A Guideline for the Clinical Management of Opioid Use Disorder

2023 Update

BRITISH COLUMBIA | Ministry of Health

BRITISH COLUMBIA CENTRE ON SUBSTANCE USE
Networking researchers, educators & care providers

The British Columbia Centre on Substance Use would like to respectfully acknowledge that the land on which we work is the unceded territory of the Coast Salish Peoples, including the traditional territories of xʷməθkwəy̓əm (Musqueam), Sḵwx̱wú7mesh (Squamish), and səl̓ílwətaɬ (Tsleil-Waututh) Nations.

We recognize that the ongoing criminalization, institutionalization, and discrimination against people who use drugs disproportionately harm Indigenous Peoples, and that continuous efforts are needed to dismantle colonial systems of oppression. We are committed to the process of reconciliation with Indigenous Peoples, and recognize that it requires significant and ongoing changes to the health care system.

We hope that this guideline contributes to a system of substance use care that provides safe, respectful, evidence-based care.

A Guideline for the Clinical Management of Opioid Use Disorder

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Target Audience: Physicians, nurses and nurse practitioners, pharmacists, policy makers, health care administrators, allied health care professionals, and all other clinical and non-clinical personnel with and without specialized training in addiction medicine, who are involved in the care and management of individuals, families, and communities affected by opioid use.

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About the British Columbia Centre on Substance Use

The BC Centre on Substance Use (BCCSU) is a provincially networked resource with a mandate to develop, implement and evaluate evidence-based approaches to substance use and addiction. The BCCSU's focus is on three strategic areas including research and evaluation, education and training, and clinical care guidance. With the support of the province of British Columbia, the BCCSU aims to help establish world leading educational, research and public health, and clinical practices across the spectrum of substance use. Although physically located in Vancouver, the BCCSU is a provincially networked resource for researchers, educators and care providers as well as people who use substances, family advocates, support groups and the recovery community.

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Disclaimer for Health Care Providers

The recommendations in this guideline represent the view of the provincial guideline committee, arrived at after careful consideration of the available scientific evidence and external expert peer review. When exercising clinical judgment in the treatment of opioid use disorder, health care professionals are expected to take this guideline fully into account, alongside the individual needs, preferences, and values of patients and their families, and in light of their duties to adhere to the fundamental principles and values as outlined in the Canadian Medical Association Code of Ethics, especially compassion, beneficence, non-maleficence, respect for persons, justice and accountability, as well as the required standards for good clinical practice of the College of Physicians and Surgeons of BC or the British Columbia College of Nurses and Midwives (BCCNM) and any other relevant governing bodies. The application of the recommendations in this guideline does not override the responsibility of health care professionals to make decisions appropriate to the circumstances of an individual patient, in consultation with that patient and their guardian(s) or family members, and, when appropriate, external experts (e.g., specialty consultation). Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

Legal Disclaimer

While the individuals and groups involved in the production of this document have made every effort to ensure the accuracy of the information contained in this treatment guideline, please note that the information is provided "as is" and that the Ministry of Health (MoH), Ministry of Mental Health and Addictions (MMHA), and the BCCSU make no representation or warranty of any kind, either expressed or implied, as to the accuracy of the information or the fitness of the information for any particular use. To the fullest extent possible under applicable law, the MoH, MMHA, and the BCCSU disclaim and will not be bound by any express, implied, or statutory representation or warranty (including, without limitation, representations or warranties of title or non-infringement).

The Guideline is intended to give an understanding of a clinical problem, and outline one or more preferred approaches to the investigation and management of the problem. The Guideline is not intended as a substitute for the advice or professional judgment of a health care professional, nor is it intended to be the only approach to the management of a clinical problem. We cannot respond to patients or patient advocates requesting advice on issues related to medical conditions. If you need medical advice, please contact a health care professional.

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EXECUTIVE SUMMARY

On April 14, 2016, the Provincial Health Officer declared a public health emergency under the Public Health Act, following an unprecedented increase in overdose-related harms due to an unpredictable, highly toxic unregulated drug supply. In response to this emergency, the Ministry of Health and the BC Centre on Substance Use (BCCSU) prioritized the development and publication of the first edition of the provincial *Guideline for the Clinical Management of Opioid Use Disorder*, which was published in February 2017 and officially adopted as the provincial standard in June 2017. Since its publication, the guideline and aligned education and implementation efforts have had an instrumental role in improving access to evidence-based treatment for individuals with opioid use disorder (OUD) in BC by providing comprehensive clinical care guidance to health care providers across the OUD care continuum in the province.

Despite significant advancements in the province's system of substance use care, drug poisoning involving opioids continues to be the leading cause of unnatural death in British Columbia, surpassing homicides, suicides, and motor vehicle collisions combined. The primary driver of this ongoing crisis is the rapidly growing toxicity and unpredictability of illegally manufactured and distributed drugs. Higher fentanyl concentrations and novel, dangerous combinations of drugs (e.g., benzodiazepines and fentanyl) have been continually detected in multiple drug surveillance data sources across the province.

In response to the escalating drug toxicity crisis, which was also exacerbated by the COVID-19 pandemic, evidence and clinical experience have continued to develop, necessitating updated clinical guidance. The second edition of the *Guideline for the Clinical Management of Opioid Use Disorder* is intended to reflect this evolution and ensure that health care providers have access to updated clinical guidance aligned with the best available evidence on interventions across the continuum of OUD care. Accordingly, this updated guideline edition includes information on oral and injectable opioid agonist treatment, antagonist pharmacotherapies, withdrawal management strategies, psychosocial interventions including bed-based treatment programs, harm reduction services and programs, and peer-based support.

In aggregate, the updates in the present edition of the guideline have been developed to ensure that OUD care is accessible and flexible enough to sustainably engage and retain patients in evidence-based care and meet the diverse and evolving needs of patients. To support a system of OUD care with the capacity to effectively accommodate diverse patient populations, the guidance provided in the second edition begins with a comprehensive discussion of the foundational principles and values of care for people with substance use disorder, including:

- Patient-centred care
- Awareness of social determinants of health
- Indigenous cultural safety and humility
- Anti-racist practice
- Trauma- and violence-informed practice
- Care centred on self-defined recovery and wellness

- Harm reduction-oriented care
- Integrated continuum of care
- Comprehensive health management
- Family and social circle involvement

In keeping with the central principle of patient-centred care, one of the overarching clinical changes in this second edition guideline is the move away from ranking opioid agonist treatment (OAT) medications as first-line, second-line, and third-line options. Instead, this guideline recommends an individually tailored process whereby clinicians discuss the risks and benefits of all three oral OAT options (i.e., buprenorphine/naloxone, methadone, and slow-release oral morphine) with patients and collaboratively select a medication that aligns with their preferences, treatment history, and other individual circumstances. This change is not intended to equate OAT medications in terms of safety and efficacy evidence, but to ensure that the full range of available evidence-based medications is considered to appropriately meet specific patient needs and preferences with reference.

Other key added content and clinical updates informed by new evidence and accumulating clinical experience include:

- Modified maximum starting doses and titration protocols for OAT medication to address the needs of individuals with higher opioid tolerance (e.g., individuals who use fentanyl)
- Low-dose induction guidance for buprenorphine/naloxone to eliminate the need for a period of withdrawal prior to medication initiation
- Guidance on the provision of monthly extended-release buprenorphine as a less intensive, more flexible option for patients who are stable on sublingual buprenorphine/naloxone
- Guidance on emergency department initiation of buprenorphine/naloxone
- Guidance on initiation and continuing care for inpatient and acute care
- Modified, more flexible guidance for addressing missed doses
- Revised, more flexible protocols for providing take-home doses of full agonist medications
- Incorporation of injectable OAT (iOAT) as an integrated component of the continuum of OUD care

A summary table of key clinical recommendations is presented below.

SUMMARY OF RECOMMENDATIONS

	Recommendation	Quality of evidence	Strength of recommendation[a]	Relevant evidence review sections
	Pharmacological Treatment			
1	Adults with opioid use disorder should be offered opioid agonist treatment as the standard of care.	High	Strong	• Section 3.2 • Section 3.2.ix (Remarks)
2	Prescribers should work with each patient to determine which of the following opioid agonist treatment medications is most appropriate based on the patient's circumstances, goals, and previous treatment experiences. • Buprenorphine/naloxone[b] • Methadone • Slow-release oral morphine	High	Strong	• Section 3.2.iv • Section 3.2.ix (Remarks) • Section 3.2.i
		High	Strong	• Section 3.2.ii
		Moderate	Strong	• Section 3.2.iii
3	Transition between opioid agonist treatment medications should be facilitated if indicated by clinical circumstances or patient preference.	Low	Strong	• Section 3.2.iv • Section 3.2.ix (Remarks)
4	Patients stable on 8mg–24mg sublingual buprenorphine/ naloxone may be offered the monthly extended-	Low	Strong	• Section 3.2.i

[a] GRADE criteria were used to ascertain and describe the quality of evidence (possible categories include: high, moderate, low, very low) and strength of recommendation. Possible designations for strength of recommendation include strong and Weak (Conditional).

- A strong recommendation implies that all patients in a specific situation would want the recommended course of action and that only a small proportion of the general patient population would not.
- A Weak (Conditional) recommendation suggests that most patients in specific situations would want the recommended course of action but many would not. In the context of this guideline, a conditional recommendation would be applicable in specific situations where factors such as strong patient preference, limiting circumstances, or contraindications would preclude the use of other generally preferable options.

Please refer to Appendix 1 for information on how the GRADE approach was applied in formulating guideline recommendations.

[b] In the absence of patient preference or other patient-specific factors that would favour other medications, buprenorphine/naloxone may be considered as the favourable option due to its superior safety profile.

	release formulation of buprenorphine if indicated by patient preference or circumstances.			(Extended-release buprenorphine) • Section 3.2.ix (Remarks)
5	Injectable opioid agonist treatment with diacetylmorphine or hydromorphone should be considered for adults with severe opioid use disorder and ongoing unregulated injection opioid use who have not benefitted from, or have declined, oral options for opioid agonist treatment.	Moderate	Weak (Conditional)	• Section 3.2.vii • Section 3.2.ix (Remarks)
6	Opioid agonist treatment should be viewed as an open-ended treatment. However, if a patient wishes to discontinue medication following a sustained period of stability on opioid agonist treatment (12 months or more), a slow taper should be offered.	Moderate	Strong	• Section 3.2.viii • Section 3.2.ix (Remarks)
7	For adults who choose to discontinue OAT, a relapse prevention plan should be collaboratively developed and implemented after a discussion of both pharmacological and non-pharmacological options.	Low	Strong	• Section 3.2.viii • Section 3.2.ix (Remarks)
8	Oral naltrexone is not a recommended treatment for adults with opioid use disorder. However, it may be offered to individuals who have declined or discontinued OAT and would prefer non-opioid treatment.	Low	Weak (Conditional)	• Section 3.3.i • Section 3.3.iii (Remarks)
9	While extended-release naltrexone is not currently available in Canada, it is an evidence-based treatment that may be considered for patients with opioid use disorder who are not interested in OAT.	Moderate	Weak (Conditional)	• Section 3.3.ii • Section 3.3.iii (Remarks)

	Non-Pharmacological Treatment			
10	Withdrawal management alone (including rapid opioid agonist tapers) without transition to opioid agonist treatment is not recommended.	Moderate	Strong	• Section 3.4 • Section 3.4.vi (Remarks)
11	If the patient chooses to pursue withdrawal management (e.g., slow opioid agonist taper), this should be conducted in an outpatient setting, followed by a collaboratively developed relapse prevention plan and referral to long-term psychosocial treatment and support.	Moderate	Strong	• Sections 3.4.iv–3.4.vi
12	Psychosocial treatment interventions and supports should be routinely offered to adults with opioid use disorder, in conjunction with pharmacological treatment.	Moderate	Strong	• Section 3.5 (3.5.i–3.5.iii)
	Harm Reduction			
13	Conversations about safer drug use, take-home naloxone, and referral to other harm reduction services should be routinely offered as part of standard care for individuals with opioid use disorder.	Moderate	Strong	• Section 3.7 (3.7.i–3.7vi)

1.0 INTRODUCTION

1.1 Background and Rationale

Opioids produce feelings of euphoria and general well-being and have been used throughout history to treat pain and a variety of different ailments.[2] In the 21st century, opioids are available as regulated, pharmaceutical medications and in unregulated non-medical forms (e.g., heroin), which have become increasingly adulterated with highly potent opioids, such as fentanyl, over time.[3] Use of opioids falls on a spectrum, from non-harmful (e.g., temporary use for pain management) to stable long-term use to uncontrolled use leading to serious health and social concerns (e.g., opioid use disorder). Movement along this spectrum can occur in either direction over the course of time and a variety of complex individual and societal factors can influence whether an individual's use produces harmful consequences.

Opioid use disorder (OUD) is best conceptualized as a chronic relapsing condition; though associated with elevated rates of morbidity and mortality, individuals with OUD have the potential for sustained long-term remission with appropriate treatment and support. Opioid use disorder is characterized by craving, uncontrolled use, and continued use despite significant consequences.[4] Most individuals also experience withdrawal symptoms when opioids are discontinued. Canadian OUD prevalence estimates are lacking. However, national survey data found that approximately 3.7 million (12.7%) Canadians used an opioid pain medication in 2018, with approximately 10% of those (351,000 Canadians) reporting problematic use, defined as using in larger amounts or more frequently than prescribed, using to get high or for reasons other than pain management, or tampering with the medication before using it.[5] Data from the British Columbia OUD Cohort[c] indicates that there was a 19.2% increase in diagnosed opioid use disorder between September 2018 and September 2020. It should be noted, however, that the factors underlying this increase are not well understood; for example, improvements in screening and documentation practices may have contributed to an increase in the number of individuals identified, but the extent of this contribution is unclear.

Opioid poisoning continues to be the leading cause of unnatural death in British Columbia, surpassing homicides, suicides, and motor vehicle collisions combined.[6] At least 32,632 Canadians died from an opioid overdose between January 2016 and June 2022.[7] Although every part of Canada has been impacted by the drug poisoning crisis, BC has seen both the highest number and the highest rate (41.3/100,000 in January–September 2021) of toxic drug deaths.[8,9] Since 2016, when a public health emergency was declared in BC, to 2022, at least 9,760 British Columbians have died from opioid toxicity.[6] Within BC, Northern Health Authority had the highest rate (58/100,000), while Fraser Health Authority had the highest number of toxic drug deaths (236 deaths) in 2022.[9,10] At the population level, BC's life expectancy at birth, which had increased by almost 3 years

[c] The opioid use disorder (OUD) cohort is an administrative database that captures all BC residents with an indication of OUD since 1996. The cohort is identified using linked population-level administrative databases, capturing provincial health insurance plan registration, physician billing records, hospitalizations, medication dispensations, emergency department visits, perinatal services for all provincial births, mortality, and cause of death.

from 2000 to 2013 (80.27 to 83.02 years of age), declined by 0.38 years from 2014 to 2016 as a direct consequence of drug toxicity deaths.[11] In 2020 alone, an estimated almost 70,000 potential years of life were lost due to unregulated drug toxicity deaths in BC, with the average age at death being 43 years old.[12] The alarming rise in toxic drug deaths has been accompanied by a host of other drug-related harms affecting communities across the province, including brain injuries from non-fatal drug poisonings, which have contributed to morbidity and mortality, as well as significant costs to the health care system.[13]

The primary driver of this crisis is the growing toxicity and unpredictability of illegally-manufactured and -distributed drugs, such as fentanyl and other highly potent synthetic opioids. While unregulated opioids are often intentionally purchased, their potency and composition are largely unknown and may differ with each purchase. Additionally, non-opioid drugs are increasingly adulterated or contaminated with fentanyl or other synthetic opioids.[14] Higher fentanyl concentrations and an increase in unexpected, dangerous combinations of drugs (e.g., benzodiazepines and fentanyl) have been observed across multiple drug surveillance data sources across the province.[d]

Fentanyl was detected in approximately 86% of overdose deaths in 2021 and 82% of toxic drug deaths in 2022, which represent substantial increases from 2012 when 3% of deaths involved fentanyl.[7] Carfentanil, a highly potent synthetic opioid used as anesthesia in large animals,[15,16] was detected in 192 drug toxicity deaths in 2021, and 126 suspected drug toxicity deaths in 2022. [7] An investigation of whether drug-related deaths between 2015 and 2017 involved prescribed or non-prescribed medications revealed that 83% of deaths involved non-prescribed opioids, with fentanyl or its analogues being the most prevalent type of opioid detected (found in 79% of deaths related to non-prescribed opioids).[17] Contamination of street drugs is ongoing and progressive, with new agents such as benzodiazepine analogues, and xylazine found in substances sold as opioids.[18]

In response to the ongoing and evolving drug toxicity crisis in which the drug supply continues to intensify in toxicity, clinicians, and researchers have pioneered innovative treatment and research protocols with the intention of improving patients' experiences of initiation and stabilization on opioid agonist treatment (OAT). Over the five years that have passed since the 2017 publication of *A Guideline for the Clinical Management of Opioid Use Disorder*, evidence, best practices, and clinical expertise have also evolved. The new 2023 guideline will reflect this evolution and ensure health care providers have access to updated recommendations and clinical guidance aligned to the best evidence on the full continuum of care for opioid use disorder.

1.2 Purpose and Scope

This document aims to update BC's first provincial guideline for the treatment of OUD, published in 2017. The original provincial guideline was the first of its kind to recommend buprenorphine/naloxone as first-line

[d] It should be noted that the existing evidence on treating opioid use disorder was developed in the context of wide-spread heroin use and availability, not the more potent fentanyl and analogues that are now ubiquitous in the drug supply in BC and elsewhere. Clinical experience indicates that best practices (e.g., dosing, titration) derived from treating individuals who use heroin are often insufficient for individuals with extremely high opioid tolerance from fentanyl.

treatment for OUD, slow-release oral morphine as an alternative treatment option for opioid use disorder, and include harm reduction services as standard of care. In addition to revised clinical recommendations informed by updated literature reviews, this edition contains principles of care, considerations for providing care to specific populations, and updated dosing and titration protocols that reflect new evidence and accumulating clinical experience.

The objective of this guideline is to support clinicians in offering the full continuum of care to treat individuals with OUD, utilizing evidence-based recommendations and clinical guidance. This guideline includes information on oral and injectable[e] opioid agonist treatments, antagonist pharmacotherapies, withdrawal management strategies, psychosocial interventions, harm reduction services and programs, and peer-based support.

Primary prevention, which includes safe prescribing of prescription opioids, is also outside the scope of this guideline. Readers are encouraged to consult the College of Physicians and Surgeons of BC's Professional Standards and Guidelines for Safe Prescribing of Drugs with Potential for Misuse/Diversion and McMaster University's *2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain*.

1.2.i Intended Audience

This guideline is intended to be used by physicians, pharmacists, nurse practitioners, nurse prescribers, and nursing and allied healthcare professionals with and without specialized training in addiction medicine. This guideline also serves as a resource for patients and their loved ones, to support treatment and wellness advocacy as well as promote system-level quality improvement. In addition, this guideline is intended to be a resource for policy makers and healthcare administrators in the development of strategies and programs to best address unmet addiction care needs within British Columbia in an evidence-based, cost-effective manner.

Additional and complementary documents for people with lived and living experience of opioid use and their loved ones have been published by the BCCSU since the release of the 2017 OUD guideline. These include From Grief to Action's *Coping Kit* (which was updated through a partnership of From Grief to Action, the Canadian Mental Health Association—BC Division, and the BCCSU); *Gone Too Soon*, for families and friends who have lost a loved one to drug-related harm; and *Opioids: A Survivor's Guide*, written by and for individuals on opioid agonist treatment.

1.2.ii Patient Populations and Settings

[e] This guideline discusses injectable opioid agonist treatment as a part of the standard continuum of OUD treatment and discusses general eligibility considerations for this treatment in reference to available literature. For comprehensive clinical guidance on providing iOAT, both as a standalone treatment and in conjunction with co-prescribed oral OAT, refer to BCCSU's *Guidance for Injectable Opioid Agonist Treatment for Opioid Use Disorder* or CRISM's *National Injectable Opioid Agonist Treatment Clinical Guideline* and *National Injectable Opioid Agonist Treatment Operational Guidance*.

The recommendations made in this guideline are applicable to the general adult patient population. Other clinical guidelines and supplementary resources have been developed to guide best practices in specific populations and settings. These include:

- *Treatment of Opioid Use Disorder During Pregnancy—Guideline Supplement*
- *Treatment of Opioid Use Disorder for Youth—Guideline Supplement*
- *Urine Drug Testing in Patients Prescribed Opioid Agonist Treatment—Breakout Resource*
- *Opioid Use Disorder: Diagnosis and Management in Primary Care* (developed in partnership with the Guidelines and Protocols Advisory Committee)
- *Guidance for Injectable Opioid Agonist Treatment for Opioid Use Disorder*
- *National Injectable Opioid Agonist Treatment Clinical Guideline*

Specific populations and communities, including Indigenous peoples, 2S/LGBTQQIA+[f] individuals, individuals experiencing homelessness, and rural and remote populations, may have unique health needs or circumstances due to biological, societal, or resource-related factors. A brief overview of additional considerations for providing care to these populations, including links to resources, has been included in Section 4.0. Guidance on co-occurring substance use and concurrent mental health issues can be found in Appendix 7: Continuing Care.

1.2.iii Guideline Uptake

As part of the clinical guideline dissemination strategy, the BCCSU initiated the Opioid Use Disorder Seminar Series—a series of in-person and virtual education events, offered within all health authorities and often co-hosted with local Divisions of Family Practice—to provide an update on the opioid overdose crisis and review the key recommendations from the provincial guideline. These sessions provided opportunities for health care providers to ask an addiction medicine expert their questions, to bring forward clinical cases for discussion, and to build local networks to support one another in this important work. To date, the BCCSU has offered 82 seminars—reaching 3,179 clinicians since April 2017. In addition, in June 2017 the BCCSU assumed responsibility for the education and training pathways for prescribers of opioid use disorder treatment in BC and created the Provincial Opioid Addiction Treatment Support Program to improve knowledge and skills in managing OUD among prescribers and increase provincial capacity for providing OAT. This work has translated to more than 1,490 new authorizations for prescribers to provide OAT between July 2017 and July 2023.

[f] The acronym 2S/LGBTQQIA+ has been used in this guideline to describe Two-Spirit, lesbian, gay, bisexual, transgender, queer, and other gender and sexually diverse individuals. This guideline has adopted the practice of placing "2S" for "Two-Spirit" at the beginning of this acronym to acknowledge Indigenous ways of knowing gender and sexuality and the long history of gender and sexual diversity in Indigenous cultures. It is important to note that not all Indigenous LGBTQ+ people identify as Two-Spirit, and that not all Indigenous cultures perceive Two-Spirit identities in the same way. Asking patients how they prefer to identify themselves rather than assuming their gender identity or sexuality is an important component of person-centred care.

1.3 Methods

A brief overview of methods used to conduct the structured review of the literature, develop recommendations for clinical practice, and assess quality of evidence and strength for each recommendation can be found in Appendix 1.

2.0 PRINCIPLES OF CARE

This section outlines several overarching principles of care, which apply to all recommendations and clinical care guidance offered in this guideline and, more broadly, to establishing positive partnerships with patients and families experiencing opioid-related harms. The principles of care are intended to serve as a general framework to support clinicians, care teams, and programs in the integration of care for OUD in their clinical practice. Clinicians and care teams are encouraged to review and adapt these principles of care as needed to fit their local context and resources available.

The principles of care identified here should not be considered an exhaustive list. There may be additional factors clinicians should take into account depending on practice setting, or when working with specific patients, families, communities, and populations (also see Section 4.0: Specific Populations).

Table 1. Summary of Principles of Care

1.	Patient-centred Care: Clinicians should strive to provide care that is respectful of the unique needs, values, and preferences of each patient. Patients should be empowered as experts in their own care.
2.	Social Determinants of Health: Opioid use disorder should be viewed within a larger societal framework that is shaped by inequities in the social determinants of health. Where appropriate, clinicians should aim to address disparities in the socioeconomic determinants of health by connecting patients with resources that meet these needs (e.g., housing, food/nutrition, financial assistance, employment).
3.	Indigenous Cultural Safety and Humility: Clinicians should make a meaningful commitment to providing culturally safe care and practicing cultural humility in order to establish safe and positive partnerships with Indigenous patients, families, and communities.
4.	Anti-racist Practices: Confronting and interrogating racist structures in health care and building awareness of one's own position within oppressive systems can help improve care engagement and health outcomes for communities facing racism.
5.	Trauma- and Violence-informed Practice: Clinicians should be familiar with and incorporate the principles of trauma- and violence-informed practice in the care and clinical management of patients with OUD with the goal of creating a safe and respectful environment that minimizes the potential for harm and re-traumatization.
6.	Recovery and Self-defined Wellness: Clinicians should validate patients' goals in OUD treatment and care, which may include recovery and/or self-defined wellness.
7.	Harm Reduction: A harm reduction-oriented approach to OUD care involves the acknowledgement and support of any steps taken by patients to improve their health and well-being. Clinicians should respect patients' decisions and goals concerning substance use, and promote strategies to minimize opioid-related harms.
8.	Integrated Continuum of Care: Opioid use disorder is understood to be a chronic, relapsing and remitting condition. This guideline supports the use of a stepped and integrated approach, in which treatment options are continually adjusted to meet changing patient needs, circumstances, and goals.
9.	Comprehensive Health Management: Opioid use disorder should be managed within a broader framework of comprehensive health care and support, including routine and ongoing medical, mental health, and psychosocial assessments.
10.	Family and Social Circle Involvement in Care: Family and social circle[g] involvement in treatment planning and decision-making should be encouraged whenever possible, and when deemed appropriate by the patient and their care team.

[g] This guideline uses the term "family" to encompass all relations that are important to the patient within their social circle, which may include romantic partners, close friends, and other people of significance who may or may not be legally recognized as family.

2.1 Patient-Centred Care

Patient-centred care is about meaningful partnership between the patient and provider. It takes into account the unique needs and preferences of each patient, and aims to and empower patients as experts in their own care.[19] Patient-centred care encompasses a variety of approaches that attempt to account for power imbalances and experiences of marginalization.

Research suggests that incorporating patient-centred approaches into the clinical management of substance use disorders can improve retention in care, treatment satisfaction, and health outcomes.[20-22] Practical strategies for incorporating patient-centred care in the clinical management of OUD include[19]:

- Collaboratively developing treatment plans
- Encouraging patients to set treatment goals that are meaningful to them (rather than imposing goals on them)
- Using a shared decision-making framework to select treatment options or interventions
- Being open to and respectful of patient agency and choice

Clinicians, care teams, and staff should be aware of and actively work to reduce the stigma experienced by individuals with OUD, including awareness of the language they use in clinical encounters and its potential to stigmatize individuals who use opioids and other substances. Clinicians and staff involved in substance use care should strive at all times to use "person-first" language and current medical terminology (e.g., person with an opioid use disorder) when interacting with patients, families, colleagues, health care professionals, and staff.[23]

While patients may choose to refer to themselves and their health conditions using language that they are most comfortable with, clinicians, other health care professionals, and non-clinical staff should avoid using non-diagnostic, outdated, or "slang" terms (e.g., "junkie", "addict", "opioid abuse", "clean/dirty") in conversation and when charting. Use of such terms by health care providers has been shown to be stigmatizing to some patients[24,25] and to influence the behaviors of subsequent clinicians when included in a medical record.[26] Stigma—both experienced and anticipated—has been associated with a reduced likelihood of accessing and staying in care[27-29] as well as receiving worse care.[26] Clinicians are encouraged to review *Respectful Language And Stigma: Regarding People Who Use Substances*, a resource jointly developed by the BC Centre for Disease Control, the Provincial Health Services Authority, and Toward the Heart, for more information.

2.1.i Reducing Barriers and Increasing Flexibility

Patient-centred care includes providing access to services and treatments without undue barriers. Commonly reported barriers to OUD treatment include lack of control or flexibility with treatment and difficulty with access.[30] Care teams should strive to assess a patient's needs and ability to access treatment and facilitate low-barrier options. Furthermore, events over recent years, including the COVID-19 pandemic and climate emergency-related phenomena (e.g., wildfire evacuations, weather warnings due to extreme heat, flooding), have demonstrated the necessity and feasibility of clinical flexibility that prioritizes patient safety and continuity of

care. Patient-centred care involves adapting, as needed, during local or global emergencies and disruptions, to ensure that patients can continue to access life-saving treatment without putting their health at risk (e.g., waiting in extreme heat) or facing unreasonable barriers. Examples of adaptations may include extended carries; reduced urine drug testing; reduced clinic appointments or shifting toward virtual care; facilitating transfer of prescriptions to a new pharmacy; or engaging other health care providers to support medication management. Prescribers are encouraged to consult the 24/7 Line or RACE app if they need support to adapt care plans in response to states of emergency or other disruptive events. Exceptions to standard clinical care should be documented, including the rationale, patient discussion, and patient consent.

2.2 Social Determinants of Health

Social determinants of health can be understood as "the broad range of personal, social, economic, and environmental factors that determine individual and population health."[31] At a population level, this can be understood as the quantity and quality of resources a society makes available to all of its members, which include, but are not limited to: conditions of childhood; access to income; education and literacy; food, housing, and employment; working conditions; and health and social services.[31,32] Distribution of these resources tends to occur along a social gradient,[33] and is shaped by factors such as socioeconomic class and income; sex, gender identity, and sexuality; Indigeneity; race and ethnicity; citizenship status; geographic location (e.g., urban vs. rural or remote); and disability status.[32,34] These factors are often interrelated and intersectional—meaning that people occupy multiple social positions by nature of their unique identity, and that these factors interact with and impact each other.[35] People who belong to marginalized groups and/or occupy the lowest socioeconomic classes experience the most significant barriers to accessing resources, and, in turn, have the poorest health outcomes.[34]

Opioid use and OUD should be viewed within this larger social context. Higher prevalence rates of substance use and substance use disorders are observed among individuals who report adverse early childhood experiences,[36] lower socioeconomic status, identify as a racial or ethnic minority, or identify as sexual or gender minorities.[37,38]

Clinicians, care teams, and staff should have an understanding of how the unequal distribution of power, opportunity, and resources in Canadian society impacts the social determinants of health for individuals.[34] Clinicians providing care to individuals, groups, and those communities at risk of discrimination and marginalization should endeavour to identify and remove barriers to accessing care. EQUIP Health Care provides several resources as well as a Health Equity Toolkit to support health care providers to implement equity-oriented care into primary health care practice. Additionally, clinicians should aim to address inequities that may exist related to the social determinants of health by connecting patients with resources to meet their social and survival needs (e.g., housing, food/nutrition, financial assistance, employment).

2.3 Indigenous Cultural Safety and Humility

Abundant evidence has demonstrated that historic and present-day colonialism has disrupted the health and well-being of Indigenous peoples in Canada. Decades of federal policies with the sole purpose of eradicating Indigenous identities, families, communities, culture, and traditional ways of life have resulted in intergenerational trauma, racism, and discrimination.[39-41] These factors manifest as an overall increased risk of premature morbidity and mortality among Indigenous peoples in Canada relative to non-Indigenous people in Canada.[42-44] Epidemiological data that show higher prevalence rates of high-risk substance use, substance use disorders, and substance-related harms among Indigenous peoples[42,45] must also be interpreted within this broader context. More specifically, it is emphasized that Indigenous peoples are not, by nature of their genetic background and cultural identity, a "high-risk" population; rather, the settler state's approach of erasure, displacement, and assimilation of Indigenous peoples has led to significant health and social inequities and created conditions where some individuals use alcohol and other substances to cope.[46,47] Racism and harmful stereotypes about Indigenous peoples, particularly around substance use,[48-50] persist within the health care system in BC and can act as a deterrent to seeking out and remaining engaged in care in this population.[51-54]

If the mainstream health care system is to be effective in addressing health and social inequities experienced by Indigenous peoples, health care providers must commit to the principles of culturally safe and anti-racist care and exercise cultural humility.[55] Cultural safety is achieved when the person receiving care or accessing a service feels safe and perceives their environment as a space free from racism and discrimination. Achieving this outcome depends on respectful engagement that seeks to address power imbalances inherent in the health care system. Cultural humility is a self-reflection process undertaken to understand personal and systemic biases and to develop and maintain respectful processes and relationships based on mutual trust; it requires humbly acknowledging oneself as a learner when attempting to understand another person's experience.[h] These processes move beyond the concept of cultural sensitivity[i] to consider how social and historical contexts, institutional discrimination, structural and interpersonal power imbalances, and past, current, and ongoing colonization shape health and health care experiences of Indigenous peoples.[56] It requires health care providers to be knowledgeable of the colonial history of Canada and the roots of historical, ongoing, and intergenerational trauma among Indigenous peoples, and to practice cultural humility: to be continually self-reflective of personal biases and aware of their position of power and the effects that this power dynamic may have on their Indigenous patients.[57]

Specific approaches and understandings have been identified as necessary to provide culturally safe and appropriate care to Indigenous peoples,[58] these include:

[h] Definitions adapted from the First Nations Health Authority.

[i] Cultural sensitivity respects cultural differences and involves communicating and behaving in ways that are considered polite and respectful by the person of the other culture.

- Understanding the importance of local history and the lasting and multigenerational impacts of colonization and the residential school system
- Examining, understanding, and acknowledging how health care providers' own values impact the healthcare environment and healthcare encounters
- Understanding health as encompassing physical, mental, emotional, and spiritual wellness
- Understanding the impacts of disparities in the social determinants of health
- Respecting local traditions, traditional beliefs, and healing practices, and offering to incorporate them in the patient's care plan when available and appropriate
- Recognizing and respecting differences in communication styles, which may be influenced by power imbalances as well as culturally-specific behaviours[j]
- Understanding that whole communities may be impacted by what happens to one community member, that the family unit may be a large, extended family, and that hostile healthcare experiences can influence entire communities' healthcare seeking attitudes
- Understanding that cultural healing practices may require that families be involved in the care of clients
- Approaching patient relationships with respectful curiosity
- Challenging personal assumptions, being flexible, and being open to changing how things are commonly done
- Recognizing and accommodating the need for a translator for those whose primary language is not English

As a starting point, all health care professionals and staff should undertake Indigenous cultural safety training to improve their ability to establish safe, positive partnerships with Indigenous patients and families. Care teams and staff are also encouraged to familiarize themselves with the Truth and Reconciliation Commission Reports, specifically the Calls to Action, which outline necessary actions to address the legacy of colonialism in a range of domains including health care. There are several Indigenous cultural safety training programs available to health care providers and staff in BC. PHSA hosts an online Indigenous Cultural Safety Learning Series in partnership with the Southwest Ontario Aboriginal Health Access Centre, which is guided by an advisory council of national and international Indigenous and non-Indigenous leaders. Information on this monthly webinar can be found here: http://www.icscollaborative.com/. First Nations Health Authority and the BC Patient Safety & Quality Council offer a cultural safety and cultural humility webinar series, in addition to several policies and resources that can be accessed on the FNHA website. Care providers are also encouraged to seek out resources that may be available in local health authorities. For example, the Vancouver Coastal Health (VCH) Indigenous Health program offers Foundational Indigenous Cultural Safety (ICS) Training, an in-person interactive and self-reflective group training session, to VCH staff. Additional resources and guidance on working with Indigenous populations can be found in Section 4.0.

[j] For example, less eye contact, long silences, and not answering direct questions or replying with a story or longer narrative response may be the norm for some Indigenous peoples compared to non-Indigenous populations.

2.4 Anti-racist Practices in Substance Use Care

Research has shown that members of communities that face racism are disproportionately affected by the harms associated with substance use, including criminal justice involvement, morbidity, and mortality.[59] This disparity in health and social outcomes can be directly attributed to institutional racism.[59-61] For example, although available evidence suggests similar rates of unregulated substance use among black and white individuals, black individuals are dramatically more likely to be arrested and incarcerated for drug-related charges.[59] Individuals who face racism also face more barriers to substance use treatment access, lower retention, and reduced satisfaction compared to their white counterparts, due to the experience of discrimination within the health care system.[59-61]

The implementation of an anti-racist framework for substance use care can help improve care engagement and health outcomes for populations that experience racism and other forms of marginalization.[62] By definition, anti-racism is a process of confronting and interrogating racist structures which persist within current sociocultural institutions, including the health care system.[62,63] Anti-racist practices require individuals to build awareness of their own position and role within these oppressive constructs, critically revising their own values, and actively challenging norms, policies, and practices that marginalize specific communities on the basis of race.[62,63]

Some examples of inclusive, anti-racist policies and program development considerations include:[64]

- Seek pre-implementation consultation from members of racially and ethnically diverse communities that the program serves
- Prioritize racial and ethnic diversity and equity in employee hiring and retention practices
- Mandate anti-racism training among all staff
- Build partnerships with community organizations that support members of communities that face racism

Some day-to-day service elements that support members of communities that face racism may include: [64,65]

- Provide interpretation and translation services to clients for whom language is a barrier to equitable program participation
- Ensure that patient-facing materials are written in the client's language, and at an appropriately accessible reading level
- Include a strong outreach component, as people who are new to Canada, or to a given province or territory, may be unaware of the types of substance use support services available or how to access them
- Provide space and other necessities for religious or cultural practices
- Establish a confidential and clearly-defined and communicated procedure for clients and employees to safely report racial discrimination

2.5 Trauma- and Violence-informed Practice

In the context of opioid use, research has shown that the prevalence of OUD is significantly higher among individuals who have been diagnosed with post-traumatic stress disorder[66] and that those who have been diagnosed with concurrent post-traumatic stress disorder and OUD experience a greater severity of OUD compared to those who have been diagnosed only with OUD.[67] Consistent and universal adherence to trauma- and violence-informed approaches in all aspects of clinical practice help create a supportive setting for all patients and families, whether or not they have experienced trauma or violence in their lives.[68] It should also be acknowledged that navigating the healthcare system can be a source of trauma for individuals with substance use disorders. Accordingly, it is important that all clinicians and care teams be familiar with and follow the principles of trauma-informed practice when working with patients and families affected by OUD.

The goal of trauma- and violence-informed practice is to create a safe and respectful environment that minimizes the potential for harm and re-traumatization of patients.[69] The key principles of trauma- and violence-informed practice are trauma awareness; safety and trustworthiness; choice, collaboration, and connection; and strengths-based approaches and skill building.[69]

While a universal approach to trauma- and violence-informed practice is recommended, it is recognized that some patient populations are more likely to have experienced trauma and violence than others. For example, Indigenous people, women, and/or 2S/LGBTQQIA+ populations are more likely to have experienced trauma and violence as a result of racism, discrimination, and social inequity compared to other patient populations.[70,71]

The Centre of Excellence in Women's Health's *Trauma-Informed Practice (TIP) Guide*[69] and *New Terrain* toolkit[71] and the Substance Abuse and Mental Health Services Administration's (SAMHSA) *Trauma-Informed Care in Behavioral Health Services*[72] may be useful resources for clinicians seeking to adopt trauma- and violence-informed care in their practice. The Canadian Institutes for Health Research (CIHR)-funded EQUIP Health Care research team has also published a *Trauma- and Violence-Informed Care Tool*[73] for organizations and care providers in BC, and has several webinars on incorporating trauma- and violence-informed approaches in primary and emergency care settings available on their website.

It is important to note that disclosure of violence and trauma is not a requirement for trauma- and violence-informed practice; health care providers do not need to know an individual's past experiences to provide appropriate support. Additionally, trauma- and violence-informed care is not intended to treat trauma. However, it is recommended to screen patients for trauma when appropriate and assess its impact on the patient's life.[74] Clinicians should be familiar with specialized treatment options, support services, and crisis services for individuals who have experienced trauma, and provide information and referrals to patients, should the need arise.

2.6 Self-defined Recovery and Wellness-oriented Care

The continuum of care for OUD includes care planning and services oriented towards recovery and self-defined wellness. This guideline suggests adoption of the United States-based SAMHSA's Working Definition of Recovery[75] as an overarching framework and for the purpose of developing patient-centred, recovery-oriented treatment plans: *"A process of change through which individuals improve their health and wellness, live a self-directed life, and strive to reach their full potential."*

Those seeking recovery and wellness require understanding, support, and referral to appropriate services to achieve their goals, which may include abstinence for some patients, while for others, goals may involve reducing use or safer use. In some cases, patient-identified goals may not be directly related to opioid use, such as improved health and wellness; having a safe and stable place to live; finding a sense of purpose through volunteer, educational, or employment activities; strengthening relationships with family and friends; or building social support networks.[75] Recovery and self-defined wellness-oriented care strives to respect the choices, autonomy, dignity, and self-determination of individuals in defining their personal goals and pathway and recognizes that there are multiple pathways.[76] Acknowledging and validating how individuals choose to define their recovery and wellness is an important component of this care. Recovery and wellness-oriented care emphasizes holistic, client-centered, strengths-based approaches, and can encompass a spectrum of abstinence-oriented and harm reduction management strategies.[76]

There is a diversity of recovery-oriented services in BC that can provide additional care, support, and guidance to individuals and families affected by OUD. It is recognized, however, that recovery-oriented services and the health care system have traditionally operated independently of one another, and there is a need to improve collaboration and communication between multiple service providers and programs that may be involved in an individual's care. This guideline emphasizes the importance of establishing functioning referral networks and streamlined communication pathways between these two sectors as part of a broader provincial strategy to build an integrated continuum of substance use care in BC.

2.7 Harm Reduction

Harm reduction has been defined as "policies, programmes and practices that aim to minimise negative health, social and legal impacts associated with drug use, drug policies and drug laws. Harm reduction […] focuses on positive change and on working with people without judgement, coercion, discrimination, or requiring that they stop using drugs as a precondition of support."[77] Although most often associated with the use of illegal substances, harm reduction approaches can also be applied to any activity that increases risk of adverse health, social, or legal consequences for an individual.[78]

At its core, a harm reduction approach to opioid use supports any steps taken by patients to improve their health and wellbeing, and seeks to meet patients "where they are at" in terms of willingness and ability to change.[78] Although it is understood that the only way to fully avoid all negative consequences associated with unregulated

opioid use is abstinence, it is also recognized that not all patients are able or have a goal to discontinue or substantially reduce their substance use.[78] Harm reduction requires the care provider to set aside prejudice and support patients' safety and well-being to any extent possible while accommodating each individual's goals, expectations, circumstances, and abilities. Most importantly, it means that the patient can trust that their care team will not abandon them, even if they make decisions that are contrary to the guidance from their care team.

Clinicians should promote strategies to minimize opioid-related harms rather than presenting abstinence from opioid use as the only desirable outcome of treatment. There is substantial evidence that uptake of harm reduction services is associated with significant decreases in substance-related harms, including risky behaviours, HIV and hepatitis C infection, and overdose deaths.[79-86] In addition, research has shown that participation in harm reduction services can promote entry into addiction treatment.[87-90] In BC, established harm reduction initiatives for unregulated opioid use include needle/syringe distribution programs, overdose prevention sites, take-home naloxone, supervised injection or consumption services, drug-checking services, and take-home fentanyl testing. A current listing of harm reduction services can be found on the Toward the Heart website. Clinicians should be aware of harm reduction programs offered in their local area and provide information to patients about these services. Information about harm reduction services should be offered to all patients, including those who are currently not using unregulated substances.

2.7.i Indigenous Harm Reduction

An Indigenous approach to harm reduction recognizes the social and systems-level factors that impact and shape opioid use by Indigenous peoples. This involves care providers engaging on a personal level with the realities of colonialism and structural racism and its impacts on their patients on an individual level, as well as critically reflecting on and working towards dismantling their own prejudices. In addition, clinicians should aim to work in partnership with their patients, understanding that the health system has been a site of significant harm for many Indigenous people, and endeavouring to mitigate the power dynamic between provider and person seeking care. Indigenous harm reduction practices are imbued with Indigenous knowledges and concepts of holistic and relational wellness, and are not focused on an individuals' opioid use behaviours. Indigenous harm reduction is defined as having the following characteristics[91]:

- Decolonizing—goes beyond addressing individual behaviours and interrogates the neo-colonial systems and structures that shape and constrain the lives of Indigenous peoples by centering power and control in places where it has been systematically removed. In the context of substance use care, this involves providing services that are community-led, peer-led, trauma- and violence-informed, and culturally safe
- Indigenizing—supporting programs and policies that are grounded in Indigenous knowledges, traditions, teachings, ceremonies, land, and languages
- Holistic and wholistic—creating the conditions in which Indigenous peoples can be mentally, physically, emotionally, and spiritually well by addressing social determinants of health including housing, education, cultural practices, and other psychosocial supports

- Inclusive—actively opposing "hierarchies of worthiness" imposed by colonial value structures. This involves respectful and non-judgemental care regardless of age, gender, sexuality, literacy levels, socioeconomic status, criminal backgrounds, spiritual belief, and substance use behaviours
- Innovative and evidence-based—combining Indigenous and mainstream approaches into effective and culturally grounded care

Within BC, the First Nations Health Authority (FNHA) has developed Indigenous harm reduction principles and practices.[92] Under the FNHA model, Indigenous harm reduction is a process of incorporating Indigenous knowledges and values into harm reduction policies and programs. The four key components of this model are:

- Relationships and care, represented by the Wolf
- Knowledge and wisdom, represented by the Eagle
- Strength and protection, represented by the Bear
- Identity and transformation, represented by the Raven.

Each of these components can be incorporated into substance use care for Indigenous patients by clinicians, care teams, and staff.

The Wolf reflects the importance of building relationships with patients.[92] Clinicians, care teams, and staff can incorporate this component through offering culturally safe, person-centred, inclusive, and trauma-informed outreach care; acknowledging the importance of relationships, community, and land; and recognizing social, economic, and environmental conditions as well as the ongoing impact of colonialism.

The Eagle reflects the ongoing nature of healing and the need for continuous support.[92] Clinicians, care teams, and staff can incorporate this component through providing trauma-informed and evidence-based services that support individuals and communities where they are at and recognize the impact that shame and stigma can have on Indigenous peoples who use drugs.

The Bear reflects a strengths-based approach to care that recognizes the importance of culture as a strength.[92] Clinicians, care teams, and staff can incorporate this component by ensuring Indigenous patients have access to Indigenous Elders, cultural practices, and holistic services in their substance use care.

Finally, the Raven signifies that wellness is a journey in which individuals explore and accept their identity.[92] Clinicians, care teams, and staff can support Indigenous patients in this journey by viewing substance use as a health issue and in the context of the determinants of health, rather than a moral or criminal issue.

2.8 Integrated Continuum of Care

The continuum of care for OUD includes evidence-based pharmacotherapies, psychosocial supports and interventions, and recovery support services. Individuals with OUD may need or want to try multiple approaches of varying intensity along this continuum of care, as their needs, circumstances, and goals change, in order to reduce harm, improve health and quality of life, and support long-term recovery.

This guideline supports the use of a stepped and integrated approach, in which treatment options are continually adjusted to meet changing patient needs, circumstances, and goals. A stepped approach may include treatment intensification, transitions between different treatment options, and strategies to de-intensify treatment at the patient's discretion. Patients can opt to re-initiate pharmacotherapy, psychosocial treatment, or recovery supports at any time if their needs or circumstances change.

Primary care providers and care teams should ensure that patients with OUD and their families are aware of the range of community-based and, where relevant, specialist-led programs and services that are available to them, and regularly assess interest or readiness in accessing these services. To support continuity of—and transitions in—care across the continuum, primary care providers and care teams should establish fully functioning referral pathways. Establishing protocols for communication and sharing information, with the patient's consent, between the primary care team and referral partners is strongly encouraged.

2.8.1 Longitudinal Care

Approaches to care and management of OUD have traditionally emphasized short-term and high-intensity treatment; for example, referring patients to inpatient withdrawal management or inpatient treatment programs without a plan for continuing care after discharge or completion. However, over the past two decades, there has been a greater understanding of OUD as a chronic, relapsing condition, which, like other chronic conditions, is best treated in a longitudinal fashion.

Although sometimes requiring specialist consultation, OUD is often best managed in outpatient primary care settings, using a longitudinal care approach in which patients have multiple opportunities to engage in care, patient need and preferences regarding treatment are prioritized, and counselling, social supports, and mental health services are incorporated into care.[93,94] A pre-existing therapeutic relationship (or the development of one over time) can improve engagement and retention in care.[94]

2.9 Comprehensive Health Management

As is the standard of care for any complex or chronic medical condition, clinicians should provide health management to patients with OUD. By definition, health management includes, but is not limited to: providing non-judgmental support and advice; assessing motivation and exploring barriers to change; developing and regularly reviewing a treatment and recovery plan with the patient; promoting complementary strategies for managing stress; and providing referrals to specialized medical care, recovery support, and social services when requested or appropriate.[95]

Management of OUD in primary care also allows for the provision of more comprehensive care, which may include, but is not limited to:

- Screening and clinical management of co-occurring substance use disorders, concurrent mental health disorders, concurrent medical conditions, and opioid- and injection-related sequelae (e.g., prolonged QT interval, cardiovascular diseases, cellulitis, HIV, hepatitis C)

- Preventive health care (e.g., vaccinations, general health screening)
- Sexual and reproductive health services (e.g., sexually-transmitted infection screening, contraceptive counselling, family planning)
- Chronic disease management (e.g., arthritis, diabetes, cardiovascular disease)
- Referrals to specialist care
- Referrals to community-based social supports

2.10 Family and Social Circle Involvement

This guideline uses the term "family" to encompass all relationships that are important to the patient, which may include romantic partners, close friends, and other people of significance who may or may not be legally recognized as family. Family members can have an important role as partners in an individual patient's care, and should be included in decision-making processes and care at all levels, when deemed appropriate by patients and their care teams. Research has shown that families can have a pivotal role in improving treatment outcomes and sustaining benefits of treatment for substance use among youth and adults by providing additional support and structure and promoting resilience.[96-99] If a patient determines family involvement would be a positive element in their treatment plan, clinicians are encouraged to educate family members about available treatment options and resources, and provide as much patient-specific information as possible within the boundaries of confidentiality requirements. Family members involved in the care of patients are often an important source of information about the patient's clinical history and progress; this information should be recorded and utilized in the care planning process as appropriate.

