

# Opioid Agonist Therapy Guidelines for Manitoba Pharmacists

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COLLEGE OF  
PHARMACISTS  
OF MANITOBA

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## Part One: Summary of Methadone and Buprenorphine for Opioid Agonist Therapy and Analgesia

Methadone and buprenorphine are both used for opioid agonist therapy (OAT) and analgesia in adults. These guidelines will focus on the use of methadone and buprenorphine for OAT, but will very briefly discuss the use of methadone for pain management.

### Treatment Choices

- a. *OAT*: Health Canada has approved several commercially available methadone oral liquid concentrates for opioid agonist therapy.

The following products are to be used when patients are prescribed methadone for opioid use disorder:

Methadose™ 10mg/ml oral liquid	DIN 2394596
Methadose™ Sugar Free 10mg/ml oral liquid	DIN 2394618
Metadol-D® 10 mg/ml oral concentrate	DIN 2244290

Methadone powder in preparation of an oral solution can no longer be used now that commercially available products are available.

Please see **Appendix A** for the information sent to pharmacists from Manitoba Health, Seniors and Active Living regarding the methadone reimbursement procedure.

#### Further Dilution of Methadone:

Methadose™ 10mg/ml oral liquid (red, cherry flavour) does not require further dilution. However, it may be diluted further if deemed necessary by the pharmacist or prescriber.

Methadose™ Sugar Free 10mg/ml oral liquid and Metadol-D® 10 mg/ml oral concentrate **must** be diluted further with a suitable crystalline diluent to a total volume of 60 to 100mL final volume. Dilution of the unflavored formulation with distilled water is **not** appropriate.

Buprenorphine is also indicated for opioid agonist therapy in adults with opioid use disorder. Buprenorphine is available in combination with naloxone as 2 mg and 8 mg sublingual tablets in a 4:1 ratio (buprenorphine:naloxone). Buprenorphine alone is available only through Health Canada via the Special Access program.

- b. *Analgesia*: Metadol® is a commercially available product indicated for pain management by Health Canada. Methadone compounded into a capsule formulation is not a benefit through the Provincial Drug Program.

Please see **Appendix A** for the information sent to pharmacists from Manitoba Health, Healthy Living and Seniors regarding the methadone reimbursement procedure for methadone for pain management.

## Knowledge, Skill and Judgement

Pharmacists must be knowledgeable in all aspects of methadone and/or buprenorphine use when involved in the care of patients with opioid use disorder. Section 18 of the Pharmaceutical Regulation states that a member may only engage in the aspects of pharmacy practice that he or she has the requisite knowledge, skill and judgment to provide or perform and that are appropriate to his or her area of practice.

- a. *OAT*: The expectation is that the pharmacist will be knowledgeable in the use of methadone and buprenorphine for OAT. At least one pharmacist at each pharmacy shall have specialized training in OAT. If this is not possible (i.e. first 6 months) a “trained” pharmacist shall function as a mentor from another location in the interim until a pharmacist at that site has taken the training. The pharmacist with specialized training at a pharmacy is responsible for training all pharmacists who will be dispensing methadone and/or buprenorphine. For further information on the accepted training programs, please see the section on “Education and Training”.
- b. *Analgesia*: Where methadone is used for pain, the expectation is that the pharmacist will be knowledgeable in the use of methadone for analgesia. Specialized training should be considered for use of methadone for analgesia in a similar manner to methadone used for opioid use disorder. A suggested resource is the free, online, accredited course, “Methadone for Pain in Palliative Care”. For more information, please see [www.methadone4pain.ca](http://www.methadone4pain.ca).

## References

Pharmacists must have onsite or readily available references and treatment guidelines when dispensing methadone or buprenorphine for harm reduction and/or analgesia.

- a. *OAT*: Minimum requirements onsite include the College of Pharmacists of Manitoba (CPhM) “Opioid Agonist Therapy Guidelines for Manitoba Pharmacists” and the College of Physicians and Surgeons of Manitoba’s (CPSM) “[Manitoba Methadone and Buprenorphine Maintenance: recommended practice](#)” guidelines and/or standards and a reference similar to that offered by the Centre for Addiction and Mental Health’s (CAMH) “[Opioid Agonist Maintenance Treatment: A pharmacist’s guide to methadone and buprenorphine for opioid use disorder](#)”;
- b. *Analgesia*: Minimum requirements onsite include the CPhM “Opioid Agonist Therapy Guidelines for Manitoba Pharmacists” and the College of Physicians and Surgeons of Manitoba’s (CPSM) “[Manitoba Methadone and Buprenorphine Maintenance: recommended practice](#)” guidelines and/or standards.

## Witnessed Ingestion

- a. *OAT*: With respect to witnessed ingestion doses for methadone and buprenorphine, the pharmacist must directly observe the patient ingesting the medication and be assured that the entire dose of methadone has been swallowed or buprenorphine has been absorbed. A pharmacist must be present and witness release. The pharmacist must assess the patient, observe ingestion and engage the patient in a short conversation to ensure that the entire dose has been ingested. Witnessed doses of methadone and buprenorphine for harm reduction must be observed, logged with date and time in a patient specific, patient identified and confidential manner.
- b. *Analgesia*: Not applicable

## Delegation

- a. *OAT*: The act of witnessing the ingestion of methadone and buprenorphine within a pharmacy for opioid agonist therapy **cannot** be delegated by a pharmacist to a non-pharmacist staff member (technicians, assistants, etc.). A pharmacist can defer witnessing, to a methadone/buprenorphine prescriber at an established harm reduction program or another pharmacist. Under a [new federal exemption](#), all nursing designations when providing health care within a community health facility can now witness administration of methadone and buprenorphine products
- b. *Analgesia*: Not applicable.

## Deliveries

- a. *OAT*: Deliveries of methadone or buprenorphine directly to the patient by the pharmacy are generally not acceptable. If in the professional judgement of the pharmacist and upon approval from the prescriber it is determined that delivery is necessary, individual case-by-case review with justification and documentation is required. However, since the witnessing of ingestion cannot be delegated by a pharmacist, delivery to a patient and witnessing must be done by a pharmacist.

Deliveries to a facility defined under the Narcotic Control Regulations as a hospital: Pharmacists are permitted to transfer custody of narcotics, including methadone and buprenorphine, to a federally or provincially operated facility that provides health care services (i.e. hospital or prison), pursuant to a written order signed and dated by a pharmacist in charge at the facility, or a practitioner authorized by the facility to sign the order.

Deliveries to a community health facility: In 2018, Health Canada authorized two new federal [Section 56 exemptions](#) related to supplies of narcotics, including methadone and buprenorphine, to a community health facility. A community health facility is defined as a facility where health services are delivered and managed by a nurse as part of the nurse's professional practice and could be outside the scope of a hospital or prison. Examples would include a health facility in a First Nations community or a harm reduction program with a nurse providing care. Pharmacies can supply methadone and buprenorphine (both patient

specific doses and orders for clinic/ward stock) to a community health facility. Nurses at the facility can receive, provide and witness administration of these medications. Please review the section on Community Health Facilities later in this OAT Guidelines document for more information.

- b. *Analgesia*: Deliveries may be undertaken with the same precautions afforded narcotics of a similar nature and can be accepted by an agent (if appropriate).

## **Policy and Procedures Manual**

A site-specific Policy and Procedures Manual should be readily available onsite when methadone or buprenorphine is dispensed for OAT and/or methadone is dispensed for the management of pain.

## **Labelling**

All patient labels will be compliant with the provisions of *The Pharmaceutical Act and Regulations*.

- a. *OAT*: Buprenorphine and methadone labels must be clearly labelled with the patient name, dosage, proper instructions for administration, and the start and end dates. Methadone labels must also indicate the total dosage (mg) in the bottle with a notation that the dosage was made up to a set volume (if applicable), the ingestion dates, and initials of the pharmacist who verified the measured doses.
- b. *Analgesia*: Labelling needs to be completed as per a regular prescription.

## **Private Area**

- a. *OAT*: A confidential area in the pharmacy for counselling and observation of ingestion is required.
- b. *Analgesia*: An area suitable for confidential counselling is required by the CPhM Standards and Practice Direction in all pharmacies for all prescription and non-prescription medication.

## **Equipment**

It is recommended that all devices and equipment used for methadone preparation be used only for methadone.

## **Tamper Proof Seals**

Individual methadone doses delivered offsite (i.e. to an institution) must be sealed with a tamper-proof seal.

## **Carries**

It is recommended that bottles/containers for carries are returned to the pharmacy and accounted for prior to issuing further carries to prevent diversion. These bottles are not to be reused but disposed of in a safe and appropriate manner.

## Part Two: Introduction to Opioid Agonist Therapy

### Introduction

These guidelines provide an overview of the pharmacist's role in opioid agonist therapy (OAT) in Manitoba. They are intended to provide a standard framework for successfully integrating this important program into practice.

Two of the medications available for OAT include methadone and buprenorphine. Methadone and buprenorphine can bring normal functioning back to an individual with opioid use disorder since they are opioids that cause little to no euphoric effects. Additionally, these medications have a long half-life to enable suppression of the withdrawal symptoms and cravings of opioid addiction that often contribute to relapse. The choice of therapy between these two options will depend on a number of patient factors including (but not limited to):

- Severity of opioid use disorder and tolerance,
- Potential risk of harm from the chosen therapy including the risk of non-compliance,
- Concomitant health conditions and comorbidities,
- Potential for significant drug interactions with other concomitant therapies,
- Ability to access the specialized services and expertise of an opioid dependence program,
- Response to therapy,
- Ability to afford the chosen therapy,
- Lifestyle and social history<sup>1</sup> and
- Patient preference.

There are an increasing number of OAT patients in Manitoba as well as pharmacies that dispense OAT. Methadone maintenance treatment (MMT) in Manitoba began in 1970 with the treatment of one heroin addict<sup>1</sup>. In 2007, the number of patients receiving MMT in Manitoba was nearly 500.<sup>2</sup> It was estimated that there were approximately 1,200 methadone patients in Manitoba in 2014.<sup>3</sup> The provision of OAT in practice can be both rewarding and challenging.

### Harm Reduction Philosophy

The Manitoba OAT programs are based on the harm reduction philosophy. Harm reduction attempts to decrease the harmful consequences of illicit drug use to the individual, family, community and society. The goals of the program are to reduce illicit opioid use, needle sharing, criminal activity, morbidity and mortality associated with addiction.

Methadone and buprenorphine are important therapeutic tools in the treatment of opioid use disorder. They have been shown to be more effective than placebo in decreasing illicit opioid use and imprisonment. Many people stabilized on OAT can return to work or school and become contributing members of society. A portion of these patients may eventually be tapered off the program.

## Overview of Opioid Agonist Treatment

Until 2007, methadone was the only substance approved in Canada for the long term (>180 days) treatment of opioid use disorder. Buprenorphine, a partial  $\mu$ -opioid receptor agonist, can also be used in the treatment of opioid use disorder. Pharmacists are expected to be knowledgeable about both medications prior to dispensing.

Methadone is an oral substitute for opioid narcotics. It prevents withdrawal symptoms and reduces cravings. Oral methadone does not induce euphoria in stabilized patients and it can block or decrease the euphoric response to other opioids. Methadone's long half-life allows it to be dosed once daily for OAT. Since methadone is dispensed from a licensed pharmacy, it is from a safe source and of known dose and purity.

Buprenorphine is a sublingual substitute for opioid narcotics. Much like methadone, buprenorphine prevents withdrawal symptoms, reduces cravings, and blocks the euphoric response from many other opioids. Buprenorphine's long half-life and high affinity to its receptor allows it to be dosed once daily and in some cases on alternate days.

Methadone and buprenorphine-naloxone are also affordable. They are covered by most third-party payers, including Manitoba Pharmacare and the Non-Insured Health Benefits (NIHB) program. While some patients may pay up to several hundred dollars a day for illicit drugs, prescription methadone or buprenorphine-naloxone can cost significantly less.

There are many benefits to OAT, however some people feel it is inconvenient to have a witnessed dose at the pharmacy on a regular basis. Although this may be cumbersome for some patients, it can help to establish a routine which is considered part of the rehabilitation process.

Unfortunately, there continues to be much stigma associated with OAT and many people do not understand how it works. Pharmacists can play an important role in educating the general public and other health care professionals on OAT.

## Criterion for Admission to an OAT Program

Prior to admission to an OAT program, patients should be informed of all other treatment options for their opioid use disorder so they can make an informed decision.

Opioid use disorder is a psychological disorder that is defined in DSM-V<sup>4</sup> as a:

A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. Opioids are often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
4. Craving, or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.

6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous.
9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance
10. Tolerance, as defined by either of the following:
  - a) A need for markedly increased amounts of opioids to achieve intoxication or desired effect.
  - b) A markedly diminished effect with continued use of the same amount of an opioid.

**Note:** This criterion is not considered to be met for those taking opioids solely under appropriate medical supervision.
11. Withdrawal, as manifested by either of the following:
  - a) The characteristic opioid withdrawal syndrome.
  - b) Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms.

**Note:** This criterion is not considered to be met for those taking opioids solely under appropriate medical supervision.

Severity of opioid use disorder is defined in DSM-V using the above criterion and the following scale:

- **Mild:** Presence of 2-3 symptoms.
- **Moderate:** Presence of 4-5 symptoms.
- **Severe:** Presence of 6 or more symptoms.

When considering a patient for OAT, the prescriber will ensure the patient has a significant history of opioid use. This is usually confirmed with a positive urine drug screen and/or other appropriate collateral information. Typically, the patient will have greater than a one-year history of opioid use disorder and have failed abstinence treatment or have a small likelihood of benefit from non-replacement treatment. Prior failure on OAT does not preclude someone from restarting the program. The prescriber will discuss the commitment required for the program and the expectations that he/she has of the patient. The patient will be required to make an informed decision in order to participate in the program.

## Urine Drug Screens

The utility of urine drug screening is twofold. The prescriber will use the test to confirm that the patient *is not* taking illicit drugs and also to confirm that the patient *is* taking methadone or buprenorphine.

If a patient's urine sample is positive for illicit substances it may indicate lifestyle instability. Patients will most likely lose carry privileges if they produce a positive urine sample for illicit

substances. Substances that can affect carry privileges may include the illicit use of opioids, benzodiazepines, cocaine, and amphetamines. If your patient has been prescribed narcotics or benzodiazepines from another practitioner, offer to call the OAT clinic/prescriber on their behalf so that he/she is not penalized for producing a positive urine sample.

The prescriber will also look for a positive methadone metabolite or buprenorphine result on the drug screen. A sample that is negative for methadone metabolite or buprenorphine may indicate that either:

- (a) the patient is not taking his/her opioid dependence treatment properly and may diverting it or ingesting his/her carries early,
- (b) the patient has provided a tampered urine sample that is not from his/her body, or
- (c) the methadone or buprenorphine dose is very low and not being detected on the test.

