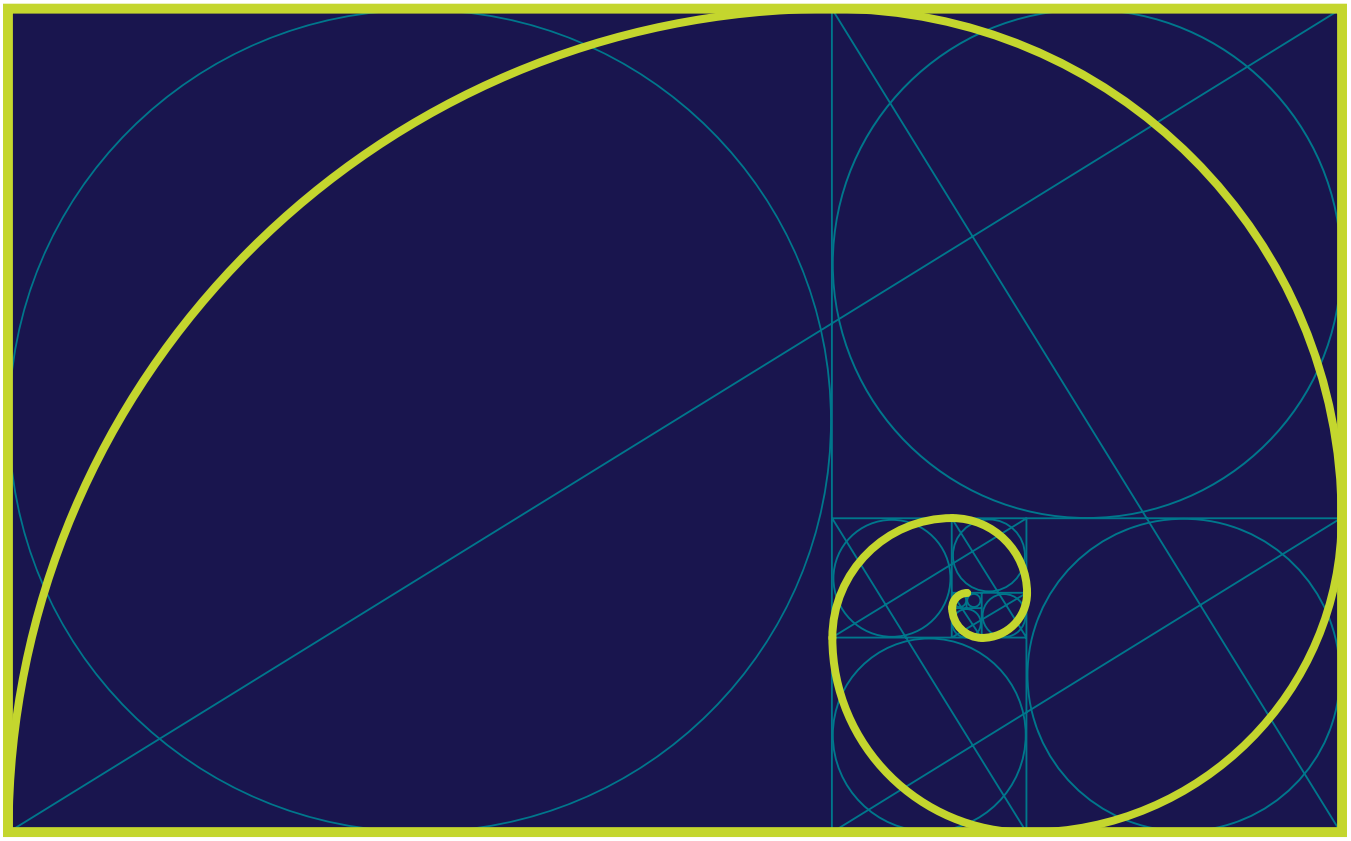
METAPHI

MENTORING, EDUCATION, AND CLINICAL TOOLS FOR ADDICTION

PARTNERS IN HEALTH INTEGRATION



RECOMMENDATIONS FOR USE OF SLOW-RELEASE ORAL MORPHINE AS OPIOID AGONIST THERAPY

AUTHORS (alphabetical)

Karan Cheema MN NP-PHC
Meldon Kahan MD CCFP FRCPC
Jason Rodgers, Peer Harm Reduction Worker
Ashley Smoke, VP, Ontario Network of People Who Use Drugs
Suzanne Turner MBS MD CCFP
Jennifer Wyman MD MPH
Maria Zhang RPh BScPhm PharmD MSc

REVIEWERS

Lisa A. Bromley MD CCFP(AM) FCFP
Katie Dunham NP
Caryn Green MD CCFP
Janelle Hannon MSW RSW
Christina Henry BA BScN RN
Cassandra Huck RPh BScPhm ACPR
Laura Jones NP
Kate Lazier MD CCFP(EM)
Andrew McLeod, Community Consultant
Charlotte Munro, Community Consultant
Patrick Nowak RN BScN
Lori Regenstreif MD CCFP(AM)
Michael Roach RN MN
Elizabeth Shouldice MD CCFP(EM) FCFP MPH
Anita Srivastava MD MSc

Version date: 01 November 2023

Suggested citation:

Cheema K, Kahan M, Rodgers J, Smoke A, Turner S, Wyman J, Zhang M. Recommendations for use of slow-release oral morphine as opioid agonist therapy. Toronto, ON: META:PHI; 2023.
www.metaphi.ca.

TABLE OF CONTENTS

Recommendations For Use of Slow-Release Oral Morphine as Opioid Agonist Therapy

SUMMARY

The toxicity of the unregulated drug supply makes access to effective opioid agonist therapy (OAT) crucial. Buprenorphine and methadone may not be suitable or effective for everyone with opioid use disorder (OUD). Slow-release oral morphine (SROM 24-hour formulation, brand name Kadian®) has been considered as a "third-line" treatment, given that the supporting evidence is limited by the quality and heterogeneity of the studies. However, current research suggests that SROM is comparable to methadone in retaining patients in treatment and reducing heroin use; other studies have reported greater treatment satisfaction, reduced cravings, fewer side effects, and reduced dysthymia.

We recommend that SROM be offered as a treatment option to individuals who have a diagnosis of OUD and are seeking OAT, within the context of a process for shared decision-making that considers the individual's health and circumstances and the evidence, merits, and risks of each type of treatment. Specific situations in which to consider SROM include the following:

- Severe OUD and/or high-risk opioid use (i.e., opioids from the unregulated supply).
- Unacceptable side effects (e.g., sedation, nausea) with other types of OAT.
- Ongoing cravings, withdrawal symptoms, and/or high-risk opioid use with other types of OAT.
- Contraindications to methadone (e.g., known history of torsades de pointes or ventricular arrhythmias on or off methadone, known or suspected congenital QT prolongation syndrome).
- Increased susceptibility to developing prolonged QT and torsades de pointes when using methadone (e.g., patients on multiple QT-prolonging medications, patients hospitalized with endocarditis or awaiting valve replacement, or with acute illness that results in electrolyte imbalances).

SROM starting doses should be based on the individual's opioid tolerance and risk of toxicity. Suggested ranges, which should be tailored to the individual's needs, are 30–50 mg for people with low tolerance or high risk for toxicity, 100–150 mg for people with moderate tolerance, and 200–400 mg for people with high tolerance. SROM doses can be increased every 48 hours. There is no maximum daily dose for SROM; while the highest dose described in the literature is 1200 mg, in our clinical experience, daily doses of over 2000 mg have been used. As with all OAT, the optimal dose aims to manage withdrawal symptoms and cravings for 24 hours without sedation or undue side effects.

Other considerations for SROM prescribing include conversions from other types of OAT, guidance regarding missed doses, and provision of take-home doses:

- Cross-tapering may be more appropriate than an abrupt stop and start transition between OAT medications. The usual final dose of SROM is between 1:6 and 1:8 of methadone to SROM.
- Missed doses: We recommend consideration of the individual's circumstances including their stability, ongoing substance use, the impact of a reduced dose, and medical and social factors. In general, we suggest no dose adjustment for up to three consecutive missed doses, and a reduction of 50% or to an initiation dose (whichever is higher) after four consecutive missed doses.
- Take-home doses: We suggest using the framework described in **META:PHI's recommendations for methadone carry doses**, which focuses on the individual's clinical and psychosocial stability, including recent substance use patterns, amount of time on therapy, and ability to store medication safely. Given the risk associated with injecting SROM pellets, we recommend caution when prescribing take-home doses for people who are injecting drugs; use clinical judgment to weigh the benefits of SROM carries against the potential risks. Take-home doses should be non-consecutive to start, with additional doses gradually being added as the person gains stability, to a maximum of six per week.

INTRODUCTION

In light of escalating opioid-related deaths associated with fentanyl and other contaminants in the unregulated drug supply (1), it is critical to ensure that people who use drugs have rapid, low-barrier access to effective, person-centered opioid agonist therapy (OAT). However, engagement and retention in treatment continue to be challenging for a variety of reasons. Frustration with approaches to methadone prescribing that reinforce stigma and barriers to care is one reason for low retention rates (2-8). Failure to meet patients' self-identified needs contributes to low treatment retention rates, which in turn are associated with high risks of relapse and death (9, 10).

