OPTIMIZING PRESCRIBING OF OPIATE AGONIST TREATMENT IN RURAL & REMOTE PRIMARY CARE TO IMPROVE TREATMENT OUTCOMES IN ADULTS WITH OPIOID USE DISORDER

by

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Abstract

Opioid use disorder (OUD) is a chronic and relapsing condition that affects people across British Columbia (BC). People with OUD are at significant risk of morbidity and mortality related to unintentional toxic drug poisonings from the fentanyl-contaminated unregulated drug supply. Despite the unabating rates of toxic drug deaths in BC, evidence-based pharmacologic interventions for OUD remain underutilized especially in rural and remote areas of the province. Opiate agonist treatment (OAT) is an evidence-based pharmacologic intervention for OUD that is within primary care provider (PCP) scope of practice to prescribe. This integrated literature review was conducted to address how in rural and remote communities, PCPs can improve treatment outcomes for adults with OUD when prescribing OAT. A systematic search of six large academic databases was conducted that yielded twelve peer-reviewed articles that met inclusion criteria. Findings are discussed based on key themes from the literature that demonstrate an undisputed understanding of the efficacy of OAT among rural PCPs, however treatment outcomes among rural patients with OUD are variable due to several high-level social, regulatory, environmental and organizational challenges that are exacerbated in rural regions. Scale-up of accessible OAT in primary care is integral to improving treatment outcomes for adults with OUD and preventing toxic drug deaths in rural and remote BC communities.

Keywords: Rural, adults, opioid use disorder, primary health care, primary care, family practice, medication-assisted treatment, opioid replacement therapy, opiate agonist treatment

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Glossary

Analogue: a chemical that is similar in structure and function to another chemical, but are different in some respects.

High-potency benzodiazepines: highly concentrated, long-acting sedative medications that are used in the pharmacologic treatment of some severe psychiatric conditions.

Buprenorphine: a partial-opioid agonist with high receptor affinity used in the treatment of opioid use disorder and pain management. Available in a combination product known as buprenorphine/naloxone.

Criminalization: a social process that involves turning the actions or behaviors of individuals into a crime or punishable offense.

COVID-19 Pandemic: a global pandemic caused by an infectious respiratory disease known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus also known as the coronavirus disease of 2019 (COVID-19).

Decriminalization: a social and legal process that removes or reduces the degree of criminal classification of an action and removes any criminal penalties associated with them. Also refers to a change in social values when a society comes to view an action as no longer harmful.

Harm reduction: an approach to policy and health-related programs that includes pragmatic strategies and a set of values that aim to reduce negative consequences associated with some social behaviors (e.g. substance use and sexual practices).

Heroin: a controlled opioid that is chemically known as diacetylmorphine and is often obtained through the unregulated drug market and used for its euphoric effects.

Hydromorphone: a pharmaceutical opioid pain medication that is five times more potent than morphine.

Fentanyl: a short-acting synthetic opioid pain medication that is 50 to 100 times more potent than morphine and is most often used intraoperatively and is found in the unregulated drug supply in the form of fentanyl and various fentanyl analogues.

Methadone: a long-acting pharmaceutical opioid medication that is used to reduce opioid withdrawal and moderate to severe pain.

Novel psychoactive substances: unregulated substances that are not controlled by the international controlled drug sanctions and have significant potential for abuse and misuse by the public.

Nurse prescriber: a registered nurse or registered psychiatric nurse who has additional training in making a diagnosis of opioid use disorder and able to prescribe opiate agonist treatment under specific circumstances as directed by their employer.

Opiate: is a substance derived from opium.

Opiate agonist treatment: a group of medications used to treat opioid use disorder by providing opioid medications that attach to the opioid receptors in the central nervous system reducing withdrawal symptoms and opioid cravings. Often involves providing an alternative to unregulated opioids that results in social and psychological stabilization from substance use.

Opioid: pharmacologic classification of all substances that are naturally derived or synthetically produced that bind to the opioid receptors in the central nervous system.

Opioid withdrawal: a syndrome that results after cessation of regular and sustained opioid use. Occurs after established physiologic dependence related to the effects from opioid receptor occupancy. Symptoms include piloerection, nausea, vomiting, diarrhea, yawning, anxiety, agitation, and eye tearing.

Opium: an organic substance that is derived from the opium poppy seed capsule.

Primary care: is a longitudinal approach to healthcare that is often the first contact people have with the healthcare system. Preventative, secondary and tertiary interventions are available in primary care.

Primary care provider: a healthcare professional that has advanced training and is able to assess, diagnose and treat common medical conditions across the life span. Physicians and nurse practitioners are the most common types of primary care providers in Canada.

Public health emergency: are specific situations that have the potential to significantly harm the public. Once declared by government officials, certain powers are enabled that allow greater access to healthcare related services and surveillance techniques aimed at reducing the spread or harm to the public.

Rurality: an expression that refers to the degree of isolation of a geographic area. Conceptualized as space or communities that are apart from urban centres.

Slow-release oral morphine: a 24-hour formulation of morphine, brand name *Kadian* that is approved for the treatment of pain management and is used off-label for the treatment of opioid use disorder.

Stigma: a social process whereby a person or group of people with similar characteristics are discriminated against or perceived as lesser than other members of society.

Stigmatization: the action of describing or treating someone or a group of people as worthy of disapproval or being discredited.

Syndemic: when the effect of two or more pandemics or epidemics occur simultaneously and exacerbate the health outcomes or burden of disease more so than if one was occurring in isolation.

Toxic drug death: unintentional fatalities that occur after a person uses substances solicited from the unregulated and contaminated drug market.

Toxic drug poisoning: fatal or non-fatal incidents caused by the significant sedating and respiratory depressant effects of highly potent fentanyl found in the unregulated drug supply. Acquired anoxic brain injury is a common secondary effect of non-fatal toxic drug poisonings.

Toxic drug supply: illegal or unregulated recreational drugs that are sold under criminalized circumstances. Lack of regulations or quality standards for illegal drug manufactures leads to utilization of highly potent and harmful substances available to the public.

Acknowledgments and Dedication

I would like to extend sincere gratitude to my project supervisor, Linda Van Pelt for her encouragement and solidarity throughout this project. Also, I am forever grateful to my partner, my parents, and my brother for their unwavering love and support throughout many difficult times; much of their efforts were often unbeknownst to them. Lastly, I would like to acknowledge my friend, colleague and mentor Dr. Geoff Bardwell, who has provided a listening ear and reassuring guidance during the process of authoring this paper.

This paper is dedicated to all the people who have unnecessarily died from the toxic drug supply due to government inaction and bad drug policy. I recognize all the unsung heroes with lived and living expertise who have done this work long before healthcare providers contributed and who continue to do so despite living with immense grief and loss from the passing of so many of their loved ones and community members.

Introduction

British Columbia (BC) is amid a severe and persistent toxic drug public health emergency driven by the contaminated and unregulated fentanyl drug supply (Tobias et al., 2021). The World Health Organization (WHO) (2021) recognizes that the introduction of synthetically-derived fentanyl as an adulterant in heroin and other substances in the unregulated drug market has resulted in unprecedented rates of toxic drug poisonings across North America (Hayashi et al., 2021; Jalal et al., 2018; United Nations, 2021). Provincial rates of toxic drug poisonings show that from January 1, 2021 to December 31, 2021 there were 2232 toxic drug deaths in BC, the highest number of deaths in one year related to the toxic drug supply since the outset of the declaration of the public health emergency (BC Coroners Service, 2022). Rural and remote regions in BC experience the greatest rates of toxic drug poisonings (BC Coroners Service, 2022). Despite ongoing efforts to address the toxic drug crisis, there has been minimal success to halt or reduce the climbing death toll. Rurality has been found to be an independent contributing factor to non-urban communities suffering distinct harms related to the toxic drug supply (Fadanelli et al., 2020; Palombi et al., 2018; Thomas et al., 2020). Although rural regions experience high mortality-rates related to toxic drug use, research, policy and program directives aimed at improving accessibility to lifesaving pharmacologic treatment for opioid use disorder (OUD) have focused on urban settings (Bardwell & Lappalainen, 2021).

Opioid agonist treatment (OAT) is an evidence-based pharmacologic intervention prescribed for people with OUD (PWOUD). An extensive amount of research has demonstrated that OAT, primarily methadone and buprenorphine, is safe to prescribe PWOUD and reduces the risk of toxic drug death, reduces infectious disease transmission (HIV and hepatitis C) and improves social functioning (Amato et al., 2005; Piske et al, 2020). Methadone and buprenorphine are

listed as WHO essential medications and their availability to PWOUD is imperative (Eibl, Gauthier et al., 2017; Sordo et al., 2017).

In a large American study, Haffajee et al. (2019) found a concerning association between rural regions with the highest rates of toxic drug deaths and low availability of providers to prescribe OAT. Low availability of OAT prescribers in rural regions contributes to reduced access to OAT. PWOUD in rural and remote communities experience added barriers of distance to pharmacies, unreliable transportation options, providers unwilling or uncomfortable prescribing OAT who are not off-set by access to low-barrier or speciality substance use clinics and fewer on-the-ground harm reduction human resources (Andrilla et al., 2019; Bardwell & Lappalainen, 2021; DeFalvio et al., 2014). One of the ways accessibility barriers to OAT are being addressed is by transitioning OAT prescribing into primary care across Canada (McEachern et al., 2016). Robust OAT delivery by rural primary care providers (PCPs) has been predicted to significantly reduce toxic drug deaths in rural and remote communities (Haffajee et al., 2019; Rosenblatt et al., 2015).

The efficacy of OAT is well established and supported by provincial and national clinical guidelines as an intervention for OUD that prevents toxic drug deaths, however only a small portion of rural PCPs are prepared to prescribe OAT (DeFlavio et al., 2015; Dooley et al., 2012; Rosenblatt et al., 2015). This paper aims to look at ways that PCPs who are already prescribing OAT to people in an office-based setting can adapt clinical practices in order to optimize health outcomes for PWOUD. The purpose of this integrated literature review is to address the research question: *In rural and remote communities, how can primary care providers improve treatment outcomes for adults with opioid use disorder when prescribing opiate agonist treatment?*

This integrative review will further explore the role of rural PCPs in the treatment of OUD. Chapter One will provide specific background, context and define associated concepts that influence the treatment of substance use conditions, specifically considering OUD. Chapter Two will review the methods used to conduct the integrated literature review that took place in several iterative and systematic stages. Chapter Three will outline the findings from the literature presented in key themes: efficacy of OAT, accessibility, stigma in rural primary care, primary care provider competence, implementation strategies and interdisciplinary team-based care. In Chapter Four a synthesis of the findings, identification of current gaps in the literature, limitations of the evidence and practice recommendations for PCPs will be discussed.

Chapter One: Background

In this chapter, key concepts related to the research question will be defined including opioids and the toxic drug supply, pathophysiology and etiology of OUD, management of OUD, expected treatment outcomes for PWOUD, and treating OUD in the context of rural and remote primary care. Important contextual concepts related to the historical, political and social factors that are contributing to the current toxic drug public health emergency will be introduced.

Opioids

The activity of using analgesics derived from plants to relieve physical, mental, emotional or spiritual pain and to bring on a sense of euphoria has been weaved into the social fabric of all civilizations, past and present (Malleck, 2015; Zhu & Ali, 2016). The term opiates refer to naturally derived substances that are most commonly known for their analgesic and calming properties (Snapp & Valderrabano, 2021). In Canada until the late nineteenth century, it was common place for individuals to self-manage pain and other ailments using tinctures and remedies made from plants, such as opium cultivated from the opium poppy (Boyd, 2021). Opium is a plant-based opiate and has historically been used to treat pain, intestinal cramping or respiratory illnesses (Boyd, 2021). As described by Thomas De Quincy in Confessions of an English Opium Eater (1821):

> Here was a panacea…for all human woes; here was the secret of happiness, about which philosophers had disputed for so many ages, at once discovered: happiness might now be bought for a penny, and carried in the waistcoat pocket; portable ecstasies might be had corked up in a pint bottle, and peace of mind could be sent down in gallons by the mail coach. (p. 73)

Opium led to the discovery of other opiates by chemically isolating properties of opium juice into new substances, including morphine and semisynthetic diacetylmorphine, also known as heroin (Boyd, 2021). Opioids refers to a class of morphine-like medications that are

characterized by being either endogenously or synthetically produced and are blocked at receptor sites in the central nervous system by naloxone, an opioid antagonist (Ritter et al, 2020). Several contemporary opioids have been engineered in an attempt to develop better analgesics with less unwanted side effects (Ritter et al., 2020; Stanley, 2014). For example, fentanyl and methadone bare less resemblance to the organic morphine molecule and are therefore referred to as full synthetic opioid-analogues. Fentanyl in particular has become one of the world's most used analgesics, most commonly used intraoperatively (Stanley, 2014). Fentanyl was synthesised in 1960 with the intent of developing a rapid acting, potent medication with the ability to provide significant analgesia with very low plasma concentrations of the drug (Stanley, 2014).

Opioids produce analgesic and euphoria effects at specific receptor sites in the brain and spinal cord known as the mu (μ), kappa (κ) and delta (σ) receptors (Ritter et al., 2020). Mu receptors are most responsible for analgesic effects of opioids and for other secondary effects (e.g. respiratory depression, constipation, euphoria, and sedation) (Ritter et al., 2020). While opioids produce powerful analgesic effects, they also cause a sense of euphoria and wellbeing, which has been suggested to also contribute to their analgesic effectiveness (Ritter et al., 2020).

Respiratory depression can be a dangerous side effect of opioids caused by activation of the μ receptor thereby reducing the sensitivity of the respiratory centres to arterial PCO2. Activation of μ receptor also inhibits respiratory rhythm in the brain stem (Ritter et al., 2020). Opioids produce a depressant response in chemoreceptors that would normally sense an increase in arterial C02 and cause a compensatory increase in ventilation rate to try and counteract the increased C02. Respiratory depression can occur even at therapeutic doses and is the most common cause of opioid poisoning deaths (Ritter et al., 2020).

Opioid tolerance refers to a pharmacological effect that occurs with repeated doses of opioids where a person requires a slightly higher dose to produce similar effects previously obtained at a lower dose. The degree of tolerance is thought to be associated with the amount of receptor occupancy, the total amount of the dose being administered, and the pharmacologic efficacy of the drug (Ritter et al., 2020). For PWOUD, repeated exposure to highly potent fentanyl is associated with more intense use of the drug reflecting the effects of tolerance produced by potent opioids (Hayashi et al., 2021).

Opioid Use Disorder

OUD is a chronic medical condition that often includes multiple periods of recovery from opioid use combined with periods of relapse (Centre for Addiction and Mental Health [CAMH], 2021). OUD may involve non-medical use of prescribed opioids or unregulated opioids such as heroin and fentanyl (BC Center on Substance Use [BCCSU], 2017). In 2017, 55,470 people in BC were identified as living with a diagnosis of OUD (Piske et al., 2020). Many people, but not all who experience toxic drug poisonings are diagnosed with OUD. The *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-5) provides internationally recognised standardized language and criteria for mental conditions (American Psychological Association [APA], 2013; Refier et al., 2013). The mainstay of criteria for substance use disorders are that the individual continues to use the substance despite significant physical and emotional symptoms and social problems related to their substance use (APA, 2013). The diagnostic criteria for substance use conditions are grouped into categories related to impaired control, social impairment, risky use, and pharmacological criteria of withdrawal and tolerance (APA, 2013), refer to Appendix A for the specific diagnostic criteria for OUD. Severity of a substance use condition is also quantified in the diagnostic criteria by tallying the number of symptom

criteria endorsed by the patient and ranges from mild to severe (APA, 2013) (see Appendix A). A diagnosis of OUD can be made by a qualified healthcare provider and is most often provided by PCPs, psychiatrists, addiction medicine specialists, or a psychologist. In Canada, addiction medicine specialists are often family physicians with additional training in substance use disorders. The term *addiction medicine specialist* will be used throughout this review; however, the author acknowledges that some commonly used terms, including the term 'addiction' or 'addict' perpetuates stigma and does not reflect the experience of people who use drugs (Buchman et al., 2017). The use of the term 'addiction' will be avoided outside the connotation of this title.

Neurobiology of Opioid Use Disorder

OUD is influenced by a complex interplay between several intrinsic and extrinsic characteristics including exposure to opioids, the effectiveness of the brain's response to stress and inherited factors. About half of people who experience OUD are initially prescribed an opioid by a healthcare provider for pain management, which initiates their opioid use (Hartung et al., 2021; Nolte et al., 2020). Despite being prescribed opioids to treat pain, people who take opioids for pain also experience the secondary anxiolytic, antidepressant and euphoric effects. When opioids bind to receptors in the central nervous system, a variety of secondary effects occur including decreased release of excitatory neuropeptides and hyperpolarization of post-synaptic neurons (Wachholtz et al., 2015). The combination of hyperpolarization and reduced neurochemical excitation leads to decreased transmission of nociceptive signals causing analgesic, antidepressant and anxiolytic effects that manifest as feelings of euphoria, increased stress tolerance and activate dopaminergic reward pathways in the brain (Ritter et al., 2020;

Wachholtz et al., 2015). However, it is clear that not all people who are prescribed opioids for short-term pain management go on to develop OUD.

Stein et al. (2017) describe the strong correlation between adverse childhood experiences (ACEs) and opioid use. Stein's et al. (2017) findings correlate with extensive evidence that higher ACE scores significantly increases in individuals' risk of engaging in opioid-related drug use behaviors (Carlyle et al., 2021; Quinn et al., 2016; van Draanen, 2020). The most common ACEs among a modest sample of PWOUD seeking treatment (n= 457) were experiencing family divorce, living with a family member who used drugs, and having an adult in the home who verbally or emotionally harmed them (Stein et al., 2017). Stressful experiences early in life can act as a catalyst for several neurobiological changes that may alter brain development leading to greater propensity for substance use conditions (Carlyle et al., 2021; Gerra et al., 2008). Stressful experiences can cause increased glucocorticoid (stress hormone) excretion and hypothalamic-pituitary-adrenal (HPA) axis dysfunction that may increase the likelihood of a person to experiment with substances or increase risk of substance use disorders (Gerra et al., 2008). The HPA axis in the brain functions by controlling the brains response to stress by regulating physiological processes that act on the hypothalamus, anterior pituitary gland and the adrenal gland (Sheng et al., 2021). Early childhood neglect, abuse or trauma can cause neurobiological injuries that increases an individual's vulnerability to stressors by reducing effectiveness of coping behaviors and ability to regulate emotions and worsen symptoms of hyperarousal (Carlyle et al., 2021). Opioids then play an important role as an external coping strategy that relieve debilitating emotional sensations and bring an immediate sense of euphoria and reward during stressful events (Carlyle et al., 2021; Derefinko et al., 2019; Quinn et al., 2016; van Draanen, 2020).

Having a family member with a prior or active substance use condition influences environmental and genetic risk factors for OUD (Nolte et al., 2020). Environmental factors such as exposure to substance use from a young age, as seen in instances where family members of children use substances (not necessarily opioids) in the home can lead to a sense of normalization of substance use (Nolte et al., 2020) and increase a person's access to unregulated substances. Opioid use in particular, has been found to have strong contributions from genetic factors based on twin studies (Nelson et al., 2016; Tsuang et al., 2001). Having a relative with OUD increases a person's risk of OUD by eight-fold (Merikangas et al., 1998).

Toxic Drug Supply

A key contributor to rising rates of toxic drug poisonings is illicitly manufactured fentanyl and fentanyl analogues that have contaminated the unregulated drug supply, rendering it toxic and places people at high risk for unintentional poisonings (Zoorob, 2019). People who use drugs (PWUD), many of whom have significant experience using heroin or other unregulated substances, are often unknowingly exposed to dangerous concentrations of fentanyl, fentanyl analogues and other dangerous adulterants such as high-potency benzodiazepines (Brar et al., 2020; Hayashi et al., 2021; Laing et al., 2021; Tobias et al., 2021).

Fentanyl is 30 to 40 times more potent than heroin and has a faster onset and short-half life (Mars et al., 2019; Stanley, 2014). Fentanyl analogues (e.g. carfentanil) are up to 10 000 times stronger than morphine (Mars et al., 2019), making soliciting the current unregulated drug supply extremely unpredictable (Brar et al., 2020). There has been some fear and misconceptions among the public in suggesting that prescribed opioids are directly causing the up-tick of toxic drug poisonings, however provincial post-mortem toxicology reports reveal that prescribed opioids have been detected in less than 2% of all toxic drug deaths, while fentanyl and fentanyl-

analogues are detected in the majority of toxic drug deaths (greater than 75%) (Crabtree et al., 2020; Socias et al., 2021; Tobias et al., 2021; Zoorob, 2019). Fentanyl recognition in drug samples detected by drug checking systems at harm reduction sites have shown that the concentration rates of fentanyl in drug samples coincides with peaks and declines in toxic drug death rates (Tobias et al., 2021). These findings strongly suggest that it is the toxic unregulated drug supply, not prescription opioids, that is the root of increased mortality for PWUD (Bardwell et al., 2021; Irvine et al., 2019; Rose, 2018). Language used to describe fatal and non-fatal overdoses has been changed to *toxic drug deaths* or *toxic drug poisonings* to reflect the unintentionality of illicit drug overdose and reduce stigma or blame on PWUD.

The unregulated drug market provides the illusion of choice to people who are purchasing substances because the vast majority of unregulated drugs contain fentanyl to some degree despite looking like or being sold as others (e.g. stimulants or heroin) (Tobias et al., 2021). Although evidence in the literature suggests that some PWOUD seek-out the strongest available product (i.e. fentanyl), the current toxic drug crisis may have separated PWOUD into two groups; those who seek out fentanyl and those who try to avoid it, which has implications when prescribing treatment options for PWOUD (Brar et al., 2020). It is estimated that of people who are exposed to fentanyl, about one half are exposed unknowingly (Hayashi et al., 2021).

There is growing concern about the escalating contamination of substances being sold as unregulated heroin or fentanyl with high-potency benzodiazepines (Beaulac et al., 2022; Laing et al., 2021). Co-ingestion of opioids and benzodiazepines increase risk of toxic drug poisoning due to the synergistic effects of combined respiratory depressant effects caused by each substance (Laing et al., 2021). High-potency benzodiazepines, namely etizolam are now recognized as a global public health threat (McAuley et al., 2022) and post-mortem detection rates of etizolam in

BC significantly increased during the COVID-19 pandemic (BC Coroners, 2021). The emergence of high-potency benzodiazepines used as dangerous adulterants in the toxic drug supply (Beaulac et al., 2022; Laing et al., 2021) increases the urgency of upscaling access to OAT across the province in order to separate people from toxic drug use. Despite the urgency and multi-level efforts, PWOUD experience challenges in accessing OAT and report that obtaining unregulated substances requires less resources than accessing safe, prescribed OAT (Bardwell & Lappalaian, 2021; Piske et al., 2020; Nosyk et al., 2021).

Stigmatization of People Who Use Drugs

Stigma is commonly identified as a barrier to health-seeking behavior in PWOUD in spite of the known risk of toxic drug use (Barry et al., 2014; Goodyear et al., 2018; Stangl et al., 2019). Stigma is understood as a negative attitude, attribute, characteristic or shared belief about a person or a group of people with a similar health condition (Goodyear et al., 2018). Stigma occurs at the individual, interpersonal, community, organizational, and policy levels and can manifest as problems in accessing and being accepted in healthcare, reduced treatment adherence, difficulty advocating for self or others and lessens the impact of protective characteristics such as resiliency (Buchman et al., 2017; Couto e Cruz et al., 2018; Stangl et al., 2019). People who experience stigma can also hold internalized negative beliefs about themselves (self-stigma), which further impacts a person's agency and how a person seeks out healthcare resources (Goodyear et al., 2018; Livingston et al., 2012). Stigma also influences the way healthcare providers interact with a person, often causing healthcare providers to act in ways that are paternalistic or authoritarian that perpetuates status loss and ultimately leads to fear of judgement and avoidance of accessing healthcare (Goodyear et al., 2018; Link & Phalen, 2001; Livingston et al., 2012).