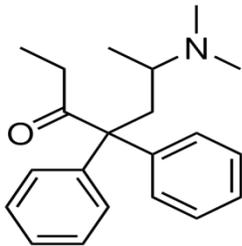
### **Overview of Methadone for Analgesia**

Methadone was originally developed in 1941 by IG Farbenindustrie in Germany. It was marketed in the United States by Eli Lilly as an analgesic by the name of Dolophine®. While methadone is a very effective analgesic, it is important to note that methadone dosed once daily is non-analgesic in a patient stabilized on MMT. Since the analgesic effects of methadone do not last as long as its suppression of opioid withdrawal, it typically needs to be administered every 8 hours for pain control.

## Part Three: Methadone and Buprenorphine Overview

### Pharmacology of Methadone

Methadone is a synthetic opioid that acts as an agonist at the mu-opioid receptor. This action is similar to morphine and heroin; however, it is structurally unrelated.



**Absorption:** Methadone has high oral bioavailability (79% range 35-100) and is quickly absorbed (30 minutes +/-15 minutes). Peak plasma levels of methadone can occur between 1 and 7.5 hours post oral dose (average peak occurs between 2.5 and 4 hours).

**Distribution:** Methadone is lipophilic and highly protein bound. It has a free fraction of 13% however there is significant inter-patient variability. Its volume of distribution is 4L/kg (range 2-13 L/kg).

**Metabolism:** Methadone has a half-life of  $35 \pm 12$  hours. Methadone is primarily metabolized by CYP P450 3A4 and to a lesser extent by 1A2, 2B6, 2C8, 2C9, 2C19, and 2D6. It is also a weak inhibitor of 2D6. Methadone's major metabolite is 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) which is inactive. It has 2 active metabolites that are produced in very small amounts and are not clinically significant.

**Excretion:** Methadone undergoes urinary and fecal excretion. Urinary excretion of methadone increases as the magnitude of the dose increases. Methadone's major metabolite EDDP is also eliminated both in the urine and feces.

Methadone's long half-life allows it to be dosed once daily for opioid agonist therapy. It should be noted that methadone takes 3 to 7 days to reach steady state; for a methadone naïve adult a daily dose as low as 40 mg can be lethal by day 3. Single doses as low as 30 mg have known to be fatal in children.

Tolerance to methadone is lost very quickly and after 3 days of missed doses, the patient must not be given their current maintenance dose. True tolerance to methadone is rarely achieved therefore most people can be maintained on the same maintenance dose for years without requiring an increase.

Cross tolerance of other opioids to methadone is incomplete and erratic. One cannot accurately predict a patient's methadone maintenance dose based on other opioid use nor should tolerance to methadone be assumed when initiating a new patient on methadone.

## Adverse Effects of Methadone

Much of methadone's side effect profile is similar to other opioids. Please see the Methadose™, Metadol-D® or Metadol® product monograph for more information.

Frequently observed but improve with time	Drowsiness, nausea, weight gain, nervousness, appetite changes
Frequently observed and persistent	Constipation, sweating, sleep disturbances, changes in sexual desire/function, dry mouth
Infrequently observed	Vomiting, dizziness, flushing, unsteadiness, itching, myalgias, arthralgias, abdominal cramping, swelling of the feet and ankles, QTc interval prolongation (usually only occurs at higher doses), dental problems

## Drug Interactions with Methadone

Methadone is primarily metabolized by CYP P450 3A4. (It is also metabolized to a lesser extent by CYP 1A2, 2B6, 2C8, 2C9, 2C19 and 2D6.) It is also a weak inhibitor of 2D6. Most interactions will be a result of induction or inhibition of CYP 3A4. Generally, these interactions can be managed by monitoring for signs of toxicity or withdrawal and adjusting the dose accordingly. The sequence of witnessed dosing of the drugs is key to evaluating the significance of the interaction. When a patient is stabilized on a drug that affects liver metabolism and methadone is introduced, the interaction may not be observed unless the drug is discontinued. In a patient on a stable methadone dose, careful consideration and monitoring is required on initiation or discontinuation of a medication known to interact with methadone.

### *Drugs with additive effects*

Extreme caution should be taken when drugs with additive adverse effects are prescribed, particularly those that can cause central nervous system or respiratory depression. In most methadone related deaths, concurrent use of sedatives such as benzodiazepines, over the counter diphenhydramine and dimenhydrinate products, and alcohol were found to have contributed to the cause of death.

### *Opioid antagonists and partial agonists*

Drugs that are opioid antagonists or partial agonists should be avoided in patients stabilized on methadone as they can precipitate withdrawal. Examples of these drugs are buprenorphine, pentazocine, butorphanol, nalbuphine, and naltrexone.

### *QTc Interval Prolongation*

**Methadone at higher doses can prolong the QT interval and concomitant use of other QT interval prolonging agents should be used cautiously.**

**Table 1: Drug Interactions with Methadone**

Drugs that may increase methadone level	
<ul style="list-style-type: none"><li>• Amiodarone</li><li>• Cimetidine</li><li>• Ciprofloxacin</li><li>• Clarithromycin</li><li>• Diazepam</li><li>• Echinacea</li><li>• Erythromycin</li><li>• Ethanol (acute ingestion)</li><li>• Fluconazole</li></ul>	<ul style="list-style-type: none"><li>• Fluvoxamine</li><li>• Grapefruit juice</li><li>• Itraconazole</li><li>• Ketoconazole</li><li>• Nefazodone</li><li>• Paroxetine</li><li>• Sertraline</li><li>• Voriconazole</li><li>• Urinary alkalinizers</li><li>• Other P450 inhibitors</li></ul>
Drugs that may decrease methadone levels	
<ul style="list-style-type: none"><li>• Abacavir</li><li>• Amprenavir</li><li>• Carbamazepine</li><li>• Cocaine</li><li>• Efavirenz</li><li>• Ethanol (chronic ingestion)</li><li>• Fosamprenavir</li><li>• Lopinavir/ritonavir</li><li>• Nelfinavir</li><li>• Nevirapine</li></ul>	<ul style="list-style-type: none"><li>• Phenobarbital</li><li>• Phenytoin</li><li>• Primidone</li><li>• Rifampin</li><li>• Risperidone</li><li>• Ritonavir</li><li>• Saquinavir</li><li>• St. John's wort</li><li>• Urinary acidifiers</li><li>• Other P450 inducers</li></ul>

The above table does not include all possible drug interactions. The table is meant as a guide and does not preclude the use of sound clinical judgment.

## Pharmacology of Buprenorphine and Naloxone

Buprenorphine is a partial opioid agonist at the  $\mu$  (mu) opioid receptor. It is associated with a reduced risk of death in overdose compared to full opioid agonists such as methadone because it has a ceiling effect and therefore a lower incidence of adverse effects such as respiratory depression<sup>5</sup>. Respiratory depression can still occur if used in combination with other medications that cause respiratory depression. Because of the ceiling effect, many clinicians consider buprenorphine to be a safer drug than methadone. However, buprenorphine's ceiling effect may also result in limitations since its effectiveness plateaus once a certain serum level is reached. Higher doses or serum concentrations will not result in additional effect.

Buprenorphine has a high affinity to the mu-opioid receptor and a slow dissociation time. Buprenorphine binds tightly to the mu-opioid receptor and it can block the effects of other opioids including morphine, oxycodone, and methadone.

**Precipitated Withdrawal with Buprenorphine:** When buprenorphine is introduced into a patient who has a full mu-opioid agonist (eg. morphine, oxycodone, methadone) in their system, it can precipitate an opioid withdrawal syndrome. Buprenorphine has both a high affinity and low intrinsic activity (i.e. it is a partial agonist) at the mu-opioid receptor. When buprenorphine replaces the full agonists at the mu-opioid receptor, it creates a net decrease in agonist effect at the receptor thus precipitating withdrawal.

**Absorption:** Buprenorphine is largely ineffective if taken orally due to an extensive first pass effect. Its bioavailability following sublingual administration is 28% to 51%. There is an onset of effects between 30-60 minutes, and peak plasma levels occur at about 90 minutes.

**Distribution:** Buprenorphine has a volume of distribution of 4-5 L/kg. It has an elimination half-life of 28-37 hours and its duration of effects is 48-72 hours. Steady state is reached in 5-10 days.

**Metabolism:** Buprenorphine is metabolized in the liver primarily by CYP3A4, and less by CYP2C8. Conjugated metabolites undergo extensive enterohepatic circulation which likely contributes to buprenorphine's long half-life.

**Excretion:** It is excreted primarily in the feces, but also in the urine.

Buprenorphine is usually dosed once daily. Due to its long half-life, it may be possible in select cases to use alternate day scheduling.

Naloxone is an opioid antagonist that is combined in a 1:4 ratio with buprenorphine to deter the injection of the sublingual tablets. Naloxone is very poorly absorbed orally and sublingually and thus has no clinically significant effects when used either way. If buprenorphine-naloxone is injected into an opioid dependant person, the naloxone component will trigger opioid withdrawal symptoms.

## **Adverse Effects of Buprenorphine**

Patients on buprenorphine may experience adverse effects similar to methadone (see section – Adverse Effects of Methadone) except they may occur to a lesser degree. Buprenorphine has also been demonstrated to carry a lower risk of overdose and death than with methadone.

## **Drug Interactions with Buprenorphine**

Buprenorphine is metabolized primarily by CYP 3A4, and to a lesser extent by CYP 2C8. Any medications that are inhibitors or inducers of these enzymes may cause varying degrees of effect on buprenorphine.

### *Drugs with additive effects to the central nervous system*

Extreme caution should be taken when drugs with additive adverse effects are prescribed, particularly those that can cause central nervous system or respiratory depression. Concurrent use of sedatives such as benzodiazepines and alcohol can markedly increase the risk of death for patients on buprenorphine.

### *QTc Interval Prolongation*

Buprenorphine can increase the QT interval (see <https://crediblemeds.org>), but likely less than with methadone.

## **Dosing Considerations**

### *Methadone:*

OAT with methadone can be divided into 3 phases: the early stabilization phase, the late stabilization phase and the maintenance phase. Overdose death from methadone in patients on methadone maintenance therapy (MMT) is most likely to occur in the early stabilization phase. This is generally due to an overestimation of tolerance and an underestimation of methadone accumulation. As mentioned earlier, cross tolerance to methadone from other opioids is incomplete and unpredictable. **“Dose Equivalency” reference tables should not be used to convert opioid intake to methadone for addiction.**

### *Early Stabilization Phase (0-2 weeks):*

This phase encompasses the first 2 weeks of the program. During this phase patients will be initiated on methadone and gradually titrated upward. The starting dose of methadone is 10-30 mg/day. The lower end of the dosing range (10-20 mg/day) should be used for those patients at higher risk of toxicity (elderly, on a drug that inhibits methadone metabolism, concomitant use of sedating medications).

The methadone dose can be increased by 5-10 mg every 3-4 days as required to suppress opioid cravings and alleviate withdrawal symptoms. It is very important not to increase the dose too quickly as the drug is accumulating for 5 days. The key is to “start low and go slow!” The pharmacist should ensure that the patient is aware of signs of toxicity and what to do about them. During this period, the patient will have all their doses supervised unless the pharmacy or clinic is closed. The pharmacist should be aware that the patient might continue using their drug of choice during this period as methadone will not yet be at a maintenance dose and will wear off before their next dose.

### *Late Stabilization Phase (2-6 weeks):*

This phase encompasses weeks two to six of the program. During this phase, the patient’s dose will be optimized and the use of other opioids should be decreased. Dose adjustments of 5-10 mg every 5 to 7 days are made depending on severity, onset and duration of withdrawal symptoms. Most patients will be on 50-80 mg of methadone during this phase. The patient will still have all doses supervised (unless pharmacy/clinic closed) during this period.

### *Maintenance Phase (6 weeks +):*

This phase encompasses the time period after the initial six weeks. By this time the patient should be on or close to their maintenance dose. The use of other opioids should be largely eliminated and the patient should not experience withdrawal effects for the full 24 hour period. When a patient is receiving their optimal methadone dose, they will not have withdrawal symptoms, opioid cravings will be reduced, euphoria from opioid use will be blocked and the patient will not have any psychomotor or intellectual impairment.

The usual maintenance dose for methadone is between 50-120 mg/day although doses upwards of 200 mg may be required in some patients. Pharmacists should be aware that potential QT interval changes are more likely to occur at doses above 100mg. Professional judgment must be used to evaluate patients who are using other medications that can also prolong the QTc interval.

If dose adjustment is required during this phase, it is usually between 5-10 mg/day every 5 to 14 days. Dosage adjustment may be required if the patient subjectively complains of withdrawal symptoms, if cravings become intense or if they relapse to opioid use. Patients should be cautioned to avoid driving or operating heavy machinery for several hours after dose increases until their body adjusts to the higher dose.

### *Buprenorphine:*

When initiating a patient on buprenorphine, induction can be done more rapidly than with methadone. Buprenorphine is safer during titration because of its partial agonist activity on the mu-opioid receptor. However, clinicians still need to remember that it takes about 5 days to reach steady state, and therefore it will take several days to feel the full effect of a dose.

#### Before first dose:

The patient must be in at least moderate opioid withdrawal before they receive their first dose of buprenorphine (as scored on the Clinical Opiate Withdrawal Scale – see **Appendix B**). This will mitigate any potential precipitated withdrawal that buprenorphine can cause in an opioid-dependent patient. A patient will likely be assessed directly by the prescriber before receiving their first prescription to ensure that they meet these requirements. Any evidence that the patient has used opioids after this assessment should be reported to the prescriber before filling the prescription. If a patient is filling buprenorphine for the first time, it is good practice to verify and document the time a patient took their last dose of opioids, the type of opioid, and, if applicable, the route (oral, IV, or intranasal) the opioid was taken.

The following chart gives suggested times to wait before initiating buprenorphine<sup>iv</sup>:

Type of Opioid	Examples	Time to wait before first dose
Short-Acting	Heroin, Morphine IR	At least 6 hr (12+ hr preferred)
Slow-Release	OxyNeo, Morphine SR	At least 12 hr (24+ hr preferred)
Long-Acting	Methadone	At least 24 hr (36-72 hrs preferred)

#### Day 1 (Initiation):

Ideally, the first dose of buprenorphine should be administered in the morning. The clinician will likely want to reassess the patient throughout the day, and may give a second dose later in the day.

The first dose is usually between 2 to 4 mg (although 6 mg has been used). After 30 to 60 minutes, the patient should be reassessed. A sudden worsening of opioid withdrawal at this stage likely indicates precipitated withdrawal and the patient should not be given a second dose that day. At that point, they may be given supportive therapy, and considered for re-induction at a later time.

If there is no evidence of precipitated withdrawal after one hour, the patient should be reassessed after 3 hours. If the patient's opioid withdrawal has only partially improved, they may be given a second dose of 2 to 4 mg either immediately or for later in the day. The maximum recommended daily dose on Day 1 is 8 mg.