In Canada, slow-release oral morphine (SROM) has historically been considered a "third-line" OAT treatment after buprenorphine/naloxone and methadone due to limited high-quality evidence for its use as an OAT medication (11); concern about increased adverse event rates and safety relative to other types of OAT; and the requirement for prolonged observed dosing with SROM due to the risks of injection of the capsules (12, 13). Another historical concern related to the difficulty differentiating prescribed morphine from heroin on urine drug tests (14). Additionally, it is likely that the structural and societal stigma associated with OUD has impeded the uptake of SROM as an OAT agent.

The 2018 CRISM National Guideline for the Clinical Management of Opioid Use Disorder (12) strongly endorsed buprenorphine/naloxone as the preferred first-line treatment for OUD when possible due to its safety profile relative to methadone, methadone as a second-line option when buprenorphine/naloxone treatment is ineffective, and methadone as a first-line therapy when buprenorphine/naloxone is contraindicated. The guideline referred to SROM as an alternative or adjunct OAT option for individuals intolerant or not responding to buprenorphine/naloxone or methadone and who remain at high risk of opioid-related harms, including overdose death. The CAMH 2021 Synthesis of Canadian Guidelines for Treating Opioid Use Disorder (13) similarly recommends initiating OAT with methadone when treatment with buprenorphine/naloxone is not preferable, and considering SROM only when buprenorphine/naloxone and methadone are ineffective, contraindicated, or declined. Both documents note that exceptions can be made at the discretion of the treating clinician, after carefully balancing the risks and benefits of treatment including the risks of not being on OAT.

Since the release of these guidelines, the presence of fentanyl and other highly potent synthetic opioids and contaminants in the unregulated drug supply have continued to drive deaths associated with drug toxicity (15, 16). Clinical experience suggests that some individuals who use fentanyl (as opposed to heroin or pharmaceutical opioids) have extremely high opioid tolerance and do not stabilize with standard approaches to buprenorphine/naloxone and methadone. In light of this reality, the British Columbia Centre on Substance Use 2022 Opioid Use Disorder Practice Update (17) recommended that clinicians carefully assess patients and discuss the advantage and disadvantages of all three oral OAT medications, regardless of the patient's previous OAT trials, and work with each patient to determine which medication is most therapeutically suitable based on their circumstances, goals, and previous treatment experiences.

The META:PHI recommendations for methadone treatment for people who use fentanyl (18) suggest that buprenorphine and methadone both be considered first-line OAT options and present strategies to achieve optimal doses of methadone and to improve engagement and retention in care. However, not everyone with OUD tolerates, desires, or stabilizes with buprenorphine or methadone (19). The strong evidence for the benefits of OAT, including protection against overdose (20), warrants reconsideration of SROM's current place in the continuum of OAT options.

Methodology

Under the auspices of **META:PHI**, a group comprised of two people with lived/living experience of SROM as OAT, three physicians, a nurse practitioner, and a pharmacist was formed to review the existing literature on SROM and formulate new evidence-informed guidance for SROM prescribing. The group's terms of reference explicitly acknowledge the value of different types of experience and education and the partnership between all members of the group as co-creators of the new guidance document.

An electronic search was conducted on PubMed and Google Scholar using subject heading search terms and keywords associated with the concepts of morphine, slow release oral morphine, Kadian®, SROM, opioid agonist therapy, and opioid substitution treatment. Key words and headings were additionally derived by reviewing the titles and abstracts of identified articles and systematic reviews. Grey literature including provincial and national guidelines for opioid agonist therapy and medication safety were included. The bibliographies of included articles were scrutinized for additional references. Articles included were limited to studies and reports published since 1996 in English.

The resulting literature regarding evidence and indications for SROM as OAT and approaches to initiation and titration of SROM was reviewed, and the group considered the experiences and perspectives of the authors around each sub-theme with the support of a moderator. Through an iterative process of discussion and refinement, the group generated the consensus-based guidance document presented below. The resulting document is not based on a GRADE framework due to the current lack of high-quality evidence. In the absence of such evidence, this document is informed by an updated review of evidence regarding the benefits and risks of SROM as OAT in the current context and by the expertise of people taking SROM as well those involved in prescribing and dispensing OAT.

EVIDENCE FOR SROM AS OAT

There are few high-quality studies evaluating SROM as OAT or comparing SROM with buprenorphine or methadone directly. We examined the literature for evidence regarding the impact of OAT with SROM on treatment retention, substance use, cravings, treatment satisfaction, mental health, pain management, pregnancy, and rapid titration. Five systematic reviews of SROM as OAT were published between 2011 and 2021 (21-25). All concluded that there were no differences in treatment retention or substance use between methadone and SROM, but also that the certainty of any treatment effects was limited due to the weakness of most study designs (crossover studies, small sample sizes, and short duration). Other aspects of treatment were not amenable to meta-analysis due to heterogeneity in study design and reporting.

Treatment Retention

A 2013 Cochrane review found no significant differences in treatment retention for SROM relative to methadone or buprenorphine (22). Two recent meta-analyses (24, 25) found no differences in treatment retention between methadone and SROM. However, other studies have reported higher rates of treatment retention for individuals on SROM. In a national prospective study of 4,778 individuals with OUD conducted in Austria (26), the two-year retention rate for those on SROM was 71%, which was significantly higher than the rate for those on methadone (47%) or buprenorphine-naloxone (48%). A prospective naturalistic German study of 189 patients who voluntarily switched to SROM from methadone or buprenorphine reported the twelve-month treatment retention rate on SROM as 60.6% (27).

Substance Use

The same meta-analyses (24, 25) found no differences between SROM and methadone in heroin use or other substance use. The German study of patients who voluntarily switched to SROM from methadone or buprenorphine reported a significant decline in heroin and alcohol use (27). A 2015 randomized crossover trial of 157 patients on methadone at baseline found that substance use and treatment retention were similar during morphine and methadone treatment (28). A small study of patients who inject heroin that chose to transition from methadone to SROM due to intolerance or dislike of methadone found that 50% reported reducing their injection drug use (29).

Cravings

Studies have shown that SROM has a greater impact on opioid cravings than methadone. A non-comparative prospective study (30) and two crossover trials (31, 32) all found that study participants reported a significant decrease in heroin cravings while taking SROM relative to methadone.

Treatment Satisfaction

Several studies have reported reductions in side effects and higher treatment satisfaction scores relative to methadone, although all of these were open-label crossover studies. In one study, patients who had side effects with methadone reported significant improvements in constipation, nausea, sweating, and reduced libido on SROM (30). In another study (31), participants taking SROM reported higher treatment satisfaction scores, with a majority of patients preferring SROM over methadone (65.9% of patients at the end of the 22-week randomized crossover trial and 83.3% at the end of the 25-week extension phase). Compared with participants taking methadone, participants taking SROM reported feeling "more normal" (33) and more clear-headed, with better ability to concentrate and work (30).

Mental Health

A systematic review found that all three OAT medications were associated with improvements in mental health compared to no treatment (34). However, different opioid agonist medications may have different effects on mood and anxiety, independent of their effect on symptoms of opioid use disorder. Compared with methadone, patients on SROM had improved measures of anxiety, depression, and overall mental health (27, 28, 35). No studies were found comparing mental health outcomes for individuals on SROM compared with those on buprenorphine.

Chronic Pain

Chronic pain is common among people with OUD. In a study of 34 patients started on OAT in a hospital in Nova Scotia, those with both OUD and chronic pain were more likely to choose SROM over methadone or buprenorphine (36). In a randomized trial, SROM was found to be as effective as oral methadone and transdermal fentanyl in managing cancer pain (37).

Pregnancy

There is only one randomized study on SROM treatment in pregnancy (38), which is now more than 20 years old. In this open-label study in which 48 pregnant patients were randomized to methadone or morphine, the SROM group experienced reductions in opioid and benzodiazepine use relative to the group on methadone. There were no differences in neonatal opioid withdrawal scores between the two groups.

Inpatient Initiation

SROM has been used to concurrently titrate methadone in the inpatient setting with patients with high opioid tolerance, such as those using high quantities of fentanyl and injecting opioids, to rapidly achieve therapeutic doses of OAT in pregnant patients. In a case series of twelve pregnant patients admitted to hospital, SROM was used in eight out of fifteen titration admissions with median doses of methadone 85 mg (IQR 70–92.5 mg) and SROM 340 mg (IQR 187.5–425 mg) at discharge (39). In a series of 34 consecutive hospitalized patients with moderate to severe OUD, seven out of thirteen patients who declined methadone and buprenorphine initiated SROM in hospital; rates of outpatient continuation of OAT were high immediately after hospital discharge (>80%) and did not differ between OAT medications (36). The ability to offer SROM may increase rates of OAT initiation among hospitalized patients.

Safety and Adverse Events

The literature around side effects or adverse events with SROM relative to other types of OAT is very limited. As a full opioid agonist, morphine would be expected to have more side effects and risks of overdose than buprenorphine. A literature review on opioids in palliative care patients (40) found that methadone was more sedating than morphine during initial titration. A study of patients starting buprenorphine, methadone, and SROM for OAT treatment in Austria found more stomach cramps, fatigue, yawning, tiredness, and insomnia in patients on SROM (41), all of which could represent undertreated withdrawal. A crossover study of safety and tolerability of SROM versus methadone for the treatment of OUD found no differences in adverse events between the two medications during the crossover or extension phases (31).