Stigma is a fundamental driver of morbidity and mortality related to substance use, as discussed by Hatzenbuehler et al. (2013) who describes stigma as a 'social determinant of health'. Stigma is comparable to other social factors that are associated with health inequalities; stigma can affect a person's access to knowledge, finances, social power, and social networks that can improve health or mitigate the effects of risk factors (Hatzenbuehler et al., 2013). Social isolation is a known risk factor associated with toxic drug death (Latkin et al., 2019; Tobias et al., 2021; Yang et al., 2022) and Hatzenbuehler et al. (2013) suggests that stigma is also a pathway that links isolation to negative population health outcomes. Couto e Cruz et al. (2018) substantiate the links between isolation, stigma and risk of toxic drug death by reporting that in a sample of 796 people who use drugs, of those who experienced stigma weekly related to their substance use had 60% increased odds of toxic drug poisoning.

People who live in rural or remote communities are at particularly risk of toxic drug death as a consequence of social isolation related to stigma due to the reduced ability to use at home or private residences related to fear of stigma from family or loved ones and lack of available supervised consumption services (SCSs) or overdose prevention services (OPSs) (Fadenelli et al., 2020; Palombi et al., 2018; Yang et al., 2022). Circumstances often arise in rural or remote communities where PWUD are forced to use substances in public areas that are isolated with no cell service (e.g. bus stops, parks) and where no help would be available if they required it (Day et al., 2006; Fadanelli et al., 2020; Thomas et al., 2020).

Drug Prohibition Policy

Canadian federal drug laws, namely the Controlled Drugs and Substances Act (CDSA) and other regulations that fall under its authority, stem from the international drug control conventions that impose international sanctions to prevent overuse and misuse (e.g. diversion) of

controlled substances (CS) while ensuring adequate accessibility for people who require them for medical purposes (Burke-Shyne et al., 2017; Nutt, 2015). All CS are categorized into one of four "schedules" and each schedule determines the degree of control over the drugs that are classified within it (Nutt et al., 2013). Drugs are classified based on the premise for potential risk of abuse of the drug by the public. All OAT medications are listed as Schedule I drugs, which have the highest degree of regulatory oversight (Courtwright, 2004). Despite the WHO listing methadone and buprenorphine/naloxone as essential medications, which indicate high priority for accessibility to those medications by people who need them, strict enforcement of these medications and people who they are prescribed to persists (DeBeck et al., 2009).

The power imbalance between enforcement of CS and those promoting access to CS for health purposes has tipped law enforcement into the sphere of healthcare by requiring intense oversight of CS through federal auditing of CS documentation and prescriptions and enforcing policies aimed at preventing diversion of CS by people they are prescribed to (Burke-Shyne et al., 2017; Wood et al., 2008). Stringent regulations of CS undermine the strides made to improve accessibility and acceptability of substance use treatment by disincentivizing OAT prescribing and perpetuating the belief that people who use drugs are not to be trusted (Collins et al., 2019). In the pursuit to further prevent diversion, people who are prescribed OAT are often subjected to invasive monitoring such as mandatory urine drug screening (UDS) and being required to take daily medication observed by a pharmacist or a nurse (del Pozo & Beletsky, 2020; Oviedo-Joekes et al., 2021). Federal drug regulations that endorse CS control over accessibility to OAT medications perpetuates criminalization of people who use substances, even when they are adhering to evidence-based treatment (Collins et al., 2019).

History of Opioid Agonist Treatment

The first Canadian federal drug law, the Opium Act of 1908, effectively criminalized the use of opioids and banned physicians from prescribing opioids to treat opioid dependency conditions (Boyd, 2021). The initial methadone prescription used to treat OUD wasn't prescribed in BC until in the mid-twentieth century after an increase of non-medical opioid use was seen among war veterans in Western Canada after the Second World War (Fischer, 2000). Despite federal prohibition of all opioid use for medical or non-medical purposes, advocacy efforts from a small number of physicians and political figures established the first opioid maintenance program through a government-funded clinic in 1969 led by Dr. Robert Halliday in Vancouver, BC (Fischer, 2000).

Methadone was the first approved medication for treatment of opioid withdrawal. Treatment guidelines based on Dr. Halliday's clinical research recommended that methadone be prescribed and administered in specialized addiction clinics only rather than by local general practitioners. The concept of specialized methadone clinics was supported by a government committee who heeded warning to physicians of the "grave risks" that could be incurred if methadone was prescribed in private practices (Fischer, 200). Federal authorities increased restrictions on physicians prescribing methadone by requiring that all methadone prescribers obtain special authorisation that limited the number of methadone prescribers, monitored all methadone prescribing and limited the number of patients on methadone (Eibl, Morin, et al., 2017). Any violations against this regulation were considered a criminal offense against the prescriber (Fischer, 2000).

Public pressure for improved accessibility to OAT began to mount in the mid-1990s when the Vancouver Health Board declared the first public health emergency related to the harms from

unregulated opioid use (Boyd, 2021; Eibl, Morin, et al., 2017; Fischer, 2000). At this time drug deaths, from mostly heroin and cocaine, peaked at a rate of 330 deaths in one year (BC Ministry of Attorney General, 1994). In response, the Office of the Chief Coroner published the Report of the *Task Force into Illicit Narcotic Overdose Deaths in British Colombia*, colloquially known as the Cain report, after the author and Chief Coroner (Boyd, 2021). Cain (1994) argued that the current enforcement approach towards substance use was demonstrated to be ineffective and by Canada following the US in a massive "war on drugs" was projected to be an expensive failure. In the report, Cain (1994) recommended a scale up of harm reduction services, fewer regulations placed on methadone prescribers and decriminalization of personal possession of substances, which bores striking resemblance to BC's Provincial Health Officer, Dr. Bonnie Henry's (2019) *Stopping the Harm: Decriminalization of People Who Use Drugs in BC.* Similarities between Henry's (2019) and Cain's (1994) reports demonstrate the longitudinal consequences of a highly politicised and poorly addressed public health issue.

Due to a significant and alarming increase in toxic drug deaths between 2015-2016, the provincial health officer in BC, declared another public health emergency on April 21, 2016 (BC Government, 2016). A public health emergency can only be declared under specific circumstances where there is an inordinate need to protect the public from immediate and harm health risks (BC Government, n.d.). Once a public health emergency is declared, health officials are authorized to act outside of the Public Health Acts usual regulations and may order immediate actions to protect the public (e.g. increased surveillance and reporting of a disease) (BC Government, n.d.).

Since the declaration of the public health emergency in 2016, several high-level policy changes have been made to increase accessibility of OAT. Changes include the removal of the

Health Canada methadone exemption from the CDSA, which was effective in increasing the number of physicians authorized to prescribe methadone (Eibl, Morin, et al., 2017). Improved prescribing standards for physicians to allow OAT to be prescribed by telehealth without an in-person visit and amendments made by the College of Pharmacists allowed pharmacists more flexibility to use clinical judgement to dispense and deliver OAT to individuals under circumstances that would have been prohibited previously (Government of Canada [GOC], 2021).

Dual Public Health Emergencies

The onset of the COVID-19 pandemic significantly disrupted the treatment of OUD and accessibility of OAT in BC (Henderson et al., 2021; Ngosa Mumba et al., 2021). Prior to COVID-19, treatment of OUD relied heavily on in-person encounters between patients and providers for assessments, non-pharmacologic interventions (e.g. motivational interviewing) and therapeutic relationship building (Komaromy et al., 2020; Leppla & Gross, 2020). COVID-19 practice recommendations from professional regulatory organizations advised providers to reduce the frequency of urine drug screening (UDS), scale-up telehealth visits, and provide longer prescriptions for take-home doses rather than daily witness ingestion (DWI) at a pharmacy in order to curb the spread of COVID-19. These recommendations contradicted the previous treatment structure and supervision of OAT, especially methadone and other full-opioid agonist medications used to treat OUD (Hughes et al., 2021; Leppla & Gross, 2020; Wang et al., 2021). Despite concerns of highly regulated medications being prescribed more frequently as take-home doses and having less frequent in-person assessments of people prescribed OAT, telehealth has demonstrated to improve the length of time people are retained on OAT (Eibl et al., 2017), and improve equitable access to OAT especially for rural and remote populations

(Eibl, Gauthier, et al., 2017; Hughes et al., 2021; Komaromy et al., 2020; Wang et al., 2021). However, restricting care provision to mostly telehealth has demonstrated to be a barrier for some PWOUD. Reduced availability of low-barrier in-person or "walk-in" appointments is causing delays in OAT initiations in people not already prescribed OAT and some clinics are not accepting new patients at all due to COVID-19 (Joudrey et al., 2021). Additionally, those who have limited or no access to technology required to use telehealth (e.g. internet, cell phones) are more significantly impacted (Joudrey et al., 2021; Wang et al., 2021).

As a result of more relaxed clinical procedures when prescribing OAT during dual health emergencies, other disciplines have been authorized to take on more responsibility in the care of PWOUD by expanding the scope of practice for pharmacists and nurses (Hong & Fairbairn, 2021). The September 2020 Order of the Provincial Health Officer identified that the rate toxic drug deaths had significantly worsened since the onset of COVID-19 due to increased toxicity of unregulated drug supply, decreased access to harm reduction services, additional barriers when accessing substance use treatment services and health risks related to withdrawal during self-isolation leading to increased risk of people using alone (BC Ministry of Health [MOH], 2020). In response to the worsening toxic drug health emergency and a lack of prescribers to meet the need of PWOUD who require pharmacologic interventions to prevent toxic drug death, registered nurses (RNs) and registered psychiatric nurses (RPNs) with additional training were authorized by the Provincial Health Officer to be able to make a diagnosis of a substance use condition and prescribe drugs, including controlled substances to treat a person with a substance use-related condition or disorder (BC MOH, 2020). In rural and small-urban settings in BC, many nurse prescribers are positioned in interdisciplinary teams that include physicians, nurse practitioners (NPs), counsellors, harm reduction workers and outreach workers to meet the

holistic needs of PWOUD and also to support safe prescribing by nurses who are new to the activity of prescribing [personal communication with A. Lavigne, June 2021]. Task-shifting OAT prescribing to RNs and RPNs demonstrates that PCPs have the knowledge, experience and skills to prescribe OAT in rural and remote PC and also creates additional interdisciplinary communication pathways between nurses and PCPs. These novel top-down policy approaches support a medical model to reduce toxic drug deaths and attempted to recruit additional healthcare professionals in prescribing pharmacologic treatment for OUD.

Opiate Agonist Treatment

Buprenorphine/naloxone, methadone and slow-release oral morphine (SROM) are evidence-based pharmacologic interventions for OUD in Canada (BCCSU, 2022) that act to reduce cravings and opioid withdrawal, and support abstinence from toxic drug use (Amato et al., 2005; BCCSU, 2017; Ngosa Mumba et al., 2021; Rosic et al., 2021). Engagement in OAT has been estimated to reduce the relative risk of all-cause mortality by 3.2 for people taking methadone and 2.2 for people taking buprenorphine/naloxone (Piske et al., 2020). Buprenorphine/naloxone has long been considered first-line treatment due to its superior safety profile as a partial-agonist with a respiratory depression ceiling effect and ease for prescribing take-home dosing (BCCSU, 2017; Socias et al., 2018), but due to the effects potent unregulated fentanyl has on PWUD's individual opioid tolerance it is now recommended that prescribers should carefully consider all three options with every PWOUD (BCCSU, 2022). Patient preference, drug-drug interactions, other comorbidities (e.g. HIV, HCV, liver failure, prolonged QTc interval), the patient's current living situation, treatment history and response to past treatments are all considerations when PCPs are mutually agreeing on an OAT medication with a PWOUD (BCCSU, 2017; Canadian Research Initiative in Substance Misuse [CRISM], 2018).

Cornerstone to OAT interventions is the opioid agonist component in the medication that reduces a person's withdrawal and cravings providing longitudinal relief and thus reduces the incentive to obtain unregulated opioids (Gauthier et al., 2018; Socias et al., 2018). Abstinence or weaning strategies that prioritize cessation of all opioid consumption is not recommended due to the association between reduced opioid tolerance and toxic drug death (Amato et al., 2005; BCCSU, 2017; Gauthier et al., 2018). Injectable OAT (iOAT) and Risk Mitigation (RM) prescribing are alternative treatments that are used to treat OUD in some practice settings (Hong & Fairbairn, 2021). Injectable OAT is considered a high-intensity treatment option that requires the individual to attend a specialized clinic multiple times per day to self-administer opioid medication (e.g. hydromorphone, diacetylmorphine or sufentanil) intravenously (BCCSU, 2017; CRISM, 2018; Nosyk et al., 2021; Oviedo-Joekes et al., 2021). Risk Mitigation (RM), also known as *Safe Supply*, is another opioid replacement option that uses a combination of short-acting hydromorphone and long-acting hydromorphone (e.g. M-Eslon) and is often prescribed as take-home doses with the goal of providing an alternative to the contaminated toxic drug supply (BCCSU, 2020; Hong & Fairbairn, 2021; Nosyk et al., 2021). Ideally, PWOUD would have access to OAT, iOAT and RM regardless of where they live in the province; however, for reasons that are outside the scope of this paper, iOAT and RM are often only accessible in urban areas (Bardwell & Lappalainen, 2021). Due to the scarcity of availably of iOAT and RM in rural regions in BC, the purpose of this paper is to explore buprenorphine/naloxone, methadone and SROM, all of which are within PCPs scope of practice.

Buprenorphine/naloxone

Buprenorphine is the active medication in the combination medication buprenorphine/naloxone used to treat OUD. In Canada, buprenorphine is most commonly

prescribed in combination with naloxone as an abuse-deterrent (Blazes & Morrow, 2020; Strickland & Burson, 2018). Naloxone is absorbed by intravenous or intramuscular routes; it has been found that naloxone does have variability in oral absorption and it cannot be concluded that naloxone in the combination medication does not have any effect by the sublingual route (Blazes & Morrow, 2020; Strickland & Burson, 2018). This small variability may explain some of the unwanted and unpredictable side effects of buprenorphine/naloxone (e.g., nausea and stomach cramping) (Strickland & Burson, 2018). Initiating buprenorphine/naloxone takes some preparation on behalf of the patient and provider to avoid precipitated withdrawal (Bell et al., 2007; Socias et al., 2018). Precipitated withdrawal is caused by the binding of a partial-agonist to the μ receptor, meaning that the biological effect on the receptor is less than a full agonist, but in the case of buprenorphine the affinity for the receptor is high (Strickland & Burson, 2019). Due to its high affinity, it will displace full agonists (e.g. heroin, morphine, fentanyl) from the receptor and be replaced by the partial agonist with less activity on the receptor leading to a sensation of opioid withdrawal (Blazes & Morrow, 2020; Carroll, 2021; Danilewitz & McLean, 2020).

Buprenorphine is also available in an extended-release depot injection administered monthly (Sublocade), a sublingual film (Subutex) and as an implant (Probuphine) (BCCSU, 2022). Buprenorphine containing medications have been found to be superior to placebo for treatment of opioid withdrawal and prevention of toxic drug death, however it has only been found to be effective at supressing unregulated opioid use at higher doses (greater than 16 mg) (Baca-Atlas & Williams, 2021; Danilewitz & McLean, 2020; Mattick et al., 2014). Retention in treatment for PWOUD prescribed buprenorphine/naloxone has varied in the literature and clinical practice (Cioe et al., 2020; Danilewitz & McLean, 2020). Many PWOUD dislike

buprenorphine/naloxone due to its taste, not wanting to risk experiencing feelings of withdrawal, and the slow titration process it can often take to get to an ideal dose (Cioe et al., 2020). On the other hand, evidence also suggests that many PWOUD prefer buprenorphine/naloxone due to more flexible dosing including more leniency with take-home dosing, greater anonymity as it is commonly prescribed in primary care, and fewer side effects compared to methadone (Cioe et al., 2020; Socias et al., 2018; Wood et al., 2019).

In terms of safety, there is evidence to suggest that buprenorphine/naloxone is more effective than other OAT medications in reducing deaths related to opioid toxicity due to its ceiling effect for respiratory depression it is considered a safer option compared to methadone (Bell et al., 2007; Sordo et al., 2017; Wang et al., 2021). However, as a partial-agonist, buprenorphine/naloxone demonstrates to be less effective at retaining PWOUD in treatment due to treatment satisfaction and people are at significantly increased risk of toxic drug death in the first four weeks after cessation of OAT, which may counteract the protective effect by increasing a person's risk of overdose when frequently on and then off treatment (Altekruse et al., 2020; Cioe et al., 2020; Sordo et al., 2017).

Methadone

Methadone is the oldest medication available to treat OUD (Eibl et al., 2015; Fischer, 2000). Methadone is a full-agonist, meaning that methadone poses the same risk of adverse events or side effects as other opioid-containing medication (e.g. respiratory depression, somnolence, euphoric effects). There is significant evidence to show that when dispensed safely, methadone is effective to reduce unregulated opioid use, reduce injection drug use and improve the health and wellbeing of PWOUD (Amato et al., 2005; Dong et al., 2020; Eibl et al., 2015; Joudrey et al., 2021). Methadone-based treatment has also been demonstrated to provide superior

retention when compared to other OAT interventions (e.g. buprenorphine) (Amato et al., 2005). However, more recent systematic reviews have found no differences in retention between buprenorphine/naloxone and methadone (Klimas et al., 2021) suggesting less of a superiority between methadone and buprenorphine/naloxone and greater individualized preference. Higher doses of methadone (greater than 80mg) have shown to provide greater retention in treatment when compared to lower doses (Amato et al., 2005; Cousins et al., 2017).

Methadone has unique pharmacologic properties, when compared to other OAT options (e.g. narrow therapeutic index, longer half-life and greater potential for drug-drug interactions) (BCCSU, 2017; CRISM, 2018). As a full-agonist, methadone has a greater risk of producing a serious sedating effect when combined with alcohol, benzodiazepines or other sedating medication. In a retrospective cohort study by Crabtree el al. (2020) that compared BC toxicology reports with provincial prescription databases, of those PWUD who experienced fatal drug poisoning, in only 7.3% of deaths was methadone detected. Out of those deaths, more than half did not have a prescription for methadone and only half of those people were prescribed an effective dose (greater than 80mg) (Crabtree et al., 2020). This confirms other findings that methadone prescribed at a dose greater than 80mg provides the most protection against toxic drug poisoning.

Patient perceptions of methadone have varied. People who are prescribed methadone report experiencing health-related concerns when taking methadone, especially over long periods of time (e.g. tooth decay, lower libido, bone pain) (Falcato et al., 2015; Johnson & Richert, 2015). Methadone is also considered less convenient in dosing due to often requiring DWI by a nurse or pharmacist (Wood et al., 2019). PWOUD, especially those who are in recovery from

unregulated drug use find this protocol stigmatizing and inconvenient when trying to go to work, school, care for family, or travel (Cioe et al., 2020; Dong et al., 2020; Wood et al., 2019).

Slow-release oral morphine

An alternative OAT option to buprenorphine/naloxone and methadone is slow-release oral morphine (SROM). For many PWOUD, balancing medication side effects (precipitated withdrawal, sweating, nausea) and other limitations of methadone (e.g. prolonged QTc, drug-drug interactions) and buprenorphine/naloxone can be a challenge. There is increasing recognition that a range of OAT options are necessary (Klimas et al., 2019). SROM is a 24-hour oral formulation of morphine, a full-agonist, that can be taken orally once daily (BCCSU, 2017). When prescribed as an OAT, SROM has demonstrated to be as effective as methadone in treatment efficacy and retention (Klimas et al., 2019). There is some low-quality evidence to suggest that SROM has greater potential for treatment retention compared to other OAT medications and that SROM is better at relieving cravings for heroin (Falcato et al., 2015; BCCSU, 2022; Klimas et al., 2019; Socias et al., 2020). SROM has been found to have a similar safety profile compared to methadone (Beck et al., 2014).

In *A Guideline for the Clinical Management of Opioid Use Disorder* (2017), the BC provincial guidelines for treatment of OUD SROM was recommended to be prescribed by a prescriber with a section 56 exemption to prescribe methadone and without a section 56 exemption to seek expert consultation before prescribing SROM. This recommendation has since expanded to allowing for prescribing of SROM to occur using clinical discretion and patient preference (BCCSU, 2022). Consultation is available in BC for any prescriber new to prescribing alternate OAT medications (e.g. Rapid Access Consultative Expertise [RACE] App, BCCSU 24/7 Addiction Line).

Table 1

Comparison of Opiate Agonist Treatment Advantages and Disadvantages

Methadone	Buprenorphine	SROM
Advantages		
-Demonstrates better treatment retention -Can titrate dose daily -Can relieve withdrawal symptoms quickly -Good pain management qualities	-Reduced risk of iatrogenic overdose -Low risk for diversion or injection -Fewer side effects -Able to switch to full-agonists -Take-home doses more accepted -Few drug-drug interactions -Easier to discontinue when ready -Due to long half-life, alternate day dosing an option -Ease of carries for rural/remote -Can transition to long-acting injectable Sublocade	-Potentially improved retention -Few side-effects -Few drug-drug interactions -Low risk of QTc prolongation -Known to reduce cravings for heroin -Daily dosing in 24hr formulation -Can be sprinkled to avoid diversion -Can titrate more quickly
Disadvantages		
-Higher risk of accidental overdose -Often prescribed as DWI -More side-effects (e.g. sweating, weight gain, erectile dysfunction, cognitive impairment) -Longer to titrate to therapeutic dose -Difficult to transition to buprenorphine -High potential for drug-drug interactions -Risk of cardiac arrhythmias	-Demonstrated lower retention rates -Risk of precipitated withdrawal -Usual doses may be suboptimal for people exposed to fentanyl -Can block analgesic or euphoric effects of other opioids due to high affinity for opioid receptors	-Higher risk of accidental overdose -Often prescribed as DWI -Higher risk of medication diversion due to full-agonist qualities

Table adapted from (BCCSU, 2017)

Treatment Outcomes

Expected treatment outcomes for people who are prescribed OAT are reduced risk of all-cause mortality and toxic drug poisonings (Rosic et al., 2021; Sordo et al., 2017; Wood et al.,

2019). Reducing a PWOUDs' risk of toxic drug poisoning is a clinical priority in the context of the fentanyl-contaminated drug supply. Prior to the emergence of fentanyl, very few studies measured mortality rate as a health outcome of OAT because death within the time frame of a clinical trial was rare (Amato et al., 2005). Proxy measures of OAT treatment success were established based on abstinence from drug use as the primary treatment goal. UDSs, self-reports of substance use and length of treatment retention measured by prescription length were all proxy indicators of treatment outcomes for pharmacologic interventions for OUD (Rosic et al., 2021). This has led to significant heterogeneity in the outcomes used to evaluate the effectiveness of OAT, which creates challenges when comparing health outcomes studies in the field of substance use disorders.

Controversy exists regarding current quantitative measures of UDS and treatment retention length. UDSs can be used clinically to confirm a diagnosis of OUD or adherence to OAT (Korownyk, Perry, Ton, Kolber, Garrison, Thomas, Allan, Bateman, et al., 2019; McEachern et al., 2019). A systematic review conducted by McEachern et al. (2019) found that there is very little evidence to support that UDS are effective at improving treatment outcomes in the medical management of OUD. Length in treatment does not accurately assess treatment outcomes for OAT due to the frequency people discontinue, re-start and initiate OAT (Lo et al., 2018; Stafford et al., 2022). There is also marked variability in length of retention in treatment regardless of the specific OAT prescribed.

Not all people who take OAT are satisfied with treatment (Cole et al., 2020; Mackay et al., 2021). Unfavourable treatment outcomes, most prominently mortality, occur for people who take OAT despite engaging in treatment (Sordo et al., 2017). Patient-centred care is a well-known approach to care provision, which means to be respectful of a patient's individual

preferences, needs and values (Barry et al., 2014; Hong & Fairbairn, 2021; Marchand et al., 2019). Patient-centred care in the context of treatment for substance use disorders includes shared decision making about pharmacologic interventions based on patients' goals and a trauma-informed approach to care (Marchand et al., 2019). Ideally, research that focuses on treatment outcomes is research that focuses on quality of patient care (Grey & Grove, 2021) however, measuring OAT treatment outcomes based on UDSs and retention in treatment length does not clearly capture patients' values, preferences or the individual's goals of care (Rosic et al., 2021). Patients' perceived satisfaction with their OAT is a significant predictor of OAT discontinuation and is positively associated with fentanyl exposure (Mackay et al., 2021), indicating that exploring patient treatment satisfaction and each patients' unique goals is critical in preventing mortality related to the toxic drug supply due to significant increase in mortality immediately after discontinuing OAT (Sordo et al., 2017).