#### Day 2 to Week 2:

On day 2, if opioid withdrawal symptoms have completely subsided, the patient can continue to take the same amount they took on Day 1 as a once-daily dose.

If the patient feels adverse effects on Day 2 (e.g. drowsiness), the dose may be lowered by 2 mg.

If opioid withdrawal symptoms are still being experienced, the dose may be titrated up 2 to 4 mg every 1 to 2 days until the patient is stabilized.

#### Maintenance:

A maintenance dose can usually be reached in one to two weeks. The maximum recommended daily dose in Canada is 24 mg. In some other countries, daily doses as high as 32 mg have been tried, but because of buprenorphine's "ceiling effect", the additional benefits at this dose are debatable<sup>5</sup>.

It is possible in some cases for patients to have less-than-daily dosing with buprenorphine-naloxone, due to its high affinity for the mu-opioid receptor. The maximum daily dose of 24 mg must still not be exceeded if using this method of dosing<sup>v</sup>.

A patient who is stabilized on 8 mg per day could potentially switch to the following regimens:

- 16 mg every second day or
- 16 mg every Monday and Wednesday, and 24 mg every Friday

#### *Extended Methadone/Buprenorphine-naloxone Maintenance*

This phase is only for long term stable patients. These patients have been socially rehabilitated and the intent of the extended program is to allow for more flexibility. Patients on this program meet the following criteria:

- a) Two consecutive years of biopsychosocial stability in a methadone maintenance program.
  - Employment or other socially productive activity
  - Absence of criminality
  - Absence of drug and alcohol abuse
- b) Reliability and honesty in keeping appointments and interactions with clinic staff.
- c) Ability to safely store medications.

These patients are seen less frequently by their methadone/buprenorphine prescriber, once every 1 to 3 months. The patients must have a negative urine drug screen on every visit or they will be reverted back to the standard program. The methadone or buprenorphine-naloxone is dispensed every 2 weeks or monthly and a witnessed dose must be taken at the time of dispensing under supervision of a pharmacist. Tablets may be given as an alternative to liquid methadone, and must be indicated by the prescriber.

#### *Choosing between Methadone and Buprenorphine*

The main advantages of buprenorphine over methadone for medication-assisted treatment of opioid dependence are:

- It is safer in overdose;
- It is associated with an improved safety profile, including less sedation;
- Those dependent on more moderate doses of opioids may reach maintenance doses of buprenorphine more quickly during substitution therapy; and
- It is more portable than methadone solutions.

The main disadvantages for buprenorphine are:

- It is generally less effective in patients who have a tolerance to higher doses of opioids;
- There is a limited range for dose titration due to its ceiling effect;
- It may precipitate severe opioid withdrawal symptoms during the initiation phase or if a patient continues to use other opioids; and
- It is generally more expensive on a dose-for-dose basis than methadone maintenance therapy<sup>5</sup>.

## **Tapering**

A patient may withdraw from OAT voluntarily after treatment goals have been met, voluntarily before treatment goals are met, or involuntarily. Withdrawal from treatment can be for a variety of reasons and pharmacists should take this opportunity to discuss the patient's treatment with them. A pharmacist can play an important role in helping patients manage side effects, etc. The pharmacist should counsel the patient on the risk of relapse of opioid use and encourage the patient to have prevention strategies in place.

### *Methadone:*

The rate of a methadone taper is usually 5-10% of the current dose every one to two weeks. Once the patient reaches 30 mg/day the taper should be slower as withdrawal effects become more pronounced. Many patients can only tolerate decreases of 1 to 2 mg every one to two weeks at this point. Patients should be monitored for signs of withdrawal and the taper should be reversed or held if cravings become too intense.

### *Buprenorphine:*

As with methadone, buprenorphine should be tapered gradually to minimize withdrawal. Tapering buprenorphine-naloxone by 1 to 2 mg per week is often suggested, although this may vary depending on how the patient responds<sup>5</sup>. To facilitate 1 mg changes, the patient or pharmacy may need to split 2 mg tablets. Ensure that any split tablets are stored properly and administered first. If split tablets are given to the patient to take home, they should be instructed to use the split tablets first. If the tablets are handled, this may accelerate the degradation of the tablet.

## **Split Dosing (Methadone only)**

Methadone prescribers may authorize "split doses" for various reasons. A very small proportion of patients may metabolize methadone rapidly (confirmed with a blood test) and some patients may be better able to tolerate the side effects of the methadone if their dose is divided. The metabolism of methadone changes in pregnant women and some may require split doses during the latter half of their pregnancy.

Authorized split doses for patients who must have every dose witnessed require the patient to attend the pharmacy in the morning for a portion of their dose and again in the evening for the remainder. Pharmacists may not dispense a carry of the remainder of the patient's daily dose unless specifically directed to do so by the prescriber in writing. If a patient requests or appears to require split dosing, contact the prescriber for authorization.

## Pregnancy

OAT with methadone is generally considered the standard of care for pregnant women with an opioid use disorder<sup>6</sup>. Buprenorphine is considered an acceptable treatment as well, especially if a patient is stabilized on buprenorphine-naloxone when they become pregnant. Opioid use disorder is dangerous for the fetus and is associated with increased risk of low birth weight, prematurity, neonatal withdrawal and sudden infant death syndrome. Opioid use disorder affects fetal health primarily through effects of variable opioid withdrawal which is associated with fetal compromise and stillbirth<sup>7</sup>. Conversely, OAT is associated with increased birth weight, decreased infant mortality and increased gestational age.

There are more studies that support the safety and efficacy of buprenorphine alone (ie. Subutex<sup>®</sup>) compared to the buprenorphine-naloxone combination product, likely due to a theoretical risk that naloxone might pose a risk to the fetus by elevating maternofetal cortisol levels. However, recent studies show that there are no statistically significant differences between the two formulations in terms of pregnancy and treatment outcomes. Furthermore, pregnancy was recently removed as a contraindication from the Health Canada-approved monograph for buprenorphine-naloxone (i.e. Suboxone). It is unnecessary to switch a patient on buprenorphine-naloxone who becomes pregnant to buprenorphine alone, unless it is clinically indicated or requested by the patient<sup>8</sup>. The prescriber needs to apply to the Special Access Programme of Health Canada to access the buprenorphine monoproduct.

The goal of OAT in pregnancy is to use a dose that will keep the patient comfortable and abstinent from illicit opioids. The patient should be maintained on OAT for the duration of her pregnancy and for several months post-partum. As metabolism changes during pregnancy the patient should be monitored for increased requirements of methadone (10-20 mg) and/or buprenorphine or the need to split the dosing (methadone only). Pharmacists can play an important role in determining when the patient needs a dose change as they will follow the patient on a daily basis. Adjustment of the dose post-partum may be required. Pharmacists can also guide the patient in making healthy lifestyle changes during this period and recommend additional resources to the patient when appropriate/necessary.

Pregnant women should *not* miss a dose of methadone or buprenorphine. The withdrawal symptoms associated with missing a dose may cause fetal distress. If a patient on methadone is feeling nauseous, recommend that she sip the methadone slowly as this may prevent emesis of the dose. It might also be beneficial for the patient to use an anti-nauseant preventatively. In some situations, it may be advisable to have the woman remain in the pharmacy until the methadone dose is absorbed. If emesis occurs during this period, then you can accurately assess what portion of the dose should be replaced. The prescriber should be contacted immediately and a replacement dose ordered. If emesis occurs after a buprenorphine dose is fully absorbed sublingually, it does not need to be replaced.

Methadone and buprenorphine cross the placental barrier and, therefore, the newborn should be monitored closely for signs of neonatal abstinence syndrome and treated with medical care.

## Breastfeeding

It is important that pharmacists continue to work collaboratively with both the methadone/buprenorphine-naloxone prescriber and patient to identify and assess the potential benefits and risks of breastfeeding while on OAT. Currently, definitive safety information is conflicting, however, pharmacists are encouraged to stay current on the latest information as more research is undertaken.

Methadone is considered compatible with breastfeeding according to the American Pediatric Society<sup>9</sup>. Even though the amount of methadone present in the breast milk is very small, it is important that the patient and their prescriber discuss the risks and benefits of breastfeeding while being maintained on methadone. There appears to be a benefit to the mother and infant, including the promotion of bonding and passing of nutrients and immunity. Because the amount of methadone in the breast milk is very small, it will not necessarily prevent all symptoms of neonatal abstinence syndrome.

However, in August 2018, Health Canada published a Summary Safety Review on Methadose and Metadol-D assessing the potential risk of serious harm in children exposed to methadone through breast milk. The Summary Safety Review can be found on the Health Canada [website](#).

There is less evidence on the safety and/or benefit of breastfeeding while using buprenorphine-naloxone. Currently, the monographs for buprenorphine-naloxone products do not recommend breastfeeding while using the product. However, the entry for “buprenorphine” at LACTMED (<http://toxnet.nlm.nih.gov>) (last revised in 2017) indicates that buprenorphine is compatible with breastfeeding. The entry for “naloxone” at LACTMED (last revised in 2015) indicates that if naloxone is required by the mother, it is not a reason to discontinue breastfeeding.

## Treatment of Acute Pain

Methadone and buprenorphine should not be considered treatments for acute pain in a person stabilized on OAT. A common misconception among health care professionals is that if a person is on methadone or buprenorphine then they do not need to be treated for their pain. Unfortunately, due to the stigma associated with drug addiction many of these patients are managed inappropriately when they present with acute pain. As many of these patients will have a history of drug seeking behavior, the problems in assessing and treating pain in somebody who is on OAT are at least threefold:

1. The objective assessment of a subjective phenomenon (pain).
2. The question whether the pain presentation of the patient suffering from opiate dependence is in fact “drug seeking” or a genuine request for relief of real pain.
3. The appropriate dose of opiate or other analgesics or adjuncts in a methadone or buprenorphine-maintained patient.

The first and second problems are best dealt with by a thorough and objective assessment of the presenting illness and its correlated pain. This is a matter of clinical judgement and includes making one’s best estimate as to the appropriate treatment for similar causes of pain in other patients.

For mild to moderate acute pain, recommend the use of NSAIDs and acetaminophen as first line therapy. These should be prescribed in the usual dosages and frequency.

For more severe acute pain, patients may be initiated on opioid analgesics (morphine, oxycodone, hydromorphone, or codeine) in doses similar to those used for other people with similar pain. Monitor the patient's pain level and adjust the dosing accordingly. Patients stabilized on OAT (greater than 3 months) will likely require higher doses (10-50%) and more frequent dosing of short acting opioids. The patient should be maintained on their usual dose of methadone or buprenorphine while being treated for acute pain. Ideally discussion should occur between any practitioner prescribing a new opioid for these patients and the methadone/buprenorphine prescriber. In addition, the pharmacist should consider notifying the methadone/buprenorphine prescriber if a patient receives a new prescription for an opioid from another practitioner.

Pentazocine, nalbuphine, and buprenorphine are partial opiate antagonists and should not be administered to patients using methadone as they will cause severe opiate withdrawal.

Tighter control of opioid prescriptions required by a patient on OAT might be achieved by:

- (a) filling the prescription at the same pharmacy that they receive their opioid agonist therapy;
- (b) dispensing the opioid more frequently (eg. daily); and
- (c) using a formulation that is less likely to be used intranasally or intravenously<sup>v</sup>.

## Overdose

Methadone overdose is a medical emergency as is any other opioid overdose. Methadone overdose is characterized by extreme sedation, stupor or coma, respiratory depression, bradycardia and hypotension. Naloxone, an opioid antagonist, is used to treat methadone overdose. The difficulty in treating a methadone overdose is the exceptionally long half-life of methadone. A naloxone infusion should be considered over repeated bolus dosing. Naloxone should be administered for a minimum of 24 hours (up to several days) followed by at least 12 hours of monitoring after the infusion is stopped. Naloxone competitively inhibits methadone at the opioid receptor thus the infusion is required until sufficient time has passed that the patient's own metabolism has cleared the methadone out of his/her system. Care should be taken to titrate the naloxone slowly so as not to precipitate severe withdrawal in the patient.

Buprenorphine is also known to cause overdose, much in the same way that other opioids can cause overdose. However, the risk of respiratory depression and sedation from buprenorphine on its own is much less than with other opioids because buprenorphine is a partial agonist and exhibits a ceiling effect in its dose response curve. The risk of overdose with buprenorphine becomes much higher when mixed with benzodiazepines. Reversing a buprenorphine overdose can be problematic because of its high affinity for the mu-opioid receptor. Naloxone, when administered in overdose, may only partially reverse the respiratory depressant effects because it needs to compete with buprenorphine at mu-opioid receptors<sup>5</sup>.

## Chronic Viral Infections and OAT

OAT is important from both an individual and public perspective with respect to HIV/AIDS and hepatitis C. As discussed earlier, opioid agonist therapy is a harm reduction strategy aimed at reducing the spread of diseases (including HIV/AIDS and hepatitis C) through needle sharing and prostitution. For the individual, OAT can help stabilize the patient and thus increase compliance with HIV medications. Many HIV medications can interact with methadone and buprenorphine, but these interactions can generally be managed by monitoring for side effects and adjusting the dose accordingly. It is especially important to closely monitor patients when their medication or dose changes or is discontinued. The pharmacist can play an important role in encouraging compliance with these medications on a regular basis. Helping this patient population manage side effects is equally important and can have a huge impact on quality of life.

## Recommended Readings

Pharmacists must have onsite or readily available references and treatment guidelines. Minimum requirements include the College of Pharmacists of Manitoba “Guidelines to Opioid Agonist Therapy for Manitoba Pharmacists”, the College of Physicians and Surgeons of Manitoba Recommended Practices “[Manitoba Methadone and Buprenorphine Maintenance](#)” document, and a resource similar to the Centre for Addiction and Mental Health (CAMH) guide: Isaac P. et al. “[Opioid Agonist Maintenance Treatment: A pharmacist’s guide to methadone and buprenorphine for opioid use disorder](#)”, 3rd Edition. Toronto: Centre for Addiction and Mental Health (CAMH), 2016. Pharmacists dispensing buprenorphine-naloxone should also review the CAMH document “[Buprenorphine/Naloxone for Opioid Dependence: Clinical Practice Guideline](#)”.

A list of additional resources can be found on the Centre for Addiction and Mental Health website at

- [http://www.camh.ca/en/education/about/services/camh\\_library/Documents/RLGmethadone.pdf](http://www.camh.ca/en/education/about/services/camh_library/Documents/RLGmethadone.pdf)
- [http://www.camh.ca/en/hospital/health\\_information/a\\_z\\_mental\\_health\\_and\\_addiction\\_in\\_formation/buprenorphine/Pages/default.aspx](http://www.camh.ca/en/hospital/health_information/a_z_mental_health_and_addiction_in_formation/buprenorphine/Pages/default.aspx)

## Part Four: Implementing Opioid Agonist Therapy in Pharmacy Practice

### Including OAT in your Pharmacy Practice

A patient's success with OAT can be linked to the interactions they have with their health care providers. All members of the health care team should monitor the patients' progress and recommend changes to their care as needed. Pharmacists must have a clear understanding of the goals of the program and a willingness to participate fully with other members of the health care team in order to contribute to their patients' success. Pharmacists are in a unique position as they will see the patient more than any other member of the treatment team. These daily interactions allow the pharmacist to monitor their patients' progress and identify actual and potential drug related problems.

