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MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

4.1 Alternative Treatment Approaches to Opioid Use Disorder Including Slow-Release Oral Morphine (Kadian®)

GENERAL CONSIDERATIONS

While Opioid Agonist Therapy (OAT) with buprenorphine/naloxone is the preferred and evidenced based first-line treatment for the management of Opioid Use Disorder (OUD), a subset of patients with this condition may benefit from treatment with methadone[1,2]. These first- and second-line options are discussed in detail throughout this manual. Occasionally, prescribers may assess a patient with OUD for whom OAT with buprenorphine/naloxone and methadone is either unavailable or unacceptable. For such patients, alternate treatment approaches exist.

It is important to note that the alternatives to first- and second-line OAT medications discussed in this chapter:

- Are not considered routine interventions.
- Lack the robust body of evidence reported for buprenorphine/naloxone and methadone.
- Should only be considered in carefully selected clinical environments and patient populations.

These alternate approaches to OUD management must be reviewed in consultation with addiction medicine specialists* in Manitoba, who have experience with these treatment modalities in our local context.

*For the purpose of this manual, an **addiction medicine specialist** is a Manitoban physician with robust training, knowledge, and clinical experience in the management of substance use disorders, including OUD, *and* who passed an addiction medicine exam proctored by the International Society of Addiction Medicine (ISAM), the American Board of Addiction Medicine (ABAM), or the American Board of Preventive Medicine (ABPM), *or* with Canadian Society of Addiction Medicine (CCSAM) certification, *or* a Certificate of Added Competence in Addiction Medicine (CCFP(AM)).

SPECIFIC CONSIDERATIONS

The alternate treatment approaches discussed in this chapter include:

1) Home-Based Withdrawal Management or "Detox"
2) Slow-Release Oral Morphine (SROM)
3) Injectable Opioid Agonist Therapy (iOAT)

HOME-BASED WITHDRAWAL MANAGEMENT OR "DETOX"

A subset of patients will seek out "detox" as treatment, or to prepare themselves for further treatment programming, for a multitude of reasons. These reasons may be circumstantial, particularly in areas where OAT is not available, and/or personal. These patients may be unwilling to commit to a longer-term structured treatment plan involving OAT with buprenorphine or methadone.

"Detox" Admission Not Recommended

Admitting such individuals to a hospital or community-based detoxification unit for abstinence-based "detox" (i.e., the abrupt discontinuation or rapid tapering of opioids over 10 -14 days) is **not recommended due to the substantial risk of serious harms**. These potential harms include death by overdose given the lost tolerance created by an abstinence-based detoxification admission. However, home "detox" may be an alternative option for some individuals. Home "detox" is defined as a self-guided process of tapering a low to moderate dose of opioids, or abstinence from opioids over a predetermined period, outside of an established clinical or institutional setting. **It is important to consider that this approach has limited evidence and carries significant risk**[3].

During a period of abstinence, symptoms of opioid withdrawal can be both physically and psychologically challenging for individuals. While opioid withdrawal is not fatal, these symptoms can be very distressing. Patients that have limited clinical and social support during their "detox" are especially vulnerable and at high risk of relapse. In as little as 3-7 days, opioid tolerance can reduce rapidly[5]. Individuals with OUD are already at a higher risk of relapse and this rapid loss of tolerance puts them at an even greater risk of fatal overdose[3,6].

Considerations for Home "Detox"

Providers and patients should decide together, where resources and patient supports permit, the treatment plan that is most appropriate. Patients wishing to pursue abstinence should consider attending a **long-term residential treatment program** (e.g., therapeutic community) following successful "detox"[4]. The therapeutic community environment provides patients with more support, time, and skill-building opportunities for additional relapse-prevention.

For patients pursuing home "detox" careful attention must be paid to:

- Initial assessment to establish appropriateness for home "detox".
- Close follow up and appropriate escalation of treatment intensity/intervention (e.g., OAT induction should ideally be readily available should the patient consent to it).
- Pharmacological management of opioid withdrawal symptoms, while remaining mindful of safe medication management (controlled dispensing) and avoiding polypharmacy (see PRESCRIBING ESSENTIALS below).
- Social and clinical supports should be optimized, based on community capacity (e.g., counselling, peer support, preferably **long-term** residential treatment after "detox").
- Relapse and overdose education, prevention, and management (e.g., take-home naloxone and other harm reduction supplies and training).

