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MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

1.4 Recommendations for the Ongoing Care of Individuals on Opioid Agonist Therapy

GENERAL CONSIDERATIONS

Once the induction and early stabilization phases of treatment have been completed, the patient is typically on a stable daily dose of opioid agonist therapy (OAT) and enters the maintenance phase of treatment. During the maintenance phase, treatment goals shift from early engagement and medical stabilization to the ongoing work of recovery. Appointments are spent managing all the biopsychosocial components of addiction treatment, with an overarching goal of establishing and nurturing clinical stability.

This section addresses key features of assessment and ongoing care during the maintenance phase of treatment. Several common issues that may arise as patients navigate life, while participating in OAT, are also discussed. Specifically, recommendations are provided for dose optimization, split dosing, rapid metabolism, prolonged QTc, missed doses, vomited doses, and rotation between different OAT medications.

SPECIFIC RECOMMENDATIONS

ASSESSING CLINICAL STABILITY

The following issues should be reviewed at follow-up appointments to assess and support clinical stability. In the earlier maintenance phase, a structured approach to follow-up will ensure that no important issues are neglected. Most issues on the list below should be reviewed at each appointment and are addressed throughout this chapter.

1) OAT Dose
2) Potential Side Effects
3) Current Substance Use

4) Urine Drug Testing (UDT)
5) Medication Review
6) Psychological Stability
7) Physical Health & Pain Management
8) Sexually Transmitted and Blood Borne Infection (STBBI) Screening
9) Social Stability
10) Treatment Goals
11) Revisit the Treatment Agreement

However, as the patient progresses in treatment and increasingly re-engages in healthy activities of daily living, follow-up appointments may be used to address the most pressing issues the patient and provider wish to discuss. Some follow-up appointments may simply be used to check in on the patient's life and to further strengthen the therapeutic alliance, often by highlighting the treatment goals realized over time.

1) OAT DOSE

The goal is to establish a stable dose of OAT medication. A stable dose is achieved when opioid withdrawal is eliminated or adequately suppressed for a complete 24-hour period following the dose, allowing patients to further engage in ongoing medical and psychosocial treatment. At a stable dose, drug cravings should be under control. The patient will likely still have regular thoughts about using (*this is very normal in early treatment*), but they should not experience regular, intense, and "physical" cravings for opioids. Opioid use will have stopped or be dramatically reduced.

The right OAT dose achieves these clinical goals without causing daytime sedation or excessive tiredness, and with minimal or at least manageable side-effects. Tolerance to common side-effects often develops over time, and reassuring patients of this in early treatment can be helpful.

Buprenorphine Dose Stability

A stable dose of buprenorphine/naloxone may be reached within the first few days of induction, but sometimes further small adjustments are required later in treatment. If it becomes apparent that withdrawal symptoms are breaking through prior to the next dose, further increases may be required. Dose increases of **2 to 4 mg may be needed up to 24 mg daily**. At this later stage of treatment, depending on the severity of withdrawal symptoms or the extent of opioid use, dose increases are typically smaller with longer intervals between increases. **A one-week interval between smaller dose adjustments allows for adequate serum accumulation to fully assess the effect of each increase**.

In some exceptional circumstances (for instance patients with higher opioid tolerance), dose increases up to an absolute maximum of 32 mg daily may be useful. It is important to note the clinical benefit associated with dose increases beyond 24 mg is significantly diminished. Therefore, if a patient does not actually benefit from increases beyond 24 mg daily, the increases should be reversed.

For patients who do identify benefit from doses between 24-32 mg daily early in treatment, it is important to later attempt a slow trial of tapering down to 24 mg after the first 6 to 12 months in treatment. Patients are often able to thrive on a lower dose once they have benefitted from treatment for an initial period. Reducing the dose to within a normal dose range may minimize side effects and the common medical complications associated with long-term opioid use.

Discomfort Despite Dose Stability

Some patients will continue to report feeling unwell, despite being at a clinically stable dose of OAT. Such distress may be described as ongoing craving, or feeling “not right”, or “not comfortable in my own skin”. It may also manifest as ongoing drug use, including intermittent opioid use. It is important to understand *if these feelings/behaviors are consistently present*, or *more episodic* and related to circumstantial or emotional triggers. For example, running into previous contacts or friends associated with drug use, or the emotional upset tied to any number of normal life experiences. Consider if an underlying mental health disorder may need to be addressed.

Generally, once withdrawal is eliminated further dose increases are rarely effective in addressing this type of discomfort, which can manifest psychologically and physiologically. Behavioral change and counselling interventions may be more effective strategies to support patients in coping with the stress and distress of early sobriety. **It is important for providers to remember that not all forms of discomfort can be addressed with medication**. A consistent strategy of non-judgmental support, framed by predictable boundaries, is often the best treatment plan. The section on Managing Co-Occurring Psychiatric Disorders offers detailed guidance to help determine if mental health symptoms are a natural part of the recovery process in opioid use disorder (OUD) or rather indicative of a psychiatric disorder requiring specific medication or psychotherapy.

Some patients, particularly those with long-standing and/or high-dose use of potent opioids, may not achieve a dose of buprenorphine/naloxone that eliminates withdrawal symptoms and significantly reduces ongoing opioid use. Such patients may need to consider switching to a different opioid agonist. Methadone has been found to be more effective in some circumstances. For inexperienced prescribers, consultation with an experienced prescriber may be helpful for advice. Transitioning from buprenorphine to methadone is discussed later in this chapter (see ROTATION OF OAT MEDICATIONS below).

