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Methadone treatment for people who use fentanyl: Recommendations[1]

Summary of recommendations

1. Indications for methadone treatment

(a) Methadone and buprenorphine are both first-line OAT options. Methadone may be preferable to buprenorphine for patients who are at high risk of treatment drop-out and subsequent fentanyl overdose. Methadone should also be considered as a first option for patients who have done well on methadone in the past; patients who do not want or have not benefited from buprenorphine; and patients for whom buprenorphine induction has not been successful.

2. Methadone dosing and titration

(a) The clinician should attempt to reach an optimal dose of methadone safely and quickly.
(b) Starting methadone at 30mg (i.e., the higher end of initial dosing guidelines) is recommended.
(c) The starting dose of methadone can be increased by 10–15mg every three to five days. Within this range, faster titration (i.e., 15mg rather than 10mg) is recommended for those who are not at high risk for methadone toxicity (e.g., not concurrently using high doses of benzodiazepines or alcohol), while slower titration is recommended for patients at higher risk of toxicity (e.g., older age, sedating medications or alcohol, patients new to methadone). Patients who have recently been on methadone dosing at higher doses (i.e., in the previous week) can be considered for more rapid dose increases based on their tolerance. Once a dose of 75–80mg is reached, the dose can then be increased by 10mg every five to seven days.
(d) Slow-release oral morphine (SROM) may be co-prescribed with methadone and can be maintained or tapered depending on clinical response. SROM should be dispensed as "observed dosing along with methadone".
(e) Patients who miss methadone doses should be assisted to resume previous doses quickly and safely. After four consecutive missed doses, the dose of methadone should be reduced by 50% or to 30mg, whichever is higher. For patients who miss five or more consecutive doses methadone should be restarted at a maximum of 30mg and titrated according to patient need. SROM at a maximum starting dose of 200mg can be added on the day of a restart, as long as the patient has not become completely opioid-abstinent.
(f) For patients who use fentanyl regularly, methadone doses of 100mg or higher are often needed.
(g) Methadone dose increases should not be delayed due to the absence of an ECG.
(h) Concurrent benzodiazepine use should be addressed and methadone dosing adjusted accordingly.

[1] The role of buprenorphine and slow-release oral morphine (SROM) as treatment options for people who use fentanyl will be presented in separate documents (although the role of SROM as an adjuvant to methadone treatment is discussed here).

3. Therapeutic considerations for treatment retention and harm reduction

(a) Use prescription management practices that promote treatment retention, including phone assessments, extending prescriptions, or leaving longer duration methadone prescriptions for 30mg at the pharmacy so patients can restart treatment.
(b) Decisions about take-home doses ("carries") may start as early as one month after initiation of OAT and should be based on an assessment of overall stability, risks, and benefits.
(c) Be aware of the limitations of urine drug testing.
(d) When determining the schedule for office visits and urine drug screens, consider both clinical need and the impact on patients' daily life.
(e) Provide treatment for concurrent psychiatric illnesses and substance use disorders.
(f) Reduce the risk of overdose through patient education, take-home naloxone, and advice on harm reduction.

4. Inpatient management

(a) OAT should be routinely offered to hospital patients with OUD.

5. Pregnancy and methadone

(a) Pregnant patients with OUD should be started on OAT as soon as possible and titrated to avoid withdrawal symptoms due to the risks of spontaneous abortion and preterm labour. When possible, hospital admission for rapid up-titration of methadone with augmenting opioids is recommended. When caring for a pregnant patient using fentanyl, contact a colleague with experience for guidance and involve the obstetrical team early whenever possible.

Preamble

Over the last five years, fentanyl and fentanyl analogues have infiltrated the illegal opioid supply across much of Canada, with devastating effects on people who use drugs. Addiction medicine providers seeking to support people who want opioid agonist therapy (OAT) have been challenged to find effective ways to use these medications to manage withdrawal, reduce cravings, and reduce overdose rates.

In 2020, a group of experienced addiction physicians in Ontario came together under the leadership of Mentoring, Education, and Clinical Tools for Addiction: Partners in Health Integration (META:PHI) to formulate a new guidance document for prescribing methadone to address the realities of opioid use in the current landscape. Using evidence from focused literature searches and expert opinion, we have made recommendations regarding issues such as methadone dosing and titration, some of which differ from previous guidelines.

This document incorporates feedback from three groups of reviewers: invited reviews from clinicians who work in various health disciplines and settings, anonymous reviews from members of the META:PHI Google Group, and feedback obtained from a focus group comprised of people with lived/living expertise and family members (see Acknowledgments section below). META:PHI recognizes the importance of meaningful collaboration with people with lived/living expertise at all stages of knowledge creation, and we acknowledge our late engagement with this group. We resolve to increase our collaborative engagement with these experts in future projects.

This document is not a comprehensive overview of methadone prescribing or an introduction to OAT; it is intended for the experienced prescriber who can apply clinical judgement with the evidence provided. Sections 4 and 5 are intended for hospital clinicians who are not experienced methadone prescribers.

Introduction

Fentanyl and its analogues have played an increasing role in opioid overdose deaths across the country over the past decade. Such high-potency, non-prescription opioids are increasingly found in the illicit and counterfeit street opioid supply, although the extent of contamination varies from region to region. In a 2020 study of 303 individuals with opioid use disorder (OUD) using harm reduction sites in British Columbia (1), 38.7% knowingly used fentanyl, 21.7% denied using fentanyl but were positive for fentanyl on urine drug screens, and 39.6% had no recent fentanyl use. A drug content research pilot of clients using harm reduction services in Montréal found that of 33 individuals whose urine tested positive for fentanyl, only three (10%) reported fentanyl use (2). Between October 2019 and March 2020, 43% of heroin samples submitted to Toronto's drug checking service contained unexpected fentanyl (3).

Fentanyl is more potent than heroin and far more lethal than oral prescription opioids. Fentanyl was found to be involved in over 70% of accidental opioid-related deaths across Canada in 2018 and 2019 (4). The rate of opioid-related deaths from fentanyl in Ontario is near this national average; Public Health Ontario reports that fentanyl and analogues contributed to 71.2% of the 1209 accidental opioid-related deaths between July 2017 and June 2018 (5). Injection-related infections such as endocarditis are also rising in North America (6). These infections have a severe impact on morbidity and mortality; in a cohort study of 149 patients admitted to a Regina hospital for complications of injection drug use, 23% left hospital early against medical advice, 27% had multiple admissions, and the one-year mortality rate was an astonishing 15% (7). Patients with infective endocarditis due to injection drug use have higher rates of readmission compared to patients with infective endocarditis not related to injection (6). As the strength and frequency of contamination of street opioids increases, achieving control of withdrawal symptoms and cravings with opioid agonist therapy (OAT) has become more challenging, raising questions about how to utilize OAT to reduce the risk of fentanyl overdose for people who use drugs. Strategies that are desirable and acceptable to people who use fentanyl or other illicitly manufactured high-potency opioids are important tools for keeping patients engaged with the health care system. In a recent study of methadone patients in Vancouver, 30.8% of the sample were dissatisfied with their care; treatment dissatisfaction was associated with fentanyl use and treatment drop-out (8). Retention in treatment is an important factor for improving access to primary care, mental health and social services, and treatment of infectious diseases such as Hepatitis C and HIV (9-13).