Most health outcomes research assume that the patient's goals of care are primarily abstinence, which for many is simply not the case nor is it attainable due to complex social-structural factors (e.g. insecure housing, trauma, pain) (Rosic et al., 2021). Also, a paradox in OUD outcomes shows that more often abstinence-related goals are positively associated with drug-taking behaviors (Rosic et al., 2021). This contradiction is not yet fully understood. Patient goals that do not include abstinence may include pain management and/or "living a normal life" free from the chaos and social instability that often is associated with substance use (Rosic et al., 2021).

Rurality

Approximately 18% of Canadians live in rural and remote communities (Bosco & Oandasan, 2016). BC reflects a similar distribution of the population with approximately 14% of

residents living rurally (Statistics Canada, 2011). The populations of rural BC are often small, dispersed and fluctuate due to population transience (BC MOH, 2015). BC geography is unique in that remoteness does not only describe population size, but also isolation as many remote communities in BC are accessible only by airplane, boat or winter (ice) road travel. Many Indigenous people live in rural and remote communities and BC First Nations make up large geographic areas in the province. The provincial health system is based on regionally delivered health services provided by five regional health authorities (BC MOH, 2016). The five regional health authorities in BC are, Vancouver Coastal Health Authority, Island Health Authority, Interior Health Authority, Northern Health Authority and Fraser Health Authority. For assessment, planning, and health surveillance purposes each health authority has been divided in to Health Service Delivery Areas (HSDA) and are sub-divided into Local Health Areas (LHA) (BC MOH, 2015). Toxic drug deaths are monitored by the BC Coroners Service based on this geographic classification system (BC Coroners Service, 2022). In 2021, The highest rates of toxic drug death by LHA were in Upper Skeena, Merritt, Enderby, Lillooet and North Thompson (BC Coroners Service, 2022) all of which are located in the Interior and Northern health authorities. Interior and Northern health authorities represent the largest number of rural and remote health jurisdictions among all five health authorities (BC MOH, 2016).

There is increasing recognition that rurality is an independent contributor as a major social determinant of health, which is magnified for people who experience other social risk factors (Canadian Institute for Health Information & Canadian Population Health Initiative, 2006; Cloud et al., 2019; Palombi et al., 2018; Rhodes, 2002). Rural communities in Canada have the highest rates of poverty, unemployment and lowest rates of people who have completed high school or post-secondary education (Canadian Institute for Health Information & Canadian

Population Health Initiative, 2006). Socio-economic factors combined with additional risk factors related to the rural environment (e.g. isolation) contribute to comparatively poorer health outcomes (Fadanelli et al., 2020; Thomas et al., 2020).

There is no international definition of rurality (Hall et al., 2006; Thomas et al., 2020) and significant variability exists in defining rurality in health literature (Bennett et al., 2019). Most definitions of rurality or remoteness are based on population size and density (Canadian Institute for Health Information & Canadian Population Health Initiative, 2006; Rost et al., 2002). This is an advantage because the information is readily available and easy to apply. However, a common critique of population-based definitions is that by limiting to population size it fails to capture the heterogeneity within rural populations and may mask problems in accessing care especially among populations with hidden barriers in accessing care (e.g. stigma, shame) (Minore et al., 2008). Measures of a community's degree of rurality that capture the challenges of "remoteness" that people may experience in accessing health services may have more merit when considering interventions for PWOUD (Minore et al., 2008). Low OAT prescriber density has been identified as large contributing barrier to PWOUD accessing OAT in rural regions of North America (Minore et al., 2008). Piske et al. (2020) corroborate the findings of low prescriber density in rural BC by demonstrating that PWOUD in rural HSDAs experience lower initiation and retention on OAT. OUD is also significantly underdiagnosed in rural primary care clinics (Cole et al., 2019; Saunders et al., 2019). It is estimated that OUD diagnoses occur approximately six-times less frequently in rural primary care than the estimated prevalence of OUD in the general population and only 1 in 5 PWOUD are prescribed OAT when diagnosed (Cole et al., 2019; Hallgren et al., 2020; Shiner et al., 2017).

For the purposes of this paper, the Rurality Index Score (RIS) is a framework that conceptualizes rurality and remoteness in a Canadian context. Calculating and applying RIS scores to communities is outside the scope of this paper, however understanding variables other than population density that contribute to the rural risk environment for PWOUD is important for future research and clinical recommendations for rural PCPs (Minore et al., 2008). When calculating the RIS, communities are given a score based on time to travel to the nearest referral centre, travel time to an advanced referral centre, community population, number of active providers, population to provider ratio, presence of a hospital, availability of ambulance services, social indicators, weather conditions and availability of select services (Minore et al., 2008). Barriers specific to PWOUD in rural communities can also be described based on the degree of rurality as conceptualized by the RIS and will be discussed further in the following section.

Rural-Specific Barriers for People Who Use Drugs

Rural environments pose distinct risks to PWUD. Ample number of articles in the literature describes the *rural risk environment* created by physical features of rural or remote communities and the impact is has on drug distribution and substance-use behaviors (Fadanelli et al., 2020; Palombi et al., 2018; Rhodes, 2002; Thomas et al., 2020). Using the RIS as a framework, rural barriers for PWUD can be described in categories of distance to travel to treatment, population to PCP ratio, number of PCPs prescribing OAT, access to emergency services, social indicators, weather conditions and availability of specialty services.

Travel Time and Distance

Distance to travel to receive pharmacologic treatment options for OUD has demonstrated to be the most common barrier PWOUD face in rural and remote communities (Lister et al., 2020; Thomas et al., 2020). A significant burden is placed on PWOUD to travel to OAT

prescribers, community pharmacies, and other harm reduction services (e.g. SCS or OPS) in order to keep themselves safe. Palombi et al. (2018) describe rural communities as "treatment deserts" and that all types of substance use treatment services, both outpatient and in-patient, are further away from rural PWOUD than for people who live in medium-sized or urban cities. The tendency of resources to be located in areas with larger populations in order to service the most people remains a health equity issue (Bardwell & Lappalainen, 2021). Inequitable distribution of mental health services results in poorer access to potentially preventative interventions considering that the etiology of OUD is often related to preceding mental health conditions and traumatic experiences requiring professional support (Rost et al., 2002). Farther distance to substance use and mental health services for rural PWOUD greatly contributes to the burden of disease in rural and remote communities (Day et al., 2006; Minore et al., 2008; Palombi et al., 2018; Wood et al., 2019).

Primary Care Provider to Person Ratio

Rural residents have less access to primary care due to lower PCP-to-person ratio compared to urban settings (Saunders et al., 2019). Access to PCPs who prescribe OAT is substantially lower in rural communities, which further exacerbates access to treatment for PWOUD (Lister et al., 2020; Palombi et al., 2018; Rosenblatt et al., 2015). PCPs are the largest group of prescribers in rural areas, however a study conducted in rural US found that less than 3% of PCPs obtained the necessary training and credentials in order to prescribe buprenorphine/naloxone (Rosenblatt et al., 2015). Even when PCPs obtain the necessary training, it does not guarantee that it will be incorporated into daily primary care practice (Anderson et al., 2021; Gadomski et al., 2020; Shea et al., 2021). The US has different credentialing processes for physicians and NPs to prescribe OAT than in Canada, however

similar findings suggest that practice characteristics other than clinician knowledge prevent implementation of OAT prescribing in primary care (Dooley et al., 2012). Common challenges include competing demands, volume of patient care, lack of time to complete training and develop clinical work flows (Andrilla et al., 2019; DeFlavio et al., 2015; Lister et al., 2020; Salvador et al., 2019). Due to multiple and complex factors, rural PCPs are often left unequipped or under prepared to prescribe OAT during office visits (DeFlavio et al., 2015).

Presence of Emergency Services

The availability and accessibility of emergency health services (EHS) in rural communities is limited. In rural regions, EHS services take longer to respond in the event of a toxic drug poisoning due to geographic distances and many EHS paramedics lack the training or resources in order to respond quickly and effectively to an overdose (Faul et al., 2015). Faul et al. (2015) analyzed the frequency of naloxone administration among paramedics based on geographical regions (e.g. urban vs. rural). They found that paramedics with basic training were less likely to administer naloxone compared to paramedics with intermediate or advanced training and subsequently in rural areas, most paramedics only have basic training (Faul et al., 2015). PWUD are also hesitant to access emergency services out of fear of legal consequences or police attendance (Ellis et al., 2020; Fadanelli et al., 2020). Often in rural communities, when an ambulance is called the police are the initial responders. Qualitative interviews with rural PWUD conducted by Ellis et al. (2020) recap several concerning scenarios where EHS are phoned to respond to a toxic drug poisoning and instead of providing life-saving measures, police search the residence for illegal contraband. Fear of police surveillance or arrest if EHS are phone to respond to an overdose prevent PWUD from accessing life-saving services, which increases the risk of death among rural PWUD (Ellis et al., 2020; Thomas et al., 2020).

Social Indicators and Weather Conditions

Nuanced social factors in rural communities contribute to accessibility of substance use services as well as substance use behaviors among PWUD. When compared to similar urban populations, rural PWUD have a higher prevalence of lifetime opioid use (Palombi et al., 2018). A variety of contextual considerations have been used to explain increased opioid use among rural populations. The rural workforce often includes greater number of people in jobs that require physical labour (e.g. construction, logging, mining) leading to an increased risk of work-related injuries requiring pain management and increased exposure to opioid medication (Cloud et al., 2019; Monnat, 2018). Economic decline in rural communities leads to less financial resources for infrastructure and population transience, which can reduce the availability of recreational activities leading to increased boredom among rural residents leading to substance use for recreational purposes (Cloud et al., 2019; Monnat, 2018). Conservative attitudes and worldviews are more common in rural and remote communities that can contribute to stigmatizing beliefs about PWUD (Richard et al., 2020). This can influence a PWOUD's choice to engage in services related to substance use or mental health and can also affect the community's willingness to locate harm reduction services in rural communities.

Availability of Specialty Services

Availability of harm reduction services that complement pharmaceutical interventions for OUD and further reduce the risk of toxic drug poisoning are limited in rural and remote communities (Bardwell & Lappalainen, 2021). Speciality harm reduction services are often not implemented in rural communities due to the notion that the cost does not justify the service for a

few, widely-dispersed people who require it (Parker et al., 2012). Rural communities also face challenges recruiting and retaining trained staff, which can limit the hours of operation and also the effectiveness of the services (Berends et al., 2010). Additionally, most harm reduction services are tailored towards people who inject drugs (e.g. needle exchange programs, indoor injection sites). However, inhalation and intranasal consumption of substances are more common routes of drug use seen in toxic drug deaths in rural communities (Bardwell & Lappalainen, 2021). Bardwell and Lappalainen (2021) argue that limited or no availability of harm reduction services that support safe inhalation has the potential to "alienate" those most at risk of toxic drug death in rural and remote settings.

Primary Care Providers

PCPs are often tasked with managing the day-to-day care of people with complex mental health, chronic conditions, chronic non-cancer pain and substance use conditions. Over the last several decades, physician opioid prescribing oversight and the utilization of opioids in the treatment of OUD has swung in excess (Cheng & DeBeck, 2017). Canada is the second largest consumer of opioids globally (Busse et al., 2017; Tilley et al., 2019) and PCPs are the main prescribers of opioid medication (Broglio & Cole, 2014). The federal government ascertains that prescribers are a contributing factor to the current toxic drug crisis (Government of Canada, 2018) by increasing the incidence rate of OUD by overprescribing and exposing people to opioid pain medication (Canadian Institute of Health Information, 2019). An Ontario study by Dahlla et al. (2011) demonstrated an association between individual physicians who prescribed high volumes of opioids and local, geographic opioid-related mortality. Dahlla et al. (2011) provide recommendations, that have been echoed elsewhere, that reducing opioid prescribing may therefore reduce opioid-related deaths. However, a controversy exists in that prescription opioid-

related mortality is extremely small (Crabtree et al., 2020; Dhalla et al., 2011) and by reducing prescribing of opioids has actually increased toxic drug deaths by exposing people to the toxic drug supply (Bardwell et al., 2021; Socias et al., 2021).

The Role of Primary Care in the Treatment of Opioid Use Disorder

PCPs are often a first point of contact for PWOUD for a variety of psychosocial and health-related needs (Kane et al., 2020). People with OUD who live in rural or remote regions frequently attend primary care appointments, but a very small number of people are diagnosed with OUD and treated appropriately by PCPs (Cole et al, 2019; Piske et al., 2020). This is problematic due to limited alternative resources PWOUD can access to obtain OAT in rural and remote regions. Although virtual and electronic health (ehealth) OAT prescribing options are growing in popularity, especially in rural and northern BC (Hser et al., 2021), evidence suggests improved health outcomes when PWOUD are provided comprehensive, wrap-around services by a PCP in their home community (Mamakwa et al., 2017; Logan et al., 2019; Kane et al., 2020).

Mathematical modelling conducted by Linas et al. (2021) estimated that rural community models are required to enroll at least 10% of all people eligible for OAT in treatment every month and retain at least 50% of people on OAT in treatment for 6 months in order to see a 40% reduction in toxic drug deaths. PCPs play a significant role in creating greater opportunity for low threshold OAT access in rural communities. Both, NPs and physicians working in primary care are critical at increasing overall OAT prescribing capacity in rural areas (Roehler et al., 2020). Prescribing full-agonist OAT is considered a non-core privilege for NPs in BC. Nurse Practitioners in BC are required to complete on-line theory modules provided by the BC Centre on Substance Use (BCCSU) and complete an in-person preceptorship with an experienced OAT prescriber in order to obtain OAT prescribing privileges (BCCNM, 2022).

Barriers & Facilitators to Prescribing Opiate Agonist Treatment in Rural Primary Care

Understanding specific barriers and facilitators to rural PCPs prescribing OAT is crucial in order to develop interventions that will break-down barriers and build-up facilitating characteristics that support OAT prescribing in primary care (Bardwell & Lappalainen, 2021; Lister et al., 2020). Improving accessibility and availability of training for rural PCPs is commonly identified as a solution to improving the number of rural PCPs who prescribe OAT (Lister et al., 2020; Logan et al., 2019; Rosenblatt et al., 2015), however findings in the literature suggest that providers degree of knowledge on treatment of OUD is not the end-point that prevents OAT prescribing in rural primary care (Andrilla et al., 2019; Salvador et al., 2019). Systems-level barriers and PCPs attitudes towards PWOUD and their beliefs regarding the efficacy of OAT have greater influence on prescribing behaviors among PCPs (Kennedy-Hendricks et al., 2016; Lister et al., 2020).

The Extension for Community Healthcare Outcomes (ECHO) practice model was developed in the rural US to help expand access to OAT in rural primary care settings by offering didactic case-based learning sessions provided by specialists to build capacity among rural PCPs (Anderson et al., 2021; Salvador et al., 2019; Shea et al., 2021). Despite the learning sessions being consolidated into 1-hour sessions over lunch hour, many PCPs find attending the sessions difficult due to competing priorities of patient care (Shea et al., 2021). Primary care sites that had leadership that supported dedicated time to OAT care provision were more likely to attend (Salvador et al., 2019). Similarly, hub and spoke practice models are integrated networks of a combination of speciality “hubs” and outlying “spokes” that consist of patient medical homes, often at rural or underserved primary care sites (Green et al., 2021; Snell-Rood et al., 2021). The hubs provide expert consultation and more intensive treatments in order to stabilize a

patient on OAT with the goal of transferring care back to the spoke site for long-term management (Green et al., 2021). Rural "spoke sites" have been difficult to recruit due to providers fears that rural sites are not equipped with support staff to address psychosocial and behavioral health needs of patients on OAT, fears that the demand for OAT services will exceed the capacity of the spoke sites and geographical distances are considered a deterrent to offering satellite OAT services (Green et al., 2021). Although rural care providers indicate that formalized support networks are an asset, results from several program evaluations indicate that the likelihood of OAT prescribing among rural PCPs is not strongly associated with the implementation of formal practice support models (Green et al., 2021; Snell-Rood et al., 2021)

System-level barriers including time, staffing and provider capacity are commonly cited as reasons providers are unable to address OUD in rural primary care (Andrilla et al., 2019; Harder et al., 2021; Lister et al., 2020); however, when addressed as priorities among leadership or through high-level policy changes can be augmented to facilitate OAT prescribing. Primary care offices that allocate specific time to OAT prescribing and dedicate administrative human resources to support providers are able to overcome OAT prescribing barriers (Andrilla et al., 2019). Encouraging younger PCPs or PCPs who are early in their careers has been suggested as an important strategy to help off-load time burden of PCPs who may be near retirement and feel overwhelmed by adding OAT-clients to their patient panel (Andrilla et al., 2018). Dotson et al. (2014) identify other system-level barriers to implementation and monitoring of evidence-based practices related to substance use. Site and staff readiness, fewer relationships with universities, low community interest and organizational capacity issues can prevent providers implementing evidence-based practices (Dotson et al., 2014). Modifications to evidence-based practices are more often required in rural settings, which increases the amount of time and clinical judgement

required to adapt practices to fit local needs (Dotson et al., 2014). System-level barriers makes prescribing OAT in rural primary care more cumbersome and time consuming, but can be augmented by high-level organizational and policy changes that prioritizes the care of PWUD.

OAT is more likely to be prescribed by PCPs in rural settings compared to urban areas where OAT is more commonly prescribed by specialty providers (Andrilla et al., 2019; Rosenblatt et al., 2015; Stein et al., 2015). Urban specialty providers are better equipped to manage PWOUD with other complex co-morbid psychiatric conditions due to greater clinical experience, but also having access to interdisciplinary team members embedded in specialty clinics. Embedding healthcare providers that address complex psychosocial issues such as social workers, outreach workers or people with lived and living expertise (PWLLE) of substance use can increase PCPs capacity to treat OUD (Lin & Knudsen, 2019). When OAT is delivered by an interdisciplinary team, patients have been found to experience improved treatment outcomes in terms of increased OAT retention rates, reduced use of unregulated drug supply, and increased patient satisfaction (Buck-McFadyen et al., 2020; Logan et al., 2019; Perry et al., 2019).

Individual provider barriers in rural areas include barriers that are unique to the circumstances of rural healthcare settings as well as barriers that are common across regions. A modest body of the scientific literature has explored PCPs attitudes and beliefs toward PWOUD and the treatment of OUD (Dooley et al., 2012; Kennedy-Hendricks et al., 2016; Lister et al., 2020). Findings indicate that the majority of PCPs acknowledge that OUD is a chronic medical condition and when treated with pharmaceutical treatment people can have positive health outcomes (Kennedy-Hendricks et al., 2017; Richard et al., 2020). Underlying negative attitudes towards PWUD among PCPs creates distance between PCPs and PWUD and lessens the sense of responsibility to treat OUD in primary care (Kennedy-Hendricks et al., 2017). Rural healthcare

providers have also been found to have more concentrated preferences for PWOUD to have complete abstinence-oriented goals or that discontinuing OAT eventually should be a treatment end-point (Richard et al., 2020). Pre-determined beliefs or attitudes among PCPs towards PWOUD reduces provider willingness to provide treatment (Franz et al., 2021) and influences patients' perceptions of the care they receive as stigmatized (Richard et al., 2020).

Providers' fears of medication diversion have acted as a barrier to prescribing opioid-containing medication for the treatment of OUD, especially take-home doses of full-agonist medications. Although the surge in number of pharmaceutical opioids prescribed during the late 1990s and early 2000s contributed significantly to the opioid crisis, there was a shift to unregulated fentanyl as the main contributor to the present toxic drug public health emergency (Socias et al., 2021). Fears of further adding to harms related to pharmaceutical opioids leads to provider avoidance of prescribing OAT to PWOUD or using restrictive prescribing practices aimed at deterring diversion (Franz et al., 2021). A recent study conducted in Vancouver, BC found that among 1100 PWUD, those who used diverted opioids had a significant reduction in frequency of fentanyl exposure related to substituting diverted pharmaceutical opioids for the unregulated toxic drug supply (Socias et al., 2021).

Barriers to OAT exist for urban and rural PWOUD alike due to political, legal, and social-structural challenges that persist despite an ongoing toxic drug public health emergency. Rural-specific environmental and social characteristics intersect with the negative consequences of OUD and exacerbate barriers for rural PWOUD. Contextual factors specific to rural PWOUD have been discussed in order to maintain focus on the research question that relates to how PCPs can improve health outcomes in the face of multiple barriers. The search strategy based on key concepts is discussed in the next chapter.

Chapter Two: Methods

A comprehensive search of the literature was conducted to obtain a thorough understanding of the research question: In rural and remote communities, how can primary care providers improve treatment outcomes for adults with opioid use disorder when prescribing opiate agonist treatment? An integrative literature review was selected to explore the research question because it can provide the broadest type of literature review methods, which allows for inclusion of an array of academic articles to develop a fulsome understanding of a multifaceted research question (Whittemore & Knafle, 2005). The search design had several iterative stages with similar methodology as described by Whittemore and Knafle (2005) that includes preliminary searches to identify the problem, a focused search of six large academic databases available online through the University of Northern British Columbia library resources, data evaluation, data analysis and presentation of the findings. Initial searches on the topic were conducted on Google Scholar to obtain a broad sense of the literature and searchability of the topic followed by a focused search for peer-reviewed articles relevant to the research question. Included articles reference lists were hand-searched to identify any further relevant articles.

Search Strategy

A population-intervention-outcome (PIO) question was used to design the search strategy. Key concepts that related to the research question components were used to develop the search terms (see Appendix B): population of adults with OUD or at risk of toxic drug poisoning, and OAT prescribed in rural or remote primary care settings by PCPs. Specific outcomes were purposely omitted from the search concepts with the intent of exploring any treatment outcomes in the context of the study population and intervention that may arise in the literature. Search

terms were developed based on the key concepts which were applied to a search strategy in each database.

A focused search was conducted of six large academic databases: Cumulative Index of Nursing and Allied Health Literature (CINHAL), MEDLINE, PubMed, PsycINFO, PsychArticles and Web of Science. Databases were selected based on the likelihood of retrieving citations relevant to the research question from disciplines of public health, medicine, nursing, social work and policy-making. The BCCSU research and publication repository was also searched for relevant articles. A peer-review of the search strategy was provided by a health sciences information specialist at the University of Northern British Columbia library to ensure comprehensiveness and completeness of the search methods.

Search Terms

Medical Subject Headings (MeSH) were used wherever possible and all sub-headings were included by expanding search terms. The MeSH for the term "remote" was not included because its meaning in databases is in reference to telemedicine or healthcare provided by phone or virtual technology rather than the concept of rurality. Instead, "remote" was used as keyword only. Keyword searches were used in databases that did not provide MeSH that matched the search concepts. For example, Web of Science and PubMed searches relied on keywords (see Appendix B).

All synonyms for each key concept were included by adding "OR" and all terms for the four key concepts were combined using "AND". The terms used to describe key concepts varied between each database, particularly the terms used to describe OAT. Synonyms for OAT and also specific pharmacologic terms and names of medications that are classified as OAT were used in each database search (see Appendix B). For the purposes of this integrated literature

review, only “buprenorphine/naloxone” and “buprenorphine” were included in the search terms for buprenorphine-containing medications because buprenorphine/naloxone is the only oral buprenorphine-containing medication that is fully covered by BC Pharmacare during the time of the literature search. Studies that included extended release injectable buprenorphine, buprenorphine sublingual film and buprenorphine implants were excluded.

Inclusion and Exclusion Criteria

No age limiters were used in order to ensure inclusion of all relevant citations and also due to variety of definitions of adults used across the literature. Articles were screened for those with study populations of adults aged 18-64 as this age group is the most represented in provincial toxic drug poisoning data at 92% of all toxic drug deaths are in this age category (BC Centre for Disease Control, 2021). Populations outside this age category, such as youth or older adults, may require OUD care from practitioners with expertise in the population type due to complexities specific to each population (BCCSU, 2018). An English Language limiter was used in Web of Science because this was the only database that retrieved titles not available in English, which is the only language spoken by the author. Any country of publication was considered in order to yield the all potentially relevant articles. Countries such as Australia, and the United States have geographical contexts, healthcare systems and social demographics that are comparable to Canadian settings and were therefore considered for inclusion.

