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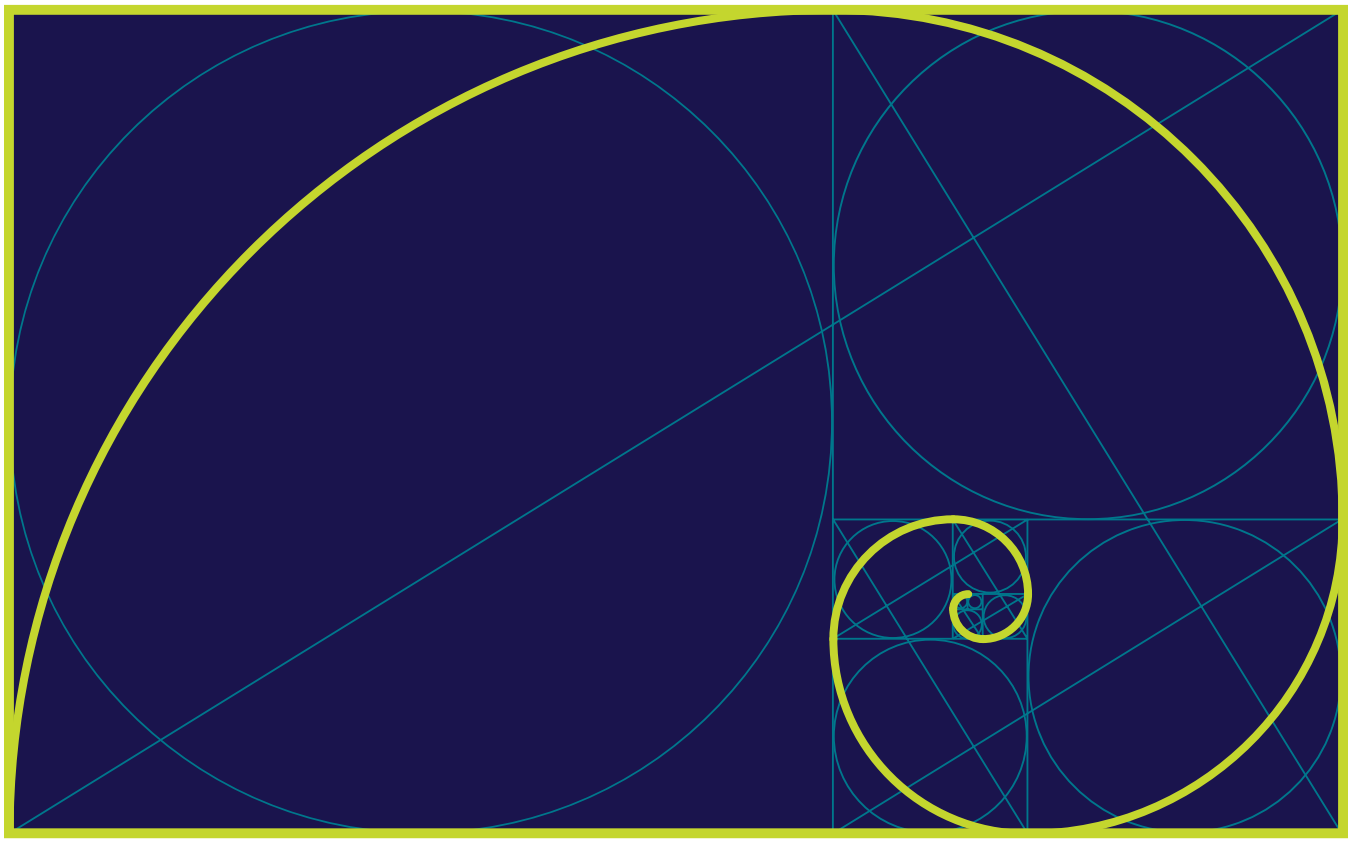

METHADONE AS OPIOID AGONIST THERAPY: GUIDANCE FOR PRESCRIBERS

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TABLE OF CONTENTS

TABLE OF CONTENTS (cont'd)

METHADONE AS OPIOID AGONIST THERAPY: GUIDANCE FOR PRESCRIBERS

SUMMARY

In order to achieve optimal benefits from methadone therapy at an individual and public health level, clinicians should work with their patients to support treatment retention. Treatment retention is increased when care is person-centered, holistic, and meets the individual's goals along the harm reduction/abstinence continuum. Clinicians should take steps to support continuity of medication, including during transitions of care between settings.

Framework

Methadone dosing guidelines should prioritize safety while also supporting early treatment engagement. The goal is to reach an effective dose in a manner that is timely, collaborative, and considers the patient's comfort, risk profile, and function. While people who use fentanyl typically have very high tolerance and are at risk of not being retained in treatment if doses are too low, people with lower tolerance or higher risks can still experience fatal overdoses from methadone. When determining initial doses, the clinician should consider the individual's opioid tolerance, risks of toxicity, and the risks of not being on methadone.

Opioid tolerance

Tolerance is difficult to establish with certainty, but it can be characterized as low, moderate, high, or very high. These tolerance categories are approximate and derived from expert opinion rather than broadly accepted criteria. When assessing opioid tolerance, clinicians should consider the potency of the opioid, the frequency of use, and the route of use (oral, nasal, smoked, or injected). Note that recent decreased access to opioids for any reason, including incarceration, hospitalization, or inpatient treatment, results in reduced tolerance within three to five days and must always be considered:

- Low tolerance: Use of low-potency opioids (e.g., codeine) or low doses of moderate-potency opioids (e.g., oxycodone 20–40 mg/day, generally < 100 morphine milligram equivalents (MME)). Also includes intermittent use of higher-potency opioids, including smoked or injected.
- Moderate tolerance: Oral use of higher doses of moderate-potency opioids and not regularly using fentanyl (e.g., oxycodone 120–160 mg/day, hydromorphone 32–64 mg/day, generally 100–300 MME when doses are known or approximated). This description recognizes that people may unknowingly use tablets that are not of pharmaceutical origin, thereby exposing them to fentanyl and other substances.
- High tolerance: Daily or near-daily use of heroin or fentanyl (smoked or injected, less than 1 g/day), regular injection use of morphine or hydromorphone, high doses of moderate-potency opioids taken orally (e.g., hydromorphone 64 mg/day or more).
- Very high tolerance: Daily use of fentanyl (1 g/day or more), smoked or injected.

Risks of toxicity

Risk for toxicity is related to age, concurrent prescribed medications and substance use, and health conditions. Clinician judgment is required to assess the degree of risk of toxicity but can be generally stratified as follows (see below for a more thorough description):

- High risk of toxicity: Advanced age, frailty, significant alcohol or benzodiazepine use (i.e., use that causes intoxication or sedation), advanced COPD, severe liver dysfunction, recent start of sedating medications, interruptions in opioid use resulting in loss of tolerance.
- Risk of toxicity: Moderate alcohol or benzodiazepine use, concurrent use of medications that are sedating or interact with methadone by prolonging the half-life, sleep apnea, liver dysfunction.
- No major risk factors for toxicity: No concurrent health conditions, substance use, or medications that increase risk.

Methadone dosing initiation and titration ranges

The following recommendations are intended to be a guide for individualized decision-making, not implemented mechanically. In individual scenarios, clinicians should assess risks and benefits and adjust doses accordingly. Clinicians should be cognizant of their own expertise; those with less experience with methadone prescribing may choose to initiate doses more conservatively.

Factors	Initial Dose	Titration	Comments
No/low tolerance OR high risk of toxicity	5–10 mg	5–10 mg q 3–5 days	Strongly consider buprenorphine Includes individuals who are not currently using opioids but are at risk of resuming use (e.g., those leaving WMS, custody, or abstinence-based settings)
Moderate tolerance AND risk of toxicity	10–20 mg	10 mg q 3–5 days	Examples: Oxycodone 80 mg x 3/day, hydromorphone 8 mg x 8/day
Moderate tolerance AND no major risk factors for toxicity	20–30 mg	< 80 mg: 10–15 mg q 3–5 days ≥ 80 mg: Up to 10 mg q 5–7 days	
High tolerance AND risk of toxicity	20–30 mg	< 80 mg: 10–15 mg q 3–5 days ≥ 80 mg: Up to 10 mg q 5–7 days	
High tolerance AND no major risk factors for toxicity	30–40 mg	< 80 mg: 15 mg q 3–5 days ≥ 80 mg: 10 mg q 5–7 days	
Very high tolerance AND no major risk factors for toxicity	40–50 mg	< 80 mg: 15 mg q 3–5 days ≥ 80 mg: 10–15 mg q 5–7 days	Daily fentanyl use of ≥1 g plus evidence of recent experience of high-dose methadone at a steady state*

*Given the lack of supporting evidence, the authors could not reach consensus on an appropriate example of a methadone dose, duration, and recency that, combined with very high opioid tolerance from daily fentanyl use of at least 1 g, would warrant an initial methadone dose of 50 mg. Clinicians should use their judgment to weigh the risks of a 50 mg starting dose against the benefits of potential improved treatment retention and symptom relief and risks of a lower starting dose for a particular patient.

Co-prescribing opioids during methadone initiation

Co-prescribing slow-release oral morphine with methadone remains an option for patients with high or very high opioid tolerance, in the context of shared decision-making. The maximum starting dose of methadone recommended when co-prescribing slow-release oral morphine is 30 mg.

Short-acting opioids can be helpful in addressing withdrawal for people with very high opioid tolerance and who have had difficulty engaging with opioid agonist therapy. In these cases, short-acting opioids should be considered a trial, in the context of a thorough risk/benefit assessment, with appropriate documentation and with the goal of optimizing opioid agonist therapy. The maximum starting dose of methadone recommended when co-prescribing short-acting opioids in the outpatient setting is 30 mg.

Missed doses

We recommend consideration of the individual's circumstances including their stability, ongoing substance use, the impact of a reduced dose, and medical and social factors. In general, we suggest no dose adjustment for up to three consecutive missed doses, a reduction of 50% or to an initiation dose (whichever is higher) after four consecutive missed doses, and a restart after five or more consecutive missed doses.

Take-home doses

We recommend using the framework described in META:PHI's document ***A New Framework for Methadone Carries***, which focuses on the individual's clinical and psychosocial stability, including recent substance use patterns, amount of time on methadone, and ability to store medication safely.

INTRODUCTION

The need for new methadone guidance in Ontario

Since 2017, Ontario, along with much of the rest of Canada, has seen devastating increases in overdose and toxicity related to the unregulated drug supply. The need to address high rates of toxicity, high opioid tolerance, and low treatment retention rates has led to novel recommendations intended to make opioid agonist therapy (OAT) more person-centered and effective, including combining methadone and slow-release oral morphine (1), more flexible approaches to take-home methadone doses (2), consideration of slow-release oral morphine as a first-line OAT option (3, 4), and higher methadone starting doses for people with very high tolerance and very low risk of toxicity (4). Furthermore, the province has been without official methadone therapy guidance since the College of Physicians and Surgeons of Ontario (CPSO) rescinded its 2011 guidelines (5) in 2021. The lack of current standards and the removal of mandatory methadone training for new prescribers has reduced some of the prior barriers to prescribing, while also leaving a vacuum for clinical guidance around best practices. The goal of this document is to provide practice guidance on methadone prescribing in Ontario that is appropriate for prescribers at every level of experience and that incorporates the perspectives of people with lived and living experience of methadone. In light of the strong evidence that methadone therapy reduces fatal and non-fatal overdoses, there is a need for updated recommendations that address the current toxicity crisis and support treatment engagement and retention for people who use opioids.

Methodology

Under the auspices of **META:PHI**, a group made up of five physicians, two people with lived experience of methadone treatment, one nurse practitioner, and one pharmacist was formed to review the literature on methadone, especially with regard to its use as OAT in the context of the current unregulated drug supply, and formulate new evidence-informed guidance for methadone prescribing. The group's terms of reference explicitly acknowledge the value of different types of experience and education and the partnership between all members of the group as co-creators of the new guidance document.

An electronic search was conducted on PubMed and Google Scholar using subject heading search terms and keywords associated with the concepts of methadone, opioid agonist therapy, opioid substitution treatment, and medications for opioid use disorder. Key words and headings were additionally derived by reviewing the titles and abstracts of identified articles and systematic reviews. Grey literature including provincial and national guidelines for opioid agonist therapy were included. The bibliographies of included articles were scrutinized for additional references. Articles included were limited to studies and reports published since 1996 in English. The resulting literature regarding indications, considerations, and dosing strategies for methadone as well as general approaches to OAT care was reviewed, and the group considered the experiences and perspectives of the authors around each sub-theme.

The 2024 *Update to National Guideline of the Canadian Research Initiative in Substance Matters (**CRISM**) for the Clinical Management of Opioid Use Disorder* (6) and the 2023 British Columbia Centre on Substance Use (**BCCSU**) *Guideline for the Clinical Management of Opioid Use Disorder* (4) both used the GRADE system to make recommendations regarding high-level therapeutic decisions such as choice of OAT, withdrawal management strategies, and approaches to harm reduction and psychosocial support. This document leans on the recommendations of both of those guidelines regarding principles of care, and the authors approached clinical recommendations with consideration of similar domains: balance between benefits and harms, patients' values and preferences, and confidence in the evidence. The purpose of this document is to provide more specific guidance regarding practical implementation of clinical care. In the absence of strong evidence for specific recommendations, this document is informed by a review of new evidence, accumulating clinical experience, and by the expertise of people with lived experience of OAT. Through an iterative process of discussion and refinement, the group generated the consensus-based guidance presented below, which has been reviewed by physician and nurse practitioner prescribers, pharmacists, nurses, clinic administrators, and people with lived experience of methadone therapy.

BACKGROUND

Approach to care

While the focus of this document is specifically on methadone prescribing, pharmacotherapy is just one aspect of OUD care. As noted in META:PHI's 2021 document *Methadone Treatment for People Who Use Fentanyl: Recommendations* (1), methadone alone does not address the many issues associated with OUD, including mental health, trauma, chronic pain, housing, poverty, and other social determinants of health. This section presents a brief outline of some aspects of a holistic approach to OUD care.

Principles of care

Holistic, safe, person-centered care that meets people where they are at is critical to engaging and retaining people in OAT care. The BCCSU *Guideline for the Clinical Management of Opioid Use Disorder* (4) presents the following overarching principles of care to support people who use opioids and their families, which align with both the META:PHI RAAM Clinic Quality Targets (7) and the Health Quality Ontario Standard for Opioid Use Disorder (8):

- Patient-centered care
- Social determinants of health
- Indigenous cultural safety and humility
- Anti-racist practices
- Trauma- and violence-informed practice
- Recovery and self-defined wellness
- Harm reduction
- Integrated continuum of care
- Comprehensive health management
- Family and social circle involvement in care

Provider-patient relationship

A critical literature review (9) found that a strong therapeutic alliance is associated with improved engagement and retention in substance use disorder treatment. Trust should be central to the relationship between a provider and a person in their care. A key component of developing trust within the therapeutic relationship is empathy, which can be defined as a process of understanding the patient's situation, perspective, and feelings, communicating and verifying that understanding, and helpfully acting on that understanding with the patient (10). Empathic listening can be embedded in every encounter. Some approaches that providers can use in their clinical relationships include the following:

- Ask about and provide encouragement for positive choices, e.g., persisting with efforts at making changes in spite of challenges.
- Engage in problem-solving about barriers to progress towards goals.
- Acknowledge strengths and resilience.
- Reduce the burden of OAT through flexible and person-centered approaches to dosing, take-home doses, appointments, and faxed prescriptions.

It can be difficult for providers to recognize their own compassion fatigue, unconscious values regarding abstinence, and preconceived ideas about "good" and "difficult" patients. Acknowledging the effort that it takes for people to continue to show up, keeping the door open, and maintaining hope are all essential in OAT care.

Holistic care

Holistic care for OUD involves offering support beyond medication, including psychosocial interventions and harm reduction strategies and supplies.

Psychosocial interventions may increase treatment retention and should be offered (but not mandated) as part of OUD care. These may include structured and/or manualized counselling that incorporates principles of psychotherapy, such as motivational interviewing (MI), cognitive behavioural therapy (CBT), interpersonal therapy (IPT), dialectic behavioural therapy (DBT), motivational enhancement therapy (MET), acceptance and commitment therapy (ACT), psychoanalytic therapy, contingency management (CM), biofeedback, twelve-step facilitation, and family/group counselling.

Harm reduction, which aims to support the health and well-being of people who use substances by meeting them "where they are" (11), is an important part of the continuum of care for people who use drugs. There are a broad range of harm reduction supplies and services that can be life-saving to people who use drugs whether their goals are to stop using, reduce their use, or reduce the harms associated with their current use. These include take-home naloxone, sterile single-use equipment such as needles, syringes, pipes, and condoms, overdose prevention sites, supervised consumption sites, virtual safe consumption (e.g., **NORS**), OAT, injectable OAT (iOAT), safer supply (prescribed pharmaceutical alternatives), and drug-checking services. Having conversations with patients about harm reduction presents an opportunity to engage with each individual in a way that respects their autonomy and goals, facilitating the development of trust within the therapeutic relationship.

Clinicians should strive to remain familiar with the trends in the unregulated drug supply in their area and should provide education to patients regarding strategies to minimize substance use–related harms. Clinics that do not have supplies on site should know where to direct clients to access supplies and provide information to patients about these services. The **Ontario Harm Reduction Distribution Program** coordinates the distribution of harm reduction supplies to core programs and public health units across the province and provides information to individuals about where they can access supplies and services.

Treatment retention

Studies have shown an association between length of methadone treatment and positive patient outcomes (12, 13). However, methadone treatment retention rates are historically low, with pooled retention rates from observational studies of 56% at six months and 47% at twelve months (14). Factors associated with lower rates of retention in care and poor outcomes include patient characteristics (e.g., comorbidities and lack of stable housing) and treatment delivery issues such as inadequate medication doses, required frequency of attendance, restricted dispensing hours, restricted access to take-home doses, and stigma (15-19). Factors associated with treatment retention and satisfaction include flexible dosing and responsiveness to unexpected changes, having holistic care in the same setting, and "the therapeutic alliance" of shared decision-making (17, 19-21). One qualitative study (17) found that the aspect of care most valued by patients surveyed about their experience with OAT treatment is "being treated like a human being" (p. 3). The authors

of this document with lived experience of OAT agree with the importance of treatment retention ("Without that, you have nothing"), creating an environment that is accessible and safe, and relationships with providers that are trusting, non-judgmental, and respectful of individual agency. The authors note the following as elements of care that promote retention:

- Convenient hours and options for drop-in visits as well as scheduled appointments ("Being on OAT should not be a full-time job")
- Options for connecting with the clinic, such as texts and email outside of appointments
- A safe environment: Welcoming and clean, no one selling drugs inside/outside the clinic, no violence, no discriminatory language, no defamatory behaviour
- Holistic care such as mental health supports, primary care, referrals, peer support groups, clothing exchanges, art therapy groups, referral to psychiatry when appropriate ("Supports are what made me stop using completely: counselling, access to a psychiatrist, help finding a physiotherapist, having referrals, even to a dentist")
- Opportunities for shared decision-making and collaborative goal-setting, e.g., "What is it you'd like to see happen and what can we do to support you in that?"
- Hiring staff with lived experience of substance use
- Have snacks available ("It's hard to get stable when you've got nothing to eat and nowhere safe to live")

Methadone: It saves your life, and without it, the other things aren't necessarily effective. In the beginning when the medicine isn't quite doing it, what keeps you going is the relationship with the practitioner and the trust. They weren't trying to watch me pee. I could have an open conversation and tell them about my drug use, my relapses and everything and it wasn't like "We're going to take away this medication that's stabilizing you and retrigger you", but "What do you need to make it better and more effective?"

Ashley Smoke

Choice of OAT agent

Multiple controlled trials, large observational studies, systematic reviews, and meta-analyses have demonstrated that OAT is effective in reducing unregulated opioid use and rates of fatal and non-fatal overdose compared with no pharmacotherapy (22-25). OAT with buprenorphine or methadone remains protective in the context of fentanyl contamination of the drug supply. A population-based study of approximately 15,000 new OAT recipients between 2016 and 2018, the period during which unregulated fentanyl became the leading cause of overdose fatalities in Canada, found rates of overdose four to ten times higher in the 30 days following treatment discontinuation compared with those of people continuing OAT (26). A retrospective cohort study of a methadone program in the US found that patients on methadone had a markedly lower risk of overdose death even if they continued to use fentanyl (27). While the strongest association is for deaths related to drug overdose, people on OAT were also at lower risk of mortality related to suicide, cancer, and alcohol- and cardiovascular-related conditions (28). OAT is also associated with reduced rates of crime and blood-borne infections (29-31).