In Ontario, all aspects of methadone prescribing have historically been tightly regulated by The College of Physicians and Surgeons of Ontario (CPSO). The 2011 CPSO methadone guidelines (14) were written for methadone prescribers, at the height of the OxyContin crisis; their intent was primarily to provide an acceptable oral opioid replacement treatment built into a contingency management approach to care, while preventing methadone diversion and iatrogenic methadone toxicity. At the time, methadone was prescribed primarily for individuals with a diagnosis of OUD who were using oral, smoked, insufflated, and injected prescription opioids and/or heroin. Prior to the rise of fentanyl in illicit markets, methadone doses of 60–100mg were usually considered adequate to reduce or eliminate cravings and opioid use for most patients, and the guidelines and dosages reflected these objectives. In the fentanyl era, newer concerns relate to the potency and prevalence of this substance, as well as the challenge of providing adequate and acceptable (oral) alternatives. There are many questions for which clinicians need guidance: How effective is OAT at reducing fentanyl use and preventing opioid overdose? Are there dosing strategies that can enhance its effectiveness? What strategies can the clinician use to retain patients who use fentanyl in treatment?

This document was initiated to address specific issues related to methadone prescribing, dose titration, and treatment retention in the context of the fentanyl crisis. The recommendations are based on the premise that clinical decisions should have the overarching objective of promoting patient engagement and retention in treatment, as duration of treatment has been shown to be a crucial predictor of outcomes (15-18). This is not an exhaustive review of all aspects of methadone prescribing. Although the CPSO discontinued its methadone policy, program standards, and guidelines in March 2021 (19), these continue to inform the

practices of Ontario prescribers who were expected to adhere to the guidelines as a standard of practice against which they would be explicitly assessed.

Holistic approaches to care

While this document focuses specifically on methadone prescribing, the authors wish to emphasize that pharmacotherapy is just one aspect of care for people with OUD. OAT is a powerful tool for reducing unwanted drug use and providing protection against overdose; however, it does not address the multifactorial issues associated with OUD including mental health, trauma, chronic pain, housing, poverty, and other social determinants of health. True holistic care for people with OUD requires a multidisciplinary approach with the goal of overall wellness as defined by the patient themselves.

Participants in the focus group emphasized that the single biggest barrier to care is stigma. People who use drugs are subject to substantial discrimination in health care settings, and this discrimination is increased for people experiencing additional axes of oppression (i.e., members of the BIPOC or LGBTQ2SAI+ community, people experiencing homelessness, etc.). Clinicians must be aware of these additional issues that patients face and provide trauma-informed, culturally appropriate, patient-centred care.

Strength of recommendations

These recommendations were developed through focused literature searches on methadone and fentanyl, as well as our collective clinical experience as methadone providers. While there is strong evidence for methadone's effectiveness as a first-line treatment for injection opioid use disorder and for dose titration, we also recommend other practices aimed at promoting retention in treatment that do not yet have a robust body of evidence due to a lack of published studies. We feel that they are appropriate considerations to address the clinical challenges posed by the risks of fentanyl in the current street opioid supply. Ultimately, prescribing decisions should be made in accordance with available evidence, standards and best clinical judgment.

Evidence on the effectiveness of methadone for people who use fentanyl

There is good evidence to suggest that OAT protects against fatal opioid overdose. A systematic review and meta-analysis of patients on OAT found a dramatic reduction in all-cause and overdose mortality (20); mortality risks were greater in the first four weeks of treatment and the first four weeks after cessation of treatment. A population-based retrospective cohort study conducted in BC had similar results (21). Using linked administrative databases, the study examined mortality among all people with opioid use disorder who received at least one prescription of methadone or buprenorphine for opioid use disorder between January 1996 and September 2018 (the large majority of the cohort was on methadone). Overall, there were 7,030 deaths (12.7% of the total cohort of 55,340 people). The relative risk of death while off OAT was 2.1 between 1996 to September 2018, rising to 2.6 after the first fentanyl-related overdose death in BC in 2012, rising again to 3.4 after fentanyl was declared a public health emergency in 2016. The mortality rate while on OAT was stable from 2010 to 2018, suggesting that being on OAT gave substantial protection from fentanyl overdose. Other studies have had similar results. In a retrospective cohort study of 17,000 individuals residing in Massachusetts who had a non-fatal overdose between 2012 and 2014 (22), those who enrolled in methadone had an adjusted hazard rate (AHR) of 0.41 for opioid-related mortality compared to those not on OAT, and those on buprenorphine had an AHR of 0.62 for opioid-related mortality. In a comparative effectiveness study looking at over 40,000 individuals with OUD and comparing six mutually exclusive treatment pathways—no treatment, inpatient detoxification or residential services, intensive behavioral health, buprenorphine or methadone, naltrexone, and non-intensive behavioural health—only treatment with buprenorphine or methadone was associated with a 76% lower risk of overdose at three months, and a 59% lower risk of overdose at twelve months. Treatment with

buprenorphine or methadone was also associated with reduction in serious opioid-related acute care use (23).

Methadone appears to protect against overdose even among patients who continue to use fentanyl. In a cohort that included 127 people who use fentanyl enrolled in a methadone program in Rhode Island, relapse to fentanyl use was common. There were no deaths in the cohort, although four people died during a period between one and six months after leaving the program (24).

Methadone protects against fentanyl overdose in at least two ways. By relieving withdrawal symptoms and cravings, methadone reduces the frequency and amount of fentanyl use, thus reducing exposure to potentially fatal doses. Secondly, it is possible that patients on long-term methadone are at least partially cross-tolerant to the respiratory depression caused by fentanyl. As well, the regular dosing of an oral, long-acting opioid such as methadone helps maintain some degree of opioid tolerance. In this way, methadone reduces the risk of overdose from a high-potency exposure following brief periods of abstinence (e.g., incarceration, lack of access, personal choice).

Methadone treatment is associated with other positive outcomes besides reduced overdose death. Methadone has been used as a treatment for opioid use disorder since the early 1960s. There have been numerous studies on its effectiveness since the 1970s and 1980s, and it is fair to say that it is by far the most extensively evaluated addiction treatment in current use. A narrative review of controlled trials and observational studies published in 1994 (25) concluded that, compared to no treatment or tapering, methadone maintenance is associated with marked reductions in illicit opioid use, crime, risky injection practices, and mortality. The review also found that treatment retention rates vary widely between clinics; clinics with higher retention rates used higher methadone doses and had more intensive medical and counselling support.

More recent literature has confirmed and strengthened our knowledge of the impact of methadone treatment on health and social outcomes. A systematic review and meta-analysis of methadone treatment in China (26) compared social outcomes at baseline and at twelve months after initiation of methadone treatment and found improvements to arrest rate, drug selling, employment, and family relationships. In a systematic review of randomized trials and observational studies (27), methadone and buprenorphine treatment during and after incarceration was associated with reduced illicit opioid use, reduced re-incarceration rates, and a greater likelihood of employment at one year. In a systematic review of twelve studies involving 16,195 people who use injection opioids, all studies found reductions in HIV risk behaviours, and increased adherence to HIV treatment (9).

