection), the naloxone precipitates withdrawal, and therefore the naloxone acts as a deterrent to non-intended use of the medication [120,190]. This minimizes diversion and prevents abuse of the medication, a unique characteristic of Suboxone [120,190]. An extended-release injectable formulation of buprenorphine is available, brand name Sublocade ®, and is used for the management of moderate to severe OUD [121]. Sublocade is administered monthly, at a minimum of every 26 days, via abdominal subcutaneous injection [121]. In 2017, the FDA

approved Sublocade for use in the United States, and in 2020 Sublocade was made available in British Columbia [121]. Due to the novelty of Sublocade® being available as an OUD treatment, a lack of research is available on alternative induction methods for this OAT option. BUP-XR is well-tolerated, with fewer clinic visits, and increased retention compared to SL buprenorphine/naloxone [191] [192,193]. In the context of the COVID-19 pandemic, Sublocade has enabled more accessible, remote healthcare for individuals with OUD seeking OAT [194]. Patients are normally prescribed a loading dose of 300mg/month for 2 months, followed by maintenance doses of 100mg/month [121]. A maintenance dose of 300mg/month can be prescribed at the discretion of the treating prescriber [121]. Buprenorphine is also available as a transdermal patch developed primarily for the management of chronic or cancer pain [124] [195]. Due to the advantages of transdermal buprenorphine, including reduced risk of diversion, increased patient adherence and compliance, and reduced frequency of medication visits, the transdermal formulation is theoretically well suited for the management of opioid dependence; practically, however, the dosing of the transdermal patches available in Canada, is a limiting factor [195].

Due to the pharmacological properties of buprenorphine and high risk for precipitated withdrawal, the induction period is the most critical for individuals starting or being transitioned onto buprenorphine. Successful induction can be defined and measured in a multitude of ways. Opioid withdrawal is commonly measured using the clinical opiate withdrawal scale (COWS); COWS is an 11-step scale that can be used in an outpatient or inpatient setting and is designed to be administered by a clinician [196]. The common signs and symptoms of opioid withdrawal collected from COWS includes resting pulse rate, sweating, restlessness, pupil size, bone/ joint aches, running nose or tearing, GI upset, tremor, yawning, anxiety/ irritability, and gooseflesh skin [196]. A score of 5-12 indicates mild withdrawal, 13-24 is moderate withdrawal, 25-36 is moderately severe withdrawal, and >36 indicates severe withdrawal [196]. Safety, treatment retention, and cessation or decreases of illicit drug use are other important factors when assessing individuals for successful induction [189].

Below, I will outline common buprenorphine induction techniques, standard and micro-induction, using sublingual buprenorphine/naloxone. Next, I will discuss the benefits and techniques of induction utilizing TD buprenorphine; this technique will be demonstrated with both patients in this case series.

STANDARD INDUCTION OF SUBLINGUAL BUPRENORPHINE/ NALOXONE (SUBOXONE®)

To avoid precipitated withdrawal, standard induction of sublingual buprenorphine-naloxone is the most common induction method [25,183,188]. This section will outline standard induction technique according

to the British Columbia Centre on Substance Use Guidelines for the Clinical Management of Opioid Use Disorder [25], the American Society of Addiction Medicine (ASAM) National Practice Guidelines for the Treatment of Opioid Use Disorder [183], and the Suboxone® product monograph [118]. The standard induction method of buprenorphine/naloxone requires patients to be abstinent from all opioids for a period of time in order to reach mild to moderate withdrawal prior to administration of Suboxone [25]. This is a major barrier for many patients seeking opioid treatment as withdrawal symptoms can be difficult to tolerate, thus the abstinence period can also lead to lower treatment retention [189].

Clinicians must instruct patients to discontinue opioids approximately 12-24 hours before the first day of buprenorphine-naloxone induction [25]. It is emphasized to patients that beginning buprenorphine induction too early can cause precipitated withdrawal, worsening any withdrawal symptoms they may already be experiencing. The risk of precipitated withdrawal is lower if the patient has signs and symptoms of at least moderate opioid withdrawal prior to their first dose of Suboxone [25]. A COWS score greater than 12 at the time of induction is recommended and associated with lower risk of precipitated withdrawal [25].

The duration of time from last opioid dose and onset of moderate opioid withdrawal (COWS score > 12) differs between short-acting, intermediate-acting, and long-acting opioids, with short-acting being approximately 12-16 hours, intermediate-acting being 17-24 hours, and long-acting being 30-48 hours or more since the last dose [25]. Table 4 below, alongside COWS, can be used to determine the most optimal time for buprenorphine-naloxone induction to begin.

TABLE 4: DURATION OF ACTION OF OPIOIDS [25]

Short-acting opioids	12-16 hours since last dose	Examples: heroin, morphine, hydrocodone, immediate-release oxycodone
Intermediate-acting opioids	17-24 hours since last dose	Examples: slow-release oral morphine, controlled-release hydromorphone, sustained-release oxycodone
Long-acting opioids	30-48 hours or more since last dose	Examples: methadone

If the patient is transitioning from methadone to buprenorphine-naloxone, it has become convention to recommend a taper to a methadone dose of <60 mg per day, ideally ≤ 30 mg per day, for a minimum of 6-7 days before induction; low dose inductions, however, do not require this [25]. Specialist supervision and inpatient settings may be recommended for higher dose methadone transfers [25,197]. It is important to emphasize to patients that induction cannot begin during acute alcohol intoxication [25,118]. For patients actively using benzodiazepines, alcohol, or other sedative medications, dosing and titration may be adjusted due to increased overdose risk associated with polysubstance use [25,118].

The commonest starting dose of buprenorphine-naloxone in a standard induction protocol is 4g/1mg buprenorphine/naloxone, equivalent to two 2mg/0.5mg sublingual tablets [25]. The starting dose will be given once the patient is in moderate opioid withdrawal (COWS > 12) and no long-acting opioids have been used for at least 30 hours, as outlined in Table 1 [25]. The starting dose may be lowered to 2mg/0.5mg buprenorphine/naloxone if the patient is currently abstinent from opioid use or there is a high risk of precipitated withdrawal [25]. The patient is at a higher risk of precipitated withdrawal when transitioning from a long-acting opioid such as methadone [25]. In contrast, the starting dose may be raised to 6mg/1.5mg buprenorphine/naloxone, equivalent to three 2mg/0.5mg sublingual tablets, if the patient is experiencing severe withdrawal symptoms at the time of induction, for example COWS score >24 [25].

Precipitated withdrawal can become evident within 30 minutes of the starting dose of buprenorphine-naloxone; therefore, patients must be reassessed 30-60 minutes after their starting dose of buprenorphine-naloxone [25]. The induction and dosing guidelines of standard induction differ depending on the patient's withdrawal symptoms during the first 24-hours of induction, as outlined in Table 5 below [25].

TABLE 5: STANDARD INDUCTION DAY 1- REASSESSMENT AFTER STARTING DOSE OF SUBOXONE [25]

Withdrawal symptoms relieved after 1-3 hours	*Day 1 induction complete. Prescribe the same total dose (Starting dose on Day 1) for the following day.*
Withdrawal symptoms not adequately relieved	*Administer additional dose(s). Maximum total of 12mg/3mg buprenorphine/naloxone may be administered on Day 1.*

Withdrawal symptoms adequately relieved after additional dose(s)	*Day 1 induction complete. Prescribe the same total dose (Combine starting dose and additional dose(s)) for the following day.*
Withdrawal symptoms not adequately treated with additional dose(s)	*Manage withdrawal symptoms symptomatically. Continue induction the following day.*

If patients develop precipitated withdrawal, clinicians and patients can choose to continue or stop the induction. This decision is made through clinical experience, severity of precipitated withdrawal, and patient preference. Continuing induction is generally preferred [25]. It is recommended to administer additional doses of 2mg/0.5mg buprenorphine/naloxone every 1-2 hours, up to 12mg/3mg buprenorphine/naloxone (daily maximum), until withdrawal symptoms are adequately relieved [25].

On Day 2 of standard induction, it is recommended to continue a once daily dose equal to the total amount of Suboxone administered on Day 1, as described in Table 6. The clinician can titrate up as needed in subsequent days, aiming for a target dose of 16mg/4mg or greater [25]. If withdrawal symptoms are present on Day 2, the clinician can administer a dose equal to the total amount administered on Day 1 and an additional 4mg/1mg buprenorphine/naloxone [25]; the steps outlined in Table 6 are followed.

TABLE 6: STANDARD INDUCTION DAY 2 [25]

No withdrawal symptoms	*Continue a once daily dose equal to the total amount of Suboxone administered on Day 1. Titrate up as needed in subsequent days, aiming for a target dose of 16mg/4mg or greater*
Symptoms relieved after 2-3 hours	*Prescribe this total dose for the next day (Day 1 total + 4mg)*
Symptoms not relieved after 2-3 hours	*A second 4mg can be administered (unless this would exceed the maximum total dose on Day 2-16mg/4mg buprenorphine/naloxone). If symptoms resolve after the second additional dose of 4mg,*

	prescribe this total daily dose the following day (Day 1 + 4mg + 4mg)
Maximum daily dose of 16mg/4mg buprenorphine/naloxone reached	*Manage symptomatically for the remainder of Day 2. Confirm that sublingual tablets are being administered correctly**

**Clinicians must instruct patients to keep the Suboxone tablet under their tongue until it dissolves. Witnessed ingestion of first dose is recommended to ensure proper intake. Patients must avoid swallowing, eating, drinking, talking, or smoking while the tablet it being dissolved. The sublingual tablets can take up to 10 minutes to dissolve.*

On following induction days, patients should reach an optimal stable dose per day that can sustain an entire 24-hour dosing interval with no withdrawal symptoms [25]. Titrate as needed, 2mg/0.5mg to 4mg/1mg at a time, up to a maximum dose of 24 mg/6mg per day, according to the BCCSU [25]. US guidelines state that a maximum dose of 32mg/8mg can be reached. Standard induction can be completed in an inpatient or outpatient setting. When considering an unobserved or home buprenorphine/naloxone induction rather than office based, careful selection of patient candidates should occur.

In conclusion, standard induction of Suboxone is the most common induction technique in North America used for people with opioid use disorder. A major barrier of standard induction is a period of opioid abstinence and withdrawal prior to the first dose of Suboxone, to prevent precipitated withdrawal. As demonstrated above, standard induction protocols and guidelines vary.

MICRO-INDUCTION OF SUBLINGUAL BUPRENORPHINE/ NALOXONE (SUBOXONE®)

To combat the challenges of standard induction, a Swiss team of psychiatrists developed the Bernese method, also known as micro induction, or micro-dosing [198]. Micro dosing does not require an abstinence period, as micro-doses of buprenorphine/naloxone are administered 1-2 times per day with a full μ-opioid receptor agonist, avoiding precipitated withdrawal [198]. Hammig et al. hypothesized that small and repetitive doses of buprenorphine will begin to accumulate at the opioid receptors due to its long binding time and high receptor affinity [199]. Therapeutic doses can be achieved within 10 days or more [198]. The patient continues using their full opioid agonists during the induction period and does not experience precipitated withdrawal [198]. A barrier of the Bernese method is the length of time is takes to reach a therapeutic dose [198]. Continued exposure to the unregulated illicit drug supply is also risky and associated with increased risk

of overdose; in the US, there are regulatory prohibitions to providing a safer, prescribed opioid to meet a patient's opioid dependence during the induction period [198].

A novel induction method, called rapid micro-induction, has been developed by The Complex Pain and Addiction Services (CPAS) Team at Vancouver General Hospital [189]. Compared to micro-dosing or the Bernese method, which takes approximately 10 days to reach a therapeutic dose, patients initiated onto Suboxone using a rapid micro-induction approach can reach a therapeutic dose of buprenorphine-naloxone in only two days. Rapid micro-induction offers many advantages to the standard induction and micro induction/ Bernese methods, including:

1. Elimination of the abstinence period prior to administration of the first dose of buprenorphine/naloxone
2. Lowered risk of precipitated withdrawal symptoms
3. Less pain and craving symptoms
4. Shorter hospital visits
5. Fewer patient-initiated discharges
6. Cost savings for the healthcare system with reduced hospital length of stay
7. Improved treatment retention
8. Faster time to achieve a therapeutic dose

Currently, there are several published case series and reports on micro-induction [200–203], as well as two ongoing randomized control trials, examining both inpatient induction and take-home induction [204189]. A systematic review that aimed to synthesize evidence on micro-induction effectiveness found high variability between regimens [205]. Starting and maintenance doses ranged from 0.03 to 1.0mg, and 8 to 32 mg respectively [205]. Among 57 patients from a total of 20 case studies and series, 54 did not experience any precipitated withdrawal [205]. The three studies that reported precipitated withdrawal symptoms among participants, described regimens overlapping with methadone [205]. Overall, the rapid micro-induction method is a patient-centered approach to initiation of OAT, making treatment more accessible to patients with opioid use disorder by reducing barriers in accessing treatment.

The rapid micro-induction technique used in an ongoing randomized control trial comparing standard and rapid micro-induction efficacy is outlined in Table 7 below. Essentially, a total of 4mg of buprenorphine-naloxone were given in split doses in the first 24 hours, and 8mg of buprenorphine-naloxone were given in the second 24 hours [189]. During hours 0-48, patients were able to receive hydromorphone PRN for

withdrawal symptoms and/or craving and/or pain. Hydromorphone is an intermediate-acting opioid medication prescribed for pain, craving and withdrawal management in the RCT. In clinical practice, the rapid micro-induction method can be used with any opioid based on clinical indication and patient preference and is not limited to hydromorphone. After the 16th dose of buprenorphine-naloxone, Suboxone 8mg SL daily was prescribed in addition to Suboxone 1-4mg SL Q3H PRN for withdrawal symptoms and/or craving and/or pain [189]. Other than buprenorphine-naloxone, all other opioids, including hydromorphone, were discontinued after the 16th dose of suboxone. A maximum dose of 32mg/8mg in 24 hours was indicated. Table 4 is an exert from the pre-printed order (PPO) for rapid micro-induction of buprenorphine-naloxone used in the ongoing RCT; the doses of suboxone and hydromorphone are clearly outlined.

TABLE 7: RAPID MICRO-INDUCTION OF SUBOXONE PROTOCOL [189]

Doses	buprenorphine* dose and interval	buprenorphine - naloxone strength to use	Quantity per dose	HYDROmorphone dose and interval
1 to 8	0.5 mg sublingual Q3H x 8 doses	buprenorphine 2 mg - naloxone 0.5 mg	1/4 tab	1 to 48 mg PO/SC/IV/IM Q1 to 3H PRN (start at the lower end of dosing range) Hold if sedated, respiratory rate less than 10 per minute, or O_2 saturation less than 92%
9 to 16	1 mg sublingual Q3H x 8 doses	buprenorphine 2 mg - naloxone 0.5 mg	1/2 tab	1 to 48 mg PO/SC/IV/IM Q1 to 3H PRN (start at the lower end of dosing range) Hold if sedated, respiratory rate less than 10 per minute, or O_2 saturation less than 92%
***buprenorphine-naloxone is dosed based on buprenorphine component.** Witness patient dissolve tablet completely under the tongue, which can take up to 10 minutes. DO NOT swallow saliva or tablet, talk or drink during this time.				

Despite these improvements from the standard induction method of sublingual buprenorphine, the following ongoing barriers have been identified:

1. Increased staff burden due to need for frequent monitoring and administration of low doses of buprenorphine/naloxone
2. Inconsistent SL dosing due to need for manual manipulation (i.e., cutting tablets) of standardized SL tablets into low doses
3. Inconsistent absorption of SL tablets due to user error potential
4. Medication administration error given the subsequential nature of the PPO

5. More limited ability for patients to manage Q3H medication dosing independently in their home environment

Given these barriers, induction methods using alternative formulations other than sublingual buprenorphine are being explored, including transdermal buprenorphine formulation.

TRANSDERMAL BUPRENORPHINE (BUTRANS®) INDUCTION

Most research and induction techniques have utilized sublingual buprenorphine-naloxone formulation for induction of buprenorphine; as described above, there are several barriers that have been identified with sublingual formulations. Transdermal buprenorphine is another option that is being explored as a bridge during the induction period. The benefits of using transdermal buprenorphine during induction include:

1. Steadier blood level concentrations of buprenorphine
2. Increased accuracy of dose administration and subsequent lower risk of precipitated withdrawal
3. Reduced burden on nursing workload with reduced frequency of dosing
4. More outpatient friendly with less reliance on patients to time their doses

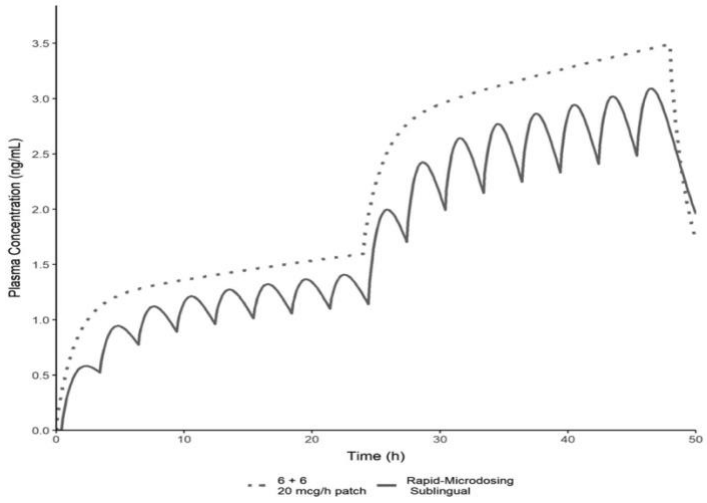
In current literature, transdermal buprenorphine patches have been shown to be effective in reducing precipitated withdrawal symptoms when transitioning from methadone onto sublingual buprenorphine/naloxone [206–210]. Other studies have shown successful induction onto SL buprenorphine/naloxone from other opioid agonists, including fentanyl, morphine, and oxycodone, using TD buprenorphine [211–213]. These inductions have been demonstrated in both an inpatient and outpatient setting. In addition, TD buprenorphine induction has been successful among individuals with a complex psychiatric history and comorbid psychiatric disorders. In published literature, the duration required to complete stabilization onto SL buprenorphine/naloxone using a TD buprenorphine bridge ranges from 2 to 13 days, and the dose of TD buprenorphine ranges from 5 to 40 mcg/h [206–210] [211–213]. A retrospective cohort study involving 41 cases of in-hospital TD buprenorphine induction to SL buprenorphine/naloxone found that 59% of cases tolerated the induction well and 32% tolerated it 'fairly well' [213]. No studies have been published on the effectiveness and safety of induction onto extended-release buprenorphine injection using TD buprenorphine.

The patients described in this case series were induced using the "IPPAS method", an induction method using TD buprenorphine patches [214]. The "IPPAS method" achieves more stable plasma concentrations

compared to the SL buprenorphine/naloxone rapid micro-induction protocol outlined in **Table 7** and is guided by pharmacokinetic modeling [214]. This method involves the application of 12 TD buprenorphine patches over a 48-hour induction period; 6 buprenorphine 20 mcg/h patches are given at 0 hours and 6 additional patches are added at 24 hours, without the removal of the patches previously applied [214]. Written informed consent was obtained from both patients.

Pharmacokinetic model simulations were done to compare the IPPAS method and rapid micro-induction buprenorphine/naloxone protocol as outlined in **Table 7**. The results of this simulation are shown in **Figure 5** below.

FIGURE 5: PHARMACOKINETIC MODEL SIMULATION [214]



This novel induction technique, called the IPPAS method, will be displayed in the two cases described below. All previously published literature has described TD buprenorphine being used during induction onto SL buprenorphine/ naloxone. This case series will show successful induction of TD buprenorphine onto extended-release buprenorphine injection. Typically, patients must be induced and stabilized onto 8-24mg of buprenorphine/naloxone for a minimum of 7 days prior to their first dose of Sublocade [121]. The method described in this case series is low barrier, faster, and more tolerable [214].

In conclusion, induction onto OAT is complex. As we have outlined, a variety of techniques and protocols have been developed to combat barriers and make treatment more patient centered. The utilization of TD buprenorphine for OAT induction has many benefits and can be used to successfully initiate patients onto sublingual buprenorphine/naloxone as well as extended-release injectable buprenorphine. Below, we will describe two patients who were successfully induced onto BUP-XR using the IPPAS method.