Methadone, sublingual buprenorphine/naloxone (buprenorphine SL), injectable extended-release buprenorphine (buprenorphine XR), and slow-release oral morphine (SROM) are all options for OAT. Both the 2018 CRISM *National Guideline for the Clinical Management of Opioid Use Disorder* (32) and the Centre for Addiction and Mental Health (**CAMH**) 2021 *Synthesis of Canadian Guidelines for Treating Opioid Use Disorder* (33) endorsed buprenorphine SL as the preferred first-line treatment for OUD when possible due to its safety profile. However, in light of more recent evidence that treatment retention is higher in patients on methadone than buprenorphine, the 2024 update of the CRISM guideline (6) states that methadone and buprenorphine are both first-line OAT options and should be offered with consideration of the differences in risks of treatment discontinuation and mortality, with SROM as a second-line treatment option (strong recommendation, moderate quality of evidence). In contrast, the BCCSU (4) has shifted away from ranking therapies, recommending instead that the choice of OAT agent be based on individual considerations in addition to the quality of evidence (high for buprenorphine SL and methadone, moderate for SROM). META:PHI's *Recommendations for Use of Slow-Release Oral Morphine as Opioid Agonist Therapy* (3) also recommend considering all three agents as primary options for OUD therapy.

Methadone versus buprenorphine SL

The CRISM 2024 guideline reviewed the results of two randomized controlled trials, eight observational studies, and four meta-analyses and concluded that methadone and buprenorphine SL are equally effective at reducing opioid use in people with OUD (6). However, there are some additional factors that should be considered when choosing between methadone and buprenorphine SL, including retention rates, risk of fatal overdose, and the risk of precipitated withdrawal (PW).

Controlled trials and systematic reviews have shown that methadone has higher treatment retention rates than buprenorphine SL (14, 34), but that buprenorphine SL is associated with lower risk of fatal overdose than methadone, especially in the first four weeks of treatment (23, 28, 35-39). These findings appear to persist in the context of a fentanyl-dominated drug supply (26).

Methadone versus buprenorphine XR

Preliminary studies suggest that buprenorphine XR has good treatment retention rates and is protective against overdose, including in people who use fentanyl (40). Buprenorphine XR produces higher and more constant serum levels of buprenorphine than buprenorphine SL, with a duration of action between 28 and 42 days (41). These properties may contribute to sustained relief of withdrawal symptoms and reductions in craving while also eliminating the need for daily medication administration, thus increasing convenience and reducing stigma associated with accessing OAT (42).

Research comparing the effectiveness of buprenorphine XR relative to methadone remains limited. A pragmatic, parallel-group, open-label, multi-centre, effectiveness superiority randomized, controlled, phase 3 trial conducted at five community-based treatment clinics in the United Kingdom compared buprenorphine XR with standard of care (buprenorphine SL 8–24 mg and methadone 60–120 mg) among 314 individuals with OUD, primarily related to heroin use (43). The authors found higher rates of abstinence for the buprenorphine XR group (a mean of 123.43 days of abstinence) compared to the standard of care groups (a mean of 104.37 days of abstinence). On subgroup analysis, participants with more severe OUD-related problems at baseline achieved fewer days of abstinence from opioids overall, but participants in the buprenorphine XR group continued to demonstrate more days of abstinence than those on standard of care. However, conclusions about the treatment effect of buprenorphine XR relative to methadone

are limited because the study did not report the results for those on methadone versus buprenorphine SL separately. Observational studies on buprenorphine XR have not demonstrated a retention in treatment benefit compared with methadone (44-46), although these studies were not designed to compare retention in treatment and may be subject to confounding. Buprenorphine XR may be a good choice for people who have difficulty attending the pharmacy regularly and those seeking less frequent interactions with the health care system. Shorter inter-dose intervals, supplemental buprenorphine SL, and extended use of the 300 mg dose as maintenance may be helpful for people initiating buprenorphine from fentanyl use (47).

Methadone versus SROM

The evidence regarding SROM as OAT is limited by the quality and heterogeneity of the studies. However, SROM appears to be comparable to methadone as OAT, with patient reports of greater treatment satisfaction, reduced cravings, fewer side effects, reduced dysthymia, and some evidence of improved treatment retention (48-52). However, in contrast to the extensive literature for buprenorphine and methadone, there is limited published evidence on the impact of SROM on overdose mortality rates, hospitalization rates, and other important outcomes. One large review using the national healthcare system database in France concluded that SROM appears to reduce opioid overdose risk to a degree similar to conventional opioid management therapy with methadone (53). SROM use was also associated with higher rates of IV drug use, hepatitis B and C, hospitalizations for bacterial infections, and overall mortality among people receiving morphine versus methadone. While the results of this study may not be directly comparable to methadone (for example, a majority of SROM prescriptions were issued by primary care providers without the level of oversight typical of methadone dispensing, and some patients included in the study received other types of morphine), these results warrant caution and further study.

Summary: Medication selection

Buprenorphine, methadone, and SROM each have features that may make them more or less appealing to individuals based on their experience with OAT, treatment goals, substance use, co-occurring health conditions, and other individual circumstances. If the patient's goal is to reduce their use or prevent overdose, any OAT is preferable to not being on therapy. Unless there are specific medical contraindications, all three medications can be considered as options for OAT.

Prescribers should work with each individual to determine which type of OAT aligns best with their goals, needs, circumstances, and concurrent health conditions. Factors such as access to a pharmacy for daily witnessed dosing or delayed access to take-home medication doses may be additional considerations, especially for people living in rural or remote areas or those with daily work, school, or family obligations. Many individuals will have previous experiences with methadone or buprenorphine SL, and they may have strong opinions about which OAT agent they want to try based on these experiences or on reports from friends. While individual preferences should inform the choice of medication, it is important to ensure that these preferences are based on adequate information and adequate previous treatment opportunities and doses; someone may report that a medication "did not work for me" without realizing that they have never received a properly adjusted, therapeutic dose. The use of a **decision aid tool** to select an OAT agent is recommended. Documentation of the risks and benefits of this treatment and the decision process should be included in the clinical record.

OAT Medication	Specific Situations	Considerations
Methadone	Previous experience with and preference for methadone Severe OUD and/or high-risk opioid use, including use of unregulated fentanyl and injection drug use Ongoing cravings, withdrawal symptoms, and/or high-risk opioid use with other types of OAT Unacceptable side effects with other types of OAT At high risk of treatment discontinuation	Use with caution in individuals with risk factors for opioid toxicity (e.g., older age, COPD, sleep apnea, concurrent use of sedating medications) or increased susceptibility to developing QTc prolongation and torsades de pointes, including history of ventricular tachycardia (54) Buprenorphine XR may also be considered for people at high risk of treatment discontinuation
Buprenorphine SL	Use of pharmaceutical opioids (prescribed/ non-prescribed) Oral opioid use Higher risk of opioid toxicity Adolescents and young adults	Buprenorphine should be considered over methadone for adolescents and young adults given the increased risk of overdose with methadone, especially in light of challenges with daily dispensing, treatment adherence and the risks of missed doses
Buprenorphine XR	People who would benefit from flexibility or reduced requirement for pharmacy visits	New models of early initiation may help achieve therapeutic doses rapidly Not recommended in pregnancy or in pregnancy-capable individuals not using contraception
SROM	Unacceptable side effects with other types of OAT Ongoing cravings, withdrawal symptoms, and/or high-risk opioid use with other types of OAT Contraindications to methadone[1] Increased susceptibility to developing prolonged QTc and torsades de pointes on methadone	Cardiac risks associated with methadone include known history of torsades or ventricular arrhythmias, known or suspected QT-prolongation, multiple QTc-prolonging medications, patients hospitalized with endocarditis or awaiting valve replacement, or with acute illness that results in electrolyte imbalances Should be avoided with renal insufficiency

[1] For a full list of contraindications, please see the **product monograph** (55).

METHADONE PHARMACOLOGY

Methadone is a full mu-opioid receptor agonist with a long duration of action. At appropriate doses, it reduces opioid use by reducing withdrawal symptoms and cravings for an average of 24 hours while also partially blocking the effects of other opioids on the mu receptor (56). It is also efficacious as an analgesic, particularly in neuropathic pain and hyperalgesia, due to its mechanism of action as an n-methyl-D-aspartate (NMDA) receptor antagonist (57). Additional mechanisms of action of methadone include inhibiting serotonin and norepinephrine reuptake. The estimated analgesic equivalent of 1 mg of methadone is 8 mg of morphine (58). However, reliable conversions between methadone and other opioids are challenging because of methadone's complex pharmacokinetics and pharmacodynamics.

Formulation: In Ontario, methadone is available for the treatment of OUD as a concentrated suspension containing 10 mg/ml of methadone. The concentrate is carefully measured by the pharmacist and diluted with up to 100 mL of a fruit drink before dispensing to deter injection. Methadone is also available as a tablet (Metadol). Metadol tablets are not covered by Ontario Drug Benefits (ODB) when prescribed as OAT; they are covered through ODB via the Exceptional Access Program for chronic or cancer-related pain.

Absorption: Methadone is detected in the blood 15–45 minutes after oral ingestion, with peak serum concentration 2.5–4 hours post-dose (59).

Distribution: Methadone is highly lipophilic. It is widely distributed and retained in the brain, gut, kidney, liver, muscle, and lung and released back into the plasma during redistribution and elimination. This property contributes to its very long elimination half-life (i.e., the time it takes to decrease the amount of substance in the body by half). Methadone also binds variably to alpha-1-acid glycoprotein, a plasma protein, which can also contribute to the variability in patient responsiveness to methadone.

Metabolism: Methadone is metabolized primarily in the liver to the inactive metabolite 2-ethylidene-1,5-dimethyl-3, 3-diphenylpyrrolidene (EDDP). Cytochrome P450 (CYP450) enzymes most involved in methadone metabolism are 3A4 and 2B6. Medications that alter the activity of these enzymes can result in either increased or decreased metabolism of methadone (see below for specific drug interactions).

Elimination: Methadone's elimination half-life is long and variable, with a range of five to 130 hours and a mean of about 20–35 hours (59). The initial dose of methadone has a half-life of up to 130 hours, meaning that it typically takes about five days (range four to ten days) to reach a steady state. Until steady state is reached, each dose increases the total drug concentration in the body; therefore, the serum level of methadone can be three times higher on Day 3 than on Day 1. With continued dosing, the enzymes metabolizing methadone are induced, shortening the half-life to an average of 22 hours (60) in a process called auto-induction (61). Methadone's elimination half-life is affected by genetic variability of the CYP450 enzymes, concurrent medications, and sex (females metabolize methadone faster than males, potentially due to differences in glycoprotein binding (62)).

Methadone Pharmacology: Clinical Pearls

- In new methadone starts in ambulatory settings, methadone is typically increased after a minimum interval of three days to allow time for a given dose to reach steady state.
- Assessment for sedation is most useful between 2.5–4 hours after methadone ingestion, which is when the serum levels peak.
- Urine drug tests typically measure EDDP, the methadone metabolite, as a marker of methadone ingestion.
- It is essential to consider drug interactions that can prolong the QTc interval, affect the speed of methadone's metabolism, or add to the patient's total serotonin load.
- Tables of CYP450 inducers and inhibitors are available at the **U.S. Food and Drug Administration website**.
- See **Credible Meds** as an example of an online resource for medications causing QTc prolongation.

Contraindications and precautions

Please refer to the **product monograph** for a full list of contraindications and precautions (55).

Contraindications to methadone initiation include the following:

- Hypersensitivity to methadone or to any ingredients in the formulation
- Known or suspected mechanical GI obstructions or ileus
- Suspected surgical abdomen
- Acute or severe respiratory depression
- Asthma with severe bronchospasm
- Acute alcohol withdrawal (alcohol withdrawal should be managed before methadone is initiated)
- Severe CNS depression, increased CSF/intracranial pressure, and head injury
- Taking MAOIs or within 14 days of MAOI therapy

The following precautions should be kept in mind:

- Methadone should be used with caution in people with severe hepatic dysfunction due to prolongation of the half-life. While stable liver dysfunction does not appear to affect methadone levels, individuals with acute decompensated cirrhosis may become very sedated. Lower starting doses and more gradual titration are advised, and dose reductions may be necessary for sedation.

- Methadone should be used with caution in individuals with risk factors for opioid toxicity, including older age, COPD, sleep apnea, and concurrent use of medications or substances that can cause respiratory depression (benzodiazepines, gabapentinoids, alcohol). In individuals with increased risks of toxicity, buprenorphine may be preferred over full-opioid agonists. When methadone is started in these individuals, lower starting doses and more gradual titration are advised, and dose reductions may be necessary for sedation.

- Methadone can cause QTc interval prolongation, which can lead to torsades de pointes (see following page).

Drug interactions

The main considerations about drug interactions are medications that act as CNS depressants, medications that are QTc-prolonging, and medications that inhibit or induce relevant CYP450 enzymes.[2]

- Methadone can cause sedation and respiratory depression when combined with sedating drugs, including benzodiazepines, alcohol, antipsychotics, gabapentinoids, and sedating antihistamines and antidepressants.
- QTc-prolonging medications (e.g., antipsychotics, tricyclics, fluoroquinolones, macrolides, ondansetron, certain SSRIs) should be used with caution in patients on methadone.[3]
- Medications that inhibit the CYP450 system should be avoided wherever possible or used with caution, as they can elevate the serum level of methadone within one or two days, resulting in adverse effects.
    - Examples of enzyme inhibitors: Antibiotics (ciprofloxacin, clarithromycin, erythromycin), antifungals (fluconazole, itraconazole, ketoconazole), SSRI/SNRIs (fluvoxamine, paroxetine), amiodarone, amitriptyline, desipramine
- Medications that induce the activity of the relevant CYP450 enzymes can result in a decrease in methadone serum levels over one to two weeks. Conversely, discontinuation of these medications can result in elevated methadone levels over one to two weeks.
    - Examples of enzyme inducers: Anticonvulsants (carbamazepine, phenytoin, phenobarbital), reverse transcription inhibitors and protease inhibitors/HIV medications (ritonavir, nelfinavir, efavirenz, fosamprenavir), spironolactone, St. John's wort (58)
- Tricyclic antidepressants and neuroleptic medications compete with methadone for binding on alpha-1-acid glycoprotein. This causes a higher proportion of unbound or free methadone, resulting in greater pharmacologic effect.
- Methadone is a weak serotonin uptake inhibitor. There have been some case reports of methadone contributing to serotonin syndrome when other serotonergic medications are used concurrently (63). However, most cases of serotonin syndrome result from multiple drug interactions (64), and methadone is unlikely to be a significant contributor (65).

Clinicians should be familiar with reliable resources for checking medication interactions and should ideally cross-reference at least two resources for consistency.[4] When interacting medications or substances are being started or stopped, prescribers should recall that enzyme induction, deinduction, and inhibition all have different time courses (66). Furthermore, the impact of a specific drug interaction also depends on whether a medication is being added to methadone or vice versa.

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[2] Tables of CYP450 inducers and inhibitors are available at the **U.S. Food and Drug Administration website**.

[3] See **Credible Meds** as an example of an online resource for medications causing QTc prolongation.

[4] Some free resources for checking medication interactions include **Credible Meds**, Drugs.com's **Drug Interaction Checker**, Medscape's **Drug Interaction Checker**, and the Toronto General Hospital's **HIV/HCV Drug Therapy Guide**.

Adverse effects

Sedation and overdose: Methadone, like all opioid agonists, can cause sedation and fatigue. Sedation is associated with high doses of methadone and concurrent use of sedating drugs, but some people experience sedation even at low doses of methadone. Methadone can also cause central respiratory depression and overdose. The risk of overdose is associated with the methadone dose, low tolerance to methadone, and risk factors for opioid toxicity, including older age, respiratory impairment, and concurrent use of alcohol or sedating drugs such as benzodiazepines. Certain medications may also inhibit the pathway by which methadone is metabolized, thereby increasing its potency, half-life, and the risk for overdose.

Respiratory: Methadone can exacerbate sleep apnea and COPD by suppressing respiration. Careful titration and monitoring is warranted.

Cardiac: Methadone can prolong the QTc interval. A QTc of ≥ 470 ms for adult males and ≥ 480 ms for adult females is considered prolonged (67). Significant QTc prolongation (i.e., > 500 msec) has been associated with potentially fatal ventricular arrhythmias (torsades de pointes) in people on methadone. However, an analysis of 5503 FDA reports of adverse events associated with methadone found only 43 reported cases of fatal arrhythmias due to methadone between 1969 and 2002 in the US; the average methadone dose was 410 mg (range 30–1700 mg), and most cases had additional risk factors, including low potassium or magnesium, structural heart disease, or being on medications that affect methadone metabolism or prolong the QTc interval (68). While it is generally thought that higher doses of methadone are associated with greater QTc prolongation, studies on the relationship between methadone dose and the degree of QTc prolongation have had conflicting results (68-72). Methadone should not be stopped abruptly in someone with a QTc interval above 500 msec; the dose can be gradually reduced with repeat ECGs, while other QTc-prolonging medications or conditions are addressed concurrently. When considering switching to an alternative OAT medication such as SROM or buprenorphine, the risks of destabilization should be weighed against the low risks of ventricular tachycardia or torsades de pointes.

Serotonin syndrome: While this is a rare adverse effect, prescribers should review the total serotonergic load for individuals on methadone to avoid the risk of serotonin syndrome.

Gastrointestinal: As with all opioids, constipation and nausea are common side effects of methadone.

Endocrine: Methadone acts on the hypothalamic-pituitary axis, causing reductions in serum testosterone and estradiol levels (hypogonadism), which also impacts bone health (73).

Weight gain: Some patients may experience a body weight increase of 5–10% during methadone therapy (74).

Dry mouth and poor oral health: There is a complex relationship between methadone and oral health. Dry mouth is a common side effect of methadone, and this side effect is one of many factors that may contribute to increased incidence of caries and other oral health conditions in people taking methadone (75). Clinicians should promote good oral hygiene and provide support for access to dental care whenever possible.

RECOMMENDATIONS FOR METHADONE THERAPY

Approach to methadone dosing

Target doses

Long-term therapy with methadone is generally the goal of care, as discontinuation of OAT is associated with higher rates of unregulated opioid use (76), overdose (77), and death (25). The optimal target methadone dose provides relief from opioid cravings and withdrawal for at least 24 hours without causing sedation. RCTs have shown a significant association between daily doses of methadone above 60 mg and retention in treatment (20), and methadone doses of 80–100 mg have also been shown to be more effective at reducing heroin use than doses of 40–50 mg (78). There is limited research on the effectiveness of methadone doses above 100 mg, but studies have shown that individuals on doses above 100 mg were more likely to remain in treatment and to reduce their substance use, including in people continuing to use heroin during OAT (79, 80). While a meta-analysis found that dose increases above 120 mg were not associated with improved retention over doses between 60–119 mg, only one of the studies considered in the analysis included doses above 120 mg (20). The BCCSU *Guideline for the Clinical Management of Opioid Use Disorder* (4) gives the optimal methadone dose as 80–150 mg, noting that this range reflects practices that predate the prevalence of fentanyl supply. This aligns with the clinical and personal experience of the authors of this document, which is that some individuals require methadone doses of above 150 mg to meet their therapeutic goals.

In light of the significant risks associated with use of high-potency unregulated drugs that typically contain fentanyl and fentanyl analogues the META:PHI 2021 document *Methadone Treatment for People Who Use Fentanyl: Recommendations* (1) recommended that methadone doses of 100 mg or higher be targeted for people who use fentanyl and that strategies such as rapid titration be used to reach an optimal dose quickly and safely (81, 82). Methadone dosing guidelines should prioritize safety (83) while also supporting early treatment engagement. The goal is to reach an effective dose in a manner that is timely, collaborative, and considers the patient's comfort, risk profile, and function.

Starting doses

Until recently, the maximum recommended initial dose of methadone in the ambulatory setting was 30 mg (32, 33), informed by observational studies that identified the first week of treatment as a period of high risk for toxicity among people starting methadone at doses higher than 30 mg. META:PHI's 2021 document *Methadone Treatment for People Who Use Fentanyl: Recommendations* (1) also recommended a maximum starting dose of 30 mg but suggested co-prescription of SROM as a strategy to achieve higher OAT doses for people with known high tolerance, those at high risk of overdose from fentanyl, or those cycling repeatedly through methadone starts. Despite the real risk of methadone-related overdose, it should be noted that non-pharmaceutical opioids from the unregulated supply have been increasingly responsible for opioid-related deaths in Ontario since 2014 (84), with fentanyl and its analogues accounting for over 99% of these deaths in 2020 (85). This reality has led to newer recommendations in both Canada and the US for higher starting doses for people with high and very high opioid tolerance and who are at risk of overdose.

Recent guidelines have suggested starting doses over 30 mg for people with established high tolerance, with the goal of achieving effective doses more efficiently and improving the chances for treatment retention. The 2023 BCCSU guideline endorses an initial dose of up to 40 mg for individuals with very high tolerance who use fentanyl and have previous experience with methadone (4). Newer guidance in the US allows initial doses of up to 50 mg methadone on Day 1 based on an individualized assessment (86).

