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

Lisa Bromley MD CCFP(AM) FCFP
Meldon Kahan MD CCFP FRCPC
Leonora Regenstreif MSc MD CCFP(AM) MScCH(AMH) FCFP
Anita Srivastava MD MSc CCFP
Jennifer Wyman MD FCFP DABAM MPH

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: Primary Care–Hospital 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.

The document was shared for review with people with lived experience using drugs, OAT providers, pharmacists, and addiction experts across Ontario. This version incorporates their input and is being posted for consideration and feedback. 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.

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

[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).

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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). Unexpected fentanyl has also been found in the Ontario supply: for example, between October 2019 and March 2020, unexpected fentanyl was found in 43% of samples expected to contain heroin that were submitted to Toronto's drug checking service (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). 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. 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 (6-10). The College of Physicians and Surgeons of Ontario (CPSO) methadone guidelines (11) were written for Ontario methadone prescribers in 2010, 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 should be viewed not as a new set of rules, but as a guide to inform clinical decisions. Our 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 (12-15). **This is not an exhaustive review of all aspects of methadone prescribing. Prescribing decisions should be made in accordance with what is known about the pharmacology of methadone;** clinicians should refer to appropriate standards and should use their best clinical judgment and all available evidence when making prescribing decisions.

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. These recommendations are based on consensus guidelines, anecdotal evidence, and clinical experience, and would therefore be classified as weak. Nonetheless, they are more appropriate for people who use fentanyl, in our view, than the recommendations of the CPSO and other medical colleges, which were written long before the fentanyl crisis and did not address the clinical challenges posed by this highly potent and dangerous opioid.

Evidence on the effectiveness of methadone for people who use fentanyl

There is good evidence to suggest that methadone protects against fatal opioid overdose. A systematic review and meta-analysis updated to September 2016 found that there was an average reduction of 25 deaths per 1000 person years among those in opioid substitution treatment with methadone (16); 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 (17). 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 Sept 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 (18), 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 reduced risk of overdose during three-month (AHR, 0.24; 95% CI, 0.14-0.41) and twelve-month (AHR, 0.41; 95% CI, 0.31-0.55) follow-up; treatment with buprenorphine or methadone was also associated with reduction in serious opioid-related acute care use during three-month (AHR, 0.68; 95% CI, 0.47-0.99) and twelve-month (AHR, 0.74; 95% CI, 0.58-0.95) follow-up (19).

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 (20).

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 (21) 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 (22) 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 (23), 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 (6). A systematic review found that in-hospital provision of methadone for people who inject drugs was negatively associated with leaving hospital against medical advice (24). In a retrospective cohort study of patients admitted to hospital for complications of injection opioid use (25), 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%).

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 (10, 26). 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 (27). In a systematic review of controlled trials comparing methadone and buprenorphine (10), 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 (28) 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. 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 (29). By the end of the study, half of the buprenorphine group had switched to methadone.

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 (16). Clinicians were advised to aim for methadone doses 60mg or above, as these were associated with

higher levels of abstinence from opioid use (11). 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, is associated with lower rates of ongoing use based on self-reports and urine drug screens (30, 31). 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 (32). 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 (32, 33), 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 (34). 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) For patients who use fentanyl daily or near-daily, consider starting methadone at the higher end of the range of initial dosing recommendations (i.e., 30mg).

Current 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 (11, 35, 36). 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.

However, methadone has a very long and variable half-life. For this reason, it is important to not exceed the recommended initiation doses of methadone. Methadone is metabolized primarily by CYP 2B6 and CYP 3A4, with CYP 2B6 primarily determining methadone's stereoselective metabolism (37). The half-life tends to be much longer on initiation of methadone treatment, declining over time with induction of the enzymes that metabolize methadone (37-39). 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 (27, 40-42).

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 (43). 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 (44). 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 (45), there is currently no helpful data to support higher starting doses of methadone for first-time methadone initiation in people who use fentanyl.