Methadone treatment initiated in hospital has been found to be beneficial for patients. A systematic review found that in-hospital provision of methadone for people who inject drugs was negatively associated with leaving hospital against medical advice (28). In a retrospective cohort study of patients admitted to hospital for complications of injection opioid use (29), being on opioid agonist therapy with methadone or buprenorphine while in hospital was associated with lower rates of leaving against medical advice (30.0% vs 59.6% for those not on OAT), and 90-day all-cause readmission rates were lower for patients who were discharged on OAT versus those not on OAT at discharge (27.3% versus 42.7%). There is evidence that being on OAT reduces the risk of injection-related infections. In a retrospective cohort study of 78,400 patients on OAT in Ontario between 2011 and 2015 (30), being continuously on OAT was associated with a significant reduced likelihood of being diagnosed with endocarditis, osteomyelitis and septic arthritis. In a study of patients hospitalized with injection-related endocarditis, those who were started on OAT had an average of 5.7 more days on intravenous antibiotic therapy than those who were not started on OAT (31).

Recommendations

1. Indications for methadone treatment

(a) Methadone and buprenorphine are both first-line OAT options. Methadone may be preferable to buprenorphine for patients who are at high risk of treatment drop-out and subsequent fentanyl overdose. Methadone should also be considered as a first option for patients who have done well on methadone in the past; patients who do not want or have not benefited from buprenorphine; and patients for whom buprenorphine induction has not been successful.

Studies have consistently shown that methadone has higher treatment retention rates than buprenorphine (13, 32). A 2017 review recommended that methadone be used as a first-line medication for patients with risk factors for treatment drop-out and overdose, such as younger age, injection opioid use, social instability, concurrent mental illness, or concurrent stimulant use (33). In a systematic review of controlled trials comparing methadone and buprenorphine (13), the average retention rates at four and six months for methadone were 73.9% and 74.0%, whereas the corresponding retention rates for buprenorphine were 45.9% and 46.0%.

As a partial mu opioid agonist with a ceiling effect, buprenorphine has a lower risk of overdose than methadone~~,~~ and for this reason the CRISM guidelines (34) recommend buprenorphine as the first-line treatment for OUD. However, the risk of iatrogenic methadone overdose is minimal compared to the risk of fentanyl overdose. In addition to its superior retention rates, methadone is also easier than buprenorphine to initiate, as patients do not have to be in withdrawal prior to initiation (or endure a prolonged duration of induction with microdosing); this makes it a good choice for patients who have their treatment frequently interrupted and require frequent OAT restarts.

In patients who are started on buprenorphine, the dose should be rapidly titrated to an optimal dose. Patients should be switched to methadone if they continue to use fentanyl or have ongoing withdrawal symptoms and cravings despite being on the maximum buprenorphine dose. There is evidence to support this stepped care approach. In one study, 96 people who use heroin were randomized to receive either methadone treatment or buprenorphine treatment, with the option of switching to methadone at the discretion of the patient and clinician. By the end of the study, half of the buprenorphine group had switched to methadone. Both groups had an identical treatment retention rate of 78% at six months, and the proportion of urine drug tests positive for heroin was 20% in both groups (35).

2. Methadone dosing and titration

(a) The clinician should attempt to reach an optimal dose of methadone safely and quickly.

Achieving a therapeutic level of medication is essential to retaining patients in treatment and to reductions in opioid use. Historically, methadone dosing was based on a "start low and go slow" approach given concerns about risks of overdose mortality in the first four weeks of treatment (20). Clinicians were advised to aim for methadone doses 60mg or above, as these were associated with higher levels of abstinence from opioid use (14). The protective benefits of methadone in people who use fentanyl warrant consideration of strategies that support retention in treatment. Flexible dosing, i.e., dosing that is individually titrated to suppress withdrawal symptoms and cravings, is associated with lower rates of ongoing use based on self-reports and urine drug screens (36, 37). Titrating the dose both rapidly and safely is critical in retaining patients in treatment and preventing overdose. People who use fentanyl are more likely than people who use prescription opioids to drop out of OAT and more likely to cycle in and out of treatment (38). Their higher treatment drop-out rate is likely due in part to the higher prevalence of concurrent substance use and mental illness among people who inject opioids (38, 39), but also to the potency of illicit fentanyl. Fentanyl is

highly lipophilic and crosses the blood brain barrier rapidly, contributing to its immediate, powerful reinforcing effect. Animal studies have shown that chronic administration of morphine does not block the reinforcing effects of fentanyl to the same degree as other opioids (40). This is likely true for methadone as well, especially at the subtherapeutic doses used in the first few weeks of methadone titration. Strategies to more promptly achieve therapeutic levels include re-evaluation of traditional starting doses, dose titration, and strategies to avoid missed doses and restarts (see below).

(b) Starting methadone at 30mg (i.e., the higher end of initial dosing guidelines) is recommended.

Previous Canadian guidelines suggest starting methadone at doses of 5–30mg depending on level of tolerance and co-existing risk factors for toxicity such as age, benzodiazepine or alcohol use, severe respiratory illness, decompensated liver disease, or co-prescription with medications that impact methadone metabolism (14, 41, 42). Given the expectation that higher doses of methadone will be required to achieve therapeutic outcomes, higher starting doses within this range (maximum 30mg) can help to shorten the trajectory to achieving therapeutic levels.

Other guidelines (43-45) set the maximum total dose for day one at 40mg for patients with established opioid tolerance.[2] However, a review (46) notes that deaths during the first week of methadone treatment with patients started at doses above 30mg have been reported by several sources (45, 47, 48). Methadone has a very long and variable half-life. Methadone is metabolized primarily by CYP 2B6 and CYP 3A4, with CYP 2B6 primarily determining methadone's stereoselective metabolism (49). The half-life tends to be much longer on initiation of methadone treatment, declining over time with induction of the enzymes that metabolize methadone (49-51). Because of this, methadone can accumulate in the serum over several days, and the window between the therapeutic dose and a fatal dose is very narrow. Multiple studies have shown that the majority of overdose deaths for patients on methadone maintenance therapy (MMT) occur during the first two weeks of treatment (33, 52-54). For these reasons, we believe that 30mg should be the maximum initial dose of methadone in a community setting; higher initial doses may at times be considered for in-patient settings with the opportunity for observation.