While there is not yet evidence to support the safety of an initial dose of 50 mg, there have been several published protocols (as well as anecdotal reports) using initial methadone doses of 40 mg and rapid titration. In a case series of 65 individuals (87), patients reporting daily fentanyl use as their primary opioid (excluding those at higher risk of overdose) received 40 mg on Day 1, 60 mg on Day 2, and 80 mg on Day 3, with dose increases of up to 20 mg every three days thereafter. Concurrent substance use, including benzodiazepine and alcohol use, was not an exclusion criterion. Among patients on the rapid induction protocol, there were no reports of sedation, medical encounters in which a patient was sedated, fatal overdoses, or nonfatal overdoses within 14 days of induction. Patients who completed the rapid protocol achieved an average dose 40 mg higher than patients who did not complete the protocol, and 85% were retained in treatment at 30 days. In another protocol (88), 154 patients with high opioid tolerance were given initial methadone doses of 30 mg and increases of 10 mg daily for two days, followed by further dose increases every seven days as required. There were no complications or deaths except in two patients who discontinued methadone. A report on a novel clinical pathway in a bridging clinic (89) describes methadone initiations in 150 cases (142 unique patients) of high opioid tolerance and moderate to severe withdrawal. Patients were started at doses of 10–50 mg (mean 28.4 mg) on Day 1 with the option of daily dose increases (mean 37.2 mg on Day 2 and 42.9 mg on Day 3); over time, the starting doses increased based on persistent observations of withdrawal and lack of sedation on Days 2 and 3. The dosing protocol most commonly used at the clinic since August 2021 is 40 mg on Day 1, 50 mg on Day 2, and 60 mg on Day 3. Overall, 57.9% of total referrals were retained in care at 30 days. The authors commented that their ability to tailor patients' initial doses and titrate more rapidly likely contributed to high engagement and retention rates, along with extended hours and comprehensive supports.

In summary, there is a role for starting doses above 30 mg in people with very high opioid tolerance. However, while current methadone initiation and titration protocols must take into account the drastically higher opioid tolerances caused by fentanyl use, not all patients seeking OAT have high opioid tolerance, and iatrogenic methadone overdose deaths do occur, typically in the first four weeks of treatment. Studies of methadone overdoses (22, 90-92) have identified low or uncertain tolerance to opioids, presence of other sedating drugs (most commonly benzodiazepines), and high starting doses (e.g., 50–55 mg) as risk factors. Determination of an initial methadone dose is an individualized decision that needs to consider the person's opioid tolerance and risks for toxicity (see section on methadone initiation).

All patients starting methadone should be given a naloxone kit either from clinic supplies if available or from their pharmacy (write a note on the prescription asking the pharmacist to dispense).

Initial assessment

The process of initiating methadone therapy begins with an assessment of the patient's substance use and their medical and mental health conditions. OAT options should be reviewed (ideally using a decision aid for shared decision-making). Information regarding the benefits and risks of methadone, particularly during the first two to four weeks of treatment, should be reviewed with the patient (ideally accompanied by a handout that the patient can take with them). A patient history should cover the following:

- Type of opioid(s), mode of use (oral, smoking, injecting), amount, and frequency
- Overdose event history (with a focus on recent events)
- Other current and past significant substance use (e.g., stimulants, alcohol, benzodiazepines, cannabis)
- Previous treatment experiences, including OAT doses and recency when possible
- Other medications
- Allergies

- Mental health history, including recent self-harm and suicide ideation/attempts, and current concerns
- Medical history, including recent hospitalizations, and current issues, including pregnancy status and contraception if appropriate
- Hepatitis C and HIV status if known, most recent testing
- Living situation social supports, employment, driver's license
- Medication coverage

While a comprehensive assessment is ideal, there are times that the intake must be abbreviated to initiate care in a timely manner, such as when people are in severe discomfort from withdrawal or when the assessment is taking place in the emergency department. At minimum, a diagnosis of OUD and informed consent regarding OAT must be confirmed. Assessments should be completed in a person-centered way, with attention to the patient's (dis)comfort, withdrawal, and reactions to questions. Shared decision-making should be used to support informed consent and autonomy. See **Appendix B** for a sample intake form.

A focused physical exam should assess the patient for signs of sedation and withdrawal.[5] Assessment of temperature, skin, and auscultation of the heart and lungs should be done in people complaining of fever, shortness of breath, or chest pain, especially in those who inject drugs.

A urine drug test is recommended when initiating methadone to identify opioid use as well as the use of other substances. Urine testing should be framed as a tool for safer prescribing and collaborative care. Point-of-care testing is preferred so that results are available to inform considerations regarding dosing.

The following tests are recommended, although treatment should not be delayed pending results:

- Baseline investigations include CBC, liver enzymes, hepatitis B, C, and HIV serology, VDRL, and urine pregnancy test in pregnancy-capable individuals.
- An ECG should be done when feasible for all patients starting methadone and should be obtained as soon as possible in people who have structural heart disease or previous heart surgery, are at risk for low potassium or magnesium (e.g., patients on diuretics), or are using drugs that can prolong the QTc interval (including antipsychotic drugs and stimulants such as cocaine and amphetamines). The recent guidelines from the BCCSU (4) notes that methadone treatment should not be delayed while waiting for an ECG unless the individual's risk is perceived to be prohibitively high (e.g., family history of prolonged QTc syndrome or sudden cardiac death).

Methadone initiation and titration

Initial doses

In determining initial methadone doses, opioid tolerance and risks for toxicity should be considered. Patients' experiences with methadone, knowledge of their own tolerance, and preferences should be discussed.

[5] See the section below on virtual care for some considerations when starting patients on methadone via telemedicine.

Opioid tolerance

Tolerance is difficult to establish with certainty, but it can be characterized as low, moderate, high, or very high. These tolerance categories are approximate and derived from expert opinion rather than broadly accepted criteria. When assessing opioid tolerance, clinicians should consider the potency of the opioid, the frequency of use, and the route of use (oral, nasal, smoked, or injected). Note that recent decreased access to opioids for any reason, including incarceration, hospitalization, or inpatient treatment, results in reduced tolerance within three to five days and must always be considered:

- **Low tolerance:** Use of low-potency opioids (e.g., codeine) or low doses of moderate-potency opioids (e.g., oxycodone 20–40 mg/day, generally < 100 morphine milligram equivalents (MME)). Also includes intermittent use of higher-potency opioids, including smoked or injected.
- **Moderate tolerance:** Oral use of higher doses of moderate-potency opioids and not regularly using fentanyl (e.g., oxycodone 120–160 mg/day, hydromorphone 32–64 mg/day, generally 100–300 MME, when doses are known or approximated). This description recognizes that people may unknowingly use tablets that are not of pharmaceutical origin, thereby exposing them to fentanyl and other substances.
- **High tolerance:** Daily or near-daily use of heroin or fentanyl (smoked or injected, less than 1 g/day), regular injection use of morphine or hydromorphone, high doses of moderate-potency opioids taken orally (e.g., hydromorphone 64 mg/day or more).
- **Very high tolerance:** Daily use of fentanyl (1 g/day or more), smoked or injected.

Risks for toxicity

The following factors influence an individual's risk of methadone toxicity:

- **Concurrent prescribed medications:** Benzodiazepines, gabapentinoids, other sedatives, and medications that interact with methadone by prolonging the half-life increase the risk of methadone toxicity.
- **Concurrent substance use:** Significant alcohol or benzodiazepine use (prescribed or non-prescribed) is a risk factor for toxicity, where "significant" can be roughly categorized as use that causes intoxication or sedation. Exposure to benzodiazepines in the unregulated drug supply is common and often results in urine tests that are positive for benzodiazepines. Benzodiazepine exposure and risks need to be individually assessed.
- **Concurrent health conditions:** Severe COPD, conditions/medications that prolong the QTc interval, and severe liver disease (evidenced by low albumin, low platelets, and elevated INR) increase the risk of methadone toxicity. No dose adjustment is recommended in mild and moderate liver disease.
- **Age:** The risk for toxicity is increased at ages 65 and older due to the greater prevalence of concurrent health conditions and medications, as well as changes in body composition and organ function (93). Note that youth aged 25 or younger should be strongly encouraged to try buprenorphine over methadone (see section on youth).

Recent overdoses are an additional consideration. People with overdoses within the past month are potentially at increased risk of overdose from prescribed methadone due to high-risk substance use; however, they may also benefit from rapid stabilization on OAT to reduce the risks of ongoing opioid use.

Clinician judgment is required when assessing the risk for toxicity with methadone initiation. The authors recognize that, as with tolerance, the risk of toxicity exists on a continuum; the following categories are intended to guide patient assessment and decision-making:

- **High risk of toxicity:** Advanced age, frailty, significant alcohol or benzodiazepine use (i.e., use that causes intoxication or sedation), advanced COPD, severe liver dysfunction, recent start of sedating medications, interruptions in opioid use resulting in loss of tolerance.
- **Risk of toxicity:** Moderate alcohol or benzodiazepine use, concurrent use of medications that are sedating or interact with methadone by prolonging the half-life, sleep apnea, liver dysfunction.
- **No major risk factors for toxicity:** No concurrent health conditions, substance use, or medications that increase risk.

Determining starting doses

Based on an assessment of the above factors, we recommend the following starting doses for methadone (monotherapy) initiation in the outpatient setting:

- **Low tolerance and/or high risk of toxicity:** Initial dose of 5–10 mg (buprenorphine should be considered in these cases)
- **Moderate tolerance and risk of toxicity:** Initial dose of 10–20 mg
- **Moderate tolerance and no major risk factors for toxicity:** Initial dose of 20–30 mg
- **High tolerance and risk of toxicity:** Initial dose of 20–30 mg
- **High tolerance and no major risk factors for toxicity:** Initial dose may be up to 40 mg
- **Very high tolerance AND no major risk factors for toxicity AND known recent experience of high-dose methadone at a steady state[6]:** Initial doses of up to 50 mg may be considered (the rationale for the higher starting dose and the patient's consent should be documented)

Clinicians should be cognizant of their own expertise; those with less experience with methadone prescribing may choose to initiate doses more conservatively.

Before planning a starting dose above 30 mg, it is advisable to obtain some form of collateral information regarding fentanyl use, which can include a urine drug test, evidence of fentanyl use on previous urine drug tests, and/or records of emergency department visits or hospitalizations associated with fentanyl use. The limitations of urine testing should be noted; for example, a urine test that is positive for fentanyl indicates exposure at some point in the last one to two weeks but is not an indicator of tolerance. People who have been recently abstinent from fentanyl may have a positive test but will have lost some of their tolerance and should be started at lower doses.

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[6] Given the lack of supporting evidence, the authors could not reach consensus on an appropriate example of a methadone dose, duration, and recency that, combined with very high opioid tolerance from daily fentanyl use of at least 1 g, would warrant an initial methadone dose of 50 mg. Clinicians should use their judgment to weigh the risks of a 50 mg starting dose against the benefits of potential improved treatment retention and symptom relief and risks of a lower starting dose for a particular patient.

Initiating methadone with SROM

As mentioned above, META:PHI's 2021 document *Methadone Treatment for People Who Use Fentanyl: Recommendations* (1) suggested co-prescribing SROM up to 300 mg with methadone 30 mg for people who use fentanyl daily. At the time of writing, guidance on higher starting doses was negligible, and this co-prescribing strategy aimed to achieve an effective dose of OAT more rapidly than relying on methadone alone. In addition to offering a higher net opioid starting dose, SROM peaks later than methadone (8–12 hours versus 2.5–4 hours), which could be advantageous. Furthermore, steady state with SROM is reached within about two days; there is no bioaccumulation of morphine. The authors with lived experience of OAT report that people who use fentanyl find that SROM augments the methadone dose, and that SROM may be more helpful with pain than methadone alone. While literature on this practice is still lacking beyond a small number of case reports (94, 95), it is the experience of the authors that co-prescribing SROM with methadone seems to help with stabilization for people who use fentanyl, and that some people prefer to stay on the combination OAT rather than tapering off SROM as methadone approaches an effective dose.

Co-prescribing SROM with methadone remains an option for patients with high or very high opioid tolerance. The maximum recommended starting dose of methadone when co-prescribing SROM is 30 mg.

We recommend that for patients with high or very high opioid tolerance, especially those who use fentanyl, prescribers discuss the option of starting methadone at a higher dose (e.g., 40 mg) versus a starting dose of 30 mg combined with SROM 100–300 mg. Potential advantages include the opportunity to increase SROM every two days rather than three. SROM may also be less risky than higher-dose methadone initiation in people with hepatic dysfunction or on medications that increase the half-life of methadone. SROM is also more expensive than methadone for people without insurance coverage, and its use may preclude people from participating in certain inpatient treatment programs. Please see META:PHI's *Recommendations for Use of Slow-Release Oral Morphine as Opioid Agonist Therapy* (3) for more guidance about prescribing SROM as OAT.

Initiating methadone with short-acting opioids

Short-acting opioids, typically hydromorphone, are sometimes prescribed alongside long-acting OAT medications, often in the context of a harm reduction intervention.[7] Individuals for whom it may be appropriate to consider co-prescribing oral short-acting opioids for a limited duration during methadone initiation and titration include those who use large amounts of fentanyl daily or those who have repeatedly discontinued or had difficulty engaging with OAT. In these cases, short-acting opioids should be considered a trial, in the context of a thorough risk/benefit assessment, with appropriate documentation and with the goal of optimizing OAT. While ideally all short-acting doses are observed, take-home doses warrant the same considerations as take-home doses of methadone with respect to an individual's ability to store and manage their medications safely (see below).

As there is currently no information on the safety of co-prescribing short-acting opioids and accelerated methadone dosing, we recommend that a maximum methadone starting dose of 30 mg should be used in patients also receiving short-acting opioids.

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[7] For guidance on prescribing short-acting opioids as a harm reduction strategy, please see *Safer Opioid Supply Programs (SOS): A Harm Reduction Informed Guiding Document for Primary Care Teams* (96).

Guidance to patients when initiating methadone

Key points to review when initiating people on methadone include expectations around the duration of methadone therapy, the importance of regular dosing, the risks of combining methadone with sedating substances such as alcohol, and caution with driving if there is any sedation:

Information for people on methadone

- Methadone is usually a long-term medication; staying on it for months to years is associated with better outcomes than trying to stop methadone quickly.
- At the beginning of methadone therapy, people usually have to go to the pharmacy every day to take their dose. People may start getting some doses to take home after about a month. There is more information for patients about how decisions about take-home doses are made in META:PHI's document ***A New Approach to Methadone Carries***.
- Methadone should be taken around the same time every day, preferably in the morning. Missing a methadone dose will result in withdrawal. Missing more than four doses will mean that the dose has to be lowered because of the risk of overdose.
- Methadone toxicity is very dangerous, especially during sleep, and can cause death. The effects of methadone are strongest about 2.5–4 hours after taking it. If there are any symptoms of toxicity such as nodding off, slurred speech, or difficulty with coordination, or if a family member notices loud snoring during sleep, it is important to get emergency help immediately.
- People should let their prescriber or pharmacist know if they throw up within 15 minutes of taking a dose.
- Methadone can make people feel sedated, and combining it with alcohol or with other sedating drugs like benzodiazepines can increase the risk of overdose.
- People taking methadone should avoid driving when feeling tired or sedated.
- It is important to let other health care providers know about methadone therapy because of medication interactions.
- Methadone is very dangerous and can be fatal if taken by someone who does not have tolerance, especially a child. Any take-home methadone doses must be kept securely in a locking device.
- Every individual and household member of an individual taking methadone should have a take-home naloxone kit.

Dose titration and stabilization

During the initiation/early stabilization period, patients should be seen once or twice per week. Methadone is typically increased every three to five days up to a dose of 80–100 mg, and then weekly, until an effective dose is achieved. The following should be assessed at each visit:

- **Dose considerations:**
  - **How long the methadone dose "lasts":** A dose increase should be considered for someone who takes methadone at 8:00 am and starts experiencing withdrawal symptoms before their next dose, with the goal of reaching a dose that provides an average of 24 hours of symptom relief.
  - **Cravings:** Thoughts and urges that make the person feel at risk of using are a reason to consider a dose increase, even if someone has been on a stable dose for a period of time.
  - **Side effects:** Sedation warrants consideration of a dose decrease or potential adjustments of other sedating medications (see **Appendix K** for information on assessing and managing methadone toxicity).
  - **Substance use:** If someone is using opioids to relieve withdrawal symptoms, a dose increase should be considered. If someone is using alcohol or benzodiazepines in risky ways, consider a dose reduction.
  - Any missed doses
- **The need for harm reduction supplies and supports:**
  - All patients should be given take-home naloxone and instructed in its use.
  - People should also be given harm reduction advice and supplies as appropriate.
- **Mood and function:**
  - If underlying mental health symptoms are not addressed, patterns of use may continue, even without withdrawal symptoms.
- **Safety:**
  - People should be advised not to drive or operate machinery until they are on a stable dose and are not sedated when the methadone level is at its peak (2.5–4 hours after ingestion).
  - Safety regarding take-home doses should be discussed (see below).

Dose increases of 5–15 mg should be considered in individuals who continue to use opioids or who report withdrawal symptoms or cravings. At higher doses and as unregulated substance use slows, dose adjustments should be reduced to 5–10 mg increments. If the person is experiencing sedation, methadone should be decreased by an amount proportionate to the level of sedation (e.g., 5–10 mg if the person is experiencing mild sedation, reduced by half (or even held) if the individual is extremely sedated in an inpatient setting).

We recommend the following specific titration schedules in the outpatient setting:

- **Low tolerance and/or high risk of toxicity:** Dose increases of no more than 5–10 mg every three to five days
- **Moderate tolerance and risk of toxicity:** Dose increases of 10 mg every three to five days
- **Moderate tolerance and no major risk factors for toxicity:** Dose increases of 10–15 mg every three to five days until the dose reaches 80 mg, and then in 5–10 mg increments every five to seven days
- **High tolerance and risk of toxicity:** Dose increases of 10–15 mg every three to five days until the dose reaches 80 mg, and then in 5–10 mg increments every five to seven days
- **High or very high tolerance and no major risk factors for toxicity:** Dose increases of 15 mg every three to five days until the dose reaches 80 mg, and then in 10–15 mg increments every five to seven days

Dose adjustments and benzodiazepines

Methadone dose adjustments should consider benzodiazepine exposure (through deliberate prescribed or non-prescribed use and/or through contaminants in the unregulated opioid supply) but do not automatically need to be slowed because of benzodiazepines. In general, we recommend not slowing the methadone titration unless the person is at high risk of toxicity. Patients should be cautioned about the risks of concurrent benzodiazepine and opioid use and offered alternative medications for management of anxiety if appropriate.

Preplanned dose increases

The prescriber may use clinical judgment to decide whether to write a prescription with a predetermined dose increase. Ideally, there should be an assessment prior to all dose increases; if this is not possible, the prescriber should use clinical judgment in balancing the risk of methadone toxicity with the risk of not reaching a therapeutic dose of methadone. For example, if an individual is restarting methadone and their tolerance of methadone is known from previous starts, it is reasonable to write one predetermined dose increase and subsequently assess the patient (see section on pharmacy considerations for suggestions on how to write preplanned dose increases). A patient should not have more than one dose increase without an assessment. If the patient is new to methadone (i.e., has not been on methadone in the past or has not taken any methadone in the past month or more), it is preferable to write a prescription for a longer duration of a starting dose and assess the patient for sedation prior to prescribing a dose increase. This will afford a new patient more opportunities to establish tolerance to the methadone.

Absence of an ECG

Methadone dose increases should not be delayed due to the absence of an ECG. A baseline ECG should be performed when feasible and repeated for individuals on doses above 150 mg methadone or with other increased risks for arrhythmias. However, the lack of an ECG should not prevent the clinician from providing dose increases as required, especially for people who continue to use fentanyl and report withdrawal symptoms and cravings. The benefits of OAT for someone at high risk of opioid-related harm outweigh the risks of a prolonged QTc interval (97-100).

Missed doses during titration

Repeated missed doses during the titration stage are a barrier to reaching a therapeutic dose of methadone. For patients who repeatedly face challenges achieving three consecutive doses, we recommend considering a dose increase for individuals with demonstrated tolerance to methadone and high-potency opioids who meet the following criteria:

- At a dose of 60 mg or less
- At least four doses in the preceding five days
- Ongoing withdrawal at the current dose
- Ongoing fentanyl use
- Lack of sedation

A dose increase immediately after a missed dose is not recommended. If a dose was missed one day before the day of the assessment, we recommend continuing that dose for one more day and prescribing a dose increase for the following day without requiring an additional clinical visit. Specify on the prescription that the pharmacist should assess the patient and hold the dose if they appear sedated. META:PHI's 2021 document Methadone Treatment for People Who Use Fentanyl: Recommendations (1) gives the following recommendations for different clinical scenarios in which someone who has taken methadone within the past two weeks is seen on Day 5 (see following page):

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
30 mg	30 mg	30 mg	miss	30 mg	45 mg
30 mg	30 mg	miss	30 mg	30 mg	45 mg
60 mg	60 mg	60 mg	miss	60 mg	75 mg
60 mg	60 mg	miss	60 mg	60 mg	75 mg
60 mg	miss	60 mg	miss	60 mg	60 mg*

*No increase on Day 6; dose can be increased when the patient has had four doses in the past five days.