(c) The starting dose of methadone should be increased by 10–15mg every three to five days., Within this range, faster titration is recommended for those who are not at high risk for methadone toxicity (e.g., not concurrently using high doses of benzodiazepines or binge-drinking 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 (11). 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 of methadone. People who use fentanyl are likely to 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 benzodiazepines as opposed to prescription, occasional, and/or accidental use.

Other dosing protocols that allow accelerated titration or additional flexibility have been described, all of which are substantially similar to the CPSO protocol. In the protocol used in the Rhode Island cohort (20), methadone is started at 30mg on day one and increased by 10mg per day until 50mg is reached; the dose can then be increased by 20mg every seven days. The American Society of Addiction Medicine (ASAM) expert panel sets the maximum dose for day one at 40mg for patients at lower risk of toxicity, as opposed to the 30mg maximum that the other protocols recommend, although the dose titration is slower than the other protocols (46). The 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 (47).

(d) Slow-release oral morphine (SROM) may be co-prescribed with methadone during the initiation and early titration phase. SROM should be dispensed as "observed dosing along with methadone" during initial titration at doses between 50mg and 200mg (47).

Co-prescribing SROM with methadone is an approach adapted from the College of Physicians and Surgeons of Saskatchewan methadone guidelines (47); although their results have not been published in peer-reviewed journals, prescribers report that this approach has been used hundreds of times with good results and no deaths during the induction period. 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 few weeks of

methadone treatment, when doses are subtherapeutic; it can be used alongside methadone because metabolites 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 not be used in patients with renal insufficiency, and other risk factors for opioid toxicity, such as heavy use of street benzodiazepines or alcohol, should be taken into consideration. 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. The CPSS guidelines recommend 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 range can be maintained or increased by 50–100mg per visit during titration of methadone. In our clinical experience, doses of 100–300mg are almost always 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 end up remaining on combination therapy, based on expert opinion; there are no established guidelines that recommend or offer guidance on combination therapy.

Use of SROM as OAT is not as yet based on established protocols. The British Columbia Centre on Substance Use (BCCSU) guidelines on OUD management provide guidance for prescribing SROM including dose titration, managing missed doses, and observed versus take-home doses (35).

(e) Patients who miss methadone doses should be assisted to resume previous doses quickly and safely. For patients who miss four consecutive doses, the dose of methadone should be reduced by 50% or to 30mg, whichever is higher; it can then be increased by up to 10mg daily for three days until reassessment, as long as the dose does not exceed the most recent dose dispensed (prior to the missed doses). For patients who miss five or more consecutive doses, the methadone should be reduced to 30mg and the patient treated as a "restart", with dose increases of 10–15mg every three to five days as discussed above. 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 due to extenuating circumstances such as a period in custody or other setting of forced abstinence.

Tolerance to methadone is partially lost after just a few days of abstinence. The current CPSO methadone guidelines (11) differentiate 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. While the CPSO guidelines recommend that if a patient misses two

consecutive doses of methadone during early stabilization the prescription should be cancelled and the patient must be reassessed in person before re-initiation of therapy, **we recommend that methadone prescriptions not be cancelled unless a patient misses four consecutive doses**. This recommendation is based on guidelines from California (48), British Columbia (49), Australia (50), and the UK (51). Use the following protocol for patients who have missed doses:

Doses missed	**Restarting dose**	**Increases**
Three or four (patient presents on day four or five)	The higher of 50% of previous dose or 30mg	10mg daily for three days, then reassess and proceed as usual
Five or more (patient presents on day six or later)	30mg	10–15mg every three to five days based on clinical judgment and patient assessment*

*Taking into account co-occurring risk of alcohol, benzodiazepine or medications that affect methadone elimination.

Repeated missed doses during the early stabilization period present a barrier to reaching therapeutic doses of methadone for craving and withdrawal symptoms. We recommend considering a dose increase for patients who repeatedly fail to achieve three consecutive doses in the early titration period under certain situations:

- At or under doses of 60mg.
- If the patient has had at least four doses within five days and on assessment reports little withdrawal relief at the current dose.
- If the patient has had continued fentanyl use and is not sedated.