Methadone Dose Stability

While buprenorphine/naloxone often allows for more rapid dose titration, **methadone induction and titration MUST be approached slowly and cautiously**, as recommended in Methadone Induction, Titration, & Stabilization. It may take several weeks to address opioid withdrawal effectively. It is important to be upfront with patients about this requirement and to discuss ways to cope with ongoing withdrawal and cravings, to help maintain engagement in treatment. Again, a stable dose is achieved when opioid withdrawal is eliminated or adequately suppressed for 24 hours, to allow patients to further engage in ongoing medical and psychosocial treatment. In the later stages of treatment most patients have substantially reduced opioid use, they are largely tolerant to methadone, and experience no withdrawal symptoms for most of the day.

With experience, prescribers can typically establish a stable dose for many patients within four to eight weeks of initiating methadone. The stable dose range for most methadone patients is 50-120 mg, however **the focus should be on clinical indicators of stability, not the dose**. Patients may occasionally ask for dose increases because of episodic subjective withdrawal symptoms, opioid cravings, or a relapse to opioid use. During the maintenance phase, or if the dose is 80 mg or higher, dose adjustments are **typically between 3-5 mg every three to seven days**. Patients who use high-potency opioids (e.g., fentanyl) regularly, may require higher overall doses and larger dose increases for stability.

Given the high degree of variability in methadone pharmacokinetics and metabolism, "the optimum methadone dose can vary significantly between patients, necessitating careful, individualized dose titration as opposed to standardized dosing regimens”[1].

Lower Methadone Doses (Below 50 mg)

Some patients stabilize at lower-than-average doses. Low maintenance doses may be suitable for some patients, such as those with lower opioid tolerance and a contraindication to buprenorphine/naloxone, or intolerable side-effects on buprenorphine/naloxone.

Some patients may choose methadone treatment despite education about the benefits of buprenorphine/naloxone. This may be due to past treatment success on methadone, or familiarity with methadone treatment due to a close family member or friend on methadone.

Treatment should not be withheld when a patient specifically requests methadone. If the patient has received adequate education about the benefits of buprenorphine/naloxone, methadone is a reasonable second-line treatment option.

Methadone doses below 50 mg are generally less effective than higher doses at reducing high-potency opioid use and retaining patients in treatment[1].

Higher Methadone Doses (Above 120 mg)

Patients may require maintenance doses above 120 mg either due to a higher innate tolerance secondary to long-standing or high-potency opioid use, or increased metabolism of methadone secondary to certain conditions or medications (see *Rapid Metabolism & Serum Levels*).

Patients on higher doses should be granted dose increases if they *consistently* report a cluster of withdrawal symptoms that occur at a predictable time at the end of a dosing interval. The cluster should include both physical and psychological symptoms. Assess the patient for other conditions that are commonly confused with withdrawal symptoms (also see *Discomfort Despite Dose Stability* section above).

Patients with particularly high tolerance of high-potency opioids (e.g., injecting or smoking primarily illicitly sourced fentanyl) may require higher doses for stabilization and treatment retention and/or Alternative Treatment Approaches to care. **Consultation with an addiction medicine specialist should be sought to best support these patients**, particularly if patients continue to have difficulty stabilizing on doses around 150 mg.

Tapering Methadone Doses

For patients who do benefit from higher doses of methadone, it is important to attempt a slow trial of tapering to a lower dose, after the first 12 months in treatment. Patients are often able to thrive on a lower dose once they have benefitted from treatment for an initial period. Reducing the dose in such cases will minimize side effects and common medical complications associated with long-term high-dose opioid use.

Clinically, some patients report feeling more alert and energetic after tapering from higher doses, and some can decrease their dose by 20-40 mg with relative ease, over time. Dose reductions should be *no more* than 5-10% of the total remaining dose every one to two weeks. The taper should be held or reversed if the patient reports persistent and uncomfortable withdrawal symptoms, to avoid risk of destabilization or relapse, even if the dose is >120 mg.

Taper attempts should also be considered in elderly patients, given age-related changes to metabolic, cardiac, respiratory, and cognitive functions. Prescribers should review the clinical picture with ageing patients to determine if a trial of a slow taper to a lower dose would be beneficial. See Recommendations for Older Patients for further guidance.

Methadone Split Doses

Split dosing should be considered rarely, in select patients, and a thorough clinical assessment is required when evaluating potential indications for split dosing. This should include review and documentation of the risks and benefits of split dosing, discussed in collaboration with the patient. **Inexperienced prescribers are strongly advised to seek expert guidance**.

If a trial of split dosing is warranted, collaboration with pharmacy is essential to discuss the indication and practical implications for pharmacy attendance/take-home doses. Further to this collaboration, the prescriber must be clear on the prescription as to which doses (i.e., AM and/or PM doses) are expected to be witnessed and take-home doses.

In determining if a trial of split dosing is appropriate in the community setting, the OAT prescriber should consider:

- The overall stability of the patient,
- The number of regular take-home doses,
- The nature and duration of the patient's condition/indication for split dosing,
- The patient's overall mobility, and
- Public safety, including the safety of other adults and children in the home.

Split dosing is *rarely recommended* in patients without sufficient clinical stability to earn take-home doses, as split dosing in such patients would require multiple trips per day to the pharmacy, which is usually impossible or impractical.

There are three *possible* clinical indications for split dosing:

- **Patients with pain**: Patients typically experience analgesia from methadone in the first 6-8 hours immediately post-dose and split dosing can be considered in *clinically stable* patients who suffer from chronic pain. **This should only be considered as an adjunct if all other non-opioid/non-pharmacological modalities of treatment are not effective or appropriate**.

