Methadone Maintenance Treatment Services
Practice Directives for Community Pharmacies

2014
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Introduction

Purpose

The primary goal of this Methadone Maintenance Treatment Services: Practice Directives for Community Pharmacies in Prince Edward Island document is to enhance the safety, consistency, and effectiveness of the methadone maintenance services provided by pharmacists in Prince Edward Island to opioid dependent individuals, contributing to improved patient and societal outcomes. The focus of this standards document will be on Methadone Maintenance Treatment (MMT) but will also discuss briefly the role of Buprenorphine.

These standards are intended to provide Island pharmacists with the processes for providing methadone in the treatment of substance dependence (i.e. MMT services) in a safe and effective manner that is compliant with the relevant legislation and consistent with best practices. While methadone is also used in the treatment of chronic pain, these standards will not address best practices in its provision for this indication except as appropriate when highlighting best practices in providing methadone to treat both chronic pain and substance dependence in the same patient.

It is recognized that there may be rare, exceptional situations, or extenuating circumstances, in which some of the provisions of these standards may not be appropriate. In such situations, where these standards are not followed, it is expected that the pharmacist will document the rationale for the deviation. Such deviations will occur only in the interest of providing optimal patient care.

Acknowledgment

These Practice Directives were developed from best practice documents from other provincial pharmacy regulatory authorities including British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, New Brunswick, Nova Scotia, Newfoundland and Labrador; and from best practice documents of the College of Physicians and Surgeons of Ontario, British Columbia and Nova Scotia; as well as from the Centre for Addiction and Mental Health’s publication, —Methadone Maintenance Therapy: A Pharmacist’s Guide – 2nd edition. The PEICP acknowledges these documents throughout the Practice Directives.

Methadone Maintenance Treatment Services- Practice Directives for Community Pharmacies, 2014
The Prince Edward Island College of Pharmacists gratefully acknowledges the work of the Methadone Committee:

- Amanda Burke
- Anne Cairns
- Dr. D. Ling
- Michelle Wyand

Support

While this document is specific to pharmacy practice, the Prince Edward Island College of Pharmacists (PEICP) recognizes that a pharmacist’s adherence to these standards will have implications for the manner in which other health care professionals provide MMT to their patients. As such, support of these standards by the other health care professionals involved in providing MMT is essential for effective collaboration towards optimal patient and societal outcomes.

The PEICP appreciates the support of the PEI College of Physicians and Surgeons for the PEICP’s Methadone Maintenance Treatment Services: Practice Directives for Community Pharmacies in Prince Edward Island:
Methadone Maintenance Treatment: Programs

Substance dependence is a medical illness. It is a chronic and relapsing disorder, not an acute condition that can be rapidly cured by detoxification. The cost of this illness to the dependent individual and to society is significant, including severe decline of the individual's physical and psychological health, unemployment, family disruption, and criminal activities, such as prostitution, vandalism, drug dealing, theft, etc. Relapses are a common part of recovery (NLPB 2007).

The main treatment options for opioid dependence are abstinence based treatments and opioid agonist therapy (also known as opioid substitution therapy) with methadone or buprenorphine.

**Abstinence Treatment**

Abstinence based treatment may consist of medically supervised withdrawal from opioids, followed by an inpatient or outpatient psychosocial treatment program, and/or 12 Step group participation (AA, CA, NA). While abstinence based treatment is less effective than MMT, patients may prefer a trial of abstinence before committing to long-term opioid agonist therapy. (CPSO, 2011)

**Opioid Agonist Therapy**

Long-acting opioids used in the treatment of opioid dependence include buprenorphine and methadone.
Buprenorphine

Buprenorphine-naloxone (Suboxone®) is a sublingual partial μ agonist that, at the appropriate dose, relieves withdrawal symptoms and cravings for 24 hours or more. Because it has a ceiling effect, buprenorphine appears to be safer in overdose compared to methadone. However, buprenorphine may also be somewhat less effective than methadone at retaining patients in treatment. (CPSO, 2011)

For any further information about training in buprenorphine, contact CAMH at (416) 535-8501 or www.camh.net.

Methadone

Methadone is a long acting orally effective opioid. In the treatment of opioid dependence, methadone is used as a substitute for heroin or other narcotics, eliminating withdrawal from and reducing cravings for opioids. Methadone does not necessarily produce a “high” and it blocks the euphoric effects of other opioids, so patients can focus on their rehabilitation without the distraction of opioid withdrawal symptoms or the hindrance of the reinforcing effects of opioid euphoria. When used in the treatment of opioid dependence, a single oral dose is effective for at least twenty-four hours. Therefore, once daily dosing is generally the optimal dosing regimen for the treatment of opioid withdrawal. (CPSO, 2011)

MMT is one component of a harm reduction approach for the health care of people addicted to heroin and other opioids. Many people on methadone can return to work and maintain a stabilized lifestyle. Eventual withdrawal from methadone is not necessarily the goal of the treatment program, although some individuals may work with their treatment team to decrease their dose and eventually stop using methadone. (CPBC, 2007)

More information on the pharmacokinetics and actions of methadone can be found in Appendix A.