As with all medical care, confidentiality requirements must be met when treating individuals with OUD.[k] This includes maintaining confidentiality from family members unless patients have granted consent for their medical information to be shared with their family.[100] Health care providers should avoid making assumptions about privacy and routinely ask patients if they prefer to include family members or friends as supportive partners in their care. If aspects of care are being kept confidential from family members, the challenges and logistics of this should be discussed with the patient. While information about a person cannot be shared with family members without a patient's explicit consent, family members can share relevant information with health care providers without violating that patient's privacy or confidentiality. A clinician can also provide education and support to a family without disclosing any information about an individual.

It is important to note that, in some cases, family involvement may not be in the best interest of the patient. Factors such as partner or parental substance use, familial abuse and violence, or dysfunctional family

[k] Doctors of BC, CPSBC, and the Office of the Information and Privacy Commissioner's BC Physician Privacy Toolkit: A guide for physicians in private practice providers more information on privacy and confidentiality for physicians. The BCCNM has practice standards regarding privacy and confidentiality for nurse practitioners, registered nurses, and registered psychiatric nurses. Clinicians should also be aware of the legislation that applies to them. Doctors of BC's "Legislative Framework for Privacy in the BC Health Care System" outlines the relevant legislation for clinicians in private practice and those subject to public sector privacy legislation.

relationships can act as barriers to engagement and retention in treatment as well as to achieving long-term recovery.[96,98,99,101] Patients should be given full discretion on whether and how they wish to include family members in their care, and if they opt not to involve family members, this decision should be respected.

In the case of youth (aged 12–25), parental participation in treatment should be actively encouraged, if appropriate, and family members should be supported with sufficient education and information about opioid use and OUD. Offering or providing referrals to group or individual sessions for parents and/or caregivers is recommended. A family history should be taken, when possible, to identify and address any mental health or substance use issues requiring treatment in the youth's family. It should also be noted that, like adults, not all youth have healthy or positive relationships with their family members. Decisions to involve family members in care should be guided by the patient's wishes and an understanding of the family dynamic. Further youth-specific guidance on family involvement in care can be found in *Treatment of Opioid Use Disorder for Youth—Guideline Supplement*.[102]

Regardless of their level of involvement in a patient's care, family members and caregivers often require support for their own health and wellness. Several resources exist for family members impacted by opioids and OUD, including From Grief to Action's Coping Kit: A guide for family members; Parents Forever, a support group for parents of adults with substance use issues in Vancouver, BC; Nar-Anon Family Groups across BC; and Here to Help's resources for family members. Further information and resources can also be found at the BCCSU's Family and Caregiver Resources page. Family members can also be referred to external specialist-led and community-based services and supports. Clinicians should be mindful of any concerns that patients may have about privacy, confidentiality, or perceived conflicts of interest if patients and family members are referred to the same specialist-led or community-based programs.

3.0 EVIDENCE REVIEW

3.1 Screening, Assessment, and Diagnosis

All patients should be screened routinely (i.e., at least annually) for substance use. Introducing substance use screening tools in a non-judgmental, conversational manner can foster trust and, in turn, improve the accuracy of self-report. Seeking the patient's consent and providing context prior to asking screening questions may also aid in building rapport. Establishing trust and safety in these initial conversations is particularly important for patients who may otherwise tend to underreport substance use, such as pregnant people, adolescents, older adults, and patients with co-occurring substance use disorders or mental health conditions.[103-105]

Regardless of the screening tool used, it is emphasized that screening alone does not improve outcomes. Provider and staff education, training, and the development of clinical pathways and processes that support early intervention among individuals who use opioids are also needed, along with a plan for any necessary diagnostic follow-up and treatment for individuals who are diagnosed with an opioid use disorder.

3.1.i Screening for Substance Use Disorders

A number of standardized screening instruments are available that have been validated in a range of clinical care settings for opioid and substance use disorders, including the 2-item Screen of Drug Use, Rapid Opioid Dependence Screen (RODS), Severity of Dependence Scale (SDS), Cutdown, Annoyed, Guilt, Eye-opener—Adapted to Include Drugs (CAGE-AID), Drug Abuse Screening Test (DAST), and Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST).

However, provider-level barriers, including time constraints, the need for extensive training and certification to administer such tools, and the requirement to calculate overall scores have been cited as impediments to the uptake of these screening tools. Moreover, many of these tools are clinician-rated only and are subcomponents of larger instruments that screen for multiple substances or other disorders (e.g., opioids, alcohol, cocaine, or psychiatric disorders).[106]

This guideline endorses universal substance use screening, using the 2-item Screen of Drug Use (see below). A positive screen should prompt an in-depth discussion of substance use patterns and a diagnostic interview using the DSM-5 criteria for OUD, as outlined below.

2-item Screen of Drug Use

A simplified screening tool for substance use disorders may circumvent the reported barriers to screening. The 2-item Screen of Drug Use tool was developed and validated to identify substance use disorders other than alcohol use disorder in primary care settings. Patients are asked to estimate their drug use in the previous 12 months.

The first question asks: "How many days in the past 12 months have you used drugs other than alcohol?" Any response of 7 or more days is considered a positive screen result. If the answer is 6 or fewer days, the administrator should proceed to the second question.

The second question asks: "How many days in the past 12 months have you used drugs more than you meant to?" Any response greater than 2 days is considered a positive screen result.[107]

The 2-item Screen of Drug Use has been validated to identify opioid use disorder in primary care settings. Using patients who screened positive for OUD by the MINI as the criterion measure, the 2-item Screen of Drug Use demonstrated 100% sensitivity (95% CI: 89.9–100), 86.3% specificity (95% CI: 84.3–88.1), 7.3 positive likelihood ratio (95% CI: 6.4–8.4), and 0 negative likelihood ratio. These results are comparable to the sensitivity and specificity of other frequently used substance use disorder screening tools in primary care settings[107]

While the 2-item Screen of Drug Use was developed to screen for substance use disorders, clinicians may also find it useful to identify patients who use substances, including opioids, but do not meet criteria for substance or opioid use disorders.[108] Clinicians should consider offering harm reduction education and supplies or referrals to other support services to patients who respond to the screening questions with numbers greater than 1 but less than the criteria for a positive screen.

Rapid Opioid Dependence Screen

The Rapid Opioid Dependence Screen (RODS) is an 8-item instrument to assess the risk of opioid dependence. Based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), criteria, the RODS was developed for use in both clinical and research settings and allows for quick, targeted screening. The RODS may be administered as a stand-alone screening tool or as a component of a larger comprehensive interview. The RODS consists of a series of questions that assesses lifetime use of opioids, and the physiological, behavioural, and cognitive factors that are associated with opioid dependence. Each positive response to a question receives 1 point. Patients may have a total possible score of 8, and a score of 3 or greater is considered a positive screen result for opioid dependence.[106]

In the initial validation study in a population of newly incarcerated, HIV-positive individuals, the RODS demonstrated 97% sensitivity, 76% specificity, 69% positive predictive value, and 98% negative predictive value. Psychometric analysis showed a strong internal consistency (α=0.92) and inter-item correlations (0.66–0.87).[106]

Similar to the 2-item Screen of Drug Use instrument, the RODS may help health care providers identify patients who use opioids but are not opioid dependent (i.e., those with a score of less than 3). Health care providers should offer patients who fall into this category counselling, harm reduction education and supplies, or referrals to other support services.

3.1.ii Diagnosis

All patients who screen positive for opioid use disorder should then be administered a diagnostic interview using the DSM-5 Clinical Diagnostic Criteria for Opioid Use Disorder to confirm the diagnosis and assess the severity

of OUD. According to studies to date, the DSM-5-TR criteria have substantial test-retest reliability in establishing the presence of OUD (Kappa coefficient=0.67; CI: 0.58–0.76) and excellent reliability in determining the severity of OUD (intraclass correlation coefficient (ICC)=0.86; CI: 0.81–0.90).[109,110]

The DSM-5-TR criteria are detailed in Appendix 2.

3.2 Opioid Agonist Treatment

IMPORTANT NOTICE REGARDING BC PHARMACARE COVERAGE

Buprenorphine/naloxone, extended-release subcutaneous buprenorphine (Sublocade), commercially available methadone[I] (Methadose and Metadol-D), and slow-release oral morphine (24-hour formulation; brand name Kadian) are all fully covered as regular benefits for those enrolled in PharmaCare Plan C (Income Assistance), Plan B (Licensed Residential Care Facilities), Plan Z (Assurance), and Plan G (Psychiatric Medications). Plan G is available to those with a family- adjusted net income below $42,000 per year (plus $3,000 per dependent) who meet the clinical criteria. A one-time Plan G exceptional coverage for 6 months can be considered for BC residents waiting for MSP coverage. Renewable Plan G bridge coverage for 3-month terms is also available under exceptional circumstances. Application forms for Plan G can be accessed here: http://www2.gov.bc.ca/assets/gov/health/forms/3497fil.pdf.

Plan Z (Assurance) is a no deductible, 100% coverage plan for all B.C. residents enrolled in MSP (not in the wait period). Exceptional Plan Z coverage is available to provide temporary Plan Z coverage of OAT for B.C. residents not yet enrolled in MSP or have enrolled in MSP but are awaiting activation of coverage. Procedure and application forms for Exceptional Plan Z coverage of OAT can be accessed here: https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare/pharmacies/plan-z.

Abundant evidence has established OAT's effectiveness in sustaining treatment retention, reducing unregulated opioid use, and minimizing risk of morbidity and mortality.[111-116] The choice of agonist treatment depends on several patient-specific factors including initial presentation, history and patterns of substance use, comorbidities (e.g., liver disease, prolonged QTc interval), drug–drug interactions, treatment preference and goals, life style requirements and restrictions (e.g., remote location of home or employment), and response to treatment. Regardless of the type of treatment administered, opioid agonist treatment should incorporate provider-led

[I] Coverage of compounded methadone 10mg/mL is determined on an individual, case-by-case basis. For further information on available methadone formulations and considerations relating to methadone formulation selection, see Appendix 3.

counselling, long-term continuing care (e.g., regular assessment, follow-up), provision of comprehensive preventive and primary care, and referrals to psychosocial treatment interventions, psychosocial supports, and specialist care as required, to optimize physical and mental wellness and support reaching patient-defined goals.

Much of the evidence supporting available opioid agonist medications pre-dates the widespread adulteration of the unregulated drug supply with fentanyl and other highly potent psychoactive substances. However, the limited available evidence demonstrates that OAT has significant efficacy in reducing the risk of overdose mortality among people with OUD who use fentanyl.[117-119] For example, a 2020 observational study (n=55,347) compared the risk of mortality between participants on OAT and those off OAT in a cohort of British Columbians who received methadone or buprenorphine between 1996 and 2018.[117] The relative risk of death among people off OAT was 2.1 times higher than participants on OAT before the introduction of fentanyl, increasing to 3.4 times higher than those on OAT in 2016, when a public health emergency was declared due to the infiltration of fentanyl in the unregulated drug supply. The mortality rate of people on OAT remained stable between 2010 and 2018, suggesting that being on OAT offered substantial protection from overdose during the fentanyl crisis.[117]

The impact of fentanyl use on OAT initiation and engagement was investigated in a 2022 secondary analysis of a Canadian clinical trial (n=272) conducted between 2017 and 2022. While unadjusted analysis suggested that baseline fentanyl exposure was associated with lower likelihood of OAT initiation [odds ratio (OR)=0.18, 95% CI: 0.08–0.36] and shorter periods of engagement in OAT [20 vs 168 days, hazard ratio (HR)=3.61, 95% CI: 2.52–5.17], adjusted models showed no statistically significant differences between participants with and without fentanyl exposure at baseline.[119] The authors concluded that both buprenorphine/naloxone and methadone are appropriate treatment options for people with opioid use disorder regardless of fentanyl exposure.[119]

Clinical experience indicates that some individuals with high opioid tolerance due to fentanyl use may require modified dosing and titration protocols, in addition to significantly higher OAT doses than were common prior to fentanyl predominating the unregulated opioid supply. In the absence of substantial evidence characterising and evaluating these modified practices intended to meet the needs of patients who use fentanyl, the dosing and titration guidance provided in this document was developed through expert consensus and in reference to accumulating clinical experience and guidance emerging in other jurisdictions—such as the Ontario-based *Methadone Treatment for People Who Use Fentanyl: Recommendations* published by Mentoring, Education, and Clinical Tools for Addiction—Partners in Health Integration (META-PHI)— as well as emerging research.[120] See Appendix 3 for guidance on dosing and titration.

3.2.i Buprenorphine

Buprenorphine is a partial opioid agonist available as both a monoproduct and a combined formulation of buprenorphine and naloxone. The naloxone component in the buprenorphine/naloxone formulation is added to deter diversion, injection use and insufflation. Due to almost complete first-pass metabolism and low sublingual availability, naloxone administered sublingually or orally has almost no pharmacological effect; but is likely to precipitate withdrawal if injected or insufflated. In Canada, buprenorphine is primarily available as a sublingual 4:1 combined formulation of buprenorphine and naloxone. An extended-release subcutaneous

buprenorphine monoproduct (Sublocade) is also available for patients who have been clinically stabilized on buprenorphine/naloxone.

Compared to placebo, a 2014 meta-analysis has shown that buprenorphine, at doses higher than 2mg/day, has significantly higher rates of treatment retention and, at doses higher than 16mg/day, significantly more effective suppression of unregulated opioid use.[116]

Compared to methadone, buprenorphine at low doses (≤6mg/day) is less effective for treatment retention than low doses of methadone (≤40mg/day), but there is no significant difference in retention rates for medium (7–16 mg/day) and high buprenorphine doses (≥16mg/day) and approximately equivalent methadone doses (40–85mg/day and ≥85mg/day).[116] Buprenorphine and methadone also appear to be equally effective for reducing unregulated opioid use.[116]

A 2016 meta-analysis comparing buprenorphine and methadone for treatment of prescription opioid dependence reached similar conclusions; buprenorphine and methadone appear to be equally effective in reducing opioid use and retaining individuals in treatment for this specific patient population, although authors note that the evidence base is limited.[121] A placebo-controlled randomized controlled trial published since this meta-analysis supports the use of buprenorphine/naloxone in individuals with opioid use disorder.[122]

While earlier meta-analyses referenced above consistently suggest that buprenorphine's treatment retention rates are comparable to that of methadone, more recent studies, including a 2022 network meta-analysis[123] and a population-based retrospective study in BC,[124] report marginally higher rates of treatment discontinuation with buprenorphine/naloxone (see also the Methadone section below).

Extended-release buprenorphine (Sublocade)

The extended-release formulation of buprenorphine (brand name Sublocade) is administered monthly via abdominal subcutaneous injection for the management of moderate to severe opioid use disorder. Extended-release buprenorphine may reduce patients' medication burden, as it is administered monthly rather than daily. It is currently indicated for patients who have been clinically stabilized on 8mg to 24mg of sublingual buprenorphine-naloxone for a minimum of seven days.

Extended-release buprenorphine is associated with significantly higher treatment retention (close to 100%) and mean abstinence percentages (over 40%) compared to placebo (5%) in individuals with moderate to severe opioid use disorder.[125] A follow-up study included both roll-over patients (n=113) and de novo patients (n=112) whose first exposure to extended-release buprenorphine was in this phase III open-label long-term study.[126] At 12 months of treatment, approximately 60% of rollover and 76% of de novo patients had ceased unregulated opioid use. Both rollover and de novo patients had similar retention rates (~51%) and similar participant satisfaction scores.[126] A 2020 longitudinal study found that participants who received 12 months of extended-release buprenorphine were significantly more likely to be abstinent at the 12-month follow-up than those who received 2 or less months of this medication (75.3% vs 24.1%; P=0.001).[127] Overall, 51% of all participants remained abstinent for 12 months. An open-label randomized clinical trial (n=119) in Australia comparing

patient-reported outcomes for individuals prescribed a different formulation of extended-release buprenorphine (brand name Brixadi/Buvidal) compared to sublingual buprenorphine/naloxone found that extended-release buprenorphine was associated with higher treatment satisfaction (p=0.002), convenience (p<0.001), and overall quality of life (p=0.03) with no significant difference in unregulated opioid use measured by self-report or urine drug tests.[128] It should be noted that extended-release buprenorphine and sublingual buprenorphine/naloxone have not yet been compared in a clinical trial. The evidence outlining the characteristics of patients who benefit from transitioning to extended-release buprenorphine is limited and continues to evolve.[127,129] Discussion of potential risks and benefits, informed consent, and regular follow-up including monitoring for cravings and withdrawal symptoms following initiation of extended-release buprenorphine should be considered key components of care.

See Appendix 3 for guidance on the titration and dosing of these buprenorphine formulations.

Other buprenorphine formulations (not covered in BC)

Subdermal buprenorphine implant (Probuphine)

A subdermal buprenorphine implant (Probuphine) allows for continuous blood levels of buprenorphine for up to 6 months following implantation.[130] According to available evidence, this formulation is superior to placebo at reducing unregulated opioid use over a 6-month period, and non-inferior to sublingual buprenorphine at preventing unregulated opioid use over a 4–6 month period.[130]

A subdermal buprenorphine implant (80mg) is currently approved for use in patients who have sustained stability on sublingual buprenorphine/naloxone at doses of no more than 8mg.[130,131] However, this formulation is being phased out in Canada and will no longer be available in BC.

Buprenorphine/naloxone film

Buprenorphine/naloxone film is a buccal film available in BC in 3 dosages[132]; however, this formulation is not currently covered by BC PharmaCare (including Plan C, G, and W), the Non-Insured Health Benefit (NIHB), or Veteran Affairs Canada.

In a randomized controlled trial, no significant differences in dose effects, adverse effects, or treatment outcomes were identified between Suboxone film and sublingual tablets.[133] Some patients may prefer the taste or faster dissolving time of the Suboxone film compared to the sublingual tablet.[134] Suboxone film produces higher bioavailability of buprenorphine compared to the same dose of the sublingual tablet; as such, switching between the two forms could theoretically lead to inadvertent over- or underdosing,[134] although actual dose changes have not been required in head-to-head trials. For this reason, switching between formulations should be done only with appropriate monitoring for symptoms of over- or under-dosing of buprenorphine.[134] Consult the product monograph for further information on switching from tablet to film.[135]

Induction dosing

Buprenorphine/naloxone treatment can be initiated through traditional induction and low-dose induction methods, both of which can be conducted at different speeds and in a range of settings, including primary care, emergency department, inpatient settings, and at home or other unobserved settings. This section provides an overview of the evidence supporting available induction methods. Detailed guidance on buprenorphine induction and dosing is provided in Appendix 3.

The traditional induction schedules provided in the buprenorphine/naloxone product monograph are approved by Health Canada[136] and have been widely used in BC. However, growing clinical and research experience indicate that more flexible induction dosing approaches—such as more rapid titration schedules—are associated with increased patient comfort and improved treatment outcomes. In keeping with the therapeutic range described in the Suboxone Product Monograph, Health Canada currently recommends a maximum starting dose of 12mg/3mg and a maximum total daily dose of 24mg/6mg of buprenorphine/naloxone; the Suboxone product monograph suggests that daily doses greater than 24mg/6mg have not been demonstrated to provide clinical advantage. However, this recommendation is based on data collected before the infiltration of fentanyl into the unregulated drug market. More recent data suggests that a daily dose of up to 32mg/8mg buprenorphine/naloxone may be reasonable and can be provided safely to address the high opioid tolerance of patients who use fentanyl.[137]

The NIDA-funded START trial (n=740)[138] allowed a flexible approach to dosing, with minimal instructions to study clinicians (e.g., maximum upper limit of 16mg/4mg buprenorphine/naloxone on Day 1, and 32mg/8mg buprenorphine/naloxone on Days 2–168). Other than recommending dose adjustment to address participant symptoms, dose escalation rates were not explicitly outlined in the START protocol, and study clinicians employed a range of induction trajectories. The analysis explored higher versus lower dose trajectories during the first three days of induction and latency to achieve a stable dose.[138] The authors found that participants who were started at a moderate dose (16mg/4mg buprenorphine/naloxone) and shifted quickly over 3 days to a high dose (16mg/4mg–32mg/8mg buprenorphine/naloxone) were three times less likely to drop out in the first 7 days than participants who were started and maintained at a low dose (8mg/2mg–16mg/4mg buprenorphine/naloxone). Participants who were stabilized at an optimal dose quickly had less opioid use in the last 28 days of treatment than those who were slowly titrated to their optimal dose, without an increase in adverse events in the first or last 28 days of treatment.[138]

Efficacy of low doses vs high doses of buprenorphine

Early studies examining the efficacy of buprenorphine have been critiqued for employing relatively low buprenorphine doses and slower induction protocols than current practice standards.[139] A 2014 Cochrane review found low doses of buprenorphine (2–6mg/day) were not as effective at retaining people in treatment compared to low doses of methadone (<40mg/day), although any dose of buprenorphine greater than 2mg/day had higher rates of retention compared to a placebo.[116]

A multi-site 2008 retrospective observational study in Italy (n=979) examined different treatment protocols across 32 treatment centres. During the induction phase, protocols indicated a first dose between 2mg and 4mg with subsequent doses ranging from 2mg–4mg. While some protocols did not impose a limit on maximum dose during the first three days of induction, others limited doses to 8mg on the first day, 16mg on the second day, and 24–32mg on the third day. Participants who received lower induction doses had significantly higher relapse rates, with 51.2% of those induced on 2mg of buprenorphine experiencing a relapse, compared to 39.2% of those induced with 4mg, 31.5% of those induced on 8mg, and 20.6% of those induced on 10mg. Nearly all participants who received an induction dose of 16mg or greater successfully completed induction. In addition, reductions in positive urine screens for cocaine and cannabis were observed as buprenorphine doses increased, with the greatest reductions seen at doses greater than 16mg.[140]

A 2022 systematic review (N=9 studies) seeking to determine factors associated with longer retention in buprenorphine treatment also found that higher doses[m] of buprenorphine/naloxone were associated with significantly higher rates of treatment retention ($p<0.01$).[141] Sub-optimal doses of opioid agonist treatment medications should be avoided, as they are a commonly cited reason for treatment disengagement.[142] An optimal dose of opioid agonist treatment medications should be understood as a dose that reduces the discomfort of withdrawal symptoms, overcomes drug cravings, reduces the use of unregulated drugs in accordance with the patient's treatment goals, and causes minimal adverse reactions in patients without inducing toxicity.[142]

Low-dose induction

Traditionally, buprenorphine induction has required a period of abstinence from opioids to ensure that withdrawal is not precipitated. This period can be both time-consuming and challenging for patients,[116,143] as it requires patients to be in moderate withdrawal prior to induction. If insufficient time has passed since last opioid use,[n] the introduction of buprenorphine, a partial agonist with high affinity for the opioid receptor, may cause precipitated withdrawal. A low-dose[o] induction that slowly up-titrates small doses of buprenorphine without cessation of all other opioids until a therapeutic dose has been reached was first described in the literature in 2016, with growing numbers of cases described since then.[144] A 2021 systematic review included 19 case studies/series and 1 feasibility study (n=57).[145] All 57 patients were able to reach a maintenance dose, and 95% (54/57) did not report precipitated withdrawal during the induction process. Twenty-six patients (46%) were co-prescribed full agonists (including methadone, fentanyl, hydromorphone, and morphine), with the rest continuing to use unregulated opioids during the induction period. Although all included patients achieved a

[m] The systematic review included studies utilizing doses of up to up to 24mg. The only studies that directly compared doses utilized doses of up to 8mg. However, the review made general conclusions about retention in higher doses studies.

[n] 12–16 hours for short-acting opioids like diacetylmorphine or hydromorphone; 48–72 hours for longer-acting opioids like methadone; ≥24 hours for suspected, confirmed, or unknown fentanyl.

[o] "Low-dose induction" is also referred to as "micro-dosing induction" or "micro-induction". This guideline will use the term "low-dose induction" in alignment with emerging literature and in the interest of consistency and clarity.

maintenance dose, some patients required multiple attempts, and return to unregulated opioid use was reported for 5 patients. The median starting dose for studies that did not report precipitated withdrawal was 0.5mg, median duration was 6 days, median maintenance dose was 16mg, and mean rate of dose change to 8mg was 1.36mg/day.[145] While the findings are promising, the overall quality of included studies was rated as poor, and the lack of standardized outcome measures and comparative effectiveness studies limit conclusions regarding effectiveness. There is significant variability and a lack of standardization in the low-dose induction protocols reported.[145]

Several case studies and case series have also reported findings in favour of the use of low-dose inductions in a variety of settings. These include successfully transitioning patients (n=6) onto extended-release buprenorphine,[146,147] a low-dose induction paired with assertive community outreach to successfully initiate a patient with multiple past treatment attempts and complex medical comorbidities onto buprenorphine/naloxone,[148] and low-dose inductions for individuals prescribed opioids for analgesia.[149,150]

Research is ongoing to produce high-quality evidence of the efficacy of low-dose induction compared to standard buprenorphine induction; two randomized controlled trials are planned to compare low-dose inductions with traditional buprenorphine/naloxone inductions, one at Vancouver General Hospital,[151] and one with four sites in BC and Alberta.[152]

Although research evidence is limited, clinical practice in many parts of BC now commonly includes using low-dose inductions as they reduce the risk of precipitated withdrawal and do not require the patient to abstain from the use of other opioids for a prolonged period. This may increase the likelihood of patient retention and satisfaction. Low-dose inductions may be especially helpful for individuals using fentanyl, as emerging evidence and clinical experience suggests that the risk of precipitated withdrawal is higher for these individuals, likely due to the unique pharmacokinetics of fentanyl.[153,154] Considerably more research is needed to compare traditional inductions to low-dose inductions in order to determine comparative efficacy and to identify specific factors that support the tailored selection of the appropriate induction approach. More research is also needed to determine optimal low-dose induction protocols.

See Appendix 3 for clinical guidance for conducting low-dose inductions based on protocols commonly utilized in BC.

Emergency department buprenorphine/naloxone induction

Individuals with opioid use disorder have high rates of emergency department (ED) utilization.[155] Data from the 2005–2014 National Surveys on Drug Use and Health in the U.S. showed that 58.2% of individuals with prescription opioid use disorder reported past-year ED utilization, with 45.1% reporting 2-4 visits.[156] Data from the BC Provincial Overdose Cohort, which examined 10,455 overdose events between January 1, 2015 and November 30, 2016, found that over half (60.4%) visited the emergency department in the year prior to overdose.[157] These high rates of ED utilization suggest that ED visits may be an opportunity to engage individuals

in OUD care. A small but growing body of evidence suggests that ED-based initiation of buprenorphine/naloxone increases engagement and retention in treatment.[158-160]

A 2015 RCT (n=329) randomized participants to one of three conditions: screening and referral to treatment; screening, brief intervention, and facilitated referral to community-based treatment services; or screening, brief intervention, ED-initiated buprenorphine/naloxone, and referral to primary care for 10-week follow up.[158] The initiation group had significantly higher treatment engagement and significantly fewer days of self-reported unregulated opioid use after 30 days, compared to the other two groups.[158] At two months, the initiation group continued to have significantly higher treatment engagement and fewer days of self-reported unregulated opioid use; however, this difference between groups did not persist at 6 or 12 months.[161] A cost-effectiveness evaluation of this study found that ED-initiated buprenorphine/naloxone is most likely to be cost-effective relative to both referral and brief-intervention.[162]

A small (n=26) 2019 study randomized patients presenting to the ED in opioid withdrawal (or soon to be) to either a clonidine or buprenorphine/naloxone group. The clonidine group were provided with clonidine in the ED and provided a 5-day discharge prescription along with a flyer and map to a rapid access addiction clinic, while the buprenorphine/naloxone group was administered up to 12mg/3mg buprenorphine/naloxone and given a prescription for a 5-day supply of buprenorphine/naloxone, a map to the nearest outpatient pharmacy, and printed information and a map for the rapid access addiction clinic.[159] At 1 month, the buprenorphine/naloxone group was significantly more likely to be receiving OAT (62% vs. 8%). In addition, more than double the number of buprenorphine/naloxone participants went for follow-up within five days at the rapid access addiction clinic (77% vs. 38%); however, this difference was not statistically significant.[159] A small number of case studies (n=3) from the California Bridge Program have shown that individuals can be rapidly inducted onto buprenorphine/naloxone in the ED following naloxone reversal of an opioid overdose, without serious adverse event.[163]

A 2019 retrospective chart review of four community hospitals in Ontario evaluated 49 patients who were eligible to receive ED-initiated buprenorphine/naloxone treatment followed by a discharge prescription of up to three daily witnessed doses and a referral to the rapid access addiction clinic; 88% (n=43) consented to the intervention.[160] Approximately 54% of those initiated on buprenorphine/naloxone attended their initial appointment at the rapid access addiction clinic. At six months, 35% remained on buprenorphine/naloxone-based OAT and 2.3% had successfully transitioned off of buprenorphine/naloxone treatment.[160] In addition, those patients in the ongoing treatment group had significantly lower ED utilization in the 6 months following initiation onto buprenorphine/naloxone.

Several programs for ED-initiation of buprenorphine/naloxone are currently in existence, in both Canada and the United States. To facilitate engaging ED patients with OUD in OAT, the BCCSU and BC Patient Safety and Quality Council worked together to launch the Learning about Opioid Use Disorder in the Emergency Department Collaborative (LOUD in the ED). The program developed three key resources: a Tool for Emergency Department Buprenorphine/naloxone Induction, a webinar series, and two new modules (modules 23 and 24) of the Provincial Opioid Addiction Treatment Support Program (POATSP).

See Appendix 4 for guidance on ED buprenorphine/naloxone induction.

3.2.ii Methadone

A substantial body of evidence has shown methadone to be significantly more effective than non-pharmacological outpatient treatment approaches in terms of treatment retention and suppression of heroin use.[164]

In terms of treatment retention, a 2022 systematic review and metanalysis (N=79) of randomized controlled trials found that methadone was marginally superior to buprenorphine for treatment retention (RR=1.22; 95% credible interval (CrI)=1.06–1.40).[123] Similarly, a 2021 population-based retrospective study utilizing administrative databases of people with who received OAT between 2012 and 2018 in BC (n=37,207) found a lower monthly discontinuation rate among individuals receiving methadone compared to those receiving buprenorphine/naloxone (10% Vs. 21%).[124]

Methadone at higher doses (i.e., between 60–120mg/day or higher) is more effective than lower doses for treatment retention and reducing heroin during treatment of OUD.[165,166] Retention in methadone treatment is associated with substantial reductions in the risk for all cause and overdose mortality in people dependent on opioids.[111]

Methadone-based opioid agonist treatment has been shown to reduce injection risk behaviours and the overall risk of hepatitis C and HIV infection among people who inject drugs.[167-169] Furthermore, among HIV-positive individuals, engagement in methadone-based agonist treatment is independently associated with increased adherence to antiretroviral therapy and improved virologic outcomes (e.g., lower HIV viral loads, higher CD4 counts), particularly at higher doses (≥100 mg/day).[170-172]

Research specifically focused on the effectiveness of methadone for managing OUD among people who use fentanyl is limited. However, a small body of observational data suggests that OAT with methadone is safe and effective in treatment retention and reduction of the risk of overdose mortality among individuals who use fentanyl.[117,118] A 2020 retrospective study (n=151) evaluated 12-month methadone treatment outcomes for patients on methadone treatment, 121 (80%) of whom tested positive for fentanyl at intake.[118] At 12-month follow-up, there were no significant differences between the fentanyl-exposed participants and other participants in terms of 1-year treatment retention (53% vs. 47% respectively), and short-term and sustained abstinence from unregulated opioid use. Importantly, although return to fentanyl use while in treatment was common, no deaths occurred among participants who were retained in treatment for the full year, while 4 known deaths occurred among participants who left treatment early. The authors concluded that OAT with methadone is safe and effective for people who use fentanyl, and may have some protective effect against drug toxicity death even in the case of continued fentanyl use.[118]

There is considerable evidence demonstrating methadone's efficacy and safety for the treatment of opioid use disorder and related harms. However, its unique pharmacological properties compared to other prescription opioids (e.g., narrow therapeutic index, long elimination half-life), and potential for interactions with alcohol

and other drugs does increase the relative risk of toxicity and adverse events. For example, in the United States, after controlling for the total number of prescriptions dispensed, methadone-related emergency room visits occur at a rate that is approximately 6 and 23 times higher than the prescription opioids oxycodone and hydrocodone, respectively.[173] However, it is important to note that these findings are not free of bias, as methadone is almost exclusively prescribed to people with OUD—a population known to have high rates of ED utilization.[155]

Moreover, although methadone accounts for fewer than 5% of all opioid prescriptions per year in the US, it is identified in more than a third of prescription-opioid-related overdose deaths.[173] This is consistent with a 2015 study in British Columbia that reported that methadone was involved in approximately 25% of prescription-opioid-related deaths in British Columbia.[120] A 2017 systematic review of mortality risk during and after OAT found that all-cause mortality for individuals on methadone was almost three times the rate of those on buprenorphine (11.3 per 1,000 person years vs. 4.3 per 1,000 person years, respectively) and overdose mortality was almost double in those in methadone treatment (2.6 per 1,000 years vs. 1.4 per 1,000 person years).[111] However, all-cause mortality dropped shortly after the first four weeks of methadone treatment. Data from the BC Provincial Overdose Cohort found that methadone was implicated in far more deaths than buprenorphine (130 cases vs. 2 cases) between 2015 and 2017, appearing in the toxicology results of 6% of the 1,789 of overdose deaths which were analysed.[174] It should be noted that these findings are not results of direct comparisons of the medications and are not free from bias.

The significantly increased risk of overdose during early stages of methadone treatment is well described (i.e., during initiation, titration, and dose stabilization). Other factors that have been associated with risk of methadone-involved overdose include[175-179]:

- Non-prescribed, diverted, and unregulated use (including unregulated use when prescribed methadone dose is insufficient to control withdrawal symptoms)
- Unsupervised or non-witnessed doses
- Combined use with alcohol and benzodiazepines
- Methadone prescribed for pain management, as opposed to treatment of opioid use disorder where doses are witnessed and titration schedules are strictly enforced

To minimize the risk of methadone-involved overdose, particularly in the first weeks of treatment, guidelines typically recommend daily witnessed dosing until patient stability on their methadone dose has been clearly established. However, this practice is based on relatively small body of evidence.[176,178,180,181] When considering the safety and utility of daily witnessed dosing, the potential adverse impact of requiring daily office visits on treatment retention—and, in turn, the risks associated with return to unregulated opioid use—should be considered. See Take Home OAT Dosing for a review of evidence on observed versus unobserved dosing.

There are currently 2 methadone options available as regular PharmaCare benefits in BC. Methadose and Metadol-D are covered as regular benefits for those enrolled in PharmaCare Plan C (Income Assistance), Plan B (Licensed Residential Care Facilities), Plan G (Psychiatric Medications), and Plan Z (Assurance). Methadose was

introduced in 2014, replacing 1mg/mL pharmacy compounded methadone. Since this formulation change, many patients who had been stable on compounded methadone 1mg/mL have reported return to unregulated opioid use due to inadequate management of withdrawal symptoms.[182-185] As a result, Metadol-D was added as a regular benefit in May 2019. In October 2019, compounded methadone became available as a third, last-resort option for individuals who had trialed regular benefit formulations without success. See Appendix 3 for more information.

Initiation dosing

Methadone carries a greater risk of all-cause mortality (adjusted mortality rate ratio [AMRR]: 2.17, 95% CI: 1.29–3.67) and opioid-related overdose related mortality (AMRR: 7.61, 95% CI: 1.81–31.94) during the first 4 weeks of treatment compared to buprenorphine.[186] The starting methadone dose will depend on factors that affect the risk of overdose, including the patient's known opioid tolerance, current opioid use, and co-occurring substance use patterns and other comorbidities. Current guidelines in many Canadian jurisdictions recommend a starting dose range of 10–30mg, with the upper end of this range recommended for individuals with increased opioid tolerance.[187,188] However, a number of more recent guidelines have allowed a maximum methadone starting dose of 40mg for patients with established high tolerance to opioids.[189-191] For example, Quebec's dosing standards recommend a maximum starting dose of 40mg based on thorough individualized assessment.[187] In the United States, the Substance Abuse and Mental Health Service Administration (SAMHSA) recommends limiting the first day dose to a maximum of 30mg for most patients, but allows a total maximum first day dose of 40mg, administered in divided doses, for patients who experience persisting withdrawal symptoms after receiving 30mg.[192] Similarly in its 2020 update, the American Society of Addiction Medicine (ASAM) has endorsed a maximum total first-day dose of 30-40mg as needed, provided that the initial dose does not exceed 30mg.[193]

The traditional upper limit of 30mg for the initial dose is informed by observational studies that identify the first week of methadone treatment as a high-risk period for methadone toxicity among patients who receive a starting dose higher than 30mg.[194-197] However, most of these studies pre-date the infiltration of fentanyl and other highly potent synthetic opioids into the unregulated drug supply and the corresponding increase in the proportion of patients with high tolerance to opioids due to fentanyl use. Although there is a lack of published studies supporting higher first-day doses of methadone, the need for modified induction protocols and higher starting doses in the era of fentanyl are widely acknowledged in clinical practice.[198]

To address the specific needs of people who use fentanyl, the Ontario-based META-PHI published a series of recommendations for *Methadone Treatment for People Who Use Fentanyl.*[188] A focus group of people with lived experience of methadone/OAT assembled by META-PHI to review the recommendations stated that 30mg is too low to make a significant impact on withdrawal symptoms among people with high opioid tolerance, and favoured starting doses in the range of 40–60mg in an outpatient setting and higher in an inpatient setting, where sedation or overdose can be monitored.[188] Although the META-PHI authors endorsed a maximum starting dose of 30mg, the authors of the document acknowledged that there are settings in which 40mg is used as a starting dose and that future updates should seek new evidence for the safety of higher starting doses.[188]

In keeping with guidelines and accumulating clinical experience in BC and other jurisdictions that support starting doses of up to 40mg,[187,189-191] and in recognition of the urgent need to engage and retain individuals who use fentanyl in evidence-based care, this guideline endorses a maximum first day dose of 40mg for individuals who use fentanyl and have established tolerance to methadone. See Appendix 3 for methadone induction guidance.

Efficacy of low dose vs high dose

Adequate methadone dosing (i.e., sufficient dose to control withdrawal symptoms for approximately 24 hours without signs of overmedication) vary significantly between patients due to variability in methadone pharmacokinetics, metabolism, and patient preference. For this reason, methadone dosing should involve careful, individualized dose titration as opposed to standardized dosing regimens.

Results from a 2009 systematic review indicate higher retention rates are associated with methadone doses ≥60mg/day compared to the retention rates at <60mg/day (OR: 1.74, 95% CI: 1.43–2.11). High doses of methadone (i.e., between 60–120mg/day or higher) have been found to be more effective than lower doses for treatment retention and reducing heroin use during OUD treatment.[165,166] While methadone dosing should be based on clinical judgment and determined on an individual basis due to differences in individual metabolism, comorbidities (e.g., liver disease, prolonged QTc interval) and drug interactions,[199] most studies have suggested that patients who take daily doses of 80mg/day or higher have optimal treatment outcomes[143,165] and that doses above 120mg/day may be required to produce full opioid blockade and fully suppress withdrawal.[200,201] The optimal methadone dose is generally between 80–150mg/day; however this dose range was established in clinical practice before the dominance of fentanyl in the unregulated drug supply. Some patients, including those who use fentanyl, may require higher doses to achieve therapeutic goals. Once achieved, a sufficient dose of methadone can require little adjustment for up to ten years.[202]

Despite this, as of 2018, 38% of patients on methadone in BC received doses of less than 60mg per day, the lower limit of what is defined as an optimal daily dose for methadone-based opioid agonist treatment.[203] This underscores the need for practice standards that adequately meet patients' needs by taking into account the increasing toxicity of the unregulated drug supply. This includes addressing barriers to reaching an appropriate individualized dose, such as titration schedules and missed dose protocols.

For induction and dosing guidelines for methadone, refer to Appendix 3.

3.2.iii Slow-release Oral Morphine

Slow-release oral morphine[p] (SROM) is widely used for pain management, but there is also a growing evidence base for its use as an OAT medication. In Canada, slow-release oral morphine for treatment of OUD has been

[p] Note: Slow-release oral morphine refers to the 24-hour formulation of extended-release morphine capsules.

eligible for coverage under Health Canada's Non-Insured Health Benefits (NIHB) program since November 2014 (now Plan W in BC), and as a regular benefit under British Columbia's provincial drug plan (PharmaCare) since June 2017.

Four systematic reviews—including two meta-analyses—of randomized trials have been published since 2013.[204-206] A 2013 Cochrane Review including three randomized trials (n=195) comparing slow-release oral morphine to methadone or buprenorphine/naloxone found no significant differences between treatments in retention, medication adherence, or non-medical opioid use.[204] However, due to the small number of trials that met inclusion criteria, the quality of this evidence was assessed as low (i.e., high likelihood that new evidence could change direction or magnitude of findings) and insufficient to make any conclusions regarding its use in clinical practice.[204] The authors also noted a higher incidence of adverse events for slow-release oral morphine compared to other opioid agonist treatments.[204]

A 2017 Norwegian systematic review compared slow-release oral morphine to methadone. Three studies (n=460) were included in the review. The study authors concluded that there is probably no or little difference in treatment retention (moderate certainty); there may be little or no difference in unregulated opioid use (low certainty); there may be little or no difference in adverse events (low certainty); there is insufficient evidence to determine effect on patient satisfaction and criminal activity.[205] Overall, the evidence was assessed as having weaknesses that conferred low certainty in evidence of effect. Thus, the authors were unable to conclude whether SROM and methadone are equivalent. This study included 2 of the 3 studies included in the Cochrane review, as well as a 2014 RCT.[207]

A 2019 systematic review and meta-analysis included both published trials and unpublished data (n=471) on two outcomes: unregulated opioid use and retention in treatment.[206] This systematic review included all of the studies included in the prior two systematic reviews, as well as unpublished data. The meta-analysis found no significant differences between SROM and methadone for both outcomes. Results from two studies also suggest that SROM is superior to methadone in reducing opioid cravings; however, this was not included in the meta-analysis. The study authors concluded that, while gaps remain in the evidence base for SROM, this meta-analysis confirms the apparent non-inferiority of SROM with methadone.[206]

Finally, a 2022 systematic review and network meta-analysis (N=79; 4 studies involving SROM) compared the effectiveness of methadone, SROM, buprenorphine/naloxone, and naltrexone in terms of treatment retention.[123] Slow-release oral morphine had the highest average percentage of treatment retention across all studies (77.6%), followed by methadone and buprenorphine/naloxone respectively (64.1% and 54.3%). However, using a Bayesian ranking framework, the authors estimated SROM's treatment retention to be superior to buprenorphine and naltrexone and marginally inferior to methadone. The authors emphasized that confidence in estimates involving SROM was very low due to the small number of high-quality trials.[123] It was also noted that SROM was compared only with methadone, and all other pairwise comparisons involving SROM were based on indirect evidence.[123]

Several non-randomized studies have also assessed the safety and efficacy of slow-release oral morphine for treatment of OUD.[208] A multi-centre study including patients intolerant to or insufficiently responding to methadone (n=67) found that transitioning from methadone to slow-release oral morphine was relatively simple and well-tolerated by patients, with significant advantages observed over time, including reduced withdrawal symptoms and cravings, and improved physical and psychological health.[209] Similarly, a small open-label crossover study (n=18) assessed outcomes of transitioning patients from methadone to six weeks of slow-release oral morphine treatment, after which methadone treatment was resumed.[210]

Compared to methadone, slow-release oral morphine was associated with improved social functioning and reduced heroin craving, with no change in heroin use, depression symptoms, and overall health scores.[210] The majority of patients (78%) expressed a preference for slow-release oral morphine over methadone, with reasons including fewer and less severe side effects, feeling more "normal", and improved withdrawal suppression, sleep quality, and energy levels.[210] Several additional small non-randomized, uncontrolled studies have reported similar improvements in quality of life, withdrawal symptoms, opioid craving, and heroin use compared to baseline or pre-treatment levels.[211-213]

A 2021 observational study (n=4778) examining OAT retention rates in the Austrian healthcare system found that SROM had a substantially higher retention rate at 2 years compared to both methadone and buprenorphine/naloxone (OR=2.141, 95% CI 1.885–2.430).[214] At the start of the two-year study period, 36% of participants started SROM (compared to 30% starting a methadone formulation and 32% starting a buprenorphine formulation). At the end of the study period, the percentage of participants on SROM had increased to 39.9%. Slow-release oral morphine appeared to be the preferable option among this larger sample of individuals on OAT in the Austrian system.[214]

The evidence supporting the use of slow-release oral morphine for opioid use disorder has some limitations, including a relatively small body of evidence of low-to-moderate methodological quality and moderate heterogeneity and risk of bias.[206] There is also an absence of data establishing the extent of SROM's impact on opioid-related mortality. Although there is a less robust evidence base supporting the use of slow-release oral morphine for opioid use disorder compared to buprenorphine and methadone, clinical judgment and patient preference should guide what medication is selected.

Finally, it is important to note that only the once-daily, 24-hour formulation of slow-release oral morphine has been studied in clinical trials for the treatment of OUD. Other formulations of oral morphine, such as twice-daily, 12-hour sustained- or extended-release formulations have not been empirically studied in this context and are not recommended at the time of publication.

Initiation and dosing

Clear, evidence-based treatment protocols for the use of slow-release oral morphine to treat opioid use disorder have yet to be established; however, significant clinical experience has led to the development of initiation protocols based on known tolerance (lower and higher; see Appendix 3).

The average dose of slow-release oral morphine has been described in randomized controlled trials. In a 2011 trial, the average dose of slow-release oral morphine prescribed to participants was 791 +/- 233mg/day (approximately equivalent to 103 +/- 30mg/day of methadone), with both of the crossover trial's groups reporting over 80% retention rates on slow-release oral morphine and an observed dose-response relationship between increasing slow-release oral morphine dose and decreasing heroin-positive urine tests.[215] An earlier randomized controlled trial gave participants 60–180mg/day of slow-release oral morphine during a 6–7-day induction period before stabilizing on an average dose of 234.66 +/-189.55mg (range: 60–800mg). Compared to rates at admission, those who received slow-release oral morphine had significantly fewer cocaine- and opioid-positive urine tests.

There is no defined maximum dose for slow-release oral morphine. The highest dose described in the literature[q] to date is 1200mg[216]; however, clinical experience indicates that patients often require doses above 1200mg to manage cravings and withdrawal symptoms, due to high tolerance developed as a result of sustained exposure to fentanyl through the unregulated drug supply.[217]

For induction and dosing guidelines for slow-release oral morphine, refer to Appendix 3.

3.2.iv Selecting an Opioid Agonist Treatment Medication

Treatment retention

Data regarding comparative treatment retention among the 3 oral OAT medications is mixed. For example, a 2021 meta-analysis (N=10 RCTs, 3 observational studies; n=5,065) found that retention rates—both length of time retained in study and presence on final day of study—are generally equal for fixed-dose oral OAT with methadone and buprenorphine/naloxone; however, the average retention rate across studies was highly variable and the evidence quality was rated as low.[218] Conversely, data from 2012–2018 in BC found that buprenorphine/naloxone was twice as likely as methadone to be discontinued (slow-release oral morphine discontinuation was not reported).[124] It is not clear, however, if those individuals discontinuing medication transitioned to another OAT medication or discontinued OAT entirely. In addition, Austrian data from 2011–2012 found that slow-release oral morphine had a significantly higher retention rate compared to both methadone and buprenorphine/naloxone.[214]

Side effects and adverse events

The partial agonist properties of buprenorphine may be preferable to full agonist options in terms of reduced overdose potential.[139] A 2015 study of more than 19 million prescriptions over a six-year period in the United Kingdom found that buprenorphine was six times safer than methadone in terms of overdose risk.[219] Other

[q] Technically, doses above 1200mg were described in a 2006 prospective, open, non-comparative multi-centre study[25]; however, doses were expressed as a mean plus standard deviation (1104 ±348mg/day). Specific doses, including max dose, were not included.

studies have associated methadone with a four-fold higher risk of fatal overdose and a significantly higher risk of unregulated use compared to buprenorphine.[220,221] Reports, an expert panel, and a 2017 systematic review have all highlighted the substantial risks of fatal overdose during methadone treatment initiation.[111,197,222] Buprenorphine has a lower potential for respiratory depression and standard doses are well below the threshold lethal dose for opioid-naïve adults compared to standard methadone doses, which often exceed the threshold lethal dose.[221] Furthermore, methadone has higher potential for adverse drug–drug interactions with many common medications (e.g., antibiotics, antidepressants, antiretrovirals).