(Bromley et al. 2021, p. 11, Table 2)

Summary

Factors	Initial Dose	Titration	Comments
No/low tolerance OR high risk of toxicity	5–10 mg	5–10 mg q 3–5 days	Strongly consider buprenorphine Includes individuals who are not currently using opioids but are at risk of resuming use (e.g., those leaving WMS, custody, or abstinence-based settings)
Moderate tolerance AND risk of toxicity	10–20 mg	10 mg q 3–5 days	Examples: Oxycodone 80 mg x 3/day, hydromorphone 8 mg x 8/day
Moderate tolerance AND no major risk factors for toxicity	20–30 mg	< 80 mg: 10–15 mg q 3–5 days ≥ 80 mg: Up to 10 mg q 5–7 days	
High tolerance AND risk of toxicity	20–30 mg	< 80 mg: 10–15 mg q 3–5 days ≥ 80 mg: Up to 10 mg q 5–7 days	
High tolerance AND no major risk factors for toxicity	30–40 mg	< 80 mg: 15 mg q 3–5 days ≥ 80 mg: 10 mg q 5–7 days	
Very high tolerance AND no major risk factors for toxicity	40–50 mg	< 80 mg: 15 mg q 3–5 days ≥ 80 mg: 10–15 mg q 5–7 days	Daily fentanyl use of ≥1 g plus evidence of recent experience of high-dose methadone at a steady state*

*Given the lack of supporting evidence, the authors could not reach consensus on an appropriate example of a methadone dose, duration, and recency that, combined with very high opioid tolerance from daily fentanyl use of at least 1 g, would warrant an initial methadone dose of 50 mg. Clinicians should use their judgment to weigh the risks of a 50 mg starting dose against the benefits of potential improved treatment retention and symptom relief and risks of a lower starting dose for a particular patient.

Methadone maintenance

During later stabilization and maintenance stages, patients should typically be seen every two to four weeks. Patients with long-term stability can be seen every one to three months.

At each visit, the following should be assessed as needed:

- Dose considerations: Withdrawal, cravings, sedations and side effects, missed doses
- Substance use, including non-opioid substances
- Suitability of take-home doses
- Need for harm reduction supplies and supports
- Mood and mental health
- Social health, including housing and food security
- Updates on medical issues, including querying cellulitis for people who inject drugs
- Medication review
- Safety for driving, operating machinery, or other types of work
- Risk of toxicity (see **Appendix K**)

A full review of the patient's physical and mental health issues and goals should take place annually:

- People who engage in ongoing high-risk activities should be offered re-screening at least annually for hepatitis C and HIV.
- Side effects of methadone include impacts on the endocrine system for patients of all genders, which can result in low testosterone, low estrogen and amenorrhea, and low bone mass. Pregnancy-capable people should be screened for contraception needs. Individuals with low testosterone can be assessed and considered for testosterone replacement therapy if appropriate (101).
- An ECG be performed annually, especially for individuals on methadone doses above 100 mg, those with structural heart disease or previous heart surgery, those using prescribed medications and/or drugs that can prolong the QTc interval (including antipsychotic drugs and stimulants such as cocaine and amphetamines), and those at risk for low potassium or magnesium.
- Medications and psychosocial supports should be assessed, including the need for psychiatric referral, opportunities for reducing polypharmacy, and connecting people to psychosocial supports such as counselling, peer-based support groups, and other psychotherapies if appropriate.

All patients should be encouraged to see their primary care provider for appropriate screening and chronic disease management. Methadone prescribers should communicate with others in the circle of care periodically to avoid overlapping or conflicting prescriptions and to support collaborative care for the patient's overall health. There should be a process for connecting unattached patients to primary care resources as needed.

Missed doses

It is important that people who miss methadone doses are supported to resume therapeutic doses as quickly and safely as possible. Although tolerance to methadone is partially reduced after just a few days of missed doses, opioid tolerance is maintained when opioid use continues. In line with META:PHI's *Methadone Treatment for People Who Use Fentanyl: Recommendations* (1) and the guidelines from the BCCSU (4), we recommend that methadone prescriptions not be altered if the person has missed fewer than four doses. We recommend that after four consecutive missed doses, the dose of methadone should be reduced by 50% or to 40 mg, whichever is higher. People who miss five or more consecutive doses should be reassessed, and methadone should be restarted at a dose that reflects their current tolerance, including their use of methadone and other opioids within the past four to seven days. For patients on a dose of at least 90 mg prior to missed doses, a restart dose of 40–50 mg may be considered, with titration according to guidelines and patient need; more aggressive titration can be considered based on clinical judgment. Patients with lower methadone doses and no regular additional opioid use should be restarted based on assessment of their tolerance and toxicity risks, as with initial dosing criteria:

Days missed	Dose	Increases
Three (person presents on Day 4)	Continue previous dose; no adjustment required	10–15 mg every three days as per usual titration protocols
Four (person presents on Day 5)	The higher of 50% or previous dose or 40 mg	10 mg daily for three days (not exceeding the most recent dose), then reassess and proceed as usual
Five or more (person presents on Day 6 or later)	Restart based on initial dosing criteria	10–15 mg every three to five days

Vomited doses

Methadone is absorbed in the stomach and can be detected in the blood as early as 15–45 minutes after oral administration. Therefore, vomited doses are generally not replaced unless the emesis was witnessed and occurred less than 15 minutes after consumption; when this occurs, doses are usually replaced with no more than 50% of the regular dose (5). In situations such as pregnancy or acute medical conditions causing nausea, it may be appropriate to provide a replacement dose if the episode of vomiting was not witnessed. Reports of repeated vomiting should prompt investigation of underlying causes and strategies to reduce nausea and the likelihood of further vomiting.

Split doses

Patients may require split methadone doses in the context of chronic pain and in situations where metabolism of methadone is accelerated resulting in withdrawal symptoms prior to 24 hours. Although split dosing is often mentioned in the methadone literature, there is little published guidance on how to divide the dose or evidence for different practices. Based on our experience, we recommend splitting the dose as a larger portion of the dose in the morning (e.g., 60% in the morning and 40% in the late afternoon). For individuals attending the pharmacy daily, this can be managed as an observed dose in the morning and a carry for the second part of the dose; requiring both doses to be observed may result in the person receiving only half their daily dose. For individuals receiving take-home doses, the pharmacy should dispense an appropriately labelled bottle for each dose. In all cases, the prescriber should specify on the prescription that on witnessed pharmacy days, the individual should receive the morning portion of their dose and take the second part of the dose as a take-home dose so that they are not moving between partial and full doses. Clinicians need to work with patients to determine the pros and cons of a trial of split doses and the safety and appropriateness of take-home doses using the general framework for decision-making regarding take-home doses below.

Split dosing for chronic pain

While some patients find that methadone provides pain relief for a full 24 hours, methadone for chronic pain management is typically dosed every eight to twelve hours. For patients on methadone who have both OUD and chronic pain who are not receiving analgesia for 24 hours, dividing the dose into two or three equal parts is an option, assuming the ability to manage take-home doses has been considered (see section on chronic pain).

Split dosing for increased clearance

Most of the clinical experience and research on split dosing is based on pregnancy (102), when methadone metabolism is increased due to the increased volume and induction of CYP3A4, and split dosing results in more sustained plasma methadone levels, reduced inter-dose withdrawal, and improved compliance with methadone therapy. Metabolism of methadone can also be accelerated due to medications such as 3A4 inducers, CYP2B6-mediated drug interactions, and genetic variants of CYP450 or of p-glycoproteins. Common medications affecting methadone metabolism include HIV medications (nelfinavir, nevirapine, ritonavir, fosamprenavir), anticonvulsants (carbamazepine, phenytoin, phenobarbital), rifampin, spironolactone, and St. John's wort (58).

While testing for rapid metabolism can be conducted by measuring peak-to-trough levels, decisions regarding split doses are typically made on clinical grounds; accelerated metabolism requiring split dosing is relatively uncommon and is used in response to reports of early withdrawal rather than prophylactically.

Take-home doses

Take-home doses of methadone (carries) have potential benefits for patients, including increased treatment retention and improvements in clinical and social stability. META:PHI's document ***A New Framework for Methadone Carries*** (2) is a consensus-based set of principles and criteria that reflects the formal literature as well as the experiences and perspectives of the authors, including people with lived experience of taking methadone. The framework is structured around criteria that are intended to be a guide for decision-making between the care provider and the person taking methadone. We recommend that take-home doses of methadone be prescribed in accordance with this framework, summarized here.[8]

[8] For a full description of the framework's development and an explanation of how to apply it, please see ***A New Framework for Methadone Carries*** (2).

The framework uses the following decision-making criteria:

- **Ability to store carries securely:** A consistent and safe place to stay, a locking device in which to store bottles
- **Amount of time on methadone:** Initiation/titration phase versus maintenance
- **Stability:** Progress towards identified goals, management of daily activities and responsibilities, management of concurrent mental health conditions
- **Frequency of missed doses:** Receiving a majority of doses (i.e., five out of seven) to ensure tolerance
- **Recent substance use patterns:** Higher-risk versus lower-risk use, recent overdoses
- **Urine drug test results:** Alignment with prescribed medication and self-reported substance use

Based on an assessment of these criteria, clinicians should determine an appropriate range of take-home doses for a particular patient at a particular time:

- **No take-home doses:** Appropriate for people who are just starting methadone therapy, are not currently clinically or socially stable, or are not able to store their medication securely
- **Up to three non-consecutive take-home doses per week:** Appropriate for people who are building stability and are able to store their medication securely
- **Four to six take-home doses per week:** Appropriate for people who are clinically and socially stable
- **More than six take-home doses:** Appropriate for people on long-term methadone therapy with consistent stability and experience with successfully managing take-home doses

The application of the criteria in the decision-making framework is shown below (2):

Criteria	No carries	Up to 3 non-consecutive carries	4–6 carries	7+ carries
Ability to store carries securely	Unstable/unsafe housing, congregate or shelter settings Unable to store carries in a manner and location that reduces the risk of inappropriate use	Consistent and safe living environment Able to store carries in a manner and location that reduces the risk of inappropriate use Locked box		
Amount of time on methadone	< 4 weeks	> 4 weeks	> 12 weeks	7–13 carries: 1 year, with at least 6 months of 6 carries 14–27 carries: 2 years, with at least 1 year of 13 carries
Stability	Not stable or stability unknown Active psychosis, suicidality	Developing stability Establishing routines around clinic/ treatment expectations Attending most appointments No acute conditions that impair judgment or ability to manage carries safely	Consistent clinical and psychosocial stability Stable routines around clinic expectations and medication management Dose is stable Stable living situations, employment, or participation in other regular activities No acute mental health conditions that impair judgement or ability to manage carries safely	
Frequency of missed doses	Frequent	Missing 2 doses per week at most	Missed doses rare	
Recent substance use patterns	Higher-risk use that is impacting health, physical safety and overall well-being Intoxicated or sedated at appointments Regular overdoses or blackouts/ memory loss	Lower-risk, not impacting immediate safety or health In alignment with goals Not intoxicated or sedated at appointments No overdoses or blackouts/memory loss in the last month	Lower-risk, not impacting immediate safety or health, and overall stability In alignment with goals Not intoxicated or sedated at appointments No overdoses or blackouts/memory loss in the last 3 months	No use of unregulated or unprescribed substances and no high-risk use of regulated or prescribed substances
Urine drug screen results	Negative for methadone or indications of tampering	Positive for methadone Consistent with self-reported substance use	Positive for methadone Consistent with self-reported substance use Generally negative for unregulated and unprescribed substances	Positive for methadone Consistently negative for unregulated and unprescribed substances

(Adapted from Lam et al. 2023, p. 16, Appendix A)

Urine drug testing

Urine drug testing (UDT) is one component of assessing an individual's current substance use and is a routine expectation of methadone care. While there is little evidence that UDT improves health outcomes (103, 104), it can provide important clinical information to providers and patients. The purpose of UDT is to confirm opioid use at the initiation of methadone therapy, verify that methadone is being taken, confirm reports of substance use, and detect the presence of other substances, including substances that the person may not know they have been exposed to. There are many drug interactions that can lead to false-positive results on point-of-care immunoassay tests. Clinicians should be aware of the risk of false positives and false negatives and refer to the product inserts for a full list of cross-reactants.[9]

Laboratory confirmatory testing with gas or liquid chromatography/mass spectrometry should be used to verify unexpected results when the results would significantly impact clinical management and to assess for relevant substances and medications that are not included in point-of-care tests.

Recent guidance documents (2, 4, 105) have highlighted the importance of ensuring that UDT is done in a flexible and person-centered way. Testing should be done in conjunction with a clinical assessment (that is, people should not have to provide samples between clinical visits) and should not be requested when the result will not impact clinical care. Prescription renewals should not be contingent on UDT. Stigma reduction and flexibility should be prioritized in the structure of UDT; patients should be able to leave urine samples at a lab, not just at the clinic, and urine samples should not be witnessed.

We recommend the UDT schedule presented in META:PHI's document ***A New Framework for Methadone Carries*** (2), which was adapted from the BCCSU document ***Urine Drug Testing in Patients Prescribed Opioid Agonist Treatment—Breakout Resource*** (105):

Treatment stage	UDT frequency
Titration, stabilization, and building carries	Usually up to four times per month, typically in conjunction with an appointment
Long-term carries, six or more	Usually every one to two months, typically in conjunction with a clinical assessment (more frequently if clinically indicated) At the request of the person receiving methadone, if they wish to know what is in their sample
Maintenance of methadone for people not receiving or working toward carries	Monthly OR more or less frequently as clinically indicated, in conjunction with a clinical assessment

Unexpected UDT results are an opportunity to inform the patient about substances they may have been exposed to without knowing it and to discuss whether any adjustments should be made to the care plan.

[9] For a list of possible causes of false-positive and false-negative results in UDT, please see page 31 of the BCCSU document ***Urine Drug Testing in Patients Prescribed Opioid Agonist Treatment—Breakout Resource*** (100).

Methadone tapering and discontinuation

Methadone doses may need to be tapered because of side effects such as sedation, constipation, sexual side effects (decreased libido), or sweating. In these situations, small dose decreases (e.g., 5 mg) can be implemented every one to two weeks with close monitoring for improvements in side effects and emerging withdrawal symptoms.

In the case of QTc prolongation > 500 msec, methadone may need to be reduced while other modifiable risk factors are addressed (e.g., electrolyte abnormalities or drug-drug interactions). If methadone needs to be reduced to a significant degree, the net opioid deficit may be managed by adding other opioids such as short- or long-acting morphine to avoid withdrawal symptoms.

Long-term methadone maintenance is generally considered to be a goal of care, since tapering off OAT is usually not successful (106) and is associated with higher rates of unregulated opioid use (76), overdose (77), and death (25). In an analysis of methadone dispensations in British Columbia, only 13% of attempted tapers were successful, defined as no return to OAT and no opioid-related hospitalizations or deaths in the year following methadone cessation (106).

However, there are many reasons that a patient may request to discontinue their methadone, including stigma, shame, and the burden of appointments and pharmacy visits (107). People on methadone are often pressured by others to discontinue methadone because of the misconception that methadone is simply switching from one drug to another (108). Whenever possible, clinicians should explain that people on methadone are far more likely to have a stable long-term recovery than people who attempt abstinence-based treatment (109). If the concerns are related to the inconvenience of methadone, strategies could include adjusting the frequency of appointments or using virtual care, finding a more convenient pharmacy, prescribing take-home doses as appropriate, or switching to buprenorphine SL or XR.

Prescribers also need to acknowledge patients' preferences and support them safely if they choose to taper (110). The low success rate of methadone tapering is due at least in part to the protracted withdrawal syndrome characterized by low mood, insomnia, and craving for opioids that accompanies dose reduction. Factors associated with successful tapers include longer time on OAT, sustained abstinence from opioids and other drugs, social stability, supportive family and friends, and slower, more flexible tapers (106, 111). For those tapering, longer stepped tapers (over one year) including planned pauses (i.e., dose decreases planned for only 25–50% of treatment weeks) are associated with higher odds of success (106) and lower rates of overdose post-taper (77).

For people who choose to taper, the following approach is suggested:

- Review the possibility of withdrawal symptoms, as well as the potential benefits of tapering, such as more energy and greater alertness. Encourage planning to deal with insomnia, persistent thoughts about opioids, urges, cravings, and triggers.
- Encourage a slow taper, e.g., decreased doses every two to four weeks (or more), with the option of adjusting the increments and pausing or discontinuing the taper at any time.
- Consider starting with a test decrease of 2–5 mg.
- Decrease methadone by no more than 10% of the total dose (e.g., 10 mg for doses of 100 mg or more, 5–8 mg for doses between 40–100 mg).
- Under 30 mg, dose decreases of 1–2 mg are usually best tolerated.

- Offer a dose increase to address symptoms such as cravings, insomnia, or dysphoria, and/or if there is resumption or increase of opioid or other substance use.
- Stop the taper at the patient's request or if the patient is finding the taper too difficult.
- For sweats and chills, clonidine 0.1 mg up to TID PRN can be effective. Benzodiazepines or z-drugs (zopiclone, zolpidem) for insomnia or anxiety should be avoided.
- The patient should be encouraged to view the taper as a success if the dose is lowered even by a small amount, and the patient is feeling and functioning as well or better on the lower dose as they did before tapering.
- All patients tapering methadone should be reminded that as their dose decreases, so does their tolerance, and that they are at risk of overdose with substantially lower amounts of opioids than they were previously used to.
- Patients completing a taper should be encouraged to check back in for ongoing support/relapse prevention. The option of restarting methadone or another type of OAT as harm reduction should be clear.

Pharmacy considerations

Clear communication between prescribers, pharmacists, and people taking OAT are important to support patient and community safety.

Prescriptions

Methadone prescriptions should include specific start and end dates and whether each dose is to be witnessed at the pharmacy or dispensed as a take-home dose.

Except in rare situations where the person does not know which pharmacy they will be attending, the prescription should specify the pharmacy and be faxed there directly.

It is helpful to add standard instructions to the bottom of the prescription where relevant, including the following:

- Dispense a carry for holidays and pharmacy closures.
- Please notify the prescriber at <contact information> of any missed or withheld doses.
- Hold the prescription and contact the prescriber at <contact information> if the client has missed four consecutive doses.

Any exceptions to usual prescribing practices should be noted so that the pharmacy does not cancel the prescription. Examples include a planned dose increase after fewer than three consecutive doses, or if the prescriber intends the prescription to be available even with multiple missed doses. If a preplanned dose increase is written (i.e., dose is to be increased prior to the next assessment), the prescriber should specify what to do if a dose is missed prior to the increase, e.g., "Dose increase: If patient misses a dose, continue prior dose; do not increase and do not cancel prescription unless four or more doses have been missed." Prescribers should specify on the prescription how they can be contacted by the pharmacist in case of prescription questions to minimize the likelihood and consequences of doses being withheld.

See **Appendix G** for a sample prescription.

Community pharmacy dispensing

General considerations that apply to all individuals on OAT and high-dose opioids include the need to confirm the correct client identity with observed dosing. It may be convenient for the client and for the pharmacy staff to have a client's photo ID scanned into the pharmacy dispensing software so that the client does not have to present a physical copy every time. For people without ID, options include using a "code" or describing the person's appearance by a unique feature (e.g., a piercing, beard, or tattoo) that can be used to confirm the person's identity at the first visit. Calling the pharmacy to let them know that the person is coming without ID is helpful. Prescribers should also inform the pharmacy if someone other than the patient will be picking up the methadone and the rationale.

Prior to every dispensed dose, all clients are assessed by the pharmacist to determine whether it is safe for them to receive an observed dose and/or a carry dose. META:PHI's document *A New Framework for Methadone Carries* (2) makes the following recommendations for these situations:

- A methadone dose should not be dispensed in situations where the risks of dispensing outweigh the benefits (e.g., when the person is significantly intoxicated or sedated or when there are concerns about their acute well-being).
- If a person appears intoxicated, the pharmacist should ask about recent substance use and provide counseling regarding self-monitoring and harm reduction. Intoxicated individuals can be asked to return later to receive an observed dose once their intoxication has resolved.
- Prescribers should make themselves available to pharmacists for case discussion as necessary, particularly after hours, to minimize consequences associated with withheld doses.
- If someone misses an observed dose on a day they were supposed to pick up carries, they should receive an observed dose on the day they attend. Carries should not be dispensed if the person has missed three consecutive doses.