#### *Community considerations and workflow*

By including OAT in your pharmacy practice, you are providing a valuable service to your patients and your community. You might choose to provide OAT to a small number of patients, perhaps beginning with those who are already patients of your pharmacy. A confidential area in the pharmacy for counselling and observation of ingestion is required.

If OAT becomes a major focus of your practice, careful planning and diligence may be required to avoid patient line-ups and patient loitering. Line-ups may not be acceptable to the surrounding neighborhood and can focus undue attention on the program. Strategies to reduce line-ups of patients outside your pharmacy include:

- Establish a regular opening time, and stick to it. Do not open the pharmacy a few minutes early because you happen to be in early. If patients begin to arrive early, let them know that they must not loiter in front of the pharmacy before opening.
- Ensure that your waiting area is large enough to accommodate the number of clients you have.
- Consider establishing "appointments" for your patients on OAT. For example, you may want to schedule half of your patients to attend the pharmacy in the morning and the other half to attend in the afternoon.

### Policy and Procedure Manual

A site-specific Policy and Procedures Manual including an OAT policy and procedure must be readily available onsite when OAT is dispensed for harm reduction and/or methadone for the management of pain.

### Education and Training

Pharmacists must be knowledgeable in all pertinent aspects of OAT when involved in care with methadone or buprenorphine to prevent errors and near misses. Section 18 of the Pharmaceutical Regulation states that a member may only engage in the aspects of pharmacy practice that he or she has the requisite knowledge, skill and judgment to provide or perform and that are appropriate to his or her area of practice. At least one pharmacist must be extensively knowledgeable at each pharmacy that provides opioid agonist therapy. The expectation is that one of the required courses listed below will be successfully completed within

6 months of initiating care. The pharmacist with specialized training at a pharmacy is responsible for training all pharmacists who will be dispensing methadone and/or buprenorphine. Successful completion of one of these courses would demonstrate compliance with Section 18 of the Regulation with respect to OAT. An exception to this rule would be for a pharmacy that must provide OAT for continuation of care. In this situation, the pharmacy would have a 6-month grace period to allow a pharmacist to take one of the required courses. In the interim any pharmacy dispensing OAT waiting for specialized training must have a “trained/knowledgeable” pharmacist functioning as a mentor who may be at another pharmacy. Pharmacists who are new to dispensing OAT should also consider asking a trained pharmacist to act as a mentor to help answer any questions they may have or to help set up their practice. Contact CPhM if assistance is needed in finding a mentor.

*Required Training for Dispensing Methadone for OAT:*

The “Opioid Agonist Therapy 101: An introduction to clinical practice” joint training program replaced the “Principles for the Provision of Opioid Dependence Treatment by Manitoba Pharmacists Certificate Program” as the required specialized opioid agonist therapy training for pharmacists dispensing methadone or buprenorphine. The CPhM, in partnership with the College of Physicians and Surgeons of Manitoba (CPSM) and the College of Registered Nurses of Manitoba (CRNM) created this multi-disciplinary training course for care providers who wish to become involved in treating those with opioid use disorder. This collaborative approach enriches discussions during the training process. It ensures that all physicians, nurse practitioners and pharmacists successfully complete training with the same high standard of knowledge and insight into the collaborative approach to treatment that serves this complex patient population best. Training together will hopefully translate into stronger and more frequent interdisciplinary collaboration in clinical practice. The two-day course provides practical knowledge and skill building exercises, including opportunities to practice interviewing mock patients with opioid use disorder in a supportive environment. Please see the CPhM website for more information on the Opioid Agonist Therapy 101 course including future offer dates, pre-requisites, and registration details. To register for the next workshop, please [visit www.cphm.ca/site/pdprograms](http://www.cphm.ca/site/pdprograms) for more information.

Those who previously completed the “Principles for the Provision of Opioid Dependence Treatment by Manitoba Pharmacists Certificate Program” are strongly encouraged to complete the new, updated program, but it is not required.

Please contact the CPhM office if you are wondering if a similar course would meet the training requirement for providing opioid agonist treatment in your practice.

*Required Training for Dispensing Buprenorphine-naloxone (not including methadone) for OAT:*

There are several training options available for pharmacists who just want to dispense buprenorphine-naloxone for OAT. In addition to reviewing The College of Physicians and Surgeons of Manitoba’s publication, “Manitoba Methadone & Buprenorphine Maintenance: Recommended Practice”, found [here](#) and The College of Pharmacists of Manitoba guidelines, “Opioid Agonist Treatment Guidelines for Manitoba Pharmacists”, pharmacists must complete one of the following:

- The two day in-person workshop, “Opioid Agonist Therapy 101: An introduction to clinical practice”, as mentioned above;
- The online, accredited Centre for Addiction and Mental Health (CAMH) program, “Buprenorphine-Naloxone Treatment for Opioid Use Disorder” formerly “Buprenorphine-Assisted Treatment of Opioid Dependence: An Online Course for Front-Line Clinicians”. Please see the CAMH website for more information: <https://www.camh.ca/en/education/continuing-education-programs-and-courses/continuing-education-directory/buprenorphine-naloxone-treatment-for-opioid-use-disorder>; or
- An addiction medicine course offered by the Canadian Society of Addiction Medicine (contact the College for more details).

### **Pharmacist - Practitioner Communication**

The methadone/buprenorphine prescriber, the patient and the pharmacist will enter into a common care plan with the rights, obligations, conditions and consequences agreed upon. A written agreement that is signed by at least the pharmacist and the patient is strongly recommended (see below – “New Patient on Opioid Agonist Therapy”).

Pharmacists who participate in OAT interact with most of their patients on a daily basis. Even those patients with carry privileges see their dispensing pharmacist more often than any other health professional, including their family physician or methadone/buprenorphine prescriber.

In order to ensure that the prescriber is making therapeutic decisions based on reliable information about the patient, you must inform the prescriber if you have concerns about the patient’s progress or success with the program. Contacting the prescriber regarding your concerns is essential to patient care.

There are several situations that should be reported to the prescriber /clinic. The following are examples of reportable situations:

- If a patient exhibits unusual behavior
- If a patient has not picked up their daily dose
- If a patient refuses all or a portion of their daily dose
- If a patient appears to be impaired or intoxicated when they arrive at the pharmacy
- If a patient has filled a prescription for opioids, or other mood-altering medications that have not been previously approved by the methadone/buprenorphine prescriber
- If a patient vomits dose after witnessed dosing (methadone only)
- Failure to provide a lock box
- Breach of treatment agreement

It is good practice to document these communications with the prescriber. This can be done either in an electronic record or on the hard copy of the prescription.

### **Methadone and Buprenorphine Approvals for Prescribers**

In order to prescribe methadone and/or buprenorphine-naloxone for OAT and/or analgesia, an approval must be obtained from the prescriber’s provincial regulatory college. Methadone

exemptions will no longer be obtained through the Office of Controlled Substances, Health Canada, as of May 19, 2018, but provincial requirements for prescribing methadone and buprenorphine remain in place.

In Manitoba, prescribers who wish to prescribe methadone for addiction must take an opioid agonist therapy training course followed by an approved preceptorship in a methadone clinic. The applications are then reviewed by the registrar of the appropriate college who may make additional recommendations. In Manitoba, physicians who wish to prescribe buprenorphine-naloxone no longer need to obtain a methadone prescriber approval first. Prescribers who wish to prescribe buprenorphine-naloxone need to complete buprenorphine-naloxone training approved by their college, and apply to the appropriate college. It is the responsibility of the dispensing pharmacist to verify that the methadone or buprenorphine-naloxone prescriber has the appropriate approval. Methadone and/or buprenorphine-naloxone prescribing approvals can be confirmed for Manitoba prescribers by phoning the CPhM at 204-233-1411. RNEP prescriber approvals can be confirmed using Nurse Check on the College of Registered Nurses of Manitoba website:

[https://members.crnmb.ca/CRNM/Services/Nurse\\_Check\\_Display/Shared\\_Content/NurseCheck/NurseCheckDisplay.aspx](https://members.crnmb.ca/CRNM/Services/Nurse_Check_Display/Shared_Content/NurseCheck/NurseCheckDisplay.aspx).

If a prescriber does not appear to have the appropriate approval, please confirm his/her status by contacting the appropriate licensing body:

- College of Physicians and Surgeons of Manitoba at (204) 774-4344 or toll free (in Manitoba) at (877) 774-4344
- College of Registered Nurses of Manitoba (204) 774-3477.

Methadone and buprenorphine-naloxone prescribing authority for out-of-province prescribers can be obtained by contacting the respective provincial colleges.

Please see the section –Hospital Prescribers, for information on prescribers of OAT for hospitalized patients.

### **M3P Prescription Program**

Methadone and buprenorphine are covered by the M3P program and must be written on the duplicate prescription form. These prescription pads are personalized and numerically recorded for the prescriber. Prescribers cannot exchange pads or write on a form that is not their own.

The prescription must contain the following information:

- The daily dose must be written both numerically and alphabetically.
- The first and last day must be clearly stated. No doses are to be given beyond the last day even if the patient missed a day and technically has a dose left.
- The total dose must be written both numerically and alphabetically.
  - The total dose requirement serves as an additional safety check to ensure the correct dose is dispensed. If the total dose is not indicated then the pharmacy should contact the prescriber to confirm and document the total dose. However, if

the prescription is written clearly with the daily dose and the start and end date, and the therapeutic intention of the prescriber is clear, pharmacists should use their professional judgment. It is important to ensure that delays in confirming the total dose do not interfere with preserving continuity of care in the patient.

- The doses to be witnessed and those to be carried must be clearly indicated either on the prescription or on an accompanying pharmacy agreement.

Where there is any discrepancy or doubt about a methadone or buprenorphine prescription, the pharmacist should verify the prescription with the prescriber.

Any changes to a patient's previously stable dose require a new prescription. A change in the witnessed dosing dates or number of carries can be taken verbally or by fax.

#### *Faxing M3P Prescriptions for Methadone or Buprenorphine*

Prescriptions for methadone or buprenorphine may be transmitted via facsimile only for the purpose of a methadone/buprenorphine maintenance program. Faxed prescriptions for methadone or buprenorphine for opioid use disorder must be written on an original M3P form with a note attached to clearly indicate the daily dosage. All faxed prescriptions must also meet the requirements of the [Joint Statement on Facsimile Transmission of Prescriptions](#) which can be found at the CPhM website. A sample template can be found in **Appendix D** that may be used for faxing prescriptions, including M3P prescriptions for methadone and buprenorphine. This form can be used by prescribers when faxing prescriptions to a pharmacy.

It is the pharmacist's responsibility to verify the origin of transmission, the authenticity of the prescription, and if not known to the pharmacist, the signature of the prescriber. Faxed prescriptions for methadone or buprenorphine may be accepted from another province as long as the above requirements are met, and faxed prescriptions are allowed in that province for OAT.

The pharmacy must keep the faxed M3P prescription and faxed written documentation together for a minimum of 5 years (electronic or hardcopy). **The original prescription no longer needs to be sent to the pharmacy in these situations.**

In rare emergency situations, a pharmacist may be asked to accept duplicate prescription forms by fax on an interim basis for methadone for analgesia. In these emergency situations, the pharmacist is required to assess each and every situation using professional judgment in direct consultation with the prescriber.

- If an emergency faxed duplicate is warranted, obtain written documentation from the prescriber, including:
  - The methadone prescriber's signature,
  - The request for fax transmission of a M3P prescription,
  - A brief description of the emergency situation, and
  - Guarantee of delivery of the original duplicate prescription to the pharmacy on a stated reasonable date.

A sample document can be found in **Appendix E** that may be used to document why a facsimile of a M3P prescription for methadone for analgesia has been accepted. This document can be sent to the prescriber to fill in, sign and return to the pharmacy.

## **New Patient on Opioid Agonist Therapy**

Upon receiving a new patient on methadone or buprenorphine, pharmacists are required to confirm that the prescription is written by a valid prescriber with the appropriate prescribing approval. The pharmacist must screen and assess the appropriateness of the treatment at the dose prescribed.

Pharmacists should review the store hours, the dispensing and dosing process, the obligations of the patient and the pharmacy, the mutual expectations including expectations for conduct and behaviour within the pharmacy, the procedure for handling missed, spoiled, lost/stolen, or vomited doses, and counselling regarding the therapy including pertinent clinical details related to safety and efficacy. This preliminary discussion is best documented by signing a two-way agreement between the pharmacy and the patient to acknowledge the mutual agreement and understanding of key elements involved in the provision of the medication. A sample agreement has been provided in the **Appendix C**. Pharmacies with highly collaborative practices may also consider a three-way agreement between the OAT prescriber, pharmacist, and patient that specifically lays out the expectations each party has of the program<sup>1</sup>. This can include the rights, obligations, conditions and consequences agreed upon.

## **Methadone Stock Solution**

All methadone prescriptions for patients being treated for opioid use disorder must be dispensed using the commercially available methadone 10 mg/ml products. **Pharmacists may no longer dispense compounded methadone (as of October 2015)** since a commercially available product has been introduced. Please see the Manitoba Health, Healthy Living and Seniors Methadone Reimbursement Procedure and Questions and Answers in **Appendix A** or contact Manitoba Health for updated information.

## **Diluting Methadone**

Diluted methadone must be prepared by staff who are competent in the processes and use of equipment to dispense the diluted solution.

Methadone that is not already in a vehicle that discourages injection must be diluted to a total volume of approximately 60 to 100 ml with a suitable crystalline diluent **such as grape flavoured Kool-Aid™, orange flavoured Tang™, or Allen's® Apple Juice**. **Dilution in a vehicle that does not easily lend itself to injection is required to minimize the risk of abuse and/or diversion for injection.** Dilution will also help mask the bitter taste of methadone. The clear, dye-free concentrate may be preferred for patients who have dye allergies, who prefer a sugar-free option, or for those who prefer an alternate flavour to cherry. **Dilution of the unflavoured oral concentrate with water is not acceptable.**

Dilution is not required for methadone formulations that are hypertonic concentrates (ie those that contain sucrose 40%), and therefore does not lend itself to injection. However, there may

be situations where dilution should be considered—for example, when dispensing small volumes where surface adhesion of the concentrate to the dispensing device or bottle may result in inaccurate or variable dose delivery, where risk of potential abuse and/or diversion is suspected, or when dispensing carries.