Title and abstract screening criteria were based on the study populations, context and interventions. Adults with OUD who reside in community settings are the target population. Any study that focused on hospitalized or incarcerated people, and people at residential or in-patient substance use treatment facilities were excluded. Studies with sample populations of adults without OUD were excluded, which mostly pertained to articles that focused on adults with

chronic non-cancer pain only. The study setting and geographical context were screened to included rural, remote or non-urban locations of health care provision. Studies that measured interventions only in urban geographic settings or failed to clearly delineate findings from rural vs. urban contexts were excluded. Lastly, studies were screened for relevant interventions, which included any type of OAT prescribed by a PCP. OAT prescribed by a specialist (e.g. addiction medicine, internal medicine, emergency physicians) or did not clearly identify the prescriber as a primary care/family practice provider were excluded. Interventions that did not include OAT (e.g. naloxone only) were excluded because there is an overwhelming amount of evidence that demonstrates OAT prevents toxic drug deaths and is the gold-standard of care for treatment of OUD, if the person is willing to engage in treatment (BCCSU, 2017; Korownyk et al., 2019). Full-text of articles were further reviewed for the same inclusion and exclusion criteria.

Table 2

Inclusion and Exclusion Screening Criteria for Articles

Inclusion Criteria	Exclusion Criteria
-Adults aged 18-64 -Adults with OUD -Primary diagnosis OUD or polysubstance use disorder/substance use disorder -English language articles -Peer-reviewed -Primary intervention is OAT prescribed in rural or non-urban office-based community health or primary care setting	-Youth younger than 18 or older adults over 65 years old, neonates -Not peer-reviewed -Study settings that included residential treatment in-patients, hospitalized patients, incarcerated patients -Studies conducted in urban only settings -Opiate agonist treatment prescribed out of pharmacies, specialty treatment clinics -Study populations with primary diagnosis of chronic pain only -Non-OAT interventions or naloxone-only interventions -Commentaries or opinion articles

Search Results

A PRISMA Flow Diagram was used to organize the search results and the number of citations retrieved from each database reflects the retrieval number with age limiters in place (see Appendix C).

Chapter Three: Findings

Twelve articles published between 2018 and 2021 were included in the data analysis for this integrated literature review. The included articles consist of 10 primary research articles both quantitative and qualitative, one systematic literature review, and one clinical practice guideline. The primary articles consisted of five quantitative studies, all of which are retrospective cohort studies (Cole et al., 2019; Gauthier et al., 2018; Hughes et al., 2021; Logan et al., 2019; Piske et al., 2020) and five qualitative studies (Andrilla et al., 2019; Kane et al., 2020; Richard et al., 2020; Saunders et al., 2019; Wood et al., 2019). Out of the qualitative studies, two explored OAT from the perspective of the patient (Kane et al., 2020; Wood et al., 2019), one from the perspective of the provider (Andrilla et al., 2019) and two that explored both patient- and provider-perspectives (Richard et al., 2020; Saunders et al., 2019). One systematic review of quantitative and mixed-methods articles and one clinical practice guideline were also included (Korownyk, Perry, Ton, Kolber, Garrison, Thomas, Allan, Bateman, et al., 2019; Lister et al., 2020).

The included studies involved a total of 67 550 unique adult patients with OUD and 65 healthcare providers from rural settings. Eight studies included patients receiving buprenorphine (Andrilla et al., 2019; Cole et al., 2019; Hughes et al., 2021; Kane et al., 2020; Logan et al., 2019; Piske et al., 2020; Richard et al., 2020; Wood et al., 2019), three studies included patients on methadone (Gauthier et al., 2018; Piske et al., 2020; Wood et al., 2019), and one study included other OAT medications other than buprenorphine or methadone, which were SROM, RM and iOAT (Piske et al., 2020). Studies that met the inclusion criteria and also considered injectable naltrexone or other OAT medications were included in the review, however the outcomes that pertain to patients taking injectable naltrexone were not included in the analysis

due to its limited use in Canada to treat OUD as well as no cost coverage by BC Pharmacare (BC MOH, 2022).

All the studies were conducted in rural settings as defined by geographic location, postal codes or characteristics defined in the RIS framework, and data was collected between Jan. 1, 1996 and June 15, 2020. One study did not explicitly identify between rural or urban settings, which was the clinical practice guideline (Korownyk, Perry, Ton, Kolber, Garrison, Thomas, Allan, Bateman, et al., 2019). This guideline was included regardless due to the value it had at directly answering the research question and a rural physician was represented on the guideline's appraisal committee, which strengthens the external validity to the research question at hand (Korownyk, Perry, Ton, Kolber, Garrison, Thomas, Allan, Bateman, et al., 2019). Seven of the articles were conducted in the United States (US), namely rural Appalachia, rural Maine, rural Pennsylvania and rural Hawaii (Andrilla et al., 2019; Cole et al., 2019; Kane et al., 2020; Richard et al., 2020; Saunders et al., 2019) and one qualitative study was conducted in two rural Australian communities (Wood et al., 2019). Two primary articles were conducted in Canada, both of which are retrospective cohort studies and used large provincial-level health databases that identified rural from urban study populations in Ontario and BC (Gauthier et al., 2018; Piske et al., 2020). As for the secondary sources, the clinical practice guideline provides additional Canadian context and clinical recommendations and the systematic literature review included only studies conducted in the US (Korownyk, Perry, Ton, Kolber, Garrison, Thomas, Allan, Bateman, et al., 2019; Lister et al., 2020). Accessibility to OAT varies dramatically between countries due to differences in regulatory policies, particularly between the US and Canada (Priest et al., 2019). Studies conducted in the US are limited in their generalisability to the BC context due to several significant regulatory differences that limit methadone dispensing to

specialty opioid treatment program clinics only, and take-home doses have tight federal criteria (Priest et al., 2019). Additionally, only a few health insurance programs cover the cost of OAT for patients in the US (Andrilla et al., 2019; Rosenblatt et al., 2015), yet is it fully covered for Medicare enrollees (Cole et al., 2019), which is similar to Canadian settings for people with Pharmacare coverage (Piske et al., 2020).

Six common themes were identified in the literature after each article was analyzed in relation to the research question, which included: the efficacy of OAT, accessibility of OAT, stigma in rural primary care, OAT implementation strategies, rural PCP competence and interdisciplinary team-based care. A detailed analysis of each article is outlined in the literature matrix (see Appendix D) with information on research design and methods, study population and context, data analysis, strengths, limitations, and key findings and recommendations made by the authors.

The majority of the articles were appraised as "High Quality" using the Critical Appraisal Skills Programme checklist (n= 10). Two articles, Kane et al. (2021) and Logan et al. (2019) were deemed "Medium Quality", which was related to small study populations that limited the external validity of both studies (n= 31, 101) respectively. The following section of the chapter will present key findings on what aspects of healthcare were found to improve treatment outcomes for PWOUD when prescribed OAT with references to the literature matrix (Appendix D). Readers can refer to the literature matrix as a reference of the author's critical analysis and summary of the findings for each article as it is discussed in this chapter.

Efficacy of Opiate Agonist Treatment

Seven articles explicitly address that OAT combined with psychosocial support is the gold-standard treatment for OUD in rural primary care (Cole et al., 2019; Hughes et al., 2021;

Kane et al., 2020; Korownyk, Perry, Ton, Kolber, Garrison, Thomas, Allan, Bateman, et al., 2019; Lister et al., 2020; Logan et al., 2019; Saunders et al., 2019). Among all eleven articles, there is undisputed evidence that supports that OAT improves PWOUD's quality of life (Kane et al., 2020; Logan et al., 2019; Wood et al., 2019), is effective in reducing toxic drug deaths (Andrilla et al., 2019; Cole et al., 2019; Gauthier et al., 2018; Hughes et al., 2021; Kane et al., 2020; Korownyk, Perry, Ton, Kolber, Garrison, Thomas, Allan, Bateman, et al., 2019; Lister et al., 2020; Logan et al., 2019; Piske et al., 2020; Richard et al., 2020; Wood et al., 2019), and provides stability from the effects of unregulated substance use (Piske et al., 2020; Richard et al., 2020; Wood et al., 2019). Three studies explored patients' perceptions of the benefits of receiving OAT (Kane et al., 2020; Lister et al., 2020; Wood et al., 2019), which include recognizing that OAT stops people from dying (Wood et al., 2019), reduces withdrawal effects and cravings for drugs (Wood et al., 2019), improves social functioning, and provides overall stability in PWOUDs' lives (Kane et al., 2020; Lister et al., 2020; Wood et al., 2019). One patient participant expressed that OAT has significantly helped in improving their overall health and wellbeing (Wood et al., 2019). One article explicitly demonstrated improved wellbeing by measuring depression and anxiety symptoms using the Patient Health Questionnaire (PHQ-9) and the Generalized Anxiety Disorder (GAD-7) validated tools before and after 3-months of buprenorphine treatment and found that rural office-based buprenorphine treatment was negatively associated with depression and anxiety symptoms (OR= -0.03, 95% CI= -0.05, -0.01, $p < .05$) (Logan et al., 2019). Findings from the included studies validate recommendations from provincial and national guidelines that OAT is gold-standard treatment for OUD.

The clinical practice guideline strongly recommends that OUD is managed as part of the full-continuum of care provided in a person's medical home (Korownyk, Perry, Ton, Kolber,

Garrison, Thomas, Allan, Bateman, et al., 2019). This recommendation was obtained from a systematic review cited in the practice guideline and is considered moderate-quality evidence. Korownyk, C., Perry, D., Ton, J., Kolber, M. R., Garrison, S., Thomas, B., Allan, G. M., Bateman, C., et al. (2019) indicate that PWOUD were more likely to adhere to an OAT program (86% vs. 67%), avoid unregulated opioids (67% vs. 35%) and have higher satisfaction of OAT services when care is provided in primary care versus at a speciality OAT clinic. Although not specific to rural primary care, there is strong agreement across all studies that prescribing OAT in primary care is effective in treating OUD. Findings from Cole et al. (2019) indicate that when OUD is diagnosed by a rural PCP then more than half (50.8%) of diagnosed PWOUD will receive OAT. Piske et al. (2020) demonstrate similar findings that out of all people in rural BC diagnosed with OUD, 61% had ever received OAT. One qualitative article demonstrates that rural PWOUD preferred obtaining OAT in primary care settings due to experiencing a greater sense of privacy because they were less likely to be identified as an "OAT client" (Kane et al., 2020) when comparing accessing OAT at a specialty substance use clinic.

Continuation and retention on OAT were measured by the number of days OAT was dispensed, which varied between studies from 3 to 12 months (Cole et al., 2019; Gauthier et al., 2018; Logan et al., 2019; Piske et al., 2020). Cole et al. (2019) demonstrates that 48.9% of those PWOUD who receive OAT by a rural PCP continued therapy for at least 6 months. Comparatively, Piske et al. (2020) show that attrition across the cascade of care for OUD (OUD diagnosis, OAT initiation, currently on OAT, retention on OAT) is greater for rural BC residents than urban counterparts; only 11% of rural BC residents with OUD were retained on OAT for greater than 12 months over the study period between 1996 and 2017. Despite general agreement across all studies that PCPs can effectively prescribe OAT and provide longitudinal care for

PWOUD, Cole et al. (2019) suggest that PWOUD prescribed OAT by a non-PCP had greater retention in therapy. Rural study participants who received the majority of their OAT from a non-PCP provider (addiction medicine specialists) were more likely to have continuity of pharmacotherapy compared to those who received the majority of OAT from their PCP (OR=1.33; 95% CI= 1.0-1.7; p= 0.04) (E. S. Cole et al., 2019). Despite contradictory findings, the overall analysis of Cole et al. (2019) and Piske et al. (2020) demonstrate reduced rates of *OAT retention* for rural PWOUD when prescribed OAT by a rural PCP (see Appendix D).

Accessibility

Access to OAT for PWOUD residing in rural settings was the most common theme elicited from the articles. Several sub-themes emerged that pertain to accessibility of OAT in rural communities which include: the impacts of distance to a prescriber (Andrilla et al., 2019; Cole et al., 2019; Lister et al., 2020), program restrictions (Andrilla et al., 2019; Korownyk, Perry, Ton, Kolber, Garrison, Thomas, Allan, Bateman, et al., 2019; Wood et al., 2019), telehealth as a promising solution (Hughes et al., 2021; Lister et al., 2020), access to a pharmacy (Gauthier et al., 2018; Lister et al., 2020) and take-home doses (Cole et al., 2019; Kane et al., 2020; Korownyk, Perry, Ton, Kolber, Garrison, Thomas, Allan, Bateman, et al., 2019; Wood et al., 2019).

Geographic Distance

Accessibility was largely contextualized from the patient perspective as limited due to geographic distance to a prescriber and restrictive program rules that required patients to complete non-prescribing tasks (e.g. UDS, pill-counts, sign contracts, attend a pharmacy daily) to obtain OAT. Quantitative findings by Cole et al. (2019) demonstrates a strong association between retention in OAT and distance to travel to the nearest OAT prescriber (OR= 0.988; 95%

CI= 0.983-0.993; $p < 0.001$). The study further extrapolates the findings by indicating that every additional mile away from an OAT prescriber is associated with 1.2% reduction in the odds of receiving OAT (Cole et al., 2019). Distance to travel to prescribers is common for rural residents, however in the study by Cole et al. (2019) those participants who traveled more than 45 miles (72.4km) were 29% less likely to continue to receive OAT daily (OR = 0.71; 95% CI = 0.56-0.91; $p = 0.007$). Lister et al. (2020) also found that from the patient perspective travel burden in terms of travel time, cost of travel and inconvenience of traveling to an OAT prescriber was a common barrier for rural PWOUD. Many rural communities have no prescribers (PCP or specialty prescriber) able or willing to prescribe OAT and are required to travel to other communities to access a prescriber (Haffajee et al., 2019; Hughes et al., 2021). A systematic review by Lister (2020) indicates that lack of any OAT prescriber is cited as the most common barrier for PWOUD in rural communities.

Rural primary care was commonly found to be perceived as a convenient location to access OAT due to closer proximity, especially when PCPs were located closer than other mental health or substance use services. Access to primary care is demonstrated to be established by rural PWOUD. Cole et al. (2019) calculated from a large study sample that adults with OUD attend just over four primary care visits per year, making PCPs well-positioned to initiate and manage a person on OAT. Study respondents from Kane et al. (2020) preferred receiving OAT in a primary care setting due to a greater sense of privacy, respect and not being labelled as an "OAT client". One respondent explained that primary care staff make PWOUD feel more human compared to other healthcare settings (Kane et al., 2020). Rural physician study respondents in a qualitative study by Andrilla et al. (2019) indicate that PCPs can gain comfort in OAT prescribing by initially prescribing only to known patients in their practice. Rural primary care

patients also perceive healthcare to be comprehensive when they were able to have their OUD addressed concurrently with other health issues including hepatitis C, mental health, dental problems, and chronic pain (Kane et al., 2020).

Program Requirements

Restrictive program requirements placed on people who are prescribed OAT by prescribers was strongly perceived by patients as limiting access to OAT. A clear paradox exists in the literature in respect to strategies used by prescribers to "effectively sustain services" (Andrilla et al., 2019, p. 116) are seen by patients to restrict access to OAT (Wood et al., 2019). People with OUD commonly cited the requirement of obtaining medication daily at a pharmacy as restrictive (Wood et al., 2019). Although daily witnessed ingestion (DWI) is a common prescribing practice aimed at preventing diversion and reducing the risk of over-sedation it is found to be perceived by patients as preventing freedom of recreation, travel and infringes on going to work and taking care of family (Kane et al., 2020; Wood et al., 2019). Wood et al. (2019) found that for PWOUD being on methadone was similar to being incarcerated; one study respondent states that, "…it's worse than um, my corrections order" (Wood et al., 2019, p. 151). In the study by Richard et al. (2020) healthcare respondents similarly perceived requirements of patients prescribed buprenorphine to attend counseling sessions as "making people jump through hoops" (Richard et al., 2020, p. 5). Other non-prescribing strategies used in OAT programs include: treatment contracts or agreements, witnessed UDSs, and random pill-counts requiring patients to keep the packaging of take-home doses and be able to provide them at any treatment visit upon request by the prescriber (Andrilla et al., 2019; Korownyk, Perry, Ton, Kolber, Garrison, Thomas, Allan, Bateman, et al., 2019; Wood et al., 2019). Physician respondents from the Andrilla et al. (2019) study suggested terminating treatment if they felt a patient was not

improving on buprenorphine; a physician respondent explains that, “I don’t discharge a patient for… a single relapsed urine specimen or relapse by history. But eventually if patients over and over… again are indicating relapse, then we’ll have to discharge them” (Andrilla et al., 2019, p. 117). The clinical practice guideline for treatment of OUD in primary care corroborates that use of prescribing activities such as DWI, UDSs, and treatment agreements are thought to be time intensive and inconvenient for patients, which risks loss to follow-up, disengagement from care, or unnecessary treatment barriers for PWOUD (Korownyk, Perry, Ton, Kolber, Garrison, Thomas, Allan, Bateman, et al., 2019). The systematic review of systematic reviews used by Korownyk, C., Perry, D., Ton, J., Kolber, M. R., Garrison, S., Thomas, B., Allan, G. M., Bateman, C., et al. (2019) to inform the clinical practice guideline showed no improvement of clinical outcomes when UDSs, treatment contracts, or DWI were used in OAT prescribing.

Telehealth

Integration of telehealth in rural primary care practice for visits related to OUD was consistently demonstrated to be an effective strategy at improving initiation and retention on OAT for PWOUD in rural primary care (Hughes et al., 2021; Lister et al., 2020). Findings from Hughes et al.’s (2021) retrospective cohort study conclude that when PCPs utilized telehealth to prescribe buprenorphine, PWOUD who lived further away from the physical location of the primary care clinic with a mean distance of 16.4 miles (26.4 km) compared to 10.7 miles (17 km) prior to telehealth, were able to maintain on medication. The emergence of telehealth in OUD treatment garnered traction during the COVID-19 pandemic. Hughes et al. (2021) demonstrate the effectiveness of one rural primary care site’s ability to integrate telehealth visits for OUD, which saw an increase in the number of people accessing buprenorphine during COVID-19 by telehealth compared to the same time period pre-COVID-19. Other potential confounding factors

including seasonal trends were controlled for using goodness of fit Chi-square tests (Hughes et al., 2021) strengthening the findings external validity outside the COVID-19 pandemic. Telehealth limits the ability to request UDSs from patients. Findings from Hughes et al. (2021) show a sharp reduction in the total number of UDSs ordered during the COVID-19 period, which was not correlated to a loss to follow-up suggesting that UDSs are not related to retention outcomes for people prescribed OAT.

Telehealth as a promising solution to improving treatment outcomes related to OAT access in rural primary care is confirmed by Lister et al. (2020) by explaining that telehealth can increase patient autonomy and access to OAT prescribers when there is limited or no local OAT prescriber options. Similar findings from Hughes et al. (2021) indicate that when a rural primary office offers telehealth buprenorphine appointments, more patients from surrounding rural communities accessed care at the site, which lead to an expansion of the site's catchment area.

Pharmacy Access

Ensuring PWOUD have convenient access to a pharmacy where OAT can be dispensed regularly demonstrated to impact treatment outcomes. Findings from two studies (Gauthier et al., 2018; Piske et al., 2020) show that access to a pharmacy that dispenses OAT is integral to OAT retention and aspects of prescribing OAT for PCPs due to considerable drug-drug interactions and complexities with tapering doses, particularly for full-agonist options. Piske et al. (2020) indicate that many rural community pharmacies are not prepared to dispense OAT. Pharmacies are required to have specialized secure storage equipment, time and staff to provide DWI, and often dispensing fees for OAT are not enough to cover additional costs and resources required by pharmacies. Gauthier et al. (2018) also support that prescriber-pharmacy partnerships are essential at improving retention for people on methadone and further explain a strong association

between onsite dispensing and retention for rural Northern Ontario patients on methadone. Many remote Northern primary care clinics are co-located with pharmacy services or in addition to prescribing also are able to dispense medications daily to patients, which are often dispensed by nursing staff (Gauthier et al., 2018). Findings from Gauthier et al. (2018) indicate that for patients who filled their methadone at an on-site pharmacy had a much greater likelihood of retaining on the medication for more than 12-months when compared to patients who had methadone filled at an off-site community pharmacy (aHR = 0.230; CI 95 % = (0.210, 0.235); $p < 0.001$). Co-location of prescribing and dispensing OAT was not found to impact other treatment outcomes (e.g. UDS or dose amounts) (Gauthier et al., 2018).

Take-Home Doses

Greater access to take-home doses of OAT, also referred to as *carries* was commonly seen to improve accessibility to OAT from the patient-perspective (Lister et al., 2020; Wood et al., 2019). Study respondents in Wood et al. (2019) indicate that being able to have OAT medication at home allowed for closer relationships with family, was more convenient than going to purchase unregulated drugs from a drug dealer and also prevented people from having to potentially interact with others in active substance use at a pharmacy that could risk them relapsing. Take-home doses are often prescribed once a person is stabilized on OAT, which is problematic because often people who are not yet stabilized on OAT require greater flexibility due to less stable social or living arrangements that can act as accessibility barriers to attending daily witnessed doses. Buprenorphine is the preferred medication to be prescribed for take-home doses because it is a relatively safer medication compared to full-agonists due to its respiratory ceiling effect (BCCSU, 2017). Kane et al. (2020) concluded that people prescribed

buprenorphine in primary care benefited from take-home doses because people had more time to spend addressing their health-related needs.

Furthermore, geographic distance from community pharmacies that dispense OAT increase demand for take-home doses in the rural-context. Distance as a rationale to prescribe take-home doses was confirmed by Lister et al. (2020) that demonstrates travel burden to OAT is the most commonly identified barrier for rural PWOUD. However, Lister et al. (2020) also found that prescribers would offer OAT less often to rural-PWOUD because they perceived distance to be a potential barrier to patients accessing the medication and therefore would not consider offering OAT. Take-home doses are a potential mitigating strategy to support rural-PWOUD in OAT initiation and retention. Treatment outcomes have not been demonstrated to be compromised when PWOUD are prescribed take-home doses (Bell et al., 2007; Cousins et al., 2017; Holland et al., 2012; Saulle et al., 2017).

Korownyk, C., Perry, D., Ton, J., Kolber, M. R., Garrison, S., Thomas, B., Allan, G. M., Bateman, C., et al. (2019) found across five randomized control trials (RCTs), there was no increase in mortality or positive UDS when OAT was prescribed as take-home doses vs. DWI. In a companion article to Korownyk, C., Perry, D., Ton, J., Kolber, M. R., Garrison, S., Thomas, B., Allan, G. M., Bateman, C., et al.'s (2019) clinical guideline, methods and findings of the systematic review of systematic reviews is described and indicate that one systematic review by Saulle et al. (2017) analysed five high-quality RCTs that examined the safety of DWI, none of the studies compared DWI to a completely unsupervised control group (Korownyk, Perry, Ton, Kolber, Garrison, Thomas, Allan, Dugré, et al., 2019). However, different levels of supervision were compared and findings indicated no difference between daily supervised doses and less restrictive monitoring (e.g. twice weekly supervised doses) (Bell et al., 2007; Fiellin et al., 2006;

Holland et al., 2012, 2014; Rhoades et al., 1998; Saulle et al., 2017). Also, all of the studies analyzed by Korownyk, C., Perry, D., Ton, J., Kolber, M. R., Garrison, S., Thomas, B., Allan, G. M., Bateman, C., et al. (2019) were conducted over 10-years ago, which limits the applicability to the current era of high-potency fentanyl that may increase motivation for medication diversion among PWUD (Socias et al., 2021). Overall, there is no indication in the literature that DWI is superior to less supervised dosing at improving treatment outcomes for people prescribed OAT in rural settings. Less supervised dosing strategies were found to be more cost-effective (Bell et al., 2007), improve patient satisfaction with treatment (Holland et al., 2012), and enhance treatment retention (Holland et al., 2014; Rhoades et al., 1998). However, this evidence is considered low-quality evidence due to lack of control groups and findings were overall small (Korownyk, Perry, Ton, Kolber, Garrison, Thomas, Allan, Dugré, et al., 2019). None of the studies examined safe storage of medication or potential of medication diversion to opioid-naïve individuals, which does not address a common prescriber concern and motivation to use DWI as a strategy to prevent unintentional medication poisoning in family members of OAT patients (Andrilla et al., 2019).