SROM is not associated with QT prolongation (31, 42), which is a significant safety concern with methadone for people who have additional risks for QT prolongation and torsades de pointes (43). Methadone has numerous drug-drug interactions associated with cytochrome P450 isoenzymes involved in its metabolism that both inhibit and potentiate its effects (44). Morphine has a limited number of drug-drug interactions; agents that can inhibit morphine glucuronidation include some benzodiazepines (lorazepam, diazepam, and oxazepam), tricyclics (clomipramine, amitriptyline, and nortriptyline), ketoconazole, nifidepine, and possibly other calcium channel blockers (45).

Conclusion

In contrast to buprenorphine and methadone, there are no systematic reviews or large observational studies on the impact of SROM on overdose mortality rates, hospitalization rates, or other important outcomes. The evidence regarding SROM as OAT is limited by the quality and heterogeneity of the studies. However, SROM appears to be comparable to methadone as OAT, with patient reports of greater treatment satisfaction, reduced cravings, fewer side effects, reduced dysthymia, and some evidence of improved treatment retention. Given this evidence, we recommend that SROM be considered as an OAT option alongside buprenorphine and methadone. Assessment of the risks and benefits of SROM should be conducted in a manner congruent with decision making for all types of OAT; no additional consultation is required. Specific recommendations regarding medication selection, initiation, titration, conversion, and treatment considerations are given below.

RECOMMENDATIONS

Choice of OAT Agent

Buprenorphine, methadone, and SROM each have features that make them more or less appealing to individuals based on their experience with OAT, treatment goals, substance use, co-occurring health conditions, and other individual circumstances. Unless there are specific medical contraindications, all three medications can be considered as options for OAT. People seeking OAT should have the opportunity to consider the features of each medication and the structures and processes with which it is delivered to make the decision that is appropriate for them **within the context of a process for shared decision-making that considers the individual's health and circumstances and the evidence, merits, and risks of each type of treatment** (46). The use of a **decision aid tool** to select an OAT agent is recommended. Documentation of the risks and benefits of this treatment and the decision process should be included in the clinical record. SROM can also be used in conjunction with methadone as combined therapy to support timely achievement of an effective OAT dose and more rapid stabilization in both community and inpatient settings (18).

Specific situations in which to consider SROM include individuals presenting with any of the following:

- Severe OUD and/or high-risk opioid use (i.e., opioids from the unregulated supply).
- Unacceptable side effects (e.g., sedation, nausea) with other types of OAT.
- Ongoing cravings, withdrawal symptoms, and/or high-risk opioid use with other types of OAT.
- Contraindications to methadone[1] (e.g., known history of torsades de pointes or ventricular arrhythmias on or off methadone, known or suspected congenital QT prolongation syndrome).
- Increased susceptibility to developing prolonged QT and torsades de pointes when using methadone (e.g., patients on multiple QT-prolonging medications, patients hospitalized with endocarditis or awaiting valve replacement, or with acute illness that results in electrolyte imbalances).

Clinicians should work with each individual to determine which type of OAT aligns best with their goals, needs, circumstances, and concurrent health conditions, as well as any previous treatment experiences. Factors such as access to a pharmacy for daily witnessed dosing or delayed access to carries may be additional considerations, especially for people living in rural or remote areas. The option (and potential challenge) of moving from one type of OAT to another as needed should also be considered. While patient values and preferences should always be a significant factor in medication selection, they have even more weight when the "best choice" is not clear based on high-quality evidence.

Pharmacology Considerations

SROM (morphine sulphate sustained release oral capsules, brand name Kadian®) is a long-acting 24-hour formulation of morphine (47). SROM is a full mu-opioid agonist developed as an opioid analgesic for the management of severe pain requiring daily, continuous long-term opioid treatment. SROM acts as a long-acting opioid because of the polymer coating on the morphine pellets contained in the capsule. This results in significantly slower absorption of morphine from Kadian® than with other formulations. Mean peak plasma concentrations (Tmax) are achieved at 8.5 hours.

---

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

The extent of absorption is unaffected by food, but mean peak plasma concentrations are slightly but not clinically significantly later (10 hours if taken with food). The terminal elimination half-life of morphine following a single dose of SROM is approximately 11–13 hours (vs. 25 hours at steady state for methadone), primarily due to the delayed absorption of the morphine pellets. Once absorbed, the plasma elimination of half-life is the same as immediate-release morphine (2–4 hours).

When given on a fixed-dose schedule, steady state is achieved within approximately 48 hours (47). SROM does not have a ceiling effect.

In a study of fourteen patients who completed transition between methadone and SROM, mean doses corresponded to a steady state oral morphine-to-methadone equivalence of 4.64 ± 1.0 (14). The magnitude and duration of opioid effects following dosing were comparable for methadone and SROM throughout a 24-hour dosing interval. SROM peaked significantly later (6.5 h ± 2.3 h) compared to methadone (2.5 h ± 1.4 h). Although the mean and median peak-to-trough plasma drug concentration ratios were significantly greater for SROM than methadone (mean 3.2 ± 1.8 vs. 1.8 ± 0.35, median 2.6 vs. 1.8), SROM provided satisfactory and equivalent degree of withdrawal suppression between doses for patients reporting both adequate and inadequate suppression of withdrawal symptoms on methadone therapy.

Morphine is metabolized mainly in the liver into normorphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), which are then eliminated via the kidneys. M6G in particular has potent analgesic and depressive effects and accumulates in individuals with renal disease, hence the need for extreme caution in people who are on hemodialysis or have clinically significant impairment of renal function.

Co-ingestion of SROM and alcohol is contraindicated due to the risk of a rapid increase in opioid plasma concentrations, which can be fatal even in opioid-tolerant people (47).

Contraindications and Precautions

Please refer to the product monograph (47) for a full list of contraindications and precautions.

Absolute contraindications to SROM include the following:

- Hypersensitivity to morphine sulfate or any of the non-medicinal ingredients.
- Acute or severe respiratory depression.
- Asthma with severe bronchospasm.
- Severe chronic obstructive pulmonary disease (COPD).
- Gastrointestinal obstruction, including ileus.
- Use of a monoamine oxidase inhibitor within the last fourteen days.
- Chronic kidney disease (GFR < 50).

The following relative contraindication and precautions should be kept in mind:

- SROM should be used with caution in people with gastrointestinal issues that affect gastric emptying (e.g., obstruction, diarrhea, abnormal gut anatomy).
- SROM should be used with caution in people with GFR between 50–90. Renal function can be acutely reduced (e.g., by dehydration or medications), thereby putting patients at risk of M6G toxicity.
- SROM should be used with considerable caution in people who drink alcohol. Co-ingestion of alcohol and SROM morphine can cause a rapid increase in opioid plasma concentrations; this is thought to occur because alcohol disrupts the sustained-release capsule.

- Morphine can have a prolonged half-life in people with hepatic dysfunction. Lower starting doses and more gradual titration is advised (48).
- SROM should be used with caution in individuals at higher risk for opioid toxicity, including older age, COPD, sleep apnea, and concurrent use of medications that can cause respiratory depression (benzodiazepines, gabapentinoids). In individuals with increased risks of opioid toxicity, buprenorphine may be preferred over full-opioid agonists. If SROM is used, the initial dose should be lower, titration should be slower, and concurrent medications should be managed/tapered accordingly.
- While the product monograph states that SROM is contraindicated during pregnancy due to the risks of neonatal withdrawal syndrome, withdrawal syndromes are associated with all opioids. For pregnant people with opioid use disorder, the benefits of OAT outweigh the risks associated with ongoing uncontrolled opioid use for the pregnant person and the pregnancy (49). People who are stable on SROM when they become pregnant should be informed that switching between OAT options during pregnancy and post-partum periods is generally not recommended (50). During pregnancy, higher doses of morphine may be required as the pregnancy progresses; tapering is not recommended.

Morphine is considered a low-risk opioid as it relates to its propensity to interact with other medications (e.g., antidepressants) in causing serotonin syndrome. This is in contrast to other opioids such as methadone, fentanyl, and tramadol, which are considered medium- and high-risk for inducing serotonin syndrome. However, this risk should be contextualized relative to other medications and substances an individual may be taking. For example, when morphine is used in combination with other medications with low or intermediate risk of serotonin syndrome (e.g., SSRIs or SNRIs), the risk of serotonergic toxicity is much lower than when combined with a monoamine oxidase inhibitor (51). Individuals at higher risk of serotonin syndrome should be informed about the range of signs and symptoms they may experience, which include excessive sweating, diarrhea, agitation, tremor, hypertension, hyperthermia, tachycardia, twitching, and involuntary muscle movements (52), and when to seek emergency care.

Dosing

The goal of SROM dosing is, as with other OAT, to support the person in finding the dose that manages withdrawal symptoms and cravings without causing sedation or other adverse effects. Initial doses and titration schedules should consider the individual's degree of opioid tolerance, general medical status, and the reliability of the relative potency estimate used to calculate the dose of morphine required. For example, a person taking daily observed methadone has a reliable ingestion pattern, although the rate of conversion from methadone to SROM has a range. For people using unregulated fentanyl, fluctuations in use and variability in the content of the street supply make it more difficult to accurately estimate an appropriate dose of morphine.