Considerations for special conditions and populations

Mental health conditions

Co-occurring mental health conditions are common in people with OUD; a recent systematic review and meta-analysis of comorbid mental disorders in people with OUD estimated a prevalence of 36.1% for depression, 29.1% for anxiety, 20.9% for attention-deficit/hyperactivity disorder, 18.1% for post-traumatic stress disorder, and 8.7% for bipolar disorder (112). Given the prevalence of mental health disorders among people with OUD, it is important that OAT clinicians identify and provide first-line treatment for psychiatric disorders and review mental health considerations regularly. A systematic review has shown that integrated treatment for concurrent disorders leads to better substance use and mental health outcomes than non-integrated treatment (113). Interventions can include supportive counseling, appropriate medications, psychotherapy, and referral to community services. When management of more complex mental health conditions is required (e.g., bipolar disorder, psychosis, OCD, treatment-resistant depression), referrals to psychiatry and community mental health services should be offered.

We recommend that clinics that provide OAT have at least one staff member who is able to provide psychoeducation, counselling, and support to individuals with mental health conditions; clinics should also work to provide connections to other services, including community mental health services, psychiatry, and primary care services with the resources to manage psychiatric illnesses. All clinicians should practice trauma-informed care.

While recognizing the substantial prevalence of trauma among people with OUD, asking about the details of a person's traumatic experiences is not recommended, as it can be retraumatizing. However, acknowledging the role that past trauma may play in people's current lives can help to build trust and reduce the sense of shame and blame that many trauma survivors carry. The principles of trauma-informed care should be central to OAT care, with the goal of creating a safe environment that minimizes the potential for harm and builds client resilience.[10]

A review of the management of mental health disorders is beyond the scope of this document, and other excellent resources are available (116, 117). The following are highlights of potential interactions between methadone and other first-line medications for mental health conditions:

- **SSRIs/SNRIs:** A population-based case control study of patients on methadone (118) found that SRIs were associated with a small increased risk of death or hospitalization from ventricular arrhythmias (OR = 1.3); the risk was attributed to prolongation of the QTc interval and inhibition of methadone metabolism. The study did not control for use of cocaine or crystal meth, which are also arrhythmogenic. An ECG should be obtained for patients taking both methadone and SSRIs/SNRIs, but methadone initiation should not be delayed pending the results. A cardiology consultation might be considered if the patient is at higher risk of QTc prolongation. Methadone is also a weak serotonin uptake inhibitor. Although rare, there are case reports of methadone contributing to serotonin syndrome when other serotonergic medications are used concurrently (63). In practice, most cases of serotonin syndrome result from multiple drugs interacting together (64), and methadone is unlikely to contribute to a significant degree (65).
- **Benzodiazepines, z-drugs, and gabapentinoids:** Benzodiazepines and z-drugs (zopiclone, zolpidem) should not be routinely prescribed due to concerns about sedation, tolerance, dependency, cognitive impairment, and increased risk of overdose (119, 120); they should be prescribed with caution and preferably for short-term use (e.g., management of alcohol withdrawal). Pregabalin and gabapentin should be prescribed with caution.
- **Antipsychotics:** Antipsychotics are associated with an increased risk of overdose and an increased risk of QTc prolongation in patients on methadone (120). They should be used with caution in patients at higher risk of overdose or QTc prolongation. Low-quality evidence suggests that aripiprazole, brexpiprazole, and olanzapine are not associated with QTc prolongation (121)

Concurrent substance use

Concurrent substance use during methadone therapy is associated with additional risks and implications for OAT safety, and may also make it more challenging for people to remain on OAT given the logistical requirements of accessing methadone. Regular assessment of opioid and non-opioid substance use at methadone assessments is an integral part of care and presents an opportunity to discuss goals and review harm reduction strategies. However, there is insufficient research on concurrent substance use during methadone therapy to guide treatment choices for improved retention and desirable outcomes.

[10] For specific guidance on asking about trauma and providing trauma-informed care, we recommend reviewing the resource *Trauma-Informed Practice & the Opioid Crisis* (114) and the article "Why, when and how to ask about childhood abuse" (115).

Methadone and stimulants

There is a high rate of concurrent stimulant (i.e., cocaine, crack cocaine, and methamphetamine) use among individuals starting OAT (122). While some research has shown that methadone treatment appears to reduce cocaine use, other studies indicate a negative association between stimulant use and retention in OAT (123-125). Stimulant use also overlaps with other factors associated with discontinuation of methadone treatment, including daily injection use, recent homelessness, recent incarceration, and not receiving income assistance (126-128). Qualitative research has shown that people use stimulants in different ways and for a variety of reasons, including to meet daily survival needs (e.g., to stay awake in unsafe environments) and to combat sedation or withdrawal from methadone or other opioids; for some people using opioids and stimulants, better management of opioid use without abstinence from either opioids or stimulants may be goals of care (129). This highlights the importance of individualizing harm reduction strategies among people who use stimulants and opioids. Co-locating OAT and treatments such as contingency management and cognitive behavioural therapy, which are associated with reduced stimulant use (130, 131), may be of benefit.

Stimulant-induced psychotic symptoms may present in people taking OAT who are using high doses of cocaine or methamphetamines. Although second-generation anti-psychotics can be used to address acute psychosis (132), QTc prolongation risk must be considered for some drugs of this class in combination with methadone.

Methadone and alcohol

Problematic alcohol use has been found in approximately one third of people with OUD (133). In addition to increased risks of overdose and mortality due to the combined sedative effects of methadone and alcohol, people with alcohol use disorder and OUD appear to have poorer psychosocial functioning and more serious medical and mental health issues (134). Addressing alcohol use with education, medications (e.g., acamprosate or topiramate, which is a mild CYP3A4 inducer), and appropriate psychosocial supports is important in the setting of OAT. Note that gabapentin should be used with caution in people taking methadone due to increased risks of fatal overdose with moderate and high daily doses of gabapentin. Naltrexone is contraindicated in people on any form of OAT.

When treating alcohol withdrawal in patients on OAT, caution is required due to the respiratory depressant effects of opioids and benzodiazepines. Consideration should be given to using shorter-acting benzodiazepines (e.g., lorazepam versus diazepam) and lower doses to manage withdrawal, and patients should be in a monitored setting. In most cases, patients experiencing concurrent alcohol and opioid withdrawal should have their alcohol withdrawal managed first due to the risk of withdrawal seizures, delirium tremens, and Wernicke's encephalopathy. Concurrent withdrawal syndromes make withdrawal monitoring scales less reliable; fixed-schedule dosing with close monitoring should be used rather than symptom-triggered dosing. In the context of concurrent OUD, alcohol withdrawal management with benzodiazepines should be completed first; low-dose methadone can be started with caution once the withdrawal has resolved.

Methadone and benzodiazepines

Use of prescribed and non-prescribed benzodiazepines is common among people on OAT, and concurrent benzodiazepine and methadone exposure is associated with increased risk of mortality. Benzodiazepine use at treatment initiation may also be associated with higher rates of OAT discontinuation; in a retrospective cohort study of people on OAT in Ontario, people taking benzodiazepines were more likely to be in the lowest income quintile, had more interactions with the health care system, more medical comorbidities and diagnoses for depression or anxiety related disorders (135). This highlights the difficulties in finding appropriate resources for patients with complex social and medical problems and the challenges of managing benzodiazepine prescriptions, which are always easier to initiate than discontinue. Although benzodiazepines have been associated with an increased risk of overdose in patients on methadone (119, 120) and do not appear to improve treatment retention (136), careful prescribing of low-dose benzodiazepines with daily dispensing may be an appropriate short-term intervention for managing benzodiazepine withdrawal experienced during reductions in fentanyl use during OAT treatment initiation.

As a general rule, benzodiazepines should be prescribed at the lowest possible dose and for the shortest possible duration (137), particularly for people co-prescribed methadone. Conditions for which long-term benzodiazepines may be indicated include some seizure disorders, spasticity, and sleep behaviour disorders such as restless leg syndrome (138); prescribing should ideally take place in consultation with an appropriate specialist. Being on a benzodiazepine should not preclude access to methadone, but it should be a factor when considering methadone dose initiation and titration. Clinicians should assess the risks and benefits of initiating, maintaining, or tapering benzodiazepines regularly. When a dose reduction or discontinuation is indicated, a gradual taper with long-acting benzodiazepines (e.g., diazepam, clonazepam) is appropriate for people with physical dependence (tolerance/withdrawal).

Hepatitis C

Hepatitis C (HCV) has the greatest burden of disease of any infectious disease in Ontario (139). Injection drug use is the major mode of HCV transmission in Canada; it has been estimated that people who inject drugs represented 60–85% of all new HCV infections from 2000–2016 (140). OAT clinics have been identified as an important setting for identifying and treating HCV (141); there is good evidence that high-quality HCV treatment can be delivered outside of specialist clinics with appropriate training (142), and that embedding HCV management into multidisciplinary and flexible care models, including OUD treatment programs, helps reduce barriers to HCV care for people who inject drugs (143).

Clinicians prescribing methadone should establish workflows that facilitate HCV testing, counselling, and treatment. Patients starting OAT should be screened for HCV, ideally using point-of-care testing or dried blood spot collection (141), along with other baseline testing; people who engage in ongoing high-risk activities should be re-screened at least annually. All patients with chronic HCV infection should be considered candidates for antiviral therapy. Clinics that do not have the capacity to deliver treatment should develop relationships with partners such as **Ontario Hepatitis C Teams**, which are embedded in communities across the province.

HCV information and resources for clinicians and patients can be found at the **Ontario Hepatitis C Elimination Roadmap** and at **CATIE**.

Acute pain

Acute pain in people on methadone should be managed using the same principles as in people not on OAT, including a comprehensive assessment, multimodal therapies, and shared decision-making (144). A brief course of short-acting opioids can be used when non-opioid pharmacologic and non-pharmacologic options are insufficient for conditions where opioids may be appropriate. Methadone alone will not provide adequate analgesia because patients on long-term methadone treatment develop tolerance to its analgesic effects (145).

General principles of management of acute pain in people on methadone are summarized below:

- Whenever possible, OAT should not be stopped during an acute pain event.
- People on methadone often require higher and/or more frequent doses of opioid analgesics because of cross-tolerance between methadone and other opioids.
- The choice of opioid should be discussed with the patient. Patients who had problematic use of oxycodone, for example, might prefer morphine or hydromorphone instead. Oxycodone with acetaminophen can be a good option to deter injection, as acetaminophen does not dissolve. Codeine should generally be avoided due to its low potency and interindividual variability.

- Three days of opioids for acute pain is sufficient for most patients; for patients with more severe pain (e.g., post-operative pain), up to seven days may be required (144).
- Whenever possible, the methadone prescriber and pain team/primary care provider should be in communication to optimize care and communicate regarding medication plans.
- When opioids are prescribed in the community (e.g., extended following discharge from hospital or for people being managed in ambulatory settings), they can be dispensed in alignment with the methadone schedule. Patients on daily observed methadone dosing would have their opioid dispensed daily.
- Timely and adequate pain control in hospitalized patients is critical; undertreatment of pain is a known reason for patients to leave the hospital before treatment completion (146). See **Appendix I** for more information on prescribing methadone in inpatient settings.

Chronic pain

The prevalence of chronic pain in patients on OAT has been estimated to be 45.3% (147). People on OAT who have concurrent chronic pain should receive a comprehensive assessment that considers the person's relevant physical and psychological conditions, as well as their social determinants of health (148). Pain management goals should focus on improvements in function and quality of life and be monitored using validated tools. Non-opioid medications and non-pharmacological therapies (such as cognitive behaviour therapy and mindfulness-based therapies) should be prioritized as first-line approaches to management of chronic pain. Self-management programs (such as the Toronto Academic Pain Medicine Institute's program) are also known to improve function and decrease perceptions of disability. A full review of the management of chronic pain is beyond the scope of this document; clinicians are encouraged to review the *Canadian Guideline for Opioid Therapy and Chronic Noncancer Pain* (149) and other appropriate resources.

Pharmacotherapy

Methadone as OAT has been shown to reduce pain in patients with comorbid chronic pain and opioid use disorder (150, 151). Methadone is a potent opioid analgesic; a systematic review of controlled trials concluded that methadone was effective for neuropathic, somatic, and cancer-related pain (152). Due to methadone's shorter duration of analgesia (relative to its duration of opioid withdrawal suppression), the American Society of Addiction Medicine (**ASAM**) recommends considering split methadone dosing for patients with chronic pain (153); a trial of split dosing can be considered in patients who report worsening pain eight or more hours after their methadone dose (see section on split dosing).

A narrative review on management of chronic pain in patients with opioid use disorder recommends that non-opioid medications such as NSAIDs and SNRIs be tried before opioids (154). Gabapentin and pregabalin should be used with caution, as the combination of methadone and gabapentinoids is associated with an increased risk of death (155).

Opioids should be co-prescribed with methadone only for severe, debilitating pain that has not responded to other modalities, and only in consultation with a specialist with experience in the patient's chronic pain condition. People taking methadone are highly tolerant to opioid analgesia; in an experimental study, patients on methadone 80–100 mg per day had no analgesic response to a cumulative dose of 32 mg IV hydromorphone (156). Thus, the analgesia provided by a supplemental opioid will likely be limited and temporary, and its benefits will be outweighed by potential adverse effects such as sedation or withdrawal symptoms.

Consultation and shared care

Addressing underlying conditions is critical, though often challenging, given the difficulties accessing primary care and specialist referrals frequently faced by people with OUD. For example, for people with inflammatory arthritis experiencing joint pain, treatment with appropriate disease-modifying medications or referral for joint replacement when appropriate is more appropriate than simply medicating the joint pain. OAT providers have a role in connecting patients with chronic pain to appropriate resources for assessment and management, such as primary care and comprehensive pain clinics (154, 157).

Pregnancy and parenting

OAT should be offered to all pregnant patients with OUD. While the product monograph (55) states that methadone is contraindicated during pregnancy (Category C) due to the risks of neonatal withdrawal syndrome, the World Health Organization has recognized that the benefits of OAT outweigh the risks associated with ongoing uncontrolled opioid use for the pregnant person and the pregnancy (158). Use of OAT during pregnancy is associated with improved birth outcomes compared to not being in treatment and actively using unregulated opioids during pregnancy (159), and a systematic review and meta-analysis found that methadone use during pregnancy is not associated with cognitive impairment, neurodevelopmental effects, or congenital defects, after controlling for smoking and other variables (160).

Pregnant patients starting methadone should be initiated at the lowest effective dose. Higher doses of methadone may be required as the pregnancy progresses; split doses are often helpful with managing withdrawal due to the increased hepatic metabolism of methadone in pregnancy. Breastfeeding/chestfeeding on methadone is safe regardless of dose and may help decrease neonatal opioid withdrawal symptoms while facilitating bonding (161). Split dosing can be maintained or once-daily dosing can be resumed after delivery, depending on patient preference.

Under Section 125 of the **Child, Youth and Family Services Act**, every person who has reasonable grounds to suspect that a child younger than 16 years of age is or may be in need of protection must immediately and directly report the suspicion and the information upon which it is based to a Children's Aid Society (CAS). Youth aged 16–17 are also eligible to receive CAS protection services, but reporting is not mandatory. Substance use and being on methadone, including during pregnancy, are not reasons in and of themselves for reporting to CAS.

Opioid use in pregnancy is heavily stigmatized, which creates a barrier to seeking care and self-disclosure of use. Pregnant people seeking care for OUD should be assured that their personal health information is confidential outside of requirements for mandatory reporting. The practice of birth alerts (notifying a hospital or birth centre of safety concerns before birth) ended in Ontario in 2020.[11] Hospitals and health care staff should still report any concerns regarding the safety and well-being of an infant, child, or youth to a CAS or an **Indigenous Child and Family Well-Being Agency**.

[11] This **blog post** by the Ontario Association of Children's Aid Societies provides the reasons behind the decision for eliminating the practice of birth alerts.

It is helpful to be aware of local child and family services, the resources and supports that they offer, and the community's perception of their work. With the patient's consent, consider working alongside these organizations for improved outcomes. For patients that choose it, there can be benefits to early self-disclosure of OAT, particularly in situations where the patient is already known to child and family services, in preparation for a smooth birthing process and return-to-home. Regardless of the path chosen, empowerment of the expectant patient is the key to maintaining trust and continuing care.

For more information and resources on supporting pregnant patients, see the BCCSU document *Treatment of Opioid Use Disorder During Pregnancy: Guideline Supplement* (162) and the Canada FASD Research Network document *Substance Use During Pregnancy: An Overview of Key Canadian Policy and Practice Areas* (163).

Youth

Youth aged 15–25 remain significantly less likely than adults to receive OAT across treatment settings (164, 165). While there is evidence to support the use of pharmacotherapy for youth with moderate to severe OUD (166, 167), it is important to consider the neurodevelopmental and psychosocial factors associated with adolescence and young adulthood that can impact both substance use and treatment (168).

When OAT is appropriate, there are strong reasons to consider buprenorphine SL before methadone in this population due to its more favourable safety profile and increased flexibility for take-home dosing. Youth typically have a shorter duration and lower intensity of opioid use; the increased risks of methadone (including overdose) must be considered in that light. Youth may also be more likely to have difficulty attending a pharmacy daily for extended periods of witnessed dosing, which can result in disruption of methadone therapy, leading to loss of opioid tolerance and ensuing risks. A study of youth on methadone in Vancouver found high levels of treatment discontinuation; missing doses and being taken off of treatment by a care provider were the most common reasons reported for methadone discontinuation (164). Buprenorphine SL is also perceived by youth to be less stigmatizing than methadone (169), which is important considering the stigma and self-stigma associated with OUD and the emerging identity of youth.

For these reasons, methadone may be considered second line for youth with OUD for whom buprenorphine SL is not effective or contraindicated, and it may be an acceptable alternative first-line option for youth with more severe OUD (e.g., sustained use of fentanyl) where discontinuation of OAT could have serious adverse consequences (168, 170). With regard to dosing, BCCSU (170) recommends an "individualized and step-wise" (p. 20) approach to determine optimal dose; prescribers without experience initiating youth on methadone should consult with a specialist with "considerable experience treating youth with OUD" (p. 21).

Other factors to consider in supporting youth in treatment include the high rates of mental health co-morbidity and of polysubstance use in this population. While family engagement has been recommended in treatment for youth due to its association with improved rates of treatment engagement, duration of abstinence from substance use, and fewer relapses (167), family dynamics can be contributors to substance use, and confidentiality and patient autonomy must be considered. Finally, the choice of treatment setting for youth may be limited by options; keeping youth out of traditional OAT clinics may be desirable to avoid socialization into higher-risk substance use circles, but few primary care/pediatric settings provide OAT care.

Setting-specific considerations

Transitions of care

Transitions between different care settings (e.g., between hospital and community, between different community providers, between correctional settings and community) can compromise continuity of care and patient safety. Because of this, it is crucial for clinicians to ensure that there is clear communication around any care transfers. For patients admitted to hospital, it is expected that the inpatient team will communicate with the community prescriber and pharmacy regarding the patient's admission, any dose adjustments, and discharge prescriptions. Direct communication (such as a phone call or secure email) between care providers is strongly recommended over a fax or assuming that a discharge report will reach the community prescriber. When care is being transferred between community prescribers, providers should ensure continuity of care by writing prescriptions until the patient's upcoming appointment.

The Digital Health Drug Repository (**DHDR**) can be helpful for obtaining collateral information about methadone dosing. It contains information about all monitored drugs billed by community pharmacies to individuals with a valid Ontario Health Number and can be accessed through ClinicalConnect, ConnectingOntario, ClinicalViewer, and some electronic medical records. However, verifying with the dispensing pharmacy is the only true method of confirming last dispensed doses, as DHDR contains billing information. Methadone doses (both observed and carries) are sometimes billed prior to dispensing to help with workflow; if a client does not appear for a pre-billed dose, it may take time for the billing reversal to be updated in DHDR. Note that DHDR does not track medications dispensed in other settings (e.g., hospital pharmacies, correctional settings); in these cases, doses can be confirmed by contacting the dispensing facility directly.

In cases where care cannot be appropriately transferred (e.g., if a patient is moving to a new community and the prescriber does not know any methadone prescribers in that community), the methadone prescription should not be stopped abruptly; the prescriber should continue prescribing until a new care provider is found or the patient decides to discontinue treatment. The prescriber may decide that it is safest to have all doses witnessed while ongoing clinical follow-up is not possible. If the patient decides to discontinue treatment, the prescriber should taper the dose gradually (as described above) rather than stopping it abruptly. Any decisions regarding cessation of care should be made in accordance with the policies of the CPSO or College of Nurses of Ontario (CNO), discussed with the patient, and documented clearly. The Ontario College of Pharmacists maintains a registry of all pharmacists that dispense methadone. Nearby pharmacists can be contacted for information on geographically co-located methadone prescribers.

RAAM clinics

Rapid access addiction medicine (RAAM) clinics are low-barrier, drop-in clinics that provide substance use–related care without requiring an appointment or referral. While META:PHI's guidance document on quality targets for RAAM clinics (7) states that RAAM clinics should aim to prescribe methadone when appropriate, managing methadone on a long-term basis can be challenging for RAAM clinics with limited hours and prescriber availability. Thus, while providers working in RAAM clinic settings should start methadone in patients for whom it is indicated, it may be necessary for these patients to eventually have their care transferred to another clinic.