After witnessing the ingestion of the undiluted methadone concentrates, the pharmacist *must* provide water to rinse the dispensing device (i.e. cup) to rinse any residual medication and must witness ingestion of the water and engage the patient in a short conversation to ensure that the entire dose has been ingested to reduce the risk of diversion by cheeking<sup>10</sup>.

Ensure that equipment or devices used for dispensing and dilution meet standards for accuracy of measuring devices. Measuring devices used in the dispensing of methadone must be accurately measured using a calibrated device that will satisfactorily minimize the error rate. Graduated cylinders are **not** an acceptable measuring device for methadone. More frequent inventory counts of methadone will further help to determine if the error rate of the measuring devices is satisfactory.

Distinctly label equipment and devices used to measure methadone and use these devices exclusively to dispense methadone where possible. Keep this equipment in a designated area to avoid mix-ups.

Pharmacy staff diluting methadone should take precautions to avoid accidental consumption of methadone during clean up and handling of methadone liquid.

The stability and sterility of some commercially available methadone products diluted with a crystalline drink such as Kool-Aid™, Tang™, or Crystal Light™ is unknown as published studies are not available. Dispensing guidelines within many provincial jurisdictions have identified the duration of stability of methadone in various diluents from a collection of past literature (see Table 2); however, available literature does not address the issue of sterility, which includes the likelihood of bacterial growth in the prepared solution stored under refrigerated or unrefrigerated conditions. The information in Table 2 is provided as best existing guidance to allow you to use professional judgment when assigning best-before dates to diluted methadone<sup>1</sup>.

Pharmacists are required to use best judgment to assign the beyond-use date for diluted products. All diluted methadone products must be refrigerated and carries are permitted a maximum expiry date of 14 days from the date of dilution. The dispensing staff must assign dates based on the earliest expiry of the ingredients used or 14 days refrigerated, whichever comes first. Dilution with fruit juices may require a shorter dating as an opened juice bottle may have a best before date that is earlier than 14 days.

Formulations prepared in juices should have an expiry that does not exceed the shelf-life of the juice under the conditions of storage recommended upon opening the bottle. In general, dispensing methadone in fruit juices or diluents not identified below or within a product monograph is discouraged due to the lack of sufficient evidence for stability and sterility upon extended storage of the mixture, especially beyond immediate ingestion upon dilution.

To avoid the potential for mix-ups during dosing, and to optimize the stability and sterility of dispensed carries, diluted methadone should not be prepared far in advance.

Note: Published guidance on the stability of methadone solutions is reported in many provincial guidelines based on a study from the early 1990s. However, there is a need for more updated testing to acknowledge both the stability and sterility of prepared products under various compounding conditions.

**Table 2: Methadone stability in various diluents for carries<sup>vi</sup>**

Diluent	Stability at room temperature (20 <sup>o</sup> to 25 <sup>o</sup> C)	Stability at refrigerated temperature (5 <sup>o</sup> C)	Period of acceptable sterility for oral consumption under refrigeration (i.e., bacterial or pathogenic growth)
Grape flavoured Kool-Aid	17 days	55 days	<ul style="list-style-type: none"> <li>• Unknown for dilution with Methadose</li> <li>• 14 days for diluted Metadol preparations</li> </ul>
Orange flavoured Tang	11 days	49 days	<ul style="list-style-type: none"> <li>• Unknown for dilution with Methadose</li> <li>• 14 days for diluted Metadol preparations</li> </ul>
Allen's Apple Juice	9 days	47 days	<ul style="list-style-type: none"> <li>• Unknown for dilution with Methadose</li> <li>• 7 days for diluted Metadol preparations</li> </ul>
Grape flavoured Crystal Light	8 days	34 days	<ul style="list-style-type: none"> <li>• Unknown for dilution with Methadose</li> <li>• 14 days for diluted Metadol preparation</li> </ul>
Grape flavoured Crystal Light with 0.1% sodium benzoate	29 days	Not available	<ul style="list-style-type: none"> <li>• Unknown for dilution with Methadose</li> </ul>

## Storage

Methadone stock solution must be stored at room temperature (15-30°C) and protected from light. Diluted preparations must be refrigerated.

Buprenorphine tablets are to be protected from light and moisture. Avoid handling tablets, as the tablets are hygroscopic and moisture can accelerate the degradation of the tablet.

## Pharmacy Storage and Security

The primary goal when selecting a storage container or site for storage of methadone solution is the prevention of mistaken consumption. If methadone doses are stored in the refrigerator of the pharmacy it is essential to ensure that all staff beverages be stored elsewhere. The containers

used to store methadone should be distinctive and recognizable. Pharmacists should avoid using similar containers to store other liquids in the dispensary. Avoid using containers that have other uses, such as distilled water bottles and beverage bottles.

As in all pharmacies that store and dispense narcotics, adequate security systems must be in place to minimize the possibility of theft and robberies. Prepared methadone doses should be labelled correctly and placed in a locked or secured fridge.

## Labelling of Prescription Bottles

All patient labels will be compliant with the provisions of *The Pharmaceutical Act and Regulations*.

Additionally, for methadone for OAT, the labelling on any take home or carry bottles needs to indicate the intended ingestion date (electronically or handwritten) and the total dosage (mg) on the bottle with a notation that the dosage was made up to a set volume (if applicable). The start and end dates of the prescription must also be indicated. For example, the sig on a label of a carry bottle may read:

“Drink the entire contents of this bottle containing 85mg of methadone mixed in Tang to a total volume of 60mL once daily (Nov. 1-Nov. 23)”. [Ingest Date: Thursday Nov 20]

Take home doses must have an adequate warning label. Please see further information on warning labels under the section - Take Home Doses (Carries).

Buprenorphine labels shall additionally indicate proper instructions for administration, which should include the intended date(s) of administration (electronically or handwritten). The start and end dates of the prescription must also be indicated. All vials must also have attached an adequate warning label. Please see further information on warning labels under the section - Take Home Doses (Carries).

## Inventory Records

All of the requirements for recording purchases of narcotics must be met for methadone and buprenorphine. Perpetual inventories are an effective means of tracking inventory levels by recording the volume of methadone solution and number of buprenorphine tablets received and dispensed. For pharmacies that dispense large amounts of methadone, reconciliation of methadone on-hand should be done more frequently (i.e. once monthly).

The Regulations of *The Controlled Drugs and Substances Act* require a pharmacist to report loss or theft of controlled substances within 10 days of discovery of said loss.

## Billing

Billing for methadone and buprenorphine shall be submitted on the day of service provision. Methadone solution must be entered into DPIN as the total number of milliliters of methadone dispensed, For example, 80mg of methadone would be billed as 8 mL (of Methadose™ or Metadol-D® 10mg/ml). Buprenorphine is entered into DPIN as the number of tablets dispensed.

If a patient is dispensed methadone, Manitoba Health requires that the total quantity of methadone (mL) received by the patient, including any witnessed doses, is entered into DPIN along with the correct days supply, on the day of service provision. Please see **Appendix A** for the Methadone Reimbursement Procedure from Provincial Drug Programs, Manitoba Health, Healthy Living and Seniors or contact Manitoba Health directly for updated information.

Missed doses of methadone or buprenorphine must be reversed in the DPIN network before the end of the business day.

It is important for pharmacists to maintain a DPIN profile that is as accurate as possible with methadone and buprenorphine, since these records are utilized by other health professionals (such as emergency care providers). However, it is ultimately the responsibility of the health care professional that is reviewing the DPIN to confirm the details of the DPIN record with the previous pharmacy, since there may occasions that a DPIN record may not reflect the situation accurately.

### **MY, MZ, and Interaction Codes Caution**

Pharmacists are to review the critical patient care codes and drug interactions that are generated by DPIN, decide on an appropriate action, and document the response in the appropriate place(s). Please note that pharmacists should still review an OAT patient's DPIN record occasionally to ensure that there is no misuse of other mood-altering medications, as some of these medications may not flag on DPIN. Any concerns should be brought to the attention of the methadone/buprenorphine prescriber, and if deemed appropriate, the prescriber of the mood-altering medication.

### **Witnessed Ingestion**

The pharmacist is responsible for:

- Confirming the patient's identity,
- Reviewing the patient's profile for pertinent concerns,
- Assessing the patient for intoxication,
- Witnessing and documenting the ingestion,
- Monitoring the patient post-ingestion for a duration based on individual patient circumstances, and
- Ongoing monitoring and troubleshooting.

#### *Positive Identification*

The pharmacist must take reasonable steps to positively identify the patient prior to dispensing OAT to the patient for the first time, or if they are unsure of their identity. It is recommended that the patient provide government issued photo identification. If the patient cannot provide the required identification, the prescriber may be contacted to assist in verifying the patient's identity. Some pharmacies that have multiple pharmacists and/or use relief pharmacists can keep a photo of the patient on file (with the patient's permission) so that the patients do not have to provide photo identification each time they come in. Addressing the patient by their full name

and stating their dose in a confidential manner is a good practice to ensure the correct person is receiving the correct dose.

### *Daily Witnessed Ingestion*

When a patient is prescribed daily witnessed ingestion or administration, they must attend a pharmacy that is open every day of the week. In most cases, the directions on the prescription will indicate which doses are to be witnessed and which doses are to be carried, however if the prescriber is unclear in his or her intentions, the pharmacist must assume daily witnessed ingestion and supervise every dose. The act of witnessing OAT administration by a pharmacist within a pharmacy is not a function that may be delegated to a non-pharmacist staff member (e.g. pharmacy technician or assistant). In the event the pharmacy is not open 7 days a week, or is closed for holidays, the prescriber must authorize the pharmacist to provide carries for the days the pharmacy is closed, or make appropriate arrangements with another pharmacy. If this is the case, communication between the two pharmacies is paramount.

The pharmacist must assess the patient prior to providing him/her with methadone or buprenorphine (see section – Intoxicated Patients).

When the patient receives methadone for ingestion, the pharmacist must maintain a sight line with the methadone until the full dose is ingested to ensure that the dose is not diverted. After the patient drinks the methadone, a short conversation is required to ensure that the entire dose of methadone has been swallowed. Confirmation that the methadone is swallowed is necessary as some patients may try to keep the methadone in their mouth until they can spit it into a container. It may be helpful to have a policy that does not allow outside drinks to be present for the witnessed dose. If water is given to the patient in a cup, ensure that the empty cup is returned to the pharmacist.

After witnessing the ingestion of the undiluted methadone (10mg/ml), the pharmacist *must* provide water to rinse the dispensing device (i.e. cup), to rinse any residual medication and must witness ingestion of the water and engage the patient in a short conversation to ensure that the entire dose has been ingested to reduce the risk of diversion by cheeking<sup>10</sup>.

When the patient receives buprenorphine for administration, the pharmacist must ensure that the sublingual tablet is placed properly under the tongue. Handling of the tablets should be minimized. Advise patients not to swallow their saliva while the tablets are dissolving. The patient may choose to split their tablets to expedite the dissolving process. If multiple tablets are required, the patient may choose to place more than one tablet under their tongue at the same time. If the patient is having difficulty with dissolving the tablets, recommend that he/she drink some water BEFORE administering the tablets. It is essential to ensure that that tablet dissolves completely under the tongue. The pharmacist should check for a “pulpy mass” under the tongue after 1 to 5 minutes, and then check again to ensure the entire tablet has been dissolved. Full tablet dissolution may take up to 10 minutes or longer. Maintain a sight line on the patient throughout the administration process. After dosing, remind patients not to drink fluid for at least five minutes, to ensure the full dose has been absorbed.

### *Intoxicated Patients*

Prior to dispensing methadone or buprenorphine to a patient, the pharmacist must assess the patient for signs of intoxication. These signs can include, but are not limited to, slurred speech, incoordination, smelling of alcohol or other unusual behaviors. If you suspect that the patient is intoxicated such that the ingestion of methadone or buprenorphine may pose a risk to the safety of the patient, the dose should be held until you can reasonably determine that it is safe for the patient to take their dose of methadone or buprenorphine. The prescriber should be notified of the situation and the course of action discussed. In most methadone- and buprenorphine-related deaths, concurrent use of sedatives such as alcohol or benzodiazepines were found to have contributed to the cause of death. Methadone or buprenorphine withdrawal, while uncomfortable for the patient, is not life threatening but methadone or buprenorphine given in combination with other intoxicating drugs can be fatal. If possible, explain to the patient that you are holding the dose because it may be dangerous to their health and clearly document your actions.

### *Refusing methadone or buprenorphine administration*

The decision to administer methadone or buprenorphine to a patient should always be subject to your professional judgment. As discussed in the previous section, if you suspect that the patient is intoxicated, dosing should be refused until the situation has resolved. If the patient has missed 3 consecutive days of methadone doses, or 6 consecutive days of buprenorphine doses, the next scheduled dose must also be held. Please see section - Missed Doses for further information.

### *Overdose due to dosing error*

It is beneficial to have two staff members (a pharmacist and a technician or assistant) independently double check the accuracy of methadone doses measured. This important step can prevent a medication error especially an overdose from occurring. Confirming the dose with the patient prior to administration can also prevent a dosing error.

A pharmacy that dispenses methadone or buprenorphine-naloxone should have a clear protocol for their staff on how to handle an accidental overdose. This protocol should include but is not limited to the following:

- make every reasonable effort to contact, inform, and follow up with the patient about the overdose,
- contact the prescriber immediately,
- encourage the patient to visit the emergency department of the hospital and be accompanied by someone knowledgeable of the incident,
- stress to the patient the reasons for going to the hospital,
- if the patient refuses to go the hospital, ensure that they are observed by someone for at least the first four hours for signs and symptoms of overdose, and
- document the incident.

Consider providing naloxone kits to patients on methadone or buprenorphine-naloxone, since this can provide an additional measure of safety against the risk of an opioid overdose.

The pharmacy should have an overdose protocol in place, so pharmacy staff understand what steps and actions to take promptly to reduce the possible harm to the patient.

### *Documentation*

Pharmacies must maintain a log of witnessed and take-home doses. There must be a clear indication on the log whether the patient is receiving methadone or buprenorphine. This log must include the time that the dose is witnessed. This information is important for both pharmacists and prescribers in assessing patients. If the patient should vomit a dose of methadone, having the exact time of witnessed dosing is helpful in deciding on a replacement dose. For stores that are open 24 hours, this information will prevent intoxication/overdose resulting from witnessed dosing times that are too close together. When methadone and buprenorphine doses are scheduled to be administered once daily, they should be administered at least 15 hours apart. The log must also state the name of the patient, a picture (if possible), and the patient's address or date of birth which can be used to verify their identity. It may be helpful to state the days they normally witness and carry on the log as well. If a patient is transferring from another pharmacy to your pharmacy it is important to know when the patient had their last witnessed dose, how many take-home doses they received, and the dose received. This should be documented on the original prescription. Some pharmacies will have the patients sign for their witnessed doses and carries in the methadone log. This is an excellent tool for preventing and resolving discrepancies. A separate sheet must be maintained for each patient to prevent confusion and maintain privacy.