Methadone is also associated with an increased risk of QT prolongation; one study estimated that up to 15% of patients receiving methadone may experience QT prolongation.[223,224] However, the maximum estimated mortality attributable to QTc prolongation is low: 0.06 per 100 patient-years.[223] Research to date has not established a clear association between buprenorphine and QTc prolongation, although some mixed results have been reported in the literature[223,225-229] While information on the clinical significance of an association between buprenorphine and QTc prolongation is also limited, available data suggests that effect of buprenorphine formulations on QTc interval does not reach the level of clinical concern and is not associated with increased risk of cardiac arrhythmia.[229,230] These findings notwithstanding, the product monograph for buprenorphine/naloxone notes that products containing buprenorphine may be associated with QTc prolongation and warns against the use of buprenorphine/naloxone in individuals with a history of long QT syndrome, as well as those taking certain classes of antiarrhythmic medications.[136] Additional guidance on drug-drug interactions that may increase risk of QTc prolongation can be found in the product monograph.[136] Guidance on a step-wise approach to assess drug interactions that may impact the QT interval can be found here.[231]

Considerations for treatment initiation

The traditional method for buprenorphine/naloxone induction requires a period of withdrawal which makes the initiation of buprenorphine/naloxone treatment significantly more challenging than full agonist options (see Appendix 3).[232] Newer low-dose induction protocols have been developed that do not require patients to reach moderate withdrawal prior to initiation. Admission to an inpatient treatment facility (i.e., inpatient withdrawal management, bed-based treatment facilities, inpatient monitoring settings) for supervised, medically-managed buprenorphine/naloxone induction may also be considered, as these facilities can provide more intensive monitoring, support, and symptom management to patients during challenging inductions.

Differences in take-home dosing considerations

Because of its partial agonist effect and superior safety profile, buprenorphine/naloxone is often prescribed as take-home dosing immediately or soon after initiation, whereas patients on methadone or SROM are required to receive daily witnessed ingestion (DWI) dosing until a stable dose is achieved for a minimum of 4 weeks. Additionally, it is easier to switch from buprenorphine/naloxone to full agonist options than from methadone and SROM to buprenorphine/naloxone.[233,234] These are factors that may make buprenorphine/naloxone a preferable option in the absence of contraindications.

Gender-related differences

While opioid use is generally more prevalent among men than women,[235] there do not appear to be significant sex-based differences in treatment outcomes for buprenorphine/naloxone compared to methadone.[236,237] A 2015 systematic review and meta-analysis of sex differences in outcomes of methadone treatment found no significant differences in opioid use, treatment retention, or methadone dosage, but did find male participants more likely to report alcohol use and female participants more likely to use amphetamines.[238] A 2019 systematic review concluded that, due to conflicting findings and heterogeneous methods, it is unclear whether there are sex-based differences in treatment retention for men and women being treated with buprenorphine.[239]

Additional information on sex and gender in relation to opioid use disorder can be found in Sex, Gender, and Sexuality in this document. For guidance on the care of pregnant people with opioid use disorder, consult the *Treatment of Opioid Use Disorder During Pregnancy—Guideline Supplement.*

Summary

As demonstrated in Table 2, below, a variety of factors are relevant in selecting an opioid agonist medication. Prescribers should work with each patient to determine which medication is best suited, based on their circumstances, goals, and previous treatment experiences.

Table 2. Decision Support Tool for Selecting OAT

	Buprenorphine-based formulations		Methadone	SROM
	Buprenorphine/naloxone	Extended-release buprenorphine		
Retention in treatment	May be slightly lower than methadone; retention improves at higher doses (above 16mg)	Substantially higher than placebo	Potentially slightly better treatment retention than buprenorphine/naloxone	Non-inferior to methadone
Initiation				
Requires withdrawal prior to induction	Traditional induction: Yes. Requires moderate withdrawal prior to induction Low-dose induction: No. Does not require prior withdrawal, allowing for comfortable start	No. Does not require a period of withdrawal, but requires prior stabilization on sublingual buprenorphine/naloxone	No. Does not require a period of withdrawal. May be easier to initiate	No. Does not require a period of withdrawal. Comparable process to methadone, with faster titration

	Buprenorphine-based formulations		Methadone	SROM
	Buprenorphine/naloxone	Extended-release buprenorphine		
Time to achieve therapeutic dose	Traditional induction: (1–3 days) Shorter time to achieve therapeutic dose Low-dose induction: (5–10 days) Takes longer to reach therapeutic dose	Two months on 300mg injections, followed by 100mg maintenance dose	(May take weeks) Longer time to achieve therapeutic dose	1–2 weeks
Requires stabilization on oral OAT prior to initiation	N/A	Requires stabilization on sublingual buprenorphine/naloxone prior to initiation	N/A	N/A
Safety				
Risk of overdose	Low. Due to ceiling effect for respiratory depression in the absence of concurrent use of central	Low. Due to ceiling effect for respiratory depression in the absence of concurrent use of	Higher. Particularly during treatment initiation	Comparable safety profile to methadone, though less well-described

	Buprenorphine-based formulations		Methadone	SROM
	Buprenorphine/naloxone	Extended-release buprenorphine		
	nervous system (CNS) depressants	central nervous system (CNS) depressants		
Drug-drug interactions	Few	Few	Higher potential for adverse drug-drug interactions (e.g., antibiotics, antidepressants, antiretrovirals)	Fewer than methadone
QT prolongation	Low likelihood	Low likelihood	Associated	Not associated
Risk of precipitated withdrawal during initiation	Yes	No	No	No
Side effects				
Side effects	Milder side effect profile	Medication adverse effects are similar to buprenorphine/naloxone	More severe dose-dependent side effect profile (e.g., sedation, weight gain,	Comparable to methadone, though less well-described

	Buprenorphine-based formulations		Methadone	SROM
	Buprenorphine/naloxone	Extended-release buprenorphine		
		Injection site pain and pruritus	erectile dysfunction, cognitive blunting)	Possibly fewer subjective side effects
Dosing				
Dosing	Health Canada-approved maximum dose of 24mg, but higher doses (up to 32mg) may be necessary for some patients Alternate day dosing possible May be suboptimal for individuals with very high opioid tolerance	First two months: Monthly dose of 300mg. Maintenance dose: Monthly dose of 100mg (though some patients may benefit from remaining at a 300mg maintenance dose)	No maximum dose specified in the product monograph	No maximum dose specified in the product monograph

	Buprenorphine-based formulations		Methadone	SROM
	Buprenorphine/naloxone	Extended-release buprenorphine		
Take-home doses	Suitable for immediate take-home doses, including take-home initiation when indicated, which may contribute to increased patient autonomy and cost savings Advantageous for rural and remote locations	N/A	Take-home dosing can be started gradually after 4 consecutive weeks of: • Medication adherence with DWI • Clinical and psychosocial stability	Take-home dosing can be started gradually after 4 consecutive weeks of: • Medication adherence with DWI • Clinical and psychosocial stability
Rotation				
Rotation	Easier to rotate from buprenorphine/naloxone to methadone or SROM	Comparable to buprenorphine/naloxone	Risk of precipitated withdrawal when rotating to buprenorphine/naloxone	Risk of precipitated withdrawal when rotating to buprenorphine/naloxone

	Buprenorphine-based formulations		Methadone	SROM
	Buprenorphine/naloxone	Extended-release buprenorphine		
			May be rotated directly to SROM	May be rotated directly to methadone
Tapering off				
Tapering off	Milder withdrawal symptoms; easier to discontinue. May be a better option for individuals with lower-intensity physical opioid dependence	Milder withdrawal symptoms Buprenorphine concentrations are decreased slowly over time following the last injection and may take months for buprenorphine to leave the system completely	More severe withdrawal symptoms	Comparable to methadone

3.2.v Initiating OAT in Inpatient Settings

Given the high rates of hospitalization among individuals with OUD, inpatient settings present a significant opportunity to engage individuals in evidence-based OUD care and promote harm reduction. However, as summarized below, there is currently a limited body of research evaluating OAT initiation in inpatient settings.

Two RCTs published in 2014 and 2019 used similar protocols to randomize participants into a 5-day buprenorphine/naloxone taper over group or a buprenorphine/naloxone OAT initiation group with inpatient dose stabilization and linkage to an affiliated OAT or primary care program.[240] The 2019 RCT (N=115) found that linkage participants (n=56) had lower rates of unregulated opioid use at days 12 (b=-6.81, 95% CI: 9.69; -3.92, *p*<0.001), 35 (b=-8.55, 95% CI: 11.63; -5.47, p<0.001), 95 (b=-7.34, 95% CI: 10.59; -4.11, p<0.001), and 185 (b=-3.52, 95% CI: 7.07; 0.27, p=0.052).[240] Linkage participants also had higher prescription buprenorphine use rates at all assessments (p<.001) than taper participants (n=59).[240] The 2014 RCT (N=139) similarly found that linkage participants (n=72) were more likely than those in the taper group to enter OAT (n=67; 72.2% vs. 11.9%; p<.001) and receive buprenorphine-based OAT at 6 months (16.7% vs. 3.0%; p=.007), and reported lower rates of previous-month opioid use at 6 months (incidence rate ratio: 0.60; 95% CI: 0.46–0.73; p<.01).[241] These findings accord with a 2015 retrospective case series (N=47) that found that just under half of the patients (n=22; 46.8%) initiated on buprenorphine successfully initiated office-based treatment within 2 months of being discharged from the hospital.[242]

The literature on inpatient methadone initiation is also scant. One 2022 retrospective cohort analysis of patients who received a medical consult and community care transition services for OUD (N=152) compared methadone to buprenorphine/naloxone for inpatient OAT initiation in terms of the duration of community-based treatment retention post-discharge.[243] Post-discharge treatment retention rate among patients who chose buprenorphine (n=106) was 37% at 2 weeks, 26% at 30 days, and 13% at 12 weeks; the retention rates for the same respective follow up times among patients who selected methadone (n=46) was 43%, 39%, and 35%. Methadone was associated with increased probability of retention in outpatient treatment as compared to buprenorphine (P<0.01). While acknowledging the limitations of this retrospective study and calling for experimental research to establish the effectiveness of inpatient methadone initiation, the authors concluded that this medication can be effectively initiated in hospital and may have a higher probability of treatment retention. [243]

Other investigations of methadone initiation in inpatient settings include a 2019 retrospective chart review from an acute pain service initiating methadone treatment in hospitalized patients with acute pain[244] and a 2019 case study from Vancouver, BC, in which a patient at St. Paul's Hospital was successfully rapidly titrated onto methadone (see Rapid Titration in Monitored Settings for more information on the protocol used).[245]

Barring specific contraindications or concerns, both traditional induction and rapid titration protocols may be used for inpatient inductions (see Appendix 3).

3.2.vi Take-home OAT Dosing

Given the significant pharmacologic and pharmacokinetic differences among OAT medications, practice standards for take-home dosing have been informed by each medication's safety profile based on the best available data. Overall, methadone has been represented in significantly more overdose deaths than buprenorphine,[120,173,174] which has led to differing regulations for dose dispensation and monitoring.

Take-home dosing has become a standard approach for buprenorphine/naloxone treatment, whereas methadone and slow-release oral morphine treatment have remained heavily reliant on the use of daily witnessed ingestion (DWI), with graduated take-home dosing provided only when patient stability[r] is clearly demonstrated and routinely assessed.[192,246]

Existing protocols that emphasize supervised dosing and restrictive criteria for methadone carries cite research associating witnessed dosing with decreased risk of methadone diversion and methadone-involved overdose.[176,178,180,181] For example, a 2010 analysis of methadone-involved deaths (n=5624) across England and Scotland between 1993 and 2008 reported that the adoption of supervised dosing policies after 1995 was associated with a four-fold reduction in methadone-related overdose deaths per defined daily dose of methadone administered, in both countries.[178] However, a 2017 systematic review (N=6 studies; n=7999 participants) evaluating DWI compared to take-home dosing for individuals on OAT with methadone and buprenorphine found no evidence showing a difference in rates of medication diversion between those who did and did not receive carries, in either buprenorphine or methadone groups.[247] Emphasizing the small number and low quality of studies, the authors called for more research to assess the risk of diversion and the impact of supervised and unsupervised dosing on patient and public safety.[247]

Although more robust research is needed to characterize the impact of take-home dosing on rates of diversion and related safety risks, its impact on treatment engagement has been described in more detail. Quick transition to take-home buprenorphine/naloxone dosing has been shown to improve treatment adherence and retention.[248,249] Conversely, restricted access to take-home methadone and SROM, and the requirement of daily travel to a pharmacy for witnessed ingestion has been widely criticized by patients and prescribers as stigmatizing and disruptive to daily life, and has been shown to act as a barrier to OAT engagement and retention.[250-253]

During the COVID-19 pandemic, protocols for take-home OAT dosing in both Canada and the United States were temporarily relaxed in order to facilitate social distancing and self-isolation without impeding access to OAT medications. These changes have presented an opportunity to evaluate the efficacy and safety of increased

[r] The term stability generally refers to the two facets of clinical stability (e.g., absence of cravings, improved sleep quality and duration, and overall wellbeing) and psychosocial stabilization (e.g., integrating new activities, re-connecting with family, and attaining safe housing). Assessment of stabilization or destabilization is patient-specific, depending on each patient's circumstances and needs and how they change over time. In the context of assessment of sufficient stability for carries during clinical visits, absence of severe sedation, ability to attend appointments, absence of severe behavioural issues at the clinic, and absence of unstable psychiatric comorbidities (e.g., psychosis, suicidality) can be indicators of clinical and psychosocial stability.

carries in the context of the current opioid overdose emergency.[254] For example, in March 2020, Substance Abuse and Mental Health Services Administration (SAMHSA), issued an exception allowing prescribers to provide up to 28 consecutive days of take-home methadone doses to patients who are stable[s] on this medication, and up to 14 methadone doses to "less stable patients".[254] In March 2022, SAMHSA extended this exemption for one year after the end of the COVID-19 Public Health Emergency in reference to reports of improved treatment engagement and patient satisfaction as a result of implementing these changes, with few incidents of unprescribed use or diversion of medication.[255,256]

Similarly, in Ontario, the Centre for Addiction and Mental Health (CAMH) released the COVID-19 Opioid Agonist Treatment Guidance in collaboration with META-PHI which recommended the expansion of access to take-home dosing in order to facilitate continuity of OAT during the pandemic. The CAMH guidance document encourages clinicians to utilize their clinical judgment of the patient's clinical and psychosocial stability and ability to safely manage carries (e.g., not sedated at the time of dose dispensation, no acute psychiatric comorbidities, ability to safely store medication), rather than urine drug tests, to determine suitability for carries. Under this guidance, patients could be assessed remotely for carries, and patients who report continued use of unregulated substances would still be allowed to get carries unless they do not meet the program's social stability criteria. Although this document did not provide specific guidance pertaining to SROM, it recommended that clinicians consider SROM carries on a case-by-case basis, modifying existing practices as needed to ensure continuity of OAT. Emerging data demonstrate a significant increase in the number of take-home doses dispensed in both Canada and the US after these changes in regulations.[256-259]

Most early evaluations of the impact of increased access to take-home dosing on treatment outcomes have reported no increase in adverse outcomes, such as overdose events or hospital admissions, associated with more relaxed take-home protocols.[256-263] For example, a 2022 cross-sectional study reported on the experiences of Ontario-based OAT patients (n=402) and prescribers (n=100) with the modified take-home dosing criteria in the six months following the release of CAMH's modified OAT guidance due to the pandemic.[259] Participating patients were most frequently prescribed methadone (30%), while 21% were prescribed SROM and the remaining patients received buprenorphine/naloxone or a combination of OAT medications. The authors found no statistically significant differences in the likelihood of self-reported opioid overdose events, emergency department visits from substance use, or hospital admissions due to substance use between individuals who received additional take-home doses and those who did not.[259] Additionally, those who received additional take-home OAT doses were no more likely to request early refills or report lost or stolen doses compared to individuals

[s] SAMHSA's general criteria for patient stability and suitability for carries include no recent unregulated opioid use, regular clinic attendance, absence of serious behavioral problems at the clinic, stable home environment, sufficient duration of OAT retention, ability to safely store medication, and assessment suggesting that the benefit of carries outweigh the risks. In response to the exemption issued due to COVID-19, many programs simplified these criteria (e.g., limited to absence of severe behavioral concerns in the clinic and ability to manage and store medication) based on clinical judgement.

who did not receive additional unsupervised doses. The majority of prescribers (68%,) reported that providing additional take-home doses improved their relationship with their patients.[259]

A 2022 Ontario-based retrospective cohort study involving 5,852 participants who normally receive daily dispensed methadone also explored the impact of increased take-home doses in response to the pandemic on treatment retention and opioid-related harm.[260] The results showed that the initiation of take-home methadone doses, compared to no change in carries, was significantly associated with lower risks of opioid overdose, (6.9% vs 9.5%/person-year; weighted hazard ratio [HR] 0.73; 95% confidence interval [CI]: 0.56 to 0.96), treatment discontinuation (51% vs. 63.6%; HR 0.80; 95% CI: 0.72 to 0.90), and treatment interruption (19% vs. 23.9%; HR 0.80; 95% CI: 0.67 to 0.95).[260]

While observational program evaluation studies to date have reported no adverse outcomes resulting from relaxed take-home dosing policies, a number of articles report an upward trend in methadone-involved overdoses[t] in the US, which corresponds with the take-home dosing policy change.[264-266] A 2023 analysis of data from the US Center for Disease Control reported a 48% increase in the number of overdoses involving methadone between 2019 and 2020.[266] However, the authors also noted the overall rise of drug toxicity deaths involving other substances during this period, and acknowledged that the change in methadone-involved deaths could be attributable to factors other than modified take-home dosing policies.[266] Similarly, a 2023 analysis of monthly overdose death databases reported a 51.7% increase in methadone-involved deaths where synthetic opioids were not implicated; however, due to the presence of a wide range of other substances, it was not possible to attribute these deaths to methadone alone.[264] Finally, a 2022 population-level analysis found a 5.3% increase in the number of methadone exposure reports to American Association of Poison Control Centers' National Poison Data System following the loosening of OAT regulations in response to COVID-19.[265] However, the authors emphasized that many other factors (e.g., Medicare and Medicaid expansion, increased number of OAT programs during this period) may have contributed to this increase.[265]

The role of more flexible take-home dosing in promoting treatment engagement and retention is an increasingly significant consideration in the current opioid overdose death crisis resulting from the high toxicity of the unregulated drug supply. In this climate, the urgency of reducing the reliance of people with OUD on unregulated drugs by removing barriers to treatment engagement and retention is vitally important, especially given the current low OAT retention rates (16% retention rate beyond 12 months, according to a 2020 cohort study in BC).[267]

In the absence of robust data determining the optimal approach to take-home dosing, this guideline endorses more restrictive criteria and considerations for methadone and SROM carries in comparison to

[t] It is worth noting that the increased presence of a medication as a "bystander" drug in toxicology reports is often an expected occurrence following increased availability or utilization; it may not be significantly concerning unless an increase in the overall drug toxicity deaths is observed.

buprenorphine/naloxone. However, it also encourages prescribers to base decisions regarding carries on an individualized and flexible assessment of each patient's needs and circumstances, and to consider the risk of treatment discontinuation along with other patient and public safety considerations, in keeping with the College of Physicians and Surgeons of BC's Safe Prescribing of Opioids and Sedatives Practice Standard. To support prescribers in doing this, this guideline presents modified take-home dosing guidance adapted from META-PHI's *A New Framework for Methadone Carries: A Person-centred Evidence-informed Approach to Take-home "Carry" Dosing*.

See Appendix 6 for detailed guidance on take-home dosing.

3.2.vii Injectable Opioid Agonist Treatment

Individuals with opioid use disorder may face a number of barriers to initiation of, and retention in, oral OAT, including inadequate management of opioid cravings and withdrawal symptoms despite appropriate OAT dose adjustments; adverse events associated with oral OAT; contraindications to one or more oral OAT medications; insufficient improvements in health, social function, or quality of life; or patient preference to not initiate oral OAT. Injectable opioid agonist treatment (with injectable diacetylmorphine or injectable hydromorphone) is a component of the continuum of OUD treatment that is generally considered for individuals with severe OUD who inject opioids and have not adequately benefitted, or are not expected to benefit, from oral OAT options for the reasons cited above.[268,269]

Meta-analyses to date have shown that, among individuals who are treatment refractory to methadone, prescription injectable diacetylmorphine—administered under the supervision of trained health professionals in a clinic setting—reduces unregulated opioid use, treatment drop-out, criminal activity, incarceration, and mortality.[270-273] A 2011 Cochrane Review that examined eight randomized controlled trials found that the supervised injection of diacetylmorphine, paired with flexible doses of methadone, was superior to oral methadone alone in retaining patients who had not previously benefited from methadone in treatment and reducing the use of unregulated drugs.[270] The authors of the Cochrane review concluded that there is value in co-prescribing diacetylmorphine with flexible doses of methadone and that, due to the higher risk of adverse events, treatment with diacetylmorphine should be considered for those who have not benefited from oral opioid agonist treatment.[270] In 2015, the lead investigators of iOAT treatment trials conducted a systematic review and meta-analysis on the efficacy of injectable diacetylmorphine, to complement the Cochrane Review.[271] Six randomized controlled trials (in Switzerland, the Netherlands, Spain, Germany, Canada, and England) were identified and included in the analysis, which found greater reductions in unregulated heroin use among individuals who received supervised injectable diacetylmorphine compared to those who received oral methadone treatment only.[271] Further supporting the use of iOAT for those who have not benefitted from oral OAT, a 2017 evidence review undertaken and released by Public Health Ontario concluded that the available literature on iOAT demonstrates efficacy for iOAT over methadone in terms of treatment retention, reduction in unregulated drug use, and reduction in criminal activities.[274]

It should be noted that, despite the evidence base supporting the efficacy of iOAT, the resource intensive nature of iOAT programs has limited its accessibility in many jurisdictions across BC.

Co-prescribed iOAT and oral OAT

Oral OAT is frequently co-prescribed with iOAT in order to prevent withdrawal and cravings between iOAT doses, particularly overnight during the longest between-dose period, as the injectable medications are relatively short-acting. Co-prescription of oral and injectable OAT helps meet the needs of patients with high opioid tolerance, and supports greater clinical stability. Another potential benefit of co-prescription of oral OAT may be the facilitation of transitions to oral OAT alone. Clinical trials have included co-prescribed methadone, however, SROM may also be considered.[u]

Buprenorphine/naloxone is generally not co-prescribed with iOAT; due to its high affinity for the opioid receptor, buprenorphine/naloxone preferentially binds to the receptor and blunts the effect of iOAT doses.

Comprehensive clinical guidance on the treatment of opioid use disorder with injectable opioid agonist treatment can be found in the BCCSU, Ministry of Health, and Ministry of Mental Health and Addiction's *Guidance for Injectable Opioid Agonist Treatment for Opioid Use Disorder* and the Canadian Research Initiative in Substance Misuse's (CRISM) *National Injectable Opioid Agonist Treatment Clinical Guideline*.

3.2.viii Treatment Duration and Discontinuation

Retention in OAT is associated with substantial reduction in all-cause and overdose mortality,[111] whereas abundant observational evidence has associated discontinuation of OAT medications with high rates of return to unregulated opioid use[275,276] and subsequent drug toxicity death.[111,277,278] In reference to these findings, national and international clinical guidelines define OAT as an open-ended treatment.[279]

The research on withdrawal management strategies to minimize the risk of relapse and related harms for patients who expressly request to discontinue OAT is limited to a small number of observational studies. For example, a 2012 population-based retrospective study involving participants who received methadone for OUD in BC (n=4,813) found that tapers that last more than 52 weeks had consistently higher odds of sustained success compared to tapers that took less than 12 weeks (OR=6.68; 95% CI: 5.13 – 8.70), regardless of time in treatment prior to initiating taper.[280] The authors also found that a stepped tapering protocol, with dose decreases scheduled for 25–50% of the weeks, provided the highest odds of sustained success (vs. <25%: 1.61 (1.22–2.14)) which was defined as no treatment re-entry, opioid-related hospitalization, or mortality within 18 months following treatment completion. However, the authors noted that the overall rate of sustained success was very low (13%).[280]

[u] See CRISM's *National Guideline for the Clinical Management of Opioid Use Disorder* for a review of evidence supporting the use of slow-release oral morphine more broadly for opioid use disorder.

A 2022 cohort study in Ontario (n=5,774) also explored taper characteristics that were associated with a lower risk of opioid overdose after discontinuation of OAT with buprenorphine/naloxone.[281] The authors found that a treatment duration of longer than 1 year prior to initiating taper (vs. ≤1 year; aHR: 0.69; 95% CI: 0.48-0.997), lower rate of taper (≤2 mg per month vs >4 mg per month, aHR, 0.65; 95% CI, 0.46-0.91), and a slower taper protocol with dose decreases scheduled in 1.75% or less of days during the taper (aHR: 0.64; 95% CI: 0.43-0.93) were associated with reduced risk of opioid overdose.[281]

Overall, available observational evidence suggests that longer duration of treatment prior to initiating a taper and a slower taper schedule may reduce the risk of return to unregulated opioid use.

3.2.ix Recommendations and Remarks for Opioid Agonist Treatment

Based on a review of evidence supporting the safety and efficacy of OAT medications, this guideline recommends the following:

Recommendation 1. Offer of OAT to all patients with OUD

Adults with opioid use disorder should be offered opioid agonist treatment as the standard of care.	
Quality of Evidence: High	Strength of Recommendation: STRONG
Remarks: • The quality of evidence for this recommendation was rated as high based on multiple systematic reviews demonstrating that OAT is effective in improving treatment retention and reducing unregulated opioid use and related morbidity and mortality • This recommendation was rated as strong based on the quality of evidence supporting the efficacy and safety of OAT and guideline committee consensus.	

Recommendation 2. Selection of oral OAT medication

Prescribers should work with each patient to determine which of the following opioid agonist treatment medications is most appropriate based on the patient's circumstances, goals, and previous treatment experiences. • Buprenorphine/naloxone • Methadone • Slow-release oral morphine	
Quality of Evidence: Buprenorphine/naloxone and methadone: High Slow-release oral morphine: Moderate	Strength of Recommendation: STRONG
Remarks: • The guideline committee emphasizes the importance of a collaborative, patient-centred approach to treatment selection.	

- However, this move away from ranking oral OAT medications is not intended to equate them in terms of safety and efficacy evidence. While available data generally supports SROM's non-inferiority to other OAT options, further research is needed to comprehensively characterize SROM's comparative risks and benefits. There is also an absence of data establishing the extent of SROM's impact on opioid-related mortality. These facts are reflected in the "moderate" quality of evidence assigned to SROM for this recommendation.
- Clinicians should offer patients consultation on the risks and benefits of all three OAT medications prior to medication selections
    - Clinicians whose current scope of OAT prescribing is limited to buprenorphine/naloxone should provide information on all 3 medications and offer appropriate referrals to a prescriber of these medications if needed
- Individual factors to consider for treatment selection may include:
    - Initial presentation
    - Comorbidities that may be a contraindication for specific OAT options
    - Drug–drug interactions
    - Treatment preferences and goals
    - Lifestyle requirements (e.g., remote location or frequent travel indicate a preference for medications or formulations that allow more flexibility with dosing and carry protocols)
    - Previous experience with OAT
- In the absence of patient preference or other patient-specific factors that would favour other medications, buprenorphine/naloxone may be considered as the favourable option due to its superior safety profile.

Recommendation 3. Transition between OAT medications

Transition between opioid agonist treatment medications should be facilitated if indicated by clinical circumstances or patient preference.	
Quality of Evidence: Low	Strength of Recommendation: STRONG

Remarks:

- Available guidelines and clinical experience support the feasibility of transition between medications if indicated by patient preference or individual circumstances.
- For example, patients stable on other OAT medications may wish to transition to buprenorphine/naloxone for a range of reasons including:
    - Fewer side effects
    - Possibility for transition to the monthly extended-release buprenorphine formulation
    - Increased treatment flexibility
- Prior to conducting the transition, clinicians should discuss the risks of switching medication, such as the risk of withdrawal and cravings during the period of transition. The risks and benefits of transition between OAT medication should be weighed carefully for patients who are stable on their current medication.

Recommendation 4. Extended-release buprenorphine

Patients stable on 8mg–24mg sublingual buprenorphine/naloxone may be offered the monthly extended-release formulation of buprenorphine if indicated by patient preference or circumstances.	
Quality of Evidence: Low	Strength of Recommendation: STRONG

Remarks:

- This recommendation has been predominantly graded based on two clinical trials demonstrating extended-release buprenorphine's effectiveness in treatment retention and reduction in unregulated opioid use.
- The extended-release formulation of buprenorphine is administered monthly via abdominal subcutaneous injection, which, according to observational findings, may be preferable for patients seeking to enhance convenience and flexibility and to reduce their medication burden.
- Data on the characteristics of patients who benefit from transitioning to extended-release buprenorphine is limited and continues to evolve. Discussion of potential risks and benefits, informed consent, and regular follow-up should be considered key components of care.
- The Health Canada-approved formulation of extended-release buprenorphine (Sublocade) is indicated for patients who have been clinically stabilized on 8mg to 24mg of sublingual buprenorphine/naloxone for a minimum of 7 days. However emerging clinical experience, represented in a number of case reports, supports the safety and tolerability of starting extended-release buprenorphine following shorter periods on buprenorphine/naloxone.
- The Sublocade Product Monograph recommends a monthly maintenance dose of 100mg following two initial monthly doses of 300mg. However, some patients (e.g., those who were previously stabilized on >24mg sublingual buprenorphine/naloxone) may benefit from an extended-release buprenorphine maintenance dose of 300mg/month.

Recommendation 5. Injectable opioid agonist treatment

Injectable opioid agonist treatment with diacetylmorphine or hydromorphone should be considered for adults with severe opioid use disorder and ongoing unregulated injection opioid use who have not benefitted from, or have declined, oral options for opioid agonist treatment.	
Quality of Evidence: Moderate	Strength of Recommendation: WEAK (CONDITIONAL)

Remarks:

- Due to the rapid onset of action and shorter time to peak effects (including respiratory depression) that is achieved with the injection of high-dose full agonist opioid medications, iOAT is generally self-administered in clinical settings with sterile supplies and under supervision of qualified staff trained to intervene in the event of an adverse event or emergency.
- Both diacetylmorphine and hydromorphone may be considered reasonable iOAT options. Selection may be made based on availability, patient preference, and prescriber judgement. If the individual is not benefitting from

the treatment or is experiencing unacceptable side effects, they should be given the option to transition to the other medication.

- In keeping with World Health Organization recommendations for other opioid agonist treatments, iOAT should be provided as an open-ended treatment.
- Injectable opioid agonist treatment can be provided alone or with co-prescribed oral OAT to adequately address patients' withdrawal symptoms and cravings.

Recommendation 6. Tapering off OAT

Opioid agonist treatment should be viewed as an open-ended treatment. However, if a patient wishes to discontinue medication following a sustained period of stability on opioid agonist treatment (12 months or more), a slow taper should be offered.	
Quality of Evidence: Moderate	Strength of Recommendation: STRONG

Remarks:

- It is well-established that individuals who discontinue OAT are at increased risk of return to unregulated opioid use and related harms including drug toxicity death. Clinicians should discuss these risks with patients and advise ongoing engagement in treatment.
- Patients who expressly wish to discontinue treatment should be advised to consider a gradual taper schedule to the extent possible.
- This is based on retrospective observational data associating longer time in treatment prior to initiating taper (≥1 year vs <1 year) and a slow rate of taper (>52 weeks vs. <12 weeks) with higher rates of successful taper and lower risk of subsequent opioid overdose.

Recommendation 7. Relapse prevention support for people who wish to discontinue OAT

For adults who choose to discontinue OAT, a relapse prevention plan should be collaboratively developed and implemented after a discussion of both pharmacological and non-pharmacological options.	
Quality of Evidence: Low	Strength of Recommendation: STRONG

Remarks:

- Patients who plan to discontinue OAT should receive information on the full range of pharmacological and non-pharmacological strategies to reduce the risk of return to unregulated opioid use and related harms, including drug toxicity death.
- Pharmacological strategies to consider may include:
    - Prescribing PRN buprenorphine/naloxone (i.e., a small "pill-in-pocket" supply to facilitate re-induction)
    - Offering PO naltrexone as maintenance treatment
- Non-pharmacological relapse prevention measures may include referral to psychosocial treatment interventions and community-based supports and programs.
- Patients should be informed that both oral naltrexone and psychosocial interventions have limited effectiveness as standalone treatment strategies. Close monitoring and other relapse prevention approaches, such as PRN buprenorphine/naloxone, should be considered in addition to any other selected relapse prevention approach.

3.3 Opioid Antagonist Treatment

3.3.i Oral Naltrexone

Naltrexone is an opioid receptor antagonist that blocks the euphoric effects of opioids at adequate doses.[282] Potential benefits of naltrexone include ease of administration, lack of induced tolerance during long-term treatment, and lack of potential for dependence or non-medical use.[283] However, as an opioid antagonist, naltrexone fully blocks the effects of all opioid medications, including opioid analgesics prescribed for pain. Additionally, the reduced tolerance to opioids facilitated by the use of naltrexone increases the risk of overdose for patients who stop taking the medication and subsequently relapse to opioid use, as demonstrated by a non-randomized study of oral naltrexone-associated mortality rates that were three to seven times higher than methadone-related mortality rates in Australia.[284]

Oral naltrexone has been shown to have limited benefits over placebo.[285] For example, a 2011 meta-analysis found no statistically significant differences in retention or abstinence rates for oral naltrexone compared to placebo or no treatment.[285] The only outcome that favoured oral naltrexone over placebo was reduced re-incarceration rates, but this finding was limited to 2 of the 13 randomized trials included in the review.[285] Based on limited data, review authors also concluded that oral naltrexone was not superior to psychotherapy alone (two studies), benzodiazepine-based treatment (one study), or buprenorphine monotherapy (one study) in terms of retention in treatment, abstinence from opioid use, and reported side effects.[285] Across studies, treatment retention rates were low with oral naltrexone treatment (28%).[285] Of note, a single randomized trial published subsequent to the meta-analysis reported a significantly higher proportion of opioid-negative urine tests among individuals on oral naltrexone (42.7%) compared to placebo (34.1%).[286]

A 2019 study randomized patients to continue oral naltrexone (n=32) or switch to extended-release naltrexone (n=28) following medication-assisted detoxification and a 50mg naltrexone challenge. Individuals randomized to extended-release naltrexone were retained in treatment for 6 months at over twice the rate of those on oral naltrexone (57.1% vs. 28.1%).[287]

Oral naltrexone is a regular benefit medication for patients enrolled in Fair PharmaCare, Plan B (Licensed Residential Care Facilities), Plan C (Income Assistance), Plan G (Psychiatric Medications), and Plan W (First Nations Health Benefits). Note that Fair PharmaCare coverage is income-based, and eligible costs may be subject to a deductible.

3.3.ii Extended-release Naltrexone

Extended-release naltrexone via monthly intramuscular injection may promote improved treatment adherence in comparison to oral naltrexone.[282] Several randomized controlled trials have found that injectable naltrexone is superior to placebo in terms of improved retention in treatment, increased abstinence rates, and decreased opioid cravings.[288-290] In addition, two systematic reviews evaluating extended-release naltrexone were published in 2018.[291,292]

One systematic review synthesized the existing literature on extended-release naltrexone induction and adherence and opioid use during treatment.[291] While acknowledging that the heterogeneity of study designs (randomized controlled trials, non-randomized studies, and cohort studies) and outcome measures were not conducive to performing a meta-analysis, the authors drew 2 key conclusions: The first is that many people aiming to initiate treatment with extended-release naltrexone do not successfully initiate treatment, likely due to the requirement to discontinue opioid use prior to initiation. The second is that the majority of those who successfully start treatment with extended-release naltrexone prematurely discontinue treatment.[291]

The other systematic review compared extended-release naltrexone to buprenorphine/naloxone and found extended-release naltrexone to be non-inferior on a variety of abstinence-related outcomes.[292] Extended-release naltrexone was also associated with a significant reduction in heroin use, but not other unregulated opioids. However, extended-release naltrexone was found to be inferior to buprenorphine/naloxone in terms of both relapse rates and discontinuation during induction.[292] These findings were based on two key studies described below.[293,294]

More recently, a 2020 systematic review and meta-analysis among justice-involved individuals, assessed the effectiveness of both oral (4 RCTs) and extended-release (7 RCTs) naltrexone in treatment retention. The findings showed that extended-release naltrexone had a statistically significant impact on treatment retention while no statistically significant change in retention was observed with oral naltrexone.[295]

A 2018 multi-site randomized controlled trial randomized participants to either extended-release naltrexone (n=283) or buprenorphine/naloxone (n=287).[293] Far fewer participants were initiated onto naltrexone than buprenorphine/naloxone (72% [204/283] vs. 94% [270/287]). While per-protocol analysis found similar 24-week relapse rates across groups (52% for extended-release naltrexone vs. 56% buprenorphine/naloxone), extended-release naltrexone relapse rates were higher than buprenorphine/naloxone (65% vs. 57%) in intent-to-treat analysis. The difference was almost entirely accounted for by early relapse in those participants unable to successfully initiate treatment with extended-release naltrexone. Per-protocol analysis of urine drug tests and opioid abstinent days found little difference. Participants' self-reported cravings were lower with extended-release naltrexone initially, but comparable to buprenorphine/naloxone by week 24.[293]

This accords with a 2017 multi-site non-inferiority trial which randomized participants to either extended-release naltrexone (n=80) or sublingual buprenorphine/naloxone (n=79) and found extended-release naltrexone to be non-inferior in terms of retention, proportion of opioid-negative urine drug tests, and use of heroin and other unregulated opioids.[294] It should be noted, however, that the trial was only 12 weeks long, meaning that any conclusions drawn can only be made about short-term abstinence from unregulated opioid use. A secondary analysis of this study with 36-week follow-up, published in 2022, compared the changes in life satisfaction scores in the two groups and found a moderate increase in life satisfaction in both randomized treatment groups, with a significant difference between the groups in favor of the extended-release naltrexone group within the first 8 weeks of the study.[296] However, this difference diminished and the scores equalized in subsequent weeks.[296]

At present, extended-release naltrexone is not available in Canada. However, it should be noted that 52% of participants in two Vancouver-based cohort studies of people who use unregulated drugs reported a high level of willingness to take extended-release naltrexone.[297] Since, this medication is substantially more expensive than traditional daily-dosed medications used to treat opioid use disorder, the assembly of expert therapeutic guideline committees may be warranted to identify patient populations who would most benefit from extended-release naltrexone, if made available.

3.3.iii Recommendations and Remarks for Opioid Antagonist Treatment

Based on the available evidence base for opioid antagonist treatment options, this guideline makes the following recommendations:

Recommendation 8. Oral naltrexone

Oral naltrexone is not a recommended treatment for adults with opioid use disorder. However, it may be offered to individuals who have declined or discontinued OAT and would prefer non-opioid treatment.	
Quality of Evidence: Low	Strength of Recommendation: Weak(Conditional)
Remarks: • Available evidence suggests that oral naltrexone has limited benefit over placebo. However, it may be considered as a last resort option for patients who prefer or require non-opioid treatment options (e.g., due to employment requirements). • Patients should be informed of the risk of return to unregulated use and related harms, including drug toxicity death. • Clinicians should be informed, while naltrexone blocks the effect of opioids, it does not alleviate opioid cravings or withdrawal symptoms • Oral naltrexone may be considered in the context of an overall relapse prevention plan, after a discussion of all available options, including PRN buprenorphine/naloxone.	

Recommendation 9. Extended-release Naltrexone

While extended-release naltrexone is not currently available in Canada, it is an evidence-based treatment that may be considered for patients with opioid use disorder who are not interested in OAT.	
Quality of Evidence: Moderate	Strength of Recommendation: Weak(Conditional)
Remarks: • A growing body of evidence has shown extended-release naltrexone to be superior to placebo in terms of treatment retention, abstinence, and reducing cravings, and non-inferior to buprenorphine/naloxone on a variety of abstinence-related outcomes. • Extended-release naltrexone may be a suitable option when OAT medications are not appropriate due to individual circumstance (e.g., in the case of patients in safety-sensitive professions) • The guideline committee endorses the utility of this medication as a non-opioid option in the continuum of OUD care if it becomes available in Canada.	

3.4 Withdrawal Management

IMPORTANT SAFETY NOTICE

Withdrawal management[v] *alone is not an effective treatment for opioid use disorder, and offering this as a standalone option to patients is neither sufficient nor appropriate.*

As will be reviewed in detail below, rates of dropout and relapse to opioid use are high, regardless of treatment modality used.[298-300] Furthermore, the risks of serious harms, including fatal and non-fatal overdose and HIV and hepatitis C transmission, are higher for individuals who have recently completed withdrawal management compared to individuals who receive no treatment.[79,167,301] To support informed decision making, patients who request withdrawal management alone should be provided with clear, concise information about the known risks to personal and public safety, and be engaged in supportive, constructive discussion about safer treatment options. Withdrawal management alone is not recommended.

3.4.i Alpha$_2$-adrenergic Agonists

Compared to placebo, alpha$_2$-adrenergic agonists (e.g., clonidine, lofexidine, guanfacine, tizanidine) have been found to be effective for reducing the severity of opioid withdrawal symptoms and increasing the probability of completing withdrawal management; however, the majority of patients will relapse to opioid use if only a withdrawal management strategy is used.[299,302] Signs and symptoms of withdrawal appear to resolve earlier with alpha$_2$-adrenergic agonists in comparison to tapered methadone doses. The chances of completing withdrawal management are similar between alpha$_2$-adrenergic agonists and methadone, but alpha$_2$-adrenergic agonists tend to require shorter treatment durations. However, compared to methadone tapers, alpha$_2$-adrenergic agonists are somewhat less effective in mitigating withdrawal symptoms, and are more likely to present adverse effects such as hypotension.[299] Compared to buprenorphine/naloxone, alpha$_2$-adrenergic agonists are less effective at mitigating withdrawal symptoms, as they take a greater amount of time to reduce symptoms and reduce significantly fewer symptoms in that time. The likelihood of treatment success, treatment completion, and abstinence from unregulated opioids and other drugs during withdrawal management is also significantly lower for alpha$_2$-adrenergic agonists tapers when compared to buprenorphine/naloxone tapers.[303]

[v] Sometimes referred to as "detoxification" or "detox"

Prescribed in the United Kingdom and United States, lofexidine has been shown to have equivalent efficacy to clonidine for mitigation of opioid withdrawal symptoms and completion of opioid detoxification. Compared to clonidine, individuals prescribed lofexidine appear to have a lower incidence of alpha$_2$-adrenergic agonist-related hypotension.[304] Lofexidine could be considered as an alternative treatment for patients who do not respond to clonidine should it become available in Canada.

3.4.ii Buprenorphine Taper

Like tapering off opioids with methadone, an opioid agonist taper involving buprenorphine/naloxone appears to reduce the severity of withdrawal symptoms, but most patients still relapse to opioid use if a strategy involving only withdrawal management is employed. For instance, participants in the Prescription Opioid Addiction Treatment Study demonstrated significantly lower sustained abstinence rates eight weeks after tapering off buprenorphine/naloxone (8.6%) compared to abstinence rates during buprenorphine/naloxone treatment (49.2%).[305] A 2018 single-site randomized controlled trial demonstrated that participants who were linked to ongoing buprenorphine/naloxone maintenance treatment following a buprenorphine/naloxone-managed withdrawal protocol reported significantly lower rates of unregulated opioid use after 3 months compared to those who were not linked to maintenance treatment.[306]

Buprenorphine may offer some advantages over methadone when used during a taper, specifically offering faster symptom relief.[235] There does not appear to be a significant difference in terms of withdrawal symptom severity,[235] withdrawal treatment completion (RR:1.04, 95% CI: 0.91–1.20), or average treatment duration (mean difference [MD]: 1.30 days, 95% CI: -8.11–10.72)[307] for individuals managed with buprenorphine compared to methadone.[235]

Compared to alpha$_2$-adrenergic agonists, buprenorphine appears to offer more effective relief of withdrawal symptoms, as indicated by the lower overall withdrawal score (standardized mean difference [SMD]: -0.43, 95% CI: -0.58 to -0.28), longer retention in treatment (SMD: 0.92, 95% CI: 0.57–1.27) and greater likelihood of completing treatment (RR 1.59, 95% CI 1.23–2.06).[307] There does not appear to be a significant difference between buprenorphine and alpha$_2$-adrenergic agonists in adverse effects (RR 0.93, 95% CI 0.70–1.26),[307] except in comparison with clonidine, which is associated with higher rates of drop-out due to side effects.[235]

3.4.iii Methadone Taper

Tapering off opioids with methadone appears to reduce the severity of withdrawal symptoms; however, the majority of patients still relapse to opioid use if a strategy involving only withdrawal management is employed.[308] For example, clinical trials report relapse rates ranging from 53.1–66.7% at 1 month, and 61.1–89.2% at 6 months post-methadone taper.[309-311]

Methadone at tapered doses does not appear to differ from other pharmacological treatments (e.g., alpha$_2$-adrenergic agonists, other opioid agonists) in terms of severity of withdrawal symptoms, adverse effects,

withdrawal completion, or sustained abstinence. Compared to placebo, tapered methadone appears to be associated with less severe withdrawal symptoms and lower rates of drop-out.[312]

It is important to note that wide variations in the literature were a major limitation when comparing tapered methadone to other treatments (e.g., different studies assessed different outcomes of withdrawal management using methadone versus other treatments, which did not allow for exact comparisons between treatment approaches in certain contexts).[312]

3.4.iv Other Considerations for Withdrawal Management Only

Given that withdrawal management alone is not recommended, it is the consensus of the committee that, in cases where it is preferred, most individuals with opioid use disorder should be offered community-based, outpatient withdrawal management as opposed to rapid inpatient withdrawal management. This is consistent with the American Society of Addiction Medicine placement criteria that emphasize meeting a patient's clinical needs with the most appropriate and least restrictive care setting and intensity.[103] Outpatient withdrawal management programs permit a slower, more flexible, and individualized approach to tapered agonist reduction compared to inpatient withdrawal management, while still allowing for dose readjustment and stabilization in the event that withdrawal symptoms, cravings, or relapse to unregulated opioid use occur. Outpatient withdrawal management is also less disruptive to the patient and their family, and offers the opportunity to continue with their normal routine of daily living, providing a more realistic environment for the development of coping strategies and support systems on reduction or cessation of opioid use.

Traditional assumptions that certain treatment modalities can be delivered only in a particular setting may not be applicable or valuable to patients. Many of the traditional placement criteria that favour inpatient rather than community-based withdrawal management services (e.g., individuals with comorbid mental health issues) should not necessarily apply in the case of opioid use disorder. In these cases, rapid inpatient opioid withdrawal may leave individuals even more vulnerable to opioid-related harms—including fatal overdose—when discharged from a highly structured treatment setting and returned to their home environment where cravings and desire to use may be high and unregulated opioids easily obtained, particularly if no follow-up substance use disorder care is provided.[313,314] Instead, like all patients without serious comorbidities, these patients can be referred to long-term inpatient or outpatient addiction services, where possible and appropriate, rather than short-term inpatient withdrawal management.[315]

Withdrawal management alone (i.e., without transition to opioid agonist treatment) is not effective and often leads to high rates of relapse rapidly post-treatment, which, increases the risk of HIV and hepatitis C transmission, morbidity, and mortality.[79,167,301] As the first point of engagement in clinical care, opioid withdrawal management can serve an important role as a bridge to treatment, but is not recommended unless a strategy is in place for referral to ongoing OUD treatment, given the risks associated with withdrawal management alone.

Specifically, a meta-analysis found higher HIV incidence among individuals undergoing withdrawal management alone as compared with individuals receiving no treatment.[167] Other past research has shown that individuals who have received inpatient opioid withdrawal management are at increased risk of death from drug overdose compared to those who received no treatment.[301] This phenomenon is believed to be due to loss of tolerance to opioids and is consistent with the increased risk of fatal opioid overdose observed following release from incarceration.[316] Furthermore, relapse to opioid use is common among patients undergoing withdrawal management alone, as evidenced by a large US-based observational cohort (n=990) that reported significantly lower rates of sustained abstinence at six-years follow-up for outpatient detoxification (12%) compared to other treatment approaches (18–21%).[308,317]

For individuals who choose withdrawal management over long-term agonist treatment, including those with high opioid tolerance, consider initiating buprenorphine/naloxone treatment to address withdrawal symptoms and slowly tapering under outpatient supervision. Individuals who are unsuccessful with this approach may be offered ongoing opioid agonist treatment. In order to reduce the risk of fatal overdose among patients who decline long-term opioid agonist treatment, patients and families should also be advised to undergo take-home naloxone training, a safe and effective intervention to prevent fatal overdose.[318,319] As individuals experience reduced tolerance following cessation of opioid use, clinicians should offer further information on vitural overdose prevention services, such as the Lifeguard app, and in-person overdose prevention sites. For more information on take-home naloxone and other harm reduction strategies please refer to Harm Reduction Programs and Services.