For context, recent guidelines have suggested starting methadone at higher doses than previously recommended for people with high opioid tolerance due to fentanyl use as a means to achieve effective doses more efficiently and increase treatment engagement and retention. The Alberta Virtual OAT program recommends a starting dose of 30–50 mg for people with recent fentanyl use confirmed by urine testing and previous methadone experience[2], and guidelines from both Québec (53) and British Columbia (54) recommend a starting dose of up to 40 mg for people with known very high tolerance). Using the mid-range of accepted conversion rates (1:4–1:8) between SROM and methadone (31, 33, 41), 200 mg of morphine would be equivalent to approximately 33 mg of methadone. META:PHI recommendations (18) suggest co-prescribing methadone 30 mg along with up to 200 mg of SROM for people who use fentanyl with high opioid tolerance, which would be equivalent to a total Day 1 dose of approximately 380 mg morphine.

---

[2] Personal communication, Dr. Nathaniel Day, 2023.

The guidance in this document regarding dose initiation and titration is based on clinical experience and expert clinical consensus and refers specifically to the 24-hour once-daily formulation of SROM. Individual factors including opioid tolerance, concurrent substance use, medications, and other medical conditions should be taken into account when determining an appropriate starting dose.

SROM as Monotherapy in the Outpatient Setting

SROM starting doses should be based on the individual's opioid tolerance and risk of toxicity. We recommend starting doses of **200–400 mg for people who use fentanyl regularly and have very high opioid tolerance**. People with moderate opioid tolerance or moderate risk of toxicity (e.g., those using opioids less intensively or those with risk of toxicity due to benzodiazepine or alcohol use) can be started at doses between 100–150 mg per day. Doses may start as low as 30–50 mg in people using lower doses of oral pharmaceutical opioids, not using opioids regularly, not currently using opioids but at risk of returning to use, or those at higher risk of toxicity due to co-morbidities or use of other sedating medications.

Titration also depends on the individual's opioid tolerance and concurrent risks. Dose increases should be separated by at least 24 hours. SROM can be titrated in increments of 50–200 mg every 48 hours or 100 mg daily until a dose of **800 mg is reached**. Above 800 mg, doses can be adjusted by 50–200 mg every 48 hours based on clinical judgment and patient needs. All dose titration planning should consider the risks of ongoing opioid use (i.e., overdose while off OAT) and treatment discontinuation, tolerance, and the need to stabilize effectively.

Table 1: SROM initiation and titration according to level of tolerance and toxicity risk

OPIOID TOLERANCE	STARTING DOSE	TITRATION
Low tolerance or high risk for toxicity	30–50 mg	50 mg every 48 hours
Moderate tolerance	100–150 mg	50–100 mg every 48 hours
High tolerance	200–400 mg	100 mg daily OR 200 mg every 48 hours to 800 mg Thereafter 50–200 mg every 48 hours

There is no maximum dose for SROM. Although the highest dose described in the literature is 1200 mg (55), in our clinical experience, daily doses over 2000 mg have been used. As with all OAT, the optimal dose aims to manage withdrawal symptoms for 24 hours without sedation or undue side effects.

In most cases, people should be assessed prior to each dose increase, but if an individual has had minimal response to a dose and is at low risk for toxicity, then one to two pre-planned dose increases can be given before the next assessment (e.g., increase by 100 mg every day for three days). The prescription should advise pharmacists to contact the prescriber if the individual appears sedated or has missed doses.

SROM Combined With Methadone in the Outpatient Setting

For people with high opioid tolerance who are choosing to start methadone as their primary OAT, co-prescribing SROM has been suggested as an option to achieve effective therapeutic OAT doses more rapidly (18), as maximum initial methadone doses have historically been capped at 30 mg. In this context, the usual starting dose of SROM is **100–200 mg** along with 30 mg of methadone. Dose titration is typically in increments of 100 mg every 48 hours. SROM can be continued or tapered once the methadone dose is stable.

SROM as Monotherapy in the Inpatient/Monitored Setting

For patients admitted to hospital, opioid tolerance and need are initially established with short-acting morphine on the first day of admission. Following a protocol used in some recent case reports (39, 56), we recommend oral immediate-release morphine (e.g., 50 mg) every two hours as long as the patient is not overly sedated (**POSS** 1 or 2 while awake; see **Appendix A**) with additional morphine 50 mg PRN if requested for pain, withdrawal, or cravings. On Day 2, the patient receives 50% of the total Day 1 dose of morphine as SROM and continues standing immediate-release morphine as needed and PRN doses as required. On Day 3, the SROM dose is calculated as the Day 2 SROM dose plus 50% of the total Day 2 immediate-release morphine; immediate-release morphine is then reduced to PRN only.

Conversions

Clinicians may suggest switching to SROM if people have persistent difficulty stabilizing and/or experience cravings, low mood, anxiety, or side effects with methadone or buprenorphine. SROM and methadone can also be combined to assist with stabilization both in early titration and later treatment. Just as SROM can be added to augment the effect of methadone, methadone can be added to SROM therapy to assist with stabilization when monotherapy is not effective.

Converting From Methadone to SROM

The transition from methadone to SROM can be made gradually with a cross-taper or abruptly with a stop-and-start approach; there is no clear evidence for one approach over the other from the limited literature. The majority of the literature (31, 33, 35) reports on stopping methadone and initiating SROM the next day in the context of observational trials. An abrupt stop and start may result in higher rates of withdrawal while doses are being adjusted; this approach may be more appropriate for a monitored setting where withdrawal can be managed with short-acting morphine. Individual circumstances such as medical stability, tolerance, experience with SROM, and opportunities for monitoring and reassessment should be considered. The usual final dose of SROM is between 1:6 and 1:8 of methadone to SROM.

Cross-Taper Transition

One study's (29) cross-tapering protocol was based on unpublished simulation studies conducted by Mundipharma Research Limited, which showed that overlapping methadone and SROM results in peak concentrations above the steady state peak concentrations for methadone alone; consequently, participants switching from methadone to SROM were started on SROM at 25–30% of the anticipated final SROM dose (using a 1:6 ratio) along with 50% of the usual methadone dose and were cross-tapered from there *(see Table 2 on page 12)*:

Table 2: Sample cross-taper transition

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

A more gradual approach is to increase SROM by 50 mg and reduce methadone by 10 mg every three to four days, with monitoring and adjustment for withdrawal, cravings, and side effects.

Individual circumstances including tolerance, medical stability, availability of monitoring, and opportunities for reassessment should be considered when planning the taper. The increments and frequency of methadone reduction and SROM increases can be slowed as needed (e.g., dose adjustments every three to five days, extending the process to seven to ten days) to achieve a smooth transition, with the goal of avoiding destabilization.

Stop-and-Start Transition

Methadone can be stopped and SROM started the next day (24 hours later) at a dose equivalent to **1:4–1:6** and then titrated as necessary (57). At lower starting doses (1:4), SROM can be increased daily for three days and every two days thereafter. At higher starting doses (1:6), SROM can be increased every 48 hours as needed. The usual final dose of SROM is between 1:6–1:8 (58). One study (59) had substantially higher conversion ratios (1:11.8–1:17), but these are not supported elsewhere in the literature.

Table 3: Sample stop-and-start transition

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

Converting From SROM to Methadone

We recommend that transitions from methadone to SROM be made gradually with a cross-taper rather than a stop-and-start approach due to differences in pharmacokinetics and respiratory tolerance between SROM and methadone. To avoid toxicity, a conservative ratio of 12:1 or 10:1 SROM to methadone is recommended, with lower ratios for individuals with comorbidities that could affect methadone tolerance or safety (54). A suggested approach is to replace 100 mg of SROM with 10 mg of methadone in increments, with the rate of conversion depending on the starting dose, the reasons for the taper, and patient factors. For example, for someone on 1000 mg SROM, the dose of SROM could be decreased to 800 mg with the addition of 20 mg methadone. Methadone can be increased and SROM decreased every three to five days, with regular reassessment.

Converting From Buprenorphine to SROM

There is no established conversion of buprenorphine to morphine equivalents. A recent study suggests an initial ratio of 1:42.3 buprenorphine to SROM and a final ratio of 1:58 (59). For example, 8 mg buprenorphine would be equivalent to 338 mg SROM.

Given the limited evidence regarding buprenorphine to SROM ratios, SROM can be initiated and titrated according to the individual's level of tolerance and toxicity risk as described above. For example, individuals still using fentanyl while on buprenorphine have higher opioid tolerance than those who have been abstinent from opioids. At the same time, the increased risks of respiratory suppression with a full-agonist opioid relative to buprenorphine should be considered, and the starting dose should be reduced by 25–50% to account for differences in cross-tolerance. SROM can be started the day after the last buprenorphine dose; there is no risk of precipitated withdrawal. SROM can then be titrated every 48 hours as per usual protocols.

There is no current guidance for depot buprenorphine; we recommend that once withdrawal symptoms present (typically day 21–28), SROM can be started at lower doses of 30–60 mg and titrated every 48 hours accordingly.