Date	Time	Dose (mg)	Drink (✓)	Number of Carries	Pharmacist's Initials	Patient's Signature

See Appendix F

### **Guest Doses**

Occasionally, you may be asked to accept a patient on a temporary basis to be medicated at your pharmacy. This may be for a variety of reasons such as vacation or business travel. In these cases, the patient can either not be provided with enough carries for the entire duration of travel or they are not stable enough to have carries for the entire duration of travel.

Pharmacists can dispense OAT pursuant to an out-of-province prescription if they confirm the following:

- The prescription is authentic, current, and appropriate;
- For methadone and/or buprenorphine prescriptions, that the out-of-province prescriber has authority to prescribe narcotics within their provincial jurisdiction, and meets the prescribing requirements for OAT within his/her province.

Please note that, as with other medications covered under the M3P program, pharmacists can fill prescriptions for methadone or buprenorphine that are written on forms used in the province or territory where the practitioner resides. Prescriptions written by authorized practitioners in other provinces and territories need only meet the requirements in place in their jurisdiction for the prescription to be filled in Manitoba. Faxed prescriptions for methadone or buprenorphine

may be accepted from another province as long as the prescription is for the sole purposes of opioid agonist therapy and the facsimile includes a note from the prescriber clearly indicating the daily dosage. All faxed prescriptions must meet the requirements indicated in the [Joint Statement on Facsimile Transmission of Prescriptions](#) which can be found at [www.cphm.ca](http://www.cphm.ca).

Communication between the temporary and regular pharmacy is imperative at the beginning and ending of the dosing interval. This communication is required to prevent double dosing and/or missed dosing. Information on time and amount of last witnessed dose as well as any carries provided must be communicated between pharmacies. The “guest” is required to present identification to the temporary pharmacy prior to receiving any methadone or buprenorphine to ensure positive identification. If there is a valid prescription at the regular pharmacy covering the period the patient will be at the temporary pharmacy, this prescription must be cancelled and the methadone/buprenorphine prescriber must issue a new prescription for the temporary pharmacy. If/when the patient returns to the regular pharmacy, a new prescription is required.

### **Take Home Doses (Carries)**

A “carry” refers to a dose of methadone or buprenorphine that the patient is authorized to take home for self-administration. Take home medication or “carries” are given to stable patients to reduce disruption in and improve the quality of the patients’ daily life. These doses are consumed unsupervised at home. Carries are considered privileges and are given as a reward to stable patients. These patients must demonstrate to the prescriber that they are clinically stable and are able to store the medication safely.

The patient is the only person who can pick up his/her carries. These carries should be signed for by the patient in a methadone/buprenorphine log. Typically, the patient will have a supervised dose on the day he/she picks up the carries. Under exceptional medical or social circumstances, and only with the authorization of the methadone/buprenorphine prescriber, the pharmacist himself/herself may consider delivering the methadone or buprenorphine to the patient to witness the required dose and deliver the carries. Patient confidentiality and safety of the pharmacist should be considered when deciding to deliver and witness opioid agonist therapy. Direct supervision of methadone ingestion or buprenorphine administration by a pharmacist cannot be delegated with the exception of deferring to a methadone/buprenorphine prescriber at an established harm reduction program or another pharmacist.

The number of carries each patient receives is dependent on clinical stability, duration of time in the opioid agonist therapy program and the ability to safely store the medication. Patients who receive methadone will not receive carries during the first 2 months of treatment with the exception of possibly a Sunday carry. After the initial 2-month stabilization period patients may be granted up to 1 additional carry per month, to a maximum of 6 carries per week. Should the patient become unstable while receiving carries the number of carries may be decreased. This can be for a variety of reasons including missed appointments, positive urine drug screen(s), inability to store medication safely, and/or unacceptable behavior in the pharmacy or clinic.

The College of Physicians and Surgeons of Manitoba (CPSM) is working to develop a new CPSM Recommended Practice Manual specifically for use of buprenorphine/naloxone for OAT

in Manitoba. Representatives from the College of Pharmacists and the College of Registered Nurses are also collaborating on this document.

Due to frequent requests for guidance, CPSM has recently published the draft Take-Home (Carry) Dosing Recommendations document for prescribers to follow in advance of publication of the full Recommended Practice Manual.

The risks associated with buprenorphine/naloxone take-home doses are limited relative to methadone, and deaths due to buprenorphine/naloxone are very rare. The document reviews recommendations for routine take-home dosing as well as special considerations when take-home doses may be initiated earlier than usual or for longer periods of time.

### [CPSM Take-Home \(Carry\) Dosing Recommendations](#)

#### *Storage of Carries*

Methadone and buprenorphine can be harmful or fatal if taken by a child or an adult who is not tolerant of opioids. Accidental poisoning can be prevented by these simple safeguards. Methadone must be dispensed from the pharmacy in a bottle with childproof caps and stored in a lock box by the patient. Tackle boxes and small tool boxes with a lock work well for this purpose. When initiating methadone carries, the pharmacist must request the patient show them the lock box prior to the patient receiving his/her first carry, unless the pharmacist can confirm that this has already been done by the prescribing clinic. This must be documented in the patient's file. Patients should be routinely counseled on the importance of safe and secure storage of methadone carries.

Patients should be advised to store methadone carries diluted with juice or crystalline solution in the refrigerator.

Buprenorphine overdoses have been reported in children who have swallowed or sucked the tablets. Patients who receive take-home doses of buprenorphine for the first time must be counseled to properly store their take-home doses safely and securely. A lock box may be required by the prescriber or the prescribing clinic.

#### *Documentation for non-childproof caps*

Should the patient request non-childproof caps, this must be documented on their file and the pharmacist should reinforce the importance of safe medication storage and the patient's responsibility in ensuring no other persons have access to their methadone or buprenorphine. As per section 81 of the Pharmaceutical Regulation, the patient must declare in writing that they do not want childproof caps and it must be reasonable given the patient's circumstances.

#### *Warning Labels*

Counsel patients that methadone or buprenorphine is very dangerous if consumed by anyone other than themselves. Methadone and buprenorphine are hazardous substances when consumed by a child or adult who is not tolerant to opioids.

All methadone or buprenorphine dispensed as carries must have an adequate warning label. The warning label must state that the amount of drug contained could cause serious harm or toxicity if taken by someone other than the patient. Some pharmacies insert a warning directly into the directions on the prescription label. There are commercially available warning labels or you can create auxiliary labels such as:

“Warning: Methadone (or buprenorphine) can be fatal when taken in individuals for whom it is not prescribed.”

“Warning: The contents of this bottle may cause harm or toxicity if taken by someone other than the person whose name appears on the prescription label.”

### *Destruction of Empty Methadone Bottles*

The pharmacy is required to dispose of all bottles and containers used for methadone doses in a safe and appropriate manner. Using a medication disposal company such as Stericycle is recommended. If the pharmacy disposes of the bottles themselves, they must ensure that the patient information and most of the label is removed, and that medication is not remaining in the bottle.

## **Diversion**

Diversion of take home doses of methadone or buprenorphine can have fatal consequences if taken by a person naïve to opioids. In most cases, methadone or buprenorphine is diverted to friends and family who are experiencing opioid withdrawal but are not on the program, or sold for profit. It is also taken by some people for the psychoactive effects that can occur at doses higher than a person’s tolerance.

Some tactics for preventing/minimizing diversion include:

- Having the patients return their empty carry bottles to the pharmacy. The bottles should be counted to ensure all the bottles are returned and none have been given away.
- Requiring the patient to present their remaining take-home doses to the pharmacy at random intervals.
- Educating the patient on the dangers of taking methadone or buprenorphine if you have not developed a tolerance to it.
- Requiring the patients to present their lock box (for methadone) prior to dispensing take home doses for the first time. Storage of methadone in a locked box will prevent accidental ingestion by someone who may think it is simply juice (especially children).
- Methadone and buprenorphine must always be dispensed directly to the person. Friends or family are not allowed to pick up someone else’s methadone or buprenorphine.
- Maintaining a sight line on the patient at all times when they are given their methadone to be ingested. Some patients may try to “pocket” their dose, or spit it into another container.
- When buprenorphine is administered, ensure that you inspect under the patient’s tongue for a “pulpy mass” at 1 to 5 minutes, and again at the end of the dissolution to ensure that it is gone. A visual on the patient throughout the dissolution process should also be enforced.

## **Vacation Supply**

A methadone/buprenorphine prescriber may prescribe a larger than normal carry supply for a patient going on vacation. This supply can be for a maximum of 2 to 4 weeks. This extended supply is only given to patients who are stable and are deemed appropriate for a high number of carries (four to six carries, attending the pharmacy once to twice weekly)<sup>11</sup>. For non-stable patients the prescriber may organize for them to “guest dose” at another pharmacy in the location they will be visiting. The pharmacy receiving the “guest” must ensure they have all pertinent information regarding the time and amount of the last dose. A new prescription is required by the interim pharmacy. Please see “Guest Doses” for more information.

## **Counselling**

Counselling can provide patients with medication information, reinforce prior knowledge and dispel myths and misconceptions. In order to communicate effectively with patients, pharmacists need a strong knowledge base. Sufficient time and a private counselling area enable the pharmacist to maximize the benefits of counselling. A private counselling area is required for witnessing OAT as other people may see the medication being consumed and may inquire as to what the patients are consuming. This puts both the patient and the pharmacist in an uncomfortable position. The pharmacist must respect the patients’ rights to privacy and this type of situation can be avoided with a private counselling area.

Daily dispensing of OAT provides the unique opportunity to have an on-going dialogue with your patients. It also requires innovative counselling as the basics will have been covered with the initial dispensing.

Prior to dispensing the dose, the pharmacist should assess the patient for signs of intoxication. This should be done simply by observing their mannerisms, speech, and appearance during a brief conversation. If the patient is receiving methadone, the pharmacist must have another short conversation after the patient ingests the dose to ensure the patient has swallowed the methadone. It is extremely difficult to talk without swallowing. These conversations provide pharmacists with the opportunity to emphasize the benefits of methadone treatments and provide support for the patient. By initiating dialogue, you can have a positive impact on the patients’ treatment goals, compliance, management of adverse effects, and lifestyle choices. This can become a very rewarding part of your practice as you develop a trusting relationship with your patients.

## **Replacement Doses**

Replacement of lost, stolen, or misplaced methadone or buprenorphine “carries” cannot be provided. Only in an extraordinary circumstance can an exception be made. The pharmacist must assess the situation, evaluate the need for the replacement dose and contact the prescriber to discuss the situation. Direct communication with the prescriber is required and must result in a new prescription being written and received if replacement medication is to be dispensed.

## Vomited Doses

When a patient reports that they vomited a methadone dose, that dose should not automatically be replaced. In order for vomited methadone doses to be replaced, emesis should be witnessed by the pharmacist or another health care professional. The prescriber should be contacted and provided with as much information as possible about the incident (time the dose was taken, time of vomiting, etc.). This is important in determining how much of the dose should be replaced if the prescriber chooses to do so. Methadone prescribers can authorize replacement doses by sending a prescription order to the pharmacy on an M3P form via fax (as previously discussed) or with an original prescription.

For patients who feel they might vomit their dose, recommend that they consume the methadone slowly in small sips. This can decrease the risk of vomiting. Have them remain in the pharmacy for 30 minutes post dose to ensure that the full dose is absorbed. If they do vomit their dose in this period then you will be in a better position to recommend a replacement dose to the methadone prescriber.

Methadone is rapidly absorbed after oral witnessed dosing. The following chart may be used as a guideline for replacing vomited doses.

Time after Consumption of Dose	Replace
<15 minutes	50-75%
15-30 minutes	25-50%
>30 minutes	Do not replace

Pregnancy is a special circumstance and the vomited dose usually is replaced in the pregnant woman. Please see section - Pregnancy for more information.

Buprenorphine is absorbed sublingually. Therefore, if a patient vomits after the complete dissolution of a buprenorphine tablet sublingually then there is no need to replace their dose.

## Missed doses

Methadone or buprenorphine doses that are not consumed or picked up on the prescribed day are considered cancelled and must be reversed on DPIN before the end of the business day. If a patient misses their dispensing day they cannot receive the missed amount when they return to the pharmacy in the future.

If a patient misses a scheduled witnessed dose and they have regularly scheduled carry doses, the prescriber may require the patient to witness a dose on one of their scheduled carry days. For example, if a patient is normally scheduled to witness doses Mondays and Tuesdays and carry doses for Wednesday through Sunday, and they miss their scheduled Monday witness dose, they may be required to add a witnessed dose on one of their scheduled carry days between Wednesday and Sunday. Contact the prescriber to see if this applies to your patient.

Pharmacists, emergency room physicians, private practice physicians and prescribers utilize DPIN to provide current information about a patient's medication history. Reversing doses that

are not picked up before the end of the business day ensures that DPIN is as accurate as possible.

Missed methadone or buprenorphine doses may indicate a serious problem (eg. relapse to other drugs) with the patient and the **prescriber/clinic should be notified about any missed doses**. The prescriber may require the patient to make up their missed witnessed dose on one of their regular “carry” days.

If a methadone or buprenorphine dose is missed on the day before a planned dose increase, the increased dose should not be given. The prescriber should be contacted to provide a new prescription for the previous dose. Alternatively, if this is not feasible, the prescriber can give authorization to continue to use the previous prescription at the previous dose if the end date has not passed.

Patients who miss their methadone for 3 or more consecutive days must not be given a dose until they have been assessed by their methadone prescriber. Due to the variability and unpredictable loss of tolerance to methadone, the prescriber will need to be contacted for a new prescription at a lower methadone dose. The following is a guideline for assessing appropriate methadone doses.

1 or 2 days missed: Patient may be given their regular maintenance dose.

3 days missed: Patient’s dose should be cut by 50% or restarted at 30 mg or less if original dose was less than 60 mg. The patient can be titrated back up to their maintenance dose by no more than 10 mg per day<sup>5</sup>.

4 or more days missed: Patient should be restarted at 30 mg or less and can be titrated up to their maintenance dose by 10 mg every 3 days or as otherwise directed by the prescriber<sup>5</sup>.

**Patients who miss their buprenorphine for 6 or more consecutive days must not be given a dose until they have been assessed by the buprenorphine prescriber.** A new prescription is required after the patient misses 6 or more consecutive days. Loss of tolerance to opioids occurs with missed doses of buprenorphine, but not as rapidly as with methadone. The following table contains suggestions on the handling of missed doses of buprenorphine<sup>5</sup>:

Usual Dose	Number of consecutive days missed	Action
Any dose	5 days or less	Resume usual dose
>8 mg	>7 days	Start at 4 mg
>8 mg	6-7 days	Start at 8 mg
6-8 mg	6 or more days	Start at 4 mg
2-4 mg	6 or more days	Start at 2-4 mg

NOTE: Some prescribers or clinics may instruct pharmacies to automatically cancel their buprenorphine prescriptions earlier than the recommendations above (i.e. 5 or less missed days), and the patient will require reassessment. The pharmacy should correspond with the buprenorphine prescriber to be clear on the prescriber’s directives.