Patients who use fentanyl are highly tolerant to opioids and have considerable cross-tolerance to the sedating and respiratory suppressant effects of methadone. However, cross-tolerance to methadone is incomplete and variable, depending on previous and recent exposure to methadone as well as other substances (55). For example, while the general recommendation for opioid switching is to prescribe the new opioid at 50% of the morphine equivalent of the original opioid, when switching patients on prescription opioids for chronic pain to methadone, the recommended dose is no more than 10% of the morphine equivalent (56). This points to the extant risk that people using any given opioid may be at increased risk of methadone toxicity, despite the potency of strong opioids such as fentanyl. As well, starting a patient on methadone is often an addition rather than a rotation, since ongoing use of more potent opioids often continues in the early phase of treatment. Furthermore, the variability in the street supply makes it impossible to predict with accuracy what actual doses of fentanyl are being used. Although fentanyl is primarily metabolized by CYP3A4 (57), there is currently no helpful data to support higher starting doses of methadone for first-time methadone initiation in people who use fentanyl.

[2] The ASAM guidelines advise a first dose no higher than 30mg, with the total dose on day one no higher than 40mg.

Focus group feedback

The consensus of focus group participants was that 30mg is too low to make a significant impact on withdrawal symptoms among people with high opioid tolerance and that substantially higher initial doses (e.g., from carries) have not caused them to overdose. The group favoured starting doses in the range of 40–60mg in an outpatient setting and higher in an inpatient setting, where sedation or overdose can be reversed.

The authors acknowledge that there are settings in which 40mg is used as a starting dose and that future versions of this guidance document should seek new evidence for the safety of higher starting doses. Adding slow-release oral morphine to methadone is suggested as a strategy to help augment initial methadone doses (see Section 2d).

(c) The starting dose of methadone can be increased by 10–15mg every three to five days. Within this range, faster titration (i.e., 15mg rather than 10mg) is recommended for those who are not at high risk for methadone toxicity (e.g., not concurrently using high doses of benzodiazepines or alcohol), while slower titration is recommended for patients at higher risk of toxicity (e.g., older age, sedating medications or alcohol, patients new to methadone). Patients who have recently been on methadone dosing at higher doses (i.e., in the previous week) can be considered for more rapid dose increases based on their tolerance. Once a dose of 75–80mg is reached, the dose can then be increased by 10mg every five to seven days.

This is consistent with the titration schedule outlined in the 2011 CPSO guidelines (14). This schedule allows for a maximum dose of 45mg on day four, 60mg on day seven, 75mg on day 10, and 85 mg on day 15. Slower titration is recommended for patients at high risk for methadone toxicity (e.g., heavy, frequent alcohol or benzodiazepine use, COPD). Assessment for withdrawal symptoms and sedation, either in person or by telephone, is advisable prior to a dose increase. Note that a positive urine screen for benzodiazepines is not reason enough on its own to justify a lower starting dose or titration rate of methadone. People who use fentanyl may test positive for benzodiazepines due to contaminants in the fentanyl supply; the risk of toxicity in combination with methadone comes from concurrent heavy use of potent, illicitly made "street" benzodiazepines as opposed to prescription, occasional, and/or accidental use.

Other dosing protocols that allow accelerated titration or additional flexibility have been described. In the protocol used in the Rhode Island cohort (24), methadone is started at 30mg on day one and increased by 10mg per day until 50mg is reached on day three; the dose can then be increased by a maximum of 20mg per week. The 2008 protocol set by the College of Physicians and Surgeons of Saskatchewan (CPSS) allows for planned dose increases of 10mg every fourth day without an intervening assessment before day seven, assuming the patient is at lower risk of toxicity; it also permits the use of slow-release oral morphine (SROM) for withdrawal symptoms during the induction period (58).

Focus group feedback

Participants stated that 120mg methadone is the minimum dose necessary to reduce fentanyl use. They emphasized that rapid dose escalation is important motivation for people who use drugs to make the effort to obtain methadone rather than readily available fentanyl.

The authors acknowledge that while the titration protocol recommended in this document represents a change from previous guidelines, it may not be rapid enough to meet the goals of people who use fentanyl. Inpatient settings can allow for faster titration. SROM may be helpful to augment methadone during titration (see Section 2d). Future versions of this document will consider evidence for the safety of more rapid outpatient titration protocols.

(d) Slow-release oral morphine (SROM) may be co-prescribed with methadone and can be maintained or tapered depending on clinical response. SROM should be dispensed as "observed dosing along with methadone" (58).

Co-prescribing SROM with methadone is an approach adapted from the 2008 CPSS methadone guidelines (58), although their results have not been published in peer-reviewed journals. This technique can be helpful for patients who are cycling through methadone starts, have known tolerance, or are at high risk of overdose from fentanyl. SROM can help relieve withdrawal symptoms and cravings during the first days and weeks of methadone treatment, when doses are subtherapeutic; it can be used alongside methadone because serum levels do not accumulate in the same way that methadone does. Offering SROM to a patient who has been unable to remain on methadone treatment long enough to reach a therapeutic dose can also reassure the patient that the clinician understands the severity of their withdrawal symptoms and wants to help them. SROM should be used with extreme caution in patients with renal insufficiency due to the build-up of a toxic metabolite. As always, the risks of toxicity associated with SROM should be measured against the potential benefits of reduced fentanyl use.

SROM can be initiated on the same day as the first methadone dose. When SROM is given on a fixed dosing regimen, steady state is reached within about two days; there is no bioaccumulation of morphine. SROM doses should be titrated no more often than every two days, with increases not co-occurring with methadone dose increases. The CPSS guidelines recommended a maximum starting dose of 200mg per day, and lower doses if the patient experiences somnolence or has risk factors for morphine toxicity. This morphine dose can be maintained or increased by 50–100mg per visit during titration of methadone. In our clinical experience, doses of 100–300mg are often sufficient as augmentation for methadone; however, the higher opioid tolerance found in people who use fentanyl may warrant doses above 300mg. SROM capsules should be opened by the pharmacist and the beads sprinkled on apple sauce or into a dry cup. The prescription should specify that the SROM should be given prior to methadone dosing so that the methadone can wash the beads down. Pharmacists should be careful with observing the ingestion of the SROM dose in order to prevent diversion. SROM may be continued or tapered, depending on patient response and preference. A subset of patients who experience side effects at higher methadone doses or who do not achieve adequate control of withdrawal symptoms at full methadone doses may remain on combination therapy, based on expert opinion.

The British Columbia Centre on Substance Use (BCCSU) guidelines on OUD management provide guidance for prescribing SROM as monotherapy including dose titration, managing missed doses, and observed versus take-home doses (41). There are no established guidelines that recommend or offer guidance on combination therapy.

(e) Patients who miss methadone doses should be assisted to resume previous doses quickly and safely. After four consecutive missed doses, the dose of methadone should be reduced by 50% or to 30mg, whichever is higher. For patients who miss five or more consecutive doses methadone should be restarted at a maximum of 30mg and titrated according to patient need. SROM at a maximum starting dose of 200mg can be added on the day of a restart, as long as the patient has not become completely opioid-abstinent.