Converting From SROM to Buprenorphine

Transition from SROM to buprenorphine can be conducted with a standard initiation or with microdosing for individuals for whom avoiding withdrawal is a priority. As SROM wears off after around 24 hours, a standard buprenorphine initiation can be implemented at 24–36 hours from last SROM dose when the person is in withdrawal; conversion from SROM to short-acting morphine for one day is an extra step that can help to reduce withdrawal time and the risk of precipitated withdrawal (57). Microdosing further reduces the risk of precipitated withdrawal or withdrawal caused by abrupt cessation of SROM. When choosing a microdosing schedule (i.e., a gradual approach or a more rapid one), consideration should be given to the SROM dose, risks of withdrawal, and other patient factor. *(See Table 4 on page 14)*

Table 4: Sample conversion from SROM to buprenorphine

	GRADUAL MICRODOSING		RAPID MICRODOSING	
	SROM	**Buprenorphine**	**SROM**	**Buprenorphine**
Day 1	800 mg	0.5 mg once daily	800 mg	0.5 mg four times daily
Day 2	800 mg	0.5 mg twice daily	800 mg	1 mg four times daily
Day 3	800 mg	1 mg twice daily	800 mg	2 mg four times daily
Day 4	800 mg	2 mg twice daily	STOP	12 mg + 2 mg every three hours as needed to max 16 mg
Day 5	800 mg	3 mg twice daily		
Day 6	800 mg	4 mg twice daily		
Day 7	STOP	12 mg + 2 mg every one to two hours as needed to max 16 mg		Titrate as needed

OTHER CONSIDERATIONS

Missed Doses

Previous guidelines recommended reducing the dose of SROM by 40% with two consecutive missed doses (58), as the short half-life of morphine (2–4 hours) can lead to loss of tolerance relatively quickly. However, increasing clinical experience with SROM and concern with the risk of treatment disruption may warrant reconsideration of this approach. Clinicians should consider the individual's circumstances including their stability, ongoing substance use, the impact of a reduced dose, and medical and social factors. For example, people who continue to use unregulated opioids regularly have more ongoing tolerance than those who are not supplementing their OAT with other opioids and may also be at greater risk of discontinuing treatment if doses are reduced.

In general, we suggest following the META:PHI recommendations for missed doses with methadone (18): no dose adjustment is required for up to three consecutive missed doses, and the dose is reduced by 50% or to an initiation dose (whichever is higher) after four consecutive missed doses. After more than four consecutive missed doses, the patient would need to be reassessed and SROM would need to be restarted:

Table 5: Adjustments for missed SROM doses

DAYS MISSED	DOSE
Three (patient presents on Day Four)	Continue previous dose; no adjustment required
Four (patient presents on Day Five)	50% of previous dose or initiation dose (whichever is higher)
Five or more (patient presents on Day Six or later)	Re-start

Take-Home Doses

META:PHI's framework for methadone carry doses (60) recommends that criteria for take-home doses should prioritize safe storage, amount of time on methadone, and clinical and psychosocial stability, including recent substance use patterns. We suggest that clinicians apply these recommendations for methadone carry doses to carry doses of SROM:

- Carries are usually not appropriate for people who have been on SROM for less than four weeks, are unable to store their medication safely, are using substances in high-risk ways (e.g., recent overdoses or blackouts), have unstable mental health conditions, or frequently miss doses and appointments.
- **Up to three non-consecutive carries per week** can be appropriate for people who have been on SROM for a minimum of four weeks, are able to store medication safely (i.e., in a locked device), and are not using substances in high-risk ways (e.g., no overdoses or blackouts in the preceding month, not intoxicated or sedated at appointments). With these conditions, carries can be used to assist with maintaining treatment and building stability outside of a contingency management framework.
- **Four to six carries per week** are appropriate for people who are quite clinically and socially stable; this number is based on the increased risk associated with greater numbers of carries (particularly consecutive carries) and aligns with contingency management practices. Expectations include a minimum of twelve weeks on SROM, effective management of smaller numbers of carries, and minimal substance use with no blackouts or overdoses in the last three months.

As there is no literature on the use of more than six carries for SROM, and given the potential risks associated with larger amounts of take-home doses, we recommend a maximum of six take-home doses of SROM.

These criteria are intended to be individualized in line with clinical judgment and personal circumstances in the context of a therapeutic alliance between the patient and the prescriber; clinicians may assess the risks and benefits associated with SROM carries in ways that are either more restrictive or more flexible, depending on individual circumstances. It is critical to recognize the particular risks associated with SROM misuse or diversion. The slow-release design of SROM can be circumvented by chewing or crushing the pellets to release the entire morphine content as a bolus dose of short-acting morphine. Co-ingestion with alcohol can also lead to rapid absorption of the dose. Unlike methadone, morphine capsules can be crushed and dissolved for injection. Injection drug use is associated with systemic viral infections such as hepatitis C and HIV, soft tissue infections, bone and joint infections, infective endocarditis, vascular injury, and thrombosis. In a study of people attending addiction care and harm reduction centres in France (61), the main route of diverted slow-release morphine use was intravenous injection (93.7%). One study (62) reported that there is widespread diversion of SROM prescribed as OAT in France and found significantly higher rates of unintentional opioid overdose, all-cause mortality, hepatitis C seroconversion, hospitalization, and thrombotic complications compared with people on buprenorphine or methadone. How decisions were made regarding take-home doses for any of these OAT medications is not explained. In addition to the usual assessment of risks and benefits of take-home doses, clinicians should particularly consider the individual's history of injection drug use; decisions about carry doses should carefully weigh the benefits of SROM carries against the risks of injecting SROM (63).

Decisions about carries, as with other aspects of OAT care, should be conducted in ways that support person-centered care. Conversations about carries should take place when both the care provider and the person receiving OAT are able to fully engage in the discussion. The discussion should review the risks of carries, the conditions under which they will be added or withheld, the dangers of taking SROM in ways other than as prescribed, the dangers of sharing SROM, and the importance of safe storage and carry management. Discussion of the agreement should be documented in the patient chart; some providers have a practice of reviewing and signing the agreement with the person taking OAT (see **Appendix B** for a sample agreement).

For people receiving take-home doses, regular visits (at least monthly) should include assessment of the individual's overall stability, substance use, and effective carry management as well as urine drug tests. As with methadone, SROM carries would be reduced or removed in circumstances where an individual is not maintaining the expected level of safety and stability.

Take-home doses should be dispensed in individual, appropriately sized, child-resistant containers. Containers with tamper-proof seals should be requested if available.

Urine Testing

The purpose of urine drug testing (UDT) as part of OAT is to provide a shared reference point for care providers and people receiving OAT. Issues related to the types of urine drug testing, sensitivity, specificity, and nuances of interpretation are beyond the scope of this document and are reviewed in recent publications (58, 60, 64, 65).

For people treated with SROM, standard point-of-care tests for opioids will be positive due to morphine and/or glucuronide metabolites. Point-of-care tests for opioids are unable to distinguish morphine from heroin. Point-of-care tests for hydromorphone may also be positive; hydromorphone is a minor metabolite of morphine, which becomes relevant and can be detected with high morphine doses. Laboratory analysis with chromatography-mass spectrometry can be used to distinguish between heroin, codeine, hydromorphone, and morphine:

Table 6: Expected mass spectrometry test results for particular opioids

SUBSTANCE	EXPECTED FINDINGS ON MASS SPECTROMETRY
Morphine	Morphine (very high) Hydromorphone (variable, proportionate to dose of morphine) Codeine (trace, i.e., < 50 mg/mL)
Heroin	Heroin metabolite 6-acetylmorphine (6-MAM) Morphine (variably high) Codeine (5–10%) 6-acetyl codeine may be present as a contaminant (marker of street heroin)
Hydromorphone	Hydromorphone Hydromorphone 3-glucuronide (hydromorphone metabolite)
Codeine	Codeine (high) Morphine (low)

The British Columbia Centre on Substance Use (64) suggests a UDT frequency of monthly (or more or less frequently as clinically indicated) during titration and stabilization, and at least six to eight random tests per year for people with carries, with scheduled UDTs when clinically indicated. META:PHI (60) suggests the following UDT schedule for people taking methadone based on treatment stage:

Table 7: Frequency of UDT based on methadone treatment stage

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

We recommend a similar approach for people taking SROM: more frequent samples (i.e., one sample with each visit) during treatment titration, as the therapeutic alliance is being established, and while the individual is building carries. People receiving six carries of SROM would typically be expected to provide a sample at least once per month. Unannounced (i.e., random) urine tests may also be requested.

Other Aspects of Care

OAT should be situated in a set of services that address the needs and goals of the individual, including issues with other substance use, harm reduction education and supports, management of mental health conditions and care for co-occurring medical issues, including contraception and screening for sexually transmitted and blood-borne infections. Clinicians providing OAT should regularly review the individual's goals and treatment plan, assess opportunities for providing other types of support, and seek to connect the individual to primary and specialist care when appropriate.

Optimizing retention in care should be a priority of all OAT providers. Factors associated with retention in treatment include flexible, individualized dosing rather than a fixed-dose strategy, clinic management policies, frequency of contact with a counselor, use of cognitive behavioural therapy, and increased numbers of take-home doses (66). The frequency of office visits and urine drug screens should be based on clinical need, with consideration given to the level of disruption in people's lives and the implications for treatment retention.