Stigma in Rural Primary Care

Stigma was found to significantly influence accessibility of OAT services in rural primary care. All twelve articles identified stigma as a potential barrier to accessing OAT. Stigma was more explicitly discussed in studies that interviewed individuals with OUD and healthcare providers commonly identified community stigma and "conservative attitudes" in rural communities as being prevalent barriers to mobilizing supports for PWUD.

Patient Reported Stigma

All three studies analysing the patient experience of being prescribed OAT in rural primary care reveal that stigma related to drug use and OUD is present in rural primary care settings, which demonstrated to impact patients' perspectives on accessibility of receiving OAT from a PCP. During focus-groups conducted by Saunders et al. (2019), patients expressed concerns regarding fear of judgement and shame from PCPs if they disclosed substance use during a visit. One patient respondent expressed concerned that if they disclosed substance use then that could impact the care they received in the future especially if they required pain management: "…that's why people don't want a flag on their record… if they get hurt, they won't get any help" (Saunders et al., 2019, p. 2828). Patients who were actively using unregulated substances also feared 'getting caught' by PCPs who would potentially report them to law enforcement (Saunders et al., 2019; Wood et al., 2019). Similarly, patient respondents in Wood et al. (2019) reported feeling stigmatized by prescribers, pharmacists and pharmacy staff during health-related interactions. Findings of stigma in rural primary care is further illustrated in an interview conducted with a buprenorphine patient who states, "my past is my past, people [including healthcare providers] tend to look down on you" (Kane et al., 2020, p. 614).

Healthcare Provider Reported Stigma

Extensive evidence suggests that PWOUD experience stigma in rural healthcare settings however, healthcare providers were found to less frequently acknowledge stigma which prevents the issue from being addressed with interventions that can mitigate stigma (Saunders et al., 2019). Healthcare providers were more likely to perceive familiarity and connectedness with PWUD as essential for obtaining an honest answer regarding substance use (Saunders et al., 2019), but no studies examining healthcare provider perspectives recognized other stigmatizing

beliefs or attitudes that could potentially distance patients from healthcare. Interviews with rural healthcare providers demonstrated a high likelihood of empathy towards PWUD, especially when substance use disorders were conceptualized as a disease (Richard et al., 2020). Despite care providers expressing empathy, Richard et al. (2020) capture that often care providers believe that PWUD are to blame for their decisions to initially experiment with drugs that eventually lead to drug dependency. The emphasis on self-determination as a factor leading to substance use disorders also drives macro-level community stigma in rural settings (Richard et al., 2020). All the studies analyzed from the healthcare-perspective show that in rural settings healthcare providers underrecognize the impacts of actual or potentially stigmatizing attitudes and beliefs towards PWUD (Andrilla et al., 2019; Richard et al., 2020; Saunders et al., 2019).

Stigma Towards Opiate Agonist Treatment

Stigmatizing beliefs and attitudes from healthcare providers were found to be isolated in relation to substance use and substance use disorders (Andrilla et al., 2019) when compared to other uses for OAT such as pain management (Wood et al., 2019). Patient respondents reported that conceptualization of OAT as a pain management strategy appeared to be more accepted by healthcare providers and they found that healthcare providers were more apt to help with access OAT when was prescribed for pain (Wood et al., 2019). OAT was viewed as a necessary treatment option for PWOUD in order to "treat an underlying disease" and should be available long-term, however a common theme that emerged is that healthcare providers hope that PWOUD can eventually live a life without any opioids (Richard et al., 2020).

Although evidence from the literature indicates that the majority of OAT prescribers view OAT as a necessary treatment for OUD, stigma related to OAT medications was found among prescribers and appears to be fuelled by prescriber fears of professional discipline (Lister et al.,

2020) and being ostracised by other medical professionals for providing OAT (Richard et al., 2020). Primary care providers expressed specific fears related to patients diverting medication (Andrilla et al., 2019; Richard et al., 2020) and being audited by professional bodies for overprescribing controlled drugs (Lister et al., 2020). Results from studies conducted in the US (Andrilla et al., 2019; Lister et al., 2020) show OAT prescribers are restricted by federal regulations and fears of being audited by the Drug Enforcement Administration (DEA) resulting in prescribers being required to follow specific rules and keep comprehensive documentation on all OAT encounters adding to time constraints in primary care. Prescribers have also been found to have mistrust of PWUD, believing that people who are prescribed OAT will divert the medications and either sell them or give them to someone who is opioid-naive who could potentially overdose from the medication (Andrilla et al., 2019). Other less commonly cited stigmatizing beliefs among PCPs who prescribe OAT were concerns that they may attract other PWUD to the practice setting, that their medical colleagues perceive OAT as unnecessary and treatment for OUD should not include substituting one drug for another (Andrilla et al., 2019; Lister et al., 2020) and that they could be ostracised from the medical community if they prescribed OAT (Richard et al., 2020). On the other hand, a sentiment of frustration was found among healthcare providers who do support people in accessing OAT against those providers who are fuelling stigma by not using evidence to inform their decision making (Richard et al., 2020).

Implementation Strategies

Overcoming challenges that make implementing OAT in rural primary care practices difficult was consistently addressed in the literature. Four articles identified common implementation barriers specific to rural PCPs, which included: time constraints, cost, physical

space shortages, privacy concerns, and site readiness (Andrilla et al., 2019; Korownyk, Perry, Ton, Kolber, Garrison, Thomas, Allan, Bateman, et al., 2019; Lister et al., 2020; Saunders et al., 2019). Apprehension regarding the amount of time required to screen for substance use disorders, obtain a compressive history and complete the required paperwork was a commonly cited concern by provider respondents (Andrilla et al., 2019; Lister et al., 2020; Saunders et al., 2019). Experienced rural provider respondents legitimized this concern by indicating setting time aside for OAT is challenging when also providing high-quality primary care (Andrilla et al., 2019). Starting with only a few well-known patients and scheduling specific times for OAT prescribing are recommended in Andrilla et al. (2019) as strategies to overcome time barriers. Korownyk, C., Perry, D., Ton, J., Kolber, M. R., Garrison, S., Thomas, B., Allan, G. M., Bateman, C., et al. (2019) also indicate that spending lengthy time counselling patients on OAT does not improve treatment outcomes. Brief motivational interviewing is time-effective for PCPs and was found to demonstrate treatment retention more so when compared to extended psychosocial interventions (Korownyk, Perry, Ton, Kolber, Garrison, Thomas, Allan, Dugré, et al., 2019). PWOUD also identified wait-times as a deterrent to seek-out OAT (Lister et al., 2020; Wood et al., 2019). Incorporating telehealth visits into rural primary care was demonstrated by Hughes et al. (2021) as a way to reduce overall clinic volume and improve access to appointment-times for OAT. Due to quantitative measures captured by Hughes et al. (2021), patient satisfaction with care or the overall quality of care provided by telehealth is not captured.

Providers had concerns that the compensation provided for OAT visits did not reflect the amount of time required during an OAT visit (Andrilla et al., 2019; Lister et al., 2020). Those articles published in the US found that Medicaid coverage, which is publicly-funded health insurance for low-income patients, was found to not be high enough for the time required to

prescribe OAT (Andrilla et al., 2019). Delegation of grant applications to community advisory groups was regarded as a potential solution (Lister et al., 2020).

A common misconception addressed in three articles is the need for more office space that what would usually be required to provide standard primary care for activities such as UDSs and counselling. Korownyk, C., Perry, D., Ton, J., Kolber, M. R., Garrison, S., Thomas, B., Allan, G. M., Bateman, C., et al. (2019) address this by demonstrating that no additional space is required to conduct UDSs or lengthy counselling sessions (45 to 60 min) because neither show improved treatment outcomes. Hughes et al. (2021) confirmed that UDSs do not affect treatment retention after transitioning all buprenorphine appointments to telehealth and UDSs can be completed unwitnessed a local lab rather than in the primary care office. No changes in treatment outcomes were identified, other than an increase in OAT visits by phone (Hughes et al., 2021). Less frequently cited barriers by PCPs was concerns that a diagnosis of a substance use condition would lead to the patient experiencing stigma (Saunders et al., 2019). A PCP respondent in Saunders et al. (2019) expressed concern that their diagnosis would be visible to other care providers in the health system if documented in an electronic medical record (EMR). Fear of patients being stigmatized by other clinic staff due to a diagnosis of substance use disorder was also palpable in the article by Logan et al. (2018).

Rural Primary Care Provider Competence

Four articles included in the literature review described rural PCPs as having less training, experience and confidence in managing treatment for OUD compared to urban PCPs or specialty providers (Cole et al., 2019; Lister et al., 2020; Piske et al., 2020; Saunders et al., 2019). One study suggests that lack of competence and confidence in treating substance use disorders among rural PCPs leads to screening avoidance due to fear of a positive diagnosis

(Saunders et al., 2019). Piske et al. (2020) conducted a retrospective cohort study of all people diagnosed with OUD in BC and found that between 2001 and 2017 there was a significant increase in the number of people diagnosed with OUD, which indicates that overall prescribers gained confidence in screening and diagnosing for OUD. However, rural PWOUD remain considerably less likely to receive a diagnosis in primary care. Findings from Piske et al. (2020) confirmed that 96% of PWOUD diagnosed in BC obtained a diagnosis at an urban care site, and 4% of PWOUD obtained their diagnosis at a rural site. Although, Piske et al. (2020) do not specify between primary care or specialty clinics, the disparity demonstrates stark differences in OUD diagnosis rates between urban and rural regions in the province. For people who are diagnosed with OUD, the assumption is that they could be eligible to receive OAT as an intervention for OUD, however only 61% of rural PWOUD ever received OAT compared to 75% of urban PWOUD (Piske et al., 2020). Similarly, findings from Cole et al. (2020) indicate that PWOUD who are prescribed OAT by non-PCP (e.g. specialists) are more likely to continue on OAT for at least 6 months. Lister et al.'s (2020) review further confirms that, rural PCPs were also more likely to prescribe buprenorphine compared to other OAT options, which suggests that other potential variables influence PCP prescribing. Despite full-agonists demonstrating slightly increased likelihood of OAT retention (Korownyk, Perry, Ton, Kolber, Garrison, Thomas, Allan, Bateman, et al., 2019; Piske et al., 2020), partial-agonists continue to be prescribed more often in rural primary care (Lister et al., 2020). Because so few articles examined full-agonist medication prescribing in rural primary care, no causal inferences can be made to suggest why this occurs. As the literature review included mostly studies conducted in the US, this result has other confounding variables specific to US prescribing regulations that limits PCPs prescribing full-

agonist medication; regardless, a practice gap is evident among both American and Canadian rural PCPs in offering comprehensive pharmacologic interventions for OUD.

Buprenorphine/naloxone and methadone are recommended to be offered by all Canadian PCPs for the treatment of OUD in primary care (Korownyk, Perry, Ton, Kolber, Garrison, Thomas, Allan, Bateman, et al., 2019). Despite this clear recommendation, other articles identified a knowledge to practice gap, especially among rural PCPs. Several articles address this gap by suggesting practice interventions that include: the "hub and spoke" model, finding a local mentor, starting with less complex patients (Andrilla et al., 2019), accessing Extension for Community Healthcare Outcomes (ECHO) learning models (Saunders et al., 2019), and prescribers collaborating closely with pharmacists who are experienced with OAT (Gauthier et al., 2018; Piske et al., 2020). Recommendations for addressing knowledge gaps among rural PCPs and strategies to implement in practice will be further discussed in the discussion and recommendations sections of this paper.

Interdisciplinary Team-Based Care

Approaching OUD treatment from a holistic perspective that includes mental, emotional, and spiritual supports is an important aspect of comprehensive care for PWOUD (Kane et al., 2020; Korownyk, Perry, Ton, Kolber, Garrison, Thomas, Allan, Bateman, et al., 2019; Logan et al., 2019). This was reflected across the studies by patient and healthcare study populations. In Logan et al.'s (2019) program evaluation from a rural West Hawaii Community Health Centre that offered buprenorphine prescribed by PCPs found that offering short behavioral health sessions by a social worker or counsellor for patients receiving buprenorphine supported PWOUD in setting and achieving goals, planning activities, and obtaining or maintaining recovery from substance use. The authors verified the effectiveness of integrating behavior

health or brief counselling sessions by measuring participants mental health symptoms before and after 3-months of treatment (GAD-7 and PHQ-9), both of which improved with treatment (Logan et al., 2019). Patient respondents also voiced greater treatment satisfaction when able to access co-located wrap-around supports that address food security, housing and financial needs (Kane et al., 2020).

Patients with concurrent mental health diagnoses pose particular challenges to rural PCPs and also demonstrate poorer treatment outcomes when prescribed OAT (Cole et al., 2019; Logan et al., 2019). Treatment retention was found to be less likely for people with concurrent diagnoses of schizophrenia or other psychotic disorders (OR= 0.43; 95% CI = 0.56-0.91; p = 0.0007) (Cole et al., 2019). Lack of adequate numbers of trained staff who can provide wrap-around supports to people with complex concurrent disorders was found to be a common barrier for rural primary care sites offering OAT (Andrilla et al., 2019; Lister et al., 2020). Some prescribers required patients attend counselling while being prescribed OAT (Andrilla et al., 2019; Richard et al., 2020). However, findings in Korownyk, C., Perry, D., Ton, J., Kolber, M. R., Garrison, S., Thomas, B., Allan, G. M., Bateman, C., et al. (2020) argue that lengthy counselling sessions (greater than 45-60min) demonstrate no greater improvement in treatment outcomes compared to those patients who receive brief motivational interviewing during OAT visits with PCPs. Some of the success of Logan et al.'s (2019) integrated primary care OAT program was attributed to offering assertive outreach. Staff that are available to connect with people who have additional barriers including mental health challenges is suggested by Logan et al. (2019) as a way to mitigate risk of medication discontinuation.

In order to address OUD from a holistic perspective, there was agreement across articles that an interdisciplinary team that includes PWLLE in substance use is required (Kane et al.,

2020; Lister et al., 2020; Saunders et al., 2019). Utilization of PWLLE in care teams is cost-effective, reduce the need for additional specialized training and improve accessibility to care (Lister et al., 2020). Limited evidence on implementing PWLLE in rural primary care teams to improve treatment outcomes was found among the articles, which identifies a gap for future research.

Chapter Four: Discussion

This integrated literature review examined the scientific literature in relation to the research question: in rural and remote communities, how can primary care providers improve treatment outcomes for adults with OUD when prescribing OAT? The following chapter will provide a synthesis of the evidence and address any gaps identified after reviewing the literature. Limitations of the literature and a consolidation of the recommendations for clinical practice will be outlined in the final section of the chapter.

Synthesis of the Evidence

The research question examines how rural and remote PCPs who are already prescribing OAT as a pharmacological intervention for OUD can adjust prescribing practices to ensure PWOUD are offered interventions with the best possible treatment outcomes. Despite rural residents having increased risk of toxic drug poisoning (BC Coroners Service, 2022), a paucity of access points to OAT is available to rural PWOUD (Bardwell & Lappalainen, 2021; Piske et al., 2020; Rosenblatt et al., 2015). As a result, rural and remote PCPs are projected to significantly increase access-points to OAT for rural residents (Haffajee et al., 2019; Rosenblatt et al., 2015). It is well documented in the literature that rural PWOUD experience unique barriers when accessing OAT that are distinct from urban regions (Altekruse et al., 2020; Bardwell & Lappalainen, 2021; Beachler et al., 2021; Fadanelli et al., 2020; Palombi et al., 2018; Thomas et al., 2020). Findings from this integrated literature review demonstrate that the strategies PCPs can employ to improve access to OAT for rural residents are superficially understood (Andrilla et al., 2019; Green et al., 2021; Lister et al., 2020; Saunders et al., 2019). A wide range of articles focuses on identifying rural barriers to prescribing OAT (Andrilla et al., 2019; DeFlavio et al., 2015; Dhanani et al., 2022; Green et al., 2021; Hutchinson et al., 2014;

Lister et al., 2020), however few studies examined novel strategies or health system changes outside increasing PCP training or access to specialty consultation for PCPs. Many of the prescribing strategies that are employed to minimize potential harms (e.g. UDS, DWI) show limited or low-quality evidence for improving health outcomes and are perceived by patients as cumbersome, demeaning and inconvenient that makes daily adherence challenging (Cioe et al., 2020; Korownyk, Perry, Ton, Kolber, Garrison, Thomas, Allan, Bateman, et al., 2019; Korownyk, Perry, Ton, Kolber, Garrison, Thomas, Allan, Dugré, et al., 2019; Wood et al., 2019). Rural PCPs are positioned to help mitigate some of the barriers rural PWOUD face when accessing OAT and are able to implement strategies that improve health outcomes for people prescribed OAT. Evidence-based strategies that emerged from the literature include utilizing telehealth rather than in-person visits (Hughes et al., 2021; Lister et al., 2020), brief motivational interviewing vs. lengthy counselling sessions (Korownyk, Perry, Ton, Kolber, Garrison, Thomas, Allan, Bateman, et al., 2019), interdisciplinary teams that provide assertive outreach and address the social determinants of health (Kane et al., 2020; Logan et al., 2019; Saunders et al., 2019; Wood et al., 2019), and least restrictive supervised dosing schedules for patients (Korownyk, Perry, Ton, Kolber, Garrison, Thomas, Allan, Bateman, et al., 2019; Wood et al., 2019), particularly for those who live further away from OAT dispensing pharmacies. Providers are pressed with employing prescribing practices that both help the patient navigate barriers related to high-level regulatory and policy restrictions placed on OAT and controlled drugs with ensuring safe prescribing for the patient and the public. Several themes for discussion were distilled from the findings based on the strategies that can improve treatment outcomes for adults with OUD who are prescribed OAT by rural PCPs that take into consideration the nuances of rural and remote settings. Those themes are: the prescriber-patient treatment paradox, rural risk

environment, rural primary care as an access point to OAT, OAT treatment options in rural settings, and program and provider characteristics, all of which will be synthesized and further elaborated on in the next section of the chapter.

Prescriber-Patient Treatment Paradox

A treatment paradox exists in regards to what PCPs view as strategies that help mitigate potential risks of controlled substances to the patient and the public, are the same strategies PWOUD perceive as barriers to OAT (e.g. UDS, DWI, pill-counts, treatment contracts, terminating treatment). Andrilla et al. (2019) state that the strategies providers were found to use in order to maintain their OAT practice, comply with legal/regulatory requirements, and prevent diversion are the same strategies that patients characterize as stigmatizing, controlling and preventing them from seeking care (Kane et al., 2020; Wood et al., 2019). Providers fears of regulatory or professional audits and oversight from prescription drug monitoring programs (PDMPs) aimed at ensuring controlled substances are prescribed appropriately place prescribers in a dilemma between professional accountability and providing patient-centred care (Cheng & DeBeck, 2017; Gorfinkel et al., 2018). Prescribing restrictions are based on the historical influences of overprescribing opioid pain medication by PCPs had on establishing the current toxic drug public health emergency (Beletsky & Davis, 2017). The multi-effort supply/demand response of curtailing opioid prescriptions by monitoring prescribing of PCPs has caused significant confusion among providers (Cheng & DeBeck, 2017). An unintentional consequence of restrictive opioid prescribing policies is that PWOUD are exposed to the toxic and unregulated drug supply due to limited supply of pharmaceutical grade opioids since PDMPs have been implemented (Alpert et al., 2018; Bardwell et al., 2021; Beletsky & Davis, 2017; Socias et al., 2021). Among articles that captured provider responses, few healthcare respondents

demonstrated awareness related to how restrictive prescribing practices aimed at meeting audit requirements could be perceived as stigmatizing or act as unnecessary barriers to PWOUD when accessing life-saving medication; especially owing to the reality that PWOUD already face intersecting social determinants of health. When OAT diversion does occur by patients, motivations to divert are influenced by feeling morally obligated to help others who are experiencing opioid withdrawal or provide other PWUD with safer alternatives to unregulated substances (Bardwell et al., 2021; Johnson & Richert, 2015; Richert & Johnson, 2015). Increased awareness among PCPs about the lack evidence to support restrictive prescribing practices and the potential harms they employ can improve accessibility to OAT for rural PWOUD.

Lister et al. (2021) highlight that rural providers offer OAT less frequently to PWOUD because it is assumed that due to geographic distances they will be unable to travel to a community pharmacy for DWI. However, use of daily supervised doses has not been found to reduce diversion, in fact there is no evidence to support any difference in diversion when OAT is prescribed as pick-ups every two or three days compared to daily (Bell et al., 2007; Holland et al., 2012, 2014; Korownyk, Perry, Ton, Kolber, Garrison, Thomas, Allan, Dugré, et al., 2019; Rhoades et al., 1998). Other than the Canadian clinical practice guideline, no study examined the efficacy of take-home dosing as a way to mitigate travel burden for rural people prescribed OAT. However, all of the studies that examined the patient-perspective cited take-home dosing as a strategy to improve accessibility to OAT for rural PWOUD (Kane et al., 2020; Lister et al., 2020; Wood et al., 2019). Future research that examines the safety and treatment outcomes of take-home doses for rural PWOUD would be a significant asset to rural PCPs. PCPs require more explicit evidence to inform prescribing take-home doses to improve OAT adherence in context of high travel burdens to get to community pharmacies.

Rural Risk Environment

Ample evidence found within the literature review corresponds with themes of rurality as an independent risk factor for poorer treatment outcomes for people prescribed OAT (Cloud et al., 2019; Fadanelli et al., 2020; Palombi et al., 2018; Thomas et al., 2020). Characteristics that are described in the literature as contributing to the rural risk environment were found to be correlational; no causal evidence was interpreted due to the difficulty to control for external environmental factors and the heterogeneity among rural and remote communities. Concentrated stigma towards PWUD and geographic distances are commonly discussed in the literature as characteristics that contribute to poorer treatment outcomes in rural and remote communities, which is evident by higher rates of toxic drug deaths in largely rural health authorities (e.g. Northern Health Authority) compared to largely urban health authorities (e.g. Vancouver Coastal Health), which are 53 and 50 per 100 000 respectively (Cole et al., 2019; Lister et al., 2020; Piske et al., 2020; Richard et al., 2020; Wood et al., 2019). Rural PCPs in particular are concerned about toxic drug use among their patients (Andrilla et al., 2019; Harder et al., 2021; Saunders et al., 2019), however from the analysis there are mixed approaches towards PWUD in rural settings that demonstrates the effects of concentrated stigma, lack of anonymity and criminalisation of rural PWUD (Fadanelli et al., 2020).

The concept of 'risk environment' is commonly described in the literature examining the effects of rural geographic locations on substance use behaviors (Cloud et al., 2019; Cooper et al., 2009; Thomas et al., 2020). Initially described by Rhodes (2002), as the interaction between social and structural characteristics that interact to increase the changes of substance use-related harm, the rural risk environment relies heavily on accepted social norms, values and beliefs in communities (Rhodes, 2002). Spatial constraints in rural care settings were found to influence

patients' perception of confidentiality in clinics (Kane et al., 2020; Lister et al., 2020; Wood et al., 2019). In settings where patients were identified as a PWOUD, either by being required to provide UDSs in spaces with little anonymity or be identified as a PWOUD can be a deterrent to seek care (Kane et al., 2020). Rural primary care clinics that did not request UDSs from patients do not differ in treatment outcomes, and avoids patients from being unintentionally identified as a PWOUD in general primary care offices (Hughes et al., 2021; Kane et al., 2020; Korownyk, Perry, Ton, Kolber, Garrison, Thomas, Allan, Bateman, et al., 2019).