CASE 1

A 52-year-old man on disability, residing in supported housing, was admitted to a tertiary care hospital for acute kidney failure. His past medical history included hepatitis C, laparoscopic cholecystectomy for gallstones, left knee injury, and a previous nasal fracture. His substance use history included stimulant and opioid use disorders for 10 years, starting with daily cocaine and intermittent heroin use. Two years prior, he had transitioned to using unregulated fentanyl. Prior to admission, he was using 200 mg of intravenous and inhaled unregulated fentanyl per day. He had past trials of OAT with 80 mg of methadone per day but discontinued treatment as he felt fentanyl helped him "balance out" the effects of stimulants. He had also been offered SL BUP/NX, but the fear of withdrawal symptoms during the induction period had discouraged him from taking it. Three days prior to his admission, he had been treated at a detox facility, where he experienced abdominal pain, nausea, and vomiting. He had returned home, where he resumed fentanyl use. On the day of admission, he reported that he last used cocaine the same morning and last used fentanyl the day prior. His urine drug screen tested positive for fentanyl, methadone, opiates, and cocaine.

On the day of admission, he received 8-16 mg oral (PO) hydromorphone every 1 hour (q1h) as needed for the management of pain and opioid withdrawal. He expressed that his goal was abstinence from unregulated opioids, noting that lately he was using opioids primarily to prevent withdrawal symptoms. Furthermore, he was interested in the BUP-XR depot because he found daily medication administration challenging.

He subsequently completed a TD buprenorphine induction over 48 hours while continuing to receive hydromorphone as needed. The full titration schedule is outlined in Table 8 below. On the first day of induction, six 20 µg/h TD buprenorphine patches were applied to the patient's back. After 24 hours, six additional patches were applied. All patches were removed 48 hours post induction, and he received 4 mg SL BUP/NX. He then received 300 mg SC BUP-XR four hours later. No precipitated withdrawal occurred during the induction period, as indicated by his low scores on the Clinical Opiate Withdrawal Scale (COWS), ranging from 0 to 5.[12] He continued to receive 4 mg SL BUP/NX once daily for ongoing withdrawal management, which was discontinued upon discharge. He was provided with an appointment with an outpatient addiction psychiatrist to receive his next BUP-XR injection. At discharge, he had no complaints of pain, nausea, vomiting, or withdrawal symptoms.

TABLE 8: CASE 1 TRANSDERMAL BUPRENORPHINE INDUCTION TITRATION SCHEDULE

	Buprenorphine (Transdermal Patch)		Buprenorphine/Naloxone* (Sublingual Tablet)		BUP-XR (Subcutaneous Injection)	Hydromorphone		Clinical Opiate Withdrawal Scale (COWS)
	Dosing	*Total dose*	*Dosing*	*Total dose*	*Dose administered*	*Dosing*	*Total dose*	
Admission day, preinduction						8mg x2	16mg	
Preinduction day						8mg x1 12mg x1 12mg x1	32mg	
Preinduction day						12mg x3	36mg	
Induction Day 1	6 x 20 mcg/h	120mcg				12mg x3 16mg x1	52mg	
Induction Day 2	6 x 20 mcg/h	120mcg				12mg x1	24mg	Mean: 2.5 Range: 0-5
Postinduction stabilization	Discontinued		4mg OD PRN	4mg	300mg SC	12mg x3	36mg	Mean: 2.75 Range: 0-4
Postinduction stabilization			4mg OD PRN	4mg		Discontinued		Mean: 0.34 Range: 0-1
Postinduction stabilization, discharge day			4mg OD PRN	4mg				Mean: 3.5 Range: 3-4

**Expressed as mg of buprenorphine component*
BUP-XR = buprenorphine extended-release injection
Q__ H= every __ hours
OD = once a day
PRN = as needed
PO = by mouth
SC = subcutaneous

CASE 2

A 34-year-old woman, receiving social support for disability, and living with her mother in a private residence, was admitted to the same tertiary care hospital for asthma exacerbation and pneumonia. Her medical history included asthma, brachial plexopathy, and a right-hand fracture in 2018. Psychiatric history was significant for major depressive disorder (treated with sertraline), and self-reported ADHD. Her substance use history included opioid and stimulant use disorders, beginning four years prior. On admission, she reported smoking approximately 1 gram of unregulated fentanyl, and an unknown amount of methamphetamine daily. She denied intravenous drug use or history of overdose. Past opioid agonist treatment included BUP-XR depot injections (Sublocade®), and more recently switching to a 500 mg daily dose of slow-release oral morphine (SROM, Kadian®). However, despite treatment with SROM, she continued to use fentanyl due to ongoing cravings and withdrawal symptoms. She reported that her last fentanyl use was on the day of admission. Her urine drug screen was positive for fentanyl and opiates, and negative for cocaine, benzodiazepines, cannabis, and amphetamines.

On the day of admission, she was treated with azithromycin and ceftriaxone by the internal medicine team for her pneumonia. She received 500 mg of SROM once daily, as well as the following medications for withdrawal management: 10-20mg of oral morphine every 4 hours as needed, 8-32mg of oral hydromorphone every 3 hours as needed, and 4-16mg of subcutaneous hydromorphone every 3 hours as needed. She reported a goal of abstinence from unregulated opioids, and subsequently underwent a TD buprenorphine induction over 48 hours onto SC BUP-XR. The full titration schedule is outlined in Table 9 below. On the first day of induction, six 20 µg/h TD buprenorphine patches were applied on the patient's back. After 24 hours, six more patches were applied. After 48 hours, all twelve patches were removed, and the patient received 4 mg SL BUP/NX. After 50.5 hours, she received a 300 mg SC injection of BUP-XR. No precipitated withdrawal occurred during the induction period, as indicated by her low scores on the Clinical Opiate Withdrawal Scale (COWS), ranging from 1 to 5, which indicates minimal objective withdrawal symptoms. The patient noted that she tolerated the induction well and denied any side effects. A follow-up appointment was scheduled with her general practitioner for her next BUP-XR injection.

TABLE 9: CASE 2 TRANSDERMAL BUPRENORPHINE INDUCTION TITRATION SCHEDULE

	Buprenorphine (Transdermal Patch)		Buprenorphine/Naloxone* (Sublingual Tablet)		BUP-XR (Subcutaneous Injection)	Kadian/Morphine		Clinical Opiate Withdrawal Scale (COWS)
	Dosing	*Total dose*	*Dosing*	*Total dose*	*Dose administered*	*Dosing*	*Total dose*	
Induction Day 1	6 x 20 mcg/h	120mcg				Kadian - 500mg PO Morphine - 10mg PO	Kadian – 500mg Morphine – 10mg	Mean: 1.33 Range: 1-3
Induction Day 2	6 x 20 mcg/h	120mcg				Kadian 500mg	Kadian – 500mg	Mean: 3 Range: 1-5
Postinduction, discharge day	Discontinued		4mg OD PRN	4mg	300mg SC	Discontinued		Mean: 1 Range: 1

**Expressed as mg of buprenorphine component*
BUP-XR = buprenorphine extended-release
q __ h = every __ hours
OD = once a day
PRN = as needed
PO = by mouth
SC = subcutaneous

DISCUSSION

Here I have presented two patients with a history of severe opioid use disorder and heavy fentanyl use who were successfully induced onto extended-release buprenorphine injection after a 48-hour induction with transdermal buprenorphine, using the novel IPPAS induction method. Both patients reached a therapeutic dose of buprenorphine without a period of opioid withdrawal being required and experiencing minimal precipitated withdrawal.

Compared to micro-induction techniques using sublingual buprenorphine/naloxone, the IPPAS induction method has some major advantages. Unlike micro-induction techniques which can involve administration of SL tablets every three hours, the IPPAS method simply involves once-daily administration of TD patches. By decreasing the frequency of buprenorphine administration, the IPPAS method drastically reduces the nurse and staff workload by minimizing the need for frequent monitoring in an inpatient setting. In an outpatient setting, the TD buprenorphine approach allows for an independent and less overwhelming induction compared to micro-induction, as the patient can manage a once-daily administration more smoothly. This method relies less on the patient timing their own dosing schedule through a home induction, thus reducing patient administration error and possible precipitated withdrawal due to such errors. Overall, a major advantage of the IPPAS method compared to SL buprenorphine induction methods, including standard and rapid micro-induction, is the simplicity of the protocol. The number of patches required for administration, totalling at twelve throughout induction, may be deemed burdensome; availability of higher-dosage TD buprenorphine patches would combat this inconvenience. Currently, higher-dosage patches are available in Europe (Transec® 35, 52.5, and 70 mcg/ hour) and are indicated for pain management only, however, are not available in North America [214]. In this case series, Butrans® 20 mcg/hour was used.

TD buprenorphine induction does not require manual manipulation of standardized SL tablets as required in the micro-induction technique. Splitting these tablets into lower doses can lead to inconsistent SL dosing. In addition, inconsistent absorption of SL buprenorphine can be seen with incorrect administration of the tablets. In an inpatient setting, administration is often witnessed by the nursing staff to ensure correct technique, which subsequently increases staff workload. Some hospital settings have noted significant barriers to implementation of rapid micro-induction due to splitting of tablets; this included inaccuracy of dosing, staff confusion, increased need for staff education, and excessive waste of the split medication [215].

Another major advantage of TD buprenorphine induction includes elimination of the abstinence period prior to administration of the first dose of opioid agonist treatment. As described in Case 1, the

patient expressed significant concern regarding the withdrawal period during the induction process. This is a major barrier and deterrent for many patients seeking opioid agonist treatment, as withdrawal can be extremely uncomfortable. The IPPAS method achieves a therapeutic dose of OAT more quickly, in only 48-hours, which allows for shorter hospital visits and cost savings for the healthcare system. In addition, this allows for fewer patient-initiated discharges due to extended hospital visits and improved treatment retention.

The use of TD buprenorphine also allows for steadier blood level concentrations of buprenorphine compared to rapid micro-dosing of SL buprenorphine as per the pharmacokinetic model simulation outlined in Figure 5. A more stable plasma concentration lowers the risk of precipitated withdrawal symptoms. In addition, the pharmacokinetic modelling displays complete rapid micro-induction administration accuracy with doses being administered every three hours; in both an inpatient and outpatient setting, this can be unrealistic due to staff or patient error. Errors can further reduce the plasma buprenorphine concentration steadiness throughout induction.

Limitations to TD buprenorphine induction include potential safety concerns due to the large amounts of TD buprenorphine patches required for induction. The patches may be diverted or misused. In addition, there is potential concern for patients or staff to forget to remove patches, leading to adverse effects, more significantly in an outpatient setting. To combat these safety concerns, patient and staff education is essential for TD buprenorphine induction, as with all other induction methods.

All currently published literature on TD buprenorphine induction shows successful induction onto SL buprenorphine/naloxone or successful transition from methadone to SL buprenorphine/naloxone. This case series adds to the current literature as it demonstrates a successful induction onto extended-release buprenorphine injection through similar methods using TD buprenorphine. This displays the potential for TD buprenorphine induction to be used for initiation of a variety of buprenorphine formulations including sublingual and injection.

The choice of buprenorphine formulation for long-term opioid agonist treatment is dependent on clinician recommendation as well as patient preference, influenced by past experiences and perceptions of treatment. Both patients described in this case series chose the monthly buprenorphine injection, Sublocade®. A major advantage of depot extended-release buprenorphine injection is convenience of administration. Unlike sublingual buprenorphine that requires attendance for daily administration at the pharmacy, Sublocade® requires monthly attendance, at a minimum of every 26 days. This allows for a more

conventional lifestyle, as pharmacy visits do not need to be factored into the patient's employment, study, or travel. In addition to this, daily pharmacy visits can increase stigmatization and discrimination experienced by the individual. Although this can be seen as a major advantage for many people suffering with OUD, some find that the daily healthcare visits, social interactions at clinic, and staff support, can be extremely beneficial to their recovery and care. In conclusion, the routine and daily dosing ritual can be of comfort and support for some patients [194]. Another advantage of Sublocade® is the reduced risk of diversion. A disadvantage for some, however, is the painful administration of the subcutaneous injection; those with a fear or anxiety of injections can find this significantly worrisome.

Due to the high opioid tolerance among fentanyl-using populations, the need for additional opioids is often required in conjunction with buprenorphine induction to reduce opioid withdrawal symptoms. In the two cases described in Chapter 3, PRN hydromorphone for Case 1 and Kadian/Morphine for Case 2 were given during the induction period in-hospital. Some patients with OUD may continue to use illicit opioids until their withdrawal and craving subsides and their opioid requirements are met by the opioid agonist medication of choice. To apply this TD buprenorphine induction protocol to outpatient settings, further research is needed to determine effective techniques to meet opioid requirements of patients during induction and reduce unregulated opioid use during this time; studies should investigate the efficacy of long-acting and short-acting PRN opioids during TD induction.

CONCLUSION

This case series provides support for the efficacy and safety of 48-hour transdermal buprenorphine induction of OAT among fentanyl-using populations. Overall, this case series explores a novel induction method that minimizes barriers to OAT initiation by eliminating an opioid withdrawal period, minimizing precipitated withdrawal, shortening the induction period, and simplifying the induction regimen. In addition, this induction method reduces nurse workload, and reduces staff and patient administration error. Given these advantages, the IPPAS method is hypothesized to be a beneficial protocol for an outpatient setting as well as inpatient. There is a need for further research among larger patient populations to assess the safety and efficacy of the IPPAS induction method using TD buprenorphine in different settings and patient demographics, including youth with OUD. The major limitation of this case series is the small sample size; future research is needed to systematically evaluate this induction approach.

CHAPTER 4: A QUALITATIVE STUDY ON THE EXPERIENCES, BARRIERS, AND UNDERSTANDING OF OPIOID AGONIST TREATMENT AMONG YOUTH WITH OPIOID USE DISORDER IN VANCOUVER, BRITISH COLUMBIA

INTRODUCTION

While qualitative literature on the experiences and perceptions of youth on OAT is sparse, there is a significant body of literature on adult populations. Access to medication, healthcare staff relationships, and choice of medication are some of the major themes explored in current literature, as identified in this narrative review. Societal, internalized, and structural stigmatization of OUD and OAT are overarching themes that heavily impact access to treatment, healthcare relationships, and choice of medication for many individuals.

Overall, OAT satisfaction is essential for patient safety; a Canadian cohort study found that patients who were dissatisfied with their OAT, were more likely to be exposed to fentanyl [216]. This study highlights the importance of optimizing OAT satisfaction in the context of the ongoing opioid overdose crisis in North American, with the increased prevalence of fentanyl and fentanyl analogue use [216].

ACCESS TO OAT

Convenience of OAT services is essential for treatment access and retention; clinic or pharmacy location, type of dispensing space, and service hours are some important factors that contribute to convenience [217]. A qualitative study on patient experiences of supervised methadone consumption for methadone maintenance therapy found that inconvenient access was a major deterrent to receiving care [217]. Due to the risk of diversion and overdose, patients on methadone are infrequently given take-home doses, and therefore require daily clinic attendance [218]. Take-home dose restrictions have been compared to that of jail, describing MMT as 'liquid handcuffs', concluding that a lack of take-home doses creates a deterrent for accessing MMT [218]. MMT is commonly dispensed in a designated MMT consumption site rather than a community pharmacy; a qualitative study on methadone supervised consumption found that community pharmacies were preferable, more discreet, and less stigmatized than designated MMT consumption sites [217]. Some participants also discussed potential "triggers" associated with MMT consumption sites; while attempting to distance themselves from people who use drugs, they were confronted daily with drug use and injecting supplies near the dispensary [217]. An Irish qualitative study

found that some patients receiving MMT found treatment to be a barrier in finding suitable employment or staying employed, due to the stigmatization and disruption of daily witnessed ingestion [219]. To address policy development of methadone treatment, clinic opening hours need to be considered, to support clients in leading satisfying lives [220]. Similar take-home dose restrictions are placed on buprenorphine-naloxone. In a qualitative study on patient preferences of buprenorphine versus methadone, thematic analysis found a shared desire for take-home doses of buprenorphine, as well as methadone [221]. Take-home doses, commonly referred to as 'carries', allows for a more patient-centered approach with increased autonomy over the patients' treatment experience [221].

Another major barrier in accessing medication-assisted treatment for opioid use disorder is lengthy waitlists for treatment [222]. In BC, rapid access clinics play a vital role in providing timely, low barrier access to medical treatment and addiction specialists [90]. Referral to rapid access clinics typically takes a few days [90]. Outside of BC, individuals seeking treatment can remain on waitlists for months as the demand for treatment remains significantly above available capacity of addiction services [222,223]. During the COVID-19 pandemic a shift from in-person to telehealth counseling services was made for MOUD treatment; 31% of patients reported one or more barrier to telephone counseling [224]. The most common barriers identified included a preference for traditional office visits, unstable phone or computer availability, and lack of privacy when talking on the phone [224].

RELATIONSHIPS WITH HEALTHCARE STAFF

Positive relationships with pharmacists and dispensing staff are found to be incredibly important and contribute significantly to positive OAT experiences [225] [217]. A Canadian qualitative study on MMT program experiences found that participants emphasized the significance of supportive and nonjudgmental staff and counselling access [226]. In a study that aimed to explore patients' experiences of injectable opioid agonist treatment (iOAT), similar results were found, with strong healthcare provider relationships being an emergent core concept [227]. The ability to 'open-up' and 'be a part of care' were two vital processes identified in developing healthcare provider relationships while on iOAT [227]. A participant of a South African study on the first low-threshold OAT centre described their positive experience with treatment staff as "the first time [they] have been treated as human beings. [They] have always been discarded by society", highlighting the profound impact that healthcare staff have on patients [228]. To optimize relationships with healthcare staff, improved provider education and an integrated system of care is essential [229].

STIGMATIZATION OF OAT

Societal, structural, and internalized stigmatization of OAT can heavily impact individuals suffering from OUD. As discussed above, shame and stigmatization surrounding accessing treatment services can be a deterrent for many individuals seeking a life described as "conventional and respectable", as 'carriers' are infrequently given, and community pharmacies are often unavailable for daily witnessed ingestion [230]. Internalized stigmatization of OAT among individuals suffering with OUD also carry significant weight, as the negative public discourse surrounding OAT and OUD can be extremely impactful [231]. The belief that long-term medication is a 'failure' of recovery is a common stigmatizing belief [231]. The pharmacological management of opioid use disorder is often seen as "substituting an illegal drug for a legal one" [232]. These deeply entrenched beliefs are described in some literature as the 'anti-medication' bias and can be seen throughout the field of addiction medicine [233]. This can be seen in a variety of settings, including prisons; a systematic review on barriers of OAT program implementation in prisons found that fear of patient stigmatization was a major barrier to program delivery [234]. It is important to recognize and address internalized stigmatization in a healthcare setting, as this can hugely impact an individual's interest in pharmacological treatment, which has been shown to significantly reduce the morbidity and mortality of people misusing opioids [41,42]. In addition to OAT-related stigma resulting in a reluctance to initiate, access, or continue pharmacological treatment, it has also been shown to result in relationship conflicts, lower self-esteem, and distrust of the healthcare system [221].

With the discrimination and stigmatization of OAT and OUD seen at a societal and structural level, it is not surprising that individuals struggle with internalized stigmatization. An important example of societal internalization is the Not-In-My-Back-Yard (NIMBY) phenomenon, "in which residents of a neighborhood designate a new development [including harm reduction services or addiction treatment facilities] as 'inappropriate or unwanted' for their local area" [235,236]. The NIMBY phenomenon was highlighted recently with the relocation of an MMT clinic to a gentrified neighborhood in Toronto, Ontario, that led to increased police surveillance and stigma in the community for those requiring access to the clinic [237].