Tolerance to methadone is partially lost after just a few days of abstinence. The CPSO methadone guidelines (14) differentiated between early stabilization (zero to two weeks) and late stabilization/maintenance phases with respect to management of missed doses. Early stabilization is the riskiest period of MMT with respect to opioid overdose, but also arguably the most important in terms of engagement in therapy. The 2011 CPSO guidelines recommended cancelling the methadone prescription after two missed doses during early stabilization and three consecutive missed doses during later stabilization. In contrast, we recommend that methadone prescriptions not be cancelled unless a patient misses four consecutive doses (see Table 1). This recommendation is based on guidelines from California (59), British Columbia (60), Australia (61), and the

UK (62). It is important to communicate changes from previous guidelines to the pharmacist to ensure that prescriptions are managed as planned. Adjustments for missed SROM doses follow a different schedule. The BCCSU guidelines recommend a reduction in SROM dose of 40% after two missed doses, 60% after three missed doses, and 80% (or a starting dose, whichever is higher) after four missed doses; reassessment before an increase in SROM dose is recommended.

Table 1: Adjustments for missed methadone doses

Days missed	Dose	Increases
Three (patient presents on day four)	Continue previous dose; no adjustment required	10–15mg every three days as per usual titration protocols
Four (patient presents on day five)	The higher of 50% of previous dose or 30mg	10mg daily for three days (not exceeding the most recent dose), then reassess and proceed as usual
Five or more (patient presents on day six or later)	Restart: 30mg +/- SROM maximum 200mg	10–15mg every three to five days

Repeated missed doses present a barrier to reaching therapeutic doses of methadone. The CPSO guideline required three consecutive doses before a dose increase in order to establish tolerance. We recommend consideration of dose increases for patients who repeatedly face challenges achieving three consecutive doses, particularly those who have previously demonstrated tolerance to methadone and high-potency opioids, in the following situations:

- At or under doses of 60mg.
- If the patient has had at least four doses within five days.
- Patient reports little withdrawal relief at the current dose.
- Continuing fentanyl use.
- Lack of sedation.

We do not recommend a dose increase immediately after a missed dose. If the dose was only missed the day prior to the day of the assessment, continue that dose for that same day, and prescribe a dose increase for the following day without an additional clinical visit. Specify on the prescription that the pharmacist should assess the patient and hold the dose if they appear sedated. Consider the following clinical scenarios where a patient who has been on prescribed methadone within the past two weeks is seen on Day 5:

Table 2: Potential dose adjustment with missed doses

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

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

Focus group feedback

The consensus of the focus group was that methadone doses should be maintained beyond four days of missed doses.

The authors recognize that there are risks associated with lowering the methadone dose. Clinicians are encouraged to use their judgment and consider individual patient circumstances (e.g., intercurrent opioid use, benzodiazepines and other sedating medications, patient's pattern of tolerance based on past experience, etc.) when a patient has missed five consecutive days of methadone.

(f) For patients who use fentanyl regularly, doses of 100mg or higher are often needed.

RCTs have shown that higher doses of methadone are associated with significantly greater retention in treatment; specifically, patients on daily doses less than 60mg were 4.8 times as likely to leave treatment as those on doses up to 80mg per day (63). The therapeutic dose range for methadone is generally thought to be 60–120mg; this range is based on a meta-analysis that found that patients on doses between 60–119mg had longer retention in treatment that those on doses below 60mg (64). However, only one study in the meta-analysis included patients on doses greater than 120mg. Controlled trials have demonstrated that methadone doses of 80–100mg are more effective at reducing heroin use than doses below 60mg (65). While it is plausible that higher doses of methadone may be needed for people who use fentanyl, there is limited research on the effectiveness of methadone doses above 100mg. In a study on people who use fentanyl participating in a methadone program in Rhode Island (24), the dose was increased to 140mg in patients who continued to use fentanyl daily; the authors report that this intervention had inconsistent results. In a retrospective cohort study, high doses of methadone (mean dose 211mg) were prescribed to patients who continued to use illicit substances (66). The high-dose patients had marked reductions in substance use compared to the general methadone clinic population; however, the average dose of the latter group was only 65mg.

To our knowledge, the only trial that examined the effectiveness of higher methadone doses was the Randomized Injection Opioid Therapy Trial (RIOTT) in the UK (67). Subjects in this trial were treatment-refractory methadone patients who continued to use heroin almost daily while on methadone. Subjects were randomized to receive either injectable heroin, injectable methadone, or optimized oral methadone. The mean dose of methadone for those in the oral methadone group was 107mg; 69% of patients randomized to oral methadone remained in the trial at 26 weeks, which is superior to most methadone retention rates and was comparable to retention rates for those in the injectable methadone and heroin arms. The RIOTT study suggests that optimizing methadone doses (to above 100mg) will increase retention in treatment and may be associated with reductions in heroin/fentanyl use in a significant number of patients, and may lead to improvements in other outcomes, such as non-opioid drug use. All subjects in the RIOTT study received counselling, which could account for some of the improvements observed in the methadone groups.

Given this evidence, we recommend increasing the dose above 100mg in patients who are using fentanyl daily or almost daily. Increased doses are suggested even if the patient does not report withdrawal symptoms; the dose required to suppress cravings is higher than the dose required to relieve withdrawal symptoms. Doses above 120mg may be helpful as long as the patient is not experiencing sedation or side effects; if the patient is experiencing sedation, severe constipation, or sweats, the dose should be held or lowered, and SROM can be added if the methadone dose is subtherapeutic.

A patient may decline a methadone dose increase if they do not want the euphoric effects of fentanyl blocked by a higher methadone dose. In these cases, it is appropriate to discuss the risks and benefits of maintaining versus increasing the dose of methadone. Focusing on reducing the risk of overdose by

maintaining tolerance through daily dosing and encouraging test-dosing and fewer high-risk exposures can all help to reduce opioid-related harms while supporting treatment retention.

(g) Methadone dose increases should not be delayed due to the absence of an ECG.

There is limited evidence on the utility of baseline ECG screening (68). In addition, studies on the relationship between methadone dose and the degree of QTc prolongation have had conflicting results (69-73). Thus, while a baseline ECG is helpful, initiation of methadone and dose increases should not be delayed if clinically indicated and an ECG is not available. High doses of methadone can be QT-prolongating, and ECG screening is advised for patients who are on doses above 150mg; who are at increased risk for arrhythmias (e.g., current endocarditis, history of cardiac surgery, previous ventricular arrhythmia, or other cardiac conditions); or who are taking other medications that could prolong the QT interval (74-76). However, the lack of an ECG should not prevent the clinician from providing dose increases as required, especially in patients who continue to use fentanyl and report withdrawal symptoms and cravings. The benefits of opioid agonist treatment for a patient at high risk of overdose or morbidity and mortality outweigh the risks of a prolonged QTc interval (75-78). In patients with a history of arrhythmia, cardiac disease, or medications that prolong the QTc (e.g., antipsychotics (79)), an ECG should be strongly considered.

If a patient has a prolonged QTc interval (above 500mmsec) then a trial of slowly reducing the methadone dose and monitoring the QTc interval could be considered. Another option is to consider transitioning to morphine or buprenorphine treatment, as both are considered lower-risk drugs for increasing the QTc interval (80).

(h) Concurrent benzodiazepine use should be addressed and methadone dosing adjusted accordingly.