3.4.V Psychosocial Treatment Interventions Provided Alongside Withdrawal Management

Psychosocial treatment interventions appear to be beneficial adjuncts to opioid withdrawal management.[320] When offered in addition to pharmacologically-supported withdrawal management (e.g., opioid agonist taper), psychosocial treatment interventions such as contingency management and psychotherapeutic counselling may be effective in improving treatment retention and completion, sustaining abstinence from unregulated opioids, and reducing opioid use during treatment.[320] However, there is currently limited evidence due to small sample sizes and heterogeneous assessment and outcome measurements. There is also insufficient evidence to favour any specific psychosocial treatment modality, including which psychosocial treatment is most effective for particular patient populations. This is due, in part, to the diverse populations and the variety of psychosocial interventions examined in the existing literature.[320] Therefore, further research and patient-specific approaches are needed with regard to psychosocial treatment interventions. Importantly, while psychosocial treatments may improve rates of treatment retention and completion, psychosocial treatment interventions provided during opioid withdrawal management likely do not protect against the elevated risk of HIV infection or fatal overdose if withdrawal management alone is pursued, due to high rates of relapse post-treatment and the negligible benefit of withdrawal management alone.[167,301,305,321]

3.4.vi Recommendations and Remarks Related to Withdrawal Management

As detailed below, this guideline recommends against withdrawal management alone. For patients who expressly wish to pursue withdrawal management, slow outpatient opioid agonist tapers should be considered, followed by long-term psychosocial OUD treatment for relapse prevention.

Recommendations 10. Withdrawal management alone

Withdrawal management alone (including rapid opioid agonist tapers) without transition to opioid agonist treatment is not recommended.	
Quality of Evidence: Moderate	Strength of Recommendation: STRONG

Remarks:

- Withdrawal management alone (i.e., without transition to opioid agonist treatment or continuing substance use disorder care) is not effective; the vast majority of patients who undergo withdrawal management relapse soon after treatment completion, which increases their risk of HIV and hepatitis C transmission, morbidity, and mortality.
- Patients who request withdrawal management alone should be provided with clear, concise information about these risks, and be engaged in supportive, constructive discussion about safer treatment options.

Recommendation 11. Setting and duration of withdrawal management

If the patient chooses to pursue withdrawal management (e.g., slow opioid agonist taper), this should be conducted in an outpatient setting, followed by a collaboratively developed relapse prevention plan and referral to long-term psychosocial treatment and support.	
Quality of Evidence: Moderate	Strength of Recommendation: STRONG

Remarks:

- When discharged from a highly structured inpatient withdrawal management setting and returned to familiar environment where cravings may be high and unregulated opioids easily available, individuals may be particularly vulnerable to opioid-related harms—including fatal overdose.
- Outpatient withdrawal management programs permit a slower, more flexible, and individualized approach to tapered agonist reduction compared to inpatient withdrawal management, while still allowing for dose readjustment and stabilization if withdrawal symptoms, cravings, or relapse to unregulated opioid use occur.
- Outpatient withdrawal management is also less disruptive to the patient's daily routine.
- Consider initiating opioid agonist treatment to address withdrawal symptoms and slowly tapering under outpatient supervision. The risks of withdrawal management alone and the benefits of being maintained on OAT should be periodically revisited in the course of the taper while respecting patient autonomy.
- Patients undergoing withdrawal management should be offered referral to psychosocial treatment interventions and community-based supports.

- In order to reduce the risk of fatal overdose among patients who decline long-term opioid agonist treatment, patients and families should also be advised to undergo take-home naloxone training, a safe and effective intervention to prevent fatal overdose.

3.5 Psychosocial Interventions and Supports

This section provides a review of evidence pertaining to non-pharmacological interventions for patients with OUD. In this context, psychosocial interventions include:

- Psychosocial treatment options for substance use disorders (e.g., contingency management, cognitive behavioural therapy)
- Bed-based treatment and supportive recovery programs

3.5.i Psychosocial Treatment Interventions

The evidence supporting psychosocial interventions is often mixed, which may be due to inconsistency in the delivery of the intervention and methodological limitations of studies examining psychosocial interventions. Available meta-analyses and clinical trials examining the effectiveness of psychosocial interventions for treating OUD do not deviate from this trend.

A 2011 Cochrane Review of 35 RCTs (n=4319) found that, compared to OAT with standard medical management and counselling, the addition of structured psychosocial treatment interventions to OAT did not improve retention in treatment, abstinence from opioid use during or after treatment, or adherence.[322] When analyses were stratified by type of psychosocial treatment intervention (i.e., behavioural [n=24]; psychoanalytic [n=4]; counselling [n=7]; and other [n=2]), pooled results remained non-significant for all comparisons and outcomes.[322] The authors concluded that there was high-quality evidence that the addition of structured psychosocial treatment interventions to standard OAT does not improve retention or abstinence rates, and moderate-quality evidence that adjunct psychosocial treatment interventions do not improve adherence over standard OAT incorporating clinician-led medical management.[322] It is emphasized that the control interventions described in the included studies involved a counselling component in addition to OAT; this conclusion applies to specific structured psychosocial interventions offered as an addition to standard psychosocial support for patients with OAT.

More recently, a 2020 systematic review used network meta-analysis (N=48 RCTs; n=5,404) to compare the effectiveness of 20 unique psychosocial interventions used as adjuncts to OAT in sustaining treatment retention. The meta-analysis showed that the addition of rewards-based interventions, such as contingency management, to OAT was superior to OAT-only.[323] There were no statistically significant differences between other psychosocial interventions; the majority of studies found no significant difference between OAT with adjunct psychosocial interventions as compared to OAT alone. The authors also compared the impact adjunct psychosocial interventions on opioid use patterns (18 studies for changes in opioid use and 35 studies for

abstinence) and found that included ancillary psychosocial interventions had no statistically significant impact on opioid use outcomes as compared to OAT alone. While calling for more high-quality RCTs to establish more definitive conclusions the authors suggested that contingency management be considered as an adjunct to OAT where appropriate.[323]

These findings align with the results of available clinical trials, which have yielded mixed results.[324] For example, 4 RCTs evaluating OAT with adjunct cognitive behavioural therapy (CBT) found no difference in treatment retention and abstinence compared to standard OAT,[325-328] although a subsequent sub-analysis of one trial did report that the addition of CBT to OAT was associated with a significant increase in mean number of opioid-free weeks in individuals with prescription OUD.[329] Of 4 RCTs assessing OAT with ancillary contingency management, 2 trials reported significantly higher attendance and retention rates, longer periods of continuous abstinence, and reductions in non-medical opioid use with prize-based contingency management[330,331]; 1 trial reported significantly higher 12-month retention rates with contingent take-home doses[332]; and 1 trial reported no difference in retention, continuous abstinence, or non-medical opioid use for prize-based CM versus standard OAT.[327] Of 2 RCTs that evaluated OAT with ancillary counselling, 1 found that ancillary counselling led to significantly higher 12-month retention rates in patients with no previous OAT experience,[333] while another found no difference in attendance rates, adherence, or non-medical opioid use with ancillary counselling compared to standard OAT.[334,335] A 2019 open-label RCT randomized OAT patients to either personalized psychosocial intervention (a flexible toolkit of change methods, including recovery activities, contingency management, and clinic attendance) along with treatment as usual (n=135) or just treatment as usual (n=135) and found that 16% (n=22) of the intervention group had a treatment response, compared to 7% (n=9) in the treatment as usual group (adjusted log odds: 1.20, 95% CI 0.01–2.37; p=0.048).[336] Treatment response was defined as no reported opioid or cocaine use in the past 28 days and at least one negative urine drug test. Participants in the intervention group also reported significantly more opioid-free days (adjusted log odds: 0.39, 95% CI 0.15–0.62).[336]

Considered together, available evidence does not provide consistent evidence that ancillary psychosocial treatment interventions improve patient outcomes over OAT incorporating standard medical management, although some studies involving contingency management approaches have yielded promising results. Ongoing research is needed to better understand the role and effectiveness of psychosocial treatment interventions in the clinical management of opioid use disorder. Findings to date do, however, underscore that **a patient's decision** not to participate in ancillary psychosocial treatment interventions should never preclude or delay provision of evidence-based pharmacological treatments.[337]

Assessment and monitoring of emotional and mental health is an essential component of care for patients with OUD, particularly given the high prevalence of concurrent mental health diagnoses in this population (e.g., post-traumatic stress disorder, depression, anxiety).[335,338-340] While the evidence for ancillary psychosocial treatment interventions in the general patient population is equivocal, there may be benefits for some individuals, including more complex patient populations typically excluded from RCTs. There is some evidence that the addition of psychosocial treatment interventions can improve both substance use and mental health outcomes for

individuals with concurrent disorders, including alcohol and other substance use disorders, post-traumatic stress disorder, and severe mental illness (e.g., schizophrenia, schizoaffective disorder).[341-343] However, due to the small number of trials, this evidence is considered to be low quality, with considerable heterogeneity between trials and pooled-effect sizes that are generally small to moderate in scale.

Further research is required to assess the effect of specific types of psychosocial support (e.g., housing, employment, and legal support services) on treatment outcomes. Although systematic reviews have examined the impact of providing supports for various social needs; previous studies have demonstrated that addressing housing and other survival needs has a significant positive impact on patient outcomes.[344-346] There is likely a benefit to OUD treatment being offered in the context of interdisciplinary care teams that are equipped to address these needs when possible.

3.5.ii Bed-based Treatment and Supportive Recovery Programs

There are no systematic reviews or meta-analyses considering the impacts of bed-based programs (also called residential or inpatient treatment) or supportive recovery treatment programs for individuals with opioid use disorder. The overall dearth of evidence does not mean that bed-based treatment is ineffective, but rather that the intervention has been under-studied, thus requiring review of individual studies. There are also no large clinical trials comparing bed-based treatment to other interventions, and few rigorous evaluations that identify specific characteristics of effective bed-based treatment programs or patient characteristics that may predict appropriateness of bed-based treatment referral.

Observational cohort studies in the UK have found that relapse is relatively common among clients discharged from bed-based treatment for opioid use disorder. For example, a 2010 study examining the outcomes of a six-week bed-based treatment program in Ireland that included methadone-based withdrawal management, psychosocial therapy (i.e., group, individual, and/or family therapy) and an aftercare component found that 80% of participants reported relapse within one month, with 59% relapsing within one week of discharge. Younger age, not completing the full six weeks of treatment, greater heroin use prior to treatment, history of injecting, and not enrolling in aftercare were associated with a shorter time to relapse. Similarly, in the 2000 National Treatment Outcome Research Study (NTORS), approximately 57% of clients reported heroin use within 30 days of discharge, with 31% relapsing to regular levels of heroin use at 1-year follow-up. However, for the full cohort of individuals who attended bed-based treatment for alcohol or substance use disorders, the NTORS study did find that, at 4–5 years follow-up, injecting rates dropped from 61% at intake to 29% at follow-up, while abstinence from heroin use increased from 23% to 49% across the same period.[347] Overall, individuals who completed bed-based treatment also demonstrated improvements in terms of safer injection practices, psychological and physical health, and reductions in criminal behaviour at 4–5 years follow-up.[348]

Studies of bed-based treatment in the United States also present varied results. One 2004 longitudinal study of abstinence-based treatment programs found similar rates of retention, completion, and patient satisfaction among individuals in outpatient and bed-based treatment programs.[349] A 2013 study found that a four-week bed-based treatment program significantly decreased several maladaptive cognitive and behavioural patterns

that may contribute to ongoing substance use problems in adults with opioid use disorder.[350] A 2014 randomized clinical trial found that a combination of community reinforcement and family training in addition to bed-based withdrawal management using buprenorphine, particularly when involving the adult patient's parents, was positively and significantly associated with improved retention in treatment and reductions in opioid and other drug use.[351] Therefore, patients may benefit from bed-based treatment that involves fostering family and other social connections.

Although the 2002 outcomes of the NTORS cohort study found that bed-based treatment was associated with reduced rates of non-fatal overdose at one-year follow up (7%) compared to pre-treatment rates (22%),[352] providers should be aware of risks associated with loss of tolerance for patients who attend residential treatment programs when not receiving OAT. For instance, a retrospective study of Massachusetts admissions data from 2013–2015 found twice as many individuals experienced an opioid overdose in the first two weeks following discharge from bed-based treatment compared to the following two-week time period.[353] Similarly, a 2016 national cohort study in England found that risk of fatal overdose was twice as high for patients who completed psychosocial treatment only (outpatient or bed-based treatment) compared to patients who had received OAT.

There is growing advocacy for the provision of OAT in supportive recovery services. [215–217,222–224] However, there have been barriers to integrating OAT and recovery-oriented services, as these approaches have evolved from distinct communities of practice, siloed service delivery systems, and—in some cases—divergent belief systems.[216] In the past, many clients receiving OAT were excluded from recovery-oriented services and programs, including supportive recovery residences, as they were not considered to be in "true recovery."[217] Patients benefit when OAT clinics and recovery programs work collaboratively.

Studies indicate that a minority of bed-based treatment facilities offer OAT. A retrospective cohort study of 36 publicly funded bed-based treatment facilities in Ontario from 2013–2016 determined that, while a slight majority (55.6%) of facilities allow patients to be on OAT during bed-based treatment, 75.5% of those facilities do not prescribe or dispense on-site, 8.5% only prescribe on-site, 13% only dispense on-site, and only 3% both prescribe and dispense on-site[354] Similarly, a 2020 cross-sectional study of bed-based treatment facilities in the United States found that only 33.3% of facilities offered buprenorphine and 2.1% offered methadone. Overall, 60% of facilities provided no form of medication for opioid use disorder (including extended-release naltrexone), and only 1.3% of facilities provided buprenorphine, methadone, and extended-release naltrexone.

There is limited evidence regarding the effects of OAT and other medications for opioid use disorder on patient outcomes in bed-based treatment facilities. A cohort study analyzing the mortality risks of patients who completed withdrawal management between 2012 and 2014 found that patients who participated in subsequent bed-based treatment had reduced all-cause mortality compared to those who received no further treatment (adjusted hazard ratio [AHR]=0.63, 95% CI: 0.47–0.84).[355] When bed based-treatment was combined with medication for opioid use disorder (buprenorphine, buprenorphine/naloxone, methadone, or naltrexone), all-cause mortality was further reduced (AHR=0.11, 95% CI: 0.03–0.43). Similarly, opioid-related mortality was reduced in patients who received subsequent bed-based treatment (AHR:0.69; 95% CI:0.50–0.94) and bed-based

treatment combined with medication for opioid use disorder (AHR:0.14; 95% CI:0.03–0.55).[355] In a 2020 cohort study examining the feasibility and effectiveness of incorporating medication for opioid use disorder into bed-based and day treatment programs based on the 12-step program, a majority (71%) of participants opted to receive some form of medication. Treatment adherence between medication groups did not differ significantly one-month post-treatment, with 87% of buprenorphine/naloxone participants, 80% of extended-release naltrexone participants, and 65% of oral naltrexone participants reporting adherence (p=0.39). Among participants who completed follow up at 6-months post-treatment, 72% of buprenorphine/naloxone patients, 53% of extended-release naltrexone patients, and 29% of oral naltrexone patients reported adherence. Buprenorphine/naloxone patients were significantly more likely to report medication adherence than oral naltrexone patients (p<0.01).[356]

3.5.iii Recommendation and Remarks Related to Psychosocial Interventions and Supports

Recommendation 12. Psychosocial treatment interventions and supports

Psychosocial treatment interventions and supports should be routinely offered to adults with opioid use disorder, in conjunction with pharmacological treatment.	
Quality of evidence: Moderate	Strength of Recommendation: STRONG
• As a standard of care, patients should be offered access to psychosocial treatment and supports as part of their OUD care plan. However, a patient's decision not to participate in ancillary psychosocial treatment interventions should never preclude or delay provision of evidence-based pharmacological treatments. • While the evidence for ancillary psychosocial interventions in the general patient population is equivocal, emerging studies involving adjunct contingency management approaches have yielded promising results for treatment retention and opioid use-related outcomes.	

3.6 Peer Support

Peer support in the provision of OUD care may include peer navigators and peer support workers in OAT programs as well as peer-based support groups, such as Narcotics Anonymous, SMART Recovery, and LifeRing.

Peer support workers

The evidence on peer support workers is limited; however, *"Nothing About Us Without Us": Greater, Meaningful Involvement of People Who Use Drugs: A Public Health, Ethical, and Human Rights Imperative* identifies several important benefits to peer involvement especially relevant for the provision of OAT. These include more patient "buy-in" to the program; the ability for patients' needs to be recognized and addressed; service delivery that meets the needs of patients by being realistic, low-barrier, and useful; and providing a sense of ownership for peers.[357] A 2018 qualitative study of a peer-run overdose response program in emergency shelters in Vancouver, BC, identified several factors that lead to increased feelings of safety from peer workers compared to non-peer paid staff, including social safety due to shared experiences, an absence of uneven power dynamics, and a perception of being cared for that contrasted with their everyday experiences.[358] A 2019 qualitative study of peer workers in overdose prevention sites in Vancouver found that peer workers help create a sense of community characterized by safety, inclusivity, and comfort.[359]

Peer-based support groups

Peer-based support groups are widely available community resources often recommended as an adjunct to clinical management of substance use disorders, or as a source of additional guidance and support following treatment (e.g., aftercare). A widely recognized example is Narcotics Anonymous (NA), an international fellowship of support groups comprised of individuals in recovery, which offers emotional support and a structured "12-step" approach to achieving abstinence. Research and evaluation of peer-based support has primarily focused on 12-step facilitation approaches, which refers specifically to 12-step programs led by a trained professional, such as a substance use counsellor. There have been no well-designed, controlled studies of the effectiveness of these groups in supporting treatment goals of individuals with OUD, although a small number of observational studies have reported associations between active participation in 12-step programs and improved treatment outcomes among individuals with substance use disorders.[360-362]

It should be noted that the 12-step facilitation model has been occasionally supportive of the use of OAT for the treatment of OUD. Underlying philosophical conflicts, if present, can also negatively affect engagement and disclosure and deter regular attendance. If patients identify incompatibilities between personal beliefs and 12-step facilitation as barriers to participation, alternative options can be provided when possible. For example, peer support groups with a secular mandate (e.g., SMART Recovery, LifeRing), or groups for specific populations (e.g., youth, women, Indigenous peoples, individuals with concurrent mental health issues) may be locally available; however, it is noted that the efficacy of these support groups has not been empirically studied.

While the evidence base is limited, 12-step groups, which are widely accessible in both urban and rural settings, may be beneficial to patients and families in navigating life changes and challenges related to treatment and recovery.

3.7 Harm Reduction Programs and Services

Broadly defined, harm reduction refers to policies, programs, and practices that aim to reduce the adverse health, social, and economic consequences of licit and unregulated substance use. In BC, established harm reduction initiatives include safer consumption and safer sex supplies distribution programs, take-home naloxone, drug checking, overdose prevention sites, and supervised consumption services. Including these harm reduction approaches within the continuum of addiction care provides additional mechanisms for promoting health and safety in diverse patient populations, including individuals who are not interested in receiving OAT or those who continue to use unregulated opioids while receiving OAT. Clinicians can take several actions to increase awareness of harm reduction services among patients, starting with routinely including information and education about harm reduction and safer injection or smoking practices when appropriate in discussions with patients and families. In order to provide informed referrals, clinicians should also be aware of harm reduction programs available in their local area and services provided. A current listing of harm reduction services in British Columbia that provide sterile needles, syringes, and other consumption supplies; overdose prevention training; and take-home naloxone kits can be found on the Toward the Heart website.

3.7.i Distribution of Safe Consumption Supplies

The distribution of sterile injection equipment to people who inject drugs via needle and syringe programs has been widely implemented across a number of countries in an effort to prevent HIV and hepatitis C infections, reduce needle sharing and re-use, and decrease the number of discarded needles and syringes in communities. Sterile injection equipment may be distributed through fixed sites, pharmacies, machines, outreach programs, or home visits. The effectiveness of the distribution of sterile injection equipment through needle exchange programs is well-established.[363] A 2014 systematic review and meta-analysis reported a 34% reduction in risk of HIV transmission among individuals who participated in needle and syringe programs (pooled effect estimate 0.66, 95% CI: 0.43–1.01) compared to those who did not participate or who participated less frequently. In the same meta-analysis, a sensitivity analysis that included only studies assessed to be of high quality supported these findings and reached statistical significance (pooled effect estimate 0.43, 95% CI: 0.22–0.81).[364] In regards to hepatitis C infections, a 2011 meta-analysis found that receiving one or more sterile needles for each reported injection was associated with a 52% reduction (aOR 0.48, 95% CI: 0.25–0.93) in the odds of new hepatitis C infection when compared to receiving less than one sterile needle for each reported injection. When participants received one or more sterile needles for each reported injection in combination with OAT, the odds of new hepatitis C infection were further reduced by nearly 80% (aOR 0.21, 95% CI: 0.09–0.52) and there was a 48% reduction (aOR: 0.52, 95% CI: 0.32–0.83) in needle sharing practices compared to participants who received less than one sterile needle per reported injection and did not receive OAT,[84] underscoring the importance of offering harm reduction supplied alongside OAT.

Although there are currently no dedicated studies examining the impact of safer inhalation supplies distribution, there is a vital need for the expansion of this service across BC as an increasing portion of people who use drugs have reported that inhalation is their preferred mode of drug consumption. The BC Coroners Service reported evidence of smoking as a mode of drug consumption in 67% of BC residents who died of unregulated drug poisoning in 2023.[365] The 2021 Harm Reduction Client Survey (n=537) conducted by the BC Centre for Disease Control also found that 64% of responding harm reduction service clients in 2021 identified smoking or inhalation as their preferred mode of drug consumption while 14% expressed a preference for injection.[366] According to this report, 20% of respondents who smoked drugs in the past 6 months used a second-hand pipe and 6% injected drugs when they were unable to access unused smoking equipment. [366] The use of second-hand or non-sterile smoking equipment exposes people who smoke drugs to infection and the development of pulmonary and respiratory problems.[367,368] Given the risks affecting a significant portion of people who use drugs, the BCCDC includes safer smoking and inhalation equipment among its harm reduction services. This service is incorporated in an increasing number of supervised consumption and overdose prevention sites across BC. Guidance for ordering, distribution, and use of safer smoking supplies are available through the Toward the Heart website.

3.7.ii Take-home Naloxone

Take-home naloxone refers to naloxone that is administered outside of a health care setting by non-health care professionals (e.g., people who use drugs, friends, family members) who have received training to administer naloxone in the event of an opioid overdose. Findings from a 2018 systematic review indicate that take-home naloxone is effective in preventing opioid-related overdose deaths and that participating in take-home naloxone training results in increased knowledge of naloxone administration and recognizing, preventing, and responding to an opioid-related overdose. Given the effectiveness of take-home naloxone, the authors advocate for the continued implementation of take-home naloxone programs.[369] The BC Take-Home Naloxone program, for example, is estimated to have averted 226 deaths between Jan 1 and Oct 31, 2016, preventing an additional 33% of the deaths that occurred during that time period.[370] Moreover, a 2015 meta-analysis of 9 studies estimated that 9.2% of take-home naloxone kits distributed would be used within 3 months for every 100 PWUD who have received naloxone training and kits.[371] Clinicians should provide take-home naloxone kits and education directly to patients or refer patients to the BC Take-Home Naloxone program, where patients and anyone at risk of responding to an overdose can learn where to receive free take-home naloxone kits and training.

3.7.iii Supervised Consumption Sites and Overdose Prevention Sites

Supervised consumption sites, which include supervised injection and inhalation sites, provide sterile supplies and a safe, hygienic space for PWUD to consume previously obtained unregulated drugs under the observation of health care providers or other trained staff.[372] While supervised consumption sites had long operated without the approval of the federal government, Health Canada began issuing exemptions under section 56.1 of the CSDA to allow supervised consumption sites in Canada to operate legally, with Insite receiving the first exemption in 2003.[373,374]

Multiple systematic reviews have evaluated the relationship between the use of supervised consumption sites, specifically supervised injection sites, and individual- and community-level outcomes.[85,372,375] Both 2014[85] and 2017[372] systematic reviews found supervised consumption use to be associated with safer injection behaviours, including decreases in syringe sharing, syringe reuse, and public injection, and an increased use of sterile injection supplies. Moreover, supervised consumption site use is associated with an increase in referrals to treatment centres, withdrawal management programs, and OAT.[85,372] Importantly, supervised consumption sites are associated with a decrease in fatal overdoses, and no fatal opioid overdoses have been reported at any supervised injection site.[85] At the community level, the implementation of supervised injection sites is not associated with increased crime, violence, or drug consumption in the areas surrounding the site.[85]

Most recently, a 2021 systematic review (N=22 studies) on the effectiveness of supervised injection facilities for harm reduction and community outcomes reaffirmed these findings.[376] The authors found supervised injection facilities were mostly associated with significant reductions in opioid overdose morbidity and mortality (n=5), significant improvements in injection behaviors and harm reduction (n=7), significant improvements in access to addiction treatment programs (n=7), and no increase or reductions in crime and public nuisance (n=7).[376]

Similar to supervised consumption sites, overdose prevention sites provide a safe, hygienic space for people to consume previously obtained unregulated substances under the supervision of trained staff, peers, and health care professionals. Unlike supervised consumption sites, overdose prevention sites in BC do not require an exemption from the federal government to operate. A provincial order issued in response to the opioid overdose public health emergency permits overdose prevention sites to operate temporarily.[377] Overdose prevention sites generally have lower expenditures, can be implemented more quickly, and are often lower barrier compared to supervised consumption services. Evaluations of overdose prevention sites have yet to be completed, but data indicates these services are increasingly utilized by people who use drugs, and drug toxicity deaths at overdose prevention sites are extremely rare (two deaths recorded to date). [378]

The BC Ministry of Mental Health and Addiction's Overdose Emergency Response Centre and BC Centre for Disease Control have also developed a Provincial Episodic Overdose Prevention Service Protocol, which provides guidance and support to staff members at a range of health care and social service settings who encounter people in need of episodic overdose prevention services on site. This service, which was developed in the context of the COVID-19 pandemic, is intended to support people at risk of overdose who have difficulty accessing a designated supervised consumption or overdose prevention site. The impact of this service has not yet been evaluated.

3.7.iv Drug Checking

Drug checking refers to a service in which street-obtained drugs are chemically analyzed and information regarding their contents is shared with the person using the drug checking service. Drug checking can be conducted using multiple technologies either at an on-site location or at a laboratory where samples are dropped off or shipped for analysis. Drug checking services may include a brief counselling component and serve as an initial point of contact with health care and other services.[379]

Drug checking services have recently expanded in BC in response to the increasing dominance of fentanyl in the unregulated drug market. A 2018 cross-sectional survey examining the uptake of drug checking services at Insite in Vancouver found that drugs were checked in nearly 1% of visits, with nearly 84.1% of drugs reported to be heroin testing positive for fentanyl.[380] Similarly, data from a 2018 pilot program of two supervised consumption sites in Vancouver demonstrated that nearly 2% of clients utilized the drug checking services at the SCS between October 2017 and April 2018, with 90.6% of all samples believed to be heroin testing positive for fentanyl.[381]

Data from two 2018 observational studies indicate that people who use drugs are willing to use drug checking services.[382,383] However, research on the impacts of drug checking on service users' substance use behaviors or health outcomes is limited.[384] Data from a 2018 survey suggest that people who receive a positive test result for fentanyl are significantly more likely to plan to reduce their drug use upon injecting (OR: 9.35, 95% CI: 4.25–20.65); however, they are not more likely to dispose of their drugs (OR: 1.60, 95% CI: 0.79–3.26).[380] A 2022 systematic review (N=90 studies) also found that drug checking services influenced the behaviour of people who use drugs, particularly when drug checking results are unexpected.[384] However, the authors noted significant limitations in the available literature, including the fact that the majority of studies were cross-sectional.[384]

3.7.v Prescribed Safer Supply: Emerging Programs

In response to the ongoing overdose crisis, novel approaches have been piloted to reduce harms related to the use of unregulated opioids for individuals in care who have not benefited from traditional OAT approaches. In July 2021, the Ministry of Mental Health and Addictions, Ministry of Health, and Office of the Provincial Health Officer released *Access to Prescribed Safer Supply in British Columbia: Policy Direction*, which contains policy directives to enable access to pharmaceutical alternatives to unregulated drugs through regional health authority-run and federally funded programs. In support of this directive, and in partnership with the provincial government, the BCCSU has developed a range of protocols and practice support tools for the provision of different forms of prescribed safer supply as a means of reducing the risk of drug toxicity events and deaths. Visit BCCSU's Prescribed Safer Supply page for further information.

3.7.vi Recommendation and Remarks for Harm Reduction Services and Programs

Recommendation 13. Harm reduction

Conversations about safer drug use, take-home naloxone programs, and referral to other harm reduction services should be routinely offered as part of standard care for individuals with opioid use disorder.	
Quality of Evidence: Moderate	Strength of Recommendation: STRONG
Remarks: • A growing body of research has shown that harm reduction services such as the distribution of sterile injection equipment, take-home naloxone, and supervised consumption and overdose prevention sites facilitate safer drug use practices and significantly reduce the risk of drug toxicity deaths and transmission of HIV and Hepatitis C.	

- Drug checking services have also demonstrated their utility in monitoring the composition of unregulated drugs. While evidence on the impact of drug checking on substance use behaviour is limited, this service can help clients make informed decisions regarding the safety of the unregulated substances they plan to use.
- Clinicians should routinely include information and education about harm reduction resources and safer injection practices when appropriate in discussions with patients and families.
- In order to provide informed referrals, clinicians should also be aware of harm reduction programs available in their local area and services provided.

4.0 SPECIFIC POPULATIONS

The recommendations in this guideline should be considered applicable and relevant to the general adult patient population; however, there are additional considerations when working with specific patient populations. This section provides strategies for working with the following patient populations: Indigenous peoples, 2S/LGBTQQIA+ populations, and people in safety-sensitive positions, as well as sex/gender considerations, and referrals to guidance for the treatment of pregnant people, youth, and older adults, and individuals in correctional settings with OUD. This section is not intended to provide prescriptive clinical practice guidance for management of OUD in these patient populations, rather, it provides an overview of general considerations for establishing positive partnerships and providing patient-centred, safe, and effective care. Links to online resources have been provided where available.

Prescribers and allied health providers are encouraged to connect with an addiction medicine specialist for advice and guidance on complex cases. The Rapid Access to Consultative Expertise (RACE) line connects physicians and nurse practitioners with an addiction specialist (Vancouver area: 604-696-2131; toll-free: 1-877-696-2131; Monday to Friday, 0800-1700). The 24/7 Addiction Medicine Clinician Support Line (778-945-7619) provides telephone consultation to physicians, nurse practitioners, nurses, and pharmacists who are involved in addiction and substance use care and treatment in BC and to any frontline service provider working in Indigenous communities in BC, and is available 24 hours a day, 7 days a week, 52 weeks a year to provide rapid response for time sensitive clinical inquiries.

4.1 Indigenous Peoples

A Note on Terminology: The source material reviewed in this section uses several different terms to describe the Indigenous Peoples in what is presently known as Canada, some of which are legal terms directly tied to the Canadian constitution and various acts (e.g., Section 35 of the Constitution Act, 1982; the Indian Act, R.S.C. 1985). This terminology has been reproduced here for consistency and accuracy.

In Canada, the term Indigenous peoples is considered inclusive of all the Peoples of Turtle Island[w] and all their descendants, and includes those that have status[x] or not, and those who self-identify as Indigenous. It is important to be aware of the diversity that exists between and among Indigenous peoples in Canada. When possible, using a name that reflects a specific peoples, community, or Nation is preferable over the collective term "Indigenous".

The term Aboriginal originates from Section 35 of the Constitution Act, 1982, wherein the Aboriginal peoples in Canada are defined as "Indian, Inuit and Métis Peoples". This collective term refers to not a single group, but three very different and distinct groups. The term reflects the legal and social responsibility of the Federal Government to these groups, and excludes those who are not formally recognized by the Government of Canada. In the section below, it is used to specify that health data being reported is specific to people who are registered under the Indian Act, R.S.C. 1985.

First Nations is the preferred collective term that replaced "Indian" in Section 35 of the Constitution Act, 1982. It refers to Indigenous peoples in Canada who are neither Métis nor Inuit. First Nations Peoples can include both status and non-status Indians. Clinicians need to be aware of this distinction when referring to health care benefits, programs, or services that are only accessible to status Indians.

Inuit Peoples are Indigenous peoples in northern Canada (Nunavut, Northwest Territories, Quebec, and Labrador).

Métis Peoples are a distinct Nation from other Indigenous peoples in Canada, and have roots in mixed Indigenous and European ancestry. Métis peoples have common descent, history, language, and culture tied to a specific territory. Being of mixed decent in and of itself does not make an individual Métis.

[w] Turtle Island refers to the continent of North America.

[x] "Status" is a legal term for a person who is registered as an "Indian" under the *Indian Act*, or a person who belongs to a First Nation or Indian Band that signed a treaty with the Crown; this can be denoted as "Status, Registered or Treaty Indian" or "Status, Registered, or Treaty First Nations". This term has origins and connection to colonial policies.

According to the 2021 Census, more than 1.8 million people in Canada self-identify as Aboriginal, making up 5% of the Canadian population, up from 4.9% in 2016.[385] Census data shows that Aboriginal peoples are growing in Canada, though this growth was not as rapid as in years past.[385]

Historical and present-day colonialism, combined with discriminatory federal policies that disrupted generations of Indigenous peoples' cultures and communities, has conferred a higher risk of morbidity and mortality from various health concerns.[40,42,43] Specifically, First Nations people in BC face a disproportionate burden of substance-related harms. This disparity existed prior to the current drug toxicity crisis[386] and is increasing in recent years: 15.9% of all toxic drug deaths in 2021 occurred in First Nations people, compared to 14.7% in 2020, while First Nations people comprise only 3.3% of the population.[387,388] The proportions of harms by gender is also different in First Nations people compared to non-First Nations counterparts in BC. Toxic drug deaths in First Nations people were higher in men (68%) in 2020,[389] which is same trend seen in non-First Nations people, where men accounted for 81% of the deaths.[390] Furthermore, data from 2020 showed that First Nations men experienced 4.3 times more fatal poisonings than non-First Nations men, and First Nations women experienced 9.9 times more fatal poisonings compared to non-First Nations women.[387] In addition to facing a high burden of substance-related harms, cohort studies in BC have found that provision of evidence-based care for OUD is low in Indigenous people. A 2011 prospective cohort study of young Indigenous people found that less than a quarter (23.4%) of those reporting lifetime opioid use had ever been on methadone.[391] This aligns with a 2007 cohort study of people who inject drugs, which found that Aboriginal people were less likely to receive methadone treatment than non-Aboriginal people (AOR: 0.60, 95% CI:0.45–0.81).[392]

Recent research has highlighted the important role of culturally safe and informed approaches to reduce disparities in substance use care for Indigenous populations.[70,393] This guideline strongly recommends that all health care professionals and staff undertake Indigenous cultural safety and cultural humility training to improve their ability to establish safe, positive partnerships with Indigenous patients, families, and communities (see Indigenous Cultural Safety). The Calls to Action from the Truth and Reconciliation Commission Reports, recommendations in the In Plain Sight Report, and Calls for Justice from the National Inquiry into Missing and Murdered Indigenous Women and Girls Final Report outline the necessary actions to address the legacy of colonialism in a range of domains including health care. A human rights-based approach is also essential, due to Canada's history of discriminatory, unethical, and harmful treatment of Indigenous peoples in the mainstream health care system.[49] In addition to incorporating Indigenous cultural safety and cultural humility in standard medical practice, several principles of providing ethical care to Indigenous peoples have been identified in the literature[394]:

- Respecting the individual and their authority over their own health and healing journey
- Practising conscious communication, active listening, and paying close attention to how a person responds to questions and conversation, both in their speech and body language, to ensure patient comfort and safety
- Using interpreters if fluency in English or French is a barrier to communication

- Involving family members in decision-making and as key sources of support, and respecting an individual's definition of family, which can include many extended relations
- Recognizing that some individuals may prefer alternative methods for communicating and receiving information about their health—the practice of "offering truth"[y,395] and honouring a patient's decision on the type of information they wish to receive and how they wish to receive it may be helpful in this context
- Practising non-interference in a patient's decision-making, unless there has been a clear misunderstanding—strong advice or persuasive language from a person in a position of power (e.g., clinician to patient) can be interpreted as coercive
- Respecting that Indigenous peoples have the inherent and recognized right to access cultural practices as part of their health care

The Society of Obstetricians and Gynaecologists of Canada's (SOGC) Consensus Guideline for Health Professionals Working With First Nations, Inuit, and Métis[396] may be a useful clinical resource. While this guideline does include specific guidance on sexual and reproductive health care for Indigenous peoples, the majority of recommendations are relevant and applicable to general clinical practice and the Canadian health care system at large. Clinicians who provide care to Indigenous peoples should be familiar with the First Nations Benefit Program (Plan W) and the Non-Insured Health Benefits program, including eligibility and coverage requirements, and the exceptions and special permissions needed in some cases.[z] Clinicians should also be aware of regional and provincial resources available to Indigenous patients, families and communities in BC. There are several First Nations substance use treatment centres that offer culturally-based services in BC. Detailed information for each treatment centre, including eligibility requirements, can be found on the FNHA website. Each regional health authority in B.C. has an Indigenous or Aboriginal Health Program, which offer tailored services and programs to support Indigenous patients and families in accessing health and wellness services:

- Fraser Health
- Interior Health
- Island Health
- Northern Health
- Vancouver Coastal Health

[y] The practice of "offering truth" recognizes that a patient may wish to receive little information or as much information as possible about their diagnosis, prognosis, and treatment. A patient's desired knowledge of their medical condition exists along a continuum and clinicians should ensure they discuss the type of information a patient wants to receive and how the patient wants to receive that information before sharing a diagnosis and beginning treatment.

[z] Eligibility for Plan W extends to include all First Nations people (who have a status number) who are residents of British Columbia (excluding persons who receive health benefits by way of a First Nations organization pursuant to self-government agreements with Canada). Examples of individuals who may not be eligible for Plan W coverage but would be eligible for Non-Insured Health Benefits include Inuit peoples or First Nations people who are temporary residents of British Columbia and/or those who are registered in BC but are currently living in another province.

Indigenous peoples in the Lower Mainland can also be referred to the Metro Vancouver Indigenous Services Society (MVISS), which offers culturally-based and trauma-informed individual, group, and family counselling, and other Indigenous healing and support services. The Metro Vancouver Aboriginal Executive Council (MVAEC) also maintains a directory of Indigenous programs and services (including substance use and recovery services) on their website.

4.1.i Access to Cultural Practices

Indigenous approaches to health are holistic, relational, and seek to balance physical, spiritual, mental, and emotional wellness.[40] However, many clinicians who provide substance use care subscribe to a biomedical approach that is disease- and individual-focused—an approach that has been acknowledged as largely incongruent with Indigenous worldviews.[397] Conventional substance use care has been shown to be less effective for and potentially harmful to Indigenous people, with some suggesting this is partially attributable to the lack of cultural practices incorporated into treatment interventions[398] and delivery of care that does not adhere to Indigenous values and worldviews.[40] The value of using the teachings of Mi'kmaq Elder Albert Marshall's "Two-Eyed Seeing" approach, which respects and integrates the strengths of both Indigenous knowledge and Western medicine,[399] has been increasingly recognized in holistic wellness and substance use care for Indigenous peoples.[397] Further reading on this approach is available online.

There is widespread agreement among Indigenous Elders and healers, as well as researchers, that the inclusion of cultural practices in substance use care is essential to promoting healing for Indigenous peoples.[400] Indeed, substance use treatment interventions that incorporate Indigenous cultural practices have been found to improve the physical, mental, emotional, and spiritual health of Indigenous people (e.g., reduced substance use, reduced rates of mental health issues, improved relationships, increased participation in cultural practices).[400] Indigenous patients have an inherent right to access cultural practices as part of their health care, as acknowledged and highlighted by Call to Action #22 of the Truth and Reconciliation Commission, which calls on the health care system to recognize the value of Indigenous cultural practices and to use them in collaboration with Indigenous Elders and healers when delivering care to Indigenous people.[401] In recognition of this, clinicians, care teams, and staff should ensure Indigenous people can access cultural practices as a component of their OUD care:

- Clinicians should inquire with Indigenous people about their interest in including cultural practices as part of their OUD care, while understanding that Indigenous people have differing levels of involvement and interest in cultural practices.
- Some Indigenous people may already be engaged in cultural practices, whereas others may have no interest in accessing cultural practices. In either situation, clinicians should offer support to the patient and be aware that the patient's preferences for accessing cultural practices may change over time.
- If a patient is already engaged in cultural practices, clinicians should, with the consent of the patient, work collaboratively with the patient's Elder or healer in care planning.

- Patients who do not have an Elder or healer may be connected to one within the care setting, if available, or in the community.
- Clinicians may also inform patients of any sacred spaces that are available to Indigenous people in the care setting (e.g., All Nations Sacred Space at St. Paul's Hospital in Vancouver, BC, the All Nations Healing Room at the Royal Jubilee Hospital in Victoria, BC, and the Hummingbird Healing Room at the Red Fish Healing Centre for Mental Health and Addiction in Coquitlam, BC). Any patient requests to access a specific cultural practice or medicine should be satisfied within a timely manner.

A diversity of cultural practices can be integrated into substance use treatment interventions, depending on resources, capacity, and expertise, including smudging, storytelling, teachings, fasting, carving, beadwork, land-based activities, pow-wows, traditional foods and medicines, language, talking circles, drumming, singing, community feasts, sweat lodges, and prayer.[397] Clinicians may also choose to have the Four Sacred Medicines (cedar, sage, sweetgrass, and tobacco) freely available to Indigenous patients in their clinic. It is important to be mindful that traditions and cultural practices can vary across Indigenous groups and communities; clinicians should take care not to assume there is a pan-Indigenous culture.

Health authorities, hospitals, and First Nations Treatment Centres may be able to provide or link patients to patient navigators, interpreters, or sacred spaces. This may include connecting the patient to cultural supports in the community, working in partnership with the patient's Elder or healer, or providing a space for the patient to engage in cultural practices. Indigenous patient navigators or liaisons can support patients and their families, clinicians, and care teams by[402,403]:

- Connecting patients with Elders and other cultural supports
- Facilitating communication between patient and care teams
- Assisting with referrals within the health authority and to community organizations, acting as an advocate on the patient's behalf
- Liaising with Indigenous communities and organizations
- Arranging for translators
- Guiding patients through the health care system
- When patients are eligible, connecting patients to First Nations Health Benefits (Plan W) at FNHA for medical and other coverage

For more information on Indigenous cultural practices in clinical settings, clinicians can refer to Vancouver Coastal Health's *Aboriginal Cultural Practices: A Guide for Physicians and Allied Health Professionals Working at Vancouver Coastal Health*. To find community organizations that offer cultural practices, clinicians can refer to Metro Vancouver Aboriginal Executive Council's directory. Additionally, Friendship Centres offer cultural practices to Indigenous people across BC. Please see Indigenous Cultural Safety for further guidance on providing culturally safe care. Clinicians, care teams, and staff may also refer to the First Nations Health Authority to learn more about Indigenous wellness and cultural practices.

4.2 Sex, Gender, and Sexuality

Sex and gender[aa] are important determinants of health and influence the physiological and psychosocial aspects of many health conditions, including substance use disorders. Several clear trends regarding gender and opioid use have been identified, related to harms from opioid use, risk factors, and access to services.

One is that opioid poisonings, both fatal and non-fatal, tend to be higher among men than women, with men representing 78% of drug-related deaths in 2022 in BC.[390] While the reasons for this difference are unclear, several possible explanations have been offered. These include the higher likelihood of ingesting opioid medications through non-prescribed routes of administration (though these rates are high among both men and women),[404] obtaining unprescribed prescription opioids,[404,405] escalating opioid medication doses,[406] and concurrent use of alcohol.[407] Men are also more likely to have been arrested or under legal supervision[407], which can lead to loss of tolerance and disruption of income, in turn resulting in greater harm when opioid use is resumed.

Women, too, face their own set of risks and gender-specific factors related to opioid use, including significant psychiatric, economic, and infectious disease vulnerabilities compared to men.[408] Psychiatric vulnerabilities include higher rates of bipolar disorder,[408] major depression,[404,408,409] anxiety/panic disorder,[404,408,409] post-traumatic stress disorder,[404] and history of suicidal behaviour.[408] Economic vulnerabilities include significantly higher rates of sex work,[408] higher likelihood of being financially dependent on someone else,[408] and higher likelihood of being unemployed.[404,407] Increased infectious disease vulnerabilities are due to a higher likelihood of sharing injection equipment.[408]

Additional vulnerabilities and risk factors women face include higher rates of family and social functioning impairment,[404] pain despite chronic opioid analgesia,[410] prescription opioid use in response to negative or difficult emotions,[404] opioid use to cope with physical symptoms,[404] concurrent amphetamine use,[407] and physical and sexual abuse histories,[408] as well as a known association between chronic physical pain in women and experiences of trauma and violence, including in women on OAT.[411]

It is noteworthy that, as a result of ongoing colonization, discrimination, and racism, Indigenous women are at substantially higher risk of drug toxicity death than non-Indigenous women. More than 32% of First Nations people who died as a result of drug toxicity in 2020 were women while women represented only 16.6 % of drug toxicity deaths in the general population.[412]

In addition to the vulnerabilities identified above, a recent study of overdose prevention sites (OPS) in Vancouver, BC, found that many OPS are experienced as male-dominated or "masculine" spaces, despite the intention of being gender-neutral. Women reported routinely experiencing harassment from men at OPS,

[aa] Sex generally refers to the classification of a person as male, female, or intersex at birth, usually based on the appearance of their external anatomy, whereas gender refers to one's internal, deeply held sense of their gender, which may or may not align with the sex they were assigned at birth.

including from men accessing OPS who had previously victimized them.[413] Thus, women may face barriers to accessing OPS, which may be alleviated by offering women-only services or hours.

The above-identified trends and relationships underscore the importance of sex/gender-informed and gender-inclusive care. The Centre of Excellence in Women's Health has several resources available through their Trauma Gender Substance Use Project, including a *Gender-Informed Approaches to Substance Use Resource List*, the *New Terrain Toolkit*,[71] and the *Trauma-Informed Practice and the Opioid Crisis*. Clinicians and care teams should also be familiar with and offer patients the option of sex/gender-specific substance use treatment and support services in their communities, if available and as appropriate.

4.2.i. 2S/LGBTQQIA+ Populations

Two-spirit[bb], lesbian, gay, bisexual, trans, queer, questioning, intersex, asexual and other gender and sexually diverse people (2S/LGBTQQIA+) face unique challenges as a result of social prejudice and discrimination, internalized stigma, and lack of health care provider competencies specific to these groups.[414,415] For example, due to the persisting heteronormative and often stigmatizing practices in the health system, trans individuals tend to feel unsafe in healthcare settings and may delay accessing care. As a result, gender-diverse and sexually diverse individuals tend to access care with more complex substance-related problems[416,417] and greater physical and mental health care needs[418,419] than individuals who do not identify as 2S/LGBTQQIA+. Some 2S/LGBTQQIA+ individuals report disproportionate rates of substance use,[420-422] and enter treatment with greater severity of substance use problems.[423] Suggested explanations for these disproportionate rates include the stress of being in a minority group, dealing with social prejudice and discrimination, internalized stigma, and lack of cultural competence in the health care system.[423,424] Data on OUD specifically in 2S/LGBTQQIA+ individuals is lacking; however, given the high rates of substance use in some 2S/LGBTQQIA+ communities, OUD treatment should be culturally sensitive and include an awareness of the issues that 2S/LGBTQQIA+ individuals are likely to face.