CHOICE OF MEDICATION

The list of available opioid agonist medications and routes of administration available to people with OUD is lengthy, and can be overwhelming; generally, patient preference and prescriber

recommendation inform an individual's choice of medication. Studies comparing methadone and buprenorphine medications for OUD have found that treatment goals, prior OAT experiences, and a desire to avoid methadone clinics and associated stigma, contribute significantly to OAT decision-making [238]. In addition, the reasons for deciding between buprenorphine and methadone are often grounded in an individual's perceived pharmacological differences between the medications [239]. Among those with a goal of abstinence from opioids, many choose buprenorphine over methadone, based on their perception that methadone is more addictive and leads to worse withdrawal symptoms upon discontinuation [238]. The non-sedating effect of buprenorphine, allowing for more clear-headedness, offers a state of normalcy and convention, that many describe as being unachievable on methadone [239]. The long-term nature of methadone is seen as another deterrent, compared to the potential short duration of treatment of buprenorphine [240]. The commonest reason for choosing methadone is found to be the familiarity of the medication, and a positive experience with reduced withdrawal and craving symptoms [241]. The myth that methadone 'rots your teeth and bones' was a deterrent for some, although this concept is not supported by research [241]. Some individuals describe a strong aversion to the taste of SL buprenorphine tablets [242]. In addition, the challenges of induction onto buprenorphine, present as another barrier [242]. Understanding of the differences between risk of fatal overdose between these medications, makes buprenorphine a more appealing treatment for many [241]. The ability to suppress withdrawal symptoms during induction and regular use, in addition to the stigma associated with their use, were important factors when deciding between methadone and buprenorphine [241]. Overall, current literature suggests a preference for buprenorphine over methadone [238–240].

While SL buprenorphine is more commonly prescribed, BUP-XR and buprenorphine implants are becoming more available; several qualitative studies describe perceptions of these newer medications. Qualitative studies on patients' experiences on BUP-XR found that depot buprenorphine allowed patients to avoid stigma experienced at pharmacies and clinic, time to engage in activities by relieving them of OAT regimens, and savings from pharmacy fees of daily dosing [243] [244]. For some, BUP-XR prescription caused disruption of important daily social and practical supports available at pharmacies and clinics, constrained control over the dosing, and loss of income via diversion of takeaway doses [244]. Employment rates among individuals on BUP-XR have shown to double after 12-months of treatment; this highlights the potential benefit of reduced pharmacy visits [244]. A U.S. study assessing perceptions and preferences for BUP-XR and implantable medications in comparison to short acting medications for OUD, including Suboxone, found that many participants "expressed concern about invasive administration and loss of control over their treatment" if choosing injectable or implantable medications [245]. A U.K. qualitative study on the perceptions

of BUP-XR found that participants who wanted to avoid drug-using associates had more positive perceptions of the medication [246].

PERCEPTIONS, BARRIERS, AND EXPERIENCES OF OPIOID AGONIST TREATMENT AMONG YOUTH

Current literature on the barriers, perceptions, and facilitators of opioid agonist treatment among youth with opioid use disorder is limited. While some of the qualitative research findings among adults, as discussed above, can be applied to young people with OUD, there are unique OAT experiences and barriers among youth that have been identified in literature.

A study exploring self-reported treatment goals of youths found that tapering or stopping pharmacological treatment was the most reported treatment goal [247]. This is heavily connected to youth's desire for a 'normal' life and future, without long term pharmacotherapies for opioid use [247 248]. Other goals while on OAT found in the study included avoidance of recreational substances, management of OUD symptoms, improvement of mental health, and gaining employment [247]. In contrast, some youth emphasize the importance of the 'extra happiness' that opioids or OAT provide them, by reducing physical pain and mental health symptoms [248].

Youth experience unique barriers and stigmatizing beliefs held by family members and healthcare providers. An exploration of young adults with OUD found that many families held stigmatizing views of medication treatment, which unfortunately resulted in lower engagement and retention of OAT [249 250]. In addition to family member involvement, government services, teachers, or other trusted adults may also be involved in the treatment decisions of youth [249]. Overall, navigating these differing opinions can be difficult, and lead to reduced access to OAT [249]. Many healthcare providers view OAT as a 'last resort' for youth, due to the misperception that one addiction is being replaced with another; the providers will often wait until the individual had experienced a relapse, non-fatal overdose, or severe adverse effects because of their opioid use before considering OAT [180 249]. This is a major barrier for young people accessing medication treatment [249]. Overall, qualitative research is particularly well suited for this area of limited research.

The research question(s) that grounded and guided the interview guide were molded throughout the writing process and narrative review of current literature. This study attempts to answer the following three research questions:

1. What are the barriers and facilitators that youth with OUD experience when accessing and staying on OAT?
2. What knowledge, understanding, and misconceptions do youth with OUD have on OAT?
3. What are the opinions and perceptions of different forms of OAT among youth with OUD?

METHODS

This section will introduce the research methodology that was used for this qualitative research study. A qualitative approach to this research was used to gain a deeper understand of the experiences, perceptions, and barriers of OAT among youth with OUD, giving a voice to the results. The appropriateness of the constructivist approach we used will be described in greater detail below, as well as study recruitment, data collection, data analysis, reflexivity, and ethical considerations.

STUDY AIM

The primary aim of this qualitative study was to investigate the experiences, barriers, and understanding of opioid agonist treatment among youth, aged 16-24, with opioid use disorder in Vancouver, British Columbia. We sought to identify 1) knowledge and understanding, 2) barriers and facilitators, and 3) opinions and perceptions of opioid agonist treatment among youth with opioid use disorder.

METHODOLOGY AND RESEARCH PARADIGM SELECTED

Because the purpose of this research study was to gain a deeper understanding and examine the experiences and perceptions of OAT among youth, the most appropriate approach to this research was qualitative. Qualitative research "collects open-ended, emerging data with the primary intent of developing themes from the data" and seeks to understand relationships between the data [251].

This study was conducted under a constructivist paradigm. Constructivist investigations "gather a range of in-depth accounts with the aim of building a detailed picture of how a particular phenomenon is understood by those who have personal experience of it" [252]. The constructivist paradigm acknowledges that knowledge is subjective, and there is a diverse range of interpretations of reality; in conclusion, there is no overarching 'truth' [252].

REFLEXIVITY AND RESEARCHER CHARACTERISTICS

The multidisciplinary research team consisted of myself, a Master of Research and medical student; in addition, a medical researcher with the Complex Pain and Addiction Services at Vancouver General Hospital, two addictions psychiatrists, a pharmacist, and two PhD researchers specializing in both qualitative and quantitative research. The principal investigator of this study was an addictions psychiatrist who works with both youth and adults in Vancouver, British Columbia. As the primary interviewer and data analyst of this study, reflecting on my own reflexivity was important.

In a qualitative, constructivist study, researchers cannot separate themselves from the research; instead, it is important to acknowledge the role of the researchers in the co-construction of knowledge with the participants of the study. We recognize the potential influence of the prior experiences and assumptions of the researchers in shaping the outcomes of this study [253].

STUDY SETTING, RECRUITMENT, AND DATA COLLECTION

Twelve semi-structured qualitative interviews were conducted from April 2022 to June 2022 with twelve individual youth with opioid use disorder. The study was conducted in Vancouver, British Columbia. Recruitment for the study took place at Foundry Vancouver-Granville Clinic. Foundry BC is British Columbia's community-based integrated health and social network that offers young people, aged 16-24, access to mental health and substance use support, primary care, peer support, and social services [254]. Purposive sampling was used. To be eligible for the study, patients had to be between 16-24 years old, be a patient at Foundry Vancouver-Granville clinic, have a current diagnosis of OUD according to DSM-5 criteria and CRAFFT screening, and have capacity to consent. Individuals with and without OAT experience were included in this study. As Vancouver, Canada is one of the most affected regions of the opioid public health crisis, further research among these populations is especially significant [255].

Prospective participants were identified by the nursing and clinical staff at Foundry Vancouver-Granville, and capacity to consent was determined by the nursing staff at Foundry Vancouver-Granville clinic, based on their clinical assessment skills [256]. Once an eligible patient was identified, the clinical staff member briefly explained the study to the patient and offered them a letter of initial contact. If the patient expressed interest in participating in the study, the nurse directed them to the research team. A research

team member further explained the study, obtained written informed consent, and answered study questions that the eligible participant may have had. Once written informed consent was given, participants completed a semi-structured interview in a private office space at Foundry Vancouver-Granville clinic. Interviews ranged from 22 to 40 minutes in duration. Hannah Schneiderman and James Wong conducted the interviews. Approximately 18 patients were approached for recruitment. Recruitment ended when thematic saturation was reached.

Throughout the interview process, the clinical staff and research team emphasized that patient participation in the study was entirely voluntary and would not affect their current treatment. The participants were informed that they were able to withdraw from the study at any time throughout the interview process without giving a reason. The interviewer explained that quotes from the interviews would be anonymized and only used to illustrate the analyses of the study. In addition, the interview content would not be disclosed to clinical staff members unless a participant expressed intent to harm oneself or others. All participants were provided a $20 CAD honorarium for their time, commensurate with the participants time in the study, as well as minimum wage in British Columbia ($15.20/hour). This study was funded by the University College Cork, School of Medicine. The interview was recorded using a Sony ICDPX370 IC Voice Recorder. COVID-19 safety standards set by the BC Centre for Disease Control, and Vancouver Coastal Health Infection Prevention and Control were followed throughout the study. In accordance with the BREB Safe Research Guidelines, all participants were given a copy of the Safe Research Plan. This study was approved by the Behavioural Research Ethics Board of the University of British Columbia (H21-03769).

By considering participant vulnerability and research risk, this study was deemed 'high' risk. Participant vulnerability was 'high' as this study is involving youth between the ages of 16-24 years old with OUD. The research risk for this study was deemed 'medium' due to the content of the semi-structured interview. Participants may have experienced some emotional distress from the interview, as they were being asked to recall past experiences relating to substance use. If participants required support post-interview, the healthcare team at Foundry was able to provide that.

Data was stored securely, as per the BREB guidelines and UCC research data management policy. The audio recordings of the semi-structured interviews were immediately transferred to a secure computer at Vancouver General Hospital Research Pavilion. The audio recordings on the recorder were immediately wiped. The data on the computer (i.e., audio recordings, transcriptions, analyzed data) have been kept safe in a secure room at Vancouver General Hospital Research Pavilion. Record of consent was kept separately

from the data, also in an office at the Research Pavilion. All data is password protected and encrypted. Signed consent forms will be retained for 10 years and audio recording will be retained for 10 years after publication of this thesis.

INTERVIEW GUIDE

The interview guide was developed through an iterative process. This process involved reviewing the literature on opioid agonist treatment perceptions, experiences, and understanding, and collecting expert opinions from clinicians and researchers in the field, and co-investigators on the current project, Dr. Pouya Azar, Dr. Martha Ignaszewski, and Dr. Kirsten Marchand. Decisions were made, in collaboration with named experts, to focus the topic guide, ground the interview, and allocate sufficient time for discussion of each research question. The interview used an inductive approach with open-ended questions; the inductive approach is in keeping with the constructivist paradigm used in this research. The interview began by eliciting information on demographic data, past opioid use history, and opioid agonist treatment history. The background characteristics of the twelve participants, including socio-demographic data, opioid use, and OAT history, can be viewed in Table 10. All names used in this thesis are pseudonyms.

The interview guide covered the same domains of interest across all interviews; however, questions were tailored to participants' previous experience with specific opioid agonist medications. In some interviews, safe supply medications were also discussed. The full interview guide can be viewed in Appendix 1: Interview Guide.

Using open-ended questions, participants were asked to discuss their experiences, perceptions, and understanding of opioid agonist treatments including Suboxone, Sublocade, Methadone, and Kadian. As patients with and without previous OAT experience were eligible for this research study, the interview guide was tailored with probe questions for both demographics; all recruited participants did have previous OAT experience.

DATA ANALYSIS

Recorded interviews were transcribed verbatim using NVivo Transcription Software and further edited by Hannah Schneiderman [257]. Thematic Analysis (TA) using Braun and Clarke's six-phase approach was used to code and develop themes with the transcribed data [258]. Thematic analysis was used to identify, analyze, and report patterns within the collected data [258]. An inductive, qualitative descriptive analysis was

done. NVivo Qualitative Data Analysis Software (Release 1.6.2) was used as a data management tool to assist in data analysis, acting as a data repository. Excerpts from the interviews were selected to highlight the major themes and sub-themes.

The six phases of TA include familiarization, coding, searching for themes, reviewing themes, defining, and naming themes, and producing the report [258]. Firstly, familiarization was done by listening to, transcribing, reading, and re-reading the transcript data; essentially, actively immersing in the data. The second phase, coding, was done on an ongoing basis as data was being collected. We aimed to give "full and equal attention to each data item, and [identify] interesting aspects in the data items that may form the basis of repeated patterns", or themes [258]. Once all the transcripts were familiarized and coded, and data saturation was reached, we began to search for themes and sub-themes within the coded transcripts. This involved "collating all the relevant coded data extracts within the identified themes" [258].

The fourth phase of TA involved refining and reviewing the themes we identified previously; at this stage, we identified that some themes did not have enough data to support an entire theme, but rather a sub-theme, or some themes "collapsed" into each other [258]. In addition, some themes were identified to be too broad, and thus we divided the theme into multiple sub-themes or multiple major themes. The fifth phase, defining and naming themes, was subsequently completed. This involved "identifying the 'essence' of what each theme [was] about, as well as the themes overall" [258]. A detailed analysis of each theme and sub-theme was written, ensuring that each theme had a clear definition. The last and final phase of TA, producing the report, was completed once the themes were refined. During the sixth phase, we ensured to "provide sufficient evidence of the themes within the data", choosing "particularly vivid examples, or extracts, which capture[ed] the essence" of the themes and sub-themes [258].

Hannah Schneiderman, James Wong, and Samer Rihani were responsible for data analysis. Analysis evolved with further data collection, transcription, coding, and feedback from the research team. Some selected coded transcripts were further reviewed by Dr. Pouya Azar, Dr. Martha Ignaszewski, Dr. Colm O'Tuathaigh, and Dr. Niamh Coakley who have extensive experience in addiction psychiatry, as well as medical and qualitative research.

RESULTS

PARTICIPANT CHARACTERISTICS

The characteristics of the study participants are displayed in Table 10 below. All participants had used opioids or fentanyl; seven participants specified use of fentanyl in the past, while all other participants described using “down”, heroin, hydromorphone (“dillies”), and/or oxycontin. It is important to note that most illicit opioids obtained in Vancouver, BC now consist of the synthetic opioid fentanyl, however, individuals may still refer to using heroin or “down”, a slang term for illicit opioids, rather than fentanyl [259]. All participants were on an opioid agonist treatment at the time of the interview. Eight participants had previous OAT experience other than their current treatment with either the same medication or a different opioid agonist medication. Six participants had used opioids for over 5 years. Six participants were using opioids while on OAT at the time of the interview, and three participants specified fentanyl use while on their current OAT. Nine participants disclosed additional main substances of use other than opioids, including alcohol, methamphetamine, cocaine, cannabis, and MDMA. Ten participants were living in BC supportive housing. Eight participants identified as First Nations and /or Indigenous. The mean age of participants was 22 years old and ranged from 17-24. Seven participants identified as male. The accounts of the study participants reflected four major themes and six sub-themes detailed below, as identified during thematic analysis.

TABLE 10: PARTICIPANT BACKGROUND CHARACTERISTICS

Pseudonyms	Chris	Dan	James	Jay	Sam	Drew	Jennifer	Josie	Jules	Samuel	Samantha	Jeff
Age	22	24	24	23	17	22	24	20	21	24	22	21
Gender	Male	Male	Male	Non-Binary	Male	Male	Female	Female	Female	Male	Female	Male
Pronouns	He/Him	He/Him	He/Him	They/Them	He/They	He/Him	She/Her	She/They	She/They	He/Him	She/ They	He/Him
Ethnicity	Native, White	Native, Jamaican	White	White	Native	White	Native	Native, Vietnamese	Ukrainian	Native	Jamaican, Columbian, Irish, Native	Native
Accommodation	Supportive Housing	Supportive Housing	Supportive Housing	Rental Home	Family Home	Supportive Housing	Supportive Housing	Supportive Housing	Disability Housing	Supportive Housing	Transitional Home	Emergency Shelter
Employment	Unknown	Disability	Unemployed	Employed full-time	Unemployed	Unknown	Unknown	Unemployed	Volunteer work	Unemployed	Re-employment program	Unemployed
Time on OAT	2 years	Unknown	3 months	9 months	3 months	1 day	1 year	2 years	5 years	2 months	6 months	3 years
Opioid misuse duration	6 years	Unknown	3 months	7 years	2 months	5 days	1 year	5 years	5 years	6 years	12 years	6 years
Previous treatment experience other than current OAT	Suboxone, Methadone	Kadian, Suboxone, Sublocade	None	Suboxone	Suboxone, Methadone	None	None	Suboxone, Methadone	Suboxone, Kadian	Kadian, Suboxone	Suboxone	Suboxone
Current substance use	Daily fentanyl use	Daily opioid use	Daily methamphetamine and alcohol use	Daily cocaine and opioid use (hydromorphone), infrequent alcohol use	Daily alcohol and cannabis use	Recent hydromorphone use	Unknown	Daily benzodiazepine and methamphetamine use	Abstinent	Irregular opioid use	Daily fentanyl use	Daily fentanyl use
Current medication	Kadian and Hydromorphone	Methadone and Dilaudids	Methadone	Sublocade	Sublocade	Suboxone	Suboxone	Sublocade	Sublocade	Methadone	Suboxone	Methadone
Main substances of use	Fentanyl	Down	Alcohol, methamphetamine, fentanyl	Alcohol, hydromorphone, fentanyl, oxycontin, cocaine	Alcohol, cannabis, hydromorphone	Cocaine, hydromorphone, MDMA	Methamphetamine, down, cocaine	Heroin, fentanyl, crystal meth	Heroin, fentanyl, methamphetamine	Down	Fentanyl	Down
Interview Duration	36 min	25 min	29 min	39 min	35 min	23 min	22 min	33 min	40 min	26 min	40 min	28 min

Table 11 below outlines the major themes and sub-theme that we will discuss in greater detail in the sections below. The first major theme describes the ways in which youth 'prepare' for initiation onto OAT, while the second major theme describes the effects of opioid agonist treatment on the personal relationships and social lives of youth with OUD. The third major theme involves the advantages, disadvantages, and barriers of the various OAT options, and the experiences of youth navigating the choices of medications, often through trial and error. Finally, the fourth major theme describes the educational and supportive roles of healthcare workers for youth on OAT, in addition to areas for further education and clarification among young people regarding OAT.

TABLE 11: MAJOR THEMES AND SUB-THEMES

Major Themes	*Sub-Themes*
Preparedness to Begin OAT	Altered Enjoyment from Opioids and Awareness of the Consequences
	Mental Health and OAT: A Tool in the Toolbox
	Perceptions of OAT that Lead to Stigma
Effects of OAT on Personal Relationships and Social Life	Distancing from People who Use Opioids and the Downtown East Side of Vancouver
	Reconnecting and Repairing Relationships with Those Supportive of Recovery
Navigating the Pharmacological Treatment Options	Naloxone: "It very much complicates things"
	Barriers of Suboxone and Methadone
	Variability of Length of OAT Duration
The Role of Healthcare Workers	Education and Support
	Desire for Further Education on OAT

PREPAREDNESS TO BEGIN OAT

'Preparedness' to begin opioid agonist treatment encompasses the thoughts and experiences of youth in the weeks to months leading up to their first dose of OAT and the steps they took to become 'ready' to start treatment. Many opioid-dependent youth who participated in this study described 1) altered enjoyment from opioids and an increased awareness of the consequences of opioid misuse prior

to initiation onto OAT, 2) addressing mental health related difficulties connected to their opioid use and finding mental health resources to support them while on OAT, and 3) addressing internalized, stigmatizing beliefs of OAT that did not serve their recovery.