Methadone alone does not constitute effective treatment of opioid dependency. Effective MMT services should comprise the following components:

- an appropriate methadone dose
- routine medical care
- treatment for other substance dependence
• counselling and support mental health services
• health promotion, disease prevention and education
• linkages to other community-based services
• outreach and advocacy
  (CPSO, 2011)

**Expected Role of the Pharmacist**

Before beginning the provision of methadone maintenance services, pharmacists need to consider the activities they are expected to undertake and establish a plan of how to address the associated time and physical space requirements.

The expected activities of pharmacists providing MMT include but are not limited to:

• methadone dispensing (including witnessed administration 7 days a week*)
• Providing assistance with methadone dosing
• Educating and counselling patients on the use of methadone
• Patient monitoring and support
• Thorough record keeping
• Communicating progress of treatment to the physician (i.e., missed / lost doses, patient behaviour, treatment plan changes etc.)
• Providing input to the physician or treatment team on authorization of carries, etc.

(*For stores that are not open 7 days a week, see “Pharmacy Hours” for recommended options.)

Just as it is required for the safe and effective care of patients with other clinical conditions, it is essential that pharmacists providing MMT are competent in this clinical area, including an understanding of:

i. Substance dependence
ii. Opioid abuse and opioid dependence
iii. Opioid withdrawal and its management
iv. Harm reduction treatment strategy
v. Methadone (i.e., chemistry, pharmacokinetics, pharmacology, therapeutics, etc.)
vi. Methadone maintenance therapy
vii. Expected activities of the pharmacist providing MMT
viii. Methadone dosing issues (including management of overdose, dosing in special and emergency circumstances, etc.)
ix. Inter-professional collaboration (i.e., working with the treatment team)
x. Pharmacy legislation, guidelines and practice directives pertaining to MMT service
xi. Community support and referral resources

Pharmacy Hours

When a patient is prescribed daily witnessed ingestion of methadone, they should ideally attend a pharmacy that is open every day of the week. Pharmacies which are open only five or six days each week will have to adjust their practices for patients for whom take-home methadone carry doses (i.e. “carries”) is not appropriate. (CPBC, 2007)

Options include:

- opening for one or two hours so patients can pick up their daily dose
- co-ordinating weekend witnessed ingestion with another pharmacy and the prescribing physician. In this situation, **communication between the weekday dispensing pharmacy and the weekend pharmacy should occur, when appropriate, to ensure continuity of dosing.**
Treatment of Substance Dependence vs. Treatment of Pain

For optimal effectiveness of MMT and to minimize risks to individual patients and the public, it is important that established guidelines and standards are followed when providing methadone to patients with substance dependence issues regardless of the indication.

It is important that pharmacists are diligent in determining the true indication for methadone when it is prescribed and take appropriate steps to determine whether the indication for the methadone prescription is for the treatment of pain or for MMT. This may require communication with the prescribing physician.

The analgesic effect of methadone does not last as long as its effect on suppression of opioid withdrawal. As such, methadone typically needs to be administered every eight hours for pain control. In contrast, once daily dosing is generally the optimal dosing regimen for MMT. (CPSNS, 2006) (CPSO, 2011)

Use of Methadone to Treat Pain in MMT Patients

There may be situations where a patient who is receiving methadone for the treatment of substance dependence is subsequently prescribed methadone for the treatment of pain. In these situations, the dosing regimen of the methadone will be consistent with that required for pain control (i.e. divided doses, every eight hours). In these situations, neither the stated indication nor the dosing regimen themselves are the sole determinants of how the methadone should be provided to the patient.

** When the dosing interval / medical history provides reasonable evidence that the patient may be receiving methadone for pain, but may also have substance abuse issues, best practice is to follow these standards for the provision of methadone to that patient to enhance the safety and effectiveness of the treatment for the patient, and to minimize risks to the public. (CPSNS, 2006)

Example 1: A patient who is strongly suspected to have opioid substance abuse issues presents with a prescription for methadone for pain, written similar to a prescription for any other narcotic (e.g. no witnessed ingestion specified, etc.)
Example 2: A patient stabilized on methadone for substance dependence presents with a prescription for methadone written for pain.

In both these circumstances, methadone should be provided in accordance with the Methadone Maintenance Treatment Services-Practice Directives for Community Pharmacists in PEI.

When methadone is prescribed strictly for pain control to patients who do NOT have substance dependence issues:

- The patient is not required to drink doses in the pharmacy unless specifically noted on the prescription.
- A larger quantity than what would be provided for MMT may be prescribed.
- The methadone prescription may be written on a regular physician prescription and not on the MMT Prescription Form (Appendix B).
Legal Issues

Physician Authorization

Physicians must have special authorization issued by the Office of Controlled Substances, Health Canada, to prescribe methadone for maintenance therapy, detoxification or analgesia.