Strategies for working with 2S/LGBTQQIA+ individuals include actively communicating that services are available for 2S/LGBTQQIA+ patients, building relationships with organizations serving diverse marginalized communities, and using inclusive language in forms and clinical materials and during appointments.[423] Although substance use disorder treatment for 2S/LGBTQQIA+ individuals is similar to that for other populations, additional factors must be considered, including acknowledging and affirming the patient's feelings about their sexual and gender identities and the impacts of stigma and discrimination in their lives.[425] Other strategies include respecting that identities are fluid and tailoring care accordingly; mirroring the language that your

[bb] Two-Spirit is a term used by some North American Indigenous societies to describe people with diverse gender identities, gender expressions, gender roles, and sexual orientations. Dual-gendered, or 'two-spirited' people have been and are viewed differently in different Indigenous communities. Definition borrowed and lightly adapted from Qmunity's "Queer Terminology from A to Q". Additional information on Two-Spirit individuals can be found on the Two Spirit Journal website.

patients use (e.g., to refer to themselves, their relationships, and bodies); not assuming sexual activity levels or motives for substance use; and being affirmative—recognizing the ways that individuals successfully practice harm reduction in their lives. 2S/LGBTQQIA+ individuals may also have experienced discrimination in the health care system and thus require extra sensitivity from health care providers in order to build trust.[425] Prescribers should make themselves aware of local support groups and resources for 2S/LGBTQQIA+ individuals. When feasible, gender-affirming and supportive bed-based, outpatient, or harm reduction services that are designated for 2S/LGBTQQIA+ clients can reduce barriers to accessing care. Additional information and guidance can be found in the Substance Abuse and Mental Health Services Administration's publication, *A Provider's Introduction to Substance Abuse Treatment for Lesbian, Gay, Bisexual, and Transgender Individuals*. Health care providers may also benefit from taking the 2S/LGBTQQIA+ module in the BC Centre on Substance Use's Addiction Care and Treatment Online Course.

A non-judgmental approach, active demonstration of awareness of and sensitivity toward trans issues, and a reinforcement of confidentiality can help trans people feel safe approaching care providers.[426] Other ways to demonstrate trans awareness and sensitivity include placing trans inclusive brochures and posters in waiting rooms, asking about gender identity on intake forms (and avoiding conflating gender and sex[cc]),[426] and using open-ended questions about sexuality and gender.[425] Additional strategies include being reflexive and acknowledging personal biases; recognizing an individual's intersecting identities (e.g., race, disability, gender, sexuality) and how they may compound and impact patients' experience of health care; and making gender neutral bathrooms available. More information on working with trans, two-spirit, and gender diverse patients can be found in Trans Care BC's *Gender-affirming Care for Trans, Two-Spirit, and Gender Diverse Patients in BC: A Primary Care Toolkit*. Additional resources include the Trans Care Program, provides clinician education, medical forms, clinical resources, patient materials, and linkages to care; UBC CPD's Gender-Affirming Primary Care course; Sherbourne Health Centre's *Guidelines and Protocols for Hormone Therapy and Primary Health Care for Trans Clients*;[427] and the Canadian Professional Association for Transgender Health. The RACE line and eCASE can also provide patient-specific guidance.

4.3 Youth

The lack of tailored, age-appropriate approaches to and options for substance use care have consistently been cited as barriers to engaging youth in treatment.[428,429] Strategies that primary care clinicians and care teams can use to improve retention and engagement in care in youth include: emphasizing confidentiality within and across services; including family members and other caregivers (e.g., trusted Elders, teachers, outreach workers, counsellors, as well as friends and romantic partners) in care when appropriate; fostering respect, trust, and the

[cc] Sex generally refers to the classification of a person as male, female, or intersex at birth, usually based on the appearance of their external anatomy, whereas gender refers to one's internal, deeply held sense of their gender, which may or may not align with the sex they were assigned at birth. A person's sex should not be assumed to match their gender, for example, that a person will have specific genitalia or reproductive anatomy based on their gender identity.

development of longitudinal therapeutic relationships; offering the full scope of pharmacotherapy when indicated; providing referrals to youth-oriented psychosocial treatment interventions and supports; and ensuring timelines are adequately discussed with youth and that treatment is provided without a pre-determined end date.[430-436] Inclusion of peer support staff or referrals to peer support services in the community may also support a youth-centered approach to care.[437,438]

While this guideline is intended to be applicable to all adults age 18 and above, there are unique considerations for adolescents (age 12-17) and young adults (18-25), collectively referred to as "youth", that are not addressed in this document. Specific guidance for the screening, assessment, and treatment of OUD in youth (aged 12-25) can be found in the BCCSU, Ministry of Health, and Ministry of Mental Health and Addiction's *Treatment of Opioid Use Disorder for Youth--Guideline Supplement.*[102]

4.4 Pregnancy

Specific guidance for the treatment of OUD in pregnant individuals is outside the scope of this guideline. See the BCCSU, Ministry of Health, and Ministry of Mental Health and Addiction's *Treatment of Opioid Use Disorder During Pregnancy—Guideline Supplement*.[439] Care providers can access the Rapid Access to Consultative Expertise (RACE) line or 24/7 Addiction Medicine Clinician Support Line to receive specialist advice for pregnant clients.

4.5 Corrections

Specific guidance for the treatment of OUD in correctional settings is outside the scope of this guideline. However, health care providers should be aware of the importance of maintaining care for patients who transition in and out of correctional settings. The following general principles should guide care for people transitioning in or out of correctional settings:

- Addiction care provision in correctional settings should adhere to the principle of community equivalence.
- For individuals who are engaged in OAT in the community at the time of entry into the correctional system, OAT must be continued without interruption or delay once incarceration begins.
- Correctional health services should establish a plan to ensure continued care in the community prior to the release of an individual receiving treatment for OUD while incarcerated.
- Prison-based care programs should collaborate with community-based services and provide individuals about to re-enter the community with referrals for continued treatment and support.

4.6 Older Adults

While this guideline is intended to be applicable to all adults age 18 and above, there are unique considerations for older adults (age 65 and above). For specific guidance on prevention, screening, assessment, and treatment

of OUD in older adults, as well as an overview of the issues unique to this population, please refer to the Canadian Coalition for Seniors' Mental Health's *Canadian Guidelines on Opioid Use Disorder Among Older Adults*.

4.7 Individuals Experiencing Homelessness

Housing is an important determinant of health that has been linked to a variety of poor health outcomes. Research indicates that living situations such as homelessness and marginal housing (e.g., single-room occupancy housing) are associated with a higher prevalence of chronic and infectious diseases and poorer overall mental and physical health. Estimates of substance use among individuals experiencing homelessness vary depending on the population and definition of homelessness used, but there is consistent evidence that individuals experiencing homelessness report disproportionate rates of substance use. A 2008 meta-analysis of international studies found that 4.5–54.2% of individuals experiencing homelessness reported non-alcohol substance use, substantially higher than the estimated overall prevalence of substance use.[440] Within BC, 8,665 people were enumerated as homeless in 2020/21 and over two-thirds (67%) of respondents indicated they had some form of addiction, although both of these numbers are considered to be underestimates.[441]

Current evidence suggests substance use and homelessness are mutually-reinforcing, but evidence is mixed regarding causality, including the temporality and magnitude of the relationship between substance use and homelessness.[442] However, housing instability that precedes substance use is linked to increased drug use intensity, including initiation into injection drug use. Compared to the general population, individuals who experience homelessness have higher substance-related mortality rates, including opioid overdose as a leading cause of death.[443,444]

Individuals experiencing homelessness face significant barriers accessing and being retained in OUD care, despite utilizing health care services—particularly emergency services—more frequently than housed individuals.[445] Further, people experiencing homelessness face challenges in accessing health care services, including lack of knowledge regarding care options, lack of transportation, lack of child care, and previous and anticipated experiences of discrimination in health care settings.[445] Specific aspects of OUD care (e.g., frequent appointments with clinicians, daily visits to a pharmacy to pick up OAT medication) present further barriers to treatment access for individuals who experience homelessness. Clinicians can better support individuals who experience homelessness by working collaboratively with patients to determine a treatment plan, providing flexible appointments, and prescribing take-home doses of medications, if appropriate (see Appendix 6 for details on take-home dosing).[dd] People who experience homelessness who present in emergency departments may be candidates for an emergency department buprenorphine/naloxone induction (see Emergency Department Buprenorphine/Naloxone Induction and Appendix 4). Clinicians should connect patients with

[dd] Take-home doses can be considered for patients that demonstrate clinical and psychosocial stability and are able to safely store the medications. For take-home methadone or slow-release oral morphine, evidence of medication adherence for at least 4 weeks is also required.

resources to meet their other health, social, and survival needs (e.g., specialist care, housing, food/nutrition, financial assistance, employment, outreach services) as requested or appropriate.

4.8 Rural and Remote Populations

Approximately 14% of British Columbians live in rural areas of the province.[446] Notably, 30.3% of Indigenous people in BC live in rural areas and another 40.1% of Indigenous people live on-reserve.[447] While data on the prevalence of OUD in rural and remote populations is lacking, 2015–2016 data from BC's Provincial Overdose Cohort indicates a non-fatal overdose rate of 53.1 per 100,000 people and a fatal overdose rate of 8.7 per 100,000 people in rural areas[ee] and a non-fatal overdose rate of 18.1 per 100,000 people and a fatal overdose rate of 4.8 per 100,000 people in remote areas[ff].[448] These rates are substantially lower than urban areas, where the non-fatal overdose rate is 182.9 per 100,000 people and the fatal overdose rate is 20.5 per 100,000 people.

Several environmental and social factors are thought to predominantly influence opioid use in rural areas of the United States, but there is a lack of comparable research in Canada. In rural areas, widespread use of prescription opioids is partially attributable to the normalization of prescription opioids in heavy-labour occupations, which, in part, results from heightened rates of occupational injury.[449,450] In addition, an older population that is more likely to experience increased chronic pain is also thought to contribute to the normalization of opioid use in rural areas.[450] There are extensive social and family networks present in rural and remote settings that are associated with protective factors for substance use as well as negative influences that may faciliate initiation into opioid use and diversion of prescription opioids.[449] A lack of economic opportunity that results in unemployment and financial hardships further contributes to opioid use in rural and remote communities.[450]

There are unique barriers to both accessing and providing OUD care in rural and remote areas. The most commonly reported barrier to substance use care is the lack of medication treatment services, followed by increased travel times, stigma, and general lack of resources (e.g., internet access) and local services.[451,452] The shortage of health care providers, including those trained to provide OAT, leads to lengthy wait-times for entry into care. Rural and remote area are less likely to have clinics or pharmacies within their communities, necessitating patients travel long distances to access OUD care, which can be costly and time-consuming for patients. Moreover, individuals who live in rural and remote communities are more likely to be undiagnosed and untreated for substance use disorders, and more likely to report unmet substance use care needs.[453,454] Individuals who must travel from rural and remote settings to urban settings to receive substance use care are more likely to experience a relapse and more likely to become incarcerated.[449] At the provider level, health care

[ee] Rural is defined as a population of 1,000–20,000 people; communities may have some specialized acute services, residential care and assisted living, limited inpatient care, primary and community care, and basic and urgent emergency care, depending on the size and needs of the community.

[ff] Remote is defined as a population of 0–1,000 people; communities may have nurse-led care, first aid, mobile primary and community care. Some remote communities are too small and dispersed to maintain health services, requiring community members to access health care in other communities.

providers in rural and remote areas are also less likely to have received training in OUD care and, as a result, are less likely to offer their patients evidence-based treatments, particularly opioid agonist treatment.[455] Limited availability and support from other rural health care providers, specialists, and support staff further hinder the delivery of OUD care.

Several strategies have been identified for providing effective OUD care to patients in rural and remote settings. Care providers can determine how to adapt the recommendations in this guideline in order to reduce barriers for patients. For example, flexible and early take-home dosing can be considered in situations where daily visits to pharmacy are not feasible due to distance or other limitations. All adaptations to the recommendations should have a clear rationale, take patient and community safety into consideration, and be documented. Additionally, nurses can play a key role in increasing access to and retention in OUD care in rural and remote settings, as they are often the primary care providers in these communities. In the United States, where nurse practitioners have had authority to prescribe buprenorphine since 2016, there has been a marked increase in the number of buprenorphine providers in both urban and rural counties.[456] More than 50% of the new buprenorphine providers in rural areas were nurse practitioneres and physician assistants. In BC, as part of the provincial response to the overdose crisis, temporary regulatory exceptions were granted in 2020, permitting an expanded scope of practice for registered nurses (RNs) and registered psychiatric nurses (RPNs). In 2023, a new designation of certified practice for opioid use disorder for RNs and RPNs was approved by the BC College of Nurses & Midwives. Certified Practice Opioid Use Disorder RNs and RPNs can diagnose OUD and prescribe buprenorphine/naloxone, methadone, and slow-release oral morphine. This expansion of scope will likely facilitate greater access to evidence-based treatment, particularly in rural and remote areas.

Another strategy is the wider adoption of virtual care (often called telehealth) in delivering OUD care (see below for further detail). Virutal care enables providers to consult with patients from a distance, eliminating the need for—and additional costs of—patient travel to other communities. While telehealth has demonstrated effectiveness in rural populations, few studies have been conducted examining OUD care specifically.[450] However, a 2017 cohort study in rural Ontario found retention rates of participants who received remotely delivered OAT to be significantly higher (50%) compared to those who received opioid agonist treatment through in-person visits (39%), at 1 year (aOR: 1.27, 95% CI: 1.14–1.41, p<0.001). The authors suggest the higher retention rates are attributable to increased acceptability and convenience to patients as they can remain in their communities to initiate and be maintained on opioid agonist treatment.[457] A virtual OUD care program in Alberta had a retention rate of 90% at 6 months and 58% at 12 months and was able to reduce wait-times from 6 days to 0 days, highlighting the significant potential to increase access to care in rural and underserved areas.[458]

4.8.i Virtual Care

Virtual care may be used, when appropriate, along with in-person appointments, collaboration with pharmacists, nurses, and specialists, to reduce travel time for patients, facilitate referrals without onerous travel, increase access to care, facilitate physical distancing (e.g., during pandemic-related restrictions), and support retention in care. Virtual care for substance use care may help engage patients by improving access and convenience and has

been shown to be at least as effective as in-person treatment in terms of retention, therapeutic alliance and substance use, during the COVID-19 pandemic.[459] However, some individuals may not be able to utilize virtual services due to barriers such as inability to access a telephone, computer, or high-speed internet. These barriers may be particularly challenging in certain groups, including racial minorities, the elderly, and those with low levels of education.[460]

Clinical judgment and patient circumstances should guide when and if virtual care is appropriate. Virtual care can be used to provide OAT prescriptions as well as follow-up and ongoing care. The current practice standard indicates that physicians can prescribe OAT if they have:

- a longitudinal treating relationship with the patient, or
- performed and documented a comprehensive assessment themselves (either by virtual care or in-person) and will be available to the patient for follow-up and are able to provide ongoing care that includes comprehensive management of the OUD.

Nurses may also provide OUD care through virtual technology. More information can be found on the BCCNM website.

Virtual care can help improve the accessibility and continuity of OUD care. However, virtual-only substance use care alone and in perpetuity will not meet CPSBC's *Standard on Virtual Care*. Regulated health professionals should regularly consult their College's standard or guidance on virtual care to ensure that they are aware of and meeting their professional obligations.

4.9 Individuals Subject to Workplace-related Legislation

Individuals subject to provincial or federal workplace-related legislation or who are otherwise limited in their treatment options due to the requirements of their jobs (e.g., regulated health care professionals, pilots) may not have access to the full continuum of care for OUD (i.e., OAT) if they wish to remain active in their position. Clinicians should discuss the risks and benefits of each treatment option and the full continuum of care with each patient, with the understanding that alternative treatment programs (e.g., opioid antagonist medications and/or psychosocial treatments) may enable patients to maintain their employment.

Under current regulations, patients who opt for OAT may require modification of workplace duties. Clinicians should work collaboratively with patients and consult with regulatory bodies and other entities (e.g., relevant regulatory colleges, Canadian Medical Protective Association) regarding obligation to notify employers in these circumstances.

It should be emphasized that workplace substance use-related policies that have precluded individuals in safety-sensitive occupations from receiving OAT have emerged without a firm evidence base or sufficient evaluation.[461]

There are currently jurisdictions, including some US states, that allow healthcare providers to receive buprenorphine-based treatments, and there is no substantial evidence associating use of buprenorphine/naloxone among health care providers with medical errors or other concerns.[461]

Barriers to accessing OAT carry a high risk of return to unregulated opioid use, which, in turn poses significant danger to personal and public health and safety. In view of these risks, the BC Coroner's Service Death Review Panel has recommended a revision of policies that have discouraged workers from seeking substance use care and precluded individuals in safety-sensitive positions from using evidence-based medications despite the absence of any compelling evidence that they significantly affect safety or workplace performance.[462]

Further work to identify and guide best practices for the treatment of OUD in this context is greatly needed.

CLINICAL GUIDANCE (APPENDICES)

Preface

The following appendices have been developed to support clinical practice using a different methodology from the process utilized for the main body of the guideline. The clinical guidance provided here has been derived through guideline committee consensus following iterative discussions in reference to existing evidence and national and international evidence-based clinical practice guidelines. The content presented in the appendices is also informed by the opinion of expert reviewers, personal communication with study authors, and a review of position papers and practice bulletins issued by recognized addiction medicine professional organizations and authorities. In addition, where appropriate, Health Canada-approved drug product monographs, and previous and current guidance from the College of Physicians and Surgeons of BC (CPSBC) and Health Canada were consulted to ensure compliance with provincial and national safety regulations and standards for practice.

APPENDIX 1: METHODS

A1.1 Funding

Guideline development activities were entirely supported by funding provided by the BC Ministry of Mental Health and Addictions and the BC Ministry of Health to the BCCSU. No support was received from the pharmaceutical industry or associated stakeholders for guideline development.

A1.2 Committee Membership

The first edition of the BCCSU *Guideline for the Clinical Management of Opioid Use Disorder* (2017) was developed by an interdisciplinary committee of 28 experts with representation from each health authority, the Ministry of Health, BC Corrections Services, and the First Nations Health Authority. In keeping with the BCCSU's commitment to regular review and update of clinical guidelines, the OUD guideline committee was reconvened in 2019 in order to begin the update process.

In 2020, the work of the committee was paused due to the COVID-19 pandemic, which shifted the BCCSU's focus to addressing emergent needs related to the dual public health emergencies. The guideline update work resumed in May 2022. At this point, the committee list was revised to ensure member availability and improve geographic and disciplinary representation. Ultimately, the re-assembled OUD committee responsible for the development of the second edition of the guideline consisted of 31 members (5 existing members and 26 new members).

This committee includes representation from each regional Health Authority in BC, the Provincial Health Services Authority, the First Nations Health Authority, BC Ministry of Health, and Ministry of Mental Health and Addictions. The committee was composed of experts in the fields of substance use care, psychiatry, family practice, nursing, pharmacy, recovery-oriented systems of care, and health care administration and policy, as well as people and family members with lived experience.

Conflict of interest policy

In line with Guidelines International Network's Principles for Disclosure of Interests and Management of Conflicts,[463] committee members were required to disclose all sources and amounts of direct and indirect remuneration received in the past five years from industry, for-profit enterprises, and other entities (i.e., direct financial conflicts) that could introduce real, potential, or perceived risk of bias. In addition, committee members were asked to report possible indirect conflicts of interest, such as academic advancement, clinical/professional revenue, and public standing that could potentially influence interpretation of evidence and formulation of the strategies contained in this guidance.

Conflict of interest summary

In terms of indirect sources of potential interest or bias, one committee member is involved in research evaluating opioid agonist treatment. Of the 31 individuals on the committee, 24 members disclosed expertise and/or experience with the topics of the guideline. This pertained to clinical practice (e.g., addiction medicine clinician or service provider), personal experience, academic publications, and public advocacy. In addition, 4 committee members reported that their clinical revenue could potentially be influenced by the guidance in this document. Upon review, of those who disclosed potential indirect conflicts of interest or bias, none were deemed to be of sufficient relevance or weight to warrant exclusion from the committee.

A1.3 Guideline Development Process

The OUD guideline committee had its initial meeting for the development of the OUD guideline's second edition in November 2019. In this meeting, the outline, scope, and planned major revisions of the guideline were provisionally approved by committee consensus with reference to the results of a preliminary literature search conducted earlier in that year. Subsequently, 3 working groups were formed to develop updated clinical guidance for:

1) Initiation, titration, and dosing of OAT medications
2) Continuing care considerations for patients on OAT
3) Take-home dosing considerations

Decisions made in the initial committee meeting and subsequent email communications informed literature searches and reviews and the drafting process. However, this work was put on hold in March 2020 due to the COVID-19 pandemic, before the committee was able to review the first draft.

Upon resumption of the OUD guideline development work in 2022, an updated systematic literature search was conducted by an information specialist in consultation with committee co-chairs and medical writers, and the draft guideline was updated accordingly.

Between September 2022 and January 2023, each working group conferred over email and, in the case of working groups 1 and 3, video conference to discuss and approve draft guideline contents and recommendations. During this process, targeted literature searches and reviews were conducted to address specific working group concerns. The full draft of the guideline was reviewed in the course of two revision rounds and a full committee meeting to reach consensus in January 2023.

Consistent with best practices for guideline development, the AGREE-II instrument[464] was used throughout development and revision phases to ensure the guideline met international standards for transparency, high quality, and methodological rigour.

A1.3.i Literature Search Strategy

The second edition of the OUD guideline expanded on the structured literature search that was conducted for the first edition in 2016. For the development of the present edition, updated systematic literature searches were performed in December 2019 and May 2022.

Using a search strategy approved by committee co-chairs, an information specialist performed the literature searches for the following databases: Medline, Embase, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials via Ovid; CINAHL and PsycINFO via EbscoHost. Search date limits started at 2016 to identify studies published after the literature search conducted for the previous edition of the guideline.

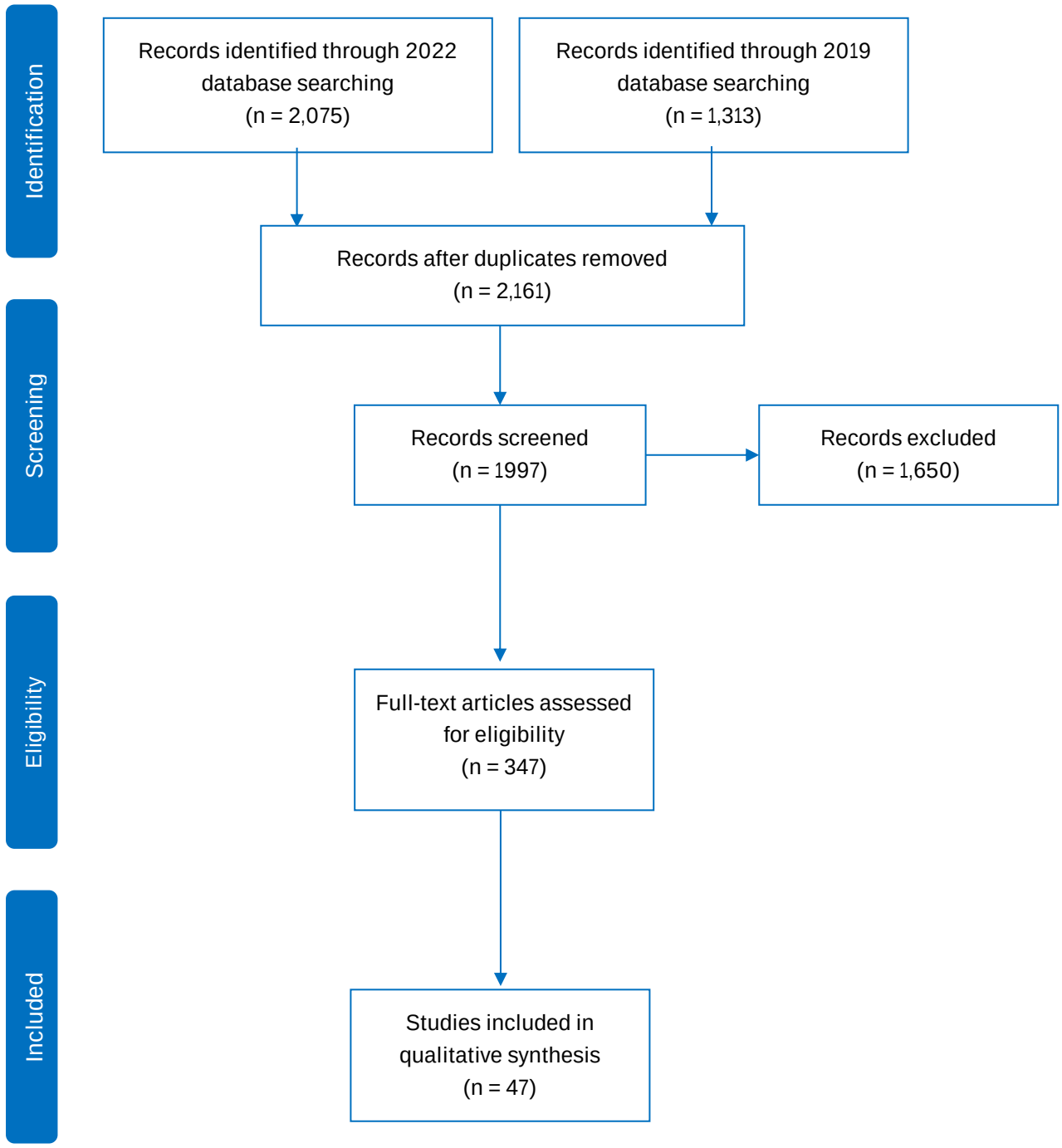
Studies were excluded if they did not meet inclusion criteria established *a priori* or if they were already included in high-quality systematic reviews and meta-analyses. There was no search of unpublished research. Additional details of the search strategy are provided below.

In December 2022, a supplementary targeted search of peer-reviewed and grey literature was performed by an information specialist to address specific questions posed by working groups concerning starting OAT doses, strategies to address missed doses, and developments in take home dosing policies and protocols.

A3.3.ii Study Selection and Critical Appraisal

Two medical writers independently screened and identified eligible studies. Discordance between reviewers on inclusion or exclusion of individual studies was resolved through discussion with no need for arbitration. A PRISMA flowchart is included below. One reviewer used validated assessment tools (e.g., AMSTAR-2, Cochrane Risk of Bias Tool, Downs and Black checklist) to evaluate study quality. The writers then updated the evidence summaries for review by each of the working groups.

PRISMA Flow Chart— May 2022 Literature Search



A3.3.iii Development and Approval of Recommendations

After reviewing and providing feedback on the evidence summaries, each working group determined through consensus whether the recommendations should be accepted without modification, adapted, or removed. For adaptations to existing recommendations or the development of new recommendations, the working groups used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool[465] to score recommendations.

Grade quality of evidence

Initial estimates of quality are based on a traditional hierarchy of evidence, whereby meta-analyses of randomized clinical trials are assigned the highest score, followed by individual clinical trials, quasi- or non-randomized trials, observational studies and reports, and expert opinion, which is assigned the lowest score. Factors that lowered confidence in the estimated effect of an intervention included risk of bias, inconsistency across the RCTs, indirectness, and publication bias; factors that increased confidence include large effect sizes and an observed dose-response effect. The final quality ratings are reflective of the estimated effect of an intervention as reported in the literature with consideration of biases and limitations of the evidence base as identified by the committee.

Table 3. GRADE Quality of Evidence

Quality of Evidence	Definition
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

Strength of recommendation

To determine strength of recommendations, the GRADE system takes into account the quality of evidence as well as additional factors, such as clinician, patient, and policy maker's values and preferences, costs and cost-effectiveness, risk-benefit ratios, and feasibility.[466]

Table 4. GRADE Strength of Recommendation

Strength of Recommendation	Definition
Strong	Implies that all patients in a specific situation would want the recommended course of action and that only a small proportion of the genera patient population would not.
Weak (Conditional)	Implies that most patients in specific situations would want the recommended course of action but many would not. In the context of this guideline, conditional recommendation would be applicable in specific situations where factors such as strong patient preference, limiting circumstances, or contraindications would preclude the use of other generally preferable options.

Once approved by committee chairs, the full-text draft guideline and graded recommendations were compiled and circulated to the full committee. The committee was given three weeks to submit written feedback on the draft guideline. Feedback was collated and incorporated into a revised draft for external review.

External review and stakeholder consultation

The draft guideline was circulated for review and comment to relevant experts and stakeholders in provincial, national, and international jurisdictions as identified by the committee. As per policy, all external reviewers completed disclosure of interest forms prior to review. Feedback from the external reviewers was reviewed by the co-chairs and incorporated into the guideline.

Update schedule

In order to ensure that advancements in the field reach the intended audience in a timely and effective manner, the guideline committee will review and update the guideline regularly.

A1.4 Search methodology

Two limited but systematic literature searches were conducted in December 2019 and May 2022 to identify literature based on the research questions listed below with regard to the management of opioid use disorders. The literature search conducted in May 2019 expanded on the search conducted in 2016 for the first edition of the guideline. The guideline development process was put on hold due to the COVID-19 pandemic shortly after the completion of this search. To address the time gap in the development process, an updated search was performed in May 2022 using the same research questions and inclusion criteria, which was reviewed and approved by the committee chairs. Since the PubMed search site had made significant changes to its functionality in 2020, the same publication date limits (2016 onwards) were applied in 2022 to ensure that no relevant finding would be missed due to these changes; however, the articles identified in the 2019 search were considered duplicates and removed from the results of the 2022 search to avoid redundant work. The PRISMA chart and

summary of identified items presented in this appendix presents aggregate results of the literature searches performed for the second edition of the OUD guideline.

Peer reviewed articles and papers were identified by searching health-related databases with international coverage (Medline, Embase, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials via Ovid; CINAHL and PsycINFO via EbscoHost). Database-dependent subject headings and text words were used in the search.

Specific search parameters (e.g., inclusion/exclusion criteria, jurisdictions, time frame, languages of publication) were developed in consultation between the information specialist, BCCSU staff, and guideline committee co-chairs during initial planning stages.

Table 5. Inclusion and Exclusion Criteria for the 2019 and 2022 Literature Searches

Research Question	Include	Exclude
1. Should individuals with opioid use disorder be offered buprenorphine/ naloxone as the preferred first-line option for opioid agonist treatment?	• Population: Adults with opioid use disorder • Intervention: Long-term ("maintenance") treatment with buprenorphine or buprenorphine/naloxone • Comparator: Long-term ("maintenance") treatment with placebo, methadone, treatment as usual, no treatment • Outcomes of Interest: Primary— Retention in treatment, abstinence or reduction in illicit opioid use Secondary—side effects, adverse events, morbidity and mortality Other—Direct and indirect costs, health service utilization • Study type: Meta-analyses, systematic reviews, randomized controlled trials	• Articles not in English • Age: under 18 • Pregnancy

2. Are there specific individuals with opioid use disorder who should preferentially receive depot buprenorphine or injectable buprenorphine rather than sublingual buprenorphine/naloxone?	• Population: Adults with opioid use disorder • Intervention: Long-term ("maintenance") treatment with or buprenorphine/naloxone • Comparator: Long-term ("maintenance") treatment with buprenorphine monoproduct (depot [Subutex] buprenorphine, injectable buprenorphine [Sublocade]), Treatment as usual • Outcomes of Interest: Primary— Retention in treatment, abstinence or reduction in illicit opioid use Secondary—side effects, adverse events, morbidity and mortality Other—Direct and indirect costs, health service utilization • Study type: Meta-analyses, systematic reviews, randomized controlled trials	• Articles not in English • Age: under 18 • Pregnancy
3. Should individuals with opioid use disorder who are not benefitting from buprenorphine/naloxone be offered the option of transitioning to methadone?	• Population: Adults with opioid use disorder • Intervention: Long-term ("maintenance") treatment with buprenorphine or buprenorphine/naloxone; transition from buprenorphine or buprenorphine/naloxone to methadone • Comparator: Long-term ("maintenance") treatment with placebo, methadone, treatment as usual, no treatment; treatment as usual • Outcomes of Interest: Primary— Retention in treatment, abstinence or reduction in illicit opioid use; Secondary—side effects, adverse events, morbidity and mortality; Other—Direct and indirect costs, health service utilization • Study type: Meta-analyses, systematic reviews, randomized controlled trials	• Articles not in English • Age: under 18 • Pregnancy
	• Population: Adults with opioid use disorder	

4. Should individuals with opioid use disorder be offered methadone as a first-line treatment option when buprenorphine/naloxone is not preferred?	• Intervention: Long-term ("maintenance") treatment with methadone • Comparator: Long-term ("maintenance") treatment with placebo, buprenorphine, buprenorphine/naloxone, treatment as usual, no treatment • Outcomes of Interest: Primary— Retention in treatment, abstinence or reduction in illicit opioid use; Secondary—side effects, adverse events, morbidity and mortality Other—Direct and indirect costs, health service utilization • Study type: Meta-analyses, systematic reviews, randomized controlled trials	• Articles not in English • Age: under 18 • Pregnancy
5. Should individuals with opioid use disorder who have achieved sustained clinical and social stability on methadone, and who express a desire for lower-intensity treatment or treatment simplification, be offered the option of transition to buprenorphine/naloxone?	• Population: Adults with opioid use disorder • Intervention: Long-term ("maintenance") treatment with methadone, transition from long-term ("maintenance") treatment with methadone to buprenorphine or buprenorphine/naloxone • Comparator: Long-term ("maintenance") treatment with placebo, buprenorphine, buprenorphine/naloxone, treatment as usual, or no treatment; treatment as usual • Outcomes of Interest: Primary— Retention in treatment, abstinence or reduction in illicit opioid use Secondary—side effects, adverse events, morbidity and mortality; Other—Direct and indirect costs, health service utilization • Study type: Meta-analyses, systematic reviews, randomized controlled trials	• Articles not in English • Age: under 18 • Pregnancy
6. Should individuals with opioid use disorder who have not benefitted from	• Population: Adults with opioid use disorder • Intervention: Long-term ("maintenance") treatment with slow-release oral morphine	• Articles not in English • Age: under 18

treatment with first- and second-line treatment options (buprenorphine/naloxone and/or methadone) be offered the option of opioid agonist treatment with slow-release oral morphine?	• Comparator: Long-term ("maintenance") treatment with placebo, methadone, buprenorphine, buprenorphine/naloxone, treatment as usual, or no treatment • Outcomes of Interest: Primary— Retention in treatment, abstinence or reduction in illicit opioid use Secondary—side effects, adverse events, morbidity and mortality; Other—Direct and indirect costs, health service utilization • Study type: Meta-analyses, systematic reviews, randomized controlled trials	• Pregnancy
7. Should individuals with opioid use disorder be offered the option of withdrawal management as a stand-alone treatment?	• Population: Adults with opioid use disorder • Intervention: Tapered dose regimens of opioid agonist treatments (buprenorphine, buprenorphine/naloxone, or methadone, SROM) or alpha$_2$-adrenergic agonists (clonidine, lofexidine) • Comparator: Tapered dose regimens of treatment as usual (for within-class comparisons of opioid agonist treatments and alpha$_2$-adrenergic agonists), tapered dose regimens of symptomatic medications (e.g., anti-anxiolytic, anti-emetic, anti-diarrheal, and/or non-opioid analgesic medications), no pharmacological treatment, or long-term ("maintenance") opioid agonist treatment. • Outcomes of Interest: Primary—completion of or retention in treatment, sustained abstinence from or reduction in opioid use Secondary—side effects, adverse events, morbidity, and mortality • Study type: Meta-analyses, systematic reviews, randomized controlled trials	• Articles not in English • Age: under 18 • Pregnancy

8. Should individuals with opioid use disorder who wish to pursue withdrawal management be offered the option of an extended opioid agonist taper (that is, a gradual dose reduction over a period of one month or more) in an outpatient or residential setting?	• Population: Adults with opioid use disorder • Intervention: Buprenorphine, buprenorphine/naloxone, or methadone taper regimens administered at variable amounts, duration, or rates. • Comparator: Where applicable, treatment as usual (for within-class comparisons or opioid agonist tapers) or long-term ("maintenance") opioid agonist treatment. • Outcomes of Interest: Primary—completion of or retention in treatment, sustained abstinence from or reduction in opioid use Secondary—side effects, adverse events, morbidity, and mortality • Study type: Meta-analyses, systematic reviews, randomized controlled trials	• Alpha2-adrenergic agonist taper regimens • Articles not in English • Age: under 18 • Pregnancy
9. Should individuals with opioid use disorder who have sustained clinical stability on—but wish to discontinue—opioid agonist treatment be offered the option of a long-term stepped tapering schedule (i.e., individually tailored, alternating schedule of gradual dose reduction and stabilization periods with a total duration of months to years)?	• Population: Adults with opioid use disorder • Intervention: Buprenorphine, buprenorphine/naloxone, or methadone taper regimens administered at variable duration, rates, and schedules. • Comparator: Not applicable • Outcomes of Interest: Completion of or retention in treatment, sustained abstinence from or reduction in opioid use. • Study type: Meta-analyses, systematic reviews, randomized controlled trials	• Articles not in English • Age: under 18 • Pregnancy

10. Should individuals with opioid use disorder who are engaged in opioid agonist treatment be offered the option to access or participate in psychosocial treatment interventions?	• Population: Adults with opioid use disorder • Intervention: Psychosocial treatment interventions are defined as structured and/or manualized counselling that incorporates principles of psychoanalytic therapy, cognitive behavioural therapy, interpersonal therapy, dialectic behavioural therapy, contingency management, biofeedback, hypnotherapy/subliminal, twelve-step facilitation, family/group counselling delivered in conjunction with long-term opioid agonist treatment. • Comparator: Treatment as usual—long-term opioid agonist treatment with methadone, buprenorphine, or buprenorphine/naloxone. • Outcomes of Interest: Primary— Retention in treatment, abstinence or reduction in illicit opioid use Secondary—side effects, adverse events, morbidity and mortality Other—Direct and indirect costs, health service utilization, quality of life, mental health, social functioning, risk behaviours, HIV and hepatitis C infection, and criminality • Study type: Meta-analyses, systematic reviews, randomized controlled trials	• Studies of psychosocial treatment interventions or supports delivered in conjunction with withdrawal management – short-term opioid agonist or alpha2-adrenergic agonist tapers. • Articles not in English • Age: under 18 • Pregnancy
11. Should individuals with opioid use disorder who have achieved cessation of opioid use be offered the option of treatment with naltrexone to prevent lapse or relapse to illicit opioid use?	• Population: Adults with opioid use disorder • Intervention: Long-term (“maintenance”) treatment with oral naltrexone; long-term (“maintenance”) treatment with extended-release injectable naltrexone • Comparator: Long-term (“maintenance”) treatment with placebo, methadone, buprenorphine, buprenorphine/naloxone, treatment as usual, extended-release injectable naltrexone, or no treatment; long-term (“maintenance”) treatment with placebo,	• Articles not in English • Age: under 18 • Pregnancy

	methadone, buprenorphine, buprenorphine/naloxone, treatment as usual, oral injectable naltrexone, or no treatment. • Outcomes of Interest: Primary—completion of or retention in treatment, sustained abstinence from or reduction in opioid use Secondary—side effects, adverse events, morbidity, and mortality. • Study type: Meta-analyses, systematic reviews, randomized controlled trials	
12. Should individuals with opioid use disorder be offered harm reduction services?	• Population: Adults with opioid use disorder • Intervention: Direct and indirect (information, referral, and/or linkage with services) provision of harm reduction services (e.g., supervised consumption sites, take-home naloxone, overdose prevention education, safer injection education, HIV and hepatitis C prevention education, sterile injection or smoking supplies distribution, drug checking). • Comparator: Non-provision of harm reduction services (where applicable) • Outcomes of Interest: Primary—morbidity and mortality, fatal and non-fatal overdose events, HIV and hepatitis C infection, risk behavior • Other—direct and indirect costs, health service utilization, and criminality	• Articles not in English • Age: under 18 • Pregnancy

Limitations:

- Grey literature resources were not searched for this phase of the literature search, although this search was supplemented with targeted structured searches of grey literature.

Identified items

Table 6. Items Identified by Database or Resource Type in the May 2022 Search

Database Name	Number of items Identified	Number of items (Duplicates Removed)
Medline	544	541
Embase	584	194
CDSR	9	1
CCRCT	437	91
CINAHL	280	27
PsycINFO	221	33
Total – All Sources	2075	887

APPENDIX 2: DSM-5-TR CRITERIA FOR OPIOID USE DISORDER

A. A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:
1. Opioids are often taken in larger amounts 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 recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous.
9. Continued 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, 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. Note: This criterion is not considered to be met for those taking opioids solely under appropriate medical supervision.
11. Withdrawal, as manifested by either of the following: a. The characteristic opioid withdrawal syndrome (refer to Criteria A and B of the criteria set for opioid withdrawal). b. Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms. Note: This criterion is not considered to be met for those individuals taking opioids solely under appropriate medical supervision.

Specify if:

- In early remission: After full criteria for opioid use disorder were previously met, none of the criteria for opioid use disorder have been met for at least 3 months but for less than 12 months (with the exception that Criterion A4, "Craving, or a strong desire or urge to use opioids," may be met).
- In sustained remission: After full criteria for opioid use disorder were previously met, none of the criteria for opioid use disorder have been met at any time during a period of 12 months or longer (with the exception that Criterion A4, "Craving, or a strong desire or urge to use opioids," may be met).

Specify if:

- On maintenance therapy: This additional specifier is used if the individual is taking a prescribed agonist medication such as methadone or buprenorphine and none of the criteria for opioid use disorder have been met for that class of medication (except tolerance to, or withdrawal from, the agonist). This category also applies to those individuals being maintained on a partial agonist, an agonist/antagonist, or a full antagonist such as oral naltrexone or depot naltrexone.
- In a controlled environment: This additional specifier is used if the individual is in an environment where access to opioids is restricted.

Code based on current severity/remission: If an opioid intoxication, opioid withdrawal, or another opioid-induced mental disorder is also present, do not use the codes below for opioid use disorder. Instead, the comorbid opioid use disorder is indicated in the 4th character of the opioid-induced disorder code (see the coding note for opioid intoxication, opioid withdrawal, or a specific opioid-induced mental disorder). For example, if there is comorbid opioid-induced depressive disorder and opioid use disorder, only the opioid-induced depressive disorder code is given, with the 4th character indicating whether the comorbid opioid use disorder is mild, moderate, or severe: F11.14 for mild opioid use disorder with opioid-induced depressive disorder or F11.24 for a moderate or severe opioid use disorder with opioid-induced depressive disorder.

Specify current severity/remission:

- (F11.10) Mild: Presence of 2–3 symptoms.
- (F11.11) Mild, In early remission
- (F11.11) Mild, In sustained remission
- (F11.20) Moderate: Presence of 4–5 symptoms.
- (F11.21) Moderate, In early remission
- (F11.21) Moderate, In sustained remission
- (F11.20) Severe: Presence of 6 or more symptoms.
- (F11.21) Severe, In early remission
- (F11.21) Severe, In sustained remission

APPENDIX 3.0: TITRATION AND DOSING

A3.1 General Guidance

All prescribers wishing to provide the full scope of OAT to patients in BC are required to complete the Provincial Opioid Addiction Treatment Program (POATSP) and a clinical preceptorship in order to have full prescribing privileges.[gg] The POATSP online course offers two dedicated training pathways for potential OAT prescribers: 1) the Physicians and Nurse Practitioners' Education and Training Pathway, and 2) the Registered Nurses and Registered Psychiatric Nurses' Education and Training Pathway. Allied health professionals are also encouraged to complete POATSP, or access specific modules as needed for information and support in providing high quality, evidence-based care to patients on OAT.

All prescribers are also encouraged to consult with an addiction medicine specialist experienced in prescribing OAT as needed; this may include contacting an Addiction Medicine Consult Team, the RACEapp, or 24/7 Addiction Medicine Clinician Support Line. Nurses, midwives, front-line workers in Indigenous communities, and pharmacists may also access the 24/7 Addiction Medicine Clinician Support Line for guidance in the care of patients on OAT.

The general considerations outlined in this section are applicable to all oral OAT medications. Medication-specific information is provided in Buprenorphine-specific Guidance, Methadone-specific Guidance, or Slow-release oral morphine-specific Guidance in this appendix.

Detailed guidance on the provision of iOAT is beyond the scope of this guideline. For comprehensive iOAT guidance, refer to the CRISM *National Injectable Opioid Agonist Treatment Clinical Guideline*.

A3.1.i Assessment

The baseline assessment considerations provided in this section are applicable to all candidates for OAT, regardless of the choice of medication. For medication-specific contraindications, cautions, and considerations, refer to dedicated sections for buprenorphine, methadone, and slow-release oral morphine in this appendix.

Contraindications to opioid agonist treatment

- Allergy to any components of the drug product

[gg] Nurse practitioners and physicians must complete POATSP in order to prescribe methadone and slow-release oral morphine. While NPs and physicians are not required to complete POATSP to prescribe buprenorphine/naloxone, prescribers are strongly encouraged to do so in order to ensure that they are able to support their patients along the full continuum of care for opioid use disorder. Registered nurses and registered psychiatric nurses must complete the nursing pathway of POATSP in order to prescribe any OAT medication.

Cautions for OAT medications

- Concurrent use of other CNS depressants
- Severe respiratory insufficiency (e.g., acute or severe bronchial asthma, status asthmaticus, chronic obstructive airway, acute respiratory depression, or cor pulmonale)
- Acute alcohol intoxication
- Acute psychosis
- Hypotension, prostatic hypertrophy, or urethral stricture
- Myxedema coma, untreated hypothyroidism, or adrenal cortical insufficiency (e.g., Addison's disease)
- Acute gastrointestinal conditions (e.g., bowel obstruction, diarrhea, abnormal gut anatomy) that affect the amount of time medication remains in the stomach
- Head injuries or history of seizures
- Pregnancy and breastfeeding
    - For guidance on the selection and dosing of OAT medications for pregnant patients, as well as relevant monitoring and support considerations for this population, refer to the BCCSU Guideline Supplement on the *Treatment of Opioid Use Disorder During Pregnancy*.

Patient assessment process

The patient assessment process should include:

- A baseline assessment, which will inform treatment planning and medication selection
- Continuing care assessment and testing procedures, which will aid in identifying and managing comorbid conditions and adjusting the treatment plan as needed

Tests that are listed under continuing care requirements (e.g., renal and liver function, sexually transmitted infections) may be performed at baseline but should not be viewed as a prerequisite for initiating care.

Baseline assessment

- Physical and mental health assessment including:
    - Past medical history (e.g., ask about HIV, hepatitis C, liver dysfunction, COPD, arrhythmias, overdoses, seizures, any other acute or chronic conditions)
    - Mental health (e.g., ask about depression, anxiety, PTSD, psychosis, violence, suicidality)
    - Allergies
- DSM-5-TR confirmed diagnosis of opioid use disorder (see Appendix 2)

- Urine drug test (to confirm the presence of opioids and to identify other relevant substances such as benzodiazepines)[hh]
- NOTE: Although baseline UDT is best practice, it may be reasonable to forgo prior to initiating OAT in the following scenarios:
    - Sufficient collateral information is available (e.g., prior documentation of OUD or OAT on PharmaNet, recent overdose)
    - Opioid agonist treatment is initiated through telehealth in a remote setting where requiring UDT would pose an unreasonable barrier to initiating treatment
    - Patient has been abstinent but is at risk of return to opioid use
- The clinical rationale for initiating OAT prior to obtaining UDT results should be documented
- For more information, refer to the BCCSU's Breakout Resource – Urine Drug Testing in Patients Prescribed Opioid Agonist Treatment
- Pregnancy test (where applicable)
- Comprehensive review of substance use history including assessment for other substance use and substance use disorders (e.g., alcohol, tobacco, cocaine, amphetamine, and benzodiazepine use disorders); route of administration; frequency and amount of use; overdose and other harms; past treatment history; exploration of the role of each substance in the patient's life; and the patient's goals related to each substance
- Review of concurrent use of CNS depressants, including alcohol, benzodiazepines, and sedatives (both prescribed and unregulated)
- Review of PharmaNet and other requirements outlined in CPSBC's Practice Standard for Safe Prescribing of Opioids and Sedatives.
    - According the CPSBC, clinicians should refer to the BCCSU's A Guideline for the Clinical Management of Opioid Use Disorder and the CPSBC's Prescribing Methadone practice standard when initiating and implementing OAT. There are currently no CPSBC practice standards for buprenorphine/naloxone or slow-release oral morphine.
- **Explore and document patient's treatment goals** and incorporate into the treatment plan; patient goals should form the basis for assessing patient progress in follow-up visits
- Document treatment choice and rationale for opioid agonist medication selected

[hh] Benzodiazepines should be included in urine drug tests for individuals who use unregulated opioids and/or those who are on OAT. However, clinicians and patients should be aware that some benzodiazepines and benzodiazepine analogues (e.g., alprazolam, clonazepam, etizolam, temazepam, triazolam) may not be detected in standard urine drug tests despite the patient having been exposed.

Continuing care

- Laboratory tests: CBC; renal and liver function panels; HIV and hepatitis A, B, and C serology; syphilis, gonorrhea, and chlamydia tests;
    - Consider assessing liver function tests soon after initiation in individuals with a history of severe liver dysfunction
    - If patients have pre-existing hepatitis or hepatic dysfunction, it may be necessary to repeat liver function tests 4 weeks after treatment initiation to check for elevated liver enzymes
    - Note that laboratory tests are not a requirement for treatment initiation, but may be offered as indicated in the course of treatment
    - ECG may be indicated for some patients on methadone

A3.1.ii General Eligibility Criteria

- Opioid use disorder diagnosis
- Informed consent

A3.1.iii Treatment Selection and Initiation

Prior to initiation, discuss the risks and benefits of all 3 oral OAT options to assist treatment selection, including information on:

- Medication side effects and other medication-specific risks
- Requirements and limitations related to take-home doses and management of missed doses

Following medication selection, collaboratively develop a treatment plan with each patient and obtain informed consent.