Altered Enjoyment from Opioids and Awareness of the Consequences

Many participants described a concerning, dark period, involving increasingly dangerous opioid use behaviours, prior to their decision to begin treatment. This frequently involved increased fentanyl use, or a shift from less potent opioids to fentanyl use. Jay described their opioid use the week leading up to initiation onto Sublocade, compared to their past opioid use which they deemed as less problematic, not requiring treatment:

> "I was so fucking blasted all the time [in the weeks leading up to initiation onto OAT], that I just didn't give a shit, like, how anyone treated me or anything", while in the past, "I wasn't doing anything like, dangerous or stupid. I wasn't like unhinged or anything. I wasn't using fent [i.e., fentanyl] or anything at the time. I was just using hydromorphone" (23-year-old White non-binary person, Jay)

Some participants explained that they began to dislike using opioids, which was when they felt ready and decided to start treatment. With a goal of achieving abstinence from opioids on Suboxone, Drew described his dislike for getting high that led to initiation onto treatment:

> "It was just uncomfortable. It felt like my brain was swelling. It felt like I couldn't think, at all, about anything. And the withdrawal was like that too. Like, I just can't think" (22-year-old White male, Drew)

While Drew aimed to achieve complete abstinence from illicit opioids, many participants of the study did not have the same goals as Drew. At the time of interview, half of all participants were using opioids while on OAT, highlighting that some youth start OAT to reduce their illicit usage and risky behaviours, without an expressed goal of abstinence. Therefore, it is important to note that preparedness to stop illicit opioid use is substantially different from starting OAT. Uncontrolled withdrawal symptoms that began to heavily impact on their lifestyle, including employment, was another common reason for initiation onto treatment. When Sam was asked by the interviewer what kind of individual would benefit from pharmacological treatment, he described:

> "Somebody who's having, like, violent withdrawals or someone who doesn't like using anymore. The feeling isn't good anymore" (17-year-old Indigenous male, Sam)

Some also talked about an increased cognizance of opioid overdose, or a recent personal non-fatal overdose experience, that acted as a 'wakeup call' to initiate onto treatment, in attempts to adopt safer opioid use practices, abstain from opioids, or prevent an opioid-related death. When asked by the interviewer about his reasons for initiating onto Sublocade, Sam explained:

> "I wanted a way to prevent overdosing. I've gotten close to overdosing… so I went to the hospital, and I got evaluated there. And um, they gave me stuff for my severe nausea and vomiting. And they advised me not to use again. But of course, I still did, over the few months after that" (17-year-old Indigenous male, Sam)

Josie had similar overdose experiences to Sam. These experiences created an increased awareness of the dangers of opioid use, influencing her to begin OAT. Josie explained that:

> "There was a person [at her accommodation] who was living [at her accommodation] and yeah, he just easily passed away and that was so fast, like it was like a blink of an eye. And when I first overdosed, it was like I was out for 20 minutes with no heartbeat. And it's scary, so, when I went on Sublocade it was like an eye opener that you can be safe when using" (20-year-old Indigenous and Vietnamese female, Josie)

While opioid overdose was a traumatic event that led many to seeking help, physical danger was another. Jules and Samantha described similar thoughts and experiences relating to their physical safety while on illicit opioids, with a history of sexual assault, harassment, and threats while using opioids:

> "One of these days I'm going to be so sick, and I'm going to be down in an alleyway and not give a shit what happens as long as I get a taste of something. So, I said, fuck, ok, I love her too much [points at dog]. It's gotten too bad" (22-year-old Jamaican, Columbian, Irish, and Native female, Samantha)

> "Drugs put you in areas and situations that sometimes end up with you being hurt. Other things do too, but like, you do things you wouldn't normally do. Like, I wouldn't have been

down there [i.e., Downtown East Side of Vancouver], and I wouldn't have followed a strange man [down an alley] because he was going to give me drugs" (21-year-old Ukrainian female, Jules)

While withdrawal symptoms, opioid-related overdose prevention, and a dislike for opioids are motivating factors to begin pharmacological treatment, many participants described that an overall positive mindset when starting treatment was essential. Dan explained how your mindset before beginning treatment affects your success on treatment:

"It's just like how you think about [OAT], because if you go into it thinking negative, you're automatically not going to, like, come through it, like come out of it. So, if you go into it positive, you're going to come out of it thinking that you can do it and you can come out of it" (24-year-old Indigenous and Jamaican male, Dan)

Essentially, preparedness precedes the initiation of pharmacological treatment, and is linked to the motivating factors for beginning OAT. Regardless of previous OAT experience or newness to OAT, all participants described specific motivations and/ or impactful events leading up the initiation of their current treatment.

Mental Health and OAT: A Tool in the Toolbox

Another important component relating to the preparation of initiation onto treatment, is addressing the complex relationship between mental health and opioid misuse, while accumulating additional resources and tools to combat mental health difficulties apart from OAT. Establishing the reasons or triggers for opioid misuse is often the first step. For many individuals, mental health and addiction are heavily connected, as described by Jay:

"I never used opioids to get high… I think the biggest thing for me was just, like, the ability to handle my emotions better" (23-year-old White non-binary person, Jay)

If opioids are used to combat mental health difficulties that arise day to day, the initiation of opioid agonist treatment can take away an essential and long-standing coping tool. Therefore, to adequately 'prepare' for initiation onto OAT, mental health must be addressed. James described feeling inadequately prepared prior to his initiation onto Methadone:

> "I think a lot of it [i.e., opioid misuse] was mental health related for me. I suffer with schizophrenia, depression, multiple personality disorder. The list goes on and on. My treatment [i.e., methadone], was a treatment for my addiction. It's addressing the addiction issue, but it wasn't addressing the mental health issues behind it" (24-year-old White male, James)

Similarly, Jules described going to a detoxification facility, feeling inadequately prepared for her mental health difficulties and suicidal ideation. She relied heavily on her opioid use to deal with this:

> "I would want to kill myself. Like I couldn't keep myself alive. I went to detox because I really wanted to get clean. But within 24 hours, I was at the point where I was going to hang myself. So, I left, and I ended up using again because that was the only way to keep me alive" (21-year-old Ukrainian female, Jules)

Jay had a different experience to James. In combination with their initiation onto Sublocade, Jay described accessing mental health resources, including therapy, that allowed them to treat their OUD while simultaneously addressing underlying mental-health related issues and traumas that led to their OUD:

> "The most important treatment is the resources available. If it was just treatment [i.e., Sublocade], I don't think that it would be very helpful. But having that with therapy and everything that I'm going through, is really starting to make a difference… it doesn't feel like I'm just sort of slapping a Band-Aid on the problem" (23-year-old White non-binary person, Jay)

Many participants concluded with a similar sentiment to Drew, viewing OAT as a 'tool in their toolbox' rather than a 'one stop shop' to recovery:

> "Counselling is equally as important as taking Suboxone [i.e., opioid agonist treatment]. I think it's mostly a tool" (22-year-old White male, Drew)

While OAT was not viewed as a psychiatric medication, some participants explained that OAT did help with staying stable mentally, as described by Jules:

> "It's not mental health medication [i.e., Sublocade], but it helps me be able to handle, like, rough situations better because my addiction brain is like, more shut down. But part of that is

like not drinking, not using, going to my appointments, being by myself" (21-year-old Ukrainian female, Jules)

Unfortunately, many participants described extreme difficulties with finding suitable psychiatric medications. This impacted on their opioid use recovery. Jules explained:

"I'm very severely mentally ill. It took eight years for my [psychiatric] meds to finally start working" (21-year-old Ukrainian female, Jules)

Overall, most youth talked about OAT for addiction being a 'tool' rather than a cure, as it does not address the underlying mental health issues that often lead to, or fuel continued opioid misuse. Some participants said that counselling or therapy was just as important as OAT. Others explained that being on the correct medication for their mental health diagnoses was essential.

An acute housing crisis led many youths to opioid misuse, as homelessness played a major role in the participants mental health decline and exposure to opioids. Obtaining stable housing prior to starting OAT was essential for many participants. As Samuel described, his opioid misuse was most severe when he was homeless. He was able to reduce his illicit opioid use when he found stable housing:

"It [i.e., opioid use] got kind of bad when I was homeless, but after [finding housing], it's kind of leveled out. It's like, uh, it's uh, I guess, sort of like where I am now" (24-year-old Indigenous male, Samuel)

Some participants said that they felt overwhelmed trying to tackle everything in life all at once, going on to explain that once they began OAT, they needed to tackle additional tasks (i.e., housing, school, work, sobriety, relationships, therapy). This led to feelings of overwhelm, which impacted on their mental health. Others said that it's helpful not having to be in a treatment facility and being able to focus on more than just recovery. Jay explained how opioid agonist treatment allows for more broad recovery, as compared to rehabilitation facilities and withdrawal management that they experienced in the past:

"The nice thing is, I'm not rushed too, I can sort of get my shit together. It's not like a withdrawal where everything has to happen all at once. Or even rehab, where I go, over a few months, and I like completely focus only on that one thing. I can sort of focus on the other things and build all of that, before I get completely sober" (23-year-old White non-binary person, Jay)

In conclusion, counselling, medication, and stable housing are adjuvant factors which influence preparedness to begin OAT.

Perceptions of OAT that Lead to Stigma

Addressing stigmatizing, internalized thoughts on OAT is important for preparedness to begin treatment. The most common internalized stigma that was mentioned by many participants, was the belief that one addiction, illicit opioids, is being substituted for another addiction, opioid agonist treatment. Essentially the belief that you are still using, even when you are on OAT. As described by Jay:

> "Sublocade still, like, it's not that it gets you high, but it has some of the same benefits. So, I guess it's not really being sober. Like, I wouldn't call it that… it's sort of like when people quit smoking, they always vape and shit, it's sort of, I don't know, similar to that" (23-year-old White non-binary person, Jay)

While many participants held similar beliefs to Jay, some explained that their negative perceptions of pharmacological treatment shifted once they began OAT. This means that their beliefs were left unaddressed prior to initiation onto OAT, acting as a possible barrier to treatment-seeking. As described by James:

> "I had like a negative view towards it. Like when I was in treatment [i.e., a detox facility, not on OAT], I thought people who were staying sober, but while on Suboxone of Methadone, I thought they weren't really sober… I don't think that now, but before I might have" (24-year-old White male, James)

Individuals seeking pharmacological treatment may be influenced or pressured by peers that hold these negative, stigmatizing beliefs of OAT. Jay went on to explain:

> "People always make fun of people calling themselves sober, and they're on Sublocade" (23-year-old White non-binary person, Jay)

Overall, many participants described stigmatizing societal views of OAT as one and the same; being on OAT or not being on OAT, you are still seen as an addict.

EFFECTS OF OAT ON PERSONAL RELATIONSHIPS AND SOCIAL LIFE

Common goals for youth while being on pharmacological treatment involved personal relationships. This looked different for each participant, but commonly involved 1) distancing themselves from the Downtown East Side of Vancouver and their previous social circles who used opioids, and 2) reconnecting and repairing relationships with people who don't use drugs and/or are supportive of their journey to recovery.

Distancing from People who Use Opioids and the Downtown East Side of Vancouver

Participants described the need to cut out or leave behind toxic relationships from their lives, including family members, friends, and partners, commonly due to drug use and abuse. While this was beneficial for their recovery on OAT, many participants found this to be extremely isolating, as their social interactions prior to OAT initiation were often centered around drug use. Since becoming abstinent or lowering usage of opioids while on OAT, being surrounding by people who use drugs was triggering and lonely. They couldn't participate in an activity they previously found enjoyable and bonding. In addition, some found that discontinuing opioids led to exclusion from their previous social circle and friend groups. Many participants explained that removing themselves from the DTES of Vancouver was beneficial, as most of their drug using relationships were located there. This was distressing for many participants of the study, as they struggled to find companionship and community that supports their new goals and aligns with their lifestyle. Jay explained how the people they previously perceived as friends, excluded, and distanced themselves from Jay when they stopped using and carrying fentanyl:

> "As soon as I wasn't carrying a quarter kilo with me every day, they just didn't give a shit" (23-year-old White non-binary person, Jay)

Similarly, Josie explained how her relationship with her family, and particularly her mother, had been affected by initiation onto OAT and her goals of opioid abstinence:

> "I started using when I was 15 years old, and I was born into a family of addiction. And my mom was using while I was born, so I was withdrawing as a newborn. So, I guess I got back into it… like now that I'm on treatment, I barely ever see my mother… when I was using, it was something we had in common, so we could use together. And that was like, that was our way of communicating and stuff" (20-year-old Indigenous and Vietnamese female, Josie)

Similarly, when asked by the interviewer "Who introduced you to down [i.e., opioids]?", Jennifer answered:

"Well, my friends. They're not so much friends now. But the ones who quit using are still my friends" (24-year-old Indigenous female, Jennifer)

James highlighted that his life in recent years was surrounded by people who use drugs. This emphasizes how difficult it is to distance yourself from that circle, even while on treatment:

"I've always been very anxious and depressed. I think I was undiagnosed as a child… and I think you get to that certain point in life where you're, you're homeless, you don't have money, you don't have a whole lot to do and then you meet people, and then sooner or later, you're going to get introduced to hard drugs, right?" (24-year-old White male, James)

Reconnecting and Repairing Relationships with Those Supportive of Recovery

Others described finding or reconnecting with supportive friends and family during recovery who encouraged OAT. Some talked about repairing relationships that were strained while they were using illicit opioids. Jay explained that they began to reconnect with supports who did not use drugs:

"I think they're just all very happy to see me sort of have stability, have a job, be able to accomplish projects" (23-year-old White non-binary person, Jay)

Some participants explained that while being on OAT, their social functioning improved, and they were able to repair relationships with family members and friends. Chris explained how starting OAT helped him to spend quality time with loved ones:

"I was able to still act normal… I didn't have to, you know, be falling asleep and falling out of my chair while I'm trying to sit next to my loved ones, trying to watch a movie or something" (22-year-old White and Indigenous male, Chris)

Similarly, Jules explained that a major goal while on OAT was to repair relationships that she couldn't maintain previously. Jules explained how she wished to be a present role-model for her brother, as she was prior to starting opioids:

"I always wanted to get better. I wanted to be able to have a life. And like, for my little brother. I helped raise him, and like, just yeah" (21-year-old Ukrainian female, Jules)

Although this was less commonly described in the interviews, one participant explained that he initiated onto OAT with a friend. They were supporting one another in recovery. At the time of interview both Dan and his friend started treatment that day:

> "One of my bros, they just started treatment today. And he wants to get back into bodybuilding. So, we're basically like building each other up to get clean. So yeah, it's great" (24-year-old Indigenous and Jamaican male, Dan)

While being on OAT, this is a time for some participants to discover healthy relationships, possibly for the first time. Jules explained:

> "I want to be able to work on healthy coping skills. I want to be able to work on healthy relationships and healthy friendships, so people don't hurt me again… I want to understand healthy relationships" (21-year-old Ukrainian female, Jules)

Overall, balancing their recovery on OAT with personal relationships was a struggle for many participants.

NAVIGATING THE PHARMACOLOGICAL TREATMENT OPTIONS

Navigating the abundance of opioid agonist treatment options while attempting to find what works best for the individual can be a challenge, and often involves trial and error. Every participant described a unique experience with different treatment options, with most acknowledging that what works best for them, may not work for another person on OAT; it is an individual and unique experience. Factors such as drugs of choice, length of opioid use, and goals for abstinence or reduced usage are some of the many factors that influence an individual's experience with treatment, leading to specific OAT preferences. The most common ideas described by participants in relation to navigating the various OAT options were 1) the presence of naloxone, an opioid antagonist, in relation to continued opioid use, 2) important barriers of Suboxone and Methadone, and 3) variability of length of pharmacological treatment duration.

Naloxone: "It very much complicates things"

Medications that contain the opioid antagonist, naloxone, was viewed differently depending on an individual's goals relating to abstinence or reduced usage of opioids while being on pharmacological treatment. Since starting Sublocade, Jay had become abstinent from fentanyl, however, continued to use oxycontin irregularly. They described their reasons behind choosing Sublocade as opposed to Suboxone:

> "Because Sublocade is just buprenorphine, Suboxone has naloxone in it, so it very much complicates things with the Suboxone, at least for me… at least when I use now, the nice thing is I don't get nearly as messed up or anything" (23-year-old White non-binary person, Jay)

Chris described his negative experiences of Suboxone while continuing to use fentanyl daily. He subsequently was initiated onto Kadian, slow-release oral morphine, which resolved these issues:

> "It took away the good feeling that I got, and I really, really hated that. I wasted money on that. Taking Suboxone, I wasted my money, the money I tried to spend on myself to feel good. I wasted a lot of money taking Suboxone" (22-year-old White and Indigenous male, Chris)

James described similar views of Suboxone to Chris and Jay, and therefore, James chose Methadone as opposed to Suboxone:

> "I don't want to go on Suboxone. And that was because, if you do go back to using again, they put something in the Suboxone, an opioid blocker, and you have to end up, like, using more product to get high" (24-year-old White male, James)

Overall, naloxone was viewed as a barrier to treatment for many individuals interviewed in this study, among those without a goal for abstinence in particular.

Barriers of Suboxone and Methadone

While the presence of naloxone was a commonly described disadvantage of Suboxone among those with a desire for continued opioid use on OAT, some disadvantages of methadone also arose during interviews. James described that a common deterrent from methadone as a treatment option is the more severe withdrawal symptoms of methadone as compared to medications containing buprenorphine:

> "I think one of the negatives would be the withdrawal symptoms from methadone are said to be like up to seven times worse than the withdrawal from heroin" (24-year-old White male, James)

Like James, Jeff explained that he doesn't want to be on Methadone for a prolonged period because of the severe withdrawal symptoms from Methadone:

> "I hear methadone isn't the greatest for withdrawals either, so soon enough, I'm going to have to stop that before things get really bad" (21-year-old Indigenous male, Jeff)

Another disadvantage of Suboxone identified during interviews was severe precipitated withdrawal during initiation onto Suboxone. Samuel explained:

> "Probably the disadvantage of Suboxone is that you have to, like, completely stop [all opioids] before you start taking [Suboxone], so there's no precipitated withdrawal. And then with methadone, it's like, it's different, like there's no precipitated withdrawal" (24-year-old Indigenous male, Samuel)

Another disadvantage of Suboxone, as described by some participants, was the strong aversion to the taste of sublingual buprenorphine tablets, and the inconvenient length of time for dissolution of the tablets. Sam and Jules explained their primary reason for transitioning away from Suboxone:

> "It was very hard to use, like I had to put it under my tongue and make sure the whole thing melted, and that took a long time" (17-year-old Indigenous male, Sam)

> "Keeping it under my tongue made me gag" (21-year-old Ukrainian female, Jules)

While some participants described convenient access to daily OAT consumption through home delivery programs, others explained that daily pharmacy visits were inconvenient, disruptive, and impractical. As described by James, inconvenient access to OAT, both Suboxone and Methadone, can result in missed doses of pharmacological treatment:

> "It's kind of a hassle having to go to the pharmacy every day, to be honest with you, because it interferes with your daily schedule, right? Like the pharmacy is open from nine to five. So, I have to make sure I'm going there from nine to five. And I'll be honest, there was a few, more than a few times, where I just forget and then it would be past five o'clock and then I would miss my dose" (24-year-old White male, James)

Like James, Jules described daily pharmacy visits being a major barrier for her:

> "I can't go into a pharmacy every day. I've never been able to go into a pharmacy every day, and I'm never going to be, right?" (21-year-old Ukrainian female, Jules)

Missed doses due to inconvenient access was found to be a major complication, as patients could go into withdrawal and were far more likely to use opioids. Overall, each participant had unique experiences with the different treatment options. Common barriers of medications containing buprenorphine included

precipitated withdrawal during induction, the taste of SL tablets, and Suboxone containing the opioid antagonist naloxone. A barrier of methadone was the severe withdrawal symptoms during discontinuation or missed doses. Both Methadone and Suboxone often required daily pharmacy visits, which could result in missed doses. Sublocade combats this barrier for many, as a monthly injection is required rather than daily visits. There was large variability with each medication providing adequate withdrawal and craving management.