  In certain situations, clinically stable patients who suffer from acute or post-operative pain may also benefit from temporary split dosing. However, once the pain is improved/resolved, once-daily dosing should be resumed. The section Managing Acute, Chronic, & Perioperative Pain provides detailed recommendations for managing pain in the context of OAT. Inexperienced providers are strongly encouraged to consult with an addiction medicine specialist when considering split dosing for pain.

- **Pregnant patients**: Dose increases may be required during pregnancy as the body and metabolism change, particularly in the third trimester and especially in pregnant patients on methadone. Some patients may report ongoing withdrawal symptoms in the evening or overnight despite dose titration, and split dosing may be effective in addressing this scenario. Typically, the smallest dose that eliminates withdrawal is prescribed as the second dose in this context. Patients in the third trimester must be assessed regularly by the treatment team to ensure appropriate and timely dose adjustments are made, including split dosing if required. See the Treatment of OUD in Pregnancy chapter for further guidance.

- **Rapid metabolizers**: Split dosing can also be considered in patients with clinically relevant symptoms of rapid metabolism, or those who take medications known to significantly induce methadone metabolism (see **hepatic inducers** section of Methadone Pharmacology). Consultation with an experienced prescriber and/or pharmacist is recommended. See section below for further details.

Rapid Metabolism & Serum Levels

Rapid methadone metabolism may occur in a small portion of patients, who otherwise would be expected to stabilize but continue to experience withdrawal near the end of their 24-hour dosing interval. While most patients will tolerate and adjust to this mild withdrawal, some require further investigation and intervention if suitable, such as split dosing or switching to other treatments (e.g., buprenorphine). Consulting with an experienced OAT prescriber can be helpful to navigate such cases.

Rapid metabolism is clinically suspected when patients on methadone report sedation or early signs of methadone toxicity at the dose peak (typically 2-4 hours after dosing), and then experience withdrawal at the end of the dosing interval the following morning.

It may be clinically useful for OAT providers to schedule a time to observe the patient when the emergence withdrawal can be witnessed – this should occur following a *witnessed* dose at a *confirmed* time. Similarly, if post-dose sedation is reported as part of the issue, arrange a visit to assess for sedation when peak methadone levels are anticipated, typically 2-4 hours after a *witnessed* dose. The patient's pharmacist may be able to assist in this process (e.g., confirming the time of the preceding witnessed dose).

In these situations, further dose increases risk the patient developing more pronounced methadone toxicity, or even overdose.

If clinical observation and collateral information raises suspicion of rapid methadone metabolism, serum methadone levels should be ordered when possible and available[2]. A peak/trough ratio of > 2:1 may be indicative of rapid metabolism. **However, it is important to note that peak/trough levels are not a definitive measure of rapid metabolism in all patients, given the high degree of variability in methadone pharmacokinetics and metabolism. Assessment of the patient's whole clinical picture is needed to effectively determine if rapid metabolism is contributing to their difficulty stabilizing.**

Collecting accurate peak and trough serum methadone levels also requires planning and pharmacy collaboration:

- Arrange for three to five consecutive days of *witnessed* ingestion of methadone at a consistent time of day.
- Draw the trough level just before the next scheduled ingestion.
- On the same day, draw the peak level approximately four hours post dose.

These written instructions, along with local laboratory locations and operating hours, should also be provided to the patient to assist them in the process. Calling the lab to discuss what is desired, may also facilitate accurate results.

2) POTENTIAL SIDE EFFECTS

Asking patients about possible side effects at follow-up appointments and addressing their concerns through reassurance, education, and medical management promotes treatment adherence and retention. Nausea, constipation, fatigue or drowsiness, headache, sweating, and sexual dysfunction are the most common side effects. Asking about these routinely and normalizing the experience can facilitate discussion around topics that patients may find uncomfortable to bring up.

Side effects are often dose-dependent, so a dose reduction may be appropriate management. However, if a dose reduction would put the patient's stability at risk, medical management with other medications or lifestyle strategies may be preferred. See the respective ADVERSE EFFECTS & MANAGEMENT sections of the chapters on Buprenorphine Pharmacology and Methadone Pharmacology for a practical approach to managing common side effects.

3) CURRENT SUBSTANCE USE

Review current substance use patterns during follow-up appointments, including checking on substance use disorders in early remission. Brief motivational interviewing techniques can be effective to highlight successes and create awareness of how ongoing substance use is impacting the patient's life or stated goals. Support the patient to set manageable goals for change, however small they may be. Asking them to actively track substance use in a private journal can be insight building and a small step toward change. See Managing Polysubstance Use for further guidance.

Remember that relapse is a common and normal part of substance use disorders as chronic diseases, and that periods of instability are manageable. For patients in early remission, discuss practical relapse prevention strategies. Additional supportive counselling and/or mutual-help groups can also be effective ways to support behaviour change and early remission.

4) URINE DRUG TESTING

UDT should be performed at most assessment appointments. Under certain circumstances, practitioners may also opt to perform a pill/bottle count at appointments if there is concern about diversion of take-home medications.

See the Use of UDT in the Management of OUD for a general approach to testing, including the recommended frequency and important issues to consider when interpreting results.

An advantage of using point-of-care UDT cups/strips is the immediate availability of results. This allows for open discussion with the patient at the time of the appointment, rather than when results are received from the laboratory at a later date. This is particularly useful if results are unexpected or suggest illicit substance use, as it allows for more timely discussion and adjustments to the treatment plan (as needed) during the appointment.

If the appointment is being conducted virtually, the patient may be asked to attend a local lab to submit a sample. Patients may experience practical challenges around attending off-site labs and thus collecting samples in this manner can be more challenging.