If the dose was only missed the day prior to the day of the assessment, continue that dose for that same day, and schedule a dose increase for the following day. 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 the patient is seen on Day 5:

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**

*Patients can be scheduled for a dose increase on the following day.

**If patient is assessed by prescriber or pharmacist and conditions are met.

(f) Take steps to optimize the dose. For patients who continue to use fentanyl or heroin regularly, doses of 100mg or higher may be needed in some cases.

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/day (52). 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 (53).

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 (54). 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 (20), 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 (55). 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 (56). 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 optimising 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) For patients on a moderate to high methadone dose, do not delay dose increases if unable to obtain an ECG.

High doses of methadone can be QT-prolongating, and ECG screening is advised for patients who are on doses above 150mg; who are at high risk for arrhythmias due to infective endocarditis, cardiac surgery, previous torsades de pointes, or other cardio-pulmonary complications of injection drug use; or who are taking other medications that could prolong the QT interval (57-59). 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 risk of death from fentanyl overdose far exceeds the risk of torsades de pointes. A Cochrane review found no evidence that ECG screening improves outcomes in methadone patients (60), and one of the studies in the review estimated the risk of death from ventricular arrhythmias among methadone patients to be 0.06 per 100 patient years (61). We recommend that dose increases not be delayed while waiting for an ECG unless there is clinical suspicion; if an ECG is deemed necessary prior to increasing the dose, consider co-prescribing SROM, which is not QT-prolongating.

(h) Identify and manage concurrent benzodiazepine use and adjust methadone dosing 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, or overdose that does not respond to naloxone. If benzodiazepine or etizolam exposure is prolonged and daily, patients are at risk for benzodiazepine withdrawal if they stop daily fentanyl use. Etizolam withdrawal should be suspected if the patient reports daily anxiety and insomnia not significantly relieved by methadone dose increases. 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 "Xanax bars" (counterfeit tablets containing 2–4mg of alprazolam, but of unpredictable strength and quality) or other pharmaceutical benzodiazepines 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 (13, 14, 62), and the National Institute for Drug Abuse (NIDA) recommends a minimum of twelve months in treatment for best outcomes (15).

Retention in treatment is greater with flexible individualized dosing rather than a fixed-dose strategy (53). 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) (63).

(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. The prescriber may consider leaving a prescription for a starting dose of methadone (up to 30mg) with the pharmacy without requiring assessment by a provider. Patients may be less likely to drop out of treatment altogether if there is a methadone prescription available to them. An extended prescription of 30mg for up to 30 days will make it easier for patients to re-engage in treatment if they can access interim doses.

Failing to extend a prescription due to a missed appointment is punitive and puts patients at increased risk of relapse and overdose.

(b) Prescribe take-home doses with due caution, beginning after at least one month of observed daily dosing.

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 (64). Thus, the carry schedule for a particular patient should be based on an evaluation of the potential risk versus the potential benefit. The CPSO carry schedule requires a full two months of daily supervised dosing before take-home doses can be added at a rate of one per month (11). We believe that the minimum requirement should be reduced to **one month** of observed daily dosing before allowing take-home doses, and that there should be a **more flexible approach** to increasing and decreasing carries that is based primarily on a clinical assessment of social stability and an individual's ability to manage carries safely. Carries are not recommended in people who continue to use fentanyl; are using illicit

substances, alcohol, or benzodiazepines in high-risk ways; have had a recent overdose; or have an unstable psychiatric co-morbidity.

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

Urine drugs screens are one important measure of a patient's 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.

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. During methadone titration, urine testing more than once a week is not required, 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.

In general, random urine screens are considered to be more useful than scheduled testing (65).

(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. It is reasonable to see a patient frequently (i.e., once or twice a week) 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 (66-68). 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 (69). Once methadone doses are in the 60–80mg range and the patient is in the maintenance phase, urine testing does not need to be done more often than **once monthly**, except in the following situations:

- The patient requests a dose change.
- The patient would like take-home doses.
- The patient requests regular testing for their own knowledge, for work, or for education around contaminants in their drug supply.