Variability of Length of OAT Duration

While deciding between opioid agonist medications was a complex process for many individuals, another important concept related to the navigation of pharmacological treatment was the length of OAT duration. All participants were asked the question: "How long do you see yourself on treatment?". Answers varied greatly; some participants said that they envision themselves on treatment for a short period of time, while others for the rest of their life. The majority, however, did not have a clear idea of how long they needed to be on treatment for, or what was recommended before treatment cessation. Overall, there was variability with desired length of OAT duration, and some answers included:

> "Indefinitely at this point" (24-year-old White male, James)

> "At least a year… I'm not sure, likely more than a year, but that's the minimum" (17-year-old Indigenous male, Sam)

> "Just until, I don't know, just until I stop feeling bad. Like I just take it when I feel, like, a little bit nauseous or dizzy or something. So as soon as that goes away, then I'll stop taking it" (22-year-old White male, Drew)

> "Maybe a couple of months?" (24-year-old Indigenous female, Jennifer)

> "I don't know, maybe till I'm twenty-five and see how steady I am. I have been, even recently, thinking about it because I have been doing so well, but I still think I'm pretty fragile in the recovery of my opioid use. So, it's a bit of like a tricky decision to make" (20-year-old Indigenous and Vietnamese female, Josie)

Most participants explained that they would prefer to not be on medication, however, they want to act responsibly and remain on OAT until the time is right, as described by Jules:

> "If I need it, I'm not going to risk my life, right? I'm not going to relapse because I choose not to be on it. But like, no one really wants to be on medication their whole life if they don't need it, need it" (21-year-old Ukrainian female, Jules)

Jules went on to explain that an indicator for the discontinuation of OAT would be stability in various aspects of life:

> "I would have to be very mentally stable [to discontinue pharmacological opioid treatment]. Hence, the next two years. Counselling groups, learning skills, having a routine, getting used to like, being busier, helping others, and then slowly transitioning into working or school. But making sure I'm stable doing that before I get off [opioid agonist treatment]." (21-year-old Ukrainian female, Jules)

While Jules listed concrete examples of goals she would like to achieve prior to discontinuation of OAT, many participants were not as clear, like Josie:

> "I don't know, maybe till I'm twenty-five and see how steady I am. I have been, even recently, thinking about it because I have been doing so well, but I still think I'm pretty fragile in the recovery of my opioid use. So, it's a bit of like a tricky decision to make" (20-year-old Indigenous and Vietnamese female, Josie)

Most participants did not have extensive conversations about the length of their treatment for their OUD with their healthcare team. This is a major contributing factor to the large variability and uncertainty of participant answers.

THE ROLE OF HEALTHCARE WORKERS

The importance of positive healthcare worker-patient relationships while on OAT was described by most participants. Education and support were two vital roles of healthcare staff, as identified during interviews. The desire for further education and understanding of OAT and OUD in a reliable setting, such as a pharmacy or clinic, was another important concept in relation to the role of the clinical staff.

Education and Support

Many participants explained how important the initial interactions were with their doctors and nurses when initiating onto OAT. Chris described his initial interaction with his healthcare team as a positive and informative experience, explaining that:

> "They told me to sit down and to have a conversation with them. And they initially… they brought out an empty pill bottle, and showed me the um, like the name of it. And then they brought, like, one of the pills just to show me… what it would look like" (22-year-old White and Indigenous male, Chris)

Chris went on to highlight the positive impact of the prescribing physician during their first interaction:

> "[The physician] definitely understood my… happiness, and he definitely cared, cared a lot for it. He definitely showed a lot of compassion for his job and for the people here [i.e., at the clinic] and for me" (22-year-old White and Indigenous male, Chris)

Chris's accounts of his first encounter with his healthcare team demonstrates the importance of patient-centered language and investing adequate time for patient education. Another important concept described by many participants was how a positive mindset of pharmacological treatment can affect perceptions of treatment staff and compliance. Dan explained how his willingness to start treatment influenced his perceptions of healthcare staff as being more helpful and collaborative:

> "When I went on [OAT] being positive and being like, I can get out of it [i.e., abstain from opioids], it was more easy going into it, because instead of thinking all these staff are just here to boss you around, you're going into it like, these people are trying to help you get out of, like, addiction and actually trying to get you back into a stable lifestyle" (24-year-old Indigenous and Jamaican male, Dan)

Dan went on to explain that he believed his willingness to continue opioids impacted his treatment by healthcare staff on OAT:

> "If you are having negative thoughts about [OAT], and you were with the staff, they kind of already know that you are like, having thoughts of using [opioids]. So, like, they kind of don't really try hard with, like, getting you out of it, because they see like, you're a lost cause" (24-year-old Indigenous and Jamaican male, Dan)

In contrast to Dan's experiences, Josie described a close relationship with her addiction counsellor that positively impacted her opioid use and willingness to start treatment. This highlights the importance of building strong, long-term relationships:

> "[My addiction counsellor] was really helpful to maintain. She gave me reassurance to not overdose, because "if you use, you die" she'd say, and if you die, you have no more chance in the world. She would always be a great listener and like, listen to my cravings and understand where I would be coming from." (20-year-old Indigenous and Vietnamese female, Josie)

The idea of trust was a major concept for many when talking about their healthcare team. Jules explained that in order to obtain carries and build relationships, you need "trust. You have to trust the doctor. The doctor has to trust you". She further explained:

> "I'm very honest. So, once I had a doctor, I got carries quick. So, I told them, yeah, I used. Yes, I didn't take the Suboxone that day. And like, that teaches, like shows them, that like, if something happens, you're going to tell them. You're not going to keep taking the medication and possibly overdose" (21-year-old Ukrainian female, Jules)

Overall, many participants explained that most of the OAT education they were given in a clinical setting was when they first started treatment. They appreciated when their doctor took the time to explain about treatment side effects, pharmacology, and various OAT options, and spend a considerable amount of time with them. Some participants talked about the importance of receiving praise and support from their healthcare team, while other participants explained that clinic staff members can be perceived as intimidating or unsupportive prior to establishing trust with the team.

Desire for Further Education on OAT

While many participants described informative sessions with their healthcare team on OAT, analysis of the interviews also identified a desire for further education among youth on OAT. The most common area for further education was a greater understanding of long-term effects of pharmacological treatment, as outlined by Sam and Drew:

> "I do wish I knew what the long-term effects [of OAT] are and how long, how many years it could last, and things like that" (17-year-old Indigenous male, Sam)

> "I'd like to know more about the long-term effects" (22-year-old White male, Drew)

Others described a desire for further education of opioid and OAT pharmacology, which could be beneficial when deciding between medications that contain an opioid antagonist. When asked by the interviewer "Is there anything you wish you knew more about?", Drew explained:

> "The mechanism of action. Like I don't really know what an opioid receptor is responsible for and, like, its network" (22-year-old White male, Drew)

Finally, some participants held some common myths that may have not been addressed by healthcare staff, including James:

> "Apparently [methadone] like, decreases your bone density" (24-year-old White male, James)

Many participants expressed a desire for further education on OAT. They would like to know more about long-term and short-term side effects, pharmacology of OAT, and OAT during pregnancy. Many participants found most of their information on OAT from clinic staff or online resources, and some from treatment facilities, including detoxification and rehabilitation facilities.

DISCUSSION

The findings of this study highlight the complexities involving individual experiences of initiation and retention of opioid agonist treatment, as well as the unique barriers of OAT that young people with OUD experience. There are several important findings from this study worthy of discussion: (1) participants described various forms of preparation prior to initiation onto OAT that functioned to assist with OAT retention; (2) building healthier personal relationships and distancing from drug-using social circles was a common goal for youth on OAT, while there were concerns of social isolation; (3) perceived advantages and disadvantages of the various OAT options creates unique experiences for each individual navigating the pharmacological choices; and (4) healthcare staff function to support youth with treatment retention, education and emotional support, while there is still room for improved education.

The first important finding of this study was the mental and psychological preparation necessary for successful retention of opioid agonist treatment; this included addressing stigmatizing beliefs of OAT. Many participants held a common belief, known as the 'anti-medication' bias, where pharmacological treatment for OUD is viewed as simply replacing one addiction for another [180]. Qualitative studies on adult populations

have shown similar findings, describing these stigmatizing beliefs as a major barrier for treatment-seeking individuals [231] [232] [233]. The anti-medication bias can be seen among healthcare providers as well, manifesting as a reluctance to prescribe opioid agonist medications [249]. This study had similar findings; Sam, for example, had a delayed initiation onto OAT after a non-fatal overdose. This is a common experience for many young people with OUD and can put individuals at an increased risk of overdose or relapse. Acknowledging and addressing these beliefs is essential for combatting the stigma associated with OAT. First, acknowledging that this is a common belief among both patients and healthcare workers allows for improvements in education of OAT, essentially, debunking common misperceptions of pharmacological treatment. Improving education will function to increase the amount of young people accessing OAT, thereby reducing the morbidity and mortality of this at-risk population [41,42]. While stigma affects both young people and adults, youth may experience greater judgement and influence from adult figures, than that of adults [249]. Therefore, addressing stigmatizing beliefs within family members, teachers, and trusted adults involved in the care of the young person may also help to lower treatment-seeking barriers. Essentially, young people are often at greater risk of influence or pressure from both peers and adult figures [249]. This finding has implications for both education of healthcare providers and treatment for young people with OUD.

Another finding linked to preparation prior to OAT initiation, was the importance of mental health related resources, psychiatric medications, and personal reflection on the connection between mental health difficulties, triggers, and opioid misuse. As described in current literature, young people are substantially less likely to receive behavioural health services following an opioid related overdose, compared to adults [180]. Although psychosocial treatment interventions are recommended in clinical practice youth guidelines, there is a greater emphasis on timely OAT initiation. The effectiveness of psychosocial services among adult populations is divided in literature, with some studies showing little benefit [109] [110]. The findings of this study support the efficacy and profound impact of psychosocial services, including therapy and counselling, among young people as a combined treatment with OAT. Early recognition and diagnosis of mental health disorders among youth is also extremely important.

The second important finding is the effect of OAT on personal relationships and the social lives of young people with OUD. While many participants in this study found that healthy, supportive relationships allowed for greater treatment retention, others found that distancing themselves from their previous drug-using social spheres caused severe feelings of isolation. Feelings of shame may come up for some as they attempt to repair relationships that were dismantled while struggling with their opioid misuse; behaving in

secrecy to obtain or use opioids, becoming less invested in relationships that exist outside of their drug-using sphere, and missing social obligations to use opioids, are some ways in which their relationships may have been impacted. Social isolation is particularly worrisome for young people, as there is a strong association between depression and anxiety, and social isolation; as well, reduced cognitive development is seen among young people in social isolation [260]. Unfortunately, for many participants, relationships with family members were particularly complicated, as many families struggled with generational substance abuse. Current literature shows that over 12% of children are exposed to substance use disorder(s) from at least one parent or guardian [84]. These findings suggest that family and social support are essential for young people, particularly during the transitional period of OAT initiation.

The third important finding of this study were the perceived advantages and disadvantages of the various OAT options, particularly Methadone and Suboxone, which created individual experiences for young people navigating the pharmacological choices. As seen in current literature, Methadone was perceived to be more addictive, leading to worse withdrawal symptoms upon discontinuation [238]. While current qualitative literature on adult populations suggests a preference for medications containing buprenorphine over methadone, this study found that youth who continued to use opioids while on OAT often preferred methadone [238–240]. Those with a goal of abstinence, often preferred buprenorphine, either Suboxone or Sublocade. While discussing the difficulties of navigating the various treatment options, many participants described a concern for long-term OAT. There is limited research on the optimal length of opioid agonist treatment [261]. Length of OAT duration should be discussed more with young people, in a collaborative way, as many wish to be on treatment for a finite amount of time due to the barriers and stigmas associated with long-term pharmacological treatment [247].

The fourth finding is the importance of education and support from healthcare workers among youth on OAT. Other studies among adult populations have shown similar findings, emphasizing the need for supportive and non-judgmental staff [226]. The concept of being 'a part of care' was seen in this study; Jules, for example, described the importance of collaboration between patient and provider, particularly when attempting to access carries [227]. Many participants emphasized the impact of early education while starting treatment and the appreciation they had for staff carving out time specifically to explain what they may expect from treatment; similar findings were found in another qualitative study on youth [262]. While these findings are encouraging, many participants described a desire for further education. These findings suggest that long-term and short-term side effects, and the pharmacology of opioids and opioid agonist

treatment, should be discussed in greater detail with youth, as many participants desired reliable information on these topics.

CONCLUSIONS

In conclusion, the data from this qualitative research study on the experiences of OAT among youth with OUD offers valuable information. This information can be used to inform future research efforts, clinical practice, and policy change to improve the treatment and social supports available for young people struggling with opioid misuse.

LIMITATIONS

As with all qualitative research, the findings of this study are not generalizable. Therefore, further investigations among different patient populations of young people are recommended, including different cultural and geographical contexts. Although this study data is not generalizable, we have included a rich description of the context to allow the reader to make their own decisions about transferability to other contexts. Another limitation is that the study sample was recruited from a single treatment facility in Vancouver, BC.

Because the interviews took place at Foundry Vancouver-Granville clinic, where recruitment was done, and interview questions were largely related to pharmacological treatment that was commonly provided to participants by Foundry clinic, there is a potential for social-desirability bias. Participants may have felt a need to under-report undesirable effects of OAT or negative experiences with healthcare staff, due to a fear of speaking more directly about their negative experiences in treatment, despite efforts being made by research staff to create a safe and non-judgmental environment.

FUTURE DIRECTIONS

Future research is essential to further develop our understanding of young people with OUD, and their experiences seeking and retaining OAT. This research found that social support, including mental health resources and stable housing, was a critical factor for treatment initiation and retention. Future research is needed to improve social supports available to young people in various demographic and cultural contexts. Another important theme found in this research was the shifts in personal relationships and social circles

due to opioid-use changes and initiation onto OAT; future research is needed to establish how to support young people socially, for example, by connecting them with other youth with similar recovery goals.

Comparing youth and adult populations is an interesting research prospect, to highlight the unique barriers that youth experience compared to that of adults. Particularly, comparing the internalized stigmatizing beliefs that youth and adults hold can be beneficial to inform age-appropriate healthcare education and support. Research focusing on specific opioid agonist medications or safe supply medications, rather than OAT in general, is valuable to delve further into the perceptions of specific pharmacological treatments. Although this study did not exclude youth without experience on OAT, we did not recruit any participants without OAT experience; research on young people who misuse opioids without OAT experience can provide valuable information on barriers to treatment access for the first time. These thoughts and experiences may be forgotten by participants who have had extensive experience on OAT for many years.

Due to the concerning fourth wave of the opioid crisis, research focusing on polysubstance use behaviours is essential. As seen in this study, many participants on OAT are using substances other than opioids. Developing a further understanding of polysubstance use among young people, specifically those with an OUD on OAT, is essential. Another characteristic of the fourth wave is mental illness co-morbidities becoming more evident among those with opioid/stimulant use disorders [29]. Research focusing more heavily on mental health and psychiatric co-morbidities among youth with OUD, and how this relates to treatment-seeking and retention, is another important area for further research.

REFERENCES

1. Trescot AM, Datta S, Lee M, Hansen H. Opioid Pharmacology. Accessed November 13, 2022. www.painphysicianjournal.com

2. Ba GRH, Baskett TF, Frcsc MB. History of Anesthesia In the arms of Morpheus: the development of mor-phine for postoperative pain relief. *CAN J ANESTH*. 2000;47:4-367.

3. Bandyopadhyay S. An 8,000-year History of Use and Abuse of Opium and Opioids: How That Matters For A Successful Control Of The Epidemic ? (P4.9-055). *Neurology*. 2019;92(15 Supplement).

4. Dhaliwal A, Gupta M. Physiology, Opioid Receptor. *StatPearls*. Published online July 25, 2022. Accessed December 25, 2022. https://www.ncbi.nlm.nih.gov/books/NBK546642/

5. Nafziger AN, Barkin RL. Opioid Therapy in Acute and Chronic Pain. *The Journal of Clinical Pharmacology*. 2018;58(9):1111-1122. doi:10.1002/jcph.1276

6. Campbell CM, Edwards RR. Ethnic differences in pain and pain management. *Pain Manag*. 2012;2(3):219-230. doi:10.2217/pmt.12.7

7. Hoffman KM, Trawalter S, Axt JR, Oliver MN. Racial bias in pain assessment and treatment recommendations, and false beliefs about biological differences between blacks and whites. *Proc Natl Acad Sci U S A*. 2016;113(16):4296-4301. doi:10.1073/PNAS.1516047113/-/DCSUPPLEMENTAL

8. Chou R, Fanciullo GJ, Fine PG, et al. Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain. *Journal of Pain*. 2009;10(2). doi:10.1016/J.JPAIN.2008.10.008

9. Pergolizzi J, Böger RH, Budd K, et al. Opioids and the Management of Chronic Severe Pain in the Elderly: Consensus Statement of an International Expert Panel with Focus on the Six Clinically Most Often Used World Health Organization step III Opioids (Buprenorphine, Fentanyl, Hydromorphone, Methadone, Morphine, Oxycodone). *Pain Practice*. 2008;8(4):287-313. doi:10.1111/J.1533-2500.2008.00204.X

10. Gladden RM, O'Donnell J, Mattson CL, Seth P. Changes in Opioid-Involved Overdose Deaths by Opioid Type and Presence of Benzodiazepines, Cocaine, and Methamphetamine — 25 States, July–December 2017 to January–June 2018. *MMWR Morb Mortal Wkly Rep*. 2019;68(34):737-744. doi:10.15585/MMWR.MM6834A2

11. Rgen Jage J. Opioid tolerance and dependence-do they matter? Published online 2004. doi:10.1016/j.ejpain.2004.11.009

12. Rosenblum A, Marsch LA, Joseph H, Portenoy RK. Opioids and the Treatment of Chronic Pain: Controversies, Current Status, and Future Directions. doi:10.1037/a0013628

13. Bart G. Maintenance Medication for Opiate Addiction: The Foundation of Recovery. *J Addict Dis*. 2012;31(3):207. doi:10.1080/10550887.2012.694598

14. Ellis RJ, Rahman T, Sherman J, Hurd YL. SnapShot: Neurobiology of opioid use disorder. *Cell*. 2021;184. doi:10.1016/j.cell.2021.02.039

15. Dafny N, Rosenfeld GC. Neurobiology of Drugs of Abuse. *Conn's Translational Neuroscience*. Published online 2017:715-722. doi:10.1016/B978-0-12-802381-5.00052-X

16. Kosten TR, George TP. *R E S E A R C H R E V I E W S-T H E N E U R O B I O L O G Y O F O P I O I D D E P E N D E N C E • 1 3 The Neurobiology of Opioid Dependence: Implications for Treatment*.