5) MEDICATION REVIEW

An important component of the OAT intake assessment is establishing a plan for managing other sedating/psychoactive medications prescribed to the patient starting OAT. This plan often involves ongoing tapers or medication adjustments to simplify polypharmacy regimens over time and reduce/control the use of less desirable medications such as benzodiazepines/Z-drugs.

Ongoing care appointments are ideal opportunities to review the medication management plan with the patient, stay on track with planned tapers, and discuss/address any difficulties that may arise. See Managing Polypharmacy, Benzodiazepines, Alcohol & Polysubstance Use for discussion of issues related to medication management, specifically AN APPROACH TO POLYPHARMACY IN THE CONTEXT OF OAT.

6) PSYCHOLOGICAL STABILITY

The patient should be periodically assessed for co-occurring mental health symptoms, possible mental health conditions, and the ability to emotionally regulate while navigating life stressors. When the patient is no longer experiencing the cycle of intoxication and withdrawal, symptoms of anxiety, depression, and insomnia may improve spontaneously over time. Many of these symptoms may have been related to withdrawal symptoms and the feelings of helplessness and desperation that accompany active substance use disorder. Conversely, previously unrecognized mental health issues that were masked by drug use may become more apparent in time.

Know Resources & Refer

Once the patient has established trust with their care providers, they may be more forthcoming with other issues, so ongoing assessment and treatment planning are crucial. Appropriate pharmacotherapy and referral to culturally appropriate and trauma-informed counselling services may be indicated. Practitioners should be familiar with local resources for counselling services, e.g., CBT, DBT, and services with a focus on trauma recovery. Many patients new to treatment also benefit from focused work to build emotional regulation and distress-tolerance skills.

Referral for psychiatric consultation, with psychiatry services knowledgeable about substance use disorders, should be considered in more complex cases.

Peer support networks such as 12-step groups and alternatives can also be valuable support to patients in recovery. Remind patients that working on self-care and coping skills are the building blocks of recovery, along with participation in OAT.

See Managing Co-Occurring Psychiatric Disorders for further insight on navigating mental health issues in patients with OUD.

7) PHYSICAL HEALTH & PAIN MANAGEMENT

Patients starting OAT often suffer from undiagnosed physical health problems that have been neglected in the context of living with OUD. Practicing self-care is a cornerstone of recovery and referral to primary care can assist in facilitating routine medical care if the OAT provider does not offer primary care services.

Pain management issues form part of the scope of practice of OAT providers, and as such, they need to play an active role in the management of acute, chronic, and peri-operative pain for patients on OAT. See Managing Pain in OAT for specific guidance in this topic.

8) STBBI SCREENING

OAT providers must offer comprehensive screening for STBBIs to all patients with OUD. Initial and intermittent STBBI screening, including treatment referrals as appropriate, form an important part of ongoing OAT care. This can occur periodically after intake, based on ongoing risk assessment. Initial intake screening should include testing for HIV, hepatitis A, B, and C, as well as syphilis, chlamydia, and gonorrhea, including throat and rectal swabs if indicated.

Patients at significant and ongoing risk of infection should be offered STBBI screening every 6 to 12 months. Repeat testing may be customized based on individual risk factors. Please see the chapter Prevention, Screening, & Management of HIV & Hepatitis C in Individuals with OUD for further guidance.

9) SOCIAL STABILITY

Advocacy and practical support around psychosocial issues is an important part of ongoing OAT care. This includes issues related to relationships with family and friends, housing, finances, transport, employment, education, medication coverage, and navigating social services.

Support and referral to other agencies should be provided as needed.

10) TREATMENT GOALS

Goals of treatment should be reviewed periodically. It can also be useful to identify short- and long-term goals with the patient. It is important to recognize that the provider's goals of treatment may not be the same as the patient's goals or priorities. Cessation of drug use or complete abstinence from non-prescribed substances may be a later goal along the treatment continuum, or it may not be realistic or achievable for some patients, but they can still benefit from harm-reduction and involvement with the OAT program. Patient goals should be documented and honored in a non-judgmental fashion.

Discussing the patient's goals in a supportive manner can contribute to patient buy-in when addressing the provider's treatment goals. Collaboration, finding common ground, and celebrating small gains is the foundation of an effective therapeutic relationship.

11) REVISIT THE TREATMENT AGREEMENT

Reviewing adherence to the treatment agreement keeps safety, mutual expectations, and boundaries at the forefront of care. The fundamentals of succeeding in treatment include:

- Attendance at appointments as scheduled.
- Attendance for UDT at the agreed upon frequency.
- Regular attendance at the pharmacy for witnessed doses and to receive take-home doses, as applicable.

Revisiting these expectations and why they are important is time well spent with patients. Review the schedule of take-home doses with the patient and assess whether this should be adjusted. Discuss the reason for changes in a transparent manner.

Treatment agreements are effective tools to review behavioural/safety expectations with patients when initiating OAT and throughout the course of care, particularly if concerns arise that may warrant changes to the treatment plan. See the Comprehensive Assessment chapter section on treatment agreements for further guidance. If the patient is not adhering to the treatment agreement, explore barriers and potential solutions. Consider whether this might be due to an active substance use disorder, work/life responsibilities, or other reasons that need to be addressed.

The Continuum of Stability

Patients engaging with OAT care will present along a continuum of clinical stability. The same patient's stability may also change over time. Even when patients are not achieving many of the treatment goals identified and promoted by providers, clinically unstable patients can still benefit from OAT care from a harm reduction perspective.