PRESCRIBING ESSENTIALS: AVOIDING POLYPHARMACY

For the purpose of this manual, polypharmacy is defined as the concurrent prescribing of five or more medications with sedating and/or psychoactive properties.

Notwithstanding this definition, it is important to note that the inherent risks of polypharmacy also apply in situations where licit substances (e.g., alcohol and cannabis) and/or illicit drugs/prescription medications, and/or over-the-counter medications with sedating/psychoactive properties, are combined with prescribed medications with similar properties. It is important for the prescriber to educate patients regarding these risks on a regular basis. See Managing Polypharmacy, Benzodiazepines, Alcohol, & Polysubstance Use in OAT for further guidance.

Assessment & Consultation

The high risk of fatal overdose during, and immediately after, pursuing opioid abstinence means the *significant risks* associated with home "detox" must be carefully weighed against the benefits.

Providers and patients need to be aware that maintaining long-term abstinence is difficult and relapse rates are high[1]. Careful documentation, patient selection, and consultation with addiction medicine specialists, are all critical to optimize patient safety and outcomes.

If home-based "detox" towards abstinence is the chosen treatment plan for OUD, whenever possible, ensure patients and their families are informed about all treatment options available. They should have information about and access to ongoing addiction care, namely, conversion to OAT if abstinence is not sustainable and/or if opioid use recurs.

Pharmacological Management of Opioid Withdrawal

The withdrawal symptoms experienced during home-based "detox", in the context of OUD and pursuing abstinence, can be pharmacologically managed with:

- Tapering doses of long-acting opioids, including buprenorphine/naloxone or methadone.

  Please note that when buprenorphine/naloxone or methadone is used in the context of home-based "detox", **the same regulatory requirements apply as for patients taking these medications long-term as OAT** (i.e., prescribing approvals are required to prescribe these medications and the witnessed dosing/dispensing requirements are the same as for OAT patients).

- Alpha-agonists (e.g., clonidine) for diaphoresis and insomnia (note that these are all off-label uses of clonidine).
- Antiemetics (e.g., ondansetron) for nausea.
- Non-opioid analgesia (e.g., acetaminophen and/or ibuprofen) for myalgia.
- Antidiarrheals (e.g., loperamide) for diarrhoea.

The management of opioid-withdrawal symptoms in the early induction phase of OAT is discussed further in other chapters of this manual. Specifically, see the chapters on Conventional Buprenorphine Induction and Methadone Induction further details.

SLOW-RELEASE ORAL MORPHINE (24-Hour Formulation, Kadian®)

Slow-release oral morphine (SROM) lacks robust evidence for the treatment of OUD when compared to first- and second-line OAT medications like buprenorphine/naloxone and methadone[2,7]. Offering SROM to patients with OUD as a first- or second-line treatment option is **not recommended**.

However, SROM can serve as a third-line treatment option for carefully selected patients with OUD. Occasionally, a patient's rural/remote living situation, unique circumstances, medical comorbidities, or severity of disease may warrant consideration of SROM treatment.

Populations in whom SROM could be considered include:

1) Patients with continued opioid use, in the context of adequate therapeutic trials of first- and second-line treatment options (buprenorphine/naloxone and methadone), with significant ongoing instability (i.e., first- and second-line treatment options have been unsuccessful).

2) For patients with suspected or confirmed OUD awaiting further assessment or treatment, to provide controlled once-daily dosing of opioids as an *interim and time-limited bridging option* to a **confirmed** OAT induction appointment or addiction specialist consultation visit.

3) In the context of a tapering regime for select patients as part of a home-based "detox" program (see section above), especially when buprenorphine/naloxone and methadone are not available or acceptable to the patient. In this context, SROM must be **daily witnessed** at a pharmacy, community health facility, or nursing station.

4) As a discharge option from hospital for patients with OUD who were not interested in engaging with OAT care, but who were prescribed harm reduction opioids during their hospital admission to facilitate medical treatment. Under these circumstances, SROM is prescribed as:
    - A **daily witnessed** bridge to OAT intake/assessment, or
    - A structured daily-witnessed opioid taper to zero.

5) Patients who are experiencing ongoing opioid withdrawal symptoms while on OAT with methadone and who may benefit from the addition of oral extended-release morphine in the context of:
    - A prolonged QTc preventing further titration of methadone, or
    - As a *temporary bridge* while methadone continues to be titrated up to a more effective dose.