17. Levitt ES, Williams JT. Desensitization and Tolerance of Mu Opioid Receptors on Pontine Kölliker-Fuse Neurons. *Mol Pharmacol*. 2018;93(1):8-13. doi:10.1124/MOL.117.109603

18. Williams JT, Ingram SL, Henderson G, et al. Regulation of m-Opioid Receptors: Desensitization, Phosphorylation, Internalization, and Tolerance. Published online 2013. doi:10.1124/pr.112.005942

19. Pergolizzi J v., Varrassi G, Paladini A, LeQuang JA. Stopping or Decreasing Opioid Therapy in Patients on Chronic Opioid Therapy. *Pain Ther*. 2019;8(2):163-176. doi:10.1007/S40122-019-00135-6

20. Benarroch EE. Locus coeruleus. doi:10.1007/s00441-017-2649-1

21. Lueptow LM, Shashkova EC, Miller MG, Evans CJ, Cahill CM. Insights into the Neurobiology of Craving in Opioid Use Disorder. *Curr Anesthesiol Rep*. 2020;10(4):378-387. doi:10.1007/s40140-020-00420-7

22. Zsoldos E, Ebmeier KP. Aging and Psychological Stress. *Stress: Concepts, Cognition, Emotion, and Behavior: Handbook of Stress*. Published online March 30, 2016:311-323. doi:10.1016/B978-0-12-800951-2.00039-X

23. Merikangas KR, Stolar M, Stevens DE, et al. *Familial Transmission of Substance Use Disorders*. https://jamanetwork.com/

24. Psychiatry.org - DSM. Accessed November 15, 2022. https://www.psychiatry.org/psychiatrists/practice/dsm

25. A Guideline for the Clinical Management of. Accessed April 12, 2022. http://www.bccsu.ca/care-guidance-publications/

26. Greiner MG, Dixon LB. The Stigma of Addiction. *https://doi.org/101176/appi.ps72901*. 2021;72(9):1105-1106. doi:10.1176/APPI.PS.72901

27. Vadivelu N, Kai AM, Kodumudi V, Sramcik J, Kaye AD. OTHER PAIN (A KAYE AND N VADIVELU, SECTION EDITORS) The Opioid Crisis: a Comprehensive Overview. Published online 1916. doi:10.1007/s11916-018-0670-z

28. Belzak L, Halverson J. Health Promotion and Chronic Disease Prevention in Canada Research. *Policy and Practice*. 2018;224(6). doi:10.24095/hpcdp.38.6.02

29. Jenkins RA. The fourth wave of the US opioid epidemic and its implications for the rural US: A federal perspective. *Prev Med (Baltim)*. 2021;152(Pt 2). doi:10.1016/J.YPMED.2021.106541

30. Vital Signs: Overdoses of Prescription Opioid Pain Relievers --- United States, 1999--2008. Accessed April 12, 2022. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6043a4.htm

31. Increases in Heroin Overdose Deaths — 28 States, 2010 to 2012. Accessed April 12, 2022. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6339a1.htm

32. Gladden RM, Martinez P, Seth P. Fentanyl Law Enforcement Submissions and Increases in Synthetic Opioid–Involved Overdose Deaths — 27 States, 2013–2014. *MMWR Morb Mortal Wkly Rep*. 2019;65(33):837-843. doi:10.15585/MMWR.MM6533A2

33. Ciccarone D, Justine MPH[. The Rise of Illicit Fentanyls, Stimulants and the Fourth Wave of the Opioid Overdose Crisis. doi:10.1097/YCO.0000000000000717

34. O'Donnell JK, Halpin J, Mattson CL, Goldberger BA, Gladden RM. Deaths Involving Fentanyl, Fentanyl Analogs, and U-47700 — 10 States, July–December 2016. *MMWR Morb Mortal Wkly Rep*. 2019;66(43):1197-1202. doi:10.15585/MMWR.MM6643E1

35. B.C. experiences record loss of life due to drug toxicity | BC Gov News. Accessed April 12, 2022. https://news.gov.bc.ca/releases/2021PSSG0099-002356

36. Overdose Death Rates | National Institute on Drug Abuse (NIDA). Accessed March 1, 2022. https://nida.nih.gov/drug-topics/trends-statistics/overdose-death-rates

37. Highlights for the 2020 National Survey on Drug Use and Health.

38. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database of Systematic Reviews*. 2014;2014(2). doi:10.1002/14651858.CD002207.PUB4/MEDIA/CDSR/CD002207/IMAGE_N/NCD002207-CMP-007-04.PNG

39. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev*. 2009;2009(3). doi:10.1002/14651858.CD002209.PUB2

40. Lawrinson P, Ali R, Buavirat A, et al. Key findings from the WHO collaborative study on substitution therapy for opioid dependence and HIV/AIDS. Published online 2008. doi:10.1111/j.1360-0443.2008.02249.x

41. Degenhardt L, Randall D, Hall W, Law M, Butler T, Burns L. Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: Risk factors and lives saved. *Drug Alcohol Depend*. 2009;105(1-2):9-15. doi:10.1016/J.DRUGALCDEP.2009.05.021

42. Sordo L, Barrio G, Bravo MJ, et al. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *BMJ*. 2017;357:j1550. doi:10.1136/BMJ.J1550

43. Ministry of Public Safety & Solicitor General Illicit Drug Toxicity Deaths in BC. Published online 2022. Accessed March 2, 2022. https://www2.gov.bc.ca/gov/content/life-

44. Hospitalizations and Emergency Department Visits Due to Opioid Poisoning in Canada Hospitalizations and Emergency Department Visits Due to Opioid Poisoning in. Published online 2016. Accessed March 3, 2022. www.cihi.cacopyright@cihi.caISBN978-1-77109-526-6

45. New app shows young people bear the burden of the drug toxicity emergency. Accessed April 12, 2022. http://www.bccdc.ca/about/news-stories/stories/2021/mortality-app-drug-toxicity-emergency

46. Alinsky RH, Zima BT, Rodean J, et al. Receipt of Addiction Treatment After Opioid Overdose Among Medicaid-Enrolled Adolescents and Young Adults. *JAMA Pediatr*. 2020;174(3):e195183-e195183. doi:10.1001/JAMAPEDIATRICS.2019.5183

47. Jalali MS, Botticelli M, Hwang RC, Koh HK, McHugh RK. The opioid crisis: A contextual, social-ecological framework. *Health Res Policy Syst*. 2020;18(1):1-9. doi:10.1186/S12961-020-00596-8/FIGURES/1

48. Jones CM, McCance-Katz EF. Co-occurring substance use and mental disorders among adults with opioid use disorder. *Drug Alcohol Depend*. 2019;197:78-82. doi:10.1016/J.DRUGALCDEP.2018.12.030

49. Strang J, Mcdonald R, Hedrich D, Simon R. Preventing opioid overdose deaths with take-home naloxone. doi:10.2810/357062

50. Latowsky M. Complexity of risk determination. *CMAJ : Canadian Medical Association Journal*. 2005;172(3):309. doi:10.1503/CMAJ.1041366

51. SAMHSA'S CENTER FOR THE APPLICATION OF PREVENTION TECHNOLOGIES Demographic Risk Factors for Opioid Overdose. Accessed December 13, 2022. http://www.samhsa.gov/capt/

52. Fischer B, Brissette S, Brochu S, et al. Determinants of overdose incidents among illicit opioid users in 5 Canadian cities. *CMAJ*. 2004;171(3):235-239. doi:10.1503/CMAJ.1031416

53. VanHouten JP, Rudd RA, Ballesteros MF, Mack KA. Drug Overdose Deaths Among Women Aged 30–64 Years — United States, 1999–2017. *MMWR Morb Mortal Wkly Rep*. 2019;68(1):1-5. doi:10.15585/MMWR.MM6801A1

54. Mason M, Soliman R, Kim HS, Post LA. Disparities by Sex and Race and Ethnicity in Death Rates Due to Opioid Overdose Among Adults 55 Years or Older, 1999 to 2019. *JAMA Netw Open*. 2022;5(1):e2142982-e2142982. doi:10.1001/JAMANETWORKOPEN.2021.42982

55. Differences in Rates of Drug Overdose Deaths by Race - MN Dept. of Health. Accessed December 13, 2022. https://www.health.state.mn.us/communities/opioids/data/racedisparity.html

56. Alberta Health Opioids and Substances of Misuse among First Nations People in Alberta. Published online 2017.

57. Overdose Data and First Nations in BC Preliminary Findings.

58. First Nations Toxic Drug Deaths Doubled During the Pandemic in 2020. Accessed November 14, 2022. https://www.fnha.ca/about/news-and-events/news/first-nations-toxic-drug-deaths-doubled-during-the-pandemic-in-2020

59. Kariisa M, Seth P, Jones CM. Increases in Disparities in US Drug Overdose Deaths by Race and Ethnicity: Opportunities for Clinicians and Health Systems. *JAMA*. 2022;328(5):421-422. doi:10.1001/JAMA.2022.12240

60. M DF. Epidemiology of Emergency Department Visits for Opioid Overdose: A Population-Based Study. *Mayo Clin Proc*. 2014;89.

61. Xiang A, Hou W, Rashidian S, et al. Association of Opioid Use Disorder With 2016 Presidential Voting Patterns: Cross-sectional Study in New York State at Census Tract Level. *JMIR Public Health Surveill*. 2021;7(4). doi:10.2196/23426

62. van Draanen J, Tsang C, Mitra S, Karamouzian M, Richardson L. Socioeconomic marginalization and opioid-related overdose: A systematic review. *Drug Alcohol Depend*. 2020;214:108127. doi:10.1016/J.DRUGALCDEP.2020.108127

63. Social Determinants of Health - Google Books. Accessed December 13, 2022. https://books.google.ie/books?hl=en&lr=&id=AmwiS8HZeRIC&oi=fnd&pg=PT11&ots=y0Jx41PuF0&sig=q2ucKZAcYHxbMV42ofSDTFGzLVo&redir_esc=y#v=onepage&q&f=false

64. Cacciola JS, Alterman AI, Rutherford MJ, McKay JR, Mulvaney FD. The relationship of psychiatric comorbidity to treatment outcomes in methadone maintained patients. *Drug Alcohol Depend*. 2001;61(3):271-280. doi:10.1016/S0376-8716(00)00148-4

65. Rose C, Shahanaghi A, Romero-Gonzalez M, et al. Mortality associated with opioid overdose: A review of clinical characteristics and health services received in the year prior to death. *Psychiatric Services*. 2019;70(2):90-96. doi:10.1176/APPI.PS.201800122

66. Zhu Y, Mooney LJ, Yoo C, et al. Psychiatric comorbidity and treatment outcomes in patients with opioid use disorder: Results from a multisite trial of buprenorphine-naloxone and methadone HHS Public Access. doi:10.1016/j.drugalcdep.2021.108996

67. Leung K, Xu E, Rosic T, Worster A, Thabane L, Samaan Z. Sensitivity and specificity of self-reported psychiatric diagnoses amongst patients treated for opioid use disorder. *BMC Psychiatry*. 2021;21(1). doi:10.1186/S12888-021-03489-4

68. Prince JD. Correlates of Opioid Use Disorders among People with Severe Mental Illness in the United States. *Subst Use Misuse*. 2019;54(6):1024-1034. doi:10.1080/10826084.2018.1559192

69. Ellis JD, Pittman BP, Mckee SA. Co-occurring opioid and sedative use disorder: Gender differences in use patterns and psychiatric co-morbidities in the United States HHS Public Access. *J Subst Abuse Treat*. 2020;114:108012. doi:10.1016/j.jsat.2020.108012

70. Bogdanowicz KM, Stewart R, Broadbent M, et al. Double trouble: Psychiatric comorbidity and opioid addiction-All-cause and cause-specific mortality. *Drug Alcohol Depend*. 2015;148:85-92. doi:10.1016/J.DRUGALCDEP.2014.12.025

71. Drake RE, Mueser KT, Brunette MF. Management of persons with co-occurring severe mental illness and substance use disorder: program implications.

72. Kinner SA, Milloy MJ, Wood E, Qi J, Zhang R, Kerr T. Incidence and risk factors for non-fatal overdose among a cohort of recently incarcerated illicit drug users. *Addictive behaviors*. 2012;37(6):691. doi:10.1016/J.ADDBEH.2012.01.019

73. Wang X, Zhang T, Ho WZ. Opioids and HIV/HCV Infection. doi:10.1007/s11481-011-9296-1

74. Pergolizzi J MPLJBF. Illicitly Manufactured Fentanyl Entering the United States. . Published online 2021.

75. Morales KB, Park JN, Glick JL, Rouhani S, Green TC, Sherman SG. Preference for drugs containing fentanyl from a cross-sectional survey of people who use illicit opioids in three United States cities. *Drug Alcohol Depend*. 2019;204. doi:10.1016/J.DRUGALCDEP.2019.107547

76. Wilson N, Kariisa M, Seth P, Smith H, Davis NL. Drug and Opioid-Involved Overdose Deaths — United States, 2017–2018. *MMWR Morb Mortal Wkly Rep*. 2020;69(11):290-297. doi:10.15585/MMWR.MM6911A4

77. Ciccarone D. Editorial for "US Heroin in Transition: Supply Changes, Fentanyl Adulteration and Consequences" IJDP Special Section. *Int J Drug Policy*. 2017;46:107. doi:10.1016/J.DRUGPO.2017.06.010

78. Definition of Youth. Accessed December 25, 2022. http://undesadspd.org/Youth.aspxfacebook.com/

79. Center for Behavioral Health Statistics S. *Key Substance Use and Mental Health Indicators in the United States: Results from the 2020 National Survey on Drug Use and Health*.; 2021.

80. Lyons RM, Yule AM, Schiff D, Bagley SM, Wilens TE. Risk Factors for Drug Overdose in Young People: A Systematic Review of the Literature. *J Child Adolesc Psychopharmacol*. 2019;29(7):487-497. doi:10.1089/CAP.2019.0013/ASSET/IMAGES/LARGE/FIGURE1.JPEG

81. Edlund MJ, Forman-Hoffman VL, Winder CR, et al. Opioid abuse and depression in adolescents: Results from the National Survey on Drug Use and Health. *Drug Alcohol Depend*. 2015;152:131-138. doi:10.1016/J.DRUGALCDEP.2015.04.010

82. Biederman J, Faraone S v., Monuteaux MC, Feighner JA. Patterns of Alcohol and Drug Use in Adolescents Can Be Predicted by Parental Substance Use Disorders. *Pediatrics*. 2000;106(4):792-797. doi:10.1542/PEDS.106.4.792

83. Lipari RN, Horn SL van. Children Living with Parents Who Have a Substance Use Disorder. *The CBHSQ Report*. Published online August 24, 2017. Accessed November 14, 2022. https://www.ncbi.nlm.nih.gov/books/NBK464590/

84. Orford J, Velleman R, Natera G, Templeton L, Copello A. Addiction in the family is a major but neglected contributor to the global burden of adult ill-health. *Soc Sci Med*. 2013;78(1):70-77. doi:10.1016/J.SOCSCIMED.2012.11.036

85. Winstanley EL, Stover AN. The Impact of the Opioid Epidemic on Children and Adolescents. *Clin Ther*. 2019;41(9):1655. doi:10.1016/J.CLINTHERA.2019.06.003

86. Daley DC, Smith E, Balogh D, Toscaloni J. Forgotten but Not Gone: The Impact of the Opioid Epidemic and Other Substance Use Disorders on Families and Children. *Commonwealth*. 2018;20(2-3):1. doi:10.15367/COM.V20I2-3.189

87. Phillips M, DeBeck K, Desjarlais T, et al. Inability to Access Addiction Treatment Among Street-Involved Youth in a Canadian Setting. *Subst Use Misuse*. 2014;49(10):1233. doi:10.3109/10826084.2014.891618

88. Marchand K, Tallon C, Katan C, et al. Improving Treatment Together: a protocol for a multi-phase, community-based participatory, and co-design project to improve youth opioid treatment service experiences in British Columbia. *Addiction Science and Clinical Practice*. 2021;16(1). doi:10.1186/S13722-021-00261-7

89. Opioid agonist therapy: a synthesis of Canadian guidelines for treating opioid use disorder. Published online 2021.

90. Taha S. Best Practices across the Continuum of Care for the Treatment of Opioid Use Disorder. Published online 2018. Accessed July 14, 2022. www.ccsa.ca•www.ccdus.ca

91. Addressing Opioid Use Disorder in General Medical Settings. Published online 2018. Accessed November 24, 2022. https://www.ncbi.nlm.nih.gov/books/NBK535277/

92. Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. doi:10.1097/ADM.0000000000000166

93. Kosten TR, Baxter LE. Review article: Effective management of opioid withdrawal symptoms: A gateway to opioid dependence treatment. *American Journal on Addictions*. 2019;28(2):55-62. doi:10.1111/AJAD.12862

94. Chou R, Dana T, Blazina I, Grusing S, Fu R, Bougatsos C. Interventions for Unhealthy Drug Use—Supplemental Report: A Systematic Review for the U.S. Preventive Services Task Force. *Interventions for Unhealthy Drug Use—Supplemental Report: A Systematic Review for the US Preventive Services Task Force*. Published online 2020. Accessed December 25, 2022. https://www.ncbi.nlm.nih.gov/books/NBK558205/

95. Screening, Brief Intervention, and Referral to Treatment (SBIRT) | SAMHSA. Accessed November 20, 2022. https://www.samhsa.gov/sbirt

96. Fujita AW, LaRosa A, Carter A. Treating Withdrawal and Pain in Inpatients With Opioid Use Disorder: A Brief Educational Intervention for Internal Medicine Residents. *MedEdPORTAL*. 2021;17:11123. doi:10.15766/MEP_2374-8265.11123

97. Jennings L, Warner T, Bacro-Duverger B. Identification and Treatment of Opioid Withdrawal and Opioid Use Disorder in the Emergency Department. Published online 2020. doi:10.15766/mep_2374-8265.10899

98. Winhusen T, Wilder C, Kropp F, Theobald J, Lyons MS, Lewis D. A brief telephone-delivered peer intervention to encourage enrollment in medication for opioid use disorder in individuals surviving an opioid overdose: Results from a randomized pilot trial. *Drug Alcohol Depend*. 2020;216. doi:10.1016/J.DRUGALCDEP.2020.108270

99. Lam JA, Lee HIS, Truong AQ, et al. Brief video intervention to improve attitudes throughout medications for opioid use disorder in a correctional setting. *J Subst Abuse Treat*. 2019;104:28-33. doi:10.1016/J.JSAT.2019.06.001

100. Fatkin T, Moore SK, Okst K, et al. Feasibility and Acceptability of Mindful Recovery Opioid Use Care Continuum (M-ROCC): A Concurrent Mixed Methods Study. *J Subst Abuse Treat*. 2021;130:108415. doi:10.1016/J.JSAT.2021.108415

101. Wiercigroch D, Sheikh H, Hulme J. A rapid access to addiction medicine clinic facilitates treatment of substance use disorder and reduces substance use. doi:10.1186/s13011-019-0250-1

102. Srivastava A, Clarke S, Hardy K, Kahan M. Facilitating rapid access to addiction treatment: a randomized controlled trial. *Addict Sci Clin Pract*. 2021;16:34. doi:10.1186/s13722-021-00240-y

103. [PDF] Connecting in the community: outreach programs for people who use drugs. Accessed November 24, 2022. https://www.researchgate.net/publication/263075059_Connecting_in_the_community_outreach_programs_for_people_who_use_drugs

104. Torres-Lockhart KE, Lu TY, Weimer MB, Stein MR, Cunningham CO. Clinical Management of Opioid Withdrawal. Published online 2022. doi:10.1111/add.15818

105. GowingL WJ. Cochrane Library Cochrane Database of Systematic Reviews Alpha 2-adrenergic agonists for the management of opioid withdrawal (Review). Published online 2016. doi:10.1002/14651858.CD002024.pub5

106. Jahagirdar D, Campbell K. Alpha2-Adrenergic Agonists for the Reduction or Discontinuation of Opioids or Opioid Substitution Therapy: A Review of Clinical Effectiveness and Guidelines. *Alpha2-Adrenergic Agonists for the Reduction or Discontinuation of Opioids or Opioid Substitution Therapy: A Review of Clinical Effectiveness and Guidelines*. Published online February 23, 2018:1-26. Accessed May 31, 2022. https://www.ncbi.nlm.nih.gov/books/NBK531931/

107. CRISM National Guideline for the Clinical Management of. Accessed April 17, 2022. http://www.cihr-irsc.gc.ca/e/44597.html.

108. Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. *Cochrane Database of Systematic Reviews*. 2011;(4). doi:10.1002/14651858.CD001333.PUB4/INFORMATION/EN

109. Sureshkumar K, Dalal P, Kailash S, Rudhran V. Relapse in opioid dependence: Role of psychosocial factors. *Indian J Psychiatry*. 2021;63(4):372. doi:10.4103/PSYCHIATRY.INDIANJPSYCHIATRY_383_20

110. Amato L, Minozzi S, Davoli M, Vecchi S. Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence. *Cochrane Database of Systematic Reviews*. Published online October 5, 2011. doi:10.1002/14651858.CD004147.PUB4

111. Wild TC, Hammal F, Hancock M, et al. Forty-eight years of research on psychosocial interventions in the treatment of opioid use disorder: A scoping review. *Drug Alcohol Depend*. 2021;218:108434. doi:10.1016/J.DRUGALCDEP.2020.108434

112. State Efforts to Improve the Continuum of Care for Substance Use Disorder and Opioid Use Disorder - National Governors Association. Accessed December 11, 2022. https://www.nga.org/publications/state-efforts-to-improve-the-continuum-of-care-for-substance-use-disorder-and-opioid-use-disorder/

113. Mpofu E, Ingman S, Matthews-Juarez P, Rivera-Torres S, Juarez PD. Trending the evidence on opioid use disorder (OUD) continuum of care among rural American Indian/Alaskan Native (AI/AN) tribes: A systematic scoping review. *Addictive behaviors*. 2021;114. doi:10.1016/J.ADDBEH.2020.106743

114. Yedinak Id JL, Goedel Id WC, Paull Id K, et al. Defining a recovery-oriented cascade of care for opioid use disorder: A community-driven, statewide cross-sectional assessment. doi:10.1371/journal.pmed.1002963

115. Medications for Opioid Use Disorder Save Lives. *Medications for Opioid Use Disorder Save Lives*. Published online May 16, 2019. doi:10.17226/25310

116. Kreek MJ. Methadone-Related Opioid Agonist Pharmacotherapy for Heroin Addiction: History, Recent Molecular and Neurochemical Research and Future in Mainstream Medicine. *Ann N Y Acad Sci*. 2000;909(1):186-216. doi:10.1111/J.1749-6632.2000.TB06683.X

117. Hatcher AE, Mendoza S, Hansen H. At the Expense of a Life: Race, Class, and the Meaning of Buprenorphine in Pharmaceuticalized "Care." *Subst Use Misuse*. 2018;53(2):301. doi:10.1080/10826084.2017.1385633

118. SUBOXONE ® (buprenorphine and naloxone) Product Monograph. Accessed October 31, 2022. www.indivior.com

119. Shulman M, Wai JM, Nunes E v. Buprenorphine Treatment for Opioid Use Disorder: An Overview. *CNS Drugs*. 2019;33(6):567. doi:10.1007/S40263-019-00637-Z

120. Orman JS, Keating GM. Buprenorphine/Naloxone. *Drugs 2009 69:5*. 2012;69(5):577-607. doi:10.2165/00003495-200969050-00006

121. Sublocade (extended-ReleaSe bupRenoRphine) infoRmation. Published online 2020. Accessed March 14, 2022. https://www.cpdnweboms.ca.