In the extremely unstable patient, the provider may truly question if the patient is benefitting from treatment. If this is the case, an overall more in-depth risk-benefit assessment can be conducted to decide if treatment should be continued. This risk-benefit assessment, decision, and the associated risks should be documented. When in doubt, a second opinion from an experienced colleague should be sought and documented as well. Seeking input from the pharmacy team may also provide a valuable additional perspective, as pharmacy staff typically see the patient more frequently. See Discontinuing Treatment for guidance on managing safety concerns in unstable patients and recommendations around involuntary withdrawal of treatment.

FREQUENCY OF ASSESSMENTS

The frequency of assessments will vary according to the stability of the patient and any changes in management that need to be monitored. In the initial months of treatment, appointments at intervals of one to four weeks are often required. More frequent appointments will be needed when the patient is unstable or when treatment changes are made.

For the most stable patients, with no changes in treatment, follow-up appointments every three months are appropriate. Clinical judgement should be applied.

Patients may have difficulty attending regular in-person appointments in certain situations, such as:

- Rural and remote living where geographic distance and transport are barriers,
- Health or mobility issues that make attendance at the clinic difficult,
- Work or childcare responsibilities that make attendance difficult, and/or
- Extreme social instability that interferes with keeping appointments.

Blended Models & Flexibility

The practitioner should be prepared to be flexible and employ novel approaches to providing OAT in the above circumstances, to promote equity in access to care. **This can include a blended model of virtual appointments, on screen and/or by phone, and in-person assessment**. Occasionally, partnerships with local healthcare providers who are willing to assist with in-person assessment may also be a useful strategy. Remember to ask for collateral information from the pharmacist and utilize UDTs that can be submitted at a local laboratory.

Drop-in capacity, if possible, is also a useful strategy to engage patients who struggle to keep scheduled appointments. If feasible, providers should schedule clinics with a combination of booked visits for patients who rely on scheduling appointments around work, childcare, or other responsibilities, and flexible drop-in time to see patients who present without an appointment, and to discuss cases as a team.

Seeking patient input regarding the ideal frequency and type of clinic appointments is also important. Often the final decision is a compromise between what the provider feels is ideal for quality care and what the patient feels they can reasonably manage.

ECG MONITORING FOR PROLONGED QTc

Methadone and buprenorphine, to a lesser degree, may cause QTc interval prolongation. In rare cases, a prolonged QTc interval can result in serious cardiac arrythmia (i.e., torsades de pointes).

The Centre for Addiction and Mental Health (CAMH) guideline, *Opioid Agonist Therapy: A Synthesis of Canadian Guidelines for Treating Opioid Use Disorder*, recommends obtaining an electrocardiogram (ECG) before initiating OAT and throughout ongoing care when monitoring is warranted, however, **lack of access should not be a barrier to receiving OAT**[2]. Providers should use clinical judgment, risk-benefit analysis in collaboration with the patient, and document the rationale for treatment decisions and attempts at obtaining ECGs.

Dose Dependent & Often Multifactorial

The effects of methadone on QTc prolongation are dose dependent. Doses above 100 mg/day are frequently reported in cases of torsade de pointes, and some case reports show that the QTc interval normalizes when methadone is discontinued or reduced in dose[3]. However, when possible, modifiable risk factors like drug-drug interactions should be rectified first.

The risk of torsade de pointes is often increased when other risk factors for QTc prolongation are present. Collaborating with pharmacists and other care providers around polypharmacy and risk factors can help mitigate the overall risk in patients with concerning QTc intervals. In addition to a higher dose of methadone, other risk factors for QTc prolongation include:

- The presence of other drugs that prolong QT interval,
- Hypokalemia,
- Female sex,
- Advancing age,
- Genetic predisposition,
- Hypomagnesemia,
- Heart failure, and
- Bradycardia[4].

Frequency of Monitoring

CAMH recommends considering the following conditions when deciding to obtain additional ECGs and to determine frequency of monitoring[2]:

- Patient has a family history of prolonged QTc or sudden death.
- Patient has had previous arrhythmias/hospitalizations.
- Patient has unexplained symptoms that suggest cardiac involvement (e.g., syncope, presyncope, palpitations, seizure activity, blurred vision without other explanations) or a predisposition to poor cardiac health.
- Patient is initiated on (or already takes) medications known to prolong the QTc interval.
- Patient is using illicit substances known to prolong the QTc interval (e.g., cocaine, methamphetamine).
- Patient develops a medical condition that increases the risk of QT prolongation (e.g., excessive vomiting).
- Methadone daily dose meets or exceeds 120 mg.

For patients requiring higher doses of methadone to stabilize, where daily doses exceed 120 mg, more frequent monitoring of QTc is recommended, if obtaining ECG is feasible. For QTc intervals between 450 msec to 500 msec, review the risks and benefits of ongoing care, monitor more frequently, and consider dose reductions of other QTc prolonging medications preferentially over changes to the OAT medication. Consulting a cardiologist is recommended if the QTc interval exceeds 500 msec[2].

Benefits of OAT May Outweigh Theoretical Risk

It is important to review the risk and benefits of continued treatment with the patient and collaborate on the best approach. Some patients may elect to accept the theoretical risk of a prolonged QTc over jeopardizing their stability or recovery, particularly if asymptomatic. Discuss transitioning patients on methadone to buprenorphine/naloxone, or possibly slow-release oral morphine (SROM) if buprenorphine is not appropriate. If dose reductions or changes are made, monitor more closely for destabilization or relapse.