OAT programs should ensure that clients have naloxone kits, provide counseling on harm reduction strategies, and offer harm reduction supplies.

PHARMACY CONSIDERATIONS

Prescriptions

SROM (24-hour formulation, brand name Kadian®) is available in 10, 20, 50, and 100 mg strengths. The prescription should include wording that advises the pharmacist to use whatever combination of strengths are available to make the total daily dose rather than specify the individual number of capsules for each strength, as pharmacy inventories vary.

As with methadone, prescriptions for SROM should include specific start and stop dates and observed vs. take-home days. The prescription should request that SROM carries be individually packed as daily take-home doses in containers with tamper-proof seals (see **Appendix C** for a sample prescription). The prescriber may also consider communicating directly with the pharmacy to ensure that they have sufficient inventory to initiate and provide continuous care.

While prescriptions do not need to stipulate that SROM is being prescribed as OAT, identifying OAT as the indication, especially when the clinician does not have a relationship with the pharmacy receiving the prescription, may help the pharmacist to contextualize the dosing in light of current chronic pain guidelines and avoid delays in dispensing of the medication.

Capsules do not need to be opened with pellets poured into a cup for observed dosing. For people taking SROM and methadone, it is common to write that methadone should be taken after the SROM capsules.

Community Pharmacy Dispensing

General considerations that apply to all individuals on OAT and high-dose opioids include the need to ensure the correct client identity with observed dosing. It may be convenient for the client and for the pharmacy staff to have a client's photo ID scanned into the pharmacy dispensing software so that the client does not have to present a physical copy every time.

SROM **pellets** must be swallowed whole. Disruption of the pellet by chewing, crushing, or dissolving will cause rapid release and absorption of a potentially fatal dose of morphine. Many programs have a protocol of opening SROM capsules and sprinkling the pellets onto a small amount of soft food. This practice was initially implemented for people with difficulty swallowing and has been adopted to potentially reduce the likelihood of diversion of SROM capsules. In the outpatient setting, the opening of capsules creates a workflow issue for pharmacists (opening many capsules into cups that may retain pellets during dosing due to static, obtaining yoghurt or apple sauce) and a barrier for people taking SROM (having to wait until the pharmacist has time, stigma of taking a medication in unique and obvious ways). **We recommend that capsules be swallowed whole for observed doses, followed by a swallow of liquid to ensure that the whole dose has been ingested.**

Pharmacists may be required to assess someone who appears unwell and make a decision about whether it is suitable for them to receive an observed dose and/or a carry. In any situation where risks outweigh the benefits (e.g., significant intoxication, sedation, or behavioural issues that raise concerns about an individual's acute well-being), the dose should be held. If possible, the pharmacist should ask directly about recent substance use and provide counseling regarding self-monitoring and harm reduction. If the individual appears intoxicated, they can be asked to return later the same day; once their intoxication has resolved, they can receive their observed dose but not their carries later in the same day.

While there is no requirement for the person who is prescribed SROM to be reassessed by a prescriber prior to receiving their dose, the prescriber can support the pharmacist by providing their contact information for case discussion, particularly after hours, to minimize consequences associated with withheld doses. Prescribers should be notified of any missed or withheld doses, as this would impact decisions regarding carry safety.

As a standard practice at dispensing pharmacies, if a person misses an observed SROM dose on a day they were supposed to pick up carries, they should receive an observed dose on the day they attend. Carries should not be dispensed if the person has missed three consecutive doses.

Challenges in Inpatient Settings

In the inpatient setting, additional concerns relate to people who inject drugs and have PICC lines. Injecting SROM into PICC lines is dangerous due to the beads, which do not dissolve fully; for people at risk of injecting SROM, the likelihood and risks of injecting should be discussed, and consideration given to choosing an alternative opioid for treatment. For patients that are not able to switch to an alternative treatment, education should be provided regarding the possible risks (e.g., specific types of infections such as fungal infections associated with lower heating protocols used with SROM) and evidence regarding safer injection practices specific to SROM (67-69).

Absorption of SROM requires a functional gastrointestinal tract. SROM (Kadian® capsules) should not be given to people with ileus or post-bowel surgery until bowel activity has resumed; immediate-release preparations may temporarily be used cautiously. SROM should not be used in people with NG tubes; the capsules do not go through NG tubes, and opening the capsules to push the beads can lead to blockages of the tube. People who do not absorb the full dose of SROM can then receive too high a dose when the tube is removed and the full dose is absorbed. If maintaining OAT with morphine is appropriate, M-ESLON can be substituted with BID dosing.

Not all hospitals have SROM on formulary or in an appropriate range of capsule strengths. Consultation with a hospital pharmacist and engagement of a local champion may be helpful when inpatient teams are not experienced with using SROM in order to build local expertise and advocate for necessary changes with hospital leadership.

Drug Shortages

Shortages of SROM of variable duration have occurred over the past number of years. When SROM is unavailable, the dose can be converted to M-ESLON and divided into twice-daily dosing. Care must be taken to avoid double-dosing, as M-ESLON releases morphine over a twelve-hour period rather than a 24-hour period.[3] No adjustments or reductions for differences in opioid tolerance are required (i.e., 200 mg SROM dose can be switched to 100 mg BID M-ESLON). Note that the literature on SROM as OAT is based only on the 24-hour formulation (i.e., Kadian®), not other intermediate-acting formulations.

[3] **https://www.ismp-canada.org/download/presentation-may2018.pdf**

Transitions of Care

Clinicians should be aware of situations that can compromise continuity of care and patient safety, including transitions of care between community providers, transition between hospital and community (especially in the setting of involuntary discharges), and prescriptions from multiple providers (e.g., in acute pain situations/hospital settings). When patients are admitted and discharged from hospital, it is the responsibility of the inpatient team to initiate communication with the community prescriber and pharmacy.

Collateral information regarding dosing should also be used when available. **The Digital Health Drug Repository (DHDR)** contains information about all monitored drugs (i.e., narcotics and controlled substances), regardless of payor, when the approved identification used was a valid Ontario Health Number. DHDR can be accessed through ClinicalConnect, ConnectingOntario, ClinicalViewer, and some electronic medical records. The DHDR may be useful in identifying the prescribers and pharmacies involved in the patient's care and their contact information but cannot be used to definitively determine if the patient actually received an observed and/or carry dose of SROM; prescriptions may be processed prior to the patient receiving an observed dose (and then later reversed if the patient misses a dose). Clinicians should contact the community pharmacy directly to confirm last observed dose. Medications administered in hospital are not noted within DHDR.

APPENDIX A:
Pasero Opioid-Induced Sedation Scale (POSS) with Interventions[4]

S = Sleep, easy to arouse

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

1 = Awake and alert

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

2 = Slightly drowsy, easily aroused

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

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

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

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

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

[4] Pain Assessment and Pharmacologic Management, by C. Pasero and M. McCaffery, 2011, St. Louis, MO: Mosby/Elsevier. Copyright (1994) by Chris Pasero. Also available as a **separate document**.

APPENDIX B:
Sample Agreement For Receiving Carries

In order to receive take-home doses ("carries") of my slow-release oral morphine (SROM), I understand and acknowledge the following:

1. There are expectations around my stability and my ability to store medications in a safe manner that must be met in order to receive take-home doses of SROM. This is because of the risks of SROM to people who do not have tolerance to it, and the risks to me if it is not taken properly. A single dose of SROM can be dangerous or fatal if consumed by someone who is not tolerant of that dose, especially if taken by a child. If I miss too many doses, I can also lose tolerance to the medication. If I take more than prescribed on a single day or if I chew, crush, or inject my dose, this can also be dangerous or life-threatening.
2. When considering whether to prescribe carries, my care provider is concerned about my safety and the safety of my community. To assess my ability to manage carries safely, my care provider will consider:
   a. My housing
   b. How long I have been taking SROM
   c. How often I miss doses
   d. My stability (for example, how I am managing appointments, medication, work, school)
   e. My substance use
   f. My urine drug test results
   g. Other factors that could affect my ability to manage carries safely, such as mental health changes
3. The number of take-home doses I receive will be based on my stability and ability to manage carries safely. As my stability increases and I have more experience managing carries safely, the number of carries will be gradually increased. If my stability decreases or I have difficulty managing carries safely, the number of carries will be decreased. These decisions are made in discussion with my prescriber, balancing the importance of the treatment working in my life, with the importance of my safety and the safety of the community.
4. In order to receive carries, I will need to manage my use of drugs and alcohol so that the impact to my health, safety, and stability is minimized, and such that it does not interfere with my ability to manage and store carries.
5. Urine drug testing is a routine part of SROM treatment. Urine drug tests provide information about what substances I have been taking or exposed to, which helps me and my prescriber develop the best treatment plan for me. I agree to provide a urine sample when requested. I understand that if my urine sample shows signs of tampering or indicates that I am not taking SROM as prescribed, I will lose my carries.
6. I will bring my carries to my clinic or my pharmacy within 24 hours of being asked to do so. If I do not without a valid reason, I may lose access to carries.
7. In order to receive carries I need to have a safe and consistent place to stay, not staying on the street.
8. I will store my SROM securely in a locking device (locked box, locked cabinet, or safe) that cannot be accessed by other people. I will keep my medication out of sight and out of reach.
9. I agree not to share, trade, sell, or loan my SROM under any circumstances. Any of these is a reason for my carries to be withdrawn indefinitely.
10. If carries are lost, they will typically be replaced with observed doses, and a review of the carry agreement will take place. If carries are lost, they will be reinstated gradually.