We recommend that RAAM clinicians that are unable to provide long-term methadone therapy due to resource limitations develop relationships with local OAT prescribers in order to facilitate transfers of care for stable patients. When transferring care, it is essential to ensure that the patient has access to their medication throughout the transition; the RAAM clinic provider should continue to prescribe methadone until the patient begins seeing the new prescriber. For all patients whose care will eventually be transferred, we recommend discussing this eventual transfer with the patient as early as possible in care; being transparent about the plan from the beginning will help create trust in the relationship.

We recommend that prescribers in RAAM clinic settings use the following methods of ensuring that patients have ongoing access to methadone:

- Consider an extended initial methadone prescription (up to 14 days) in case a person does not return for follow-up.
- Have a system for arranging follow-up to align with the end of a methadone prescription and for reaching out to patients who do not follow up as expected.
- Collaborate with pharmacists to ensure good communication and prescription continuity:
  - Ask pharmacists to fax a renewal request before a prescription ends.
  - Ask pharmacists to communicate with you regarding missed doses.
- **Do not discontinue methadone abruptly.** If a patient needs to be discharged to another OAT setting, continue prescribing methadone until care is transferred to the new setting.

Northern First Nations, Inuit, and Métis Communities

Individuals living in First Nations, Inuit, and Métis communities in remote areas generally receive buprenorphine (SL or XR) as OAT, as methadone is typically not available. Health care providers serving Indigenous patients in non-remote settings should consider whether the patient is likely to be travelling or returning home to a community where methadone will not be available before initiating methadone; buprenorphine is preferable in these situations to avoid interruptions in therapy.

Virtual care

The use of virtual care for OAT increased significantly with the social distancing requirements of the COVID-19 pandemic (171, 172). This has facilitated the removal of typical barriers to substance use–related care due to socioeconomic and structural issues, including stigma (173). Evaluations have shown that virtual care effectively decreased wait times (174), increased the number of new OAT starts, increased appointment attendance (175), increased retention in treatment, and increased patient satisfaction (174, 176-178). It also removes barriers of transportation and improves flexibility for the patients (176). These benefits were expected to be particularly beneficial for rural and remote regions (178) and youth (175).

Lack of "digital literacy" and access to electronic devices and phones have been described as barriers to virtual care (178, 179). It has also been suggested that virtual care feels impersonal and makes it hard to build rapport (176, 178). Other concerns included infrastructure development and costs, virtual care training requirements, and health information protection (176). Concerns regarding increased medication diversion and overdose related to virtual care have not been demonstrated by the literate to date (176, 180).

There is general agreement that, given its safety profile, buprenorphine SL can be safely started through virtual assessment and either transitioned to longitudinal care (180-183) or continued through virtual care (173, 184). The provision of methadone through virtual care varies; many programs require an initial in-person appointment, though some will support initiation of methadone via a video assessment (176, 181). Phone-based care for methadone prescriptions, though generally reserved for stable, long-term patients (173, 176, 185), can be used to connect with patients who miss an appointment to reduce treatment interruption as an element of patient-centered, harm reduction–oriented care.

When providing access to methadone through virtual care, supporting information to ensure tolerance should be reviewed before initiating medication (174, 185). This can be gathered through platforms such as Connecting Ontario, where information on recent clinical or hospital visits for substance-related reasons and UDTs ordered by other clinicians may be visible. Clinicians can also request that patients provide a urine sample at a clinic location with staff available to conduct a UDT or at a local lab. The highest-risk patients likely benefit from in-person services due to the support of face-to-face connections and access to physical exams. While they may connect through virtual care, ideal infrastructure would allow these individuals to be redirected to low-barrier in-person services, with at minimum psychosocial supports being made available through virtual care at the initial touch-base (171, 176).

Primary care

There is good evidence that primary care providers (PCPs) can provide methadone treatment safely and effectively and that patients strongly prefer receiving treatment in a primary care setting. A scoping review of randomized trials and observational studies found that stable patients receiving methadone in primary care settings versus specialized settings had higher ratings of treatment satisfaction and similar rates of treatment retention and unregulated substance use compared with those receiving methadone in specialized addition settings (186). Patients on methadone have higher rates of medical and psychiatric comorbidity than matched control patients not on methadone (187) but are significantly less likely to receive screening for cancer or monitoring for diabetes (188); incorporating OAT care into the primary care setting (the patient's "medical home") increases access to screening as well as chronic disease management. However, a qualitative study found that even PCPs who are willing to prescribe methadone feel they lack the necessary training and support (189).

Methadone prescribers can work with PCPs to help reduce some of these barriers to care, starting with working collaboratively throughout methadone treatment to ensure positive connections with primary care providers are fostered:

- Communicate with the patient's PCP through intermittent progress updates or when there is a change in treatment to maintain communication. Sharing information about prescribed medications and interactions is important to ensure that care is a collaborative effort.
- Discuss the possibility of transferring stable patients to the PCP, particularly those who need screening and/or chronic disease management.
- When transferring a patient, provide clear communication regarding the person's methadone dose and take-home schedule. Discuss the role and frequency of urine monitoring, which can be done through the lab without the need for point-of-care testing. Ideally communicate with the PCP verbally and not only by letter.
- Offer to be available by email or phone for questions that might arise, and to reassess the patient if requested.
- Remind primary care physicians of the OHIP service codes for patients on methadone.

PCPs can support collaborative care with methadone prescribers by sending information regarding new diagnoses, medication changes, and investigations completed. When taking on a patient on methadone, the PCP can speak with the pharmacist for additional information regarding the patient's history on methadone and recent dose changes. Patients who pick up medication frequently are often well known to the pharmacy staff, who can provide useful insight into any logistical issues with prescriptions and how the person appears to be doing. PCPs can ask the pharmacy for a copy of the last methadone prescription sent by the previous prescriber. This can be used as a template for future prescriptions, minimizing disruption in continuity during transfer of care.

PCPs can find resources and courses about substance use health care through many organizations, including **META:PHI**, **BCCSU**, **CAMH**, and **Project ECHO**. Family physicians can also access peer mentoring through the **OCFP Peer Connect Mentorship**.

Correctional facilities

Up to 80% of the federal prison population in Canada has a substance use issue, with opioids being a significant contributor (190, 191). People with OUD are at an elevated risk of justice system involvement due to the intersection of possession charges and behaviours linked to substance use, such as theft or other non-violent crimes.

Justice system encounters and incarceration represent periods of increased vulnerability to harms for individuals with OUD; events around arrest, detainment, and court appearances can be chaotic, resulting in missed OAT doses, and those not on OAT may undergo severe withdrawal. The subsequent loss of tolerance and intense cravings mean that any exposure to unregulated opioids inside a facility or soon after release can lead to an overdose or other injection-related harms (192).

Interventions to improve the lives of people with OUD who experience incarceration can be considered in terms of three stages of opportunity: pre-arrest (planned or unplanned), incarceration, and post-release.

Pre-detention

For individuals with a known upcoming period of detention, ensure optimal OAT dosing with methadone (or buprenorphine SL) if they are not already therapeutic. SROM and/or short-acting opioids are not available in correctional settings; therefore, individuals on these therapies should ideally be switched to methadone or buprenorphine SL and titrated to a therapeutic dose prior to incarceration.

Incarceration

People who are incarcerated are at high risk for opioid overdose during incarceration due to reduced tolerance through periods of forced abstinence and/or OAT disruptions. Individuals who use opioids are more likely to continue drug use while incarcerated compared to those who use other types of drugs (193), and the risks of injection-related infections are also elevated due to using non-sterile materials to inject (194). For prescribers and other staff working inside correctional facilities, it is important to ensure that assessment for OUD happens as early as possible, that OAT is initiated or continued promptly, and that doses are titrated to therapeutic levels (typically minimum 80 mg for methadone).

Preparing for release

The risk of death due to drug toxicity is extremely high during the first two weeks after release (195). The two most important evidence-based strategies to reduce this risk are OAT and provision of naloxone kits. Doses of OAT should ideally be optimized in the two weeks prior to a scheduled release. Buprenorphine XR is one option, particularly for those already taking buprenorphine SL. For people taking methadone, adjusting the dose to at least 80 mg is recommended. Correctional facilities should ensure that individuals are released with a one-week minimum prescription for their OAT. Staff should identify a pharmacy that is convenient for the patient and connect with the patient's community prescriber promptly to ensure that dose information and end dates are clear. Community prescribers and clinics should take steps to ensure that individuals released from corrections can be seen promptly and without needing to navigate barriers to care. Individuals released without prescriptions need to be assessed within a day of release whenever possible. All incarcerated individuals with OUD should be given a take-home naloxone kit upon release and educated about loss of tolerance.

APPENDIX A: Decision Aid Tool

The purpose of this tool is to give you information about the different medications for opioid use disorder. You can use this tool with your health care provider to help you understand what your options are and which choice makes the most sense for you.

YOUR OPTIONS:

- Suboxone (sublingual buprenorphine/naloxone)
- Sublocade (injectable buprenorphine)
- Methadone
- Kadian (slow-release oral morphine)

KEY POINTS TO REMEMBER:

- Opioid agonist treatment (OAT) is taking a long-acting opioid medication to relieve opioid withdrawal symptoms and cravings. It is the most effective therapy that we know of for opioid use disorder, and taking it lowers the chance of a fatal overdose from other opioids. **Suboxone, Sublocade**, **methadone**, and **Kadian** are all options for OAT.

- **Buprenorphine** has a lower chance of side effects and lower risk of overdose compared with methadone and Kadian. It might not provide enough relief of withdrawal symptoms and cravings for people with very high opioid tolerance. Buprenorphine can be taken as a tablet under the tongue (Suboxone) or as an injection (Sublocade).
  - **Suboxone** is usually taken once a day. There are many ways to get started on Suboxone, and you do not necessarily have to be in withdrawal to get started. The dose can be increased quickly. Take-home doses are usually available much sooner than they are for methadone or Kadian. Suboxone is available at most pharmacies.
  - **Sublocade** is usually taken once a month. You get your first injection after taking Suboxone for a few days, and then the buprenorphine stays in your system for three or four weeks. You can take doses of Suboxone if the Sublocade isn't enough by itself. You will probably have to go to a clinic for your injections, although some pharmacies do injections as well.

- **Methadone** is usually taken once a day. Methadone provides more relief of withdrawals and cravings than buprenorphine. It has a higher chance of side effects and higher risk of overdose compared to buprenorphine. The dose is increased slowly, usually over four to eight weeks. It can sometimes be combined with Kadian at the beginning of treatment to help reduce withdrawal. It usually takes at least a month to start getting carries. Methadone is not available at all pharmacies.

- **Kadian** is usually taken once a day. It provides more relief of cravings and withdrawal symptoms than buprenorphine does. The dose can be increased a bit faster than methadone can. It usually takes at least a month to start getting carries. There is some evidence that Kadian has a lower chance of side effects than methadone.

FAQ

Here are answers to some of the questions you might have about these medications. As you go through this with your health care provider, think about your own health, situation, and values, and add your notes in the column on the right. Be sure to ask about anything that's unclear.

	Buprenorphine		Methadone	Kadian	Notes
	Suboxone	Sublocade			
What does it do?	Helps opioid withdrawal symptoms and cravings				
How much do we know about it?	Used in Canada since mid-2000s and has lots of research evidence	Approved for use in 2019 – not many studies yet	Has been used since the 1960s and has the most research evidence for OAT	Has been around since the 1990s mostly as a treatment for chronic pain– some studies but evidence isn't as strong for OAT use	
How do I take it?	Tablet that dissolves under the tongue	Injection under the skin of the belly	Drink (often orange-flavoured and coloured)	Capsule that you swallow whole or opened and sprinkled into a cup or food	
How often do I take it?	Usually once a day	Usually once a month	Usually once a day	Usually once a day	
Where do I take it?	Dose is taken at the pharmacy at first, then usually at home within weeks	Usually done at a clinic	Dose is taken at the pharmacy every day for at least one month, then take-home doses start gradually	Dose is taken at the pharmacy every day for at least one month, then take-home doses start gradually	
How do I start it?	Various ways: Can be started in withdrawal 12–18 hours after last opioid use OR started at a "micro" dose and increased very gradually	You have to take buprenorphine tablets at a dose of 8 mg or more for at least a day or two before your first injection	You can take your first dose anytime Sometimes combined with Kadian at the start of treatment	You can take your first dose anytime	
How fast can I increase my dose?	The dose can be increased every day	There is one standard dose of the injection	The dose can be increased every three to five days	The dose can be increased every two days	
When will I start feeling better?	You can usually get to a helpful dose within a few days if you start it in withdrawal	You will probably already be at a good dose from the tablets when you get your first injection	It can take one to two weeks to start feeling better, and one month to reach a dose that feels really helpful Sometimes Kadian can be added to methadone at the beginning of treatment, which can help reduce withdrawal	It can take one to two weeks to start feeling better, and one month to reach a dose that feels really helpful	

	Buprenorphine		Methadone	Kadian	Notes
	Suboxone	Sublocade			
How do I get it?	Many health care providers prescribe it and most pharmacies have it	Not all health care providers do injections – you might have to go to a special clinic	Not all health care providers prescribe it, and not all pharmacies have it – you might have to go somewhere new, especially if you live in a small or remote area	Not all health care providers prescribe it for OAT, but most pharmacies have it – you might have to go somewhere new, especially if you live in a small or remote area	
How much does it cost?	About $10–12 per day (covered by Ontario Drug Benefits)	$550 per month (covered by Ontario Drug Benefits with a Limited Use code)	About $6 per day (covered by Ontario Drug Benefits)	Varies by dose – an average dose (about 800 mg) would be about $21 per day (covered by Ontario Drug Benefits)	
What are the side effects?	All opioids can cause sweating, constipation, dry mouth, headache, itchiness, and weight gain as side effects All opioids can cause hormone changes, which could lead to a lower sex drive, irregular periods, erectile dysfunction, or a higher chance of getting pregnant Kadian and methadone can both make you feel sedated or high at higher doses Buprenorphine has the mildest side effects (although the injection can leave a bump on the skin and can cause brief pain and itchiness on the belly) Kadian's side effects are mostly milder than methadone's				
What are the risks?	All opioid medications (especially methadone) can affect how other medications work – make sure you tell your health care provider about everything you're taking Methadone and Kadian both have a risk of overdose, especially when taken with alcohol or benzos (like Xanax or Valium) Methadone can be dangerous for people with certain kinds of heart problems (mostly related to irregular heart rhythms) Sublocade isn't recommended as a first choice for people who are pregnant				
How well does it work?	Buprenorphine is a "partial" opioid agonist – it might not fully relieve your withdrawal and cravings, especially if you have very high opioid tolerance If Sublocade isn't enough by itself, you can take Suboxone at the same time		Methadone and Kadian are both full opioids – they may be more likely than Suboxone or Sublocade to fully relieve withdrawal and cravings		
What would happen if I used opioids while taking it?	Blocks the high from other opioids more than methadone and Kadian	Blocks the high from other opioids more than methadone and Kadian	Reduces the effect of other opioids	Reduces the effect of other opioids	

PERSONAL STORIES

"Going through opiate withdrawal, I had 3 choices. Tough it out and go cold turkey (I highly do not recommend this method!!), methadone, or Suboxone. I knew I didn't want to get high anymore and wanted to change my life. I know many people on methadone and they still got high every day. I heard from others about Suboxone and how you can't get high on it or you get really sick. That was appealing to me more for reassurance if I did go get high." — **Angela**

"I was on methadone for 7 years, and while very high doses twice a day took care of my withdrawal and helped me stay off other opioids, it never took care of the cravings, and I was very depressed, unmotivated, and still in extreme physical pain – the reason for the opioids in the first place. After a relapse to fentanyl (the only available option), I found someone willing to prescribe Kadian alongside methadone. The addition of Kadian provided the extra relief I needed for withdrawal. It eventually eliminated my opioid cravings, and it has also helped with my depression and my ulcerative colitis. I have attempted multiple medical-assisted opioid treatments, but this is the most successful treatment for me. By choosing my own path, I was able to take ownership over my well-being and I am the healthiest I have ever been." — **Ashley**

"Methadone was the only option when I started my recovery. I am glad it was an option and it helped with opiates, but it was hard to earn carries while working on cutting back other substances. Getting there before closing and sampling was a challenge living so far away from the clinic. Being on Sublocade, I now just need to come to the doctor's office once a month. The injection does sting a little, but not for long, and using ice beforehand helps. I no longer have to worry about getting to town every day and risk running into people who are still using." — **Victoria**

"I just want to emphasize that being on OAT will affect your life for a long time. They did not educate me enough on how hard and how long the withdrawal is from methadone or Suboxone before signing up – the first time I quit Suboxone, I was still having chills three months after. This means you're stuck to a doctor and a pharmacy for a long time. Counselling and proper mental health care were much more important for me than OAT. If I could go back, I would have done a treatment program rather than signing up for Suboxone." — **Kayla**

"I wasn't given a choice when I started on OAT 15 years ago, but methadone works for me in a really positive way. Maybe Suboxone would have worked for me, but I would be scared to go through withdrawal to start it. Methadone has definitely made my life much better." — **Sue**

"I wasted years of my life and missed out on so many things because of my addiction. I talked to my doctor and was put on Suboxone for the first 6 weeks of recovery, but it wasn't the right fit for me – the pain and withdrawal symptoms were persistent – so my doctor put me on methadone and it worked a lot better for me. I felt stronger, steadier, and more able to put the work into recovery. I was ok going for observed doses at first. I had a feeling of pride after earning my take-home carries – for me, that was part of the incentive. Methadone maintenance has absolutely saved my life, and take-home methadone carries allow me to have a life." — **Lorilee**

"When I made the decision to recover from years of opiate use, the option of methadone was very stigmatizing and time-consuming. I didn't want to wait at the pharmacy every morning just so that I could function. My family doctor and I came up with a plan to wean off opiates with Kadian. It was tough in the beginning, but after a few days we were able to get to the correct dose and I started to feel normal again. After 8 months of titrating my dosages down slowly, I was able to come off Kadian. Although therapy was also a big component of my recovery, there is no way I could have gotten to my appointments without Kadian. Giving people who suffer from substance use disorder more options in their recovery empowers them to make better decisions and to be a part of the way forward in the decision-making process." — **Jason**

YOUR DECISION

Now that you've thought about the differences between the medications, your feelings about what's important to you, and your health, you might have an idea of which medication you'd like to try. Which way are you leaning right now?

◯ **Suboxone** ◯ **Sublocade** ◯ **Methadone** ◯ **Kadian**

NEXT STEPS

Do you understand all the options? **Yes** ◯ **No** ◯

Do you know which benefits and side effects matter most to you? **Yes** ◯ **No** ◯

Do you have enough support and advice to make a choice? **Yes** ◯ **No** ◯

NOTES

APPENDIX B: Intake Form[12,13]

INTAKE FORM

REASON FOR PRESENTING: _____

_____

CURRENT SUBSTANCE USE: _____

Type: _____

Frequency: _____

Quantity: _____

Mode: _____

Last use: _____

HISTORY OF SUBSTANCE USE/SUBSTANCE USE TREATMENTS: _____

_____

CURRENT GOALS:

☐ withdrawal support
☐ harm reduction
☐ abstinence
☐ mental health
☐ other:

OTHER PROVIDERS: _____

_____

MENTAL HEALTH HISTORY: _____

_____

FORMAL DIAGNOSIS MADE: ☐ Yes ☐ No

_____

[12] Adapted from materials provided courtesy of the Northwestern Ontario Regional RAAM Steering Committee.

[13] Simple intake forms help ensure useful information is captured at rst visit without being overly burdensome on the client.

SUICIDE RISK/ASSESSMENT:

MEDICAL HISTORY:

MEDICATIONS:

ALLERGIES:

SOCIAL SUPPORTS:

CHILDREN AT HOME:

BASIC NEEDS:

LEGAL ISSUES:

SAFETY ISSUES:

WORK SAFETY CONSIDERATIONS:

TREATMENT PLAN:

APPENDIX C: OUD Follow-up Visit Form[14]

OPIOID USE DISORDER FOLLOW-UP VISIT FORM

MEDICATIONS:

☐ Methadone ☐ Buprenorphine SL ☐ Buprenorphine XR ☐ SROM

☐ Other: _____

Dose: ____ mg

Take-home doses: _____ Missed doses: _____

Recent dose change: _____

Side effects (including sedation): _____

Opioid withdrawal: _____

Opioid cravings: _____

Issues with carries: _____

SUBSTANCE USE, PATTERN, AND ROUTE:

Alcohol: _____

Benzodiazepines: _____

Cannabis: _____

Opiates: _____

Stimulants: _____

Other: _____

PSYCHOLOGICAL ISSUES UPDATE (IF CHANGED SINCE LAST VISIT):

Mood: _____

Sleep: _____

Energy: _____

[14] Adapted from materials provided courtesy of Women's College Hospital.