122. Neale J, Tompkins CNE, McDonald R, Strang J. Implants and depot injections for treating opioid dependence: Qualitative study of people who use or have used heroin. *Drug Alcohol Depend*. 2018;189:1-7. doi:10.1016/J.DRUGALCDEP.2018.03.057

123. Food and Drug Administration approval of sustained-release buprenorphine for treatment of opioid dependence: realizing its potential. Published online 2016. doi:10.1111/add.13539

124. Transdermal Buprenorphine (Butrans) for Chronic Pain | The Medical Letter Inc. Accessed November 28, 2022. https://secure.medicalletter.org/TML-article-1362d

125. Bell JR, Butler B, Lawrance A, Batey R, Salmelainen P. Comparing overdose mortality associated with methadone and buprenorphine treatment. *Drug Alcohol Depend*. 2009;104(1-2):73-77. doi:10.1016/J.DRUGALCDEP.2009.03.020

126. Hser YI, Saxon AJ, Huang D, et al. Treatment Retention among Patients Randomized to Buprenorphine/Naloxone Compared to Methadone in A Multi-site Trial. *Addiction (Abingdon, England)*. 2014;109(1):79. doi:10.1111/ADD.12333

127. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database of Systematic Reviews*. 2014;2014(2). doi:10.1002/14651858.CD002207.PUB4/MEDIA/CDSR/CD002207/IMAGE_N/NCD002207-CMP-007-04.PNG

128. Faggiano F, Vigna-Taglianti F, Versino E, Lemma P. Methadone maintenance at different dosages for opioid dependence. *Cochrane Database Syst Rev*. 2003;(3). doi:10.1002/14651858.CD002208

129. Soyka M. Transition From Full Mu Opioid Agonists to Buprenorphine in Opioid Dependent Patients-A Critical Review. *Front Pharmacol*. 2021;12. doi:10.3389/FPHAR.2021.718811

130. Sordo L, Barrio G, Bravo MJ, et al. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *BMJ*. 2017;357:1550. doi:10.1136/bmj.j1550

131. Oviedo-Joekes E, Brissette S, Marsh DC, et al. *Diacetylmorphine versus Methadone for the Treatment of Opioid Addiction A Bs Tr Ac t*. Vol 361.; 2009.

132. Oviedo-Joekes E, Guh D, Brissette S, et al. Hydromorphone Compared With Diacetylmorphine for Long-term Opioid Dependence: A Randomized Clinical Trial. *JAMA Psychiatry*. 2016;73(5):447-455. doi:10.1001/JAMAPSYCHIATRY.2016.0109

133. Beck T, Haasen C, Verthein U, et al. Maintenance treatment for opioid dependence with slow-release oral morphine: a randomized cross-over, non-inferiority study versus methadone. *Addiction (Abingdon, England)*. 2014;109(4):617-626. doi:10.1111/ADD.12440

134. Verthein U, Beck T, Haasen C, Reimer J. E-Mail Mental Symptoms and Drug Use in Maintenance Treatment with Slow-Release Oral Morphine Compared to Methadone: Results of a Randomized Crossover Study. Published online 2014. doi:10.1159/000368572

135. Falcato L, Beck T, Reimer J, Verthein U. Self-reported cravings for heroin and cocaine during maintenance treatment with slow-release oral morphine compared with methadone: A randomized, crossover clinical trial. *J Clin Psychopharmacol*. 2015;35(2):150-157. doi:10.1097/JCP.0000000000000288

136. Hämmig R, Köhler W, Bonorden-Kleij K, et al. Safety and tolerability of slow-release oral morphine versus methadone in the treatment of opioid dependence. *J Subst Abuse Treat*. 2014;47(4):275-281. doi:10.1016/J.JSAT.2014.05.012

137. Martin JA, Campbell A, Killip T, et al. QT Interval Screening in Methadone Maintenance Treatment: Report of a SAMHSA Expert Panel. *J Addict Dis*. 2011;30(4):283-306. doi:10.1080/10550887.2011.610710

138. The College of Physicians & Surgeons of Manitoba Opioid Agonist Therapy Recommended Practice Manual Alternative Treatment Approaches to Opioid Use Disorder Including Slow-Release Oral Morphine (Kadian®).

139. Ignaszewski MJ. The Epidemiology of Drug Abuse. *J Clin Pharmacol*. 2021;61(S2):S10-S17. doi:10.1002/JCPH.1937

140. Ivsins A, Boyd J, Beletsky L, McNeil R. Tackling the overdose crisis: The role of safe supply. *International Journal of Drug Policy*. 2020;80. doi:10.1016/J.DRUGPO.2020.102769

141. CAPUD. Accessed November 24, 2022. https://www.capud.ca/

142. Risk Mitigation in the Context of Dual PubliC health emergenCies Update to Interim Clinical Guidance. Published online 2022. Accessed November 28, 2022. https://www.bccsu.ca/COVID-19

143. Alter A, Yeager C, Analyst O. COVID-19 Impact on US National Overdose Crisis. Accessed December 11, 2022. http://odmap.org/Content/docs/news/2020/ODMAP-Report-May-2020.pdf

144. Ahamad K, Bach P, Brar R, et al. AAAAAAA RRRRRRRRR ((( ). Accessed March 6, 2022. www.bccsu.ca/covid-19

145. Willows M, Brasch J, Sobey P, Tanguay R, Martell D. Is All "Safe Supply" Safe? *Canadian Journal of Addiction*. 2020;11(1):30-31. doi:10.1097/CXA.0000000000000079

146. Ivsins A, Boyd J, Mayer S, et al. "It's Helped Me a Lot, Just Like to Stay Alive": a Qualitative Analysis of Outcomes of a Novel Hydromorphone Tablet Distribution Program in Vancouver, Canada. *J Urban Health*. 2021;98:59-69. doi:10.1007/s11524-020-00489-9

147. Krawczyk N, Fawole A, Yang J, Tofighi B. Early innovations in opioid use disorder treatment and harm reduction during the COVID-19 pandemic: a scoping review. *Addiction Science and Clinical Practice*. 2021;16(1):1-15. doi:10.1186/S13722-021-00275-1/TABLES/3

148. Salamanca-Buentello F, Cheng DK, Sabioni P, Majid U, Upshur R, Sud A. Mal/adaptations: A qualitative evidence synthesis of opioid agonist therapy during major disruptions. *International Journal of Drug Policy*. 2022;101:103556. doi:10.1016/J.DRUGPO.2021.103556

149. Bardwell G. Open Access Substance Abuse Treatment, Prevention, and Policy. doi:10.1186/s13011-022-00494-y

150. Expert Opinion on Drug Safety Reducing the harm of opioid overdose with the safe use of naloxone: a pharmacologic review. Published online 2015. doi:10.1517/14740338.2015.1037274

151. Non-Prescription Naloxone Now Available Outside of Pharmacies | College of Pharmacists of British Columbia. Accessed April 12, 2022. https://www.bcpharmacists.org/news/non-prescription-naloxone-now-available-outside-pharmacies

152. Frequently Asked Questions: Access to naloxone in Canada (including NARCAN™ Nasal Spray) - Canada.ca. Accessed April 12, 2022. https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/narcan-nasal-spray-frequently-asked-questions.html

153. Opioid Overdose Treatment - NARCAN® (naloxone HCl) Nasal Spray. Accessed April 12, 2022. https://www.narcan.com/

154. Diagnosing and treating opioid dependence | MDedge Family Medicine. Accessed November 22, 2022. https://www.mdedge.com/familymedicine/article/64873/addiction-medicine/diagnosing-and-treating-opioid-dependence

155. Samhsa. SAMHSA Opioid Overdose Prevention TOOLKIT Opioid Use Disorder Facts Five Essential Steps for First Responders Information for Prescribers Safety Advice for Patients & Family Members Recovering From Opioid Overdose.

156. Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. doi:10.1097/ADM.0000000000000166

157. Supervised Consumption Services Literature Review. Published online 2016.

158. Jozaghi E, Andresen MM. *Should North America*[?]*s First and Only Supervised Injection Facility (InSite) Be Expanded in British Columbia, Canada?* Vol 10.; 2013. doi:10.1186/1477-7517-10-1

159. Marshall BD, Milloy MJ, Wood E, Montaner JS, Kerr T. Reduction in overdose mortality after the opening of North America's first medically supervised safer injecting facility: A retrospective population-based study. *The Lancet*. 2011;377(9775):1429-1437. doi:10.1016/S0140-6736(10)62353-7

160. Potier C, Laprévote V, Dubois-Arber F, Cottencin O, Rolland B. Supervised injection services: What has been demonstrated? A systematic literature review. *Drug Alcohol Depend*. 2014;145:48-68. doi:10.1016/J.DRUGALCDEP.2014.10.012

161. Kerr T, Mitra S, Kennedy MC, McNeil R. Supervised injection facilities in Canada: Past, present, and future. *Harm Reduct J*. 2017;14(1):1-9. doi:10.1186/S12954-017-0154-1/METRICS

162. Interactive map: Canada's response to the opioid crisis. Accessed April 12, 2022. https://health.canada.ca/en/health-canada/services/drugs-medication/opioids/responding-canada-opioid-crisis/map.html#wb-auto-8

163. Pauly B, Wallace B, PaganID F, et al. Impact of overdose prevention sites during a public health emergency in Victoria, Canada. Published online 2020. doi:10.1371/journal.pone.0229208

164. Wallace B, Pagan F, Pauly B (Bernie). The implementation of overdose prevention sites as a novel and nimble response during an illegal drug overdose public health emergency. *Int J Drug Policy*. 2019;66:64-72. doi:10.1016/J.DRUGPO.2019.01.017

165. Public Perception of Harm Reduction Interventions. Accessed November 22, 2022. www.phac-aspc.gc.ca/sti-its-surv-

166. Watson TM, Bayoumi A, Kolla G, et al. Police Perceptions of Supervised Consumption Sites (SCSs): A Qualitative Study. *Subst Use Misuse*. 2012;47(4):364-374. doi:10.3109/10826084.2011.645104

167. Hyshka E, Bubela T, Wild & TC. Prospects for scaling-up supervised injection facilities in Canada: the role of evidence in legal and political decision-making. Published online 2013. doi:10.1111/add.12064

168. Cruz MF, Patra J, Fischer B, Rehm J, Kalousek K. Public opinion towards supervised injection facilities and heroin-assisted treatment in Ontario, Canada. *International Journal of Drug Policy*. 2007;18(1):54-61. doi:10.1016/J.DRUGPO.2006.12.001

169. Debeck K, Wood E, Zhang R, Tyndall M, Montaner J, Kerr T. Substance Abuse Treatment, Prevention, and Policy Police and public health partnerships: Evidence from the evaluation of Vancouver's supervised injection facility. Published online 2008. doi:10.1186/1747-597X-3

170. Fishman M, Wenzel K, Scodes J, et al. Young Adults Have Worse Outcomes Than Older Adults: Secondary Analysis of a Medication Trial for Opioid Use Disorder. *J Adolesc Health*. 2020;67(6):778-785. doi:10.1016/J.JADOHEALTH.2020.07.038

171. Minozzi S, Amato L, Bellisario C, Davoli M. Maintenance treatments for opiate -dependent adolescents. *Cochrane Database Syst Rev*. 2014;2014(6). doi:10.1002/14651858.CD007210.PUB3

172. Guideline Supplement Treatment of Opioid Use Disorder for. Accessed December 22, 2022. http://www.bccsu.ca/care-guidance-publications/

173. Robinson CA, Wilson JD. Management of Opioid Misuse and Opioid Use Disorders Among Youth. Published online 2020. doi:10.1542/peds.2019-2056C

174. Pilarinos A, Bromberg DJ, Karamouzian M. Access to Medications for Opioid Use Disorder and Associated Factors Among Adolescents and Young Adults: A Systematic Review. *JAMA Pediatr*. 2022;176(3):304-311. doi:10.1001/JAMAPEDIATRICS.2021.4606

175. Woody GE, Poole SA, Subramaniam G, et al. Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth: a randomized trial. *JAMA*. 2008;300(17):2003-2011. doi:10.1001/JAMA.2008.574

176. Marsch LA, Bickel WK, Badger GJ, et al. Comparison of pharmacological treatments for opioid-dependent adolescents: a randomized controlled trial. *Arch Gen Psychiatry*. 2005;62(10):1157-1164. doi:10.1001/ARCHPSYC.62.10.1157

177. Marsch LA, Moore SK, Borodovsky JT, et al. A Randomized Controlled Trial of Buprenorphine Taper Duration Among Opioid-Dependent Adolescents and Young Adults HHS Public Access. *Addiction*. 2016;111(8):1406-1415. doi:10.1111/add.13363

178. Polsky D, Glick HA, Yang J, Subramaniam GA, Poole SA, Woody GE. Cost-effectiveness of Extended Buprenorphine-Naloxone Treatment for Opioid-Dependent Youth: Data from a Randomized Trial. *Addiction (Abingdon, England)*. 2010;105(9):1616. doi:10.1111/J.1360-0443.2010.03001.X

179. Hadland SE, Bagley SM, Rodean J, et al. Receipt of Timely Addiction Treatment and Association of Early Medication Treatment With Retention in Care Among Youths With Opioid Use Disorder. *JAMA Pediatr*. 2018;172(11):1029-1037. doi:10.1001/JAMAPEDIATRICS.2018.2143

180. Westenberg JN, Tai AMY, Elsner J, et al. Treatment approaches and outcome trajectories for youth with high-risk opioid use: A narrative review. Published online 2021. doi:10.1111/eip.13155

181. Feder KA, Krawczyk N, Saloner B. Medication-Assisted Treatment for Adolescents in Specialty Treatment for Opioid Use Disorder. doi:10.1016/j.jadohealth.2016.12.023

182. Nairn SA, Audet M, Stewart SH, et al. Interventions to Reduce Opioid Use in Youth At-Risk and in Treatment for Substance Use Disorders: A Scoping Review. *Can J Psychiatry*. 2022;67(12). doi:10.1177/07067437221089810

183. NATIONAL PRACTICE GUIDELINE For the Treatment of Opioid Use Disorder.

184. Elkader A, Sproule B. Buprenorphine Clinical Pharmacokinetics in the Treatment of Opioid Dependence. *Clin Pharmacokinet*. 2005;44(7):661-680.

185. Liu S, O'donnell J, Gladden ; R Matt, Mcglone L, Chowdhury ; Farnaz. Trends in Nonfatal and Fatal Overdoses Involving Benzodiazepines — 38 States and the District of Columbia, 2019–2020. Published online 2019. Accessed October 25, 2022. https://www.

186. Sun EC, Dixit A, Humphreys K, Darnall BD, Baker LC, MacKey S. Association between concurrent use of prescription opioids and benzodiazepines and overdose: Retrospective analysis. *BMJ (Online)*. 2017;356. doi:10.1136/BMJ.J760

187. Bachhuber MA, Hennessy S, Cunningham CO, Starrels JL. Increasing benzodiazepine prescriptions and overdose mortality in the United States, 1996-2013. *Am J Public Health*. 2016;106(4):686-688. doi:10.2105/AJPH.2016.303061

188. (No Title). Published online 2018. doi:10.1503/cmaj.170958

189. Wong JSH, Nikoo M, Westenberg JN, et al. Comparing rapid micro-induction and standard induction of buprenorphine/ naloxone for treatment of opioid use disorder: protocol for an open-label, parallel-group, superiority, randomized controlled trial. *Addict Sci Clin Pract*. 2021;16:11. doi:10.1186/s13722-021-00220-2

190. Chiang CN, Hawks RL. Pharmacokinetics of the combination tablet of buprenorphine and naloxone. *Drug Alcohol Depend*. 2003;70(2 SUPPL.). doi:10.1016/S0376-8716(03)00058-9

191. Frost M, Bailey GL, Lintzeris N, et al. Long-term safety of a weekly and monthly subcutaneous buprenorphine depot (CAM2038) in the treatment of adult out-patients with opioid use disorder. *Addiction (Abingdon, England)*. 2019;114(8):1416-1426. doi:10.1111/ADD.14636

192. Lee JD, Malone M, McDonald R, et al. Comparison of Treatment Retention of Adults With Opioid Addiction Managed With Extended-Release Buprenorphine vs Daily Sublingual Buprenorphine-Naloxone at Time of Release From Jail. *JAMA Netw Open*. 2021;4(9). doi:10.1001/JAMANETWORKOPEN.2021.23032

193. Haight BR, Learned SM, Laffont CM, et al. Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2019;393(10173):778-790. doi:10.1016/S0140-6736(18)32259-1

194. Buprenorphine: extended-release formulations “a game changer”! Published online 2021. doi:10.5694/mja2.51098

195. Modak T, Modak T, Sarkar S. Transdermal buprenorphine patch: Potential for role in management of opioid dependence. *Asian J Psychiatr*. 2019;40:88-91. doi:10.1016/J.AJP.2019.02.002

196. Nida. Clinical Opiate Withdrawal Scale. Accessed October 31, 2022. http://www.drugabuse.gov/nidamed-medical-health-professionals

197. Lintzeris N, Monds LA, Rivas C, et al. Transferring Patients From Methadone to Buprenorphine: The Feasibility and Evaluation of Practice Guidelines. doi:10.1097/ADM.0000000000000396

198. Hämmig R, Kemter A, Strasser J, et al. Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: the Bernese method. *Subst Abuse Rehabil*. 2016;7:99. doi:10.2147/SAR.S109919

199. Microdosing of Buprenorphine for Induction (the Bernese Method) | BC Pharmacy Association. Accessed November 2, 2022. https://www.bcpharmacy.ca/tablet/fall-18/microdosing-buprenorphine-induction-bernese-method

200. Hamata B, Griesdale D, Hann J, Rezazadeh-Azar P. Rapid Micro-induction of Buprenorphine/Naloxone for Opioid Use Disorder in a Critically ill Intubated Patient: A Case Report. *J Addict Med*. 2020;14(6):514-517. doi:10.1097/ADM.0000000000000675

201. Hämmig R, Kemter A, Strasser J, et al. Substance Abuse and Rehabilitation Dovepress Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: the Bernese method. Published online 2016. doi:10.2147/SAR.S109919

202. Klaire S, Zivanovic R, Barbic SP, Sandhu R, Mathew N, Azar P. Rapid Micro-Induction of Buprenorphine/Naloxone for Opioid Use Disorder in an Inpatient Setting: A Case Series. *Am J Addict*. 2019;28(4):262-265. doi:10.1111/AJAD.12869

203. Perez Martell J, Sri Konakanchi J, Sethi R. Treating opioid use disorder with rapid micro induction technique of sublingual buprenorphine/ naloxone in an outpatient setting-a case report Treating opioid use disorder with rapid micro induction technique of sublingual buprenorphine/naloxone in an outpatient setting-a case report. *J Addict Dis*. 2022;40(3):439-443. doi:10.1080/10550887.2021.1996153