It is recommended that the prescriber should be contacted for direction after at least 3 consecutive days of buprenorphine are missed, as there is a possibility that the patient has become unstable. If it is known that the patient has relapsed to opioid use after missing doses of buprenorphine, consult with the prescriber and delay the next dose of buprenorphine for at least 12 hours after the most recent opioid use, *and* until opioid withdrawal symptoms are evident.

For patients that are on less-than-daily dosing of buprenorphine, the management of missed doses can be more challenging. Essentially, patients need to be given enough buprenorphine to last until the next scheduled dose. For example, if a patient who normally takes 16 mg of buprenorphine on Monday and Wednesday, and 24 mg on Friday misses Monday, then they should be given 8 mg on Tuesday. If the same patient misses Friday, then they should be given 16 mg on Saturday. The prescriber must be contacted and a new prescription written if required.

If a patient on less-than-daily dosing of buprenorphine misses two consecutive alternative-day doses, then the prescriber should be contacted and the patient will likely need to be switched back to once-daily dosing, and possibly a lowered dose.

## **OAT in Hospital**

As the number of patients on OAT increases so do the number of encounters with the hospital system. Patients on OAT may be admitted for addiction related problems or for other medical or surgical issues. Regardless of the reason for the admission it is important that these patients receive the same standard of care as that of any other patient. Unfortunately, the stigma surrounding opioid agonist therapy exists not only in the lay public but also among health care professionals which can lead to the mismanagement of this patient population. The most common area for mismanagement is pain. Please refer to “Treatment of Acute Pain” for more information.

### *Continuation of Care*

Upon admission of a patient on opioid agonist therapy to the hospital, the patient’s pharmacy should be contacted to verify the date, time and dose of the last dose, and to also notify the pharmacy of the admission. If the patient has missed 3 or more consecutive days of methadone, or 6 or more consecutive days of buprenorphine, then the attending physician should be notified and the dose adjusted accordingly in consultation with the patient’s community methadone/buprenorphine prescriber. It is possible that a patient who is receiving multiple carries as an outpatient is not consuming their entire dose each week. In the interest of patient safety, it may be prudent to offer these patients a dose reduction to prevent possible overdose with the witnessed dosing of their full maintenance dose. This should be done in a non-judgmental and non-confrontational manner. Alternatively, in a methadone patient only, methadone may be given in split doses on the first 2 days and held if sedation is present. Upon discharge, the patient’s regular pharmacy should be contacted. See “Discharge from Hospital” below for more information.

### *Hospital Prescribers*

At times, patients receiving methadone/buprenorphine for opioid use disorder or pain may be admitted to hospital when there is no practitioner on staff authorized to prescribe OAT. Attending physicians with narcotic prescribing privileges practicing in a hospital setting can prescribe methadone/buprenorphine for continuation of therapy as long as the patient is an inpatient of the hospital, is under their care and, is currently on methadone/buprenorphine in the community. They are able to prescribe methadone/buprenorphine at the same or lower dose for continuation of patient care in the hospital.

For methadone, all dose increases, new starts or restarts in hospital should be undertaken by an approved methadone prescriber. In the case of buprenorphine, dose increases, new starts or restarts are permitted in hospital if the hospital practitioner documents a discussion with the patient's approved community prescriber or an approved prescriber who is a member of the HSC Addiction Consult team.

Any methadone/buprenorphine prescribed by the hospital practitioner must be prepared and dispensed by a hospital pharmacist who practices at a pharmacy that is affiliated with the hospital where the patient has been admitted.

The patient's community OAT prescriber must be kept informed that the patient has been hospitalized and any methadone/buprenorphine dose changes made by the hospital practitioner must be discussed with the community OAT prescriber. A practitioner in a hospital setting, who does not have a methadone/buprenorphine approval from their college, cannot provide a discharge methadone/buprenorphine prescription to the patient.

The prescriber/clinic and community pharmacy need to be notified as soon as possible after discharge. The hospital practitioner must coordinate with the community OAT provider to ensure the patient has a valid outpatient prescription for methadone/buprenorphine. To prevent a possible overdose, the prescriber and community pharmacist should verify when the patient last received his/her methadone/buprenorphine dose in hospital.

A hospital practitioner can, *at their discretion*, prescribe a "pass med" to an inpatient who is temporarily leaving the hospital and is returning back to the hospital. The methadone/buprenorphine must be dispensed by the hospital pharmacy and the patient must still be a patient of the hospital. Methadone/buprenorphine should only be provided as a "pass med" if the patient was previously receiving carries in the community and need to meet the requirements of a carry dose in the community.

### *Initiating OAT in hospital*

Methadone initiated or restarted in hospital must be done by a prescriber experienced in addictions and with a valid full methadone approval from his/her college. In the hospital setting, methadone may be titrated at a faster rate than that used in the community if the patient has adequate levels of monitoring. It is still important to remember that the drug is accumulating in the system for five days and that opioid cross tolerance is incomplete and unpredictable.

In the case of buprenorphine, new starts or restarts are permitted in hospital if the hospital practitioner documents a discussion with the patient's approved community prescriber or an approved prescriber who is a member of the HSC Addiction Consult team.

#### *Provision of opioid agonist therapy within the hospital*

The nursing staff should be made aware of the requirements for observing doses and that methadone or buprenorphine should not be left at the patient's bedside. Inserting explicit directions into the medication administration record for observing doses can be helpful.

#### *Discharge from Hospital*

When a patient is discharged from a hospital setting where they have received OAT as an in-patient, careful planning is important to facilitate a seamless transition back into the community.

Before discharge, the hospital staff should ensure that the patient can restart their OAT as an out-patient. They should communicate with the community pharmacy and community methadone/buprenorphine prescriber so that the patient can obtain a new prescription for their treatment as an out-patient.

A notation with details about the hospitalization should always be made on the patient's methadone/buprenorphine administration log by the community pharmacist, so that if the patient presents at the community pharmacy without warning, the pharmacist on duty will know to contact the hospital first.

Before resuming opioid agonist therapy in a patient who is discharged, the community pharmacy should verify:

- that the patient is officially discharged,
- the dose and time of the last witnessed dose in the hospital, and
- whether the patient has any remaining carry doses from before the hospitalization.

If an OAT prescription was not cancelled and instead put on "hold" in the community pharmacy, and there are no relevant changes in the patient's treatment, the prescription may be activated after consultation and confirmation with the community OAT prescriber.

Generally, it is safer to cancel or put a "hold" on community prescriptions for methadone or buprenorphine on admission to hospital. Ideally, the community methadone prescriber should reassess the patient on discharge and write a new prescription. Circumstances may have changed because of the hospitalization, and changes to the dose or carry schedule may be warranted.

### **Transfer of Custody to Hospitals, Prisons, and Community Health Facilities**

Pharmacists are permitted to transfer custody of narcotics, including methadone and buprenorphine, to a federally or provincially operated facility that provides health care services (ie. hospital or prison), pursuant to a written order signed and dated by a pharmacist in charge at the facility, or a practitioner authorized by the facility to sign the order. See subsection 35(1) of the NCR for more details. The person in charge of the health services at the hospital or prison

is responsible for ensuring that guidelines are in place to meet the requirements for security and safe and effective administration of the doses.

In September 2018, Health Canada issued two new federal exemptions to expand access of OAT to community health facilities. A community health facility is defined as a facility where health care services are delivered and managed by a nurse as part of the nurse's professional practice and outside the definition of a hospital. An example might include a health centre in a First Nations community.

Previously, a nurse could only conduct activities with controlled substances when working in a hospital setting. The new exemptions under Subsection 56(1) of the CDSA authorize:

1. [Nurses who provide health care services at a community health facility to conduct certain activities with controlled substances;](#) and,
2. [Persons in Charge of a hospital and pharmacists to supply controlled substances \(including methadone and/or buprenorphine\) to a community health facility.](#)

All nursing designations in Manitoba (RNs, LPNs and RPNs) providing health care at a community health facility may now receive, provide and administer controlled substances including the witnessed administration of methadone and buprenorphine products used for OAT.

In particular, the exemption for nurses provides them with the authority to possess, sell, provide, administer, transport, send and deliver controlled substances while providing health care services at community health facilities under certain conditions. These conditions pertain mainly to record keeping for all activities conducted with the controlled substances, keeping controlled substances secure when storing, receiving and returning as well as reporting to Health Canada of any loss or theft of controlled substances.

Pharmacies and hospitals can supply to a community health facility individually labelled, patient-specific doses as well as orders for clinic/ward stock. When clinic stock of methadone and/or buprenorphine is ordered by an authorized prescriber at a community health facility, a nurse working at the community health facility and an authorized prescriber or pharmacist must both sign the order for clinic stock. This order may be a separate document accompanied by a valid M3P prescription (duplicate prescription) signed by an authorized prescriber, or the nurse and authorized prescriber may sign the M3P form itself.

Pharmacies or hospitals that supply methadone or buprenorphine to a community health facility shall record the brand or specified name of the substance, the quantity supplied, the date of transport, the name of the person and company transporting the substance, the name and address of the person who ordered the substance, and the name and address of the facility receiving the substance.

Pharmacies or hospitals must take all necessary steps to protect against the loss or theft of methadone and buprenorphine during transport. There must be a chain of signature system in place that records signatures, full names, and dates of receipt. Individual bottles of methadone must have a tamper-proof seal, and final packaging of methadone and buprenorphine doses must also include a tamper-proof seal (eg. tamper-proof tape could be used).

Below are links to the exemptions and supplementary information and please review carefully, noting all terms and conditions that apply to these exemptions.

[Subsection 56\(1\) Class Exemption for Nurses providing Health Care at a Community Health Facility](#)

[Subsection 56\(1\) Class Exemption for the Person in Charge of a Hospital and/or a Pharmacist who Supplies Controlled Substances to a Community Health Facility](#)

[Supplementary Information](#)

## **Incarceration**

The provision of opioid agonist therapy in correctional facilities provides for continuation of the harm reduction philosophy. An important goal is to prevent transmission of blood borne pathogens such as HIV and HCV. Injection drug use is known to be high among inmate populations and therefore it is believed that opioid dependence treatment can help prevent the spread of HIV and HCV. The National Task Force on HIV, AIDS, and Injection Drug Use recommended the following (2001):

- Continuation of methadone in patients previously stabilized on methadone prior to incarceration.
- Make OAT available to those inmates who are in opioid withdrawal.
- Evaluate the need for OAT prior to release and ensure transfer to an appropriate community program upon release.

While buprenorphine is not specifically mentioned in the above recommendations, it is also currently being used in correctional facilities when patients stabilized on buprenorphine are incarcerated.

If your pharmacy is providing methadone or buprenorphine to a correctional facility you must ensure that the patients are receiving the correct dose. If the patient has been stabilized on OAT prior to incarceration you must contact the dispensing pharmacy to verify the date, time and dose of the last drink. If a patient has been diverting his/her methadone or buprenorphine, giving the usual prescribed dose in the correctional facility can result in sedation or death. Methadone should be dispensed with a tamper proof seal prior to being delivered to the correctional facility.

Upon release from a correctional facility, seamless care is important to ensure that the patient is prevented from experiencing withdrawal, which can put them at risk of relapse. Typically, it will fall on the community pharmacy or methadone/buprenorphine prescriber to determine when the patient was released and the amount and time of their last dose.

If an OAT prescription was not cancelled and instead put “on hold” in the community pharmacy, and there are no relevant changes in the patient’s treatment, the prescription may be activated after consultation and dose confirmation with the community prescriber.<sup>iv</sup>

Generally, it is safer to cancel or put a “hold” on community prescriptions for methadone or buprenorphine-naloxone when patients are incarcerated. Ideally, the community methadone

prescriber should reassess the patient on release and write a new prescription. Circumstances may have changed, and changes to the dose or carry schedule may be warranted.

## Part Five: Appendices

### Appendix A: Manitoba Health, Healthy Living and Seniors: Methadone Reimbursement Procedure and Questions and Answers



#### ***Information for Pharmacists*** **Methadone Reimbursement Procedure - Update** **Provincial Drug Programs** **Manitoba Health, Seniors and Active Living**

***Effective April 20, 2017***

- The Provincial Drug Programs' (PDP) Methadone Reimbursement Procedure, which came into effect on October 16, 2014:
  - enhances patient safety by ensuring a more consistent and clear indication in the patient's Drug Programs Information Network (DPIN) history of the dose of methadone prescribed for and dispensed to the patient; and
  - ensures a consistent process for adjudication and reimbursement of methadone preparations by PDP through DPIN.
- This procedure aligns with methadone policies in other jurisdictions.

#### **Methadone for Opioid Dependence:**

- "Methadone powder in preparation of an oral solution", PIN 909190, was delisted on October 22, 2015.
- Methadose\* is currently listed and Metadol-D\* 10 mg/ml Oral Concentrate will be listed (**effective April 20, 2017**) as an unrestricted Part 1 benefit for opioid dependence.

<b>Methadose* 10 mg/ml oral liquid</b>	<b>DIN 2394596</b>
<b>Methadose* Sugar Free 10mg/ml oral liquid</b>	<b>DIN 2394618</b>
<b>Metadol-D** 10 mg/ml oral concentrate</b>	<b>DIN 2244290</b>

- Pharmacy operators must indicate the quantity of methadone dispensed as the **total number of milliliters (ml)** of Methadose\* or Metadol-D\*\* dispensed. • Pharmacy operators must specify in DPIN the total days supply of Methadose\* or Metadol-D\*\* provided to the patient.
- If a patient is dispensed Methadose\* or Metadol-D\*\* carries, the total quantity of Methadose\* or Metadol-D\*\* received by the patient must be entered into DPIN along with the correct days supply. There should be a single entry into DPIN, and not separate entries on the same day.

For example: An M3P prescription is presented for methadone 2240 mg to be dispensed as 80 mg OD for 28 days.

This can be entered as daily or weekly:

<b>Daily</b>	<b>Weekly</b>
Quantity Dispensed: 8 ml	Quantity dispensed: 56 ml
Day's Supply: 1	Day's Supply: 7

- Pharmacy operators will be reimbursed the ingredient cost plus their usual and customary professional fee.
- Pharmacy operators must record and keep a copy of the documentation in a retrievable manner, indicating how all calculations/billings were done, and tracking of all dosages dispensed.
- Methadone compounded into a capsule formulation is not a benefit through PDP.

### **Methadone for Pain Management:**

Metadol\*\*\* tablets will be considered as a Part 3 benefit for the management of severe cancer related or chronic non-malignant pain that is not well controlled by short and long-acting Morphine and Hydromorphone as well as Fentanyl products, and for use as a replacement for other narcotic analgesics in palliative care patients who are requiring frequent and continuous dosing of short-acting opiates.