6) Patients with concurrent OUD and **confirmed** chronic pain, who may benefit from a trial of additional opioids (with better 24-hour analgesic benefit) for chronic pain management, as an alternative or in-addition to once-daily methadone.

Additional Recommendations for SROM Use

There an several **important recommendations** that prescribers must acknowledge if pursuing SROM as a third-line option for select patients.

- SROM refers to the **24-hour formulation** of the extended-release morphine capsules (i.e., brand name Kadian®). Other forms of oral morphine (e.g., 12-hour sustained- or extended-release formulations) have not been studied empirically for treating OUD, and thus are not to be used in this context.

- **SROM is typically dispensed/witnessed once daily**, **for all indications discussed in this document**. If due to any reason, including patient or provider preference, SROM is to be dispensed/witnessed at a time of day when the pharmacy is closed (e.g., evenings), that does **NOT** justify the authorization of carry doses beyond the recommendations in this guidance document.

Otherwise stated, the same witnessed dosing and carry recommendations apply, as per the *Stability & Take-Home Dosing* section below. This means that the patient **MUST** have pharmacy/nursing station/community health facility access at the time of day they plan to attend for witnessed ingestion of SROM. Additionally, the absolute minimum of three witnessed doses per week would still apply to patients who qualify for carries and who may otherwise take SROM in the evenings on a regular basis.

- **SROM must be dispensed via witnessed ingestion**, **for all indications discussed in this document** (unless being dispensed as a carry for patients who qualify for take-home doses as outline in the stability section below).

  Additionally, a note must also be included on the prescription instructing pharmacists/nurses to "open and sprinkle" all witnessed doses of Kadian® capsules (e.g., into a medicine cup or onto soft food, like applesauce) before administering the contents to the patient in the pharmacy/nursing station/community health facility. If SROM pellets are dispensed in a medicine cup, this must be followed by at least 30 mL of water to ensure all the pellets have been swallowed. This approach is aimed at optimizing compliance with therapy and minimizing diversion risk.

  Prescribers are strongly encouraged to contact the pharmacy to review the treatment plan and the instructions for witnessed ingestion because crushing, chewing, or dissolving SROM pellets can cause the rapid absorption of a potentially fatal dose of morphine sulphate.

- In remote/rural living environments with no access/limited access to OAT (and other OUD treatment resources) via a pharmacy, nursing station, or community health facility, **preferential consideration may be given to liberal dispensing of buprenorphine/naloxone to engage and support patients with OUD**. Unwitnessed SROM is not an appropriate alternative in this setting due to the potential patient and community safety risks.

  Such patient presentations should be discussed with a specialist to determine how to best connect the patient to an OAT prescriber who can develop and manage an appropriate treatment plan, with assistance from local care providers. Collaboration between an experienced OAT prescriber and a local clinician will typically be required to facilitate such a treatment plan, especially if the OAT prescriber does not practice in the community where the patient is seeking treatment.

OAT Prescribing Approvals & SROM Use

Brief time-limited prescribing of SROM does not require a CPSM prescribing approval, but it *does* require expert consultation. Prescribing SROM as third-line treatment option for OUD and associated contexts, requires *both* consultation and OAT prescribing approvals for methadone and buprenorphine/naloxone.

Detailed recommendations are as follows:

- In populations 2 and 3 above – prescribing SROM as a time-limited bridging option to a confirmed OAT induction appointment or addiction specialist consultation, or prescribing SROM as part of a home-based "detox" tapering regime – does not require a CPSM prescribing approval. **However, prescribing SROM for these indications MUST be done in consultation with an addiction medicine specialist. Such consultative discussions must be clearly documented in the patient's medical record**. **This also applies to dose titrations over time**. The prescriber must also include the indication on the M3P prescription, as well as the phrase "… as discussed with Dr _____ (name of addiction medicine specialist)".

- Prescribing SROM for chronic non-cancer pain management in the absence of OUD, as an alternative to other long-acting opioids (to lessen the pill/dosing burden), *does not* require a specific CPSM prescribing approval. The indication must be noted on the M3P prescription to provide relevant context to the pharmacy.