People who use fentanyl can be exposed to benzodiazepines in three different ways:

1. Benzodiazepine or benzodiazepine analogues added to street supply. Etizolam, a benzodiazepine analogue not legally available in Canada, is commonly added to street fentanyl without the user's knowledge. Alprazolam, meclonazepam, and other benzodiazepines and benzodiazepine-like drugs have also been found in urine drug tests of people who use fentanyl and on analysis of drug samples. The clinician should suspect benzodiazepine or benzodiazepine analogue exposure if the patient reports sedation that is distinct from their usual opioid sedation, overdose that does not respond to naloxone, or benzodiazepine withdrawal symptoms (e.g., anxiety and insomnia) not significantly relieved by methadone dose increases when fentanyl use is stopped. Unless the patient is at high risk for methadone or benzodiazepine toxicity (COPD, elderly, alcohol consumption), methadone dose titration should not be delayed, as this will prolong exposure to etizolam. Gradual decreases in fentanyl use will be associated with an inherent etizolam or benzodiazepine taper. In rare cases, etizolam withdrawal may be managed by tapering doses of clonazepam, dispensed daily along with methadone.

2. Daily use of illicit benzodiazepines. People who use opioids may also be using pharmaceutical or counterfeit benzodiazepines (e.g., "Xanax bars") recreationally or to self-manage anxiety or withdrawal symptoms. We recommend not slowing the methadone titration unless the patient is at high risk for methadone or benzodiazepine toxicity (e.g., benzodiazepine use disorder) or shows signs of sedation. Patients should be cautioned about the risks of concurrent benzodiazepines and opioids and offered alternative medications for management of anxiety if appropriate.

3. Therapeutic dose of prescribed benzodiazepines. For patients taking prescribed benzodiazepines, we recommend not adjusting the methadone titration unless the patient is at high risk for methadone or benzodiazepine toxicity, e.g., a patient on a very high prescribed benzodiazepine dose. The risks of fentanyl use far outweigh the risks of toxicity from a therapeutic benzodiazepine dose. The methadone prescriber should work with the benzodiazepine prescriber to manage the patient's anxiety disorder with medications such as SSRIs and pregabalin. A slow benzodiazepine taper may be considered once the patient is stable.

3. Therapeutic considerations for treatment retention and harm reduction

Optimizing treatment retention should be a priority of all OAT programs. Numerous studies have shown the importance of length of treatment; outcomes for patients who receive fewer than 90 days of treatment with methadone are not significantly different from those who do not enter treatment (16, 17, 81), and the National Institute for Drug Abuse (NIDA) recommends a minimum of twelve months in treatment for best outcomes (18).

Retention in treatment is greater with flexible individualized dosing rather than a fixed-dose strategy (64). This meta-analysis found that predictors of dose include prior frequency and amount of drug use, diagnosis of post-traumatic stress disorder or depression, greater number of previous opioid detoxifications, and living in a region where street heroin is high in purity. Other factors associated with retention in treatment included clinic management policies, frequency of contact with a counselor, use of cognitive behaviour therapy, and use of contingency management (i.e., increased number of take-home doses) (82).

(a) Use prescription management practices that promote treatment retention, including phone assessments, extending prescriptions, or leaving longer duration methadone prescriptions for 30mg at the pharmacy so patients can restart treatment.

Prescriptions should be managed in a way that prioritizes patient retention. Assessments can be done on the phone or virtually. For patients who miss multiple appointments, pharmacists are helpful partners in care who can assess the patient and communicate with the prescriber. For established patients who repeatedly miss four or more doses, the prescriber may consider issuing a prescription for a standing dose of methadone (up to 30mg) with the pharmacy that can be re-initiated without a new assessment by the prescriber, as long as the patient has not missed more than seven consecutive days of methadone. Patients may be less likely to drop out of treatment altogether if there is a methadone prescription available to them. Communication with the pharmacist is especially important with new prescribing practices and when the pharmacist is being asked to use their judgment in assessing the patient and implementing a treatment plan. Failing to extend a prescription due to a missed appointment is punitive and puts patients at increased risk of relapse and overdose.

(b) Decisions about take-home doses ("carries") may start as early as one month after initiation of OAT and should be based on an assessment of overall stability, risks, and benefits.

Take-home doses are valued by people on OAT; work and other activities that promote functional addiction recovery are more achievable when the requirement to attend a pharmacy daily is removed. However, carries are not without risks, including community overdose deaths: Between 2015 and 2017, 93 people not on a methadone program died of a methadone-related overdose in British Columbia (83). Thus, the carry schedule for a particular patient should be based on an evaluation of the potential risk versus the potential benefit. The carry schedule outlined in the previous CPSO guidelines required a full two months of daily supervised dosing before take-home doses can be added at a rate of one per month (14). We believe that the minimum requirement can be one month of observed daily dosing before allowing take-home doses, and that a more flexible approach to increasing and decreasing carries should be used, based primarily on a clinical assessment of social stability and an individual's ability to manage carries safely. Carries are generally not recommended in people who continue to use illicit substances (including fentanyl), alcohol, or benzodiazepines in high-risk ways. This includes people who have had a recent overdose; appear intoxicated or sedated when assessed; have an unstable psychiatric co-morbidity; or are injecting opioids. However, non-consecutive carries may be utilized with patients who use substances (including opioids) in ways that are not high risk, as per the COVID-19 OAT guidelines (84).

Focus group feedback

Participants felt that carries should be provided almost immediately to make methadone more compelling than fentanyl: "My drug dealer is closer than my pharmacy, and he's open later. The only thing closer is my fridge." Participants also felt that carries are essential for people to work and live their lives and should be based on trust and not urine samples. They strongly disagreed with the notion of carries as contingency management.

The authors contend that, although this document does not recommend initiating carries at the onset of methadone treatment, the recommendation to base decisions about carries on clinical judgement creates substantial flexibility. Decisions about carries should be made based on ongoing evaluation of their benefits relative to risks for the individual, as well as the risk to the public from possible diversion.

(c) Be aware of the limitations of urine drug testing.

Urine drugs screens are one means of assessing substance use and stability; however, clinicians should be aware of their limitations and use urine drug screens in ways that contribute meaningfully to clinical decision making. Many contaminants in the opioid supply and some illicit opioids, including fentanyl derivatives such as carfentanil, may not be detected on point-of-care tests. Furthermore, the absence of benzodiazepines in a sample does not rule out benzodiazepine exposure, as point-of-care test sensitivity varies with benzodiazepine types; for example, while diazepam is fairly reliably detected in point-of-care testing, clonazepam is often not detected unless the patient is taking high doses. In addition to confirming patient self-reports of use, urine drug screens sometimes identify substances the person did not know they were using or being exposed to. Urine testing should always be an option for patients who find it helpful and reinforcing to see their results and for those concerned with possible exposure to contaminants in their drug supply

When assessing methadone doses, discussion regarding withdrawal symptoms, dose duration and effectiveness, patterns of use, and reports or signs of sedation are more important factors in clinical decision making than the results of a urine test. Urine testing should not be required for dose adjustments, and doses should not be withheld if a patient does not provide a urine sample. Urine testing is an expectation for people who want take-home doses on a regular basis.