Common social ideologies found among rural community members in the present review was viewing drug use as a moral issue rather than a medical diagnosis, especially among law enforcement officers (Richard et al., 2020). The belief that substance use is a choice or moral failing creates opportunity for blame and othering of PWOUD (Kane et al., 2020; Richard et al., 2020; Wood et al., 2019). Societal stigma and PWOUDs perceptions of their community members attitudes towards them creates self-stigma and influences how PWOUD approach their own care (Hatzenbuehler et al., 2013; Kane et al., 2020; Latkin et al., 2019). Negative attitudes towards people with substance use disorders and their treatment was found to influence the degree to which providers and patients engage in OUD treatment (Andrilla et al., 2019; Lister et al., 2020; Richard et al., 2020).

Providers fears of patients diverting OAT for the purposes of obtaining a euphoric high can result in punitive approaches such as termination of treatment when a provider suspects a patient is diverting medication (Andrilla et al., 2019; Lin et al., 2018; Richard et al., 2020) however, OAT diversion was found to occur more often out of patients' concern for others (Bardwell et al., 2021; Socias et al., 2021). Reframing negative beliefs that all PWOUD are seeking OAT with

an intent to divert medication will reduce discrimination and perceived stigma related to OAT and therefore improve accessibility to OAT (Bardwell et al., 2021; Richard et al., 2020).

Comparing degrees of stigma between rural and urban communities is largely undocumented in substance use research, but has been documented in the field of HIV by comparing stigma experienced by people with HIV in rural and urban communities and concluded that geographic place does influence patients' experience of stigma (Gonzalez et al., 2009; Heckman et al., 1998; Kalichman et al., 2017). People living with HIV in rural areas have reported lower quality of life ratings, greater challenges accessing resources related to HIV care and mental health however, community size based on population density alone did not explain those differences (Gonzalez et al., 2009; Heckman et al., 1998). HIV-related stigma was found to be experienced the greatest for people living in small rural communities and rural people with HIV also experienced greater internalized stigma (Kalichman et al., 2017). Although no research exists that the author is aware of that explicitly compares rural PWUD to urban PWUD's experience of stigma, rural PWUD have reported significant internalized stigma related to how they perceive being viewed by fellow community members, healthcare providers and law enforcement, which indicates clear complexities between rural acquaintanceship and risk that rural PWOUD perceive discrimination that influences accessing OAT in primary care or at pharmacies (Kane et al., 2020; Lister et al., 2020; Richard et al., 2020; Wood et al., 2019).

Abstinence is a commonly discussed as a sought-after treatment outcome for OUD among health outcome studies (Holland et al., 2014; Logan et al., 2019; Rosic et al., 2021). Robust themes of abstinence-based treatment approaches from prescribers, healthcare providers and rural community members are of particular concern considering that only a small percent of PWOUD obtain complete remission from opioid use (Piske et al., 2020). Abstinence-only

perspectives exacerbate stigmatizing beliefs towards PWOUD (Richard et al., 2020; Wood et al., 2019). Treatment outcomes that embody a harm reduction approach, for example, quality of life indicators and patient-determined goals or achievements, are more attainable for PWOUD (Hooker et al., 2022). Attainable goals instil hope for both prescribers and PWOUD in that positive treatment outcomes do not require abstinence from substance use.

Treatment adherence is significantly impacted by increased travel burden rural PWOUD face when accessing OAT. Geographic distance is the most prominent accessibility barrier rural PWOUD face; every additional mile a person must travel to an OAT provider or a dispensing pharmacy reduces their likelihood of engaging in or maintaining on OAT (Cole et al., 2019). This finding was consistent throughout the literature and when recognized by PCPs, feasible telehealth and dispensing strategies can be implemented in primary care to reduce travel burden for PWOUD. When PCPs in rural communities choose not to prescribe OAT in their practice, this gap impacts all people in the surrounding area. Lack of OAT providers in rural communities require PWOUD to go to the next closest OAT provider to receive OAT, which is often outside the community (Gauthier et al., 2018). PCPs refusing to prescribe OAT reduces OAT-prescriber density as well as perpetuates stigma towards rural PWOUD, which directly contributes to increasing the rates of toxic drug deaths in rural areas (Haffajee et al., 2019). Isolation as a result of the concurrent effects of geographic distance and stigma pose overwhelming hurdles that PWOUD must overcome in order to access OAT (Cole et al., 2019; Fadanelli et al., 2020; Wood et al., 2019), which can be mitigated by rural PCPs through the use of telehealth appointments and dispensing OAT in locations that are convenient to patients (Gauthier et al., 2018; Hughes et al., 2021).

Rural Primary Care as an Access Point to Opiate Agonist Treatment

Since 2001, the provincial rate of diagnosis for OUD has increased 3-fold, however only modest improvements in rates of initial engagement in OAT have occurred during the same time period (Piske et al., 2020). Increasing rates of diagnosis reflects improvements in screening for OUD, which may be attributed to increased awareness of OUD lending to the current public health emergency (Piske et al., 2020). Treatment initiation and retention on OAT have shown to be where the greatest improvements can be made in rural BC (Piske et al., 2020). Systematic universal screening for OUD in primary care is recommended as way to identify who is at risk for OUD and is necessary for diagnosis, treatment and secondary prevention of toxic drug deaths (Saunders et al., 2019). Data from administrative health records show that often PWOUD have multiple health-related contacts before diagnosis, and sadly nearly all people who experienced fatal toxic drug poisoning had contact with a community-based healthcare provider within the last year prior to their death (Otterstatter et al., 2018). Primary care is an important access point for screening, diagnosis and initiating OAT, particularly because those PWOUD left untreated are likely to die from toxic drug poisoning (Harder et al., 2021; Otterstatter et al., 2018; Piske et al., 2020).

A unanimous sentiment from PWOUDs' responses is that accessing OAT should be convenient (Kane et al., 2020; Lister et al., 2020; Wood et al., 2019). Most rural and remote communities in BC have PCPs, making primary care accessible to PWOUD. In Canada, it is expected that PCPs are equipped to prescribe buprenorphine/naloxone and methadone (Korownyk, Perry, Ton, Kolber, Garrison, Thomas, Allan, Bateman, et al., 2019) and it is well documented in the literature that treating OUD is feasible in primary care (Andrilla et al., 2019; Buck-McFadyen et al., 2020; Korownyk, Perry, Ton, Kolber, Garrison, Thomas, Allan,

Bateman, et al., 2019; Logan et al., 2019). Rural PWOUD are found to prefer seeing a PCP for OAT-related visits due to an increased sense of privacy versus going to an OAT-clinic where people can be identified as an "OAT-client" simply for attending the site (Kane et al., 2020).

Misconceptions made by providers of where PWOUD access services in rural communities may lead to missed opportunities to offer OAT in rural primary care. Often, PCPs who are novice to OAT prescribing assume that PWOUD do not attend primary care clinics, however evidence suggests that rural PWOUD attend primary care visits frequently (Cole et al., 2019). Although rural communities lack comprehensive mental health resources, have fewer community pharmacies and specialty harm reduction programs, rural primary care is an access-point for people to obtain life-saving pharmacologic interventions that abates the lack of other ancillary harm reduction services (Haffajee et al., 2019; Irvine et al., 2019; Rosenblatt et al., 2015). System-level challenges including geographic distance, transportation, treatment service setting, and regulatory frameworks that influence providers utilizing DWI are the strongest predictors for PWOUD discontinuing OAT (Mackay et al., 2021). Also, if rural PWOUD need to travel to urban centres in order to receive treatment, then they are at increased risk of OAT discontinuation, exposure to unfamiliar drug suppliers, and increased risk of first-time injection drug use (Day et al., 2006). Unnecessary travel for PWOUD can be avoided when rural PCPs prescribe OAT in people's home communities.

Opiate Agonist Treatment Options in Rural Settings

In BC, several medications are available for the treatment of OUD. The current standard of care involves using first-line medications, which are buprenorphine/naloxone or methadone in conjunction with psychosocial supports (BCCSU, 2017). SROM, iOAT and RM prescribing has increased in frequency mostly in urban settings due to the detrimental need for PWOUD to be

prescribed OAT that resolves opioid cravings and provides a sense of satisfaction with care in order to ensure retention in treatment (Hong & Fairbairn, 2021; Mackay et al., 2021). Patient treatment satisfaction has been demonstrated to be associated with OAT retention, reduced substance use and improved overall quality of life (Mackay et al., 2021). Dissatisfaction with treatment can occur with any type of OAT. Individual preference, number of supervised doses, amount of opioid-use and fentanyl exposure are all potential factors that contribute to OAT satisfaction (Bardwell et al., 2021; Brar et al., 2020; Cousins et al., 2017; Mackay et al., 2021).

Limited access to the full continuum of OAT options in rural areas contribute to reduced rates of patient treatment satisfaction and medication adherence. Pharmacologic options have been found to be limited in rural communities due to lack of program infrastructure, pharmacy capacity to stock or dispense medications, prescriber knowledge of options and limited training available for providers or limited drug coverage (Thomas et al., 2020). Both Canada and the US has seen a significant increase in buprenorphine prescribing in rural and remote areas by PCPs (Furst et al., 2021; Mamakwa et al., 2017). Buprenorphine/naloxone prescribing is more or less integrated in rural primary care and PCPs with little to no experience or knowledge with prescribing buprenorphine/naloxone have demonstrated to be able to offer effective care (Mamakwa et al., 2017). Patient satisfaction with buprenorphine/naloxone is variable, which is evident by lower adherence rates compared to other OAT options (Amato et al., 2005) and patient self-reports (Cioe et al., 2020). The availability of methadone in rural areas varies significantly across North America. In the US, methadone is only approved to be dispensed from a designated opioid treatment clinic and distribution of opioid clinics in rural regions differs by state (Furst et al., 2021). In Canada, methadone prescribing is within PCP scope of practice (Korownyk, Perry, Ton, Kolber, Garrison, Thomas, Allan, Bateman, et al., 2019) and Health

Canada's removal of the requirement for providers to obtain a methadone exemption has made prescribing methadone more accessible to non-specialty providers (Eibl et al., 2017).

Results of the literature search revealed that there is a dearth of evidence that explores treatment outcomes of methadone prescribing among PCPs in rural Canadian settings (Dooley et al., 2012; Lister et al., 2020). Out of the literature available, a study by Dooley et al. (2015) found a high willingness to prescribe methadone among PCPs and that willingness to prescribe methadone was not associated with the providers degree of expertise in treating OUD. Willingness to prescribe methadone among PCPs was found to have a strong negative association with abstinence-orientated values (Dooley et al., 2012), which indicates investments in PCP-training may not address core-values that have a greater influence on rural prescribing behaviors (Kennedy-Hendricks et al., 2016; Salvador et al., 2019). Similar findings from evaluation studies of Extension for Community Healthcare Outcomes (ECHO) program models and rural "hub and spoke" models that aim to improve provider skills in prescribing OAT ha2022-08-29 2:33:00 PMve found that those providers who engage in educational or supportive programs already have a high desire to deliver OAT (Salvador et al., 2019; Snell-Rood et al., 2021). Furthermore, rural PCPs have not been found to be significantly less comfortable treating OUD compared to their urban counterparts (Harder et al., 2021). System-level barriers are consistently identified as root-causes to the limited up-take of OAT prescribing among OAT-hesitant providers (Cole et al., 2021; Salvador et al., 2019; Snell-Rood et al., 2021).

The lack of OAT options available in rural areas impacts treatment outcomes for PWOUD. Based on the information available, inferences can be drawn between limited OAT options being associated with poor treatment adherence and therefore toxic drug mortality risk (Haffajee et al., 2019; Irvine et al., 2019; Rigg et al., 2018). To the author's knowledge, no

articles have been published that examines treatment outcomes for rural PWOUD using alternative OAT options such as SROM, iOAT or RM prescribing. This finding reflects Bardwell and Lappalainen's (2021) commentary that recognizes the lack of research on the effectiveness of alternative strategies in rural settings to inform clinical practice is contributing to the rural-urban disparities of treatment accessibility in BC.

Program and Provider Characteristics

Finally, characteristics of programs and providers that enhance accessibility to OAT, patient satisfaction and patient health outcomes during treatment in rural areas are identified as being non-stigmatizing and non-judgemental, value strong trusting therapeutic relationships, convenient, and address concurrent disorders (Buck-McFadyen et al., 2020; Ellis et al., 2020; Kane et al., 2020; Logan et al., 2019; Saunders et al., 2019; Wood et al., 2019). Actual and perceived stigma is concentrated in rural communities (Ellis et al., 2020; Kalichman et al., 2017; Thomas et al., 2020). It is common for rural PWOUD to describe anxiety related to how community members, law enforcement, pharmacists and healthcare providers may perceive them differently in the form of discrimination based on their history of substance use (Ellis et al., 2020; Palombi et al., 2018; Wood et al., 2019). Stigma is a complex phenomenon and past experiences of stigma strongly influence health decision-making and perceived accessibility of healthcare services even if stigmatizing behaviors are not enacted (Fadanelli et al., 2020; Goodyear et al., 2018; Hatzenbuehler et al., 2013). Emphasis on stigma reduction in rural emergency departments, primary care settings and in harm reduction programs in the form of using trauma-informed care, including PWLLE, ensuring confidentiality, and increasing professional knowledge of how to approach PWOUD are recommended strategies to reduce actual and perceived stigma in clinical settings (Buck-McFadyen et al., 2020; Ellis et al., 2020;

Lister et al., 2020; Logan et al., 2019). Improving access to training opportunities for providers has demonstrated to reduce stigmatizing attitudes, beliefs and language among healthcare providers that leads to stigmatizing care experiences for PWOUD (Andrilla et al., 2019; Lister et al., 2020; Livingston et al., 2012; Saunders et al., 2019). The ability of providers to identify restrictive prescribing practices that hinder actual or perceived access to OAT is essential to mitigate any treatment paradox between prescriber safety-related goals and patient-goals that negatively affect patient satisfaction and therefore treatment outcomes (Richard et al., 2020; Wood et al., 2019).

Trust between patients and providers is described as an essential characteristic in order for PWOUD to initiate health-seeking behaviors for treatment of OUD (Ellis et al., 2020; Kane et al., 2020; Saunders et al., 2019). Fear of negative consequences for disclosing substance use in the form of healthcare providers informing law enforcement of patients' drug-related activities or fear of future mistreatment is a common and unnecessary barrier (Ellis et al., 2020; Saunders et al., 2019). Trust between PCPs and patients is essential to people's health and welling, however breeches of confidentiality are reported in rural communities, particularly when relationships between primary care and law enforcement or emergency department staff become blurred and patient information related to drug use is shared (Ellis et al., 2020). Information sharing is often well-intentioned, however when that information is utilized in a way that further stigmatizes patients in emergency department or criminal justice settings it perpetuates social isolation and fear among PWOUD that can lead to high risk substance use behaviors and toxic drug poisonings (Thomas et al., 2020). Rural PWOUD are acutely aware of social-structural characteristics that may strengthen or hinder trust between providers and patients (Ellis et al., 2020), which is unique to rural settings (Saunders et al., 2019). For rural patients, weak rapport

with PCPs may be perceived as a barrier in order to feel comfortable disclosing substance use and conversely, relationships that are close-knit with little anonymity can also can amplify concerns about stigma (Saunders et al., 2019). Therapeutic rapport is a dynamic process between PCPs and patients and rural PWOUD have unique considerations PCPs must weight when navigating trust-building in order to improve accessibility to OAT (Ellis et al., 2020; Kane et al., 2020; Saunders et al., 2019).

Two retrospective program evaluations of OAT programs integrated into rural primary care demonstrate the feasibility and effectiveness of implementing interdisciplinary care teams into office-based primary care settings (Buck-McFadyen et al., 2020; Logan et al., 2019). Sizable value is added to patient care when PWOUD are able to access holistic services at one centralized location (Kane et al., 2020; Logan et al., 2019). Wrap-around programs improve mental health symptoms (Kane et al., 2020), and patients report satisfaction with ease of access to medical and social services (Gauthier et al., 2018; Kane et al., 2020). For many rural PCPs, lack of team support to address mental health concerns and the social determinants of health is a barrier to effectively retaining a person on OAT (Andrilla et al., 2019; Buck-McFadyen et al., 2020; Lister et al., 2020; Logan et al., 2019). By nature, rural healthcare systems have less workforce to draw from and challenges hiring and retaining qualified staff limit the ability to implement interdisciplinary substance use services in rural primary care (Clark et al., 2002; Parker et al., 2012). Strategies that can improve ease of access to OAT in primary care that do not require interdisciplinary teams include optimizing telehealth visits, avoiding unnecessary investigations or requirements of PWOUD when prescribing OAT (e.g., UDS), and consider initiating take-home doses as soon as possible or when requested by PWOUD (Hughes et al., 2021; Korownyk, Perry, Ton, Kolber, Garrison, Thomas, Allan, Bateman, et al., 2019; Lister et

al., 2020; Wood et al., 2019). Implementing capacity to dispense OAT in primary care clinics is also advantageous for OAT retention, especially for remote communities that do not have access to a community pharmacy (Gauthier et al., 2018). Low rates of OAT retention in rural regions suggest that PWOUD require more supports after initially being prescribed OAT by PCPs (Piske et al., 2020). Additional supports, especially during the first year of OAT can meaningfully improve treatment outcomes for PWOUD (Piske et al., 2020).

Limitations

Several limitations have been identified by this integrated literature review that affect the generalisability of the findings. All the included studies were conducted in either Canada (n=4), the US (n=7) or Australia (n=1), all of which have diverse regulatory, healthcare, and historical contexts. American studies are less comparable to Canadian contexts due to differences in regulatory oversight of methadone and buprenorphine prescribing, which will significantly impact the external validity of the American studies (Priest et al., 2019). In the US, methadone is highly regulated and can only be prescribed and dispensed in speciality treatment centres (Cole et al., 2019), whereas in Canada and Australia methadone and buprenorphine/naloxone is prescribed in primary care making OAT comparably more accessible (Piske et al., 2020). Buprenorphine is also tightly regulated in the US and providers are required to obtain a waiver that limits the number of patients who can be prescribed buprenorphine to either 30 or 100 on a provider's panel (Rosenblatt et al., 2015). Regulatory contexts limit the generalisability of studies conducted in the rural US, which is problematic due to the majority of studies that address treatment outcomes for rural PWOUD originate from the US.

Heterogeneity among rural and remote communities' limits generalizability of the findings, which is identified as a limitation in nearly all the included studies (Richard et al.,

2020; Saunders et al., 2019; Wood et al., 2019). BC has some unique characteristics that warrant further examination. Although outside the scope of this review, First Nations communities have been disproportionally impacted by the toxic drug crisis across BC (Nosyk et al., 2021), and further examination of the treatment needs of rural BC First Nations people is required to address this disparity. Lister et al. (2021) suggest that future research must focus on the treatment needs of racialized and minority rural populations. A closer look at focused rural regions that have been particularly hard-hit by toxic drug deaths is warranted in order garner a better understanding of region-specific risk-factors in order to find the most appropriate interventions (Lister et al., 2020).

Sampling limitations that are specific to retrospective cohort study designs likely influenced the outcomes of the quantitative study findings included in the integrated review. Study populations that are based on health administrative diagnostic codes rely heavily on data inputted by clinicians often in the form of billing codes (Cole et al., 2019). Patient cases can be misclassified that leads to an underestimation of the total study population of people with OUD. Provider types can also be misclassified (Cole et al., 2019; Piske et al., 2020), which limits the precision that study interventions were conducted by PCPs, findings in this review may misclassify OAT prescribing by PCPs that may have occurred by speciality providers. The distinction between PCP and specialty OAT provider was rarely made by study authors. When provider characteristics were clearly described and the study context was similar to rural or remote office based primary care, then the study was included in the review. In Piske et al. (2020) case-finding algorithms were used to minimize classification error. Overall, the sample sizes of the studies analysed were small and included participants from single clinics or single

clinic networks that may not represent all office-based rural primary care settings further limiting generalisability of the findings (Gauthier et al., 2018; Hughes et al., 2021).

Lastly, no studies were found that examined the effect take-home doses has on treatment outcomes for rural PWOUD, namely treatment retention. Although, all the articles that look at treatment facilitators from the patient perspective highlighted that take-home doses could help mitigate the negative impacts of geographical distance or transportation barriers to getting to a brick and motor location where OAT is dispensed, few studies demonstrated how rural patient voices or perspectives are included in program implementation (Lister et al., 2020). Research in the field of rural substance use interventions remains novel as evident by the only relevant articles found in the search that address the research question were published after 2018. In order to advance evidence-based practice among rural primary care providers prescribing OAT, further research is required to demonstrate that novel interventions such as take-home doses are effective at meeting the needs of rural PWOUD and ensuring treatment continuity to prevent toxic drug deaths.

Recommendations

In order to synthesize recommendations for practice to improve treatment outcomes for adults with OUD in rural primary care settings, each recommendation was organized by the themes distilled from the literature as shown in Table 3: Provider-patient treatment paradox, rural risk environment, rural primary care as an access point to OAT, OAT treatment options in rural primary care, program and provider characteristics.