If the patient does not wish to alter treatment options, the risk of mortality from non-retention on OAT may outweigh the mortality risk of the prolonged QTc[2]. Clinical judgment should be applied, taking into consideration the patient's wishes. When in doubt, a second opinion from an experienced colleague should be sought and documented as well.

CONSIDERATIONS FOR BUPRENORPHINE EXTENDED-RELEASE FORMULATIONS

Sublocade® (buprenorphine extended-release injection, or depot) or Probuphine® (buprenorphine implant) can enhance medication adherence and convenience for some patients. These options can be explored with both clinically stable patients and those struggling with stability and/or regular pharmacy attendance (see MISSED OAT DOSES below).

CAMH notes that there is not yet evidence about the long-term safety and effectiveness of depot or implant buprenorphine therapy and encourages prescribers to review existing evidence to counsel patients accordingly for informed consent[2]. Patients may find these options preferable for less frequent medication administration. If patients switch to depot or implant buprenorphine therapy, consider the overall medication management plan for patients on other sedating/psychoactive medications and determine a reasonable dispensing schedule for these medications.

Other considerations include the patient's comfort with an invasive procedure or device and available medication coverage options[2].

Depot buprenorphine therapy can be considered in patients stabilized on 8-24 mg sublingual buprenorphine/naloxone daily, for at least 3-7 days. The injection does not require abstinence from other opioids before initiation, but it is preferable. Alternatively, the subdermal implant can be considered in patients stabilized on ≤ 8 mg of sublingual buprenorphine/naloxone daily, noting the implant requires a period of abstinence from opioids before initiation[2].

MISSED OAT DOSES

Missed doses of OAT (due to patients not attending the pharmacy for witnessed self-administration and possible take-home doses) can indicate a variety of problems that warrant exploration, including:

- Relapse to substance use,
- Psychosocial instability,
- Financial reasons (e.g., the patient is unable to pay for the prescription),
- Limited access to the pharmacy due to geographic distance or mobility issues,
- Limited pharmacy hours,
- Work hours resulting in an inability to attend the pharmacy,
- Lack of transportation, and/or
- Childcare or other caregiver issues.

Pharmacists must report missed doses to the prescriber/clinic staff daily. Missed doses present an opportunity to reach out to the patient and reassess stability, particularly if doses are missed frequently or unexpectedly. The prescriber should explore reasons for missed doses and make every effort to problem solve with the patient. This may include switching to a pharmacy with different hours and/or closer to home, work, school, or even on a more accessible bus route. Re-evaluate take-home dosing candidacy and schedules, depending on patient stability. Note that more flexibility exists with buprenorphine formulations.

Document the patient's reasons for frequently missing doses and potential attempts at solutions. If there has been a significant relapse to substance use, treatment intensification should be offered to the patient, along with discussion of relapse-prevention and harm-reduction strategies.

After 6 consecutively missed days of buprenorphine/naloxone, 3 consecutively missed days of methadone, and 2 consecutively missed days of SROM, the pharmacist will cancel the OAT prescription. A new prescription will be required from an approved prescriber to restart OAT.

Providers should use clinical judgement to determine if in-person assessment by the prescriber or nurse, and/or collateral information from the pharmacist, is indicated to assess withdrawal and recent drug use, and to conduct point-of-care UDT.

Risks of precipitated withdrawal when restarting buprenorphine/naloxone must be weighed against the benefits of resuming OAT as soon as possible. Similarly, when restarting methadone, a risk-benefit assessment based on the unique patient situation should guide decisions about in-person assessment and the best approach to resuming OAT.

Buprenorphine Missed Doses

If the patient is on buprenorphine/naloxone and sufficiently stable, but struggling to attend the pharmacy due to work or family responsibilities, consider accelerating the provision of take-home doses as outlined in Take-home Dosing Recommendations.

Additionally, consider and discuss alternative treatment approaches, as appropriate:

1) Alternate-day dosing is an option for patients who are clinically stable at doses ≤ 12 mg/day (e.g., 12mg/day could be prescribed as 24 mg every other day) and who require/desire less frequent visits to the pharmacy for dosing. This approach should be balanced with the challenges of managing missed doses. The patient should be assessed for sedation when given this higher dose and timely communication with the pharmacist is paramount to discuss the plan[2].

2) Consider switching to an extended-release buprenorphine formulation if the main reason for alternate-day dosing is to facilitate fewer pharmacy visits, and if the patient is not a candidate for accelerated take-home doses. Assess and discuss with the patient if switching to the extended-release monthly injection or the six-month subdermal buprenorphine implant would be suitable and preferable.

Given the partial agonist properties of buprenorphine, re-stabilizing a patient after missed doses does not require the same vigilance as for methadone, but prescribers must stay mindful of loss of tolerance to buprenorphine after 6 or more consecutively missed days[1,2].

Again, **pharmacists must notify the prescriber/clinic staff of any missed doses daily**.

The following is recommended for consecutively missed daily doses of buprenorphine:

- For **≤ 5 consecutively missed days**, continue the same buprenorphine/naloxone dose. The current prescription remains valid. The pharmacist must report all missed doses to the prescriber/clinic team daily and if providers are able contact the patient, they can advise them to return to the pharmacy as soon as possible to resume buprenorphine dosing *before* or *by day 6*.

  If the patient has relapsed to substance use (of opioids or other substances) offer assessment and treatment intensification as appropriate. With relapse to full opioid agonist use, as the number of missed consecutive daily doses increases, the theoretical risk of precipitated withdrawal also increases. However, experientially, the benefits of resuming buprenorphine/naloxone within this time frame tend to outweigh this theoretical risk, even with resuming dosing on day 6.