- In populations 1, 5, and 6 above – when SROM is prescribed as a third-line treatment option for OUD, or in addition to methadone, or in the treatment of patients with concurrent OUD and chronic pain – **the treatment plan must be reviewed in consultation with an addiction medicine specialist**. Such consultative discussions must be clearly documented in the patient's medical record. This also applies to dose titrations over time. Additionally, when using SROM as a third-line treatment option for these populations with OUD, **the prescriber must have CPSM prescribing approvals for the use of methadone and buprenorphine/naloxone in the context of OAT**. This requirement is consistent with national guideline recommendations around the use of SROM as a third-line treatment for OUD[1,4].

Assessment & Documentation

A thorough risk-benefit assessment, documented in a detailed manner, is critical to ensure the treatment plan involving SROM is the safest and most appropriate option for the patient. Providers should clearly document the relevant benefits and risks discussed with the patient. Providers must also ensure they have documented all relevant components of specialist consultation as part of the decision-making process.

Induction & Titration of SROM

SROM starting doses are between 30-200 mg PO per day, with dose increases every 24-48 hours.

SROM can be titrated up by 100 mg every 24-48 hours, based on documented clinical response/Clinical Opiate Withdrawal Scale (COWS), ongoing opioid use, and documented evidence of retention/engagement in treatment[2,7].

The average total daily SROM dose range can be as broad as 200-1,200 mg per day[2,7,8]. The most recent guidance from the British Columbia Centre on Substance Use (BCCSU) *OUD Practice Update* indicates the titration approach should be determined by clinical discretion, individual circumstances, and frequent assessment; patients should be assessed in-person or virtually (with video) prior to any dose increases. Additionally, BCCSU recommends, "Prescribers should use caution, with respect to side effects, when prescribing above 1,200 mg and clearly document the rationale for doses above 1,200 mg"[8].

For patients who are switching from methadone to SROM, use a methadone-to-morphine ratio of 1:4 on day 1 (i.e., 60 mg methadone = 240 mg morphine) and titrate upward based on symptoms and cravings. Stabilization dose ranges are reported to be between 1:6 and 1:8 [2].

Stability & Take-Home Dosing

A patient is considered clinically stable once they reach the lowest dose of SROM required to achieve reasonable control of opioid withdrawal symptoms for 24 hours and adequate suppression of illicit opioid use. The criteria for clinical stability can be summarized as follows:

- Absence of opioid withdrawal symptoms and significantly reduced cravings.
- Absence or significant reduction in illicit substance use (self-reported and supported by urine drug testing).
- Financial and/or employment stability.
- Housing stability.
- Improvements in self-care and wellness practices.
- Strengthening of supportive relationships.
- Improvements in mental and physical health.

SROM is typically dispensed via daily witnessed dosing. Daily witnessed doses are self-administered under the direct supervision of a pharmacist, approved prescriber, or a nurse, until the patient demonstrates clinical stability to be *considered* for take-home doses. Once clinical stability has been achieved, take-home doses may be considered on a *case-by-case basis* in patients for whom daily witnessed dosing creates a barrier to ongoing participation in treatment. Take-home doses should be awarded in a gradual fashion, similar to current guidance for authorizing Methadone Take-Home (Carry) Doses. However, contrary to the guidance for methadone carries, **the maximum number of weekly take-home doses that may be awarded to patients on SROM is four. In other words, a minimum of three daily-witnessed doses per week must be maintained at all times to promote safety and stability.**

To receive SROM carries, patients must also have a lock box or the ability to store their medication supply safely in a locked cabinet at home.

Misses Doses

As with other opioids, including OAT, loss of tolerance can result from missed doses of SROM. Close collaboration with pharmacists, regular assessment, and clinical judgment are essential to lessen the risk of over-sedation/overdose if patients miss doses[2,7]. There is a lack of clinical evidence to guide the management of SROM missed doses and re-induction protocols. Clinical judgment should consider the total daily dose, number of missed doses, and the possibility of diversion or other opioid use surrounding missed doses[7].

After two or more consecutively missed days of SROM the pharmacist will cancel the prescription. Restarting SROM requires clinical assessment and frequent follow-up by the prescriber. **A new prescription with clear instructions to guide the restart is required**. A collaborative discussion between the prescriber and pharmacist regarding the plan and further monitoring can build in additional safety. The examples outlined in the PRESCRIBING ESSENTIALS box below require daily assessment for signs of intoxication or withdrawal.