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

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

Date

Patient (Signature)

Patient (Printed Name)

I confirm that:

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

HCP (Signature)

HCP (Printed Name)

APPENDIX C:
Sample SROM Prescription

Rx

Mary Smith, MD,
CCFP, DBAM, FCFP
Toronto Family Practice
123 Valley Road West #440
Toronto Ontario M1P 2P3
CPSO: 11111
Tel: 416-555-1234
Fax: 416-555-4321

Jane Doe DOB: 15/05/1958

Written: 2023-06-24
Prescription ID: 010203

Toronto, CA-ON
416-555-0022
Health Ins.# 1234-001-123-WR

KADIAN 100MG
750mg PO DAILY: RX VALID SEPT 1-6 INCLUSIVE
Qty: 7 DAY SUPPLY (7500 mg) Repeats: 0
Active Ingredients:
MORPHINE SULFATE 100.0 MG
Form: CAPSULE (SUSTAINED-RELEASE)
Route: PO
DIN: 02184451

NOTES: PHARMACIST: PLEASE USE COMBINATION OF AVAILABLE CAPSULES TO COMPRISE THE TOTAL DAILY DOSE
OBSERVED DOSES
MONDAY/WEDNESDAY/FRIDAY/SATURDAY/SUNDAY
TAKE-HOME DOSES TUES/THURS
PLEASE DISPENSE TAKE-HOME DOSES IN INDIVIDUAL TAMPER-PROOF CONTAINERS
CAPSULES DO NOT NEED TO BE OPENED FOR INGESTION
PLEASE NOTIFY PRESCRIBER REGARDING ANY MISSED DOSES

Signature: _____

Mary Smith, MD, CCFP, DBAM, FCFP
Pract. No. 0101234

REFERENCES

1. Gomes T, Murray R, Kolla G, Leece P, Kitchen S, Campbell T, et al. Patterns of medication and healthcare use among people who died of an opioid-related toxicity during the COVID-19 pandemic in Ontario. Toronto, ON: Ontario Drug Policy Research Network; 2022.
2. Frank D, Mateu-Gelabert P, Perlman DC, Walters SM, Curran L, Guarino H. "It's like 'liquid handcuffs": The effects of take-home dosing policies on Methadone Maintenance Treatment (MMT) patients' lives. Harm Reduct J. 2021;18(1):88.
3. Al-Tayyib AA, Koester S. Injection drug users' experience with and attitudes toward methadone clinics in Denver, CO. J Subst Abuse Treat. 2011;41(1):30-6.
4. Sohler NL, Weiss L, Egan JE, López CM, Favaro J, Cordero R, et al. Consumer attitudes about opioid addiction treatment: a focus group study in New York City. J Opioid Manag. 2013;9(2):111-9.
5. Villafranca SW, McKellar JD, Trafton JA, Humphreys K. Predictors of retention in methadone programs: a signal detection analysis. Drug Alcohol Depend. 2006;83(3):218-24.
6. Gomes T, Campbell TJ, Kitchen SA, Garg R, Bozinoff N, Men S, et al. Association Between Increased Dispensing of Opioid Agonist Therapy Take-Home Doses and Opioid Overdose and Treatment Interruption and Discontinuation. Jama. 2022;327(9):846-55.
7. Bell J, Strang J. Medication Treatment of Opioid Use Disorder. Biol Psychiatry. 2020;87(1):82-8.
8. Bartoszko J, Strike CJ. Primary care and methadone patients in treatment for five years or more: The patient and physician perspective. Toronto, ON: CPSO; 2012.
9. Connery HS. Medication-assisted treatment of opioid use disorder: review of the evidence and future directions. Harv Rev Psychiatry. 2015;23(2):63-75.
10. Timko C, Schultz NR, Cucciare MA, Vittorio L, Garrison-Diehn C. Retention in medication-assisted treatment for opiate dependence: A systematic review. J Addict Dis. 2016;35(1):22-35.
11. Kimmel S, Bach P, Walley AY. Comparison of Treatment Options for Refractory Opioid Use Disorder in the United States and Canada: a Narrative Review. J Gen Intern Med. 2020;35(8):2418-26.
12. Bruneau J, Ahamad K, Goyer M-È, Poulin G, Selby P, Fischer B, et al. Management of opioid use disorders: a national clinical practice guideline. Canadian Medical Association Journal. 2018;190(9):E247-E57.
13. Centre for Addiction and Mental Health. Opioid Agonist Therapy: A Synthesis of Canadian Guidelines for Treating Opioid Use Disorder. Toronto, ON. 2021. Available from: **www.camh.ca**
14. Mitchell TB, White JM, Somogyi AA, Bochner F. Comparative pharmacodynamics and pharmacokinetics of methadone and slow-release oral morphine for maintenance treatment of opioid dependence. Drug Alcohol Depend. 2003;72(1):85-94.

15. Ontario Agency for Health Protection and Promotion (Public Health Ontario), Office of the Chief Coroner, Ontario Forensic Pathology Service, Ontario Drug Policy Research Network. Opioid mortality surveillance report: analysis of opioid-related deaths in Ontario July 2017-June 2018. Toronto, ON: Queen's Printer for Ontario; 2019. Available from: **https://www.publichealthontario.ca/-/media/documents/O/2019/opioid-mortality-surveillance-report.pdf**

16. British Columbia Coroners Service. BC Coroners Service Death Review Panel: A review of illict drug overdose. Vancouver, BC: Government of British Columbia; 2018. Available from: **https://www2.gov.bc.ca/assets/gov/birth-adoption-death-marriage-and-divorce/deaths/coroners-service/death-review-panel/bccs_illicit_drug_overdose_drp_report.pdf**

17. British Columbia Centre on Substance Use. Opioid Use Disorder Practice Update. Vancouver, BC: British Columbia Centre on Substance Use; 2022. Available from: **https://www.bccsu.ca/wp-content/uploads/2022/02/Opioid-Use-Disorder-Practice-Update-February-2022.pdf**

18. Bromley L, Kahan M, Regenstreif L, Srivastava A, Wyman J. Methadone treatment for people who use fentanyl: Recommendations. Toronto, ON: META:PHI; 2021. Available from: **www.metaphi.ca**

19. Socias ME, Wood E. Evaluating Slow-Release Oral Morphine to Narrow the Treatment Gap for Opioid Use Disorders. Ann Intern Med. 2018;168(2):141-2.

20. Pearce LA, Min JE, Piske M, Zhou H, Homayra F, Slaunwhite A, et al. Opioid agonist treatment and risk of mortality during opioid overdose public health emergency: population based retrospective cohort study. BMJ. 2020;368:m772.

21. Jegu J, Gallini A, Soler P, Montastruc JL, Lapeyre-Mestre M. Slow-release oral morphine for opioid maintenance treatment: a systematic review. Br J Clin Pharmacol. 2011;71(6):832-43.

22. Ferri M, Minozzi S, Bo A, Amato L. Slow-release oral morphine as maintenance therapy for opioid dependence. Cochrane Database Syst Rev. 2013(6):Cd009879.

23. Mosdøl A, Ding KY, Hov L. NIPH Systematic Reviews. Alternative Opioid Agonists in the Treatment of Opioid Dependence: A Systematic Review. Oslo, Norway: Knowledge Centre for the Health Services at The Norwegian Institute of Public Health (NIPH); 2017.

24. Klimas J, Gorfinkel L, Giacomuzzi SM, Ruckes C, Socias ME, Fairbairn N, et al. Slow release oral morphine versus methadone for the treatment of opioid use disorder. BMJ Open. 2019;9(4):e025799.

25. Lim J, Farhat I, Douros A, Panagiotoglou D. Relative effectiveness of medications for opioid-related disorders: A systematic review and network meta-analysis of randomized controlled trials. PLoS One. 2022;17(3):e0266142.

26. Busch M, Klein C, Uhl A, Haltmayer H, Cabanis M, Westenberg JN, et al. Retention in the Austrian opioid agonist treatment system: a national prospective cohort study. Harm Reduct J. 2021;18(1):25.

27. Lehmann K, Kuhn S, Baschirotto C, Jacobsen B, Walcher S, Gorne H, et al. Substitution treatment for opioid dependence with slow-release oral morphine: Retention rate, health status, and substance use after switching to morphine. J Subst Abuse Treat. 2021;127:108350.

28. Verthein U, Beck T, Haasen C, Reimer J. Mental symptoms and drug use in maintenance treatment with slow-release oral morphine compared to methadone: results of a randomized crossover study. Eur Addict Res. 2015;21(2):97-104.

29. Bond AJ, Reed KD, Beavan P, Strang J. After the randomised injectable opiate treatment trial: post-trial investigation of slow-release oral morphine as an alternative opiate maintenance medication. Drug Alcohol Rev. 2012;31(4):492-8.

30. Kastelic A, Dubajic G, Strbad E. Slow-release oral morphine for maintenance treatment of opioid addicts intolerant to methadone or with inadequate withdrawal suppression. Addiction. 2008;103(11):1837-46.