Medication-specific guidance can be found below.

A3.1.iv Take-home Naloxone

All patients starting opioid agonist treatment should be offered training and a take-home naloxone kit (or information on where to acquire one). Take-home naloxone kits are available at no cost through the BCCDC and most provincial harm reduction programs. A list of sites can be found on the Toward the Heart website. Some patients may opt to purchase naloxone from a pharmacy, health care site, treatment centre, or community agency without a prescription. All patients enrolled in the First Nations Health Benefits (PharmaCare Plan W) are eligible for access to naloxone—including intranasal naloxone—and injection supplies from pharmacists at no cost and without a prescription.

A3.1.v Stabilization

An effective stabilization dose is reached when withdrawal symptoms are controlled for more than 24 hours, cravings for opioids are reduced or eliminated without causing excessive sedation or other intolerable side effects, and the patient reports a general level of comfort. Each patient's personal treatment goals (e.g., reduction vs. cessation of unregulated opioid use) should also inform what constitutes an effective dose in their case.

A3.1.vi Missed Doses

See medication-specific guidance on addressing missed doses in this appendix.

While necessary in certain circumstances to ensure patient safety, OAT dose reduction or restart may present a barrier to treatment retention. To facilitate continued treatment, it is important to discuss the protocol for missed doses with the patient at initiation, and develop strategies to support medication adherence. If dose reduction or restart is indicated to ensure patient safety, explain the rationale for this decision to the patient, clarifying that dose adjustment and restart are not punitive measures, and that the goal is to get them back up to an effective dose as quickly as is safe.

A3.1.vii Specialist Consultation

Clinicians are encouraged to access the Rapid Access to Consultative Expertise app (RACEapp) or the 24/7 Addiction Medicine Clinician Support Line (778-945-7629) to speak with an addiction medicine specialist regarding any questions or concerns.

A3.2 Buprenorphine-specific Guidance

A3.2.i Buprenorphine/naloxone-specific Contraindications

- Allergy to buprenorphine, naloxone, or any other components of the drug product

A3.2.ii Buprenorphine/naloxone Pharmacology

- Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor
- Naloxone, which is an antagonist at the mu-, delta-, and kappa-opioid receptors, is added to dissuade injection use or insufflation. Due to almost complete first-pass metabolism and low sublingual availability, naloxone administered sublingually or orally has almost no pharmacological effect; however, it is available when injected or insufflated and will likely precipitate withdrawal
- Buprenorphine/naloxone is available in tablets containing a 4:1 ratio of buprenorphine and naloxone

    - 2mg tablet=2mg buprenorphine/0.5mg naloxone
    - 8mg tablet=8mg buprenorphine/2mg naloxone
- Buprenorphine tablets are administered sublingually
- Tablets can be split or combined to achieve target doses
- Buprenorphine/naloxone is generally taken once daily, though due to its favourable safety profile and pharmacological properties, it can also be prescribed at more frequent doses or on alternate-day schedules
- Half-life of approximately 24–42 hours

A3.2.iii Buprenorphine/naloxone Induction

Traditionally, buprenorphine/naloxone induction has been conducted in clinic settings and required a period of abstinence from opioids prior to induction, in order to prevent precipitated withdrawal. However, this period of withdrawal—which may range from at least 12 hours to 72 hours depending on the type of opioid at baseline—can be both time-consuming and difficult for patients. This method has become even more challenging in the era of fentanyl and other synthetic opioid analogues, which carry an unpredictable risk of precipitated withdrawal, typically necessitating 48 hours of withdrawal prior to the first buprenorphine/naloxone dose.[153,154] In order to reduce these barriers to successful induction, many clinicians have increasingly moved away from traditional induction protocols and now use low-dose induction[ii] protocols (which do not require a period of withdrawal) or take-home induction approaches.

This section on buprenorphine/naloxone initiation begins with low-dose induction protocols, followed by traditional inductions and considerations for home induction, respectively. Guidance on emergency-department buprenorphine/naloxone induction is provided in Appendix 4. In all cases, prescribers should discuss all induction options with the patient and select the appropriate method collaboratively.

Guidance on dosing for the extended-release subcutaneous buprenorphine formulation (Sublocade), is provided in the section on Extended-release buprenorphine in this Appendix.

Low-dose induction

While the literature on low-dose buprenorphine/naloxone induction is currently limited to several case series, growing evidence and clinical experience in BC highlight the important role of this approach. While research is ongoing to determine optimal low-dose[ij] induction protocols, a number of protocols have been developed that are in use across BC care setting.

[ii] Low-dose induction is also referred to as "micro-dosing induction" or "micro-induction" in the literature.

[ij] Low-dose induction is also referred to as "micro-dosing induction" or "micro-induction". This document predominantly uses the term "low-dose induction" to reflect emerging terminology.

Tables 7 and 8 offer examples of commonly utilized low-dose induction protocols.

Table 7. Sample 7-day Low-dose Induction Protocol

Day	Buprenorphine/naloxone Dose	Other opioids
1	0.5mg/0.125mg two times	Continue full agonist use
2	0.5mg/0.125mg three times	Continue full agonist use
3	1mg/0.25mg two times	Continue full agonist use
4	2mg/0.5mg two times	Continue full agonist use
5	2mg/0.5mg three times	Continue full agonist use
6	4mg/1mg three times	Continue full agonist use
7	12mg/3mg once	Stop other opioid use

Table 8. Sample 8-day Low-dose Induction Protocol

Day	Buprenorphine/naloxone Dose	Other opioids
1	0.5mg/0.125mg two times	Continue full agonist use
2	1mg/0.25mg two times	Continue full agonist use
3	2mg/0.5mg two times	Continue full agonist use
4	3mg/0.75mg two times	Continue full agonist use
5	4mg/1mg two times	Continue full agonist use
6	6mg/1.5mg two times	Continue full agonist use
7	8mg/2mg two times	Continue full agonist use
8	16mg/4mg once	Stop other opioid use

Note: May be preferable for some patients due to consistent BID dosing during induction

Additional low-dose induction protocols are available from the BC Pharmacy Association, published in the Canadian Medical Association Journal, and reported in peer-reviewed studies (see supplemental material to Moe, et al., 2021). In the absence of a widely established evidence-based protocol, clinicians may consult the 24/7 Addiction Medicine Clinician Support Line or RACEapp for specialized support.

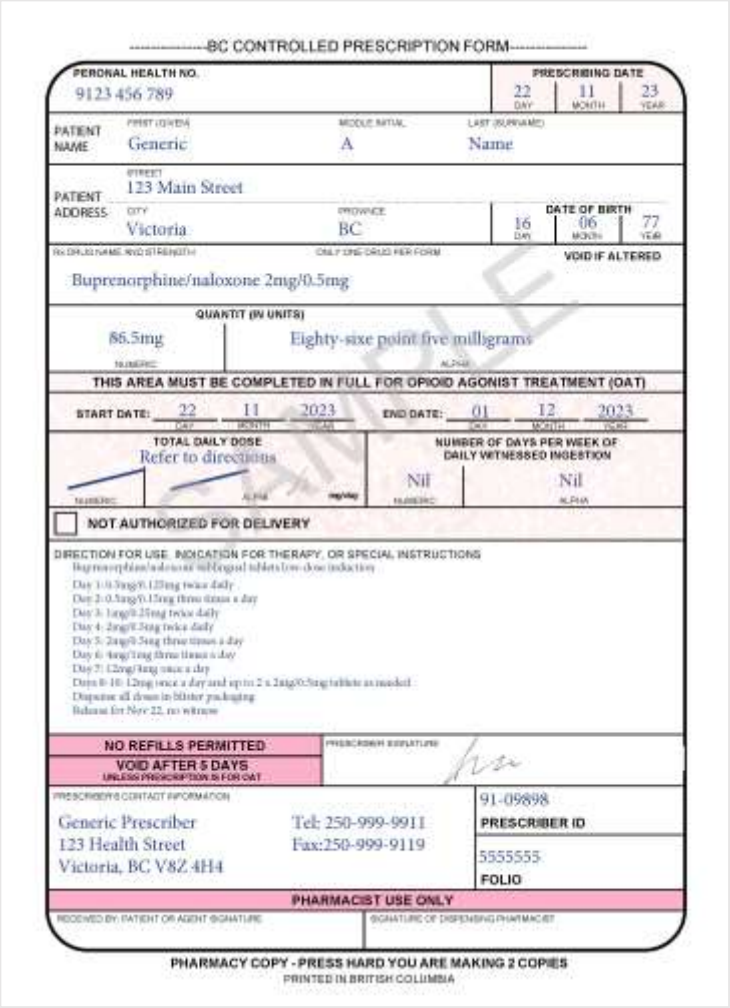
If clinically indicated, co-prescribing a full agonist (e.g., SROM, hydromorphone, methadone) during low-dose induction can help reduce or eliminate patients' reliance on the unregulated drug supply and reduce the risk of overdoses while titrating the buprenorphine/naloxone dose.

Mild to moderate withdrawal symptoms are not uncommon during low-dose induction, and can generally be managed by slowing down the titration process or providing adjunct medications to mitigate withdrawal (e.g.,

dimenhydrinate, clonidine, ibuprofen). It is important to maintain close contact with the patient throughout the titration process in order to make necessary adjustments in a timely manner.

To reduce patient confusion regarding dosing, prescribers should include instructions for blister packaging in prescriptions for low-dose inductions.

The following is a sample prescription for low-dose induction:



----------BC CONTROLLED PRESCRIPTION FORM----------

PERSONAL HEALTH NO.: 9123 456 789

PRESCRIBING DATE: 22 (DAY) | 11 (MONTH) | 23 (YEAR)

PATIENT NAME: Generic | A | Name

PATIENT ADDRESS: 123 Main Street

CITY: Victoria | PROVINCE: BC

DATE OF BIRTH: 16 (DAY) | 06 (MONTH) | 77 (YEAR)

VOID IF ALTERED

Buprenorphine/naloxone 2mg/0.5mg

QUANTITY (IN UNITS): 86.5mg (NUMERIC) | Eighty-six point five milligrams (ALPHA)

THIS AREA MUST BE COMPLETED IN FULL FOR OPIOID AGONIST TREATMENT (OAT)

START DATE: 22 | 11 | 2023 END DATE: 01 | 12 | 2023

TOTAL DAILY DOSE: Refer to directions

NUMBER OF DAYS PER WEEK OF DAILY WITNESSED INGESTION: Nil | Nil

NOT AUTHORIZED FOR DELIVERY

DIRECTION FOR USE, INDICATION FOR THERAPY, OR SPECIAL INSTRUCTIONS

Buprenorphine/naloxone sublingual tablets low-dose induction

Day 1: 0.5mg/0.125mg twice daily
Day 2: 0.5mg/0.125mg three times a day
Day 3: 1mg/0.25mg twice daily
Day 4: 2mg/0.5mg twice daily
Day 5: 2mg/0.5mg three times a day
Day 6: 4mg/1mg three times a day
Day 7: 12mg/3mg once a day
Days 8-10: 12mg once a day and up to 2 x 2mg/0.5mg tablets as needed
Dispense all doses in blister packaging
Release for Nov 22, no refills

NO REFILLS PERMITTED
VOID AFTER 5 DAYS
UNLESS PRESCRIPTION IS FOR OAT

PRESCRIBER'S SIGNATURE

PRESCRIBER'S CONTACT INFORMATION
Generic Prescriber
123 Health Street
Victoria, BC V8Z 4H4
Tel: 250-999-9911
Fax:250-999-9119

91-09898 PRESCRIBER ID

5555555 FOLIO

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SAMPLE

A3.2.iv Traditional Induction

Traditional inductions have been widely used in BC and have an established evidence base. While traditional inductions have historically been conducted in clinical settings, they are increasingly completed at home, as the requirement of office attendance can be a barrier for many patients (see Home Induction for relevant criteria and considerations for unobserved inductions).

Traditional induction protocols typically allow the patient to reach a therapeutic dose within one day after medication initiation, which may be preferable if there has been a significant time period since the patient's last opioid use or if the patient is experiencing severe withdrawal symptoms. Additionally, patients who have previous experience with successful traditional buprenorphine inductions may prefer this method due to its familiarity and established history. However, many patients may find this induction method challenging due to the required period of withdrawal prior to medication initiation in order to minimize the risk of precipitated withdrawal. In particular, traditional induction may not be the preferred option for patients who currently use fentanyl or other intermediate- and long-acting opioids (e.g., methadone) that require longer periods of pre-initiation withdrawal. Prescribers should discuss the risks and benefits of all induction options with patients, and support informed decision-making.

Preparation

- Instruct patient to discontinue opioid use prior to the first day of scheduled induction. In order to avoid precipitated withdrawal, patient should reach moderate withdrawal (COWS score>12)[kk] prior to induction. In general, the duration of time between last opioid dose and onset of moderate withdrawal is as follows:

Box 9. Recommended Duration of Time Since Last Opioid Use to Prevent Precipitated Withdrawal

Short-acting opioids	≥12 hours since last dose	*Examples: heroin, oxycodone, hydromorphone*
Intermediate-acting opioids	≥24 hours since last dose	*Examples: slow-release oral morphine, fentanyl* (confirmed or suspected)*
Long-acting opioids	48–72 hours or more since last dose	*Example: methadone*

* Note on fentanyl: Although fentanyl has a rapid and intense onset with a relatively short duration of action (1–2 hours),[467] it has a long terminal half-life, likely due its lipophilic nature (which enables its rapid distribution into the body's tissues).[468] Emerging evidence and clinical experience suggests that inductions may be particularly challenging in patients using fentanyl.[153,154] For such patients, time elapsed since last use may be a more relevant indicator for safe buprenorphine/naloxone initiation than the COWS score. A 2022 Vancouver-based case series involving fentanyl-exposed patients reported 3 cases where patients experienced unexpected precipitated withdrawal following

[kk] The COWS tool is provided in Appendix 8.

buprenorphine/naloxone initiation despite reaching COWS>12 prior to induction.[153] Based on these findings, a 48-hour period of abstinence prior to traditional induction may be preferable in order to minimize the risk of precipitated withdrawal, regardless of the COWS score.[153] However, the patient's tolerance of the pre-induction withdrawal period and their risk of drop out should also be considered. In general, a minimum of 24 hours of withdrawal from fentanyl is recommended for people who use fentanyl. Patients should be supported to sustain this withdrawal period for as long as tolerable beyond the 24-hour point in order to minimize their risk of precipitated withdrawal. Alternatively, a low-dose induction method may be preferable for fentanyl-exposed patients.

- Emphasize to patient that starting buprenorphine/naloxone too early may worsen withdrawal symptoms
- Ensure patient is aware to not drive or operate heavy machinery during induction and the early titration phase
- Emphasize that induction cannot take place during acute alcohol intoxication, and that dosing and titration may be adjusted or reduced for patients who are actively using alcohol, benzodiazepines, or other sedative medications due to increased overdose risk
- Utilize the Clinical Opiate Withdrawal Scale (COWS; see Appendix 8) to assess withdrawal symptom severity
- If possible, plan induction of buprenorphine/naloxone for earlier in the week to allow for monitoring and re-assessment over the week (if prescriber is not available on weekends)
- For patients transitioning from methadone to buprenorphine/naloxone, see the Methadone to Buprenorphine/naloxone section

Day 1

1. The risk of precipitated withdrawal is lower if the patient has signs of at least moderate opioid withdrawal (COWS>12), before receiving the first dose of buprenorphine/naloxone.

    a. For a COWS score of 12 or less, consider postponing the first dose of buprenorphine/naloxone until later in the day or the following day, when the patient is demonstrating more severe withdrawal.

2. Table 10 presents recommended starting doses in reference to common practice.[ll]

[ll] It is important to note that, to date, no universally applicable evidence-based titration protocol has been established. Clinicians report that each individual's titration is different, depending on their particular circumstances (e.g., opioids used, time since last use). The general starting doses provided here should be combined with individualized assessment.

Table 10. Initial Buprenoprhine/naloxone Dose Based on Risk of Precipitated Withdrawal

Indication	Starting Dose	Total Starting Dose
Concern about precipitated withdrawal	One 2mg/0.5mg buprenorphine/naloxone tablet	2mg/0.5mg buprenorphine/naloxone
Low risk of precipitated withdrawal	Two 2mg/0.5mg buprenorphine/naloxone tablets	4mg/1mg buprenorphine/naloxone
• Patients who use fentanyl are at higher risk of precipitated withdrawal, possibly due to the lipophilic nature of fentanyl.[153,468,469] Start these patients at 2mg/0.5mg buprenorphine/naloxone. • For patients at lower risk of precipitated withdrawal (e.g., recently completed withdrawal management, known time of last opioid use, fentanyl-negative UDT), consider a higher starting dose of 4mg/0.5mg buprenorphine/naloxone.		

3. Offer patient education on taking the sublingual buprenorphine/naloxone tablet. While not necessary, you can offer to witness the ingestion of the first dose to ensure that the tablet is appropriately taken and fully dissolved.
    - *Instruct the patient to keep the tablet under their tongue until it dissolves, which may take up to 10–15 minutes, and to avoid swallowing, talking, eating, drinking, or smoking during this time.*

4. Since precipitated withdrawal (see Managing Precipitated Withdrawal below) can become evident within 30 minutes of the first dose of buprenorphine/naloxone, reassess 30–60 minutes from the time of first dose.
    a. If withdrawal symptoms are adequately relieved after 1–3 hours: Day 1 is complete. Prescribe the same total dose for the following day.
    b. If withdrawal symptoms are not adequately relieved after 1–3 hours: Administer additional doses 2mg/0.5mg to 4mg/1mg at a time.
        - The Suboxone Product Monograph suggests a maximum total of 16mg/4mg buprenorphine/naloxone on Day 1. However, more recent clinical experience suggests that a higher maximum Day 1 dose may be needed to adequately address persisting withdrawal symptoms in people with high opioid tolerance, including those who use fentanyl.
        - If uncertain about the need for an additional dose, consider prescribing 2mg/0.5mg buprenorphine/naloxone tablets as take-home doses in case withdrawal symptoms occur later in the evening.
    c. If withdrawal symptoms are adequately relieved with additional dose(s): Day 1 is complete. Prescribe the same total dose for the following day.
    d. If withdrawal symptoms are not adequately treated with additional dose(s): manage withdrawal symptoms symptomatically (see step 5, below) while continuing to dose with buprenorphine/naloxone.

5. When needed, short-term symptomatic relief may be offered. For example:
    - Clonidine tablets (instruct patients to take 0.1–0.2mg every 4 hours PRN for <12 hours)
    - As-needed (PRN) oral anti-emetics, antidiarrheals, NSAIDs, or acetaminophen can also be considered

For challenging inductions (e.g., severe concurrent substance use disorders, challenging co-morbidities), referral to an inpatient withdrawal management program, community withdrawal management team, or a bed-based facility for induction can be considered.

Day 2 onward

1. Assess withdrawal symptoms to determine Day 2 starting dose.
    - If no withdrawal symptoms present since last dose:
        - Continue a once-daily dose equal to the total amount of buprenorphine/naloxone administered on Day 1.
        - When necessary, titrate up by 2mg/0.5mg–4mg/1mg buprenorphine/naloxone as needed.
    - If withdrawal symptoms present since last dose:
        a. Administer dose equal to the total amount administered on previous day, plus an additional 2mg/0.5mg–4mg/1mg buprenorphine/naloxone.

2. Assess the presence of withdrawal symptoms at 2–3 hours after first dose.
    - If symptoms are relieved 2–3 hours after first dose:
        - Day 2 is complete. Prescribe this total dose for the next day.
    - If symptoms are not relieved 2–3 hours after first dose:
        - Give 2mg/0.5mg–4mg/1mg buprenorphine/naloxone every 1–3 hours as needed
            - According to the therapeutic range described in the Suboxone Product Monograph, the daily maximum dose of buprenorphine/naloxone is 24mg/6mg. However, this recommendation is based on data collected before the infiltration of fentanyl into the unregulated drug market. More recent data suggests that a daily dose of up to 32mg/8mg buprenorphine/naloxone may be reasonable and can be provided safely to address the high opioid tolerance of patients who use fantanyl.[137]
        - If patient has already reached the maximum daily dose of 32mg/8mg buprenorphine/naloxone and is still experiencing withdrawal symptoms, provide symptomatic management for the remainder of Day 2 (see Step 5, Day 1 above).
        - If withdrawal symptoms are not relieved with initial or repeated buprenorphine/naloxone doses, it is important to confirm that tablets are being taken and/or administered correctly (i.e., placed under tongue, waiting for tablet(s) to dissolve completely, no swallowing, eating, drinking, or smoking until tablet has fully dissolved).
3. On the following induction days, if withdrawal symptoms, craving, or unregulated opioid use persists, continue dose increases as per the above schedule.

- Titrate as needed by 2mg/0.5mg–4mg/1mg buprenorphine/naloxone at a time to achieve an optimal stable daily dose that can sustain an entire 24-hour dosing interval with no withdrawal symptoms and no medication-related intoxication or sedation.
- Hold buprenorphine/naloxone dose if intoxicated or sedated.
- Historically, the typical therapeutic daily dose has been 24mg/6mg buprenorphine/naloxone per day. However, due to the prevalence of exposure to fentanyl and other highly potent synthetic opioids, daily doses of up to 32mg/8mg may be needed in some cases.[137]

4. Once optimal dose is achieved, follow up as needed.

A3.2.v Home Induction

Where safe and appropriate, prescribers can consider unobserved traditional induction or "home" induction as a means of addressing office attendance barriers and avoiding unnecessary disruptions to patients' daily lives (e.g., work, school, child-care, disability).

- Prior to home induction, a discussion of the risks and benefits of home induction must be conducted, and the patient's verbal consent secured.
- During home induction, clinicians should ideally be able to provide regular follow-up and support via telephone or video within regular clinic hours. Patients with previous experience taking buprenorphine/naloxone may require less intensive support.
- Patients should be provided with clinic/office contact information and in-person education and written instructions for dosing and timing, including use of the Subjective Opioid Withdrawal Scale (SOWS, see Appendix 9) to assess withdrawal symptoms and determine when to start induction (SOWS score ≥17), if appropriate.
- Patients and/or support people should be instructed to contact the office immediately in the event of any problems and be willing to come in for clinical assessment as required.

Patient education for home initiation

A patient handout is available to help guide patients through home induction. General instructions for home induction include:

- Wait until moderate withdrawal occurs to prevent precipitated withdrawal
  - At least 12 hours for short-acting opioids (e.g., heroin, hydromorphone, oxycodone)
  - At least 24 hours for intermediate-acting and slow-release preparations (e.g., slow-release oral morphine) or for confirmed or suspected fentanyl
  - At least 48–72 hours for methadone
- Do not use any opioids or other sedatives during initiation (e.g., alcohol, benzodiazepines, or z-drugs)
- Put the tablet(s) under your tongue and let them dissolve completely
- Do not consume food or drink while the tablet is dissolving. Avoid smoking

- Do not give up if symptoms persist after the initial doses. After taking 4 or more tabs, most people will start feeling improvement of withdrawal symptoms
- Return to care (specialist, general practitioner, or emergency department) if symptoms of precipitated withdrawal develop and you are unable to cope
    - Prescribers should provide preliminary information on the possibility of precipitated withdrawal, its cause, and how to identify and manage it

A3.2.vi Managing Precipitated Withdrawal

Precipitated withdrawal can occur when the first dose of the partial opioid agonist buprenorphine/naloxone is administered to a patient who has been using full agonist opioids (e.g., heroin, fentanyl, oxycodone) before they have achieved a moderate stage of opioid withdrawal. Because buprenorphine has a high affinity but low intrinsic activity at the mu receptor, it is able to rapidly displace other full agonist opioids that are present at the opioid receptors, which can result in a net decrease in overall opioid effects. The sudden replacement of the full agonist opioid with buprenorphine and rapid decrease in net opioid agonist effects can precipitate significant opioid withdrawal symptoms.

If a patient develops precipitated withdrawal, the clinician and the patient may decide to continue, delay, or stop the induction. An emerging fourth option for addressing precipitated withdrawal involves the provision of high-dose buprenorphine/naloxone.[470-472]

All options for managing precipitated withdrawal are outlined below. Deciding between these options can be guided by clinician experience, patient preference, and severity of precipitated withdrawal. All options should include supportive treatment, reassurance that symptoms will resolve, and careful explanation of what has occurred to patients.

Actions to take in all cases of precipitated withdrawal:

- Explain to the patient what has occurred
- Discuss the options presented below and engage in shared decision making in developing a plan for management
- Offer non-opioid adjuncts to treat withdrawal symptoms
    - Clonidine tablets (instruct patients to take 0.1–0.2mg every 4 hours PRN for <12 hours)
    - PRN oral anti-emetics, antidiarrheals, NSAIDs, acetaminophen can also be considered
- Specialty consultation (e.g., the RACEapp or 24/7 Addiction Medicine Clinician Support Line) may be contacted for support

Option 1: Continue induction

1. Administer additional doses of 2mg/0.5mg buprenorphine/naloxone every 1–2 hours until withdrawal symptoms are resolved.
2. Inform the patient that additional doses of buprenorphine/naloxone can initially result in worsening of withdrawal symptoms before improvement. Offer non-opioid adjuncts for symptom management.

Option 2: Delay induction

1. If patient chooses to continue, consider waiting a few hours to allow full agonist to clear opioid receptors before administering the next buprenorphine/naloxone dose.
2. Offer non-opioid adjuncts to treat withdrawal symptoms as needed.
3. Continue up to the Day 1 maximum or until withdrawal symptoms are resolved.

Option 3: Stop induction

1. Provide reassurance that symptoms will resolve as the buprenorphine dissociates from the mu opioid receptors and the full agonist can resume its activity.
2. Offer non-opioid adjuncts and/or short-acting full opioid receptor agonists to treat withdrawal symptoms as needed.
3. Offer to discuss a plan for a future induction attempt or an alternate form of OAT.

Option 4: High-dose buprenorphine/naloxone

1. Provide additional doses of buprenorphine/naloxone in close succession, typically ranging from 8mg/2mg to 24mg/6mg in total.[470-472] Several high doses of buprenorphine/naloxone may be necessary.

Providing high-dose buprenorphine/naloxone is an emerging practice that is rapidly gaining acceptance. A 2022 case study described the case of a patient experiencing precipitated withdrawal following an initial buprenorphine/naloxone dose of 4mg/1mg.[470] The withdrawal symptoms worsened with an additional 4mg/1mg dose taken one hour later and she called her clinic in distress. She was treated with an additional 8mg/2mg of buprenorphine/naloxone followed by another two doses of 2mg/0.5mg provided in short succession, resulting in complete resolution of her precipitated withdrawal symptoms.[470] Another case study presented the case of a patient who experienced precipitated withdrawal after receiving 8mg/2mg of buprenorphine/naloxone (i.e., an initial test dose of 2mg/0.5mg, followed by 6mg/1.5mg and hour later).[471] The patient was given an additional dose of 8mg/2mg upon the diagnosis of precipitated withdrawal, which reduced withdrawal symptoms from COWS=33 to COWS=5. Five hours later, another dose of 8mg/2mg was provided. This brought the first day total dose to 24mg/6mg buprenorphine/naloxone and resolved withdrawal symptoms.[471]

A3.2.vii Stabilization

- Given buprenorphine/naloxone's safety profile, consider providing take-home dosing immediately or as soon as possible following induction. Always educate patients on risks to self and others when giving take-home doses.
- Continue to assess as needed. Decrease interval of follow-up as clinical stability is achieved.
- Follow-up assessments should include adequacy of dosage, side effects, substance use (via patient report and, when indicated, urine drug testing; see Appendix 5), and quality of life
- For clinically stable patients at stable doses, one can consider:
    - Alternate day dosing can be considered for patients who are on a stable daily dose of up to 12/3mg.
        - For example, a patient who receives a stable daily dose of 8mg/2mg could transition to taking 16mg/4mg on alternate days.

A3.2.viii Missed Doses

Due to buprenorphine's partial agonist properties, adjusting and re-titrating a patient's buprenorphine/naloxone dose following missed doses does not require the same degree of vigilance as full agonists. However, missed doses can still contribute to a loss of tolerance to buprenorphine and dose adjustment and re-titration may be required.

There are two missed dose protocols for buprenorphine/naloxone, based on whether the patient has returned to full agonist use since their last buprenorphine/naloxone dose. Prescribers are encouraged to schedule an appointment to assess clinical and social stability and to check for any signs of return to use. Reasons for missed doses should be clearly documented.

BC pharmacists are required to notify prescribers of missed doses and clinicians must review and document PharmaNet profiles. Under current regulations, the dispensing pharmacy is also required to cancel the prescription and notify the prescribing clinician if the patient misses:

- 6 consecutive days of buprenorphine/naloxone, without return to full opioid agonist use OR
- 4 consecutive days of buprenorphine/naloxone, with return to full opioid agonist use

Without return to full opioid agonist use

For missed doses without return to full agonist opioid use, the following considerations are advised for patients who wish to resume buprenorphine/naloxone:

- 5 or fewer consecutive once-daily missed doses, without return to full agonist opioid use:
    - No change in dose is required. Resume previous dose without dose reduction.
    - The reasons for the missed doses should be discussed and documented at the next visit.
- 6 or more consecutive once-daily missed doses, without return to full agonist opioid use:
    - Buprenorphine/naloxone should be held pending virtual or in-person assessment, and the remainder of the prescription should be cancelled.

- Reasons for missed doses should be discussed and documented during the subsequent clinical visit, with attention to supporting the patient for better OAT retention.
- Re-titration is required. The re-titration process should be individually tailored; the goal is to re-titrate to previous stable dose within a few days.

Table 11. Protocol for Missed Buprenorphine/naloxone Doses Without Return to Full Opioid Agonist Use

	Suggested protocols
≤5 without return to full agonist use	Resume without dose reduction
≥6 without return to full agonist use	Re-titration is required. The re-titration process should be individually tailored with the goal to re-titrate to previous stable doses within a few days.

With return to full opioid agonist use

For missed doses with return to full agonist opioid use, the following considerations are advised for patients who wish to resume buprenorphine/naloxone:

- One to three consecutive once-daily missed doses, with return to full opioid agonist use:
  - No change in dose is required. It is likely safe to continue buprenorphine/naloxone without re-induction.
  - The reasons for the missed doses should be discussed and documented at the next visit.
  - The decision to continue buprenorphine/naloxone may also depend on additional factors, including the amount of the last buprenorphine/naloxone dose and the amount and time of the most recent full agonist use.
  - Providers may seek specialist consultation to discuss patient-specific factors, particularly if the patient experiences significant discomfort upon resumption of medication.
- Four consecutive once-daily missed doses, with return to full opioid agonist use:
  - Buprenorphine/naloxone should be held pending virtual or in-person reassessment, and the remainder of the prescription should be cancelled.
  - Reasons for missed doses should be discussed and documented during the subsequent clinical visit, with attention to supporting the patient for better OAT retention.
  - Clinicians should discuss the risk of precipitated withdrawal with the patients and weigh them against the benefits of continuing buprenorphine/naloxone. Less experienced providers are encouraged to first contact RACEapp or 24/7 Addiction Medicine Clinician Support Line to discuss patient-specific factors in order to select between resumption and re-titration of buprenorphine/naloxone. For patients who prefer to continue buprenorphine/naloxone, a test dose and plan for managing precipitated withdrawal should be discussed.
- Five or more consecutive once-daily missed doses, with return to full opioid agonist use:
  - Buprenorphine/naloxone should be held pending virtual or in-person reassessment, and the remainder of the prescription should be cancelled.

- Reasons for missed doses should be discussed and documented during the subsequent clinical visit, with attention to supporting the patient for better OAT retention.
- A new induction may be required; proceed as described in Low-dose or Traditional Induction, above.

Table 12. Protocol for Missed Buprenorphine/naloxone Doses with Return to Full Opioid Agonist Use

	Suggested protocols
≤3 days with return to full agonist use	Safe to continue buprenorphine/naloxone without re-induction
4 days with return to full agonist use	Discuss the risk of precipitated withdrawal and weigh them against the benefits of continuing buprenorphine/naloxone
≥5 days with return to full agonist use	New induction may be required

Alternate day schedule

- For missed doses with an alternating day schedule, follow missed doses protocol above. Patients should be returned to a daily dose schedule, possibly at a lowered dose, to re-stabilize prior to resuming an alternating day schedule.

A3.2.ix Overdose Considerations

Although buprenorphine/naloxone overdose is rare, emergency department clinicians and first responders should be aware that patients with a buprenorphine/naloxone overdose may present with typical signs and symptoms of opioid toxicity that may be less responsive to naloxone due to the pharmacodynamics of buprenorphine (i.e., high affinity for opioid receptors, long duration of action).[473] Naloxone is still recommended in the event of an overdose, but repeated doses (initial dose may range up to 2mg, repeated every 2-3 minutes) or continuous intravenous administration may be required to reverse an overdose.[473,474] In addition, as naloxone will be metabolized more rapidly than buprenorphine, patients must continue to be monitored closely for re-emergence of overdose symptoms.

A3.2.x Extended-release Subcutaneous Buprenorphine (Sublocade)

Extended-release buprenorphine is an extended-release formulation of buprenorphine that is administered monthly via abdominal subcutaneous injection for the management of moderate to severe opioid use disorder. Extended-release buprenorphine was made available in British Columbia on April 30, 2020. Extended-release buprenorphine is fully covered as a regular PharmaCare benefit under PharmaCare Plans B, C, G, and Z. This

formulation is indicated for adult patients (age≥19 years) who have been inducted and stabilized on sublingual buprenorphine/naloxone. For this patient population, extended-release buprenorphine may reduce the burden of medication on their daily lives, as it is administered monthly rather than daily.

There are two dose strengths of extended-release buprenorphine: 100mg/0.5ml and 300mg/1.5ml, both of which are provided in a prefilled syringe with a 19-gauge 5/8-inch (16mm) needle to be administered by a physician, nurse practitioner, registered nurse, registered psychiatric nurse, licensed practical nurse, or pharmacist.

For detailed information on requirements for prescribing and administering extended-release buprenorphine, refer to the BCCSU bulletin on Sublocade (Extended-release Buprenorphine) Information.

General initiation and dosing information

This section provides brief guidance on dosing and administration of extended-release buprenorphine in reference to the Sublocade Product Monograph.[475] The manufacturer of Sublocade requires that all prescribers interested in prescribing Sublocade complete training through www.sublocadecertification.ca. The manufacturer's website provides additional information on Sublocade.

- Patients should generally be inducted and stabilized on sublingual buprenorphine/naloxone (8–24mg/day) for a minimum of 7 days prior to receiving extended-release buprenorphine.
    - Qualifying note: While the product monograph requires a 7-day stabilization on buprenorphine/naloxone prior to extended-release buprenorphine initiation,[475] emerging evidence supports the feasibility of a more rapid transition to extended-release buprenorphine, which may facilitate treatment retention.[476,477]
- Patients starting extended-release buprenorphine should be prescribed 300mg for the first two months, followed by a maintenance dose of 100mg/month from the 3rd month.
    - Qualifying note: According to recent updates to the product monograph, patients who have been stable on 8mg/2mg–18mg/4.5mg of sublingual buprenorphine/naloxone may begin to receive their maintenance dose of 100mg/month once a month after a single induction dose of 300mg.[mm]
- Prescribers may consider providing supplemental sublingual buprenorphine/naloxone for patients who continue to experience opioid withdrawal and cravings.
    - There is evidence of significant fluctuation in plasma concentration and mu opioid receptor occupancy prior to reaching stability on extended-release buprenorphine.[1] This may result in

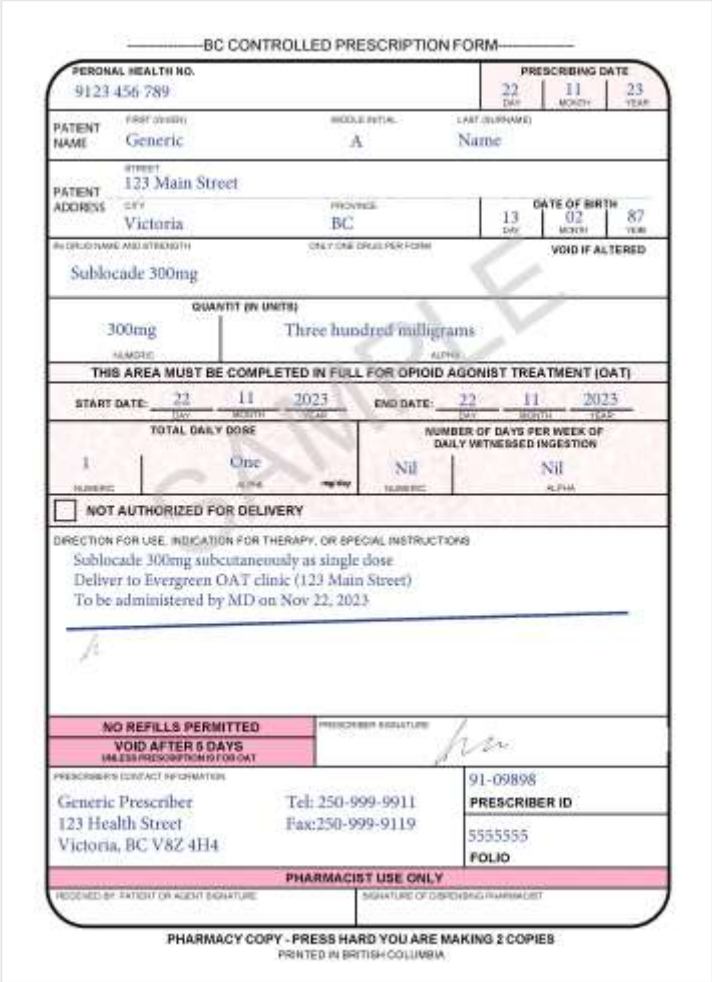
[mm] If patient is still experiencing cravings or withdrawal symptoms after the initial 300-mg dose, consider giving 300 mg as the second dose

the emergence or persistence of some withdrawal symptoms in the initial months of treatment, which can be addressed with sublingual buprenorphine/naloxone top off.

    - Prescribed supplemental dosing should be determined on a case-by-case basis and may vary over time. A 2021 case series (n=40) reported supplemental sublingual doses ranging from 4mg to 24mg as needed in 25% of participants.[476]

- At the discretion of the treating prescriber, the maintenance dose may be increased to 300mg/ month if the patient experiences ongoing opioid cravings or ongoing unregulated opioid use.
    - In published clinical trials, the 300mg/month maintenance dose did not provide additional efficacy compared to the 100mg/month dose, and was associated with a higher incidence of adverse events and study discontinuations.[125] However, one study comparing the benefits of 300mg and 100mg monthly extended-release buprenorphine found that, although there was no difference in efficacy for participants who did not inject drugs, the 300mg/month dose was associated with higher rates of treatment retention and abstinence from unregulated drug use specifically among participants who injected drugs.[478] A 2021 case series (n=40) examining the process and outcomes of treatment with Sublocade in a low-threshold clinic also reported that 25% of patients were receiving a maintenance dose of 300mg/month.[476] More research is required to characterize the effectiveness of higher doses among individuals with established opioid tolerance who inject opioids.
- Extended-release buprenorphine doses must be administered monthly. A minimum length of 26 days is required between doses. (See Missed extended-release buprenorphine doses for guidance on addressing delays)

A sample prescription for extended-release buprenorphine is provided below.



BC CONTROLLED PRESCRIPTION FORM

PERSONAL HEALTH NO.: 9123 456 789
PRESCRIBING DATE: 22 (DAY) 11 (MONTH) 23 (YEAR)
PATIENT NAME: Generic A Name
PATIENT ADDRESS: 123 Main Street; Victoria; BC
DATE OF BIRTH: 13 (DAY) 02 (MONTH) 87 (YEAR)
VOID IF ALTERED
Sublocade 300mg
QUANTITY (IN UNITS): 300mg (NUMERIC); Three hundred milligrams (ALPHA)
THIS AREA MUST BE COMPLETED IN FULL FOR OPIOID AGONIST TREATMENT (OAT)
START DATE: 22 (DAY) 11 (MONTH) 2023 (YEAR)
END DATE: 22 (DAY) 11 (MONTH) 2023 (YEAR)
TOTAL DAILY DOSE: 1 (NUMERIC); One (ALPHA); mg/day
NUMBER OF DAYS PER WEEK OF DAILY WITNESSED INGESTION: Nil (NUMERIC); Nil (ALPHA)
☐ NOT AUTHORIZED FOR DELIVERY
DIRECTION FOR USE, INDICATION FOR THERAPY, OR SPECIAL INSTRUCTIONS
Sublocade 300mg subcutaneously as single dose
Deliver to Evergreen OAT clinic (123 Main Street)
To be administered by MD on Nov 22, 2023
NO REFILLS PERMITTED
VOID AFTER 6 DAYS UNLESS PRESCRIPTION IS FOR OAT
PRESCRIBER SIGNATURE
PRESCRIBER'S CONTACT INFORMATION
Generic Prescriber
123 Health Street
Victoria, BC V8Z 4H4
Tel: 250-999-9911
Fax:250-999-9119
91-09898 PRESCRIBER ID
5555555 FOLIO
PHARMACIST USE ONLY
RECEIVED BY: PATIENT OR AGENT SIGNATURE
SIGNATURE OF DISPENSING PHARMACIST
PHARMACY COPY - PRESS HARD YOU ARE MAKING 2 COPIES
PRINTED IN BRITISH COLUMBIA
SAMPLE

Notes:

- Administration of extended-release buprenorphine can be performed by an MD, NP, pharmacist, or nurse (RN, RPN, or LPN)
- Prescribers can consider indicating the date of administration/clinic appointment on the prescription
- To avoid errors, best practice is to write "sub cut" or "subcutaneously"[1] on the prescription
- Prescription may be written as a partfill, for example: "600mg six hundred, inject 300mg subcut once a month as a single dose by MD x 2 months (May, June), dispense 300mg in 25- to 30-day intervals."
- To avoid errors, the reduction in dose to 100mg after two months should be written as a separate prescription, ideally after reassessment

Missed extended-release buprenorphine doses

- Up to 2 weeks delay in monthly injection (i.e., up to 42 days after last dose): Occasional delays of up to 2 weeks are not expected to significantly impact treatment effect. If a patient misses a monthly extended-release buprenorphine injection, they should receive their next dose as soon as possible, and monthly injections should be resumed thereafter.
- More than 2 weeks delay in monthly injection (i.e., >42 days after last dose): Re-induction is warranted. Patient should be restarted on sublingual buprenorphine/naloxone followed by a rapid transition to extended-release buprenorphine (see General initiation and dosing information above).

A3.3 Methadone-specific Guidance

A3.3.i Assessment

Methadone-specific contraindications

- Hypersensitivity to methadone hydrochloride
- Currently taking monoamine oxidase inhibitors (MAOIs) or use within past 14 days
- Severe respiratory compromise or obstructive disease

Caution

- If pre-existing risk of prolonged QT interval (e.g., cardiac hypertrophy, concomitant diuretic use, concomitant QT-prolonging medications, hypokalemia, hypomagnesaemia), more intensive monitoring is required
    - If baseline ECG indicates a QTc interval 500 ms, seek specialist consultation to discuss if an alternative opioid agonist treatment medication should be considered (See section on baseline assessment below).

Baseline assessment

In addition to general baseline assessment considerations outlined above, complete the following:

- Order ECG if indicated. Ordering ECG is generally indicated in any of the following circumstances:
    - Prescription of 2 or more QT-prolonging medications
    - Pre-existing risk or history suggestive of possible prolonged QT interval (e.g., syncope, arrythmias, history of cardiac disease, or family history of sudden cardiac death)
    - Note: If indicated, ECG results should be obtained before initiating methadone. However, the prescription of methadone maintenance or restarts should not be delayed for the process of receiving ECG results, associated consultations, or the patient's inability to get an ECG, unless their risk is perceived to be prohibitively high (e.g., family history of congenital prolonged QT syndrome, sudden cardiac death), surpassing the risk of overdose
- Document clinical plan

A3.3.ii Methadone Pharmacology

- Full opioid agonist, with action predominantly at the mu-opioid receptor and some action at the kappa and delta opioid receptors; antagonist at the NMDA receptor
- Most frequently administered as an oral solution, generally given as a single daily dose
- Average plasma half-life is approximately 24 hours (with a range of 6–90 hours)
- The average time to peak plasma concentration and peak clinical effect is 3 hours (with a range of 2–6 hours)

A3.3.iii Formulations

There are 2 methadone options available as regular PharmaCare benefits in BC (Covered under Plans B, C, G, and Z):

- Methadose
- Metadol-D

There are also 2 methadone options that are not covered under regular PharmaCare benefits and require a Special Authority Request:

- Compounded methadone
  - Exceptional, last-resort
- Methadose Sugar-free

Methadose was introduced in 2014, replacing 1mg/mL pharmacy compounded methadone. Since this formulation change, many patients who had been stable on compounded methadone 1mg/mL have reported return to unregulated opioid use due to inadequate management of withdrawal symptoms.[182-184] As a result, Metadol-D was added as a regular benefit in 2019.

In October 2019, compounded methadone became available as an exceptional, last-resort option for individuals who had trialed regular benefit formulations without success. For individuals who have not benefited from documented, reasonable trials of two methadone formulations, and for whom methadone remains the optimal OAT option, compounded methadone 10mg/mL may be considered.

Table 13. Summary of Methadone Options

Methadose	Metadol-D	Compounded Methadone	Methadose Sugar-free
• Red, cherry-flavoured • Contains sugar • Commercial solution • Regular benefit • Interchangeable with Metadol-D	• Colourless, unflavoured • Sugar-free • Commercial solution • Traditionally diluted (e.g., in Tang, Crystal Light) • Regular benefit • Interchangeable with Methadose	• Colourless, unflavoured • Sugar-free • Compounded solution • Must be diluted (e.g., in Tang, Crystal Light) • Non-benefit. Special Authority request required. • May take time for pharmacy to receive special order	• Colourless, unflavoured • Sugar-free • Commercial solution • Must be diluted (e.g., in Tang, Crystal Light) • Non-benefit. Special Authority request required

For further information to support formulation selection and transition between formulations, see the BCCSU's bulletin on Methadone Formulations Options and Interchangeability. For specific formulation for pharmacists and prescribers on requesting and prescribing compounded methadone as a last resort option, refer to the BCCSU's Compounded Methadone Bulletin.

Interchangeability among methadone formulations

Methadose and Metadol-D are both commercially available methadone 10mg/mL products that meet the Health Professions Act definition (section 25.91) of an interchangeable drug (i.e., pharmacist are able to auto-substitute Methadose with Metadol-D or vice versa if needed to address availability issues).[nn]

Compounded methadone and Methadose sugar-free are not interchangeable with regular benefit formulations or with each other, due to the special coverage requirements. However, while compounded methadone and other

[nn] Substitutions should be considered in collaboration with the patient and in reference to their needs and preferences. In the absence of availability issues, substitutions should be avoided for patients who are stable on their current medication.

formulations cannot be used as auto-substitutes, no dose changes are required when switching between these formulations.

A3.3.iv Initiation

Initiation and dosing guidance provided in this guideline is applicable to all formulations of methadone.

During initiation, prescribers should see patients in person or virtually at least weekly to carefully monitor treatment response. Clinical assessment is necessary before adjusting methadone doses; this is due to the unique pharmacokinetic properties of methadone (long half-life, slow bioaccumulation) compared to other opioids, and the high degree of individual variability in absorption rates, metabolism, potency, and cross-tolerance with other opioids.

Depending on the patient's needs and circumstances, these assessments can be conducted virtually or in person. For example, patients with previous treatment experience with methadone face a lower risk of complications during initiation, and may be good candidates for virtual assessment.

Due to risk of overdose from drug–drug interactions, current substance use, including alcohol and prescription medications, should be reviewed with patients at every visit and confirmed with PharmaNet records. Periodic check in with the dispensing pharmacy is encouraged, in order to collect collateral information on patient wellbeing (e.g., sedation) and adherence to daily witnessed ingestion requirements.

Prior to initiation, review risks and benefits of treatment, determine starting dose based on patient-specific risk of opioid toxicity (see below), and obtain informed consent.

Determining the starting dose

The starting methadone dose will depend on factors that affect risk of toxicity, including the patient's known opioid tolerance, current opioid use, and co-occurring substance use patterns. An overview of evidence informing guidelines on methadone initiation doses is provided in Initiation Dosing.

In view of accumulating clinical experience and emerging guidance, this guideline endorses a starting dose of up to 40mg for individuals who use fentanyl and have established tolerance to methadone based on past treatment history. See Table 14 below for the full range of suggested methadone starting doses based on the patient's level of opioid tolerance.