204. Moe J, Badke K, Pratt M, et al. Microdosing and standard-dosing take-home buprenorphine from the emergency department: A feasibility study. *J Am Coll Emerg Physicians Open*. 2020;1(6):1712-1722. doi:10.1002/EMP2.12289

205. Moe J, O'Sullivan F, Hohl CM, et al. Short communication: Systematic review on effectiveness of micro-induction approaches to buprenorphine initiation. *Addictive Behaviors*. 2021;114. doi:10.1016/J.ADDBEH.2020.106740

206. Kinasz KR, Herbst ED, Kalapatapu RK. Case Report: Buprenorphine Induction Using Transdermal Buprenorphine in a Veteran With Opioid Use Disorder and Psychosis, Managing Precipitated Withdrawal. *Mil Med*. 185(10):2020. doi:10.1093/milmed/usaa068

207. de Aquino JP, Fairgrieve C, Klaire S, Garcia-Vassallo G. RAPID TRANSITION FROM METHADONE TO BUPRENORPHINE UTILIZING A MICRO-DOSING PROTOCOL IN THE OUTPATIENT VETERAN AFFAIRS SETTING. *J Addict Med*. 2020;14(5):e271. doi:10.1097/ADM.0000000000000618

208. Tang VM, Lam-Shang-Leen J, Brothers TD, et al. CASE SERIES: LIMITED OPIOID WITHDRAWAL WITH USE OF TRANSDERMAL BUPRENORPHINE TO BRIDGE TO SUBLINGUAL BUPRENORPHINE IN HOSPITALIZED PATIENTS. *Am J Addict*. 2020;29(1):73. doi:10.1111/AJAD.12964

209. Brogdon H, Facer KL, Cox EJ, Carlson RH, Wurzel JF. Rapid Transition to Buprenorphine in a Patient With Methadone-Related QTc Interval Prolongation. *J Addict Med*. 2022;16(4):488-491. doi:10.1097/ADM.0000000000000935

210. Hess M, Boesch L, Leisinger R, Stohler R. Transdermal Buprenorphine to Switch Patients from Higher Dose Methadone to Buprenorphine without Severe Withdrawal Symptoms. *Am J Addict*. 2011;20(5):480-481. doi:10.1111/J.1521-0391.2011.00159.X

211. Raheemullah A, Lembke A. Buprenorphine Induction Without Opioid Withdrawal: A Case Series of 15 Opioid-Dependent Inpatients Induced on Buprenorphine Using Microdoses of Transdermal Buprenorphine. *Am J Ther*. 2019;28(4):e504-e508. doi:10.1097/MJT.0000000000001108

212. Raheemullah A, Lembke A. Buprenorphine Induction Without Opioid Withdrawal: A Case Series of 15 Opioid-Dependent Inpatients Induced on Buprenorphine Using Microdoses of Transdermal Buprenorphine. *Am J Ther*. 2019;28(4):e504-e508. doi:10.1097/MJT.0000000000001108

213. Baumgartner K, Salmo E, Liss D, et al. Transdermal buprenorphine for in-hospital transition from full agonist opioids to sublingual buprenorphine: a retrospective observational cohort study. *https://doi.org/101080/1556365020222028802*. 2022;60(6):688-693. doi:10.1080/15563650.2022.2028802

214. Azar PWJSHMNVMPJHAAKRMMJSGGMKMAR. 48-hour Induction of Transdermal Buprenorphine to Sublingual Buprenorphine/Naloxone: The IPPAS Method. *J Addict Med*. Published online September 23, 2022.

215. Deweese JP, Krenz JR, Wakeman SE, Peckham AM. Rapid buprenorphine microdosing for opioid use disorder in a hospitalized patient receiving very high doses of full agonist opioids for acute pain management: Titration, implementation barriers, and strategies to overcomes. doi:10.1080/08897077.2021.1915914

216. Mackay L, Kerr T, Fairbairn N, Grant C, Milloy MJ, Hayashi K. The relationship between opioid agonist therapy satisfaction and fentanyl exposure in a Canadian setting. doi:10.1186/s13722-021-00234-w

217. Anstice S, Strike CJ, Brands B. Supervised Methadone Consumption: Client Issues and Stigma. *http://dx.doi.org/101080/10826080802483936*. 2009;44(6):794-808. doi:10.1080/10826080802483936

218. Frank D, Mateu-Gelabert P, Perlman DC, Walters SM, Curran L, Guarino H. "It's like 'liquid handcuffs": The effects of take-home dosing policies on Methadone Maintenance Treatment (MMT) patients' lives. *Harm Reduct J*. 2021;18(1):1-10. doi:10.1186/S12954-021-00535-Y/METRICS

219. Harris J, McElrath K. Methadone as social control: institutionalized stigma and the prospect of recovery. *Qual Health Res*. 2012;22(6):810-824. doi:10.1177/1049732311432718

220. Fraser S. The chronotope of the queue: Methadone maintenance treatment and the production of time, space and subjects. *International Journal of Drug Policy*. 2006;17(3):192-202. doi:10.1016/J.DRUGPO.2006.02.010

221. Woo J, Bhalerao A, Bawor M, et al. "Don't Judge a Book by Its Cover": A Qualitative Study of Methadone Patients' Experiences of Stigma. *Subst Abuse*. 2017;11. doi:10.1177/1178221816685087

222. Scorsone KL, Haozous EA, Hayes L, Cox KJ. Overcoming Barriers: Individual Experiences Obtaining Medication-Assisted Treatment for Opioid Use Disorder. *Qual Health Res*. 2020;30(13):2103-2117. doi:10.1177/1049732320938689

223. Sigmon SC. Interim treatment: Bridging delays to opioid treatment access. *Prev Med (Baltim)*. 2015;80:32-36. doi:10.1016/J.YPMED.2015.04.017

224. Kang AW, DeBritz AA, Hoadley A, et al. Barriers and poor telephone counseling experiences among patients receiving medication for opioid use disorders. *Patient Educ Couns*. Published online March 6, 2022. doi:10.1016/J.PEC.2022.03.006

225. Trujols J, Siñol N, Iraurgi I, Batlle F, Guàrdia J, Pérez de los Cobos J. Patient and clinician's ratings of improvement in methadone-maintained patients: Differing perspectives? *Harm Reduct J*. 2011;8:23. doi:10.1186/1477-7517-8-23

226. MacNeill L, Brunelle C, Skelding B, DiTommaso E. Experiences of Clients in Three Types of Methadone Maintenance Therapy in an Atlantic Canadian City: A Qualitative Study. *Can J Nurs Res*. 2021;53(3):211-221. doi:10.1177/0844562120924516

227. Marchand K, Foreman J, MacDonald S, Harrison S, Schechter MT, Oviedo-Joekes E. Building healthcare provider relationships for patient-centered care: A qualitative study of the experiences of people receiving injectable opioid agonist treatment. *Subst Abuse Treat Prev Policy*. 2020;15(1). doi:10.1186/S13011-020-0253-Y

228. Marks M, Scheibe A, Shelly S. High retention in an opioid agonist therapy project in Durban, South Africa: the role of best practice and social cohesion. doi:10.1186/s12954-020-00368-1

229. Oros SM, Christon LM, Barth KS, Berini CR, Padgett BL, Diaz VA. Facilitators and barriers to utilization of medications for opioid use disorder in primary care in South Carolina. *Int J Psychiatry Med*. 2021;56(1):14-39. doi:10.1177/0091217420946240

230. Radcliffe P, Stevens A. Are drug treatment services only for "thieving junkie scumbags"? Drug users and the management of stigmatised identities. *Soc Sci Med*. 2008;67(7):1065-1073. doi:10.1016/J.SOCSCIMED.2008.06.004

231. Crawford S. Shouting through bullet-proof glass: Some reflections on pharmacotherapy provision in one Australian clinic. *International Journal of Drug Policy*. 2013;24(6). doi:10.1016/J.DRUGPO.2013.07.004

232. Abadie R, Mclean K, Habecker P, Dombrowski K. Treatment trajectories and barriers in opioid agonist therapy for people who inject drugs in rural Puerto Rico. *J Subst Abuse Treat*. 2021;127:108347. doi:10.1016/j.jsat.2021.108347

233. White WL, Coon BF. Methadone and the Anti-medication Bias in Addiction Treatment.

234. Komalasari R, Wilson S, Haw S. Systematic Review A systematic review of qualitative evidence on barriers to and facilitators of the implementation of opioid agonist treatment (OAT) programmes in prisons. *International Journal of Drug Policy*. 2021;87:102978. doi:10.1016/j.drugpo.2020.102978

235. NIMBY (Not in My Backyard) | The Homeless Hub. Accessed December 27, 2022. https://www.homelesshub.ca/solutions/affordable-housing/nimby-not-my-backyard

236. Smith CBR. Socio-spatial stigmatization and the contested space of addiction treatment: Remapping strategies of opposition to the disorder of drugs. *Soc Sci Med*. 2010;70(6):859-866. doi:10.1016/J.SOCSCIMED.2009.10.033

237. Smith CBR. A users' guide to "Juice Bars" and "Liquid Handcuffs": Fluid negotiations of subjectivity, space and the substance of methadone treatment. *Space and Culture*. 2011;14(3):291-299. doi:10.1177/1206331211412238

238. Yarborough BJH, Stumbo SP, McCarty D, Mertens J, Weisner C, Green CA. Methadone, buprenorphine and preferences for opioid agonist treatment: A qualitative analysis. *Drug Alcohol Depend*. 2016;160:112-118. doi:10.1016/J.DRUGALCDEP.2015.12.031

239. Gryczynski J, Jaffe JH, Schwartz RP, et al. Patient Perspectives on Choosing Buprenorphine Over Methadone in an Urban, Equal-Access System. doi:10.1111/j.1521-0391.2012.12004.x

240. Schwartz RP, Kelly SM, O'grady KE, et al. Attitudes Toward Buprenorphine and Methadone Among Opioid-Dependent Individuals. *Am J Addict*. 2008;17:396-401. doi:10.1080/10550490802268835

241. Pinto H, Rumball D, Holland R. Journal of Substance Use Attitudes and knowledge of substance misusers regarding buprenorphine and methadone maintenance therapy. doi:10.1080/14659890701639808

242. Checkley L, Steiger S, Knight KR. "I wanted something that was more flexible": A qualitative study of patient preferences on choosing buprenorphine over methadone in a large, safety-net hospital opioid treatment program. Published online 2022. doi:10.1080/08897077.2021.2010251

243. Larance B, Degenhardt L, Grebely J, et al. Perceptions of extended-release buprenorphine injections for opioid use disorder among people who regularly use opioids in Australia. Published online 2019. doi:10.1111/add.14941

244. Barnett A, Savic M, Lintzeris N, et al. Tracing the affordances of long-acting injectable depot buprenorphine: A qualitative study of patients' experiences in Australia. *Drug Alcohol Depend*. 2021;227:108959. doi:10.1016/J.DRUGALCDEP.2021.108959

245. Saunders EC, Moore SK, Walsh O, et al. Perceptions and preferences for long-acting injectable and implantable medications in comparison to short-acting medications for opioid use disorders. *J Subst Abuse Treat*. 2020;111:54-66. doi:10.1016/J.JSAT.2020.01.009

246. Neale J, Tompkins CNE, Strang J. Prolonged-release opioid agonist therapy: qualitative study exploring patients' views of 1-week, 1-month, and 6-month buprenorphine formulations. doi:10.1186/s12954-019-0296-4

247. Chai D, Rosic T, Panesar B, et al. Patient-Reported Goals of Youths in Canada Receiving Medication-Assisted Treatment for Opioid Use Disorder. *JAMA Netw Open*. 2021;4(8):e2119600-e2119600. doi:10.1001/JAMANETWORKOPEN.2021.19600

248. Giang V, Thulien M, McNeil R, Sedgemore K, Anderson H, Fast D. Opioid agonist therapy trajectories among street entrenched youth in the context of a public health crisis. *SSM Popul Health*. 2020;11. doi:10.1016/J.SSMPH.2020.100609

249. Hadland SE, Park TW, Bagley SM. Stigma associated with medication treatment for young adults with opioid use disorder: A case series. *Addiction Science and Clinical Practice*. 2018;13(1):1-4. doi:10.1186/S13722-018-0116-2/METRICS

250. (PDF) An Exploration of Young Adults With Opioid Use Disorder and How Their Perceptions of Family Members' Beliefs Affects Medication Treatment. Accessed December 9, 2022. https://www.researchgate.net/publication/361533901_An_Exploration_of_Young_Adults_With_Opioid_use_Disorder_and_How_Their_Perceptions_of_Family_Members'_Beliefs_Affects_Medication_Treatment

251. Creswell JW. RESEARCH DESIGN Qualitative, Quantitative. and Mixed Methods Approaches SECOND EDITION SAGE Publications International Educational and Professional Publisher Thousand Oaks London New Delhi. Published online 2003.

252. Bunniss S, Kelly DR. Research paradigms in medical education research. *Med Educ*. 2010;44(4):358-366. doi:10.1111/J.1365-2923.2009.03611.X

253. O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. Standards for reporting qualitative research: A synthesis of recommendations. *Academic Medicine*. 2014;89(9):1245-1251. doi:10.1097/ACM.0000000000000388

254. Foundry - Where Wellness Takes Shape -. Accessed January 4, 2023. https://foundrybc.ca/

255. Government of Canada Actions on Opioids: 2016 and 2017 - Canada.ca. Accessed December 20, 2022. https://www.canada.ca/en/health-canada/services/publications/healthy-living/actions-opioids-2016-2017.html

256. Consent. Accessed January 2, 2023. https://www.bccnm.ca/RPN/PracticeStandards/Pages/consent.aspx

257. Best Qualitative Data Analysis Software for Researchers | NVivo. Accessed January 2, 2023. https://www.qsrinternational.com/nvivo-qualitative-data-analysis-software/home

258. Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res Psychol*. 2006;3(2):77-101. doi:10.1191/1478088706qp063oa

259. Baldwin N, Gray R, Goel A, Wood E, Buxton JA, Rieb LM. Fentanyl and heroin contained in seized illicit drugs and overdose-related deaths in British Columbia, Canada: An observational analysis. *Drug Alcohol Depend*. 2018;185:322-327. doi:10.1016/J.DRUGALCDEP.2017.12.032

260. Almeida IL de L, Rego JF, Teixeira ACG, Moreira MR. Social isolation and its impact on child and adolescent development: a systematic review. *Revista Paulista de Pediatria*. 2022;40:e2020385. doi:10.1590/1984-0462/2022/40/2020385

261. NATIONAL PRACTICE GUIDELINE For the Treatment of Opioid Use Disorder.

262. Moore SK, Guarino H, Marsch LA. "This is Not Who I Want to be:" Experiences of Opioid-Dependent Youth Before, and During, Combined Buprenorphine and Behavioral Treatment. doi:10.3109/10826084.2013.832328

263. BCCSU – British Columbia Centre on Substance Use. Accessed December 4, 2022. https://www.bccsu.ca/

APPENDIX

Appendix 1: Interview Guide

Section A: Consent and Screening

Thank you for your interest in being involved in the project we are conducting about the opinions of opioid agonist treatment, or OAT, among youth.

[Introduce yourself as a researcher]

[Explain what OAT is and confirm their understanding before continuing]

The interview will take about 30-minutes to an hour, and I will be asking questions about your experiences and opinions of OAT, as well as your thoughts about how OAT can become more accessible to youth in Vancouver. The interview will be recorded but will feel much like a conversation and is informal. If you would like to take a break, we can always take one during through the interview. We are looking forward to talking with you and getting your perspectives on this topic! The questions in the interview are broad and open-ended so that we can give you room to talk about whatever you think is most important. If you aren't sure about how to answer any of the questions, let us know and we can try to clarify for you. We can go over the consent form now before we start.

[Read the consent form]

Do you have any questions?

[Sign the consent form]

I'll now start the recording if that is alright with you?

[RECORDER ON]

Section B: Semi-Structured Interview

If it's ok with you, there are a few questions that we would like to ask to gain some background information for the study. After these questions we will move on to discuss more about your opinions of OAT.

Questions:	Probes:
Age? Pronouns? Gender Identity? Ethnicity? Housing?	What is your age? What gender do you identify as? What pronouns do you use? What is your ethnicity? In the past 4 weeks, what type of accommodation did you mainly live in?
Can you give a brief history of your opioid use	What does your current substance use look like? How has this changed over time?

from when it started?	What are the reasons you started using opioids? Continue to use opioids? (Drivers of use)

Thank you very much for answering those questions. Now, we can start by talking about your past experiences with OAT, including which medications you have been on.

Questions:	Probes:
Are you or have you been on opioid agonist treatment? Which forms of treatment have you been on? • Suboxone • Methadone • Long-acting, slow-release oral morphine (Kadian) • Buprenorphine injection for subcutaneous use (Sublocade)	How long have you been on OAT? How many times have you been on OAT? What were the reasons you went on OAT? What were the reasons you stopped OAT? How do you feel when you are on OAT? How does this compare to before you started OAT or periods when you are not receiving OAT? How long do you see yourself being on OAT? Did things change in your life once starting OAT? What are your goals while being on OAT? (Patient-reported goals) How does your experience of [OAT] compare with [OAT]? Did you notice any advantages or disadvantages of [OAT], specifically?
[OR] Have you ever considered going on OAT?	<u>Full list of probes for participants without OAT experience</u> OAT experience: Have you heard about Suboxone? Methadone? Long-acting morphine (Kadian)? Injectable therapy (Sublocade)? What would be your goals if you decided to start OAT? (Patient- reported goals) OAT knowledge and understanding: How would you describe the medication to a friend who was thinking of starting OAT? Long-term/ short-term side effects? Using down while on OAT? Where do you get your information from regarding OAT? Do you feel informed about OAT? Are there things that you wish you knew more about regarding OAT?

	OAT opinions: Is there one medication that you feel is better for you? Tell me about that. What might your future look like if you go on OAT? How do you see OAT affecting your everyday life? What do your peers think about OAT? If you were to weigh out the positives and negatives of OAT, what would that look like? **OAT barriers and facilitators:** Have you found challenges with accessing OAT? Tell me about that. How could things be improved?

Now, we would like to talk about your opinions and perspectives of OAT. In asking these questions, we hope to understand how these medications can be improved for youth.

Questions:	Probes:
If you were to weigh out the positives and negatives of being on OAT, what would that look like? Visual aid to keep participants on track: "If you were to weight the positives and negatives of opioid treatment, kind of like a balancing scale in this picture, what would that look like and why? Give specific reasons" 	Did your opinions of OAT change once you started the medication? What do your peers think about OAT? Would you recommend OAT to a friend? Tell me about that.

Now, it would be great to hear about your understanding of the medications. In asking these questions, we want to understand ways that the healthcare providers can improve knowledge and understanding so that people can become better informed and more empowered to make decisions regarding the medications that they are on.

Questions:	Probes:
What did you know about OAT before you went on it?	Has your understanding of OAT changed once you started the medication? How would you describe the medication to a friend who was thinking of starting OAT? Do you know of, or have you heard of, any long-term/ short-term side effects of OAT? What is your understanding of using down while on OAT? Where do you get your information from regarding OAT? Do you feel informed about OAT? Are there things that you wish you knew more about regarding OAT?

We would now like to ask you questions about barriers that you have found when accessing medication and staying on medication. Hearing this will be helpful to improve ways that the healthcare system can make medication more accessible in the future. We can also talk about what you found to be helpful when you were accessing OAT and staying on OAT.

Questions:	Probes:
What were the challenges of getting on OAT?	What were the benefits of getting on OAT? What were/ are the challenges of staying on OAT? What were/ are the benefits of staying on OAT? How could things be improved?

Thank you very much! We covered a lot of topics today and I really appreciate it. To sum up, we are interested in your general experience and opinions of OAT and how the healthcare system can be improved to make OAT more accessible to youth. Would you like to add any other comments?

[RECORDER OFF]

Finally, after everything we've discussed, I just wanted to make sure that you're ok and don't have any concerns about anything that we've talked about today. [Arrange gift voucher]