31. Hammig R, Kohler W, Bonorden-Kleij K, Weber B, Lebentrau K, Berthel T, et al. Safety and tolerability of slow-release oral morphine versus methadone in the treatment of opioid dependence. J Subst Abuse Treat. 2014;47(4):275-81.

32. Falcato L, Beck T, Reimer J, Verthein U. Self-reported cravings for heroin and cocaine during maintenance treatment with slow-release oral morphine compared with methadone: a randomized, crossover clinical trial. J Clin Psychopharmacol. 2015;35(2):150-7.

33. Mitchell TB, White JM, Somogyi AA, Bochner F. Slow-release oral morphine versus methadone: a crossover comparison of patient outcomes and acceptability as maintenance pharmacotherapies for opioid dependence. Addiction. 2004;99(8):940-5.

34. Moazen-Zadeh E, Ziafat K, Yazdani K, Kamel MM, Wong JSH, Modabbernia A, et al. Impact of opioid agonist treatment on mental health in patients with opioid use disorder: a systematic review and network meta-analysis of randomized clinical trials. Am J Drug Alcohol Abuse. 2021;47(3):280-304.

35. Eder H, Jagsch R, Kraigher D, Primorac A, Ebner N, Fischer G. Comparative study of the effectiveness of slow-release morphine and methadone for opioid maintenance therapy. Addiction. 2005;100(8):1101-9.

36. Brothers TD, Fraser J, MacAdam E, Morgan B, Webster D. Uptake of slow-release oral morphine as opioid agonist treatment among hospitalised patients with opioid use disorder. Drug Alcohol Rev. 2022;41(2):430-4.

37. Mercadante S, Porzio G, Ferrera P, Fulfaro F, Aielli F, Verna L, et al. Sustained-release oral morphine versus transdermal fentanyl and oral methadone in cancer pain management. Eur J Pain. 2008;12(8):1040-6.

38. Fischer G, Jagsch R, Eder H, Gombas W, Etzersdorfer P, Schmidl-Mohl K, et al. Comparison of methadone and slow-release morphine maintenance in pregnant addicts. Addiction. 1999;94(2):231-9.

39. Rodger L, Nader M, Turner S, Lurie E. Initiation and Rapid Titration of Methadone and Slow-Release Oral Morphine (SROM) in an Acute Care, Inpatient Setting: A Case Series. Preprint (Version 1) [Internet]. 2022. Available from: **https://www.researchsquare.com/article/rs-1638638/v1**

40. Cherny N. Is oral methadone better than placebo or other oral/transdermal opioids in the management of pain? Palliat Med. 2011;25(5):488-93.

41. Giacomuzzi S, Kemmler G, Ertl M, Riemer Y. Opioid addicts at admission vs. slow-release oral morphine, methadone, and sublingual buprenorphine maintenance treatment participants. Subst Use Misuse. 2006;41(2):223-44.

42. Etaee F, Tobin M, Vuppala S, Komaki A, Delisle BP, Di Biase L, et al. Effects of opioid receptor agonist and antagonist medications on electrocardiogram changes and presentation of cardiac arrhythmia: review article. J Interv Card Electrophysiol. 2022;63(2):471-500.

43. Treece JM, Madani MA, Khoury GE, Khraisha O, Martin JE, Baumrucker SJ, et al. Comprehensive Review on Methadone-Induced QT Prolongation and Torsades. Journal of Pharmacology and Pharmacotherapeutics. 2018;9(2):66-75.

44. McCance-Katz EF, Sullivan LE, Nallani S. Drug interactions of clinical importance among the opioids, methadone and buprenorphine, and other frequently prescribed medications: a review. Am J Addict. 2010;19(1):4-16.

45. Strouse TB. Pharmacokinetic drug interactions in palliative care: focus on opioids. J Palliat Med. 2009;12(11):1043-50.

46. Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. J Addict Med. 2015;9(5):358-67.

47. BGP Pharma ULC. Product monograph: Kadian capsules. 2015.

48. Chandok N, Watt KD. Pain management in the cirrhotic patient: the clinical challenge. Mayo Clin Proc. 2010;85(5):451-8.

49. Horman J, Plessis-Bélair M-C, Schurter E. Guide to Using Slow-Release Oral Morphine (Kadian®) in Opioid Agonist Therapy (OAT). In: dépendances Iusl, editor. Montréal, QC2021.

50. British Columbia Centre on Substance Use. Treatment of Opioid Use Disorder During Pregnancy: Guideline Supplement. Vancouver, BC: British Columbia Centre on Substance Use; 2018. Available from: **https://www.bccsu.ca/wp-content/uploads/2018/06/OUD-Pregnancy.pdf**

51. Opioids and serotonergic medicines: some combinations may increase the risk of serotonin syndrome. Prescriber Update [Internet]. 2022; 43(3):[32-4 pp.].

52. Foong AL, Grindrod KA, Patel T, Kellar J. Demystifying serotonin syndrome (or serotonin toxicity). Can Fam Physician. 2018;64(10):720-7.

53. Institut national d'excellence en santé et en service sociaux (INESSS). Opioid use disorder: Optimal usage guide. Québec, QC: Gouvernement du Québec; 2021. Available from: **https://www.inesss.qc.ca/fileadmin/doc/INESSS/Rapports/Medicaments/GUO_TUO_EN.pdf**

54. British Columbia Centre on Substance Use, BC Ministry of Health, BC Ministry of Mental Health and Addiction. A Guideline for the Clinical Management of Opioid Use Disorder. Vancouver, BC: British Columbia Centre on Substance Use; in press.

55. Vasilev GN, Alexieva DZ, Pavlova RZ. Safety and efficacy of oral slow release morphine for maintenance treatment in heroin addicts: a 6-month open noncomparative study. Eur Addict Res. 2006;12(2):53-60.

56. Turner SD, Lurie E, Nader M. Rapid Methadone and Concurrent Slow-Release Oral Morphine Titration in a Pregnant Fentanyl User. Canadian Journal of Addiction. 2021;12(1):29-33.

57. Ghosh SM, Klaire S, Tanguay R, Manek M, Azar P. A Review of Novel Methods To Support The Transition From Methadone and Other Full Agonist Opioids To Buprenorphine/Naloxone Sublingual In Both Community and Acute Care Settings. Canadian Journal of Addiction. 2019;10(4):41-50.

58. British Columbia Centre on Substance Use, British Columbia Ministry of Health. A Guideline for the Clinical Management of Opioid Use Disorder. Vancouver, BC: British Columbia Centre on Substance Use; 2017. Available from: **https://www.bccsu.ca/opioid-use-disorder/**

59. Baschirotto C, Lehmann K, Kuhn S, Reimer J, Verthein U. Switching opioid-dependent patients in substitution treatment from racemic methadone, levomethadone and buprenorphine to slow-release oral morphine: Analysis of the switching process in routine care. J Pharmacol Sci. 2020;144(1):9-15.

60. Lam V, Latreille S, McLeod A, Munro C, Wyman J, Zhang M. A new framework for methadone carries: A person-centered evidence-informed approach to methadone take-home "carry" dosing. Toronto, ON: META:PHI; 2023. Available from: **www.metaphi.ca**

61. Larney S, Peacock A, Mathers BM, Hickman M, Degenhardt L. A systematic review of injecting-related injury and disease among people who inject drugs. Drug Alcohol Depend. 2017;171:39-49.

62. Bertin C, Delorme J, Riquelme M, Peyrière H, Brousse G, Eschalier A, et al. Risk assessment of using off-label morphine sulfate in a population-based retrospective cohort of opioid-dependent patients. Br J Clin Pharmacol. 2020;86(12):2338-48.

63. Peyriere H, Nogue E, Eiden C, Frauger E, Charra M, Picot MC. Evidence of slow-release morphine sulfate abuse and diversion: epidemiological approaches in a French administrative area. Fundam Clin Pharmacol. 2016;30(5):466-75.

64. British Columbia Centre on Substance Use, BC Ministry of Health, Ministry of Mental Health and Addictions. Urine Drug Testing in Patients Prescribed Opioid Agonist Treatment—Breakout Resource 2021. Available from: **https://www.bccsu.ca/opioid-use-disorder/**

65. Stefan C. Urine drug testing. In: Selby P, Rieb L, Lam V, Zhang M, Bertram J, editors. Opioid Agonist Therapy: A Prescriber's Guide to Treatment. 3rd ed. Toronto, ON: CAMH; 2022.

66. Marshall K, Maina G, Sherstobitoff J. Plausibility of patient-centred care in high-intensity methadone treatment: reflections of providers and patients. Addiction Science & Clinical Practice. 2021;16(1):42.

67. Roux P, Carrieri MP, Keijzer L, Dasgupta N. Reducing harm from injecting pharmaceutical tablet or capsule material by injecting drug users. Drug Alcohol Rev. 2011;30(3):287-90.

68. Keijzer L. Reducing harm through the development of good preparation practices for the injection of slow release morphine sulphate capsules. Harm Reduction Journal. 2020;17(1):48.

69. McLean S, Bruno R, Brandon S, de Graaff B. Effect of filtration on morphine and particle content of injections prepared from slow-release oral morphine tablets. Harm Reduction Journal. 2009;6(1):37.

www.metaphi.ca