(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 (32, 33). 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 (70). 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 (71). 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 who are at risk of overdose on harm reduction strategies. We suggest the following:

- 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.

4. Inpatient management

(a) Methadone should be routinely offered to hospital patients with OUD when appropriate. Methadone can be adjusted with a rapid titration protocol by prescribers trained in addiction medicine.

Hospitalization is an excellent opportunity to offer and initiate OAT treatment. Titration of methadone can be done more quickly in an inpatient setting; patients are often motivated to engage in treatment and can be monitored throughout the day for sedation. The care team should make a plan for the patient to be seen by a community methadone provider for ongoing care. However, a data analysis of admissions to the Veterans Administration hospital system in the US found that only 2% of inpatients with OUD were given OAT while in hospital and linked to treatment on discharge (72).

While buprenorphine should be offered routinely to all patients with OUD in the emergency department, methadone or referral for methadone treatment should be offered if the patient declines buprenorphine or if buprenorphine is contraindicated.

SROM may be used as an 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.). The hospital clinician can prescribe SROM for up to a week after discharge. It should be dispensed once daily under the observation of the pharmacist.

If the prescriber is not an experienced methadone prescriber, the patient should be started at 30mg and titrated according to advice from a community prescriber. If the prescriber has training in addiction medicine, an accelerated titration protocol can be followed. Several inpatient protocols for accelerated methadone titration have been developed. In the inpatient protocol used by the Centre for Addiction and Mental Health, the initial morning dose is 10–30mg, followed by two 5mg PRN doses or one 10mg PRN dose. The next morning, the patient receives the previous day's total dose (up to 40mg) as a single dose, followed by two 5mg doses or one 10mg PRN dose. In this manner, the dose is increased by 10mg per day until discharge, when the outpatient protocol resumes. This protocol is similar to a protocol used in California (48). In a protocol used at St. Paul's Hospital in Vancouver (73), a base dose of 30mg is given on the first day with up to three 10mg PRN doses. The base dose is increased every three days as with an outpatient titration. When the total daily dose in base dose + PRN doses has been stable for several days, PRN doses can be consolidated into the base dose given once daily. Regardless of the inpatient protocol used, monitor the respiratory rate and level of consciousness three hours after each PRN dose. Slower titration is recommended in patients on benzodiazepines or other sedating drugs, patients with respiratory impairment, and other risk factors for methadone toxicity.

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 (74), 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 (75-77), 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) For patients who miss four consecutive doses, the dose of methadone should be reduced (on Day 5) by 50% or to 30mg, whichever is higher; it can then be increased by up to 10mg daily for three days until reassessment, as long as the dose does not exceed the most recent dose dispensed (prior to the missed doses). For patients who miss five or more consecutive doses, methadone should be reduced to 30mg and the patient treated as a "restart", with dose increases of 10–15mg every three to five days as discussed above. SROM at a maximum starting dose of 200mg can be added, as long as the patient has not become completely opioid-abstinent due to extenuating circumstances such as a period in custody or other setting of forced abstinence.	(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 30 mg 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) For patients on a moderate to high methadone dose, do not delay dose increases if unable to obtain an ECG.	(S6.18) The MMT physician shall order an ECG with a calculated QTc interval for patients on doses above 150 mg.
(3a) Use prescription management practices that promote treatment retention, including phone assessments, extending prescriptions, or leaving 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 45 to 60 mg. 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 is restarted on methadone 30mg on a Wednesday. The prescriber is not available for reassessment for a dose increase 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: Methadone can be started at 30mg with SROM at 100–200mg daily (unless at increased risk for sedation) and increased in three to seven days for patients who are known to the prescriber and are injecting daily. Morphine can be increased by 50–100mg per visit (along with the methadone) to a dose of 300mg. During this titration period, the morphine dose would generally be maintained (not increased) while methadone is increased, unless the clinician and patient agree that a morphine dose increase would be better tolerated and/or more effective than a methadone dose increase.

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 three or four doses.

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Leah Steele MD PhD
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Maria Zhang BScPhm PharmD MSc

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