Table 3

Recommendations for Primary Care Providers in Rural Settings to Improve Treatment Outcomes for Adults with Opioid Use Disorder

Recommendation	Implementation Strategies for Rural Primary Care	Source
Provider-Patient Treatment Paradox		
Find a mentor experienced in prescribing OAT	-Use preceptorship opportunities with experienced prescribers. -Find a mentor who has overcome similar barriers.	Andrilla et la., 2019
Coordinate and/or attend education opportunities related to treatment of OUD e.g. ECHO, Hub and Spoke Models	-Incentivize comprehensive training for rural PCPs. -Training that targets PCP attitudes and beliefs towards PWOUD and OAT.	Andrilla et al, 2019; Lister et al., 2019; Saunders et al., 2019
Conduct universal screening for substance use disorders for all patients in primary care annually.	-Early identification of OUD -Use short screening tools e.g., the Prescription Opioid Misuse Index (POMI) -Use a tablet that links screening directly to the patients' chart for confidentiality.	Cole et al., 2020; Korownyk et al., 2019; Piske et al., 2020; Saunders et al.,
Adopt a chronic disease model for OUD	-Discuss OUD as a chronic medical condition that requires evidence-based pharmacologic interventions. -Address concurrent chronic pain as multimorbidity that significantly affects quality of life. -Do not impose time restrictions on treatments or prognoses.	Piske et al., 2020; Korownyk et al., 2019; Richard et al., 2021; Saunders et al., 2019;
Reduce stigma in primary care settings through facilitated education and dialogue with all team members.	-Provide proactive education on OUD and the value of harm reduction approaches. -Empower staff with the knowledge of barriers PWOUD face accessing healthcare.	Andrilla et al., 2019

Recommendation	Implementation Strategies for Rural Primary Care	Source
Rural Risk Environment		
Reimburse patients or provide stipends for travel to clinics and pharmacies.	-Add medical transportation services to rural clinic sites. -Cover the costs of mileage for patients. -Avoid prescribing daily pick-ups if transportation is a barrier.	Lister et al., 2019; Wood et al., 2019
Address the social determinants of health with every patient with OUD.	-Ask about housing, finances, and transportation to help find interventions to address barriers. -Refer to social supports and resources in the community	Kane et al., 2020
Offer telehealth visits for OAT wherever possible, especially for patients have challenges accessing reliable transportation or childcare.	-Offer telehealth as an option -Amend any policies to support telehealth visits for prescribing OAT. -Avoid in-person UDSs at primary care sites.	Hughes et al. 2021; Lister et al., 2020; Piske et al., 2020
Limit the use of urine drug screens (UDSs).	-UDSs may be used as a clinical tool to intensify treatment if a person is found to be using unregulated substances. -UDSs not required for diagnosis.	Hughes et al., 2021; Korownyk et al., 2019
Focus on treatment retention for patients prescribed OAT.	-Provide contingency management or positive rewards for attending appointments or retaining on OAT. -Encourage or facilitate cannabis use for people taking OAT. -Eliminate punitive measures for concurrent drug use for patients prescribed OAT. -Always reinitiate OAT for patients who have previously discontinued and are interested in re-starting. -Facilitate the longest duration on OAT as possible	Korownyk et al., 2019; Piske et al., 2020

Recommendation	Implementation Strategies for Rural Primary Care	Source
Rural Primary Care as an Access Point to OAT		
Prioritize taking on new patients with OUD who present to rural primary care sites.	-Set-aside discrete time for OAT prescribing and new patient assessments.	Andrilla et al., 2019; Cole et al., 2020
Use a trauma-informed approach and recognize stigma occurs in healthcare.	-In an affirming way, ask about past experiences with OAT and healthcare. -Invite patients to share about their treatment history.	Kane et al., 2020
Proactively build trusting, therapeutic rapport with PWOUD.	-Discuss confidentiality in small communities with patients. -Set-out clear expectations with clients early in care. -Normalize discussions about substance use.	Saunders et al., 2019
OAT Treatment Options in Rural Primary Care		
Offer a full range of OAT (buprenorphine, SROM, methadone) to any patient with OUD in rural primary care practices.	-Prescribe partial and full-agonist OAT medications. -Keep provincial and national guidelines accessible as quick reference guides.	Andrilla et al., 2019; Cole et al., 2020; Kane et al., 2020; Korownyk et al., 2019; Saunders et al., 2019
Use the least restrictive prescribing strategies for rural patients (e.g. longer prescriptions, reduced patient contact, take-home doses, less frequent witnessed doses).	-Consider sustained release formulations of OAT (e.g. extended-release injectable buprenorphine). -Two or three times per week witnessed doses with take-home doses reduces travel burden. -Telehealth visits for patient contact with prescriber.	Kane et al., 2020; Korownyk et al., 2019; Wood et al., 2019;
Treatment agreements may be used to ensure shared decision-making and mutual understanding of expectations of patients and providers during OAT.	-Written contacts can be useful to communicate the clinic expectations of patients when prescribed OAT. -Treatment agreements should not be used as punitive measures. -Avoid terminating care if a patient continues to use unregulated substances despite taking OAT.	Andrilla et al., 2019; Korownyk et al., 2019

Recommendation	Implementation Strategies for Rural Primary Care	Source
Program and Provider Characteristics		
Integrate interdisciplinary team members that provide outreach services and behavioral, psychosocial supports into primary care teams.	-Delegate a staff member to contact patients who miss appointments. -Utilize group psychosocial sessions to maximize staff time. -Offer brief (15-20min) motivational interviewing sessions weekly or biweekly. -Integrate case management services that utilize trauma-informed practice. -Hire PWLLE to provide outreach to patients on OAT.	Andrilla et al., 2019; Korownyk et al., 2019; Logan et al., 2019; Lister et al., 2019; Piske et al., 2020; Richard et al., 2020
Provide on-site OAT dispensing in collaboration with interdisciplinary team members (e.g. pharmacists, nurses).	-Collaborate with local pharmacists or nurses to dispense OAT at rural primary care clinics. -Build relationships with local pharmacists in order to provide collaborative patient care. -Encourage community pharmacies to dispense OAT at primary care clinics, especially in rural or remote communities where pharmacies may not offer confidentiality during medication administration.	Andrilla et al., 2019; Gauthier et al., 2018; Korownyk et al., 2019
Ensure patient confidentiality by training all clinic staff on the harms of stigma and importance of trusting relationships for PWOUD	-Provide confidentiality and privacy training to all staff routinely. -Discuss with patients which staff can view EMRs and if they link to other databases. - Obtain informed consent before documenting results of substance use screening in linked EMRs -Acknowledge dual relationships with patients in small communities.	Kane et al., 2020; Saunders et al., 2019

Recommendation	Implementation Strategies for Rural Primary Care	Source
Establish community advisory boards to address the toxic drug public health emergency	-Coordinate stakeholders that include PWLLE to voice local needs of PWUD. -Use community in-kind resources to apply for grants to fund community initiatives (e.g. OPS, peer networks, transportation options).	Lister et al., 2019; Richard et al., 2020
Develop community interventions to address stigma related to PWOUD and OAT	-Social marketing campaigns that shift cultural norms to inclusion of PWUD. -Medical campaigns that increase connectedness to PWOUD and PWUD. -Media that focuses on OUD as a chronic medical condition that is treatable. -Empower PWOUD to share their stories to reduce interpersonal stigma related to OUD and OAT.	Richard et al., 2020

Chapter Six: Conclusion

PWOUD are at significant risk of morbidity and mortality related to the fentanyl contaminated and unregulated drug supply in BC. PCPs are positioned as an access point to OAT, which is a life-saving pharmacological intervention that reduces the risk of toxic drug death. Once OAT is universally implemented in primary care settings across rural and remote communities in BC, it is projected to help close the disparity between rural and urban rates of toxic drug deaths. Some current OAT prescribing practices among rural PCPs act as barriers to PWOUD, and the barriers are exacerbated by rural-specific characteristics. Geographic distance, lack of reliable transportation, limited mental health and harm reduction services, fewer human resources, concentrated stigma and lack of anonymity in rural communities contribute to barriers rural PWOUD face when initiating and retaining on OAT.

Despite multiple barriers, several strategies have been identified in the literature that mitigate actual or potential barriers to OAT for rural PWOUD. Rural PCPs can approach treatment of OUD using a patient-centred, chronic disease model of care that uses the least restrictive prescribing practices; this includes shared-decision making regarding the use of UDSs, selection of OAT medication, use of supervised doses and take-home doses, and referrals to support services that address mental health and the social determinants of health. Furthermore, rural and remote PCPs are community leaders and are required to address harmful stigma that PWUD experience, especially in healthcare settings in order to ensure primary care is accessible to PWUD. PWOUD frequently attend primary care, however due to fears of judgment, confidentiality breeches or future discrimination, PWOUD may not present with chief complaints of opioid use or opioid withdrawal. Safeguarding accessibility of rural primary care for PWOUD is a shared responsibility of PCPs and other healthcare staff.

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Appendix A

DSM-5 Diagnostic Criteria for Opioid Use Disorder

A diagnosis of OUD is met when a patient meets at least two (2) of the following clinical symptoms within a 12-month period:

1.) Opioids are often taken in larger amount or over a longer period than was intended.
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 or urge 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 current social or interpersonal problems caused or exacerbated but 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 opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10.) Tolerance[1], as defined by either of the following:
    a. A need for markedly increased amounts of opioids to achieve intoxication or desired effect.
    b. A markedly diminished effect with continued use of the same amount of an opioid.
11.) Withdrawal[2], as manifested by the either of the following:
    a. Opioid withdrawal syndrome
    b. Opioids are taken to relieve or avoid withdrawal symptoms.

Severity is classified as:
Mild: Presence of 2-3 symptoms
Moderate: Presence of 4-5 symptoms
Severe Presence of 6 or more symptoms

(American Psychological Association, 2013)

[1,2] This criterion is not considered to be met if a person is taking opioids solely for medical reasons e.g. pain management.

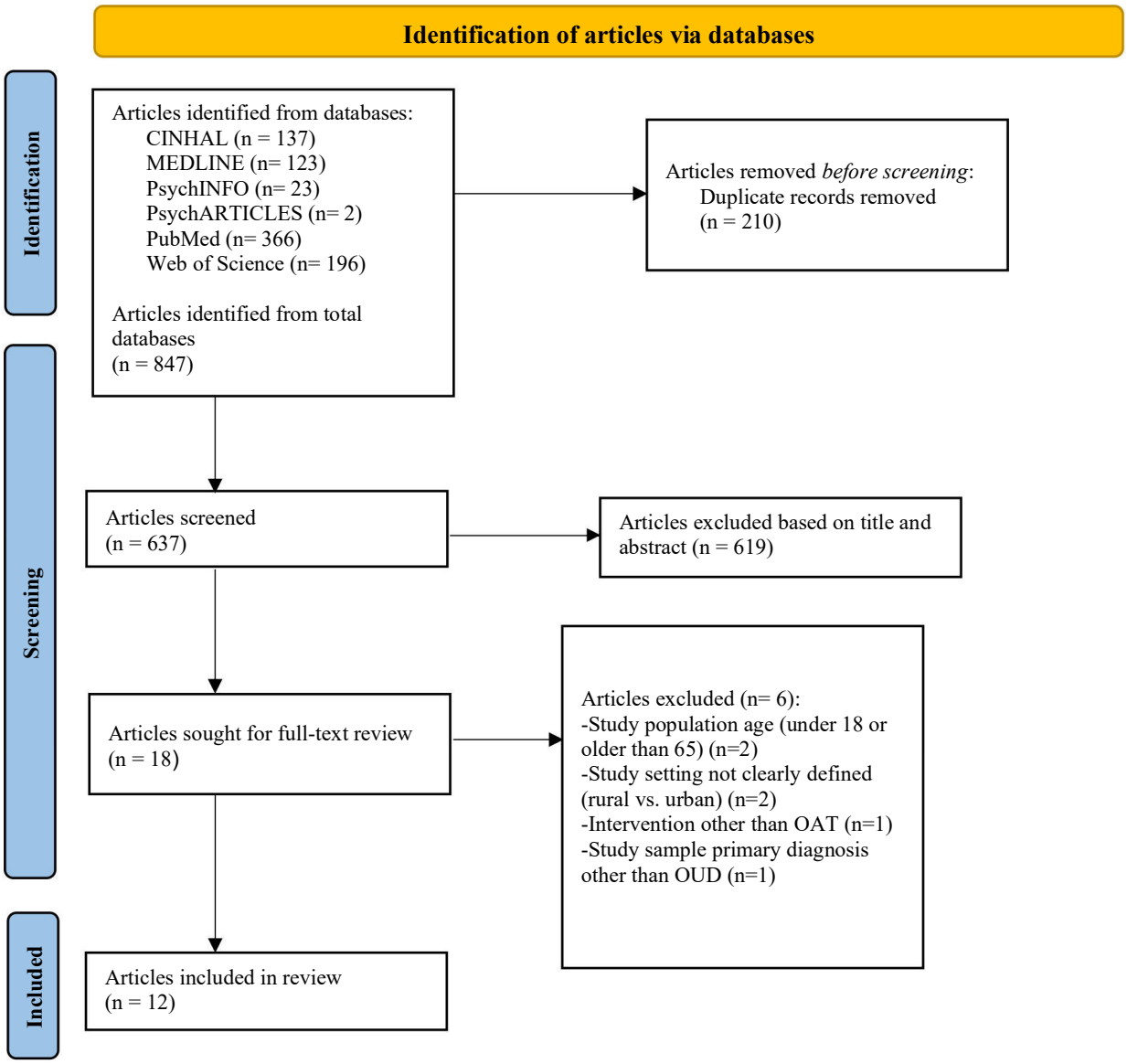
Appendix B

Database	Concept 1 (population)	Concept 2 (intervention)	Concept 3 (intervention)	Concept 4 (intervention)
CINAHL EBSCO	Analgesics-opioid, Fentanyl, Heroin, Narcotics, Opiate Overdose, Opioid Epidemic, Overdose, Recreational Drug Use, Street Drugs, Substance Abuse, Substance Use Disorder Opium	Rural Population Rural Health Personnel Rural Health Centers Hospitals, Rural Rural Health Services Rural Health Nursing Rural Areas "rural" "isolat*" "remote" "non-urban"	Primary Health Care Physicians, family Nurse Practitioners Family Nurse Practitioners Adult Nurse Practitioners Outpatient Services Outpatients Community Health Centers Community Health Nursing Community Health Services Office Visits Practitioners Office	Methadone, Dihydromorphinone, Morphine, Buprenorphine, "buprenorphine/naloxone", Analgesic, opioid, "Suboxone", "medication assisted", "substitution treatment", "maintenance treatment", "levomethadone", "methadol", "methadyl", "levomethadyl"
MEDLINE Ovid	Opioid-Related Disorders, Substance-Related Disorders, Drug Users, Opioid Overdose, Drug Overdose, Fentanyl, Heroin, Heroin Dependence, Opium, "addiction, "drug addict"	Rural Health, Rural Population, Hospitals, Rural, Rural Health Services, Rural Nursing, "rural" "remote" "non-urban" "isolat*"	Primary Health Care, Family Practice, Physicians, Family, Nurse Practitioners, General Practitioners, Community Health Centers, Outpatients, Office Visits,	Opiate Substitution Treatment, Methadone, Buprenorphine, Buprenorphine-Naloxone Drug Combination, Analgesics, Opioid, "medication assisted", "substitution treatment", "maintenance treatment", "levomethadone", "methadol", "methadyl", "levomethadyl"
PsycINFO/ PsychARTI-CLES	Opioid Use Disorder, Heroin Addiction,	Rural Health, Rural Environments,	Primary Health Care, Family Physicians,	Medication-Assisted Treatment,

	Morphine Dependence, Substance Use Disorder, Addiction, Drug Abuse, Drug Dependency, Substance Related and Addictive Disorder, Drug Abuse, Polydrug Abuse, Drug Withdrawal, Drug Overdoses, Opiates, Fentanyl, Heroin, Morphine, Oxycodone	"rural" "remote" "isolat*"	General Practitioners, Nurses, Nursing, Private Practice, Outpatients, Outpatient Treatments	Buprenorphine, "buprenorphine/naloxone", "Suboxone", Narcotic Agonists, Substance Use Treatment, "medication assisted", "substitution treatment", "maintenance treatment", "levomethadone", "methadol", "methadyl", "levomethadyl"
PubMed	Opioid, Opiate Fentanyl, Heroin, Overdose, Substance Use Disorder Opioid Use Disorder, Addiction	Rural Health, Rural, Rural Population, Remote, Non-urban "isolat*" Non-metropolitan	Primary Health Care Primary Care Office Visit Family Physicians, Nurse Practitioner, Outpatient General Practitioner, Community health centre	Opioid agonist therapy, Opiate replacement therapy, Opiate substitution treatment, Medication-assisted treatment, Methadone, Methadone maintenance therapy, Buprenorphine, Suboxone
Web of Science	"opiate", "opioid", "overdose", "withdrawal", "heroin", "fentanyl", "addiction"	"rural", "remote", "isolat*", "non-urban"	"outpatient", "primary care", "in-office", "community", "ambulatory", "nurse practitioner", "physician"	"methadone", "buprenorphine", "suboxone", "opiate agonist", "medication-assisted"

Appendix C

PRISMA Flow Diagram



Appendix D

Literature Matrix

Table 1: *Literature Review Matrix – Quantitative studies*

Author, Year, Title, Journal,	Purpose	Research Design/ Context	Outcomes Measured and Data Analysis	Strengths/ Limitations	Key Findings/ Recommendations
Hughes, P. M., Verrastro, G., Wilson Fusco, C., Gilmore Wilson, G., & Ostrach B. (2021). An examination of telehealth policy impacts on initial rural opioid use disorder treatment patterns during the COVID-19 pandemic. *Journal of Rural Health*	Aim to measure any changes in the accessibility of medications for opioid use disorder (MOUD) at a rural family practice after the implementation of policies that support telehealth visits for OUD during COVID-19 pandemic.	Retrospective, open-cohort design. N= 242 patients Patients prescribed BUP-containing medication only. Patient data extracted from EMRs at a single PC office with several providers who prescribe MOUD. Study location is a rural, micropolitan region near Appalachian Mountains USA. Population inclusion were any patient who had ever been prescribed buprenorphine and had an ICD-10 code for OUD. Study periods used as comparisons are	Outcomes Measured: - Distance patients traveled between their home and the clinic using ZIP codes - The number of visits of each patient during the time periods - Number of new patient visits during each time period Data Analysis: -Data analyzed using SAS v9.4 software -Chi-square tests and ANOVAs used to compare outcomes across all three time periods. -Comparisons from clinic data during the time periods from 2018-2019 showed expected proportions of visits during the amount of study time. -Maps made with ArcGIS Desktop	<u>Strengths:</u> - Ethics approval obtained - Clear and measurable study population inclusion criteria - Demonstrates outcomes of application of regulatory changes in a clinical practice setting. - Service location and study supports mission and values of harm reduction. - Able to control for any seasonal variability of visits or cyclic trends in patient visits. - CI used for all outcomes measured demonstrate precision of results <u>Limitations:</u> - Sample obtained from only one primary care clinic. - Patients only offered BUP, which could impact patient characteristics and severity of SU.	<u>Findings:</u> - Patients who used telehealth visits on average lived further away - An increase in the no. of patients receiving MOUD from rural areas. - Increased in clinic's overall catchment areas. - More overall visits from MOUD occurred during COVID period (581) than pre-COVID (436) and a higher proportion of visits during COVID for that time-period (45.7% vs. 40%; $p < 0.001$). - No sig. change of new patients - COVID period showed more lab visits by patients and more UDSs obtained during lab visits

Author, Year, Title, Journal,	Purpose	Research Design/ Context	Outcomes Measured and Data Analysis	Strengths/ Limitations	Key Findings/ Recommendations
		between Nov. 16 2019 to June 15 2020. Data was compared between 3 time periods; Pre-COVID (Jan. '20-Mar. 20), COVID-related changes (Mar. '20-Apr. '20) COVID (Apr. '20-Jun.'20).	version 10.7.1 for visualizing the catchment area	- Patient satisfaction with telehealth not measured. - Short study period, unable to infer long-term treatment retention or outcomes related to telehealth. - Does not take into consideration any barriers rural patients may face in filling BUP prescriptions. - Unable to identify other characteristics of the clinic that facilitated improved access by rural patients - Assumes patients live at ZIP codes listed in the clinic EMR	- Telehealth visits did not change appointment attendance - COVID showed an increase in average number of days between UDS <u>Recommendations:</u> -Utilize telehealth wherever possible. -Do not need to obtain in-person UDSs; patients can do UDS at labs, if one is required.
Gauthier, G., Eibl, J., & Marsh, D. C. (2018). Improved treatment-retention for patients receiving methadone dosing within clinic providing physician and other health services (onsite) versus dosing at community	To assess the effectiveness of dispensing OAT from on-site pharmacies by measuring retention of patients who have their OAT dispensed onsite at the clinic compared to patients who have their OAT filled offsite at a community pharmacy.	Retrospective cohort study N = 3743 patients Patients started MMT between Jan. 1 2011 and June 17, 2013 Only included patients who had never been on MMT before, excluded patients starting on BUP	Outcomes Measured: -retention by dosing records for 12 consecutive months -Considered d/c when up 30 days without a refill of OAT. Data Analysis: - Cox Proportional Hazard Model used to demonstrate RR of MMT discontinuation.	<u>Strengths</u>**:** study includes patients Rx'd MMT in PC. -Findings generalizable due to prescribing regulations in Canadian settings. -Author D. Marsh associated with Northern Ontario School of Medicine, well-published. -Covariates controlled for sex, geographic region,	-Dispensing OAT from onsite pharmacies is feasible in remote and rural PC clinics. -When OAT is filled onsite, patients are more likely to retain on MMT - median peak MMT doses greater for onsite participants compared to offsite (80mg vs. 65mg) –no difference in other important clinical end-

Author, Year, Title, Journal,	Purpose	Research Design/ Context	Outcomes Measured and Data Analysis	Strengths/ Limitations	Key Findings/ Recommendations
(offsite) pharmacies. *Drug and Alcohol Dependence*		Used electronic health records for clinics associated with Ontario Addiction Treatment Center (OATC) Context comparable to remote/rural health centres that are required to dispense OAT due to lack of community pharmacy	- MMT filled onsite, patients 77% less likely to d/c treatment before 1 year (aHR= 0.230 CI=0.210-0.253 p<0.001) - Likelihood that patients dispensed OAT onsite in rural clinics would discontinue treatment before 1 yesr (aHR=0.791 CI = 0.697-0.898) p < 0.001)	rurality, age of MMT start. -Cox proportional hazards regression to characterize the relative risk of premature treatment discontinuation Limitations: rurality of patient's location adjusted for in statistical analysis -Clinic selection was based on a single clinic network, which limits external validity due to a selection bias and confounding factors related to culture, philosophy embedded in the clinic network. - study design limits ability to define characteristics for patients that make onsite dispensing more accessible	points like dose amount or neg. UDS. -OAT should be dispensed in locations that are convenient to patients. - due to MMT being a complex medication and requiring collaboration between patient, prescriber and dispending pharmacists, convivence in having onsite dispensing. -MMT requires collaboration between prescriber and pharmacist. Recommendations: -Dispense OAT onsite at clinics where OAT is prescribed. -Collaboration between PCPs and pharmacists improves client care.
Logan, D., Lavoie, A. M., Zwick, W. R., Bumgardner, M. A., Kunz, K., & Molina, Y. (2019). Integrating addiction medicine into rural	To describe the outcomes of implementing an addiction medicine program in rural PC. -Evaluate program effectiveness by measuring patient	Retrospective cohort study Rural Hawaii, U.S. n= 101	Outcomes Measured: Mental Health (MH) symptoms using GAD-7 and PHQ-9, UDS, medication adherence Findings: patients more likely to d/c	Strengths: MH measured using validated tools. -Sample population context closely resembled research question. -Advocates for comprehensive OUD treatment in PC.	- When adults with OUD are prescribed BUP and offered counselling or other psychosocial supports, anxiety and depression are likely to improve.