SOCIAL ISSUES UPDATE (IF CHANGED SINCE LAST VISIT):

Housing: _____

Employment: _____

Social support: _____

Driving: _____

Safety: _____

MEDICAL ISSUES UPDATE (including risks/management of STBBIs):

Counselling/clinical notes:

On examination: _____

Appearance: _____

Speech: _____

Affect: _____

Mental status: _____

Signs of withdrawal/sedation: _____

Other: _____

UDT RESULTS: _____

IMPRESSION: _____

PLAN:

Rx: _____ mg from _____ to _____

Carry doses: _____

TAKE-HOME DOSE SAFETY ISSUES DISCUSSED:

☐ Yes ☐ No ☐ N/A

OTHER MEDICATIONS: _____

_____

RESOURCES/SUPPORTS: _____

_____

PHARMACY: _____

RETURN TO CLINIC: _____

APPENDIX D: Sample Methadone Carry Agreement[15]

In order to receive take-home doses of my medication ("carries"), I understand and acknowledge the following:

1. There are expectations around my stability and my ability to store medications in a safe manner that must be met in order to receive take-home doses of methadone. This is because of the risks of methadone to people who do not have tolerance to it, and the risks to me if it is not taken properly. A single dose of methadone can be dangerous or fatal if consumed by someone who is not tolerant of that dose, especially if taken by a child. If I miss too many doses, I can also lose tolerance to the medication. If I take more than prescribed on a single day, this can also be dangerous or life-threatening.
2. When considering whether to prescribe carries, my care provider is concerned about my safety and the safety of my community. To assess my ability to manage carries safely, my care provider will consider:
   - **a**. My housing
   - **b.** How long I have been taking methadone
   - **c.** How often I miss doses
   - **d.** My stability (for example, how I am managing appointments, medication, work, school)
   - **e.** My substance use
   - **f.** My urine drug test results
   - **g.** Other factors that could affect my ability to manage carries safely, such as mental health changes
3. The number of take-home doses I receive will be based on my stability and ability to manage carries safely. As my stability increases and I have more experience managing carries safely, the number of carries will be gradually increased. If my stability decreases or I have difficulty managing carries safely, the number of carries will be decreased. These decisions are made in discussion with my prescriber, balancing the importance of the treatment working in my life, with the importance of my safety and the safety of the community.
4. In order to receive carries, I will need to manage my use of drugs and alcohol so that the impact to my health, safety, and stability is minimized, and such that it does not interfere with my ability to manage and store carries.
5. If I wish to receive a larger number of carries, I will need to minimize my substance use and be abstinent from medications not prescribed to me.
6. Urine drug testing is a routine part of methadone treatment. Urine drug tests provide information about what substances I have been taking or exposed to, which helps me and my prescriber develop the best treatment plan for me. I agree to provide a urine sample when requested. I understand that if my urine sample shows signs of tampering or indicates that I am not taking methadone as prescribed, I will lose my carries.
7. I will bring my carries to my clinic or my pharmacy within 24 hours of being asked to do so. If I do not without a valid reason, I may lose access to carries.

---

[15] Adapted from ***A new framework for methadone carries: A person-centered evidence-informed approach to methadone take-home "carry" dosing***, META:PHI.

8. In order to receive carries I need to have a safe and consistent place to stay, not staying on the street.
9. I will store my methadone securely in a locking device (locked box, locked cabinet, or safe) that cannot be accessed by other people. I will keep my medication out of sight and out of reach.
10. I agree not to share, trade, sell, or loan my methadone under any circumstances. Any of these is a reason for my carries to be withdrawn indefinitely.
11. If carries are lost, they will typically be replaced with observed doses, and a review of the carry agreement will take place. If carries are lost, they will be reinstated gradually.

My signature below indicates that I agree to follow the obligations and responsibilities outlined in this agreement.

I have had the opportunity to discuss and review this agreement with my care provider and my questions have been answered to my satisfaction.

Date

Patient (Signature)

Patient (Printed Name)

I confirm that:

1. This form has been reviewed with the patient and they understand its content fully.
2. The patient was given time to ask questions about this agreement and seek clarification.
3. I will engage with my patient in discussing carry issues and use my clinical judgment along with current guidelines as a basis for treatment decisions. I will explain the reasons for decisions about initiating, increasing, or decreasing carries.

HCP (Signature)

HCP (Printed Name)

APPENDIX E: Clinical Opioid Withdrawal Scale (COWS)[16]

Date: _____ **Name:** _____ **DOB:** _____

Time of assessment				
Resting heart rate (measure after lying or sitting for one minute) 0- HR 80 or below; 1- HR 81–100; 2- HR 101–120; 4- HR greater than 120				
Sweating (preceding 30 minutes and not related to room temp/activity) 0- no report of chills or flushing; 1- subjective report of chills or flushing; 2- flushed or observable moisture on face; 3- beads of sweat on brow or face; 4- sweat streaming off face				
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				
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				
Bone or joint aches (not including existing joint pains) 0- not present; 1- mild diffuse discomfort; 2- patient reports severe diffuse aching of joints/ muscles; 4- patient is rubbing joints / muscles plus unable to sit still due to discomfort				
Runny nose or tearing (not related to URTI 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				
GI upset (over last 30 minutes) 0- no GI symptoms; 1- stomach cramps; 2- nausea or loose stool; 3- vomiting or diarrhea; 5- multiple episodes of vomiting or diarrhea				
Tremor (observe outstretched hands) 0- no tremor; 1- tremor can be felt, but not observed; 2- slight tremor observable; 4- gross tremor or muscle twitching				
Yawning (observed 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				
Anxiety or irritability (0–4) 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				
Gooseflesh skin (0–5) 0- skin is smooth; 3- piloerection (goosebumps) of skin can be felt or hair standing up on arms; 5- prominent piloerection				
TOTAL **(5–12 = mild; 13–24 = moderate; 25–36 = moderately severe; > 36 = severe)**				

[16] Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). J Psychoactive Drugs. 2003 Apr-Jun;35(2):253-9. doi: 10.1080/02791072.2003.10400007. PMID: 12924748.

APPENDIX F: Pasero Opioid-Induced Sedation Scale (POSS)[17]

S = Sleep, easy to arouse

Acceptable; no action necessary; may increase opioid dose if needed.

1 = Awake and alert

Acceptable; no action necessary; may increase opioid dose if needed.

2 = Slightly drowsy, easily aroused

Acceptable; no action necessary; may increase opioid dose if needed.

3 = Frequently drowsy, arousable, drifts off to sleep during conversation

Unacceptable; monitor respiratory status and sedation level closely until sedation level is stable at less than 3 and respiratory status is satisfactory; decrease opioid dose 25% to 50% or notify prescriber or anesthesiologist for orders; consider administering a non-sedating, opioid-sparing nonopioid, such as acetaminophen or an NSAID, if not contraindicated.

4 = Somnolent, minimal or no response to verbal or physical stimulation

Unacceptable; stop opioid; consider administering naloxone; notify prescriber or anesthesiologist; monitor respiratory status and sedation level closely until sedation level is stable at less than 3 and respiratory status is satisfactory.

[17] Adapted from ***A new framework for methadone carries: A person-centered evidence-informed approach to methadone take-home "carry" dosing***, META:PHI.

APPENDIX G: Sample Methadone Prescription

Rx

Substance Use Clinic
123 Pine St.
Anytown, ON X1X 1X1

Tel: 555-123-4567
Fax: 555-123-4568

Please inform us of immediately of any missed doses

Dr. Mary Smith

Created On: Aug 22, 2025 11:44:05 AM

For: Johnson, Jon

DOB: 1971/03/28
Health Card #: 11111111111 XY
M: (555)987-6543

Script intended for: **Pharmacy of Choice**

Methadone 10 mg/ml oral solution
40 mg O. D.
Forty milligrams
From: **Aug 22, 2025** To: **Aug 28, 2025**

Total Dose for 7 day(s): 280 mg

The pharmacist, physician or nurse must **observe** the ingestion of methadone on the **7** underlined day(s).

Sun Mon Tue Wed Thu Fri Sat

Notify prescriber regarding missed doses

Do not cancel Rx unless patient misses 4 consecutive doses

Rx

Created On: Aug 22, 2025 11:53:55 AM

For: Johnson, Jon

DOB: 1971/03/28
Health Card #: 11111111111 XY
M: (555)987-6543

Script intended for: **Pharmacy of Choice**

Methadone 10 mg/ml oral solution
50 mg O. D.
Fifty milligrams
From: **Aug 29, 2025** To: **Sep 04, 2025**

Total Dose for 7 day(s): 350 mg

The pharmacist, physician or nurse must **observe** the ingestion of methadone on the **7** underlined day(s).

Sun Mon Tue Wed Thu Fri Sat

Note planned dose increase.

If patient misses a dose prior to Aug 29 please continue previous dose (40 mg); do not increase
Do not cancel Rx unless patient misses 4 consecutive doses
Carry for Sunday and any other day pharmacy is closed

Notify prescriber regarding missed doses

CPSO (12345)

Verification #: XY123456
Printed: Aug 22, 2025 11:53AM by: **Mary Smith**

Generated by PatientVu™

APPENDIX H: Prescribing Methadone in the Emergency Department

The emergency department (ED) is an important point of access to OAT care. For patients already on methadone, being able to receive their medication while awaiting treatment can help to keep them comfortable, facilitate completion of treatment for their presenting condition, and avoid the risk of a missed dose. For patients not already on OAT who present in opioid withdrawal, regardless of the reason for their presentation, OAT should be made available. While the ED community has focused on buprenorphine SL initiation for safety and logistical reasons (especially in the US where there are significant restrictions on who can prescribe methadone), initiating methadone in the ED is an alternative for patients who use fentanyl and are not candidates for or decline buprenorphine SL. Patients do not have to commit to a particular OAT goal such as abstinence; initiation of OAT helps to address withdrawal symptoms, and although the starting dose will not fully suppress withdrawal symptoms, it is the first step on which subsequent doses can be titrated.

Supports to facilitate methadone initiation and continuation in the ED include the following:

- Having methadone on formulary and stocked in the ED
- Cards with local OAT clinic telephone numbers and hours
- Community pharmacy lists with hours and phone/fax numbers
- Contact information for local addictions specialists (community or hospital)
- Lists of local harm reduction resources with hours and contact information

The same general principles for initiating or continuing methadone doses apply in the ED as in the community, with the following notes:

- Methadone should not be given when overdose is a cause for the ED visit, including naloxone reversal of overdose. The opioids/mixed substances that caused the overdose can be temporarily reversed by naloxone but contribute to sedation again when the naloxone wears off.
- Methadone should not be given when there is altered mental status, depressed level of consciousness, or delirium.
- Methadone should not be given to patients who are acutely intoxicated.
- Patients in withdrawal from alcohol and opioids should have alcohol withdrawal treated as a priority due to the risk of seizures and should be started at lower doses of methadone while receiving benzodiazepines.
- For patients who are in significant opioid withdrawal, initiating short-acting opioids for one to two doses can be very helpful, as methadone will not take effect for at least two hours, and there is often a delay in accessing methadone from the hospital pharmacy (see below).

Patients already on methadone

Recent dispensed and witnessed doses should be confirmed by contacting the patient's community methadone pharmacy directly when possible, as information on Connecting Ontario/DHDR is not always accurate to verify the last dispensed dose. The hospital pharmacist can be helpful in contacting the community pharmacy to confirm and cancel doses and reviewing possible medication interactions. In general, the patient's community dose should be maintained (or adjusted if they have missed doses recently) while they are in the ED, including if the last dose cannot be confirmed with the pharmacy.

If the patient will be unable to access their usual methadone dose while waiting in the ED and they have not missed any doses or received methadone in the past 24 hours, that day's dose should be offered from hospital stock. If the patient has missed doses, their dose should be adjusted per the usual guidance. If the patient has missed five or more doses (i.e., patient presents on Day 6 or beyond), the patient should be offered the opportunity to restart methadone (see below). For all patients given methadone from ED stock, the patient's pharmacy should be notified so that the community dose can be cancelled for that day.

Patients not already on methadone

For people in the ED with high opioid tolerance associated with daily fentanyl use, daily opioid use ≥ 200 mg of morphine equivalents/day, in a safer opioid supply program with more than 40 mg hydromorphone/day, and/or injection of opioids, methadone can be started assuming no contraindications. Referral to an addiction medicine consult service is recommended if available but not required to initiate methadone in the ED. The clinician should confirm that the patient will be able to follow up at an outpatient clinic within five to seven days for ongoing therapy. Methadone can be started at 30 mg.

Ideally, the first dose of methadone will be given in the ED. A prescription should be faxed to a community pharmacy to last until follow-up with a community methadone prescriber is available (up to seven days). In situations where the patient is uncertain which pharmacy they will be able to attend (e.g., people in transition between housing or shelter settings), a prescription can be given to the patient to take with them to a pharmacy of their choice. A patient summary should be faxed to the appropriate clinic. A naloxone kit should be dispensed to the patient and harm reduction information/supports and resources as appropriate.

Treating opioid withdrawal in the ED

Short-acting opioids (e.g., hydromorphone) can be used in doses appropriate for the person's level of withdrawal, opioid tolerance, and risk for toxicity in the following circumstances:

- When the person is waiting for methadone or SROM initiation
- When the person has received methadone or SROM but continues to experience withdrawal
- When the person is not interested in or able to take buprenorphine, methadone, or SROM

For people with high opioid tolerance and at higher risk of toxicity (e.g., respiratory depression, hemodynamic instability, alcohol withdrawal requiring benzodiazepines, advanced age/frailty, acute kidney injury/chronic renal failure), hydromorphone can be initiated at 4–8 mg PO q 1–2 h or 2 mg SC/IV q 30 minutes as needed until **COWS** < 5.

For people at lower risk of toxicity and with high opioid tolerance (e.g., daily fentanyl use, participation in a safer opioid supply program with more than 40 mg hydromorphone/day, injection opioid use), doses of 8–16 mg PO q 1–2 h or 4 mg SC/IV q 30 min may be required.

For resources on managing opioid withdrawal and initiating OAT in the ED, please refer to META:PHI's **ED Toolkit for Opioid Use Disorder**.

APPENDIX I: Prescribing Methadone in Inpatient Hospital Units

Admission to hospital presents an opportunity to initiate or optimize OAT in patients with OUD such that when discharged, they are in better health and at less risk of opioid-related harms. Unfortunately, hospitals are often seen as a hostile and unsafe environment for people who use drugs due to stigma and negative experiences with the health care system (196). Hospital staff, including nurses, pharmacists, and physicians, may be unfamiliar or uncomfortable with methadone dosing and assessing for withdrawal and opioid-related sedation. These factors can result in patients presenting late in their illness or initiating self-discharge before completing treatment. Hospital clinicians should keep the following principles in mind:

- Maintain opioid tolerance to prevent mortality from opioid toxicity after discharge due to loss of tolerance.
- Avoid methadone toxicity.
- Both pain and withdrawal symptoms should be addressed.
- Provide a psychologically safe environment through the use of person-centred, non-stigmatizing language.

Considerations for managing methadone in hospital

The following factors may need to be considered when managing methadone in hospital:

- Acute illness, altered mental status, and inability to communicate (e.g., intubation) impacting assessment of tolerance and withdrawal
- Co-occurring withdrawal from other substances
- Electrolyte disturbances and QT prolongation
- Drug-drug interactions leading to altered methadone metabolism
- Nothing by mouth (NPO) status
- Fear or agitation over lack of pain and withdrawal relief, or anticipating lack of relief
- Staff lack of understanding of patient experience
- Use of non-medical opioids in hospital, leading to uncertainty in management plan, stigma, or conflicts with staff or hospital security
- Disconnection from community supports

In general, methadone should be administered in hospital in the same format as in the community, diluted in liquid and with nursing observed administration. The hospital should ensure adequate nursing education on safe administration of methadone (e.g., pre-dosing assessment, no doses left at bedside). Timing of dosing and any missed or declined doses should be noted in the patient Medication Administration Record (MAR). Hospitals should ensure nursing education is in place to assess for opioid-related sedation (e.g., using the POSS) and to recognize signs of methadone toxicity (unresponsiveness, laboured breathing). Naloxone (nasal/IM/IV) should always be ordered to the ward for admitted patients. Benzodiazepine and Z-class drugs should generally not be initiated for people in hospital on methadone. The pharmacist's role is important in hospital management of methadone in contacting the community pharmacy to confirm and cancel doses and review possible medication interactions.

If the patient is NPO, consult with the admitting team if low-volume concentrated methadone liquid is feasible. Consider the duration of NPO status needed. Methadone is absorbed via the rectal route without any dose adjustment necessary. For prolonged NPO status, consider opioid rotation to interim non-oral options such as buprenorphine SL or the transdermal fentanyl patch.

Methadone has numerous drug-drug interactions. Interactions of most concern are over-sedation due to combination with other sedating meds, and QTc prolongation, especially combined with other QTc-prolonging meds. The hospital pharmacy can provide guidance.

The elimination half-life of methadone can be prolonged in patients with severe liver impairment, resulting in oversedation. Patients with hepatic impairment or hepatic encephalopathy should be monitored for sedation; for new starts in patients with hepatic impairment, a lower initial dose with more gradual dose titration is recommended.

Methadone is less affected by renal impairment than other opioids. Methadone is not removed by dialysis. However, patients with advanced chronic kidney disease are more likely to have multiple comorbidities, a prolonged QTc interval, and take sodium bicarbonate supplements (alkalinization of the urine can prolong methadone excretion). Close monitoring is warranted in these patients (197).

Electrolyte disturbances (hypokalemia and hypomagnesemia) due to acute illness and other medications ordered in hospital can contribute to QTc prolongation. A QTc of ≥ 470 ms for adult males and ≥ 480 ms for adult females is considered prolonged (67). Given the ease of access, a baseline ECG is recommended for all hospital inpatients prescribed methadone. If QTc prolongation persists after correction of electrolyte abnormalities and adjustment of other QTc-prolonging medications as appropriate, the methadone dose should be reduced, and alternate OAT medications can be given instead, such as SROM with or without short-acting oral opioids. Once the patient is medically stable, methadone can be re-titrated with ECG monitoring.

Patients already on methadone

Recent doses should be confirmed by contacting the patient's community methadone pharmacy. In general, the patient's community dose should be maintained or adjusted as for missed doses in the community. If the patient has missed more than five doses and methadone is being restarted, the initial dose should be determined according to assessment of tolerance, risk of toxicity, and recency of methadone use, as with community dosing. Consider that patients who are acutely ill (e.g., sepsis, respiratory conditions) are at higher risk of toxicity and should be started more cautiously. If the dose of methadone is insufficient to relieve pain and/or withdrawal symptoms, short-acting opioids may be added to help address withdrawal and pain more safely than choosing a higher dose of long-acting opioids. Conversely, for patients with very high opioid tolerance and recent known methadone dose, methadone could be restarted at 50 mg and titrated more rapidly unless there is significant medical instability while in hospital (e.g., acute cardiac/respiratory disease, ICU admission).

Patients not already on methadone

While the same criteria for initial dosing apply (tolerance, risk of toxicity), the monitored inpatient setting offers an opportunity for more rapid methadone titration to a therapeutic level for relief of withdrawal and cravings for individuals with high tolerance. No titration guidelines exist specific to the hospital treatment setting. There are case reports and case series describing more rapid methadone titrations both in community and in hospital for people using fentanyl who have very high opioid tolerance. These include protocols such as a base dose of 30–40 mg with up to three additional 10 mg doses PRN to a maximum of 70 mg on Day 1 (198), or 30–40 mg as the Day 1 dose with 10 mg daily dose increases up to 60 mg (199). One protocol implemented for patients with routine fentanyl use in a hospital with an addiction medicine service used a maximum dose of 60 mg of methadone on Day 1 (30 mg or 40 mg as the initial dose with 10 mg q 3 H PRN to maximum 60 mg), 70 mg on Day 2 (50 mg with up to two 10 mg PRN doses), 80 mg on Day 3 (60 mg with up to two 10 mg PRN doses) and up to 100 mg on Days 4–7; of the 25 patients undergoing this protocol, none had any adverse events requiring holding a dose of methadone, naloxone administration, or transfer to a higher level of care (200).

Another rapid titration option reported in the literature combines methadone with SROM (201). The authors report on 24 pregnant women with high opioid tolerance admitted to hospital for OAT initiation and titration with the goal of achieving at least 60–80 mg of methadone. Patients were started on methadone 40 mg and increased by 10 mg daily to 70 mg, after which the dose was maintained for three days to reach steady state; 100 mg SROM was added eight hours after methadone on Day 2 to stagger peak effects. Immediate-release morphine (30–50 mg) was also offered as a standing dose every two hours and as needed for pain, withdrawal, or cravings. Approximately every two days, 50% of the immediate-release morphine was converted to SROM. There were no adverse events among the cohort, all patients remained in hospital for the duration of their titration (median length of stay twelve days), and the median daily dose of methadone at discharge was 85 mg.