Table 14. Methadone Starting Doses Based on Patient's Opioid Tolerance

Level of tolerance	Suggested starting dose
No/low tolerance | opioid-naïve High risk of toxicity. Includes patients who have completed withdrawal management, those not currently using opioids but at risk of relapse, patients with heavy use of other sedating agents, and patients with severe comorbidities that affect toxicity risks	5–10mg/day
Unknown/moderate tolerance Moderate risk of toxicity. Includes patients who use benzodiazepines or other sedatives (prescribed or unprescribed), patients with alcohol use disorder	10–20mg/day
Known high tolerance Lower risk of toxicity. Patients actively using opioids	20–30mg/day
Known very high tolerance Very low risk of toxicity. Characterized specifically by previous methadone experience and current fentanyl use	30–40mg/day*

* Higher doses may be considered with caution on a case-by-case assessment of risks and benefits; rationale for higher doses should be documented and patient's informed consent should be obtained. Close monitoring should also be arranged for patients receiving higher starting doses.

Dose escalation

- For patients with established high opioid tolerance (i.e., documented history of fentanyl use) and experience with methadone, doses may be titrated by a maximum of 15mg every 3 days.[188,479]

    - Once the daily dose reaches approximately 85mg, the titration process should be slowed to a maximum of 10mg every 3–5 days.
- For patients with lower or unknown tolerance, no active fentanyl use, or those who have no history of OAT with methadone, doses should be increased more cautiously (e.g., 5–10mg every 3–5 days.)
- After a dose increase, it can take several days for methadone to reach a steady concentration and maximum therapeutic effect, which can also cause delayed emergence of serious adverse effects like respiratory depression.
- Patients are ideally assessed at least weekly either in person or virtually during periods of frequent dose titrations.
- If there are concerns of methadone toxicity, see the patient at 3-hours post-dose. Collateral information on the patient's response to methadone can also be obtained from care providers and staff involved in the patient's care (e.g., nurses, pharmacist, case worker).

A slower dose escalation should be considered for individuals who may be at higher risk of opioid toxicity, including individuals with recent loss of tolerance (e.g., recent discharge from withdrawal management, residential treatment, or correctional facilities where they did not receive OAT), severe respiratory illness, or decompensated liver disease; individuals using high amounts of alcohol, benzodiazepines, sedatives, or prescribed medications that affect methadone metabolism (i.e., CYP inhibitors and inducers); and older adults (i.e., over 55 years of age).

A3.3.v Rapid Titration in Monitored Settings

There is scant evidence on rapid methadone titration[245,480]; however, there is growing clinical need for, and experience with, safe and successful rapid titration in monitored settings. This is likely in response to the needs of patients who use fentanyl and other highly potent synthetic opioids, for whom existing methadone dosing and titration guidelines may be insufficient to address withdrawal symptoms or support treatment retention.[188] To address the treatment needs of this population, META-PHI recommendations for *Methadone Treatment for People Who Use Fentanyl* emphasizes the need for measures to reach an optimal dose of methadone quickly and safely in order to avoid drop-outs and reduce concurrent unregulated opioid use which increases the risk of overdose in this population.[188]

The sample rapid titration protocol presented in Table X is based on the St. Paul's Hospital protocol featured in a 2019 case study.[245] It is emphasised that a rapid titration schedule such as this one should be performed in monitored settings (e.g., hospital wards, inpatient detox facilities, bed-based treatment facilities) that can accommodate greater flexibility and the ability to monitor for early signs of opioid toxicity. This protocol starts patients at 30–40mg methadone per day, with up to 3 x 10mg methadone PRN per day. Additional doses should be at least 3 hours apart, with post-dose re-assessment at 3 hours after each dose (peak effect). On the 4th day, the lowest most consistently administered total daily dose should be consolidated into the new scheduled dose with

a 10mg increase,[oo] with up to 3 x 10mg q3h PRN doses in addition. Oral hydromorphone is also given 8–24mg q2h PRN to manage acute pain and withdrawal symptoms not managed by methadone. If the patient reports continued pain or withdrawal symptoms, consider increasing the morphine dosing during the OAT titration, as adequate OAT and analgesia dosing have a protective effect against unregulated opioid use in hospital and leaving against medical advice.[481-483] In this sample protocol, the patient took all PRN doses.

Table 15. Sample Rapid Methadone Titration

Day	Methadone, scheduled (mg)	Methadone, PRN (mg)	Highest possible total Daily methadone Dose (mg)
1	30	3 x 10	60
2	30	3 x 10	60
3	30	3 x 10	60
4	70	3 x 10	100
5	70	3 x 10	100
6	70	3 x 10	100
7	110	3 x 10	140
8	110	3x 10	140
9	110	3 x10	140

During rapid methadone titration, the patient should receive pre- and post-dose assessments—for both scheduled and PRN dosing, ensuring that they are alert and showing no signs of sedation.

An alternative rapid methadone titration protocol utilized in some North American jurisdictions is presented on the Ca Bridge website.

A3.3.vi Stabilization

The optimal therapeutic dose varies widely among patients. The range commonly cited in existing guidelines is 60mg–120mg. However, this is based on evidence collected before the emergence of fentanyl in the unregulated drug supply. While there is scant evidence around relative effectiveness or best practices for methadone prescribing in the fentanyl era, clinical experience suggests that doses of 150mg or higher may be required in some patients to meet therapeutic goals.

A3.3.vii Missed Doses

Tolerance is lost rapidly when methadone treatment is interrupted or discontinued. To avoid overdose as a result

[oo] For example, 30mg scheduled dose + 3 x 10mg PRN + 10mg dose increase = 70mg scheduled dose on Day 4.

of lost tolerance, BC pharmacists are required to notify prescribers of missed doses and clinicians must review and document PharmaNet profiles. Under current regulations, the dispensing pharmacy is also required to cancel the prescription if the patient misses 4 consecutive days of methadone, and notify the prescribing clinician.

In alignment with an increasing number of guidelines suggesting that most patients who are stable on their medication can safely resume their medication after 3 consecutive missed once-daily doses,[188,192] this guideline endorses the resumption of the patient's usual dose after 3 consecutive missed once-daily doses. An assessment for dose reduction should be conducted after 4 consecutive missed once-daily methadone doses, and titration should be restarted after 5 or more consecutive missed once-daily methadone doses, as outlined below. For split dosing (BID or more frequently), prescribers should count fully missed days rather than missed doses for assessments according to the missed dose protocol. However individualized clinical judgement should be exercised any dose adjustments for patients who have missed a part of their total daily dose over a number of days.

- One to three consecutive once-daily doses missed: No change in dose is required, as long as there is no other reason to withhold methadone. The reasons for the missed doses should be discussed and documented at the next visit.
- Four consecutive once-daily doses missed: Methadone should be held pending virtual or in-person reassessment, and the remainder of the prescription should be cancelled. Reasons for missed doses should be discussed and documented during the subsequent clinical visit, and patients should receive advice and support for removing barriers to taking methadone doses as prescribed. Following assessment, methadone may be restarted at 50% of previous dose or at 30–40mg, whichever is higher (see Table 16).
- Five or more consecutive once-daily doses missed: Methadone should be held pending virtual or in-person reassessment, and the remainder of the prescription should be cancelled. Reasons for missed doses should be discussed and documented during the subsequent clinical visit, with attention to supporting the patient for better OAT retention. Restart at 30–40mg and titrate as needed according to guidelines. If clinical judgement indicates more aggressive re-titration (e.g., for patients who were on a high dose of methadone within the past 4–7 days), prescribers may seek specialist consultation. Additionally, patients should discuss the risks of more rapid titration schedules with patients, obtain verbal consent, and plan for frequent re-evaluations until the patient is stable.

Table 16. Suggested Protocol for Managing Missed Methadone Doses*

Number of consecutive missed once-daily doses	Action	Explanation	Example
1–3	No action	Up to three consecutive once-daily doses can be missed without a dose change. This means on the 4th day since the last dose, the person can receive their full dose.	Anne gets her regular dose on Monday, and then misses Tuesday, Wednesday, and Thursday. When she arrives at the pharmacy on Friday, she receives her normal dose.
4	Cancel prescription. Reassess. Can restart at 50% of dose or 30–40mg (whichever is higher)	Missing 4 consecutive once-daily doses requires the dose to be reduced by half or to 30–40mg. This means on the 5th day since the last dose, the person could receive 50% of their dose or 30–40mg following assessment by the prescriber.	Nish gets his regular dose on Monday, and then misses Tuesday–Friday and goes to the pharmacy on Saturday. His prescription must be cancelled. If he can see his prescriber today, he can resume his dose at 50% or 30–40mg.
5+	Cancel prescription. Reassess. Restart titration.	Missing 5 or more consecutive once-daily doses requires the titration to be restarted. This means on the 6th day since the last dose, the person must restart titration following assessment by the prescriber.	Zola gets her regular dose on Monday. She then misses Tues–Saturday. When she returns to pharmacy on Sunday, she is told she must see her prescriber again to restart her methadone titration.

Note: For split dosing (BID or more frequently), count fully missed days rather than doses. Use clinical judgement in adjusting dosage for patients who have missed a part of their total daily dose over a number of days.

**Adapted from the META-PHI Methadone Treatment for People Who Use Fentanyl: Recommendations*

***For patients whose risk of lost tolerance is assessed to be lower (e.g., those who have continued using other opioids since last methadone dose), a smaller dose reduction may be considered after individualised assessment of risks, benefits, and safety considerations. On the other hand, a more conservative dose adjustment schedule may be considered for individuals who have not used unregulated opioids since their last dose.*

A3.3.viii Transitioning Patients to Different Commercial Methadone Formulations

1. Discuss potential risks and benefits of the transition with your patient
2. If a shared decision is made to switch to a different commercial methadone formulation, document the discussion, decision, and your clinical rationale carefully in the patient's medical record
3. Call the patient's pharmacy and discuss the switch to ensure the pharmacy is aware of the new transition and able to fill the prescription. This will allow for easier transition for your patient

A3.4 Slow-release Oral Morphine-specific Guidance

Slow-release oral morphine (SROM; brand name Kadian) is a long-acting, 24-hour formulation of oral morphine available in BC to treat opioid use disorder. Like methadone, SROM does not have a ceiling effect, requiring a similar level of monitoring during initiation to ensure patient safety.

In the absence of clear, evidence-based clinical treatment protocols established for slow-release oral morphine, the guidance in this document is based on clinical experience and expert clinical consensus. It is important to note that only the once-daily, 24-hour formulation of slow-release oral morphine has been studied in clinical trials for the treatment of opioid use disorder. Other formulations of oral morphine, such as twice-daily, 12-hour sustained- or extended-release formulations (brand name M-Eslon), have been used in BC in response to shortages of SROM and the need for expanded harm reduction measures across the province.[484] However, these formulations have not been empirically studied in the context of OAT and are not recommended by this committee for treatment of opioid use disorder.[pp] The BCCSU's *Risk Mitigation in the Context of Dual Public Health Emergencies* and the *Opioid Use Disorder Practice Update* provide guidance on prescribing M-Eslon as a harm reduction intervention.

[pp] Clinical experience in BC in response to shortages of SROM and a single case study[22] suggest that some individuals with OUD do well on sustained-release oral morphine (e.g., M-Eslon). Further research is needed. Relevant information on SROM shortages can be found on the BCCSU website.

A3.4.i Assessment

Slow-release oral morphine-specific contraindications

- Hypersensitivity to morphine sulfate or any component of the formulation
- Known or suspected paralytic ileus
- Currently taking monoamine oxidase inhibitors (MAOIs) or use within past 14 days
- Severe respiratory compromise or obstructive disease
- Chronic kidney disease

Cautions

- Adrenal insufficiency
- Gastrointestinal issues (e.g., obstruction, diarrhea, abnormal gut anatomy) that affect the amount of time medication remains in the stomach
- Pregnancy or breastfeeding
    - People who are stable on SROM when they become pregnant should be informed that switching between OAT options during pregnancy and post-partum periods is generally not recommended. For patients starting OAT during pregnancy, SROM should only be considered when other OAT options are deemed inappropriate; this is due to the comparatively small body of literature supporting the use of SROM for this population.[485]

Additional prescribing considerations

Prescribers and pharmacists should be aware that that co-prescription of naltrexone and Kadian for OAT will not be automatically flagged by PharmaCare, due to the use of a PIN for Kadian. Additional caution should be exercised to ensure that these medications are not co-prescribed. Naltrexone is contraindicated for patients receiving SROM as it blocks the effect of opioids and may precipitate withdrawal.

A3.4.ii Pharmacology

- Slow-release oral morphine is administered via once-daily oral doses
- Slow-release oral morphine is released over 24 hours
- Peak plasma levels are achieved within 8.5 to 10 hours
- Elimination half-life: The terminal elimination half-life of morphine following a single dose of slow-release oral morphine administration is approximately 11 to 13 hours. However, this is primarily due to the delayed absorption of the pellets. Once absorption is complete, the plasma elimination half-life is the same as immediate-release morphine (2 to 4 hours)

A3.4.iii Initiation and Dosing

Administration

- Slow-release oral morphine capsules can be provided whole to be swallowed. Alternatively, based on patient preference or clinician assessment, the pellets contained in the capsule may be sprinkled into a cup for immediate ingestion.
    - Slow-release oral morphine pellets must be swallowed whole. Crushing, chewing, or dissolving capsules or pellets can cause rapid release and absorption of a potentially fatal dose of morphine sulphate.
- Following the ingestion of SROM, drinking water is preferred to acidic beverages (e.g., cola, sparkling water, coffee, orange juice), as acidic liquids may affect the absorption kinetics of the medication.

Initiation

- Because of the sustained-release properties of slow-release oral morphine (see Pharmacology section above), dosage increases should generally be separated by at least 24 hours.
- For individuals using unregulated opioids other than methadone, refer to dosing schedules below

Dosing schedules

There are a variety of dosing schedules described in the literature. The average (mean) daily SROM dose presented in the literature ranges from 235mg/day to 791mg/day, and the full range of SROM daily doses described is 60–1200mg. Clinical experience suggests that higher doses are often needed for many patients, especially in the context of fentanyl dominating the unregulated drug supply.

Clinical experience in BC indicates that the dosing and titration schedules described in the literature, while appropriate for patients requiring a more conservative titration, are often too conservative to retain patients in care. Depending on the patient's level of opioid tolerance, starting doses as high as 300mg are commonly used, with increases of up to 100mg every 24 to 48 hours. Suggested starting doses based on opioid tolerance are provided in Table 17.

Table 17. SROM Starting Doses Based on Patients' Opioid Tolerance.

Level of tolerance	Suggested starting dose
No/low tolerance | opioid-naïve High risk of toxicity. Includes patients who have completed withdrawal management, those not currently using opioids but at risk of relapse, patients with heavy use of other sedating agents, and patients with severe comorbidities that affect toxicity risks	50mg/day
Unknown/moderate tolerance Moderate risk of toxicity. Includes patients who use benzodiazepines or other sedatives (prescribed or unprescribed), patients with alcohol use disorder	100–150mg/day
Known high tolerance Lower risk of toxicity. Patients actively using opioids	200mg/day
Known very high tolerance Very low risk of toxicity. Characterized specifically by previous SROM experience and current fentanyl use	300mg/day*

*Higher doses may be considered with caution on a case-by-case assessment of risks and benefits; rationale for higher doses should be documented and patient's informed consent should be obtained.

The example protocol provided below is based on clinical experience and expertise, and is intended for individuals with known tolerance who are currently using opioids. To date, there is an absence of evidence to guide titration schedules for slow-release oral morphine. Clinical judgement based on individual circumstances should determine which titration protocol is used and frequent assessment should determine whether titration should be maintained, slowed, or sped up.

A patient should be assessed prior to dose increases. Where appropriate, virtual assessment may be considered. Clinicians are encouraged to consult the 24/7 Line or RACE app when determining a titration protocol.

Table 18. Sample SROM Titration Schedule

Day	SROM dose (moderate tolerance)
1	200mg
2	300mg
3	400mg
4	500mg
5	600mg
6	700mg
7	800mg

There is no defined maximum dose for slow-release oral morphine. The highest dose described in the literature[qq] to date is 1200mg[216]; however, clinical experience indicates that patients often require doses above 1200mg to manage cravings and withdrawal symptoms, due to high tolerance developed due to sustained exposure to fentanyl through the unregulated drug supply.[217] Prescribers should use caution with respect to side effects when prescribing above 1200mg and clearly document the rationale for doses above 1200mg. Patients should be assessed for sedation with dose increases.

For SROM prescriptions, it is no longer necessary to write "for OAT" in the Directions for Use Field if the information in the OAT shaded section indicates clearly that the prescription is for OAT. This ensures that it will be correctly entered into PharmaNet using the Product Identification Number (PIN), which indicates slow-release oral morphine is used for OAT rather than analgesia. Clinical discretion and individual circumstances should determine which titration protocol is used and frequent assessment should determine whether titration should be maintained, slowed, or sped up.

Switching from methadone oral solution to slow-release oral morphine:

- No wash-out of previous treatment is required (to minimize potential for withdrawal symptoms). Withdrawal symptoms may recur temporarily during the switch-over period.
- Determining the slow-release oral morphine dose will depend on the current methadone dose. Generally, a ratio of 1:6 to 1:8 (methadone: SROM) can be used to determine dose. Clinicians are encouraged to consult the 24/7 Line or RACEapp for case-based support to determine conversion ratio for patients receiving high methadone doses or those who use additional

[qq] Doses above 1200mg were described in a 2006 prospective, open, non-comparative multi-centre study[25]; however, doses were expressed as a mean plus standard deviation (1104 ±348mg/day). Specific doses, including max dose, were not included.

unregulated opioids.

- See Methadone to Slow-release Oral Morphine, below

A3.4.iv Stabilization

The goal is to stabilize the once-daily dose at the lowest dose that relieves withdrawal symptoms and suppresses unregulated opioid use. Currently, there is no published literature to guide treatment decisions beyond the 36-week duration of clinical trials. The guideline committee supports following similar stabilization and tapering practices as those used for methadone and buprenorphine/naloxone.

A3.4.v Missed Doses

Despite delayed absorption, the underlying short morphine half-life results in the potential for rapid loss of tolerance following missed doses and the possibility of harmful over-sedation or overdose. To mitigate this, prescribers should work very closely with pharmacists regarding missed doses and daily patient assessments.

To avoid overdose as a result of lost tolerance, BC pharmacists are required to notify prescribers of missed doses and clinicians must review and document PharmaNet profiles. Under current regulations, the dispensing pharmacy is also required to cancel the prescription if the patient misses 4 consecutive days of SROM, and notify the prescribing clinician.

In the absence of established evidence-based protocols, approaches to dealing with missed SROM doses are based on expert opinion and local clinical experience. Since this medication was a relatively new addition to the province's continuum of OUD care, previous BC guidelines provided a conservative protocol for addressing missed SROM doses, recommending that dose reductions be considered after 2 missed dose. However, increasing clinical experience with SROM has informed the revision of this protocol in order to minimize treatment disruption. This guideline endorses the resumption of the patient's usual dose after 3 consecutive missed once-daily doses. An assessment for dose reduction should be conducted after 4 consecutive missed once-daily doses, and titration should be restarted after 5 or more consecutive missed once-daily doses, as outlined below.

- One to three consecutive once-daily doses missed: No change in dose is required, as long as there is no other reason to withhold SROM. The reasons for the missed doses should be discussed and documented at the next visit.
- Four consecutive once-daily doses missed: Slow-release oral morphine should be held pending virtual or in-person reassessment, and the remainder of the prescription should be cancelled. Reasons for missed doses should be discussed and documented during the subsequent clinical visit, and patients should receive advice and support for removing perceived barriers to taking SROM doses as prescribed. Following assessment, SROM may be restarted at 50% of previous dose or the patient's initiation dose, whichever is higher (see Table 19).
- Five or more consecutive once-daily doses missed: Slow-release oral morphine should be held pending virtual or in-person reassessment, and the remainder of the prescription should be cancelled. Reasons

for missed doses should be discussed and documented during the subsequent clinical visit, with attention to supporting the patient for better OAT retention. Restart at the patient's initiation dose and titrate as needed according to guidelines. If clinical judgement indicates adjustments to the pace of re-titration (e.g., a more aggressive pace for patients who were on a high dose of SROM within the past 4–7 days or those who have continued using unregulated opioids), prescribers may seek specialist consultation. Additionally, patients should discuss the risks of more rapid titration schedules with patients, obtain verbal consent, and plan for frequent re-evaluations until the patient is stable.

Clinicians should address missed doses on a case-by-case basis, and may use a modified approach in consideration of individual factors that affect opioid tolerance. In determining dose adjustments after missed doses, clinical judgment must take into account:

- Total daily dose
- Number of missed doses
- Possibility of diversion
- Other opioid use during periods of missed dosing
- Type and amount of opioids used most recently
- Previous experience with SROM treatment

Consultation with the patient about past experiences with missed doses, restarts, and other similar circumstances is crucial in determining an appropriate missed dose schedule for each patient.

Table 19. Suggested Protocol for Managing Missed SROM Doses

Number of consecutive missed once-daily doses	Action	Explanation	Example
1–3	No action	Up to three consecutive once-daily doses can be missed without a dose change. This means on the 4th day since the last dose, the person can receive their full dose.	Anne gets her regular dose on Monday, and then misses Tuesday, Wednesday, and Thursday. When she arrives at the pharmacy on Friday, she receives her normal dose.
4	Cancel prescription. Reassess. Can restart at 50% of dose* or initiation dose (whichever is higher)	Missing 4 consecutive once-daily doses requires the dose to be reduced by half or to the initiation dose. This means on the 5th day since the last	Nish gets his regular dose on Monday, and then misses Tuesday–Friday and goes to the pharmacy on Saturday. His prescription must be cancelled. If he can see his prescriber today, he can resume his dose at 50% or at his initiation dose.

		dose, the person could receive 50% of their dose or their initiation dose following assessment by the prescriber.	
5+	Cancel prescription. Reassess. Restart titration.	Missing 5 or more consecutive once-daily doses requires the titration to be restarted. This means on the 6th day since the last dose, the person must restart titration following assessment by the prescriber.	Zola gets her regular dose on Monday. She then misses Tues–Saturday. When she returns to pharmacy on Sunday, she is told she must see her prescriber again to restart her SROM titration.
**For patients whose risk of lost tolerance is assessed to be lower (e.g., those who have continued using other opioids since last SROM dose), a smaller dose reduction may be considered after individualised assessment of risks, benefits, and safety considerations. On the other hand, a more conservative dose adjustment schedule may be considered for individuals who have not used unregulated opioids since their last SROM dose.*			

A3.5 Transitioning Between OAT Medications

Transitioning between OAT medications may be appropriate for a number of reasons including:

- No change from pre-treatment levels of non-prescribed opioid use
- Increased or re-initiated use of non-prescribed opioids while on OAT in order to manage opioid cravings or withdrawal symptoms
- Continued, increased, or re-initiated use of other substances (e.g., alcohol, benzodiazepines) to manage opioid cravings or withdrawal symptoms
- Patient wish to simplify treatment or increase flexibility (e.g., transitioning to buprenorphine/naloxone to reduce the number of required pharmacy visits)
- Other factors that impact health, wellness, or quality of life (e.g., intolerable side effects), or increased risk of harm to the patient

Any decisions to transition to a different medication should be made in consultation with the patient and based on clinical judgment and the specific needs and circumstances of the patient.

The following section provides example protocols for transitioning between OAT medications. Other than low-dose induction protocols for transitioning from methadone to buprenorphine/naloxone, which is based on a developing body of evidence represented in a 2021 systematic review,[145] these protocols are based on clinical experience and expert consensus, as there is a lack of evidence-based protocols for transitioning between OAT medications. As with all OAT, the goal when transitioning between OAT doses is to titrate to a final dose in which the patient feels comfortable and does not experience withdrawal symptoms between doses.

A3.5.i Buprenorphine/naloxone to Methadone or Slow-release Oral Morphine

Rotation from buprenorphine/naloxone to methadone or SROM is relatively uncomplicated, as methadone and SROM are full agonists, while buprenorphine is a partial agonist. Thus, there is no risk of precipitated withdrawal during this switch.

Generally, the first dose of methadone or SROM can be administered within 24 hours of the last dose of buprenorphine/naloxone, using established protocols for starting methadone treatment in opioid tolerant patients. An example protocol follows.

Table 20. Example Protocol for Transition from Buprenorphine/naloxone to Methadone

Day	Buprenorphine/naloxone dose	Methadone Dose
1	16.0mg	–
2–4	–	40mg
5–7	–	50mg
8+	–	Continue to up-titrate methadone as per initiation protocol

A3.5.ii Methadone to Buprenorphine/naloxone

There is a potential for precipitated withdrawal when transitioning from methadone to buprenorphine-containing products. This is due to buprenorphine's high affinity and lower intrinsic activity at the mu-opioid receptor, which displaces methadone and replaces the full agonist with a partial agonist.[144] Historically, it has been challenging to transition from methadone to buprenorphine/naloxone, as the terminal elimination half-life of methadone ranges from 8 to 59 hours, requiring a wait before buprenorphine/naloxone induction, to prevent precipitated withdrawal.[144,486] The requirement to be in moderate withdrawal before initiating buprenorphine/naloxone has, thus, presented a significant challenge for individuals wanting to transition to buprenorphine.

Low-dose induction is the preferred method for transitioning from methadone to buprenorphine/naloxone, as it reduces the risk of precipitated withdrawal and does not require a wash-out period. This method maintains the patient's dose of methadone while gradually increasing the buprenorphine/naloxone dose, allowing it to slowly accumulate at the mu-opioid receptors over time, gradually displacing methadone. Methadone is then abruptly stopped once the target buprenorphine/naloxone dose is reached.[144,487,488] Patients should be seen frequently to assess the titration, with speed of transition modified as needed based on symptoms.

Table 21. Sample Low-dose Induction Protocol

Day	Buprenorphine/naloxone Dose	Methadone
1	0.5mg/0.125mg two times	Continue prescribed dose
2	0.5mg/0.125mg three times	Continue prescribed dose
3	1mg/0.25mg two times	Continue prescribed dose
4	2mg/0.5mg two times	Continue prescribed dose
5	2mg/0.5mg three times	Continue prescribed dose
6	4mg/1mg three times	Continue prescribed dose
7	12mg/3mg once	Stop Methadone

*Note: A 5–7-day transition protocol may be challenging for people on higher doses (i.e., >100mg) of methadone. In such cases, a slower (up to 14 days) transition protocol should be considered in collaboration with the patient.

A3.5.iii Methadone to Slow-release Oral Morphine

Both methadone and SROM are full agonists at the mu receptor, which means that no wash out period is required. There is a lack of published research on strategies to transition between methadone and slow-release oral morphine for individuals with opioid use disorder.

When transitioning from methadone to SROM, use a 1:6 to 1:8 ratio of methadone to SROM. For patients who are currently using unregulated opioids to supplement their current methadone dose, a 1:8 ratio and a more rapid transition schedule is preferable to address their higher opioid tolerance, while a 1:6 ratio or a more gradual titration schedule may be more suitable for patients who are not using unregulated opioids.

Table 22. Rapid Transition from 100mg to SROM Using a 1:8 Ration of Methadone to SROM

Day	Methadone Dose	SROM Dose
1	100mg	–
2	–	800mg
3+	–	Continue to titrate per SROM titration protocol. For individuals continuing to use unregulated opioids: Increase dose by 100mg per day.
All doses should be daily witnessed ingestion		

Table 23. Gradual Transition from 150mg Methadone to SROM Using a 1:6 Ratio of Methadone to SROM

Day	Methadone Dose	SROM Dose
1	150mg	–
2–8	50mg	600mg
9	–	900mg
10+		Continue to titrate per SROM titration protocol: For individuals not using unregulated opioids: Increase dose by up to 100mg every 24 hours as needed.
All doses should be daily witnessed ingestion		

Table 24. Gradual Transition from 150mg Methadone to SROM Using a 1:8 Ratio of Methadone to SROM

Day	Methadone Dose	SROM Dose
1	150mg	–
2–8	50mg	800mg
9	–	1200mg
10+	–	Continue to titrate per SROM titration protocol: For individuals not using unregulated opioids: Increase dose by up to 100mg every 24 hours as needed.
All doses should be daily witnessed ingestion		

A3.5.iv Slow-release Oral Morphine to Methadone

Transitioning from SROM to methadone is challenging due to the different pharmacokinetics of these two long-acting opioid agonists. When transitioning from SROM to methadone, a conservative ratio of 12:1 or 10:1 SROM to methadone is appropriate in order to avoid inadvertent methadone toxicity. An even more conservative ratio should be used if the tolerance of the patient is unknown, if the patient does not have experience with methadone, or if they have medical comorbidities that may impact tolerance or safety. Patients should be monitored closely during transition. Example protocols follow.

Table 25. Rapid Transition from 1000mg SROM Using a 12:1 Ratio of SROM to Methadone (Not Suitable for Methadone-naïve Patients)

Day	SROM Dose	Methadone
1	1200mg	–
2		100mg
3		100mg
4		100mg
5+	Continue methadone titration as appropriate (see guidance on methadone dose escalation)	

Table 26. Gradual Cross-titration from 1000mg SROM Using a 12:1 Ratio of SROM to Methadone

Day	SROM Dose	Methadone Dose
1	1000mg	–
2–4	520mg	40mg
5–7	400mg	50mg
8–10	280mg	60mg
11+	Continue cross-titration until SROM has been completely discontinued, increasing methadone by 10mg and decreasing SROM by 120mg every 3–5 days	

Table 27. Gradual Cross-titration from 1000mg SROM Using a 10:1 Ratio of SROM to Methadone

Day	SROM Dose	Methadone Dose
1	1000mg	–
2–4	600mg	40mg
5–7	500mg	50mg
8–10	400mg	60mg
11+	Continue cross titration until SROM has been completely discontinued, increasing methadone by 10mg and decreasing SROM by 100mg every 3–5 days	

APPENDIX 4.0: EMERGENCY DEPARTMENT BUPRENORPHINE/NALOXONE INDUCTION

Individuals with OUD have high rates of emergency department (ED) utilization.[155-157] These high rates of utilization suggest that ED visits may be an opportunity to engage individuals in evidence-based OUD care and promote harm reduction. A small but growing body of evidence suggests that ED-based initiation of OAT increases engagement and retention in treatment.[158-160] See Evidence Review for a review of available research related to ED-initiation of buprenorphine/naloxone. A brief summary of the supporting evidence follows.

Over half (60.4%) of the 10,455 people who had a fatal or non-fatal overdose in BC from January 1, 2015 to November 30, 2016 had utilized ED services in the past year.[157] In 2017, 70% of the people who died from drug toxicity in the Vancouver Coastal Health region had visited an ED in the previous year.[489]

Emergency department-initiated buprenorphine/naloxone is associated with:

- Higher treatment engagement and fewer days of self-reported unregulated opioid use after 30 and 60 days, compared to screening and brief intervention or screening, brief intervention, and facilitated referral to community-based treatment[158,161]
- Significantly higher likelihood of receiving OAT compared to clonidine[159]
- Successful follow-up with outpatient clinics (54%) and successful retention in OAT (buprenorphine/naloxone) at 6 months (35%)[160]
- Lower ED utilization at 6 months[160]
- Cost effectiveness relative to both referral and brief intervention[162]

A small number of case studies (N=3) have shown that individuals can be inducted onto buprenorphine/naloxone in the ED immediately following naloxone reversal of an opioid overdose, without serious adverse events.[163]

Emerging evidence demonstrates that low-dose initiation in the ED is feasible and may improve OAT retention in comparison to traditional induction.[490]

To increase the chances of engaging ED patients with OUD in OAT, the BCCSU and BC Patient Safety and Quality Council worked together to launch the Learning about Opioid Use Disorder in the Emergency Department Collaborative (LOUD in the ED). The program developed three key resources: a Tool for Emergency Department Buprenorphine/naloxone Induction, a webinar series, and two new modules for the Provincial Opioid Addiction Treatment Support Program (POATSP). While this appendix provides a general overview of buprenorphine/naloxone initiation in EDs, prescribers are encouraged to refer to these resources for detailed guidance.

A4.1 General Considerations

- General screening and eligibility assessment guidance for buprenorphine/naloxone initiation guidance applies to ED-initiation.
- Whether an eligible ED patient chooses to initiate OAT or not, supporting connections to OUD care and treatment in this setting should be prioritized. This may include:
    - Provision of take-home naloxone
    - Emergency department initiation of buprenorphine/naloxone (low-dose or traditional induction)
    - Provision of take-home doses ("bup-to-go") in order to facilitate a home induction
    - Referral to a community prescriber or specialist to initiate other OAT (e.g., methadone, slow-release oral morphine, or injectable OAT)
    - Referral to community-based support services
    - Education on harm reduction and provision of harm reduction supplies
- For a comprehensive decision support tool containing a step-by-step pathway for guiding emergency department inductions, see the Decision Support Tool for Emergency Department Buprenorphine/naloxone Induction by LOUD in the ED.

A4.2 Screening

Patients who present with overdose, withdrawal, or other negative consequences from unregulated opioid use (e.g., cellulitis, mental health concerns) may be suitable for ED-initiation of buprenorphine/naloxone. However, broader screening of ED patients for OUD is also encouraged where possible, since potential candidates for OAT initiation may not be limited to those who present to the ED with opioid-related emergencies. Emergency department-initiation of buprenorphine/naloxone may be appropriate if the patient has opioid use disorder and if there is sufficient clinical information to indicate suitability for ED-initiation.

Eligibility

While individual program requirements may vary, eligibility for a traditional buprenorphine/naloxone induction should be met, including:

- Diagnosed opioid use disorder
- Informed consent
- Clinical Opiate Withdrawal Scale (COWS) score of >12 (at least moderate withdrawal)
- Adequate time since last opioid use, to prevent precipitated withdrawal:
    - ≥12 hours for short-acting opioids (e.g., heroin, oxycodone, hydromorphone)

- ≥24 hours for intermediate-acting opioids (slow-release oral morphine) and confirmed or suspected fentanyl[rr]
- 48–72 hours for long-acting opioids (e.g., methadone)

It is advised that patients who use fentanyl complete a minimum of 24 hours of abstinence prior to traditional induction regardless of the COWS score. Support the patient to sustain the pre-induction withdrawal period for as long as tolerable, since patients who have been using fentanyl may experience unexpected precipitated withdrawal symptoms up to 48 hours after last use.[153] If the patient prefers not to experience moderate withdrawal prior to induction, consider initiating a low-dose induction (see Appendix 3 for more information).

If a significant delay is anticipated until adequate withdrawal is achieved, consider "bup-to-go"[ss] or prescribe a home induction instead, with follow-up from their primary care provider or referral to a community OAT clinic, or rapid access addiction clinic. "Bup-to-go" may be prescribed as a low-dose or tradtional induction. See Home Induction in Appendix 3.

Patients presenting to the ED may require laboratory and other diagnostics, including a urine drug test and pregnancy test, as needed, for their care management; however, if a patient declines recommended additional testing, this should not be a barrier to receiving further care and is not required for a diagnosis of OUD.

A specialist (e.g., Addiction Medicine Consult Team, RACEapp, or the 24/7 Addiction Medicine Clinician Support Line) should be consulted in the following situations:

- Pregnancy
- Allergy to buprenorphine/naloxone
- Currently on OAT, particularly a long-acting opioid (e.g., methadone)
    i. Unless the patient requests it, changing OAT medications in the ED is usually not indicated
- Concurrent withdrawal/intoxication from one or more sedative (e.g., benzodiazepines, alcohol, z-drugs)
- Severe respiratory or liver dysfunction
- Acute medical (e.g., delirium) or psychiatric concerns (e.g., psychosis) precluding consent
- Youth under 16 years of age

[rr] Although fentanyl has a rapid and intense onset with a relatively short duration of action (1–2 hours), it has a long terminal half-life, likely due rapid distribution into the body's tissues due to its lipophilic nature.

[ss] "Bup-to-go" refers to buprenorphine/naloxone kits (usually 3-day supply) dispensed from the ED to facilitate home initiation without requirement of prescription to fill at a pharmacy. Dispensation uploaded to PharmaNet as standard practice.

A4.3 Monitoring

Following a traditional buprenorphine/naloxone induction

Pre-induction in ED: COWS administered by nurse or MD every two hours until score is >12

During induction ED: COWS administered by nurse or MD pre-dose for all doses and 1-hour post first three doses

Changes in the COWS score over time can guide how patients are titrated. At the discretion of the treating clinician, patients who still report discomfort due to withdrawal symptoms and are under-dosed may be titrated up to the suggested maximum first day dose more quickly. Always consider the possibility of precipitated withdrawal if a patient's COWS score is worsening.

Buprenorphine/naloxone administration does not discontinue once a patient's COWS score is <12. Patients should continue to receive buprenorphine/naloxone, either in the ED or as a take-home dose, until they no longer experience withdrawal symptoms or reach the maximum first day dose (see below for dosing).

Note: Initiation can occur in a low acuity area that can accommodate frequent patient assessment and medication administration. No cardiorespiratory monitoring is required.

A4.4 Initiation

Following a traditional buprenorphine/naloxone induction

If the patient is in sufficient withdrawal upon presentation to the emergency department, likely to reach significant withdrawal shortly, or would benefit from a short observation stay, start an emergency department initiation. Initiation should follow the general guidance (see Appendix 3.).[tt] Initiation can be entirely completed in the ED or continued after discharge with provision of additional doses to take home if the patient's ED stay is shorter than the time required for full induction.

Always offer non-opioid medications to alleviate withdrawal symptoms prior to the first dose or during the first few doses. Keep in mind these medications may decrease the COWS score. Options include (if no contraindication to individual medications):

- Acetaminophen (650-975mg po q6h PRN)
- Ibuprofen (400mg po q6h PRN)

[tt] Note that low-dose induction is increasingly used by community OAT providers, to avoid the need for patients to experience moderate withdrawal. See Low-dose Induction for more information.

- Loperamide
- Ondansetron or dimenhydrinate, as per standard dosing
- Clonidine (0.1-0.2mg po q6h PRN)

Home initiation (prescription or "bup-to-go") may be appropriate in the following situations:

- Patient preference
- Patient is not in sufficient withdrawal upon presentation to the ED and anticipated time to moderate withdrawal is lengthy

In these cases, buprenorphine/naloxone may be prescribed or dispensed to complete a home initiation. In addition, medications to relieve withdrawal may be prescribed, and patient information material (including an induction information sheet) should be provided. See Home Induction, above, for more information.

Buprenorphine/naloxone dosing should start with 2mg/0.5mg buprenorphine/naloxone SL and can be titrated up to a target total first day dose of 12mg/3mg to 16mg/4mg. If the patient's COWS score has consistently decreased receiving 2mg/0.5mg per hour, it may be appropriate to increase to 4mg/1mg per hour, once the patient has reached 8mg/2mg total of buprenorphine/naloxone, with no signs of precipitated withdrawal.

While the product monograph recommends a target first day dose of 12mg/3mg, clinical experience suggests that higher doses (up to 16mg/4mg) can be administered safely and may be necessary to adequately address withdrawal symptoms. The clinician's selection of total first day dose should be guided by their organization's paper or electronic order sets, patient comfort, and their comfort level in administering a higher dose. As with any medical treatment, exceptions may be made at the discretion of the treating clinician, after carefully balancing the risks benefitts of a given approach.

Table 28. Example Initiation Protocol Starting at 12pm

Time	Buprenorphine/naloxone dose	Total cumulative dose
12pm	2mg/0.5mg	2mg/0.5mg
1pm	2mg/0.5mg	4mg/1mg
2pm	2mg/0.5mg	6mg/1.5mg
3pm	4mg/1mg	10mg/2.5mg
4pm	4mg/1mg	14mg/3.5mg

A4.5 Discharge Planning

Discharge planning should start as soon as the patient agrees to initiate buprenorphine/naloxone. The following provides guidance for what could be included in discharge planning, with each patient's plan tailored to their needs and circumstances.

- Give the patient a take-home naloxone kit and provide training on how to administer naloxone
- Consolidate the patient's doses received during initiation to once daily and provide discharge prescriptions
    - If initiation has not been completed, provide remaining doses to complete initiation at home
    - Consider providing PRN additional buprenorphine/naloxone doses (either bup-to-go from the ED or as a prescription) to alleviate withdrawal symptoms (e.g., 4 x 2mg)
    - Provide a bridging prescription of 2–7 days of buprenorphine/naloxone, depending on access to follow up care
    - Provide non-opioid medications to alleviate withdrawal symptoms
- Refer the patient to continuing OAT care (OAT Clinics Accepting New Patients)[uu] and encourage the patient to pre-book a follow-up OAT appointment, either with their usual community prescriber or designated OAT clinic[vv]
- Refer to outreach support services as required or requested (if available)
- Provide the patient with information on available community resources such as harm reduction facilities (e.g., supervised consumption sites), community-based healthcare clinics, psychosocial support services (e.g., housing, nutrition), and educational materials (e.g., Opioids: A Survivors Guide)
- Send referral directly to OAT clinic, including a copy of their chart or discharge summary containing total buprenorphine/naloxone dose provided and time of last dose, and consider providing additional copy for referral to patient
    - Consider creation of referral pathways, including standard referral letters to receiving clinics
- Discuss with patient any support people who should be alerted of the treatment plan (e.g., staff at supportive housing)
- If home induction is planned, provide patient with induction information sheet

[uu] A variety of resources may be available in each hospital and community to support linkage to care and reduce barriers to retention in treatment, such as patient navigators, social workers, rapid access addiction clinics, and peer-led organizations such as the BC Association of People on Opiate Maintenance.

[vv] Cost of medication may be a barrier some patients. If required to ensure coverage, fax a signed OAT referral to BC Mental Health and Substance Use Services, along with a signed Application for PharmaCare Plan G form, or connect patient to a community prescriber who can provide support with paperwork and ongoing care.

APPENDIX 5.0: URINE DRUG TESTING

Urine drug testing (UDT) at indicated intervals is the standard of care in OAT programs and can be used to assess adherence to treatment, validate self-reported use of opioids or other substances, detect use of other substances which may affect safety (e.g., benzodiazepines), and evaluate treatment response and outcomes (e.g., abstinence from heroin or other opioids). However, the extent of the utility and effectiveness of UDT is unclear. A 2019 critical review of the literature supporting the use of UDT as a standard of care for individuals on OAT found insufficient evidence to determine UDT's effectiveness for both patient and community health outcomes[491] and called for more research to determine the relationship between UDT frequency and health outcomes.[491] This finding accords with a 2014 systematic review, which found insufficient evidence to demonstrate the utility of carrying out UDT for medical management of individuals receiving opioids.[492] This review looked at the use of UDT for both opioid analgesia and OAT. While the overall findings were insufficient to demonstrate the utility of UDT, weak evidence was found for the use of UDT in OAT.

All UDT should be accompanied by a discussion with the patient about their substance use and care plan and should be based on the principles of improved patient care and outcomes. The frequency of UDT should be determined by therapeutic need, with an understanding that more frequent testing has not been shown to decrease substance use.[493] However, a general principle of more frequent testing at the beginning may be followed.

Clinicians should use UDT when test results may impact clinical management for a given patient; however, UDT results should not be the only factor considered in clinical decisions. Urine drug testing should be used along with collateral information, self-report, and clinical assessment for the monitoring of treatment.[493] A pattern of tests positive for the prescribed medication and negative for unexpected substances suggests a treatment plan is effective, whereas the opposite indicates the need for treatment plan adjustments.[493] These may include discontinuation of take-home doses, increased psychosocial interventions and support, a higher level of care, increased patient education, a dose increase, more frequent UDT schedule, or trialing a different medication option.[493]

In the absence of clearer evidence supporting the use of UDT for individuals receiving prescribed opioids, UDT should be used for specific purposes, such as:

- Confirming unregulated opioid use during baseline assessment
- Supporting decision-making regarding take-home doses
- Confirming that the medication is being taken
- Screening for ongoing non-prescribed or unregulated opioid use, which may indicate the patient is undertreated or needs additional support
- Detecting the presence of other substances, including substances the patient may be unaware they have ingested
- Evaluating treatment response and outcomes

Information about drug testing and patient-provider expectations should be discussed with the patient when initiating OAT.[493] In particular, clinicians should emphasize—and ensure that patients understand—that UDT is performed for all patients prescribed OAT and that the results will not be used punitively or as sole grounds to discontinue treatment, but may be used to inform changes to their clinical management.

This appendix provides broad guidance on using UDT for OUD care, including suggested frequency, information on point-of-care and laboratory UDT, and information on using UDT in patient prescribed slow-release oral morphine. More detailed guidance, including general practices, ordering UDT, interpreting results, and managing unexpected results, is available in *Urine Drug Testing in Patients Prescribed Opioid Agonist Treatment—Breakout Resource*. In any instances of incongruent guidance between this guideline and the Breakout Resource, the guidance contained in this guideline supersedes the guidance in the Breakout Resource.

A5.1 Frequency

Determining the frequency of UDT should be at the discretion of the prescribing clinician. Urine drug testing frequency should be guided by therapeutic need, with an understanding that there is insufficient evidence to suggest that more frequent testing affects substance use.[493] A general principle of more frequent testing at the beginning of treatment may be followed. Generally, UDT should be performed at baseline and when patients display a change in clinical status.[493] During initiation and dose escalation, urine drug testing should be performed monthly or more or less frequently as required when clinically indicated and at the discretion of the clinician to confirm self-reported abstinence from unregulated opioid use and/or when treatment plan changes to include take-home dosing and when UDT results would change clinical management. More frequent urine drug tests are not necessarily required if ongoing substance use is fully disclosed by the patient.

Following initiation, and once a patient has stabilized on a given dose of OAT, UDT should be performed when the results would change clinical management. Patients who miss UDT appointments should be reassessed as this may indicate risk of return to unregulated opioid use or diversion.

Table 29. Suggested Urine Drug Testing Frequency

Treatment stage	UDT schedule
Initial confirmatory testing	Performed to confirm unregulated opioid use prior to initiating OAT[ww]
Buprenorphine/Naloxone	
Induction and stabilization	Monthly or more or less frequently as required and when clinically indicated
Maintenance	When clinically indicated
Take-home doses	2–4 tests per year or when there are any safety concerns Frequency of UDT is as required when clinically indicated
Methadone and slow-release oral morphine	
Initiation, titration, and stabilization	Monthly or more or less frequently as required and when clinically indicated. In circumstances where UDT is occurring less than monthly, patient safety can be increased with daily witnessed ingestion.[xx]
Maintenance	When clinically indicated
Take-home doses	6–8 tests per year or when there are any safety concerns Frequency of UDT is as required when clinically indicated

[ww] Although best practice, there may be situations in which it is reasonable to forgo prior to initiating OAT (e.g., virtual care in a remote setting with significant collateral information, where requiring UDT would constitute an unreasonable barrier; emergency department induction with significant collateral information; a patient who has been abstinent but is at risk of relapse).

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A5.2 Immunoassay-based UDT

Point-of-care urine immunoassay-based drug testing is useful for providing immediate feedback to patients, supporting real-time discussions and shared decision-making (e.g., prescribing take-home doses). Physicians are compensated through MSP (fee code P15039) for performing and interpreting point-of-care UDT as part of opioid agonist treatment up to a maximum of 26 UDT per patient per year; however, UDT should only be performed for a specific purpose and according to therapeutic need. For that reason, many patients will require far fewer than 26 UDT per year.

If point-of-care immunoassay-based UDT is unavailable or infeasible because of low patient volume or cost considerations, patients can be referred or urine samples collected in clinic can be sent to a local laboratory service for immunoassay-based UDT.

Point-of-care UDT are typically available for the following substances:

- Opiates (unspecified)
- Oxycodone
- Buprenorphine
- Methadone metabolite (EDDP)
- Fentanyl
- Hydromorphone
- Benzodiazepines (unspecified
- Amphetamines (unspecified)
- Cocaine metabolite
- Cannabinoids
- Alcohol

It is important to note that the immunoassay opiate test strip panel is designed to detect morphine or substances in which morphine is a metabolite, including heroin and codeine. The immunoassay opiate test strip cannot reliably detect synthetic and semi-synthetic[yy] opioids such as methadone or fentanyl. Individual tests for semi-synthetic and synthetic opioids are available but must be ordered separately.

Vendors typically offer a standard panel that includes tests for several substances. Clinicians should review what is included in standard panels prior to ordering and request additional single-agent test strips if a substance of interest is not included in the panel (e.g., buprenorphine, fentanyl). Given the wide-spread contamination of the street drug supply in British Columbia, point-of-care tests should include fentanyl.

Availability and accuracy of tests vary by product and manufacturer. Clinicians should carefully review the manufacturer's product insert to determine which drugs within a class are detected. A point-of-care UDT for a particular drug class (e.g., benzodiazepines or opioids) should *not* be assumed to include all possible drugs within that class. Test strip cut-offs should also be noted, as cut-offs can differ based on test settings (e.g., for medical

[yy] Although hydromorphone is a semi-synthetic opioid, many immunoassay opiate panels are able to detect it.

monitoring, opiates have a standard cut-off of 300ng/mL, while the standard cut-off for workplace testing is 2000ng/mL).