<b>Metadol*** 1mg tablet</b>	<b>DIN 2247698</b>
<b>Metadol*** 5mg tablet</b>	<b>DIN 2247699</b>
<b>Metadol*** 10mg tablet</b>	<b>DIN 2247700</b>
<b>Metadol*** 25mg tablet</b>	<b>DIN 2247701</b>

- Manitoba Health, Seniors and Active Living may conduct audits of the accounts and records of the pharmacy owner relating to methadone claims submitted by the pharmacy owner, to determine compliance with the terms and conditions of this procedure.

If you have any questions or concerns, please contact: [PDPInfo&Audit@gov.mb.ca](mailto:PDPInfo&Audit@gov.mb.ca)

Provincial Drug Programs  
300 Carlton Street  
Winnipeg MB R3B 3M9  
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## **METHADONE REIMBURSEMENT PROCEDURE**

**UPDATED (March 2017)**

***As communicated in Bulletin #91 effective April 20, 2017 – Metadol-D 10 mg/ml Concentrate (DIN 02244290) will be listed as a Part 1 benefit.***

***As communicated in Bulletin #84 effective October 22, 2015 - Methadone Powder for Compound (PIN 00909190) has been delisted.***

### **QUESTIONS AND ANSWERS**

**The Specified Drugs Regulation of *The Prescription Drugs Cost Assistance Act* indicates that Methadose\* (for opioid dependence) and Metadol\* (for pain management) are covered benefits. Effective April 20, 2017, Metadol-D 10 mg/ml Concentrate\* (DIN 02244290, for opioid dependence) will also be a covered benefit.**

**Why is the quantity in DPIN being entered in millilitres (ml) and not milligrams (mg) of methadone?**

- All Methadose or Metadol-D 10 mg/ml Concentrate prescriptions are to be entered in DPIN in millilitres. The entry in millilitres (ml) is consistent with the DPIN entry requirement for all other liquid formulations of products. The ml entry is also consistent with the entry methodology in other provincial jurisdictions, which addresses prior safety issues through a more consistent and accurate documentation of the quantity, strength and number of days supply of methadone provided to the patient in the DPIN history. By using the Drug Identification Number (DIN) of the product, DPIN can also provide drug interaction information.
- In some jurisdictions, pharmacists have both the ml and mg on the label for their patients in order to alleviate some of this concern.

For example: 100mg of methadone would be billed to DPIN as 10ml.

## **Is Methadose or Metadol-D 10 mg/ml Concentrate covered for chronic pain?**

- Methadose is currently listed and Metadol-D 10 mg/ml Concentrate will be listed (effective April 20, 2017) on the Manitoba Formulary as an unrestricted Part 1 benefit.
- The benefit status for Methadose and Metadol-D 10 mg/ml Concentrate and the delisting of compounded methadone in Manitoba is consistent with actions undertaken in other Canadian jurisdictions.

## **Do we need to dilute the Methadose or Metadol-D 10 mg/ml Concentrate?**

Methadose – cherry flavoured formulation:

- Is a hypertonic concentrate containing sucrose 40%, and the manufacturer advises that it would be difficult to distill, extract or inject. The cherry flavoured formulation can be dispensed without further dilution. However, pharmacists/prescribers may dilute this formulation at their clinical discretion.
- Dilution may be considered if a greater volume of solution is required to help prevent ‘cheeking’ the Methadose or to ensure the patient has received the entire dose.

Methadose – unflavored, dye-free, sugar-free formulation:

- Is not hypertonic; therefore, pharmacists are required to dilute this product in approximately 60 - 100 ml of a coloured, flavored vehicle such as grape flavoured Kool-Aid™ or orange Tang™. Dilution with a crystalline liquid is required to minimize the risk of abuse and/or diversion by injection. Dilution of the unflavored formulation with distilled water is not appropriate.

Metadol-D 10 mg/ml Concentrate – unflavored, dye-free formulation:

- Pharmacists are required to dilute this product in approximately 100 ml of a coloured, flavored vehicle such as grape flavoured Kool-Aid™ or orange flavoured Tang™, Allen’s® Apple Juice, Crystal Light® Tangerine-Grapefruit flavoured or Crystal Light® Lemonade flavoured. Dilution in a vehicle that does not easily lend itself to injection is required to minimize the risk of abuse and/or diversion by injection. Dilution of the unflavored formulation with distilled water is not appropriate.
- The practice of diluting Methadose or Metadol-D 10 mg/ml Concentrate with any diluent, including crystalline solution (Tang™), is not considered compounding and is not eligible for reimbursement as an extemporaneous compound.

**When we bill the Methadose and/or Metadol-D stock solution, do we submit the claim as a regular drug product or should we bill it as a compound?**

- The practice of diluting Methadose or Metadol-D 10 mg/ml Concentrate with any diluent, including crystalline solution, is not compounding and is not eligible for reimbursement as an extemporaneous compound. All prescriptions should be billed using the appropriate Drug Identification Number (DIN).

**How am I paid for Methadose and/or Metadol-D 10 mg/ml Concentrate; what should my professional fee be?**

- This procedure notes that pharmacists are to bill for the cost of the drug plus one professional fee. The professional fee would be at the same frequency as when you were dispensing the compounded methadone. If you have a fee structure for Methadose and/or Metadol-D 10 mg/ml Concentrate, whereby the fee may vary depending on the days supply provided, and whereby the same fee(s) would be charged to a cash paying customer, this is acceptable.
- The pharmacy will not be reimbursed for the cost of the diluent that is used to prepare the methadone dose for the patient.

**We get a lot of pain management people taking different doses - 1mg/ml, 5mg/ml, 10mg/ml and 50mg/ml. How could they continue receiving their pain medication if only the 10mg/ml is covered?**

- Methadose is currently listed and Metadol-D 10 mg/ml Concentrate will be listed (effective April 20, 2017) on the Manitoba Formulary as an unrestricted Part 1 benefit.
- Methadose and Metadol-D Concentrate are manufactured in a 10 mg/ml strength to allow for easy conversion.
- The benefit status for Methadose and Metadol-D 10 mg/ml Concentrate and the delisting of compounded methadone in Manitoba is consistent with actions undertaken in other Canadian jurisdictions.

**How will the change affect patients?**

- Some patients will note differences in the dispensing of Methadose or Metadol-D 10 mg/ml Concentrate versus previously compounded methadone solution, including:

*Colour change:* Methadose is available as a colourless (flavourless) or red colour (cherry) formulation. Depending on the formulation of Methadose that is dispensed and the diluent added, there may or may not be a change in the colour of the final dose dispensed to the patient. Metadol-D 10 mg/ml Concentrate is available as a colourless (flavourless) formulation and therefore the colour will be dependent on the diluent used.

*Different taste:* Methadose is available as a flavourless or cherry-flavoured formulation. Depending on the formulation dispensed, the final methadone dose may or may not have a different flavour. Metadol-D 10 mg/ml Concentrate is available as a flavourless formulation and therefore the taste will be dependent on the diluent used.

*Volume:* The final volume dispensed may be different.

*Viscosity:* Methadose and Metadol-D 10 mg/ml Concentrate may impact the viscosity or consistency of the final product dispensed to patients. Patients may perceive this change as being slightly thicker or “stickier”.

### **Are Methadose and Metadol-D interchangeable?**

- Methadose and Metadol-D 10 mg/ml Concentrate are not interchangeable. Prescriptions should be filled as prescribed by the clinician.

### **Our pharmacy system software is not designed with a decimal place for the quantity dispensed. How can I input the correct quantity of 7.5ml for a 75mg dose?**

- Please contact your pharmacy software vendor to activate the decimal point on your software if necessary. Software vendors have confirmed that decimal points can be accommodated on software systems.

### **End of Appendix A**

## Appendix B: Clinical Opiate Withdrawal Scale

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name: _____ Date and Time ____/____/____:_____	
Reason for this assessment: _____	
<b>Resting Pulse Rate:</b> _____beats/minute <i>Measured after patient is sitting or lying for one minute</i> 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	<b>GI Upset: over last ½ hour</b> 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 Multiple episodes of diarrhea or vomiting
<b>Sweating:</b> <i>over past ½ hour not accounted for by room temperature or patient activity.</i> 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	<b>Tremor observation of outstretched hands</b> 0 No tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
<b>Restlessness</b> <i>Observation during assessment</i> 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 Unable to sit still for more than a few seconds	<b>Yawning</b> <i>Observation during assessment</i> 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
<b>Pupil size</b> 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	<b>Anxiety or Irritability</b> 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable anxious 4 patient so irritable or anxious that participation in the assessment is difficult
<b>Bone or Joint aches</b> <i>If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored</i> 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/ muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	<b>Gooseflesh skin</b> 0 skin is smooth 3 piloerection of skin can be felt or hairs standing up on arms 5 prominent piloerection
<b>Runny nose or tearing</b> <i>Not accounted for by cold symptoms or allergies</i> 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	<p style="text-align: right;">Total Score _____</p> <p>The total score is the sum of all 11 items</p> <p>Initials of person completing Assessment: _____</p>

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

From: Wesson DR, Ling W J Psychoactive Drugs 2003 Apr-June; 35(2): 253-9

## End of Appendix B



## Appendix C: Sample Pharmacist – Patient Agreement

As your pharmacist(s), we believe in the principles of the methadone maintenance program, and the valuable role it can play in improving people’s lives. To help you succeed in the program we make the following promises:

- We will treat you professionally and respectfully.
- We are part of your health care team and will communicate with your methadone prescriber when necessary. The kinds of issues we will discuss with your prescriber(s) include:
  - Missing one or more drinks
  - Refusal to drink full dose of methadone
  - If you are intoxicated when you arrive at the pharmacy
  - Doses for replacement of lost, stolen or vomited methadone
  - If you see another prescriber and are prescribed mood-altering medications
- We will provide methadone to you exactly as your practitioner prescribed it. We are not able to give you extra doses, early doses, or methadone to take home unless your practitioner prescribes it.
- We are required to watch you drink your dose of methadone and have a conversation with you afterward.
- We will not dispense your methadone to anyone other than yourself and may require you to present identification.

As our patient, we have a number of expectations of you, too.

- You will attend the pharmacy during regular pharmacy hours.
- You are asked to respect our neighbourhood. Please ensure that all pharmacy packaging material and litter are disposed of in the garbage containers provided.
- All of our patients are expected to be respectful of others, including staff, other patients and our neighbours.
- You must store all take-home doses of methadone (carries) safely and securely in your home in a lock box.
- You may be refused your methadone at the pharmacist’s discretion if any of the following occurs:
  - You appear intoxicated
  - You are prescribed opioids or other mood altering medications from another prescriber without prior approval
  - If you are required to pay for your dose(s), and cannot make payment
  - If you are not being respectful to staff, other patients, or our neighbours
- If you do not take your methadone for three consecutive days you will have to see your doctor for a new prescription.

\_\_\_\_\_  
Pharmacist’s Signature

\_\_\_\_\_  
Patient’s Signature

\_\_\_\_\_  
Pharmacist’s Name

\_\_\_\_\_  
Patient’s Name

\_\_\_\_\_  
Date

\_\_\_\_\_  
Date

### End of Appendix C

## Appendix D: Facsimile Transmission of Prescriptions Template

Prescriber Name \_\_\_\_\_

Registration # \_\_\_\_\_

Clinic Name \_\_\_\_\_

Prescriber Address \_\_\_\_\_  
\_\_\_\_\_

Prescriber Telephone # \_\_\_\_\_

Prescriber Facsimile # \_\_\_\_\_

### Confidential Facsimile to:

Pharmacy Name: \_\_\_\_\_

Pharmacy Fax #: \_\_\_\_\_

Date \_\_\_\_\_

Time \_\_\_\_\_

Patient Given & Surname \_\_\_\_\_

Patient PHIN \_\_\_\_\_

Patient DOB \_\_\_\_\_

Patient Address \_\_\_\_\_

### **Rx#1**

Supply a total of \_\_\_\_ doses to be dispensed in quantities of \_\_\_\_ every \_\_\_\_ days, **OR**, refill \_\_\_\_\_ times.

### **Rx#2**

Supply a total of \_\_\_\_ doses to be dispensed in quantities of \_\_\_\_ every \_\_\_\_ days, **OR**, refill \_\_\_\_\_ times.

Prescriber Name \_\_\_\_\_

Prescriber Signature \_\_\_\_\_

Prescriber Address \_\_\_\_\_

Date \_\_\_\_\_

\*Attach M3P form for methadone or buprenorphine-naloxone if applicable

If a prescription for methadone or buprenorphine-naloxone is being faxed, the daily dosage must be clearly indicated below (in addition to being noted on the M3P form itself):

### **Practitioner Certification**

- This prescription represents the original of the prescription drug order.
- The pharmacy addressee noted above is the only intended recipient and there are no others.
- The original prescription has been invalidated and securely filed, and will not be transmitted elsewhere at another time.
- Quantity is stated in words and numerals.

This telecopy is confidential and is intended to be received by the addressee only. If the reader is not the intended recipient thereof, you are advised that any dissemination, distribution or copying of this facsimile is strictly prohibited.

Use of this form for purposes or by persons not authorized under the *Controlled Drugs and Substances Act* and its regulations is a criminal act.

**End of Appendix D**

## Appendix E: Sample Emergency M3P Documentation (methadone for analgesia)

This form is for use in the event of an emergency that requires a faxed M3P prescription (methadone for analgesia). Please complete and fax to the pharmacy with the M3P prescription. Direct consultation between the pharmacist and the prescriber must occur. The pharmacist must obtain written documentation from the prescriber prior to dispensing any medication.

Prescriber:	Patient Name:
Pharmacy and Pharmacist:	Date:

Brief Description of the emergency situation:
---

Affix M3P prescription here.

As the prescriber, I request the above named pharmacy to accept a faxed transmission of the M3P prescription form for the above named patient. I understand that the M3P prescription must be faxed to and received by the pharmacy prior to the pharmacy dispensing the medication. I guarantee delivery of the original M3P prescription to the pharmacy.
---

Prescriber's Name:
License#
Prescriber's Signature:
Date Signed:

**End of Appendix E**



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## References

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- <sup>3</sup> Personal communication, Dr. Lindy Lee. Date: October 22, 2014.
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- <sup>9</sup> The Transfer of Drugs and Therapeutics into Human Breast Milk: An Update on Selected Topics, Sach, Hari and Committee on Drugs. Pediatrics Vol 132. September 2013
- <sup>10</sup> College of Pharmacists of British Columbia, Methadone Maintenance Treatment (MMT) Frequently Asked Questions – Pharmacists, 2014.
- <sup>11</sup> College of Physicians and Surgeons of Manitoba, Manitoba Methadone and Bruprenorphine Maintenance Recommended Practice