Focus group feedback

The group felt strongly that urine samples should never be supervised. They reiterated the importance of an honest relationship between patients and providers. Specific comments were that "We also need to stop punishing people who use drugs by deciding their course of treatment off their urine sample results."

The authors agree that a relationship based on open and non-judgmental communication is the ideal therapeutic partnership. When that relationship exists and clinical stability has been established, urine samples are less relevant. Frequency of samples can be a discussion between clients and clinicians.

(d) When determining the schedule for office visits and urine drug screens, consider both clinical need and the impact on patients' daily life.

The frequency of office visits and urine drug screens should be based on clinical need with consideration to the level of disruption in patients' lives and the implications for treatment retention. It is reasonable to assess

a patient frequently (i.e., once or twice a week, virtually or in person) during early titration; however, if the patient's dose is adequate, their pattern of drug use is stable, and they are not engaged in co-located counselling, then the length of time between visits can be increased. Frequent visits can interfere with patients' work and family responsibilities and sometimes lead to treatment drop-out. Qualitative studies suggest that dissatisfaction with frequent visits and a poor therapeutic relationship with their care provider are major factors contributing to treatment discontinuation (85-87). The provider should ensure that clinical encounters are meaningful, even if they are brief; the strength of a therapeutic relationship depends on the patient feeling that the clinician cares about them and is "on their side".

There is little evidence that frequent urine drug screens are associated with better health outcomes (88). Urine testing should be used in the following situations:

- At treatment initiation/re-initiation.[3]
- The patient would like regular take-home doses.
- The patient requests testing for their own knowledge, for work, or for education around contaminants in their drug supply.

In general, there is little utility to testing more often than once per month and to having patients leave samples outside of a clinical encounter.

(e) Provide treatment for concurrent psychiatric illnesses and substance use disorders.

People who inject opioids have a high prevalence of concurrent substance use and mental illness (38, 39). Because these conditions tend to exacerbate each other, it is ideal to treat them concurrently. OAT providers should be prepared to prescribe first-line medications for psychiatric conditions (including mood disorders, anxiety disorders, and psychosis) to patients who are not having these conditions managed by another health care provider. OAT providers should also offer first-line medications for concurrent substance use disorders when indicated. The prescriber should keep in mind that atypical antipsychotics, benzodiazepines, and gabapentinoids can increase the risk of methadone-induced sedation. Supportive counseling, brief interventions, and motivational interviewing can all be readily incorporated into regular clinic visits.

Clinicians should take a trauma-informed approach to care. A "universal precautions" approach understands that trauma is common in people with mental health conditions, and any reported exposure is probably significant (89). The principles of trauma-informed care are physical and psychological safety; trustworthiness and transparency; collaboration and mutuality with levelling of power differences; and patient empowerment, voice, and choice (90). It is important to respect a patient's decision about how much they want to disclose; full disclosure of the details of the trauma history is not necessary. The clinician's response to a situation where a trauma history may be playing a role should be to acknowledge the emotions, recognize the role that past events may be contributing to current emotional reactions, take the patient's perspective, and strive to make the current situation as comfortable as possible. Motivational interviewing and behavioural therapy skills align with patient-centred, trauma-informed care. It is a way to help patients become partners in their own health care decisions.

(f) Reduce the risk of overdose through patient education, take-home naloxone, and advice on harm reduction.

All OAT prescribers should routinely counsel patients on harm reduction strategies. We suggest the following:

[3] Note that if the patient has a confirmed OUD diagnosis and OAT is indicated, a negative urine result should not stop the prescriber from initiating methadone.

- Emphasize to patients that methadone is a form of harm reduction and abstinence is not a required goal of care. If patients stop methadone in favour of other harm reduction approaches, they are always welcome to return to an OAT program.
- Advise patients to not use alone and to call 911 if someone is drowsy after using. Recommend that they use a supervised injection site if possible.
- Provide and instruct patients on the use of naloxone.
- Warn patients that derivates of fentanyl do not reliably show up on point-of-care tests.
- Warn patients that drugs sometimes contain fentanyl or derivatives even if they are not sold as such.
- Stay informed of local trends (e.g., prevalence of etizolam or carfentanil in fentanyl supply) and share information with patients.
- Learn about your public health department resources (e.g., drug-checking services, overdose prevention phone line) and share information with patients.
- Take extra time to counsel patients if they have experienced or witnessed an overdose; these events can be very traumatizing.
- Have supplies and information on safer drug use in the clinic as well as relationships with local harm reduction agencies.
- Offer testing and access to treatment for blood-borne infections.
- Provide treatment for complications of substance use such as cellulitis and abscesses when appropriate.
- Provide contraception.

4. Inpatient management

(a) OAT should be routinely offered to hospital patients with OUD.

Evidence suggests that OAT is rarely initiated in hospital. In a data analysis of admissions to the Veterans Administration hospital system in the US, only 2% of inpatients with OUD were given OAT while in hospital and linked to treatment on discharge (91). In Ontario, one major barrier to OAT initiation in hospitals is that few hospitals have an addiction consult service, and hospital clinicians may be reluctant to initiate OAT if they lack training and experience. However, hospital initiation of OAT is very safe and markedly reduces rates of leaving against medical advice, readmission, and mortality. Therefore, attending clinicians should offer OAT, including methadone when appropriate, even if the hospital does not have an addictions consult service. As described in section 1, methadone and buprenorphine are both first-line treatments. Methadone is indicated if the patient has been unsuccessful with buprenorphine treatment in the past, if the patient has continued high-risk opioid use despite an optimal dose of buprenorphine, if buprenorphine induction in hospital is unsuccessful, or if the patient prefers methadone.

Methadone can be initiated and prescribed according to the usual dosing protocol (see section 2): 30mg maximum on day one, with dose increases of 10–15mg as needed every three to five days. If the prescriber has training in addiction medicine, and the patient is not at high risk for methadone toxicity, an accelerated titration protocol can be followed (59, 92). Patients should have a slower dose titration if they are at high risk for methadone toxicity due to acute respiratory illness, sedating medications, liver or renal failure, or uncertain opioid tolerance. In high-risk patients, the starting dose should be lowered to 10–20mg, with dose increases of 10mg every three to five days. Short-acting oral opioids such as hydromorphone or morphine may be used for pain and withdrawal symptoms. Patients who show signs of sedation, even if mild, should have O2 saturations monitored and their methadone dose should be held. Consultation with an experienced OAT provider may be helpful.

SROM may be used in combination with methadone if the hospitalist is experienced in OAT. It may also be used as a monotherapy alternative to methadone and buprenorphine, particularly in hospital settings where methadone or buprenorphine administration may be logistically difficult (e.g., at smaller hospitals, on weekends, pharmacy resource limitations, etc.).

Follow-up should be arranged with a community OAT prescriber within a week of discharge. The hospital clinician should give a bridging prescription for daily-dispensed methadone and/or SROM to last until the planned appointment.