- For **≥ 6 consecutively missed days**, the prescription will be cancelled. Encourage the patient to connect with the treatment team when they are able/desire to resume OAT. A new induction will be required using either a Conventional Buprenorphine Induction or a Micro-dosing Induction, as appropriate. **A new prescription is required for the buprenorphine/naloxone restart**.

  After assessing the patient's response to dosing with the restart, the dose can be increased toward the previous stable dose more rapidly, as applicable, in the absence of other safety concerns and with reassessment as needed.

An approach to missed doses of buprenorphine/naloxone is summarized in the PRESCRIBING ESSENTIALS below.

PRESCRIBING ESSENTIALS: MISSED BUPRENORPHINE DOSING APPROACH

Missed Days	Previous Prescribed Dose	Suggested Adjustment
1-5	Any dose	Same dose (no change)
≥ 6	Any dose	Restart buprenorphine/naloxone*

*The pharmacist will cancel the prescription. A new prescription is needed to restart OAT. The pharmacist must report all missed doses to the prescriber/clinic team daily.

For patients on alternate-day dosing of buprenorphine who missed two alternate-day doses, suspend prescribing until the patient can be reassessed. Accordingly, the prescription will be cancelled, and a new OAT prescription is required. The patient should resume daily dosing, possibly at a lower dose, to restabilize before considering return to every-other-day dosing[2].

Methadone Missed Doses

As outlined above, missed methadone doses may indicate a variety of problems requiring review with patients. Tolerance to methadone is lost rapidly and may occur in as little as three days, so restarting at the previous stable dose may be excessive or dangerous[1].

Again, **pharmacists must notify the prescriber/clinic staff of any missed doses daily**.

The following is recommended for consecutively missed daily doses of methadone:

- For 1 to 2 consecutively missed days, continue the usual prescribed dose, provided there is no other reason (e.g., intoxication) to withhold methadone. The current prescription remains valid.
- **For 3 consecutive missed days, the pharmacist will cancel the methadone prescription and the patient must follow up with the prescriber/clinic team**. Remind patients of this regularly. Before restarting methadone, providers should use clinical judgement to determine if in-person assessment by the prescriber or nurse, and/or collateral information from the pharmacist, is indicated to assess withdrawal and recent drug use, and to conduct point-of-care UDT.

  A new prescription is required to restart:

  - If the usual dose is ≤ 30 mg, the patient may be continued at the same dose following appropriate assessment.
  - **For doses > 30 mg, patients can typically be restarted at 50% of their previous dose**. Generally, the reduced dose should be no less than a starting dose of 10-30 mg. After tolerance to the reduced dose has been demonstrated, the dose can be rapidly increased (by no more than 5-10 mg per day) if daily supervision occurs.

    Slower dose escalation is suggested for patients with clinical instability and/or concurrent use of alcohol, benzodiazepines/Z-drugs, or other sedative/hypnotics. The patient should be assessed as needed during titration and re-stabilization, and more frequent UDT may be warranted if clinically appropriate.
- **For ≥ 4 consecutive missed days**, **restart methadone at 30 mg or less**. Again, a new prescription is required. After assessing the patient's response to this new dose, the dose can be increased toward the previous stable dose more rapidly, in the absence of other safety concerns, with reassessment as needed.

The CAMH guideline summarizes an approach to missed methadone doses as outline in the PRESCRIBING ESSENTIALS below.

PRESCRIBING ESSENTIALS: MISSED METHADONE DOSING APPROACH[2]

Missed Days	Previous Prescribed Dose	Suggested Adjustment
1-2	Any dose	Same dose (no change)
3	Any dose	Decrease dose by 50% of previous dose*
≥ 4	Any dose	Decrease dose to 30 mg or less*

*The pharmacist will cancel the prescription. A new prescription is needed to restart OAT. The pharmacist must report all missed doses to the prescriber/clinic team daily.

VOMITED DOSES

Patients may experience nausea as a symptom of withdrawal or as a side effect of OAT, or as a symptom of another medical condition (such as commonly experienced in pregnancy). If changes to OAT medications are considered to manage nausea, the risks to the patient's stability should be evaluated, and medical management and/or lifestyle strategies may be preferred. Collaboration with the pharmacy is recommended, particularly if considering changes between different brands or formulations of medications.

Buprenorphine, Nausea, & Vomiting

If a patient vomits after their buprenorphine/naloxone is fully dissolved, no replacement dose is indicated, as the dose should be adequately absorbed sublingually.

Very rarely a patient may vomit before the tablets have fully dissolved. If this is witnessed by the pharmacist and it is reasonable to assume that the patient would not have had time to absorb the full buprenorphine dose, the practitioner may exercise clinical judgement and prescribe a replacement dose of 25-50% of the original dose. **Replacement doses require a *new* prescription**. The prescriber should note on the prescription that it is a "replacement dose".

If the patient reports persistent nausea which is not related to withdrawal, several strategies could be considered:

- Use of a non-sedating antiemetic prior to taking the buprenorphine/naloxone dose.
- A small dose reduction in the buprenorphine dose, weighed against the potential for destabilization.
- Switching to a different brand, as some patients find taste triggers nausea and the taste varies between brands.
- Switching to a different formulation, e.g., buprenorphine/naloxone film, depot or implant buprenorphine therapy.

Methadone & Vomited Doses

Vomited methadone doses are not replaced unless emesis is *witnessed* by a healthcare provider or support staff. **It is impossible to entirely empty the stomach, even with projectile emesis right after dosing, therefore full dose replacement is *not recommended***.