A5.3 Confirmatory Testing

Laboratory confirmatory testing using gas-chromatography/mass spectrometry or liquid-chromatography/mass spectrometry provides greater sensitivity, specificity, and accuracy compared to immunoassay-based testing. Confirmatory testing can determine the presence of specific drugs, particularly semi-synthetic and synthetic opioids. As such, confirmatory testing can be used to identify drugs that are not included in immunoassay panels or are not detectable in immunoassay panels (e.g., tramadol)[494] and it is useful when a patient is prescribed more than one opioid or is prescribed an opioid that has active metabolites.[495] In addition, it can be used to resolve cases of false-positive results.[496]

Confirmatory testing is only covered through MSP in cases in which the presence of the drug would significantly impact the clinical management of the patient. Because confirmatory testing is expensive, it should only be requested when clinically indicated and when accurate test results are required to make important treatment decisions.

Availability, cost, and general processes for requesting UDT for specific substances should be confirmed with local laboratory services. Clinicians must specifically indicate confirmatory testing after a positive test result on the laboratory requisition, otherwise an immunoassay-based UDT will be performed as the default option.

The results of confirmatory testing must be interpreted cautiously, given that some opioids have active metabolites.[495] For example, the presence of morphine according to confirmatory testing may be due to the metabolism of codeine, an over-the-counter opioid, rather than heroin or a non-prescribed opioid.[495,496]

A5.4 Slow-release Oral Morphine Urine Drug Testing

For patients treated with slow-release oral morphine, standard point-of-care opiate test strips and panels will be positive for morphine metabolites. Patients may have a positive UDT result for hydromorphone due to high morphine levels[zz]; however, this does not necessarily indicate hydromorphone has been taken. In addition, it is impossible to distinguish unregulated heroin use from prescribed slow-release oral morphine using these tests.[496] Clinicians can consider using specific point-of-care UDT for fentanyl to assess unregulated opioid use as needed to supplement clinical assessment and further patient–clinician discussion of ongoing substance use. LifeLabs

[zz] Morphine is metabolized to hydromorphone by a minor pathway. With low doses of morphine, the amount of hydromorphone may not be detectable. However, individuals prescribed slow-release oral morphine for the treatment of OUD are prescribed relatively high doses, which can lead to concentrations of hydromorphone well above the cut-off being detected in their urine.

and other local or hospital laboratories are able to perform confirmatory testing that can distinguish between unregulated heroin and prescribed SROM.

Mass spectrometry can distinguish between heroin, acetaminophen with codeine, and SROM as follows:

- Heroin: variably high morphine, 5–10% codeine, heroin metabolite 6-acetylmorphine (6-AM) may be present
- Acetaminophen with codeine (Tylenol #3): high codeine, relatively low morphine
- Slow-release oral morphine: very high morphine, trace levels of codeine (i.e., <50 mg/mL)
- These data may not be reported unless specifically requisitioned for individuals on SROM, point-of-care urine drug tests will be positive for the morphine metabolite and it may be difficult to distinguish on UDT between unregulated heroin and prescribed slow-release oral morphine
- However, the prevalence of fentanyl makes this less clinically important, as not many people in BC are using heroin alone if they are using unregulated opioids

A5.5 Urine Drug Testing and Virtual Care

Virtual care (e.g., telehealth, video conferencing software) is increasingly being used in OUD care. This can help reduce barriers for individuals who have to travel to see their prescriber (e.g., in rural and remote locations). It is important for clinicians to consider each patient's circumstances when ordering UDT through virtual health. Clinical judgement should be used to determine when virtual UDT is appropriate and necessary, prioritizing patient safety and the avoidance of unreasonable barriers for patients.

If UDT is clinically indicated, there are several options for clinicians to consider when ordering UDT for patients through virtual health.

- Clinicians can request that the patient present to a local laboratory to provide a urine sample.
- Patients can be directed to a clinic location that has staff available to conduct a UDT and the prescribing clinician can then follow up on the results with the patient.
- If the patient is staying in a shelter or supported housing, the staff in the shelter may be able to conduct the UDT and support the patient to connect with the prescribing clinician.
- Clinicians can also use collateral sources (e.g., Meditech, Cerner, or CareConnect) if a patient has recently had a UDT ordered by another clinician.

APPENDIX 6.0: TAKE-HOME DOSING

Take-home dosing (carries) of OAT may increase motivation to participate in opioid agonist treatment, improve treatment retention, facilitate virtual care, and enhance quality of life by increasing patient autonomy and flexibility and decreasing treatment burden. Carries also decrease costs related to daily witnessed ingestion. However, these benefits must be balanced against patient and public safety considerations. See Take-home OAT Dosing for a review of evidence informing take-home dosing guidelines.

The criteria and limitations for take home dosing of each medication should be discussed with patients prior to treatment initiation, as this information may impact treatment selection.

Considerations for individuals in rural and remote areas

Early and flexible provision of take-home dosing is a particularly important consideration for individuals who live in rural and remote communities, as daily travel to pharmacy may not be a feasible or sustainable requirement for this population. When determining the individualized criteria for take-home dosing in this population, prescribers should weigh medication safety concerns against the risks associated with loss of patient to care and their continued reliance on the unregulated drug supply.

Considerations for patients who use other CNS depressants

Due to the increased risk of overdose when full opioid agonists are combined with other CNS depressants, benzodiazepines and other sedative medications should generally not be prescribed concurrently with opioid agonist treatment, particularly when take-home doses are being considered. Clinicians should ask patients whether they are using any CNS depressants, and offer information on the risks of combining these with opioid agonists.

As per CSPBC guidance, PharmaNet should also be reviewed at each clinical visit to confirm that another care provider has not prescribed these medications.

A6.1 Buprenorphine/naloxone

Take-home dosing should be considered for all patients who meet the following criteria:

- Clinical and psychosocial stability
    - Generally, the indications of clinical and psychosocial stability include:
        - Ability to attend appointments
        - Absence of unstable psychiatric comorbidities (e.g., psychosis, suicidality)
        - Absence of severe behavioural issues at the clinic
        - Absence of severe sedation

        - Absence of high-risk or uncontrolled substance use patterns that cause frequent overdoses or blackouts
    - Point-of-care assessment of stability is patient-specific, depending on each patient's circumstances and needs and how they change over time.
- Ability to safely store medication (access to a secure lockbox or cabinet)

Take-home doses may be considered immediately for patients who meet the above criteria, as quick transition to take-home dosing is associated with improved treatment adherence and retention.[248,249] In a study of commercial claims data (n=17,159) in the US, receiving fewer (i.e., ≤15) days of take-home doses in the initial prescription was associated with increased odds of discontinuing treatment (adjusted odds ratio=1.32, p<0.01) as well as increased odds of opioid-related adverse events (suggesting relapse or overdose), the majority of which occurred after treatment discontinuation. The increased odds of opioid-related events[aaa] remained even after treatment discontinuation was controlled for.[497]

If concerns exist around the appropriateness of take-home dosing, the impact of providing or limiting take-home dosing on treatment adherence or loss to care should be considered. If take-home doses are determined to not be clinically appropriate, the rationale for not prescribing take-home doses should be carefully documented in the medical record and explained to the patient.

Individuals experiencing homelessness may especially benefit from immediate take-home dosing, as they may not be able to return to the same pharmacy each day due to the realities of homelessness and the requirement for frequent moves (e.g., from one shelter to another). Co-occurring substance use should not be considered an absolute contraindication for take-home dosing. Patients should receive education on the risks associated with co-occurring substance use and the option to initiate treatment for co-occurring substance use disorders.

A6.1.i Considerations for Safely Maintaining a Patient on Take-home Buprenorphine/naloxone

- Buprenorphine/naloxone can be initially prescribed as a 1- to 2-week supply. This is for the purpose of following up to establish the effectiveness of dosage; longer prescription intervals may be appropriate once a stable dose has been established.
- Clinicians should monitor patient for signs of increase in unregulated opioid use and new use of sedating agents (e.g., alcohol, benzodiazepines), other signs of instability, and/or diversion.
- When clinically indicated, urine drug tests (UDTs) may be requested to confirm medication adherence.
    - If UDT is indicated, assure the patient that this test is intended to confirm the presence of buprenorphine, and that the results will not be used punitively.

[aaa] Defined as at least one ED visit or inpatient admission involving opioid poisoning, dependence, or abuse within 360 days of initiation.

- When appropriate, clarify to the patient that the presence of other unregulated substances is not necessarily grounds for discontinuation of carries.

A6.1.ii Monitoring of Take-home Buprenorphine/naloxone Dosing

Patients receiving take-home buprenorphine/naloxone should be seen at least monthly to assess progress and stability. Once the patient is stable, intervals between planned visits may be prolonged (e.g., to 8 weeks) at the prescriber's discretion, provided that the patient is able to reach the prescriber remotely or in person if urgent support is needed.

Prescribers should be vigilant in monitoring for signs of increased unregulated opioid use, alcohol and other (non-opioid) substance use, psychosocial instability, and diversion. The following are considerations for follow-up and reassessment:

- Self-reported or other indication of increase in unregulated opioid use
- Missed appointments or doses, or repeated reports of lost, stolen, or vomited doses
- Requests to increase a previously effective dose
- Other evidence of diversion (e.g., tampering with blister packs, UDT negative for buprenorphine, repeated inability to provide urine samples)

Before take-home prescriptions are reduced or discontinued, the prescriber must balance the risks of destabilizing patients by enforcing daily dispensation of medication. Daily witnessing of this medication has not been shown to improve outcomes and is a recognized barrier for treatment engagement.[247] In addition, the buprenorphine/naloxone formulation was created to facilitate take-home dosing and make treatment more attractive to patients due to its safety profile and lower risk of diversion.

For patients prescribed take-home buprenorphine/naloxone showing signs of major clinical or psychosocial instability, individual patient circumstances should be considered when reducing the number of take-home doses of buprenorphine/naloxone, as limiting take-home dosing may result in loss to care. Following discussion with the patient about any underlying issues contributing to treatment instability, clinicians can consider:

- Increasing the frequency of clinical appointments in order to provide more intensive support, monitoring and assessment
- Providing referrals to adjunct psychosocial and community-based supports, as appropriate

If treatment intensification does not adequately address clinical or psychosocial instability, clinicians and patients can consider transitioning from buprenorphine/naloxone- to full agonist treatment.

Evidence of diversion should prompt a reassessment of the treatment plan, and, in some cases, reduction or discontinuation of take-home dosing with consideration of dose reduction if doses have been missed.

- A negative UDT result for buprenorphine suggests that the patient has not taken this medication for many days. In this case, discuss reasons why and, if appropriate, consider discontinuing buprenorphine/naloxone and transition to another OAT medication with the patient.
- Evidence of falsified UDT sample should prompt a supportive, non-judgmental discussion with the patient regarding whether the current treatment plan is helping them achieve their goals. A new sample should be requested to help make modifications to the treatment plan. Patients should not be asked to leave treatment.

A6.2 Methadone and Slow-release Oral Morphine

Due to their inferior safety profile, more restrictive considerations are advised for the provision of take-home methadone doses of full agonist OAT options in comparison to buprenorphine/naloxone, in order to minimize individual and public safety risks. Past guidelines set very strict criteria for access to methadone take-home doses, and discouraged any take-home SROM doses. More recent data, however, has suggested that increased access to carries can be safe for many patients who are stable on their medication, and can potentially improve treatment retention for select patients. *Ontario's META-PHI* has recently developed *A New Framework for Methadone Carries: A Person-centred Evidence-informed Approach to Take-home "Carry" Dosing*, outlining criteria and considerations for starting and extending take-home methadone doses in the interest of reducing barriers to the sustainability of methadone care for patients. The guidance provided below for methadone and SROM take-home doses has been developed in reference to these considerations.

The decision to initiate take-home doses can only be made by the prescribing clinician in collaboration with the patient and with case-by-case consideration of risks and benefits. Particular caution should be exercised when considering take-home doses for patients who are still in the titration phase; for these patients, frequent pharmacy visits may be a safety necessity.

Rationale for decisions regarding take-home doses, including confirmation that criteria listed below have been met, should be clearly documented. Clinicians must ensure that take-home doses are safe for both patients and the public, as unsafe storage, non-prescribed use, and diversion of methadone or SROM may result in lethal consequences.

A6.2.i Patient Criteria for Methadone and SROM Take-home Doses

Prior to prescribing take-home methadone or SROM doses, the following patient criteria should be met:

- Appropriate UDT results (e.g., evidence of medication adherence) for a minimum of 4 weeks
- Ability to safely store OAT medication (e.g., locked containers or cabinets)
- Clinical and psychosocial stability (i.e., ability to keep appointments and manage medication; no severe psychiatric issues, such as psychosis or acute suicidality, at the point of assessment;

no high-risk substance use patterns that cause frequent overdoses, blackouts, or hospitalizations)

Take-home methadone and SROM dosing schedules for patients who meet the above criteria should start as a single take-home dose per week. The number of take-home doses per week can be increased gradually (e.g., every 1–2 weeks). The patient will progress from 1–3 non-consecutive take-home doses, then to 4–6 consecutive take-home doses. However, clinical discretion may dictate a faster increase in the number of take-home doses in consideration of patient-specific circumstances, (e.g., wok schedules, rural or remote location, pharmacy hours, or previous successful experience with tak-home doses).

Beyond the time frames specified in Table 30, additional take-home doses can continue to be offered gradually (e.g., every 2 weeks) to patients who have consistently been able to manage previous take-home doses, sustain medication adherence, and experience improving clinical and psychosocial stability including reduction in substance use in alignment with patient's treatment goals.

Table 30. Suggested Protocol for Methadone and SROM Take-home Doses

Number of take-home doses per week	Minimum time on methadone/SROM	Conditions/Criteria
0 (Not a candidate for take-home doses)	–	Any of: • Inability to safely store medication • Unstable psychiatric illness or other acute mental health crisis • Frequent missed doses and appointments • Ongoing high-risk or uncontrolled substance use patterns (e.g., causing frequent overdoses, blackouts, or hospitalizations)
1–3 (non-consecutive take-home doses)	4 weeks	All of: • Ability to safely store medication • Evidence of medication adherence (e.g., UDT positive for methadone) • Clinical and psychosocial stability, including: ○ Ability to keep appointments and manage medication

		○ No acute behavioral or psychiatric issues at point of assessment ○ No high-risk or uncontrolled substance use patterns that cause frequent overdoses, blackouts, or other severe safety risks
4–6 (consecutive take-home doses)	12 weeks	All of: • Consistent medication adherence with rare missed doses and appropriate management of non-consecutive take-home doses • Improved clinical and psychosocial stability, including: ○ Rare missed appointments ○ Minimal unprescribed substance use, in alignment with treatment plan and patient goals, with no recent overdoses or blackouts

Adapted from META-PHI's *A New Framework for Methadone Carries: A Person-centred Evidence-informed Approach to Take-home "Carry" Dosing*.

It is advised that the first dose be provided as DWI in the pharmacy on the day the prescription is picked up. Prior to dispensation of take-home doses, patients should be informed of the risks of infection associated with injection use of medications intended for oral use. This discussion may be particularly relevant for SROM, as methadone and buprenorphine/naloxone have properties that reduce the risk of injection use (i.e., presence of naloxone, and high liquid volume, respectively).

Take-home doses should be dispensed in individual, appropriately sized, child-resistant containers. Containers with tamper-proof seals may also be available at some pharmacies, and should be requested if available.

A6.2.ii Monitoring of Take-home Dosing for Full Agonist OAT Medications

Patients receiving take-home methadone or SROM dosing should be seen at least monthly to assess progress and stability. Prescribing clinicians should be vigilant in monitoring for signs of increased unregulated opioid use, alcohol and other (non-opioid) substance use, psychosocial instability, and diversion.

When clinically indicated, UDT may be requested to confirm medication adherence, or in collaboration with a patient to gain clinically relevant information about self-reported unregulated substance use. Prior to conducting the test, clearly explain to the patient that the test is intended to confirm the presence of OAT medication, and

that the results will not be used punitively. When appropriate, clarify that the presence of other unregulated substances is not necessarily grounds for discontinuation of carries.

The following are considerations for follow-up and reassessment:

- Self-reported or other indication of increased use of unregulated opioids and other CNS depressants
- Missed appointments or doses, or repeated reports of lost, spilled, stolen, or vomited doses
- Requests to increase a previously stable dose
- Unable to attend the clinic or lab for UDTs

For patients prescribed take-home methadone or SROM showing signs of instability, prescribing clinicians should consider reduced take-home dosing days per week or complete return to DWI if appropriate, following discussion with the patient. Clinicians should also increase the frequency of clinical appointments and provide referrals to adjunct psychosocial treatment and community-based supports. If treatment intensification and adjunct support does not address issues underlying instability, clinicians and patients can consider transitioning to an alternative opioid agonist treatment.

Evidence of diversion (e.g., UDT results negative for OAT) warrants return to prescribing witnessed doses following a discussion with the patient to ensure that the medication is appropriately meeting their needs. Transition to another medication may be collaboratively considered where appropriate. In the case of negative UDT results for OAT, prescribers should assess loss of tolerance and consider restarting or resuming OAT at a lower dose, as needed, to minimize risk of overdose.

APPENDIX 7.0: CONTINUING CARE

As with any chronic condition, individuals with opioid use disorder should receive comprehensive and continuing care. This should include ongoing review and assessment of the following:

- Adequacy of dosage
- Any emerging side effects and drug–drug interactions
- Patient's treatment goals
- Physical and mental health
- Need for, and access to, harm reduction services and supports
- Psychosocial wellbeing and need for related supports including housing, relationships, finances, and connection to cultural services and supports

Ongoing periodic prescriber appointments can be used for building therapeutic relationships, providing education about harm reduction and safe injection practices, offering supports and referrals to appropriate services, and promoting health and healthy behaviours.

Urine drug testing can be used to help guide patient care, to ensure patients are aware of which substances they are ingesting if using unregulated substances, and to start a conversation on harm reduction and safety. Urine drug testing should never be used as a punitive measure; it should only be offered when clinically indicated with the informed consent of the patient. See Appendix 5 for more information on urine drug testing.

A7.1 Concurrent Mental Health Concerns

Mental health and substance use disorders frequently present concurrently. Twelve-month prevalence rates for adults in the US with substance use disorder and any concurrent mental health disorder were 43.3% in 2016,[498] while over 50% of individuals with a severe mental illness are estimated to have problematic substance use.[499] Looking specifically at opioid use disorder, an observational study of individuals receiving methadone-based OAT in Ontario found that 78.5% met diagnostic criteria for at least one comorbid psychiatric disorder, with anxiety disorders most common.[500] A 2017 meta-analysis examining the treatment of mood and anxiety disorders in individuals receiving OAT found psychotherapy and tricyclic anti-depressants most effective. Selective serotonin reuptake inhibitors (SSRIs) were not significantly better than placebo.[501]

All patients who present with opioid use disorder should be screened for concurrent mental health disorders, and those who screen positive should receive evidence-based treatment for both conditions. To support effective integrated care for individuals with concurrent substance use and mental health disorders, the Substance Abuse and Mental Health Services Administration (SAMHSA) has developed the Four Quadrant Model, an integrated and collaborative care model wherein the locus of care is dependent on the severity of each disorder.[502] In this model, mild to moderate concurrent substance use and mental health disorders are treated in outpatient care settings, while individuals who experience a more severe substance use disorder are treated in an addiction care

setting and individuals who experience a more severe mental health disorder are treated in mental health care settings.[502]

While concurrent treatment is recommended, stabilization on OUD treatment—including initiation of OAT—may be initially prioritized for patients with severe OUD in cases where simultaneous initiation of treatments is not feasible, in order to mitigate the risk of drug toxicity death.

A7.2 Ongoing Substance Use

Ongoing substance use while on OAT may be an indication to discuss the patient's treatment goals and modify treatment accordingly. Possible treatment modifications may include dose increases, transitioning to another OAT medication, or increasing psychosocial and other supports. Patients should be advised of the risk of overdose due to contamination of the unregulated drug supply with fentanyl and other highly potent synthetic opioids (including non-opioid substances such as benzodiazepines and stimulants) and receive education on harm reduction strategies and, where possible, access to a variety of harm reduction resources, including:

- Take-home naloxone (a list of locations offering naloxone kits and training is provided on Toward the Heart's Take-Home Naloxone Programs website)
- Drug checking services
- Observed consumption services
- Test strips for fentanyl and benzodiazepines[bbb]
- Overdose prevention apps, such as the Lifeguard app, if the person is using alone
- The Toxic Drug and Health Alerts text messaging system

A7.2.i Unregulated Opioids

Continued use of unregulated (non-prescribed) opioids while on OAT, ascertained by self-report or urine drug test (see Appendix 5 in this document), should be considered as a possible indication to discuss treatment modification to better meet the patient's needs. Discussions and decisions regarding ongoing unregulated opioid use should be informed by the patient's personal treatment goals; some individuals' goals may include reduction in, rather than absolute cessation of, unregulated opioid use. In such cases, harm reduction and overdose prevention measures should be discussed and reinforced.

In cases where treatment modification is indicated, clinical judgment should be used in determining what specific types of adjustment are appropriate. Modifications to address ongoing unregulated opioid use may include dose adjustment, transitioning to another OAT or iOAT medication, or increasing psychosocial

[bbb] It should be noted, however, that drug-checking and fentanyl test strips are not well validated and are not available in all areas of the province.

supports. If a patient is continuing to use unregulated opioids at the same intensity despite intensification of treatment, their reasons for continued reliance on the unregulated drug supply should be explored collaboratively, and clinical judgment should be used to determine appropriate follow up. Prescribed safer supply may be an appropriate harm reduction option to consider at this point.

A7.2.ii Stimulants

If patients are using stimulants (e.g., cocaine or methamphetamine) while receiving OAT, consider increasing psychosocial interventions and supports, such as implementing contingency management.[503] In some cases, it may be beneficial to consider combining OAT with bed-based treatment, which will facilitate the close monitoring and the incorporation of psychosocial strategies to reduce stimulant use (e.g., counselling, contingency management).[504,505]For more information on treatment options for stimulant use disorder, please see the BCCSU's Stimulant Use Disorder Practice Update.

A7.2.iii Sedatives (alcohol and benzodiazepines)

Ongoing sedative use may indicate a need to modify treatment. Clinical judgment should be used to determine which interventions are appropriate for each patient.

Alcohol

Co-occurring use of alcohol and opioids is associated with an increased risk of respiratory depression, overdose, and death.[506,507] Approximately one-third of individuals prescribed OAT for the management of opioid use disorder also meet the criteria for high-risk drinking or an alcohol use disorder (AUD).[508-511] Although alcohol use is a known risk factor for fatal overdose among individuals prescribed opioids,[512-514] and associated with suboptimal adherence to OAT,[515,516] there is limited guidance on effective management strategies for this patient population.[517]

For individuals on OAT who meet criteria for high-risk drinking but do not have an AUD, physician or nurse-delivered brief intervention has been found to reduce alcohol consumption in RCTs[518,519] and non-randomized studies.[520-522] Motivational interviewing may also be effective for reducing high-risk drinking in patients prescribed OAT.[523,524] For patients diagnosed with co-occurring alcohol use and opioid use disorders, AUD pharmacotherapy should be offered with consideration of drug-drug interactions with OAT, as applicable.

Opioid agonist treatment selection for patients with co-occurring alcohol use disorder:

Buprenorphine/naloxone may be a preferred OAT medication in this patient population due to its superior safety profile, including lower risk of respiratory depression and overdose when used alone or in combination with alcohol.[116] However, to ensure engagement in treatment, clinicians should view patient preference and individual circumstances as key consideration in mediation selection; continued unregulated opioid use poses a higher risk of harm to than any OAT medication. For more information on treating individuals with co-

occurring AUD and OUD, please see the BCCSU's Managing Co-occurring Opioid Use and Alcohol Use Disorders bulletin.

Alcohol use disorder pharmacotherapy for patients on OAT:

For individuals on OAT who also have a diagnosis of AUD, acamprosate should be considered along with evidence-based psychosocial treatment interventions and supports for treating concurrent alcohol use disorders.[525,526] Acamprosate has an established evidence base for safety and efficacy for the treatment of AUD,[525-529] and does not pose significant safety risks when used concurrently with CNS depressants.[530]

Topiramate may be considered with for the treatment of AUD in patients who are also on OAT in cases where acamprosate is not appropriate. Topiramate has not been well studied for the treatment of alcohol use disorder in patients with concurrent opioid use disorder. However, the efficacy of this medication for the management of AUD is supported by an established body of evidence,[431,432] and it is not contraindicated for patients who use CNS depressants concurrently.[531]

Caution should be exercised when considering gabapentin for alcohol use disorder treatment for a patient on OAT. Although gabapentin has a growing evidence base supporting its use for withdrawal management[532-535] and preliminary evidence supporting its use in relapse prevention for alcohol use disorder,[536-538] this medication may potentiate the euphoric effects of opioids and increase the risk of respiratory depression and overdose if used at moderate-to-high doses concurrently with opioids.[539,540] A 2017 Canadian study found that concomitant use of opioid medications and gabapentin increased the risk of fatal overdose by 49%, with moderate and high daily doses increasing the fatal opioid overdose risk by 60% compared to those with no concomitant gabapentin use.[540] If these medications are co-prescribed, clinicians should be aware of these risks and monitor patients appropriately.

Due to its effects on opioid receptors, naltrexone cannot be used to treat alcohol use disorder in patients who are on OAT. However, individuals with both alcohol use and opioid use disorders who are not taking OAT may benefit from extended-release naltrexone, as there is evidence that it is effective for both conditions.[20,541]

For more guidance on treating alcohol use disorder, see the BCCSU, Ministry of Health, and Ministry of Mental Health and Addiction's *Provincial Guideline for the Clinical Management of High-Risk Drinking and Alcohol Use Disorder*.

Benzodiazepines

Co-occurring use of benzodiazepine receptor agonists (BZRAs; benzodiazepines and z-drugs) and opioids significantly increases the risk of respiratory depression, overdose, and death.[542-545] When prescribing OAT, all patients should receive education on the risks of combining opioids and BZRAs, even if medications are taken as prescribed.

Benzodiazepines should be included in urine drug tests for individuals who use unregulated opioids and/or those who are on OAT. However, clinicians and patients should be aware that some benzodiazepines and benzodiazepine analogues (e.g., alprazolam, clonazepam, etizolam, temazepam, triazolam) may not be detected in standard urine drug tests despite the patient having been exposed.

Traditionally, prescribing OAT to patients also taking benzodiazepines has been contraindicated.[546] However, in light of the high risk of overdose death associated with unregulated opioid use, it is not advised to delay or withhold OAT for patients who use benzodiazepines or if benzodiazepine exposure through the unregulated drug supply[ccc] is suspected.[546] However, patients should not be started on OAT while sedated.[ddd]

As soon as a patient is stabilized on OAT, the prescribing clinician should review the indication for BZRA use and diagnose any underlying sedative use disorder. The clinician should inform the patient of the risks of concurrent opioid and BZRA use and offer to initiate a BZRA taper. During a BZRA taper, consider dispensing BZRAs at the same frequency as OAT medications; monitor patients closely for symptoms of opioid withdrawal, as breakthrough symptoms can emerge when BZRA dose is reduced[547]; and advise patients that any take-home OAT and BZRA doses must be safely stored (e.g., in a locked box).

Inadvertent benzodiazepine exposure and dependence

Care providers should be aware of the harms associated with inadvertent benzodiazepine exposure or dependence through the use of unregulated opioids. Since the introduction of benzodiazepine testing to BC's drug checking services in October 2018, an upward trend in the proportion of benzodiazepine-adulterated opioid samples has been observed, with a rapid increase documented since mid-2020.[548-550] In July 2022, 32% of opioid samples tested in Vancouver drug checking facilities contained benzodiazepines, which is more than 3 times the proportion (9%) of benzodiazepine-positive samples found in August 2020.[550] Vancouver Island Drug Checking Project, which uses a more advanced testing technology capable of reliably detecting benzodiazepine analogues such as etizolam, found benzodiazepines and etizolam in 46% of expected opioid samples collected in July 2022.[551] Several novel benzodiazepine analogues have been identified in drug samples that were sold as opioids, including etizolam, bromazolam, flualprazolam, and flubromazepam.[549,552] These benzodiazepine analogues can be significantly more potent than pharmaceutical-grade benzodiazepines such as diazepam (Valium) and alprazolam (Xanax).[552]

Patients who reduce or discontinue the use of unregulated opioids (e.g., individuals starting OAT) should be monitored for symptoms of benzodiazepine withdrawal. Benzodiazepine withdrawal management in such cases requires individual assessment and treatment planning. If benzodiazepine withdrawal is suspected, clinicians are

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[ccc] For more information about the prevalence and implications of benzodiazepine exposure among people who use opioids, refer to the BCCSU's clinical bulletin on Benzodiazepines and Opioids (2021).

[ddd] For guidance on OAT initiation, refer to Appendices 1, 2, and 3 of the BCCSU/MOH Guideline for the Clinical Management of Opioid Use Disorder.

encouraged to provide supportive care and contact the 24/7 Addiction Medicine Clinician Support Line or the RACE App for case-based consultation.

Patients who continue to use unregulated opioids should receive information and education regarding the risk of overdoses involving a mix of opioids and benzodiazepines. According to BC Coroner's Service toxicology reports, benzodiazepines were detected in 42% of suspected overdose deaths between July 2021 and August 2022.[553,554] Opioid-benzodiazepine overdoses result in atypical and protracted overdose events that can be difficult to reverse.[549,555]

- Patients should be informed that overdoses involving a mix of opioids and benzodiazepines are different from other opioid overdoses in that they may last for several hours even after naloxone administration; however, naloxone should always be used in the event of an overdose as it can reverse the effects of opioid overdose and restore breathing.
- Patients should also be informed that benzodiazepine analogues may not be detected through drug-checking or urine drug testing; harm reduction precautions are recommended even in the case of negative drug checking results for benzodiazepine analogues.
- Education resources for people who use drugs and members of the community for responding to a suspected overdose involving benzodiazepines are available at the Toward the Heart website:
    - Do I Keep Giving Naloxone?
    - Opioids and Benzos or Etizolam

For more information on the detection and management of overdoses involving benzodiazepines, refer to the BCCSU's Clinical Bulletin: Benzodiazepines and Opioids.

A7.2.iv Tobacco

Mortality in smokers is almost three times higher than in non-smokers,[556] and is causally linked to significant morbidity including pulmonary disease, coronary heart disease, chronic obstructive pulmonary disease, diabetes mellitus, and multiple cancers including lung, esophageal, and stomach.[557] A 2018 population-based study found that 39% of deaths in individuals with opioid use disorder were due to smoking-related conditions.[558] Disproportionately high rates of tobacco use have been found in individuals receiving treatment for opioid use disorder compared to general population prevalence rates.[559-562]

Although tobacco use disorder is commonly undertreated in addictions treatment,[563] a 2016 Cochrane systematic review found a consistent association between tobacco cessation interventions—both pharmacotherapy and counselling combined with pharmacotherapy—and tobacco abstinence in individuals in treatment and recovery for substance use disorders, with no evidence showing an effect on abstinence from alcohol and other drugs.[564] Despite common assumptions to the contrary, 44–80% of individuals receiving substance use disorder treatment are interested in tobacco cessation.[565]

Evidence-based treatments for tobacco use disorder, including nicotine replacement therapy, varenicline, and bupropion, should be integrated into primary care and opioid use disorder care.

A7.2.v Cannabis

Patients who are using cannabis recreationally may benefit from a discussion of the recommendations made in the Lower-Risk Cannabis Use Guidelines.[566] Patients who are using medicinal cannabis should be monitored by their OAT prescriber to ensure the benefits they receive outweigh the potential harms.

A7.2.vi Psychedelics

Clinical experience has shown that some individuals have tried to self-treat their opioid use disorder with psychedelics. Patients reporting psychedelic use should receive education on harm reduction and should be advised that there is no evidence to date that psychedelics can be used to treat opioid use disorders.

A7.3 Acute Care and Inpatient Considerations

Individuals with OUDs may have comorbidities which put them at increased risk for hospitalization for acute or chronic physical or mental health conditions.[567,568] This should be used as an opportunity to initiate or optimize OUD care.

Several considerations are relevant for acute and inpatient settings, which include planning, ensuring ongoing OAT dosing, initiating OAT, and pain management and perioperative considerations. Although specific to Alberta, CRISM Prairies' *Management of Substance Use in Acute Care Settings in Alberta: Guidance Document* provides guidance relevant to acute care settings in BC as well.

A7.3.i Admission to Acute Care

The following care components should be developed in order to support continuity of OUD care:

- Protocol in place for hospital staff to assess for signs and symptoms of withdrawal from substance use
- Protocol in place for acute care prescribers and addiction medicine consult services to contact the community prescriber
- Protocol in place for the hospital team providing care to access date and last dose received by patient (e.g., through PharmaNet check[eee] and call to pharmacy)

[eee] PharmaNet does not provide information about the current day's doses as pharmacies usually cancels missed doses on PharmaNet at end of day.

- Protocol to cancel the community prescription when appropriate, to avoid double-dosing as hospital medications do not appear on PharmaNet
- Protocol in place to include continuity of OUD care discharge planning (e.g., a bridging prescription, arranging follow-up appointment with a community prescriber, offering harm reduction information and supplies)
- Protocol in place to provide patients with harm reduction education and supplies, and to connect them to community-based harm reduction services (e.g., the Lifeguard app, overdose prevention sites, supervised consumption sites)

A7.3.ii Maintaining Stable OAT Dosing

Individuals on OAT who present for acute care, surgical intervention, or who require inpatient care should receive their regularly prescribed OAT, when medically safe to do so, to prevent withdrawal symptoms, cravings, destabilization, self-discharge against medical advice, and return to unregulated use.[569,570] In some cases, OAT dose adjustments may be necessary to address emerging withdrawal symptoms or opioid cravings for patients who used unregulated opioids in addition to OAT prior to admission to inpatient care. Additionally, pain management needs should be considered separately from OAT (see Pain Management and Perioperative Considerations).

Prescribers who do not have experience prescribing OAT in hospital settings may consult their Addiction Medicine Consult Team (where applicable), the RACEapp, or the 24/7 Addiction Medicine Clinician Support Line.

A7.3.iii Pain management and perioperative considerations

Adequate pain management is vitally important to successful inpatient care. Poor management of pain and withdrawal symptoms in inpatient settings is significantly associated with self-discharge against medical advice and a range of negative outcomes including worsening of illness, or exacerbation of unregulated opioid use and related risks of harm, re-admission, and death.[568]

Despite these established risks, there are, to date, no guidelines for treating acute pain in individuals with opioid use disorder, and most of the limited evidence regarding acute pain in this population concerns perioperative considerations. A 2019 review article published in *Expert Opinion on Pharmacotherapy* provides some relevant guidance for the treatment of acute pain in individuals with OUD,[570] which largely accords with guidance contained in an evidence brief from the Evidence Synthesis Program at the US Department of Veterans Affairs.[571] Available evidence and guidance, including CRISM Prairies' *Management of Substance Use in Acute Care Settings in Alberta: Guidance Document*, indicate that patients' OAT dose should be continued,[571] and may be increased, split, or increased and split to treat pain.[570,572] Methadone may be given parenterally in patients who are unable to take their doses orally.[570] The baseline OAT dose will not address acute pain.[570,571] In situations where more than one opioid is prescribed, the duration of opioid co-prescribing should be pre-determined when possible, and the patient should be informed of the timeline at the outset.[570] it should be noted that higher than average

doses of short acting opioids will likely be needed to manage acute pain in patients on OAT given their increased tolerance to opioids. Non-opioid adjuncts (e.g., clonidine)[570,573] may be considered for pain control.

The literature on perioperative conditions for individuals on OAT is limited. However, a 2019 systematic review of controlled studies, observational reports, and case studies (N=18 studies) found no evidence against continuing buprenorphine perioperatively, although the quality of evidence is weak and number of studies limited.[574] The authors of the systematic review also used a modified Delphi process to develop a clinical practice advisory for perioperative buprenorphine-maintained patients. The main recommendation is to continue buprenorphine treatment in the perioperative perioid.[569] This aligns with a 2018 review article on perioperative considerations for individuals on buprenorphine/naloxone and methadone that states that OAT medications should be continued for most patients in the perioperative period and that multimodal pain management should be used.[575] More specific guidance can be found in the article.[575] A 2019 case series (N=32) found that individuals receiving buprenorphine/naloxone prior to surgery required large doses of opioids during the early postoperative period, regardless of the type of anaesthesia used (regional, general, and combined regional/general).[576] This finding was true for both those who continued and those who discontinued buprenorphine/naloxone. Clinical experience in Vancouver, BC, indicates that hydromorphone and fentanyl are good choices for post-operative pain management when buprenorphine/naloxone is continued; this is likely due to the high affinity of these medications for the mu opioid receptor, which enables them to complete with buprenorphine receptor occupancy.

Patients on methadone may present additional challenges with regards to pain management, given the unique pharmacology of methadone.[577] These challenges include increased risk of drug-drug interactions, QT interval prolongation, and increased risk of CNS depression when increasing methadone dose or co-prescribing additional opioids.[577]

A7.4 Chronic Pain

According to available data, chronic pain affects 36–68% of individuals receiving OAT. [578-583] and is associated with higher rates of depression, anxiety, somatization,[584] and non-medical benzodiazepine and unregulated cannabinoid use.[581] Although OAT may help with pain management for some individuals,[585] patients presenting with chronic pain should have access to additional services for pain management. Additional guidance can be found in the *2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain*[586] and the *CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016*.[587]

A7.5 Long-term Effects of OAT

Patient-reported concerns with methadone include the potential for tooth decay, which has been largely understudied—and possibly under-acknowledged by care providers.[588,589] There are several side effects common to all opioid medications that can negatively impact oral health, including suppression of salivary secretion, bruxism, and masking pain of oral disease, which could delay seeking treatment.[589-592] In addition, the high-sucrose syrup used to administer some formulations of methadone could contribute to development of dental

caries in combination with the above risk factors. Although buprenorphine/naloxone is less frequently associated with oral health issues compared to methadone, a small case series (n=11) reported that sublingual buprenorphine/naloxone can reduce salivary pH and buffering capacity, which in turn, could increase risk of dental caries through repeated exposure of tooth surfaces to an acidic environment. More research is needed to confirm these findings; however, clinicians should be aware of the general risk of oral health problems in this patient population and should offer referrals to low cost or free dental care services in the local area for those who would benefit.

Long-term opioid use, including both unregulated opioid use and opioid agonist treatment, may lead to abnormalities in the endocrine system, mainly affecting the gonadal axis and leading to hypogonadism.[593-595] In line with this, low testosterone levels and erectile dysfunction have been associated with long-term opioid use (including oral opioid agonist treatment) in males.[596] Long-acting opioids and higher doses of opioids may increase the likelihood of developing hypogonadism in males.[595] For males with opioid-related hypogonadism, testosterone replacement may increase serum testosterone and improve sexual function, sexual desire, and mental health. While there are limited studies specifically examining hypogonadism in females,[595] decreased libido, amenorrhea,[595] and menstrual disturbances[593] have been reported. Osteoporosis and reduced bone mineral density can also result from hypogonadism. Opioid use may also influence the hypothalamic-pituitary-adrenal axis, including lowered blood cortisol and adrenocorticotropic hormone levels.[595] Clinicians should discuss the potential hormonal changes from chronic opioid use prior to initiating opioid agonist treatment, and be mindful of related risks in the course of treatment.

Long-term opioid agonist treatment may cause opioid-induced hyperalgesia, a decrease in pain threshold or pain tolerance after chronic opioid exposure, in some patients. Individuals who are maintained on methadone or buprenorphine may experience increased sensitivity and diminished tolerance to pain.[597,598] Opioid-induced hyperalgesia may persist in individuals even after cessation from opioid agonist treatment, although tolerance to pain may slowly improve.[598]

Opioid use has been shown to affect emotional states and reactions, due in part to mood enhancing properties such as euphoria and reduced mood disturbance. Abnormal emotional experience, defined by heightened response to unpleasant stimuli and blunted response to pleasant stimuli, is common in opioid use.[599] Long-term buprenorphine/naloxone use in particular may result in a flat affect and less awareness of being happy, sad, or anxious.[600]

A7.6 Discontinuing Treatment: Tapering OAT Medications

Individuals who have been stabilized on OAT may have a treatment goal of decreasing dosage or discontinuing opioid agonist treatment instead of remaining on OAT indefinitely. While the majority of tapers from long-term opioid agonist treatment appear to be unsuccessful, there are increased odds of success when doses are gradually reduced with longer periods of stabilization.[280] For example, an evaluation of the British Columbia methadone program found a successful taper completion rate of only 13% across 4,917 treatment episodes between 1996 to 2006, with 35% of patients re-entering treatment within 18 months and 24% subsequently hospitalized for

opioid-related reasons.[280] Longer, more gradual stepped-tapering schedules (e.g., >52 weeks) where dose reductions were scheduled to occur bimonthly or monthly were associated with significantly higher odds of success.[280] Data from 2018 found that only 3,347 of 44,427 (7.5%) people on OAT in BC had successfully tapered below 5mg per day.[203] In a 2018 study of buprenorphine tapers, 15% of patients were estimated to have completed a buprenorphine taper, with less than half of these patients completing a medically supervised taper. Most of the reported tapers were completed quickly, with patients reporting a daily dose of <8mg/day for a median of only 40 days prior to tapering. Of the patients who completed the buprenorphine taper, 61% subsequently resumed buprenorphine treatment.[601]

In addition to low completion rates, tapering off opioid agonist treatment is associated with fewer opioid negative urine samples, more days per week of unregulated opioid use, fewer consecutive weeks of opioid abstinence, and lower treatment retention compared to maintenance opioid agonist treatment.[275,602,603] There is also a significantly increased risk of overdose death immediately following discontinuation of any opioid agonist treatment.[222] Another concern with abrupt discontinuation of opioid agonist treatment is the possibility of temporarily induced pain at healed injury sites, a phenomenon that has been reported to be a barrier to opioid cessation and be a risk factor for opioid re-initiation.[604]

However, gradual tapering in a therapeutic manner at an appropriate time for the patient may be advantageous, as demonstrated by a 2005 review that found that the pooled abstinence rates for voluntary therapeutic taper patients was 48% compared to 22% among non-voluntary "non-therapeutic detoxification" patients.[605] Individuals interested in decreasing dosage or discontinuing opioid agonist treatment should be informed of the risks associated with tapering. If patients indicate that they would like to taper off opioid agonist treatment, clinicians should initiate a slow taper over the course of months to years. During the taper, clinicians should continue to offer support and referrals to appropriate services. Patients should be educated about and provided with take-home naloxone if they initiate tapering.

A7.7 OAT and Operating Motor Vehicles

The literature on OAT and cognitive performance is limited, with methodological problems and mixed findings common.[606] While the literature as it stands suggests that OAT is associated with impairment on some tests, the literature is too limited to draw firm conclusions on whether individuals receiving OAT should be restricted from driving.[607,608] Currently, people who are stable on OAT in BC are allowed to drive.

Prescribers are encouraged to inform and remind their patients that they should not drive nor operate machinery while intoxicated or sedated by any substance, including during OAT initiation and dose increases. Given that methadone generally reaches steady state after approximately 5 days of continuous use, patients should be advised against driving during the first 5 days of a dose increase. Similarly, SROM reaches a steady state after 24–48 hours of continuous use; patients should be advised against driving during the first 2 days of a dose increase.

Clinicians are required to report patients who have continued to drive, against clear clinician advice, if they have a medical condition that, in the clinician's opinion, makes it dangerous to drive.[609] In line with guidance from the Canadian Medical Protective Administration, prescribers should be familiar with the CMA Driver's Guide and use it as a guideline when determining a patient's fitness to drive and any duty to report.[610] In brief, the CMA Driver's Guide states that patients stabilized on OAT are usually eligible for Class 5 and 6 driver's licences, but a waiting period following initiation of OAT is recommended before the patient can resume driving. The guide also states that assessment and follow-up monitoring should be tailored to the individual, that clinical monitoring (e.g., UDT) should be performed to screen for co-occurring substance use, and that biological monitoring should be considered to ensure fitness to drive in the context of SUDs.

APPENDIX 8: CLINICAL OPIATE WITHDRAWAL SCALE (COWS)

For each item, circle the number that best describes the patient's signs of symptoms. Rate based the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increased pulse rate would not add to the score.

Table 31. Clinical Opiate Withdrawal Scale (COWS)[611]

Patient's Name: _____ Date and Time: ___/____/____ ____:____ Reason for this assessment: _____	
Resting Pulse Rate: _____ beats/minute Measured after patient is sitting or lying for one minute 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	GI Upset: over last ½ hour 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: over past ½ hour not accounted for by room temperature or patient activity 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	Tremor: observation of outstretched hands 0 no tremor 1 tremor can be felt but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness: observation during assessment 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds	Yawning: observation during assessment 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil Size: 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	Anxiety or Irritability: 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint Aches: If patient was having pain previously, only the additional component attributed to opiate withdrawal is scored 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	Gooseflesh Skin: 0 skin is smooth 3 piloerection of skin can be felt or hairs standing up on arms 5 prominent piloerection
Runny Nose or Tearing: Not accounted for by cold symptoms or allergies 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score: _____ (The total score is the sum of all 11 items) Initials of person completing assessment: _____

Score: 5-12=mild; 13-24=moderate; 25-36=moderately severe; >36=severe withdrawal

APPENDIX 9: SUBJECTIVE OPIATE WITHDRAWAL SCALE (SOWS)

The SOWS[612] is a self-administered scale for grading opioid withdrawal symptoms. It contains 16 symptoms, the intensity of which the patient rates on a scale of 0 (not at all) to 4 (extremely), and takes less than 10 minutes to complete.

Patient Instructions: Please score each of the 16 items below according to how you feel right now. Circle one number only.

Table 32. Subjective Opiate Withdrawal Scale

Item	Symptom	Not at all	A little	Moderately	Quite a bit	Extremely
1	I feel anxious	0	1	2	3	4
2	I feel like yawning	0	1	2	3	4
3	I am perspiring	0	1	2	3	4
4	My eyes are teary	0	1	2	3	4
5	My nose is running	0	1	2	3	4
6	I have goosebumps	0	1	2	3	4
7	I am shaking	0	1	2	3	4
8	I have hot flushes	0	1	2	3	4
9	I have cold flushes	0	1	2	3	4
10	My bones and muscles ache	0	1	2	3	4
11	I feel restless	0	1	2	3	4
12	I feel nauseous	0	1	2	3	4
13	I feel like vomiting	0	1	2	3	4
14	My muscles twitch	0	1	2	3	4
15	I have stomach cramps	0	1	2	3	4
16	I feel like using now	0	1	2	3	4

TOTAL SCORE: _____

APPENDIX 10: FUNCTIONAL OUTCOME RATING SCALES

Assessment of functional outcomes is increasingly recognized as an important component in patient care. Unlike screening, assessment of functional outcomes can occur on an ongoing basis in order to identify any changes in a patient's symptoms or functioning during treatment. Functional outcomes can encompass different concepts, including health-related quality of life (e.g., pain, physical function), psychosocial interaction (e.g., social interactions, daily tasks), or quality of life (e.g., perceived enjoyment and satisfaction).[613,614] There are a multitude of clinician- and patient-rated instruments that measure global and specific aspects of functioning,[614] and the decision of which instrument(s) to administer should be based on clinical need and the patient's preferences and treatment goals. The following list of instruments is non-exhaustive and there is not a best choice of instrument. Clinicians may find these or other instruments useful as part of care planning and follow up.

The World Health Organization Disability Assessment Schedule 2 (WHODAS 2.0) was designed to assess global functioning and impairment, and is applicable to all health conditions, including substance use. This instrument is reliant on patient self-report and evaluates the patient's ability to perform activities in 6 domains of functioning during the previous 30 days: cognition, mobility, self-care, social and interpersonal functioning, home, academic, and occupational function, and participation in society. There are 36- and 12-item versions of the instrument, both of which can be self-administered, proxy-administered, or rater-administered. The APA endorses the use of WHODAS 2.0 to assess function and includes both the 36- and 12-item self-administered questionnaires in the DSM-5. The WHODAS 2.0 has demonstrated good face validity, including replicability across countries, populations, diagnostic groups, ages, and genders. It has further demonstrated reliability and validity in discerning differences across the general population and among those with mental health issues or addictions.

The Injection Drug User Quality of Life Scale (IDUQOL) was designed to assess the complex circumstances (e.g., cultural, socioeconomic, political, medical, and geographic) that influence quality of life for people who inject drugs. The IDUQOL relies on patient self-report and contains 21 life domains that are relevant to the daily lives of people who inject drugs. Each domain is displayed on a small card that includes the name, description, and visual representation of the domain. Individuals rate themselves on each domain using a 7-point Likert-type scale that ranges from 1 (very dissatisfied) to 7 (very satisfied). The IDUQOL has demonstrated weak criterion-related validity, good internal consistency and one-week test-retest reliability, and strong convergent and discriminant validity.

The EuroQol Group's 5-domain (EQ-5D) questionnaire is a widely used instrument that measures general health status. The instrument relies on patient self-report and consists of 5 dimensions with 3 or 5 levels: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D was designed to be self-administered, but may also be interviewer-administered or proxy-administered. An extensive body of evidence supporting the validity and reliability of the EQ-5D for numerous health conditions exists, and there is growing evidence of its validity in populations of people with opioid use disorder.[615,616] The EQ-5D has demonstrated

strong concurrent validity and construct validity, and can detect clinically important changes in unregulated drug use.[616,617]

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