5. Pregnancy and methadone

(a) Pregnant patients with OUD should be started on OAT as soon as possible and titrated to avoid withdrawal symptoms due to the risks of spontaneous abortion and preterm labour. When possible, hospital admission for rapid up-titration of methadone with augmenting opioids is recommended. When caring for a pregnant patient using fentanyl, contact a colleague with experience for guidance and involve the obstetrical team early whenever possible.

It is critically important to initiate OAT in pregnant patients and retain them in treatment; OAT has been shown to improve parental and neonatal outcomes compared to detoxification and withdrawal (93), and withdrawal increases the risks of both spontaneous abortion and preterm labour. Because methadone has a shorter half-life and longer clearances during the later stages of pregnancy (94-96), consider prescribing split doses to patients in the third trimester. The severity of neonatal abstinence syndrome has not been found to be related to the methadone dose.

Summary

The recommendations given above are largely consistent (albeit different in emphasis) with the CPSO guidance document. However, we advise some novel practices, as summarized below:

New recommendation	CPSO statement
(2e) After four consecutive missed doses, the dose of methadone should be reduced by 50% or to 30mg, whichever is higher. For patients who miss five or more consecutive doses methadone should be restarted at a maximum of 30mg and titrated according to patient need. SROM at a maximum starting dose of 200mg can be added on the day of a restart, as long as the patient has not become completely opioid-abstinent.	(S6.14) If the patient misses two or more consecutive doses during the early stabilization phase, the MMT physician shall cancel all subsequent doses, assess the patient in person, and restart the patient maintaining this dose for at least three consecutive days. (S6.15) The MMT physician shall reduce the dose to 30mg or less when a patient has missed four or more doses of methadone during the late stabilization and maintenance phases. (S6.16) The MMT physician shall reduce the dose by 50% or to a dose of 30mg or less when a patient has missed 3 consecutive days during the late stabilization and maintenance phases.
(2g) Methadone dose increases should not be delayed due to the absence of an ECG.	(S6.18) The MMT physician shall order an ECG with a calculated QTc interval for patients on doses above 150mg.
(3a) Use prescription management practices that promote treatment retention, including phone assessments, extending prescriptions, or leaving longer duration methadone prescriptions for 30mg at the pharmacy so patients can restart treatment.	(S6.9) The MMT physician shall assess the patient in-person prior to each dose adjustment. (G6.3) The MMT physician should ensure doses are only increased after the patient has been assessed in person, and it is determined that the patient is experiencing cravings or ongoing opioid use, and/or a constellation of withdrawal symptoms.
(3b) Prescribe take-home doses with due caution, beginning after at least one month of observed daily dosing.	(G8.2) The MMT physician should ensure the first weekly take-home dose is prescribed only after the patient has been in the program for two months, and prior to take-home dose acquisition the patient has had at least one week without problematic substance use, as determined by history and UDS.

Clinical questions and scenarios

Q: A patient has recently started on methadone, is in the dose titration phase, and last week his dose was increased from 45mg to 60mg. He misses an appointment and shows up the next day at the pharmacy requesting his dose. He has been forthcoming with the prescriber that he is using fentanyl regularly. The pharmacist contacts the prescriber's office seeking direction. The pharmacist reports the patient is alert and not intoxicated. What should the prescriber do?

A: Rather than requiring the patient to come in for an assessment, the prescriber should extend the methadone prescription at 60mg for one week and offer the patient another follow-up visit for assessment.

Q: A patient has started methadone 30mg on May 1st and presents to the prescriber's office on May 5th requesting a dose increase. However, she has missed a dose on May 3rd. She has already had a dose today, May 5th. On assessment, she states she barely feels 30mg of methadone and continues to use fentanyl daily. She denies nodding off or sedation and looks alert. She is requesting a dose increase. What should the prescriber do?

A: The prescriber should increase the dose to 45mg on May 6th despite not having three consecutive days of doses, since she has had four of five doses, including the day of assessment. If she had not already had her dose on May 5th, she would receive 30mg on May 5th and 45mg on May 6th. An alternative is to consider adding SROM at a dose of 100–200mg to be co-administered with methadone at the pharmacy. Since SROM does not accumulate in the serum, it can provide additional withdrawal relief without the risk of accumulation with repeated dosing.

Q: A patient has been on 100mg methadone for several months. He continues to use fentanyl intermittently but attends at the pharmacy regularly and only occasionally misses one or two doses at a time. He has missed the last several appointments and typically presents later to the pharmacy requesting extensions of his prescription. He has again missed his appointment and is at the pharmacy requesting an extension of his prescription. What should the prescriber do?

A: The prescriber should make a reasonable effort to reach the patient on the phone, whether during the pharmacy visit or on the patient's phone if he has one. Collateral information about the patient's functional status can be collected from other professionals involved in the patient's care, such as the pharmacist, case managers, or outreach workers. Generally, prescriptions should be continued, because treatment drop-out can lead to fatal fentanyl overdose. If there is persistent and repeated difficulty in connecting with the patient and the prescriber has concerns about continuing the prescription, the prescriber can initiate a very slow taper, to be reversed if the patient attends.

Q: A patient who has been on methadone off and on in the last several months at doses up to 75mg is restarted on methadone 30mg on a Wednesday after missing six doses. The prescriber is not available for reassessment three days later on Saturday. Can the prescriber write a predetermined dose increase from 30mg to 45mg to start on Saturday or Sunday without reassessing the patient? What if the patient has not been on methadone in the past month?

A: 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. If the patient's tolerance of methadone is known from previous starts, it is reasonable to write one predetermined dose increase and subsequently assess the patient. The prescriber should leave clear written instructions for the patient's pharmacy. 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 longer duration of a starting 30mg prescription 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.

Q. How do you titrate SROM and methadone together?

A: For patients using fentanyl in high quantities/high-risk ways, methadone can be started at 30mg along with SROM at 100–200mg daily (assuming no increased risk for sedation). Both methadone and SROM can be increased every three days for patients who are known to be using fentanyl intensively, e.g., injecting daily. Methadone can be increased by 15mg and morphine can be increased by 50–100mg per visit to a dose of 300mg. Once at 300mg, the morphine dose would generally be maintained (not increased) during further methadone titration, unless the clinician and patient agree that an increase of morphine would be better tolerated and/or more effective than an increase of methadone.

Q: Does SROM have to be stopped once the patient gets to a certain dose of methadone? What would that level be?

A: While SROM is usually offered as a bridge while working to an adequate dose of methadone, it may be continued once an optimal methadone dose is reached if the patient is doing well, i.e., injecting less often and feeling better without sedation or side effects. The prescriber should consider patient preference and response to treatment and use clinical judgment to determine appropriate doses of both medications.

Q: How should the prescriber decide between increasing the methadone dose and adding SROM?

A: The prescriber can engage in shared decision-making with the patient.

Q: If a patient on 100mg of methadone and 300mg SROM misses two days of dosing (while continuing to use fentanyl), how would you adjust the doses?

A: For two missed days, both doses could be continued, since 200mg is the maximum starting dose for SROM. If the patient missed three or more doses, SROM should be reduced by 50% or to the previous starting dose; methadone can be continued as long as the patient has not missed more than four doses.

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