Please refer to the Pregnancy Chapter for specific guidance on vomited doses in pregnancy, as avoiding opioid withdrawal is more critical in this context.

The following is recommended for *non-pregnant* patients:

- If emesis occurs less than 15 minutes after consumption, consider replacing 50-75% of the full dose. If the dose is ≥ 120 mg, consider replacing only 50% of the full dose.
- If emesis occurs at between 15-30 minutes after consumption, consider replacing 25-50% of the full dose.
- If emesis occurs at more than 30 minutes after consumption, do not replace the dose.

After a replacement dose, the patient should be observed for 30 minutes. Repeated dose replacement increases the risk of unexpected overdose. If emesis is a recurrent reason for dose replacement, observing the patient for 15-20 minutes after dosing may be warranted[1]. Use of a non-sedating antiemetic prior to dosing may be helpful. Providers may elect to not replace a vomited dose.

All replacement doses require a *new* prescription. The prescriber should note on the prescription that it is a "replacement dose".

Again, potential underlying causes of the vomiting should be addressed, and dose reductions to offset nausea should be weighed against the potential for destabilization. Sometimes it may be helpful to speak with the pharmacist about trying a different diluent with the methadone concentrate (e.g., apple juice instead of Tang), or switching to a cherry-flavored concentrate that does not require dilution. However, remember that switching between methadone brands should be approached cautiously and in collaboration with the pharmacist. **Methadone products are not interchangeable from a clinical perspective nor a coverage perspective**.

A new prescription from an approved methadone prescriber would be required to switch a patient from one product to another. **Such changes will often require collaboration and communication between the prescriber, pharmacy team, and patient.**

A safety review completed by Health Canada found that there may be a link between switching methadone-containing products used to treat OUD and the risk of lack of effect, which may present as withdrawal symptoms, although the reason for this is unclear[5].

OAT providers should be aware that:

- Some patients may experience withdrawal symptoms after being switched from one methadone-containing product to another; these patients should be clinically managed and monitored regularly.
- Dose adjustments may be necessary in some patients.
- Withdrawal symptoms can lead to a failure to remain in treatment and subsequent problematic substance use, which can lead to serious harms.

ROTATION OF OAT MEDICATIONS

Some patients may benefit from transitioning from methadone to buprenorphine/naloxone and vice-versa, for several reasons:

- To manage intolerable side effects, patients may elect to transition between either medication.
- For more flexibility with take-home dosing and to decrease the burden of treatment, patients may elect to transition from methadone to buprenorphine/naloxone, or to eventually transition to depot or implant buprenorphine therapy.
- For safety reasons, if patients become increasingly at risk of overdose, providers may promote transitioning from methadone to buprenorphine.
- To manage withdrawal and cravings more effectively, patients may transition from buprenorphine to methadone, particularly patients with high tolerance and regular use of high-potency opioids.

Collaboration between the prescriber, patient, and pharmacist is required to review the goals of treatment and a transition plan. Recognizing the principle of patient autonomy, while promoting retention in treatment and harm reduction, is essential when making such decisions.

Regardless of the clinical approach taken, this can be a challenging process for patients and can increase risk of relapse. **Patients therefore need to be carefully selected and all appropriate options discussed**.

Prescribers who are inexperienced with transitions are advised to seek expert guidance for complex situations.

Patients Transitioning from Methadone to Buprenorphine

Transitioning from the full-agonist methadone to the partial-agonist buprenorphine can be challenging. The methadone dose should ideally be gradually tapered to ≤ 30 mg/day, and the patient should be advised to abstain from methadone for 48-72 hours prior to a Conventional Buprenorphine Induction.

Alternatively, patients may transition from methadone to buprenorphine/naloxone using a Micro-dosing Induction, as appropriate, or switching from methadone to SROM (the 24-hour formulation) for five days prior to transitioning to buprenorphine.

Again, this process can be very challenging for patients. **The risk of relapse must be discussed with the patient and the discussion documented**. **Prescribers who are inexperienced with transitioning patients from methadone to buprenorphine/naloxone are strongly advised to seek expert guidance**.

Inpatient admission for transitions may be helpful for patients with psychosocial instability, ongoing polysubstance or polypharmacy concerns, or patients with complicated or poorly managed medical conditions. See In-Hospital Care for details, specifically PLANNED HOSPITAL ADMISSIONS IN THE CONTEXT OF OUD.

Transitioning From Buprenorphine to Methadone

Comparatively, transitioning patients from buprenorphine to methadone is less complicated, going from a partial to full agonist. Generally, the first dose of methadone can be administered within 24 hours of the last buprenorphine/naloxone dose[1]. Dosing can then follow the guidance for Methadone Induction for patients with established opioid tolerance, typically 10-30 mg per day for the first three days, and titrated based on assessment of individual patient factors.

The BCCSU guideline summarizes that a "stepped care strategy (i.e., treatment initiation on buprenorphine/naloxone and escalation to methadone if necessary)" is equally efficacious and given the greater safety profile of buprenorphine, it is recommended as first-line treatment[1]. Methadone can then be explored as a second-line option for patients as needed, with SROM serving as a third-line treatment option for carefully selected patients. Please see Alternative Treatment Approaches for OUD Including SROM (Kadian®) for detailed recommendations.

IN SUMMARY

The ongoing care of patients on OAT certainly requires investment from the provider and the patient. This work necessitates therapeutic alliance, collaboration, mutual respect, and problem solving, not only between the provider and patient, but along with the whole care team, pharmacy, and community. Providers are encouraged to seek advice from experienced colleagues in challenging situations to optimize patient outcomes, as they navigate the long road of recovery.

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