Patients requiring methadone with low tolerance or high risk for toxicity should be started at lower doses (e.g., 10–20 mg) and titrated conservatively (e.g., dose increases of 5–10 mg every three days or more as required). Short-acting opioids can be used to manage withdrawal with less risk of methadone toxicity. Patients with high tolerance and low risk of toxicity, especially those at risk of leaving the hospital due to inadequate control of withdrawal symptoms or pain, could be offered a more rapid titration, such as 40–50 mg on Day 1, with 10 mg daily dose increases to 70 mg and continuing at this dose for three days. In determining the specific dose protocol, the clinician should consider additional factors such as the logistics of adding PRN methadone doses and the potential to mitigate withdrawal with other short- and long-acting opioids.

Short-acting opioids for the management of pain or withdrawal

Individuals with OUD require management of withdrawal symptoms and pain while in the hospital to address presenting health issues. The goal of administering short-acting opioids is to manage pain, prevent agitation from untreated withdrawal and self-discharge, prevent people from self-administering their own opioids while in hospital, and maintain opioid tolerance.

Doses are dependent on assessment of opioid tolerance. For a patient on a stable methadone dose undergoing scheduled surgery, short-acting opioid dosing would be similar or slightly higher than what would normally be anticipated for an opioid-naïve patient. For a patient admitted with an acute, painful condition such as epidural abscess who has been using large amounts of fentanyl or participating in a safer opioid supply program with large doses of hydromorphone prior to admission, short-acting opioid doses would be expected to be very high, e.g., hydromorphone 8–16 mg PO q 2–3 H scheduled (held if POSS ≥ 3). Some patients need at least 24–32 mg hydromorphone PO q 3 H scheduled as well as PRN doses for adequate withdrawal relief. Scheduled short-acting opioid administration is preferred over PRN, and oral doses should be observed. Parenteral opioid administration may need to be considered if the patient is NPO, if immediate relief of pain or withdrawal is needed (e.g., pain crisis), or if opioid tolerance is extremely high. As the patient stabilizes medically, methadone can be increased or short-acting opioids can be consolidated to SROM.

When ordering opioids, provide instructions to nursing staff on a brief assessment of sedation and safety of ongoing opioid dosing with the **POSS** (see **Appendix F**).

Benzodiazepine withdrawal in the context of opioid withdrawal management

Development of inadvertent benzodiazepine dependence, including dependence on novel psychoactive substance benzodiazepines found in the unregulated opioid supply, has become a challenge over the last several years (202). Benzodiazepine withdrawal can occur when people stop accessing the unregulated drug supply acutely, as during admission to hospital or withdrawal management. Benzodiazepine and opioid withdrawal symptoms overlap substantially. Typical benzodiazepine withdrawal symptoms include anxiety, insomnia, and autonomic hyperactivity; complicated benzodiazepine withdrawal can progress to seizure and delirium. When withdrawal symptoms persist or intensify despite opioid therapy, especially for people who have been accessing the unregulated opioid supply, benzodiazepine withdrawal should be considered. While full clinical guidance is beyond the scope of this document, consideration can be given to prescribing a closely managed short course of long-acting benzodiazepine for stabilization, with the goal of tapering and/or conversion to non-benzodiazepine alternatives (e.g., diazepam 5 mg TID x 2 days, 5 mg BID x days, 5 mg daily x 2 days). For people with severe symptoms or complicated withdrawal, consultation with addiction specialists is recommended.

Discharge planning

It is important to ensure smooth transition of methadone prescribing to the community and avoid treatment interruptions due to logistical reasons. While in hospital, medication coverage may need to be addressed with the assistance of the social work service. The patient's preferred community pharmacy and OAT clinic should be identified. Ideally, hospital discharges should be planned, and Friday afternoon or long weekend discharges avoided if possible. Short-acting opioids should be consolidated to long-acting opioids (e.g., SROM) before discharge. Benzodiazepines and z-drugs initiated in hospital (e.g., for management of acute withdrawal or agitation) should generally not be prescribed on discharge. A bridging methadone prescription for five to seven days or until the person can next see their prescriber should be sent, including information about the last dose given in hospital. A discharge summary including ECG results if available should also be sent. The patient should be instructed to follow up with their community methadone provider shortly after discharge. Harm reduction supports should be offered if appropriate.

APPENDIX J: Conversions Between Methadone and Other Types of Opioid Agonist Therapy

Switching between OAT medications may be appropriate if people have persistent difficulty stabilizing on their current OAT or experience ongoing withdrawal symptoms, cravings, or problematic side effects.

Converting from SROM to methadone

There are several challenges in converting from other opioids to methadone. Most of the literature comes from the chronic pain/palliative care literature and uses calculations related to equianalgesic doses. However, the conversion from other opioids to methadone with regard to equianalgesic dose is not linear. Moreover, doses of methadone for OAT target withdrawal symptoms and cravings and not pain, and it is not clear how these different parameters compare.

META:PHI's guidance document *Recommendations for Use of Slow-Release Oral Morphine as Opioid Agonist Therapy* (3) recommends a gradual cross-taper from methadone to SROM over an abrupt transition due to their differences in pharmacokinetics and respiratory tolerance as a way to prevent withdrawal and toxicity. The document recommends a SROM to methadone ratio of 12:1 or 10:1 in order to prevent toxicity, with lower ratios for people with comorbidities presenting potential safety issues (4); we recommend an even more conservative ratio for patients who do not have experience with methadone. We suggest incrementally replacing 100 mg of SROM with 10 mg of methadone with a minimum of three days between methadone increases, with regular reassessment of withdrawal and tolerance. The maximum starting dose of methadone during a conversion should be 30 mg. For example, for someone on 1000 mg SROM, the dose of SROM could be decreased to 800 mg with the addition of 20 mg methadone, followed by decreases of 100 mg SROM and increases of 10 mg methadone every three to seven days. Abrupt transitions (e.g.,1000 mg SROM to 100 mg methadone) are dangerous because despite high overall opioid tolerance, the patient is not tolerant to methadone, and without enzyme activation, methadone levels can increase and cause toxicity.

Converting from methadone to SROM

META:PHI's guidance document *Recommendations for Use of Slow-Release Oral Morphine as Opioid Agonist Therapy* (3) presents two methods of transitioning from methadone to SROM: a cross-taper approach or a stop-and-start approach. The choice between these approaches should be determined based on individual circumstances including medical stability, opioid tolerance, previous experience with SROM, and the ability to monitor and reassess the patient. The stop-and-start approach may be more suitable for situations where methadone has to be discontinued abruptly (e.g., following a ventricular arrhythmia). This approach can increase the risk of withdrawal as the SROM dose is titrated, making it more suitable for monitored settings where withdrawal can be managed with short-acting opioids. The usual final dose of SROM is between 1:6 and 1:8 of methadone to SROM. Recommended transition schedules for the cross-taper approach and the stop-and-start approach are presented on the following page (3):

	Methadone	SROM
Day 0	100 mg	
Day 1	50 mg	150 mg
Day 2	30 mg	300 mg
Day 3	20 mg	400 mg
Day 4	0 mg	500 mg
Day 5		600 mg

(Cheema et al. 2023, p. 12, Table 2)

	Methadone	SROM (Option 1)	SROM (Option 2)
Day 0	100 mg		
Day 1	0 mg	400 mg	600 mg
Day 2		500 mg	600 mg
Day 3		600 mg	700 mg
Day 4		600 mg	700 mg
Day 5		Reassess	Reassess

(Cheema et al. 2023, p. 12, Table 3)

See META:PHI's *Recommendations for Use of Slow-Release Oral Morphine as Opioid Agonist Therapy* (3) for guidance on both cross-taper and stop-and-start transitions from methadone to SROM.

Converting from buprenorphine to methadone

Methadone can be started 24 hours after the last buprenorphine SL dose; there is no risk of precipitated withdrawal. There is no established conversion of buprenorphine to morphine or methadone equivalents. One study suggests an initial ratio of 1:42.3 buprenorphine to SROM and a final ratio of 1:58 (203); using a conservative ratio of 10:1 SROM to methadone, 8 mg buprenorphine would therefore be 33.8 mg methadone. For comparison, the World Health Organization's *Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence* (204) suggested that methadone be started at 30 mg from a daily buprenorphine dose of 8 mg and above, at 20 mg from buprenorphine doses of 4–8 mg, and at less than 20 mg from buprenorphine doses below 4 mg.

Methadone should be initiated and titrated based on each individual's opioid tolerance and risk of toxicity (e.g., patients who have been using fentanyl while taking buprenorphine have greater tolerance than those who have not been using other opioids). However, clinicians should be aware of the increased risk of respiratory suppression when switching a patient from buprenorphine to a full-agonist opioid; the starting dose of methadone should thus be reduced by 25–50% to account for differences in cross-tolerance.

There is no current guidance for transitions to methadone from buprenorphine XR; we recommend that in individuals who want to start methadone (e.g., because buprenorphine XR is not managing their withdrawal symptoms), methadone should be started at lower doses of 10–20 mg and titrated every three days in accordance with usual guidelines and withdrawal symptoms.

Converting from methadone to buprenorphine

Patients may wish to convert from methadone to buprenorphine due to the convenience of more flexible take-home doses and the option of converting to buprenorphine XR. Transition from methadone to buprenorphine SL has historically been challenging due to the very long half-life of methadone and the risk of precipitated withdrawal that can occur even beyond 72 hours from last methadone dose. There are several strategies for managing the transition from methadone to buprenorphine SL. The "standard" conversion has historically been to slowly taper methadone to 20–30 mg, then discontinue methadone and wait 72 hours before starting buprenorphine with a traditional initiation. Other options include conversion of methadone to SROM for at least 72 hours followed by standard buprenorphine initiation (sometimes called a "bridge") and microdosing (also called "low-dose initiation") (205). Evidence for novel transition methods and their relative risks and benefits is still limited and requires further research.

Microdosing reduces the risk of precipitated withdrawal and withdrawal caused by abrupt cessation of methadone. When choosing a microdosing schedule, consideration should be given to the methadone dose, risk of and tolerance for withdrawal, setting (inpatient or community), and other patient factors such as mental health, safety, and social supports. Consider seeing the patient more frequently during the conversion and modify the titration as needed; methadone can typically be stopped when the patient is at 12 mg buprenorphine, and the dose of buprenorphine can be adjusted further from that point.

There are few reports of initiation of buprenorphine XR in people who have been taking methadone. The product monograph (206) recommends that patients be on a minimum of 8 mg of buprenorphine SL for seven days prior to a first injection. Some clinicians are using alternative rapid induction strategies, including injection without prior buprenorphine SL, particularly for people facing challenges with fentanyl use who are at high risk of not continuing other therapies. Rapid initiation of buprenorphine XR may also be important in people on methadone who are at high risk of discontinuing care, such as people leaving correctional institutions. One retrospective case series described a successful experience in a custodial setting starting 4 mg buprenorphine SL with the onset of withdrawal symptoms following cessation of methadone, followed by a first injection of buprenorphine XR one hour later (207). Emerging anecdotal reports of success in people using fentanyl would seem likely to extend to people on methadone, but evidence is still extremely limited.

APPENDIX K: Managing Methadone Toxicity

Methadone toxicity can occur in several situations:

- When the dose of methadone has been increased rapidly
- When methadone is started at a dose to which the patient is not tolerant
- When sedating medications (prescribed or non-prescribed) are taken along with methadone
- When an individual has deliberately or inadvertently (e.g., due to a pharmacy error) taken additional methadone
- When methadone is ingested by someone intolerant of methadone and/or opioids
- When cytochrome inducers are discontinued or cytochrome inhibitors are initiated (see section on methadone pharmacology)

What constitutes a toxic dose depends on the person's tolerance, concurrent medication use, and health status. For example, an extra dose of 20 mg in someone with low opioid tolerance during the early initiation period could be excessive. In someone on a steady dose of 75 mg, an extra 50% of their dose or mistakenly taking two doses in the same day could result in toxicity. If the exact amount ingested is not known or the risk for toxicity is unclear, it is safest to manage the person proactively. It is important to recall that methadone levels peak 2.5–4 hours after ingestion. Therefore, if the person appears sedated shortly after their dose, this will intensify over the next few hours; conversely, lack of sedation within 30 minutes after the dose does not guarantee that the person will not experience sedation within the next few hours. Most people will start to exhibit signs of overdose within five hours of ingestion, but some patients may not exhibit symptoms for up to ten hours.

Any individual who has consumed extra methadone should be assessed in person for sedation ("nodding off"), slurred speech, ataxia, and pinpoint pupils and determine appropriate next steps.

If the clinician is concerned that a patient is at risk for toxicity, we recommend the following steps:

- The clinician should explain to the individual (and a family member if possible) the significance of the risk of respiratory depression and death. Explain that methadone has a gradual onset of toxicity and that deaths often happen during sleep (208), and describe the signs of overdose (e.g., slow breathing, loud snoring).
- The person should be advised to go to the emergency department (ideally accompanied) for monitoring. A naloxone kit should be provided for transit from the clinic or pharmacy. The clinician can arrange for ambulance pick-up if appropriate.
    - If the person is unwilling to go to the emergency department, the clinician should consider completing a Form 1 and arranging involuntary assessment. Although this is not a step to be taken lightly, methadone overdose meets the requirements of a Form 1 because the person is at imminent risk of harm and substance use disorders are considered mental disorders under the Ontario Mental Health Act.
    - If this is not possible, the clinician may consider sending emergency services to the patient's home for a wellness check.
- Whenever possible, the clinician should speak with the attending emergency department team and advise that the patient should be observed for a minimum of ten hours due to the insidious onset of symptoms and potential return of sedation as naloxone wears off.

In general, patients presenting to the emergency department with opioid overdose should be treated with the lowest effective dose of naloxone required to reverse respiratory depression and maintain airway protective reflexes, not to fully reverse unconsciousness (209); excessive dosing can precipitate severe withdrawal, which can then lead to patient departure from the emergency department and recurrent overdose. When patients presenting with methadone toxicity require naloxone, intravenous administration is preferred over intramuscular or intranasal use. A naloxone infusion is required for patients who respond to initial IV boluses but subsequently deteriorate. Patients who do not adequately respond to naloxone should be evaluated for other substance use (e.g., benzodiazepines). Patients should be discharged from the emergency department only when they have normal oxygen saturation, respiratory rate, temperature and heart rate, a GSC score of 15, and can mobilize/ambulate as usual (210); the observation period following methadone toxicity may be up to twelve hours (209).

APPENDIX L: Methadone Quick Notes

Pharmacologic considerations

- Methadone is a full mu-receptor opioid agonist with no ceiling effect.
- Peak serum concentration (and therefore sedation) occurs between 2.5–4 hours.
- Methadone has a long and variable half-life (mean of 20–35 hours), so a dose that is not adequate on Day 1 can be toxic after a few days.
    - This is why methadone dose increases are typically spaced at least three days apart and patients should be reassessed for withdrawal, sedation, and side effects before each dose increase.
- Tolerance to methadone begins to decrease after three to five days.
    - For this reason, methadone doses should be decreased by 50% after four consecutive missed doses.
    - After five or more missed doses, the person should be reassessed and methadone should be restarted at a dose that reflects their current tolerance.
- Methadone is QTc-prolonging. At the beginning of methadone therapy, it is essential to consider drug interactions and medical conditions that can prolong the QTc interval.
    - **Credible Meds** is one online resource for medications that cause QTc prolongation.
- Methadone is primarily metabolized by CYP3A4 and CYP2B6. Consider the impact of co-prescribed medications that speed up or slow down methadone metabolism.
    - Tables of CYP450 inducers and inhibitors are available at the **U.S. Food and Drug Administration website**.
- Methadone is serotonergic. Consider other serotonergic medications that could add to the patient's total serotonin load.

Contraindications and precautions to methadone

Contraindications to methadone initiation include the following:

- Hypersensitivity to methadone or to any ingredients in the formulation
- Known or suspected mechanical GI obstructions or ileus
- Suspected surgical abdomen
- Acute or severe respiratory depression
- Asthma with severe bronchospasm
- Acute alcohol withdrawal (alcohol withdrawal should be managed before methadone is initiated)
- Severe CNS depression, increased CSF/intracranial pressure, and head injury
- Taking MAOIs or within 14 days of MAOI therapy

Precautions to methadone initiation include the following:

- Severe hepatic dysfunction
- Risk factors for opioid toxicity, including older age, COPD, sleep apnea, concurrent use of medications or substances that can cause respiratory depression (benzodiazepines, gabapentinoids, alcohol)

Intake

- The intake history should include substance use, concurrent medical and mental health history, medications, living situation, and social supports to help inform goal setting and therapy planning.
- An ECG, urine drug test, and baseline blood work should be done as early in therapy as possible but are not required to start methadone.
- The intake history should inform an assessment of both opioid tolerance and risk for toxicity:
    - Assessment of opioid tolerance should consider the potency of the opioid, the frequency of use, and the route of use (oral, nasal, smoked, or injected). Note that recent decreased access to opioids for any reason, including incarceration, hospitalization, or inpatient treatment, results in reduced tolerance within three to five days.
    - Assessment of risk for toxicity should include age, concurrent health conditions, and substance use and medications.
- The patient does not have to be in withdrawal to start methadone, but methadone should not be initiated if the person appears sedated or intoxicated.

Dose initiation and titration

- Starting doses should be determined based on an individual's opioid tolerance and risk for toxicity.
- Initial dosing can range from 5–50 mg, with lower doses for those with no or low tolerance and higher risk for toxicity, and higher doses for those with known high tolerance and no risk for toxicity.
- Doses can be increased by 5–15 mg every three to five days until a dose 80 mg is reached. Lower and less frequent increases are used for those with no/low tolerance and higher risk for toxicity.
- Clinicians should be cognizant of their own expertise; those with less experience with methadone prescribing may choose to initiate doses more conservatively.

ED setting

- The usual maximum starting dose is 30 mg, with a prescription for up to seven days until the patient can attend follow-up.

Inpatient setting

- Patients requiring methadone with low tolerance or high risk for toxicity should be started at lower doses (e.g., 10–20 mg) and titrated conservatively.
- Short-acting opioids can be used to manage withdrawal.
- Patients with high tolerance and low risk of toxicity, especially those at risk of leaving the hospital due to inadequate control of withdrawal symptoms or pain, could be offered a more rapid titration, such as 40–50 mg on Day 1, with 10 mg daily dose increases to 70 mg and continuing at this dose for three days.

Factors	Initial Dose	Titration	Comments
No/low tolerance OR high risk of toxicity	5–10 mg	5–10 mg q 3–5 days	Strongly consider buprenorphine Includes individuals who are not currently using opioids but are at risk of resuming use (e.g., those leaving WMS, custody, or abstinence-based settings)
Moderate tolerance AND risk of toxicity	10–20 mg	10 mg q 3–5 days	Examples: Oxycodone 80 mg x 3/day, hydromorphone 8 mg x 8/day
Moderate tolerance AND no major risk factors for toxicity	20–30 mg	< 80 mg: 10–15 mg q 3–5 days ≥ 80 mg: Up to 10 mg q 5–7 days	
High tolerance AND risk of toxicity	20–30 mg	< 80 mg: 10–15 mg q 3–5 days ≥ 80 mg: Up to 10 mg q 5–7 days	
High tolerance AND no major risk factors for toxicity	30–40 mg	< 80 mg: 15 mg q 3–5 days ≥ 80 mg: 10 mg q 5–7 days	
Very high tolerance AND no major risk factors for toxicity	40–50 mg	< 80 mg: 15 mg q 3–5 days ≥ 80 mg: 10–15 mg q 5–7 days	Daily fentanyl use of ≥1 g plus evidence of recent experience of high-dose methadone at a steady state*

*Given the lack of supporting evidence, the authors could not reach consensus on an appropriate example of a methadone dose, duration, and recency that, combined with very high opioid tolerance from daily fentanyl use of at least 1 g, would warrant an initial methadone dose of 50 mg. Clinicians should use their judgment to weigh the risks of a 50 mg starting dose against the benefits of potential improved treatment retention and symptom relief and risks of a lower starting dose for a particular patient.

Methadone management

- The goal of therapy is to reach a dose that reduces withdrawal symptoms and cravings for approximately 24 hours without sedation. This can take days to weeks.
- In the ambulatory setting, patients are often seen weekly during the first month of treatment, then bi-weekly. Each visit is an opportunity to assess the duration and effectiveness of the medication, sedation and side effects, substance use, mental health, social factors, and opportunities for harm reduction.
- All doses are typically witnessed at a pharmacy for the first four weeks of treatment (see ***A New Framework for Methadone Carries***).
- Careful prescribing and counselling can help to reduce the risks of methadone:
  - Avoid prescribing new sedating medications during initiation.
  - Always confirm whether there have been missed doses.
  - Consider co-dispensing of psychoactive/sedating medications.
  - Communicate with the pharmacy around any specific directions.
  - Counsel patients to monitor for toxicity, which can appear as "nodding off", but also as ataxia, nausea/vomiting, slurred speech, and slow breathing (including during sleep). Taking methadone in the morning is recommended.
  - Advise patients to avoid risky activities if they are experiencing any sedation, e.g., driving, operating machinery.

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