PRESCRIBING ESSENTIALS: MISSED SROM DOSING SCHEDULE[2,7]

Number of Missed Days*	Example Prescribed Dose SROM 200 mg PO OD	Prescribed Dose Example SROM 800 mg PO OD
1	200 mg	800 mg
2	120 mg (40% reduction)	480 mg (40% reduction)
3	80 mg (60% reduction)	320 mg (60% reduction)
4	40 mg or starting dose (e.g., 60 mg), whichever is higher (80% reduction)	160 mg (80% reduction)
5	Resume at initiation dose (e.g., 60 mg)	Resume at initiation dose (e.g., 60 mg)

*After ≥ 2 days, 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.

INJECTABLE OPIOID AGONIST THERAPY (iOAT, i.e., diacetylmorphine/heroin or hydromorphone)

A subset of patients with severe OUD and injection drug use (IDU) may experience ongoing cravings, withdrawal symptoms, and/or inadequate improvement in health and functional status, *despite* adequate trials of first-, second-, and third-line options for OAT. Some patients with severe injection-based OUD may not tolerate oral OAT medication due to drug reactions, severe side effects, or negative treatment experiences.

For patients who have not achieved adequate benefit from OAT trials as above, and/or who are considered treatment refractory with ongoing risk related to opioid IDU (e.g., blood borne infectious disease, overdose), injectable opioids (i.e., diacetylmorphine or hydromorphone) used under supervision in a structured and supported clinical environment have shown some benefit as a harm reduction treatment strategy[9].

Despite evidence of benefit, iOAT as a treatment option is not currently available in Manitoba and therefore will not be discussed in detail in this manual.

IN SUMMARY

While buprenorphine/naloxone and methadone remain the treatment approaches of choice for patients with OUD, there will be a subset of individuals that require alternatives to engage in care and mitigate the harms of substance use. The risks and benefits of alternative approaches must be weighed and discussed with patients, while taking into account their psychosocial contexts. Consultation with addiction medicine specialists is essential to navigate these approaches with carefully selected patients.

References

1. Bruneau J, Ahamad K, Goyer M-È, et al. Management of opioid use disorders: a national clinical practice guideline. *CMAJ*. 2018; 190(9):E247-E257. doi: 10.1503/cmaj.170958
2. Centre for Addiction and Mental Health (CAMH). *Opioid Agonist Therapy: A Synthesis of Canadian Guidelines for Treating Opioid Use Disorder.* CAMH; 2021. Available at: https://www.camh.ca/-/media/files/professionals/canadian-opioid-use-disorder-guideline2021-pdf.pdf
3. Dunlap B, Cifu AS. Clinical management of opioid use disorder. *JAMA*. 2016; 316(3):338-339. doi: 10.1001/jama.2016.9795.
4. Canadian Research Initiative in Substance Misuse (CRISM) National Guideline Review Committee. *CRISM National Guideline for the Clinical Management of Opioid Use Disorder.* CRISM; 2018. Available at: https://crism.ca/wp-content/uploads/2018/03/CRISM_NationalGuideline_OUD-ENG.pdf
5. Torres-Lockhart KE, Lu TY, Weimer MB, Stein MR, Cunningham CO. Clinical management of opioid withdrawal. *Addiction.* 2022;117(9): 2540-2550. doi: 10.1111/add.15818
6. Strang J, McCambridge J, Best D, et al. Loss of tolerance and overdose mortality after inpatient opiate detoxification: follow up study. *BMJ*. 2003;*326*(7396): 959-960. doi: 10.1136/bmj.326.7396.959
7. Provincial Opioid Use Disorder Treatment Guideline Committee. *A Guideline for the Clinical Management of Opioid Use Disorder.* British Columbia Centre on Substance Use (BCCSU) and BC Ministry of Health; 2017. Available at: https://www.bccsu.ca/care-guidance-publications/
8. British Columbia Centre on Substance Use (BCCSU). *Opioid Use Disorder Practice Update.* BCCSU and BC Ministry of Health; 2022. Available at: https://www.bccsu.ca/wp-content/uploads/2022/02/Opioid-Use-Disorder-Practice-Update-February-2022.pdf
9. Oviedo-Joekes E, Marchand K, Lock K, MacDonald S, Guh D, Schechter MT (2015). The SALOME study: recruitment experiences in a clinical trial offering injectable diacetylmorphine and hydromorphone for opioid dependency. *Substance Abuse Treatment, Prevention, and Policy*. 2015; 10(3): 1-9. doi:10.1186/1747-597X-10-3