Author, Year, Title, Journal,	Purpose	Research Design/ Context	Outcomes Measured and Data Analysis	Strengths/ Limitations	Key Findings/ Recommendations
primary care: Strategies and initial outcomes. *Journal of Consulting and Clinical Psychology*	outcomes of MH symptoms, substance use, and medication adherence.	Recruitment occurred between Dec. 2016 – May 2018 Sample included mostly Native Hawaiian people, lower socioeconomic status, long distances to travel to addiction specialty clinics.	treatment at 3 months if UDS – inconsistent, or had higher baseline depression or anxiety. -Treatment time and patient depression and anxiety were negatively associated. (-0.04, 95& CI= -0.06, -0.02 $p < 0.0001$)	-Demonstrates feasibility of interdisciplinary OUD care in PC. Limitations: PCP and BUP prescribers were separate professionals. -Framework suggests a large number of staff i.e. SW, psychologist, counsellors, MDs, behavioral health workers. -Abstinence based approach demonstrated by encouraging cessation of substance use. -Patients excluded for unexplained reasons i.e. "could not follow treatment plan". -UDS measurements not clearly defined.	-OUD treatment in PC should include pharmacotherapy and psychosocial supports. -Assertive outreach for clients who are hard-to-reach can help initiate and retain people in OUD treatment.
Cole, E. S., DiDomenico, E., Cochran, G., Gordon, A. J., Gellad, W. F., Pringle, J., Warwick, J., Chang, C. H., Kim, J. Y., Kmiec, J., Kelley, D., & Donohue, J. M. The role of primary care in improving access	-To examine the degree to which adults with OUD in rural settings are engaged in primary care. -Describe the role of PCPs in MAT delivery. -Estimate the association between distance to MAT prescribers and MAT utilization.	Quantitative Retrospective cohort study comparing Medicaid enrollees with OUD who had greater than 1 primary care visit with enrollees with OUD who had no PC visits. Rural PA, U.S. Includes patients prescribed BUP and	Outcomes Measured: PC utilization, MAT utilization, distance to nearest MAT prescriber, continuity of MAT. -Retention defined as continuity of MAT for at least 180 days Data Analysis: -unmeasured potential confounding variable discussed as	Strengths: similar study population and prescribing context which strengthens external validity. -Independent variables (distance to MAT) and dependent variables (medication adherence) clearly stated. - Sensitivity analyses completed to confirm the odds ratios and statistical	-Distance to nearest MAT prescriber was strongly associated with likelihood of receiving MAT. (OR=0.988; 95% CI=0.983-0.993; $p < 0.001$). -Distance to MAT prescriber and MAT dispensing significantly reduces continuity of MAT. -Every additional mile was associated with a

Author, Year, Title, Journal,	Purpose	Research Design/ Context	Outcomes Measured and Data Analysis	Strengths/ Limitations	Key Findings/ Recommendations
to medication-assisted treatment for rural Medicaid enrollees with opioid use disorder. *Journal of General Internal Medicine*		naltrexone. Excludes patients prescribed methadone n=7930 Medicaid enrollees 2014-2015 Aged 18-64 OUD diagnosis and at least 1 PCP visit Older adults excluded	transportation access and health status	significance of the findings. -OUD diagnosis indicates a greater likelihood a person will be prescribed MAT. Limitations: diagnostic codes have low sensitivity, high specificity = underestimate OUD incidence. -Not able to classify MMT prescribed by PCP vs. non-PCP. -inconsistent finding that enrollees who rec'd MAT from non-PCP providers were less likely to discontinue pharmacotherapy. Differences in quality of are not measurable in observational study	1.2% reduction in the odds of receiving any MAT -30% of enrollees had their OUD diagnosis recorded on a PCP visit claim. Half of that group received OAT (50.8%) -Patients who were prescribed OAT by non-PCPs were more likely to continue on MAT when compared to patients with PCP prescribers. (OR=1.33; 95% CI=1.0-1.7; p=0.04) -OUD screening suboptimal in PC. There is a need for education on recognizing, screening and diagnosing for OUD for PCPs. -MAT should be offer in locations that are convenient. -Adults with OUD frequently attend PC visits (4.1 visits per year), making PC a convenient place to prescribe MAT. -Greater distance from MAT provider (greater

Author, Year, Title, Journal,	Purpose	Research Design/ Context	Outcomes Measured and Data Analysis	Strengths/ Limitations	Key Findings/ Recommendations
					than 45m miles), co-concurrent psychiatric diagnoses and additional comorbidities increase the odds of pharmacotherapy discontinuation. - When OUD is diagnosed in PCP, more than half of people receive MAT. Higher than all people with OUD in the sample. → PCPs play a crucial role in OAT initiation.
Piske, M., Zhou, H., Min, J. E., Hongdilokkul, N., Pearce, L. A., Homayra, F., Socias, E., McGowan, G., & Nosyk, B. (2020). The cascade of care for opioid use disorder: a retrospective study in British Columbia, Canada. *Addiction*	To estimate the cascade of care for OUD in BC and to identify factors associated with OAT engagement for PWOUD in BC. -Generate an actual cascade of OUD care using individual-level health data for all PWOUD accessing care in BC.	Qualitative retrospective cohort study n=55,470 PWOUD in BC BC residents have access to fully covered BUP, and fully covered OAT services based on income. Data obtained for records between January 1, 1996 and November 30, 2017 Health records from PharmaNet, Medical	Outcomes Measured: PharmaNet (OAT dispensing), Discharge Abstract Database (hospitalizations), Medical Services Plan (MD billing), BC Vital Statistics (deaths) -followed until administrative loss (66 mos. of no records up to study cut-off) or death. -OAT defined as dispensation records of BNX, MMT, SROM, or iOAT.	<u>Strengths:</u> Clearly defined all variables and outcomes measured. -Provides insight to the entire population in BC with OUD, able to compare rural to urban. -Study context is BC-specific i.e. takes into consideration that both BUP and MMT can be prescribing in PC. <u>Limitations:</u> does not specify care between types of prescribers or types of OAT, however does advocate that common OAT (MMT & BUP) can be Rx'd by PC physicians.	-Three-fold increase in OUD diagnosis from 2001to 2017 and modest increased in OAT initiation and low-retention rates. -fewer than 3% of PWOUD obtain long-term remission = importance of harm reduction strategies - An opportunity for improved OUD identification, treatment engagement, OAT initiation and retention. - People who are accessing care for other OUD-related needs but

Author, Year, Title, Journal,	Purpose	Research Design/ Context	Outcomes Measured and Data Analysis	Strengths/ Limitations	Key Findings/ Recommendations
		Services Plan, BC Vital Statistics, Discharge Abstract Database were linked to de-identified participant codes.	Data Analysis: -First the OUD care cascade from 2012-2016 was plotted to obtain population characteristics. - Cochrane-Armitage test used for temporal trends, and $\chi 2$ tests for univariate comparisons. -Factors associated with OAT engagement were analyzed using generalized estimating equations (GEEs) to analyze factors associated with OAT -Dependent variable categories: time-variant variables; age group at first OUD diagnosis, gender; time-variant variables, which are rural region, comorbidities, year since OUD dx, ever homeless, income assistance. -alpha of 0.05 used for all tests	-Measurements are based on health data, not in-person direct care. -Rurality based on non-specific HSDA -Internal validity not validated due to PNET records often not accurate, not controlled for. -For PWOUD not engaged in OAT, does not capture harm reduction measures in PC.	not receiving OAT need specific attention. -Equipping pharmacies for OAT dispensing and increasing reimbursement rates for OAT dispensing may encourage collaboration from rural pharmacies. 4% (n=2338) of all PWOUD in BC live in rural regions. -Rural PWOUD experience greater attrition at reach stage of the cascade of care especially in OAT engagement and retention. -PWOUD who are more are younger, male, have other substance use disorders or HCV are more likely to engage on OAT.

Table 2: *Literature Review Matrix – Qualitative Studies*

Author, year, title, journal	Purpose	Research Design/ Context	Data Analysis	Strengths/Limitations	Key Findings/ Recommendations
Wood, P., Opie, C., Tucci, J., Franklin, R. & Anderson, K. (2018). "A lot of people call it liquid handcuffs" – barriers and enablers to opioid replacement therapy in a rural area. *Journal of Substance Use*	To investigate delivery of OAT services from a client perspective in rural communities in Australia.	Qualitative Semi-structured interviews conducted in 2 rural communities conducted in person. One in Victoria and one in New South Wales. N=12 Communities greater than 100km away from a regional centre Adults >18 years old and engaged in OAT (9 methadone and 3 Suboxone)	- NVivo data analysis software used - Data deidentified and coded in NVivo - Data analyzed separately by 2 researchers and compared - Themes organized into barriers and enablers and sub-themes.	Strengths: -Recruitment strategy for participants clearly stated and snowball sampling used among peers. -Interview guide added as an appendix. -Interview questions relate to my research question. "*Has pharmacotherapy change your life in any way?"* and "*Describe the moment that you decided you wanted to enrol into a pharmacotherapy program, what happened at that time?"* -Explicit examples provided from interviews as quotations to support findings and themes. -Participant demographics are clear and relate to local context – increasing external validity. -Study limitations identified, including generalisability to other rural communities due to variability. -Include a mix of patients on methadone and Suboxone. -Two researchers independently analyzed findings and themes compared for consistency.	Themes categorized into barrier and enablers of people accessing OAT. Each them was categorized into sub-themes, including: Barriers 1.) Restrictiveness – the most common reported barrier is clients feeling as though they have no freedom being required to attend a pharmacy daily. 2.) Stigma – perceived stigma by clients from prescribers, pharmacists and community members despite taking OAT. 3.) The medication – issues with dose adjustment and drug-drug interactions causing side effects 4.) The program – design, cost, wait times and daily dosing are barriers in feeling supported or ease of accessibility. Enablers 1.) Social – ability to become stable in

Author, year, title, journal	Purpose	Research Design/ Context	Data Analysis	Strengths/Limitations	Key Findings/ Recommendations
				-Findings add to a deeper understanding of the patients experience on OAT in rural communities. Limitations: -Small sample size. -Authors do not state date range of when interviews conducted. -Does not clearly indicate how research participants were compensated. -Does not clearly state any considerations of researchers/interviewer's role. -Findings similar to findings in other studies. Limited new information produced. -Sample selected only from patients who are currently engaged in OAT, which may limit responses to those who are already able to access OAT. -Recommendations for practice or future research not clearly stated	social factors e.g. finances, relationships, and recovery. 2.) Physical – stopped people from dying. 3.) Mental – OAT helped people feel normal again and improved coping. 4.) The program – daily dosing improved accountability and daily routine. 5.) Drug-use – OAT reduced other drug use 6.) The medication – seeing OAT as a pain medication made it more acceptable -Identifies the treatment paradox of delivery strategies that improve patient outcomes from the prescriber's perspective may contribute to decreased availability and acceptability for patients in rural areas. -Rural barriers identified are similar to other studies addressing rural barriers, regardless of specific community or country.
Saunders, E. C., Moore, S. K., Gardern, T.,	A feasibility study aimed at examining the implementation	Rural Maine, USA	Interview and focus group responses uploaded to Atlas.ti	<u>Strengths</u>:	Findings presented within the KTA domains:

Author, year, title, journal	Purpose	Research Design/ Context	Data Analysis	Strengths/Limitations	Key Findings/ Recommendations
Farkas, S., Marsche, L. A., McLeman, B., Meier, A., Nesin, N., Rotrosen, J., Walsh, O., & McNeely, J. (2019). Screening for substance use in rural primary care: A qualitative study of providers and patients. *Journal of General Internal Medicine*	of substance use screening using electronic health records to deliver validated screening tools by rural PCPs.	Qualitative Semi-structed interviews and focus groups Oct. 2017 – April 2018 Participants PCPs, office assistants, and patients from 3 rural health centres. Study guided by the Knowledge-to-Action framework	(8.0) software for analysis Coding from parent study used to guide adaptation using KTA framework Two researchers individually assess coded transcripts and compared findings Inter-rater reliability measured using Coding Analysis Toolkit and computed Cohen's kappa coefficient. Average kappa coefficient was 0.74 – considered good reliability Data collection supported by using a systematic matrix to organize findings by KTA domains	-Research question focuses on primary prevention strategies -Clearly identifies potential social desirability bias as a study limitation -This study is an ancillary study of two urban sites for implementation of substance use screening -A feasibility study to implement a practical approach to substance use screening in rural primary care -Participants compensated -PCP participants include physicians and NPs -Findings are applicable to rural context <u>Limitations</u>: -Considers all types of substance use, not specific to OUD -Study did not identify patients in focus groups as having lived/living experience with OUD or other substance use. -Efforts to ensure confidentiality of participants not clearly stated -Recruitment of patient participants not clearly stated.	1.) Identifying the problem -Identifies that current substance use screening practices are not systematic and offers recommendations on how to implement SU screening. -Study identifies that screening is necessary for diagnosis and treatment (secondary prevention) of substance use conditions. -Rural PCPs face exacerbated challenges compared to urban settings. 2.) Adapting to the local context -Universal SU screening recommended annually by self-administered, tablet-based format that is reviewed the PCP. 3.) Assessing barriers -Majority of patient participants identified that a trusting relationship with their PCP was the most important aspect when disclosing SU -Few PCPs focused on relationships as a facilitator for patients

Author, year, title, journal	Purpose	Research Design/ Context	Data Analysis	Strengths/Limitations	Key Findings/ Recommendations
				-Rurality not defined. Geographical context of rural study sites not explicitly stated.	-PCPs had fears of a positive finding during SU screening and felt unequipped to address SU -Time was seen as a constraint when addressing Su in a 15 to 30 min appointment -Patients fear that disclosing SU may impact future care, especially pain management. Recommendations: -Study recommends Project ECHO (extension for Community Health Outcomes) to facilitate PCP education -Strengthening PCP-patient relationships and normalizing discussions about SU recommended. -Concerns about privacy and who can access EMR information may be heightened in rural settings – a strong PCP-patient relationship suggested can mitigate these concerns.
Andrilla, C. H. A., Moore, T. E., & Patterson, D. G. (2019). Overcoming barriers to	To better understand strategies of rural physicians when providing medication-assisted	Qualitative semi-structured telephone interviews	-interviews recorded - 36 interviews reached response saturation, and 43 interviews completed.	Strengths: provides insight to perspectives of rural prescribers who are embracing OAT prescribing in PC.	Start-up is solutions-focused by finding a local mentor, starting with less complex patients first, designated specific time to

Author, year, title, journal	Purpose	Research Design/ Context	Data Analysis	Strengths/Limitations	Key Findings/ Recommendations
prescribing buprenorphine for the treatment of opioid use disorder: Recommendations from rural physicians. *The Journal of Rural Health*	treatment (MAT) in rural areas.	n= 43 rural physicians who frequently prescribe BUP for OUD. April 2016 Participants previously identified as rural MDs treating multiple patients on OAT in rural settings from a Rural Health Research Centre survey Participants from across USA	-Chi-square and t-tests for demographic info -Analysis using SAS statistical software version 9.4 Findings: Key themes include I. Getting Started II. Maintaining MAT services III. Complying with DEA requirements IV. Ensuring financial viability V. Combating diversion VI. Access to MH services VII. Overcoming stigma	- clearly states recruitment of rural physicians and obtained a sample from different areas of USA -Provides practical solutions for rural PCPs to implement OAT prescribing. -Sample selected from all rural MDs that prescribe BUP in U.S. -responses consistent across sample. Limitations: Small sample size -some recommendations are inconsistent with clinical guidelines and supported by weak evidence i.e. patient contracts, pill-counts, UDS' or terminating patients if continuing to relapse. -Abstinence-based philosophy present throughout i.e. if a person is not "responding" may need to terminate BUP, and patients' "commitment to recover". - Findings are inconsistent with other literature in terms of what is considered "accessible" OAT care. This is not discussed in the study.	OAT prescribing during week or month. -Advises on using patient contracts to help set boundaries, when contract is violated → stricter treatment plan. - Hub and spoke model, collaborating with more experienced prescribers. -At minimum PCPs should be prescribing OAT to patients already in their practice. - Large number of physicians reported using potentially harmful suggestions that are not supported by evidence e.g. random UDS, pill counts, strict outcomes if contracts broken such as termination from treatment. - Helps identify the paradox of what prescribers consider as supporting OAT practice is often considered harmful and stigmatizing to patients.
Kane, C., Leiner, C., Harless, C., Foley, K. A.,	Seeks to understand the patients experience of	Qualitative	- researchers recorded interviews using writing notes;	Strengths: - Interview guide added as an appendix and is found to	Four factors shaped patient perspectives: 1.) Societal Structure

Author, year, title, journal	Purpose	Research Design/ Context	Data Analysis	Strengths/Limitations	Key Findings/ Recommendations
Fagan, E. B., & Wilson, C. (2020). The value of treating opioid use disorder in family medicine: From the patient perspective. *Journal of American Board of Family Medicine*	receiving office-based opioid treatment with buprenorphine containing medication in a rural primary care setting.	Brief, structured interviews after office visits with PCPs Rural Appalachia U.S. Rural family medicine clinic n=30 PWOUD Jul. to Oct. 2017 Study participant inclusion criteria: PWOUD with at least 3 visits and prescribed BUP over at least 1 month.	interviews not audio recorded -thematic analysis completed independently by 3 authors and compared for reliability Findings: after content saturation, thematic analysis for four main themes decided upon by research team: I. Social structures II. Life before treatment III. Treatment history IV. Experiences in office-based treatment	be applicable to research question - explores research question from the lens of the patient. -Important contributor to the literature. -Findings are consistent with other literature that captures PWLLE experience. -internal validity established through consensus of themes and saturation from 3 researchers - confidentiality of participants clearly stated and researchers did not collect demographic information due to small sample size and small rural community. -study participants paid with a 10$ gift card Limitations: External validity jeopardized due study in non-Medicaid expansion state. -Interviews conducted at only one PC office. -Small sample size. -Authors identified inexperience and coding schema not clearly defined. - -Low incentive/payment of participants (10$)	-External controls that contributed to them feeling shame, instability, lack of personhood. 2.) Life before treatment -Chaotic feeling before being in treatment 3.) Treatment history -Treatment before OBOT, often methadone treatment -Frustration with daily dosing, required to take doses early in the morning, cost, lack of confidentiality 4.) Experience in OBOT -preferred privacy in a primary care setting -opportunity to have expanded treatment of dental care, chronic pain, mental health and hepatitis C treated -PWOUD identify transportation and Medicaid insurance coverage as barriers. -Referrals to other resources that address social determinants of health are seen as helpful. -Integrating wrap-around services into PC seen as a strength by PWOUD. -Confidentiality and not being identified as an

Author, year, title, journal	Purpose	Research Design/ Context	Data Analysis	Strengths/Limitations	Key Findings/ Recommendations
				-PCP only Rx BUP, means PWOUD may needed to transition from MMT.	"OAT client" is a strength in PC.
Richard, E. L., Schalkoff, C. A., Piscalko, H. M., Brook, D. L., Sibley, A. L., Lancaster, K. E., Miller, W. C., & Go, V. F. (2020). "You are not clean until you're not on anything": Perceptions of medication-assisted treatment in rural Appalachia. *International Journal of Drug Policy*	Aims to characterize the perceptions and attitudes towards OAT and the environmental factors that contribute to those views in rural Appalachian Ohio.	In-depth, semi-structured interviews with 34 participants between Feb. and Jul. 2018. Interviews audio-recorded and transcribed. Participants included healthcare professionals, substance use treatment providers, law enforcement agents and judicial officials. Rural Appalachia Ohio, US. A region disproportionately impacted by mortality related to opioid use. Interview candidates a part	-Risk environment framework (REF) by Rhodes (2002) used. -*Dedoose* qualitative analysis software applied -Each author coded transcripts independently and the convened to review and obtain consensus. -Coded excerpts systematically organized using a matrix. -Analysis addressed, identification of how available OAT was in rural counties, compared perceptions of OAT across participants, documented contributions of rural factors to OAT-related stigma and the drug use environment.	<u>Strengths:</u> -Interview candidates were rural partners in supporting health or drug-related services. -Recruitment occurred until thematic saturation. -Interview specifically asked about perceptions and attitudes towards OAT. -informed consent and IRB approval clearly stated. -Environmental factors consider: physical, social, economic, policy -clearly outlines the impacts of fears of diversion, which is applicable to BC rural context <u>Limitations</u>: -Research questions or guide not included in study. -Some contextual factors not applicable to Canadian setting e.g. "pill mills", and BUP regulations. -Difficult to generalize findings to other rural settings or if OAT-stigma occurs beyond the interview sample.	-Three thematic areas: 1.) OAT availability in rural Ohio, 2.) risk environment factors that impact the perceptions of OAT, 3.) stakeholder and community member attitudes and perceptions of OAT -OAT-stigma in rural Ohio occurs frequently, and is accepted socially and integrated into current policies and practices. -OAT-related stigma significantly affects accessibility and acceptability of OAT by patients -Environmental factors that impact OAT-stigma and risky substance use are; conservative culture, history of pill mills driving fears of diversion, and policies that keep OAT access from people involved in the justice system. -Abstinence-related views influences treatment of OUD

Author, year, title, journal	Purpose	Research Design/ Context	Data Analysis	Strengths/Limitations	Key Findings/ Recommendations
		of Ohio Opioid Project, a community partnership to address opioid use.		-Several people refused to be interviewed, which may have minimized the degree of conservative attitudes that exist in rural Ohio sample. -Social desirability bias as sample recruited from opioid community stakeholder group. -No PWUD included in the sample, can cannot infer how OAT-stigma described in the study creates barriers for PWUD.	Recommendations: -social-structural interventions to address the REF. -Requires multi-level approach e.g. social marketing to shift cultural norms, medical campaigns to increase social closeness to people with SUD or mental health issues, media campaigns that look at medical explanations of OUD to reduce blame. -Hosting community events with PWLLE and community members to increase social contact. -Empowering PWLLE to tell their stories. -Advocacy that addresses harmful policies, particularly OAT-related stigma.

Table 3: Literature Review Matrix – Clinical Practice Guideline

Author, title, journal	Year	Purpose	Design/ Method	Stakeholders	Findings	Strengths/ Limitations	Recommendations
Korownyk, C., Perry, D., Ton, J., Kolber, M. R., Garrison, S., Thomas, B., Allan, G.	2019	To support PCPs in managing OUD in primary care based on a shared and	Systematic review of systematic reviews for key questions generated	-13 individuals there represent various PC practice locations in Canada. -2 GPs - 1 rural GP	Recommendations relate to pharmacotherapy interventions and ancillary interventions that can be used to	Strengths: healthcare setting in all topic questions addressed is clearly defined as PC. - All guidance is patient-centred and incorporates shared	-Management of OUD should be performed in PC, which includes BUP and MMT prescribing. -A case finding tool, Prescription Opioid Misuse Index (POMI) can

Author, title, journal	Year	Purpose	Design/ Method	Stakeholders	Findings	Strengths/ Limitations	Recommendations
M., Bateman, C., de Queiroz, R., Kennedy, D., Lamba, W., Marlinga, J., Mogus, T., Nickonchuck, T., Orrantia, E., Reich, K., Wong, N., Dugre, N., Lindbald, A. J. PEER simplified guideline: Managing opioid use disorder in primary care. *Canadian Family Physician.*		informed decision-making approach with patients. Focus is on treatment of uncomplicated OUD in PC setting.	by an expert panel and a peer-review process that included people with lived experience of OUD. Followed principles of the Institute of Medicine's *Clinical Practice Guidelines We Can Trust*	- 2 inner-city family physicians - 1 addiction and pain management family physician - 1psychiatrist - 1 NP - 1 pharmacist - 1 social worker - 1 community support worker - 2 pharmacy project managers	manage uncomplicated OUD in PC. Specifically related to treatment setting, diagnosis of OUD, identifying risk factors of OUD, treatment and on-going management.	decision making. -Supporting systematic review article described methods and included systematic reviews and RCTs. Limitations: inconsistent definitions of OUD across systematic reviews -Risk of attrition bias due to high dropout rates in studies included in systematic review -end-points inconsistent and more often related to positive or negative drug use (UDS) rather than health outcomes.	be used as a screening tool. -DWI is not superior in treatment outcomes compared to unsupervised dosing or "carries" - UDS and patient contracts do not improve treatment outcomes, however can be used to help communicate care to patients. - Lengthy counselling is not superior to brief interventions such as MI.

Table 4: *Literature Review Matrix – Systematic Review*

Author, year, title, journal	Purpose	Review Design/ Methods / Quality	Study Types, Dates & Number	Context	Strengths/ Limitations	Key Findings/ Recommendations
Lister, J. J., Weaver, A., Ellis, J. D., Himle, J. A., & Lederwood, D. (2020). A systematic	This study aims to highlight the state of knowledge around medication treatment for	Systematic literature review of published, peer-reviewed articles	18 studies published between 2004-2018 included in synthesis Studies categorized into	Assessed patient and provider perspectives related to the accessibility, availability and acceptability of medication	Strengths: studies inclusion criteria included both quantitative and qualitative -results from all the included studies are	-Most common consumer-focused barrier is lack of available medication services for OAT in rural communities. -Travel burden in terms of distance, time and cost

Author, year, title, journal	Purpose	Review Design/ Methods / Quality	Study Types, Dates & Number	Context	Strengths/ Limitations	Key Findings/ Recommendations
review of rural-specific barriers to medication treatment for opioid use disorder in the United States. *The American Journal of Drug and Alcohol Abuse.*	rural OUD, identify consumer- and provider-focused barriers to medication treatment to rural OUD, and to demonstrate rural-specific policy, practice and research implications.	PubMed, psychINFO and Web of Science No date restrictions Search term concepts: urbanicity focused term AND keywords related to drug type AND treatment type Inclusion criteria: - Study data collected in USA - Findings related to PWOUD as primary diagnosis - Setting rural or compared rural/urban - Quantitative or qualitative data - Study examined	consumer-focused (n=11) or provider-focused (n=3) or both (n=4) Data extraction analyzed by barrier type: availability, accessibility, or acceptability	treatment for OUD in rural US settings.	clearly displayed in a table. -search terms listed in study; relevant to research question -the first systematic review to examine the literature on rural medication treatment for OUD <u>Limitations:</u> -only studies completed in USA were included in review, which excludes Canadian studies. -rigour of studies included in analysis not clearly described. -no quality analysis of included studies described -none of the studies look at medication treatment outcomes	is a barrier for rural PWOUD -prescribers often consider travel as a barrier and offer OAT less than for urban patients, even when they seen in same location -lack of additional workforce to support concurrent services -Prescribers are concerned about being audited, federal regulations, see OUD as too complex, fear of diversion, mistrust of PWOUD, lack of belief in the efficacy of OAT -rural pts face few options for OAT, most require travel and cost. -rural PCPs feel unprepared to deliver treatment due to lack of supports, resources and time constraints. <u>Recommendations:</u> -rapid expansion of telehealth services to treat PWOUD -policy makers soften regulations, especially those related to telehealth

Author, year, title, journal	Purpose	Review Design/ Methods / Quality	Study Types, Dates & Number	Context	Strengths/ Limitations	Key Findings/ Recommendations
		barriers to OAT				and requiring in-person visits -address capacity barriers for those clinics that are providing OAT -encourage technology assisted counseling services to address psychosocial needs -hire peer support specialists as low-cost axillary staff -co-locate OAT with other services to reduce the need to travel -reimburse transportation expenses or provide ride sharing options -health authorities incentivize addiction medicine training opportunities for PCPs -develop community advisory boards to help coordinate stakeholders and to identify funding opportunities to help build-up resources.