**Methadone Line**: (613) 946-5139** or toll free at (866) 358-0453**
(Mon-Fri 7.30am-3.30pm Eastern Time)
Fax: (613) 952-2196
Email: exemption@hc-sc.gc.ca
(**accurate at date of printing)**

Physicians who are authorized to prescribe methadone for MMT are **not** automatically authorized to prescribe methadone for pain. Pharmacists may call the federal Methadone Line for verification of a physician’s authorization for either indication.

Temporary Exemptions for Physicians of Institutionalized Patients

Any licensed physician can obtain a temporary methadone prescribing exemption from Health Canada in order to maintain continuity of care. The exemption can be applied for by calling, emailing or faxing the Office of Controlled Substances. This circumstance may arise when a patient is hospitalized or incarcerated.

The Office of Controlled Substances will typically grant the exemption the same day if contacted during business hours, or the next business day if contacted after hours. In the event that the exemption is being applied for after hours (evenings, weekends, holidays) the application approval **should not be reason for delaying methadone treatment**. The physician or pharmacist on the physician’s behalf should leave all the relevant information on the voicemail at the above number. The exemption is valid for 60 days or for the duration of the patient’s hospital stay, whichever is shorter. If the patient is hospitalized for longer than 60 days, then a new exemption is required.

The following information is required when calling/faxing for the exemption:

- Name of person calling
• Physician’s name
• Physician’s license number
• Name and address of the institution
• Phone number where the physician can readily be reached
• Patient name and gender
• Indication for methadone (MMT or analgesia)
• Methadone dose
• Date methadone ordered to start in hospital
• Phone number of the institution’s pharmacy

Pharmacy Registration

There is no special authorization required for pharmacists to order or dispense methadone. Any licensed pharmacist may order methadone from a wholesaler, providing they are not under a notice from the Office of Controlled Substances prohibiting them from buying or dispensing narcotics.

Pharmacies providing MMT services must notify the Prince Edward Island College of Pharmacists. The Pharmacist-in-Charge will login to the PEICP website and complete the registration online.

Prescription Requirements

Methadone is a straight narcotic. All federal and provincial laws and regulations that apply to straight narcotics apply to methadone. Verbal prescriptions or refills are not permitted. In PEI, all methadone prescriptions for MMT must be written on the Methadone Maintenance Prescription Fax Form and faxed to the pharmacy (Appendix B). If the prescriber wishes to make any changes to an existing MMT prescription, a new MMT prescription must be initiated and faxed to the pharmacy.

If for some reason the treatment period of a prescription overlaps with that of a previously issued prescription, instructions should be included on the new prescription to cancel the previous prescription.

MMT prescriptions must include:
  ➢ The number of doses of methadone to be provided
The daily dose in mg

- The dispensing schedule including:
  1. The dosing frequency
  2. Which doses must be administered as supervised ingestions
  3. Whether “carries” are permitted, and if so, the carry schedule

If this information is not included on the MMT prescription fax form, clarification with the prescriber is required.

Consistent with current best practices, the number of consecutive carry doses should be limited to a maximum of six (see pg. 20 Take Home Doses). An exception to this maximum can be made for reasons including the following:

1. The patient is going on vacation to an area where methadone is not readily available.
2. The patient has employment opportunities in an area where methadone is not readily available.
3. Other exceptional circumstances as agreed upon by the pharmacist and physician in collaboration.

If the number of carries prescribed exceeds six consecutive doses, the pharmacist will contact the physician and document the reason(s).
Methadone Maintenance Treatment: Pharmacy Services

The interactions a patient has with their health care providers have a significant impact on the patient’s success in a MMT program. Pharmacists are in the unique position of seeing and interacting with the patient daily. This daily interaction affords a pharmacist the opportunity to monitor a patient’s progress, identify actual and potential drug-related problems and make recommendations for changes to their care. Pharmacists who have a clear understanding of the goals of the program, of their role on the patient’s MMT team and who are committed to providing optimal care can substantially contribute to their patients’ success.

Pharmacist – Prescriber Collaboration

Effective communication and collaboration between the pharmacist and the patient’s MMT prescriber enables clinical decisions to be based on current, comprehensive patient information. Therefore, pharmacists are encouraged to develop a solid working relationship with the physicians/clinics who prescribe methadone for their patients. (CPBC, 2007)

Pharmacists will contact the prescribing physician regarding concerns about the patient’s progress, including if the patient:

- exhibits unusual behavior
- has not picked up their daily dose
- refuses all or a portion of their daily dose
- is impaired, intoxicated, or showing signs of withdrawal when they arrive at the pharmacy.
- any information or observed evidence of diversion of methadone

All communications with the physician must be documented on the patient’s profile. (CPBC, 2007) (CPSO, 2011)

Initial Pharmacist – Patient Discussion

A patient enrolling in the methadone program will be counselled in a private area in the pharmacy where conversation cannot be overheard by others, respecting the patient’s right to privacy and confidentiality.

The patient should receive an orientation to the pharmacy and be provided with the following information about methadone:
Methadone is an opioid the patient will become physically dependent upon and if the patient abruptly discontinues the medication, withdrawal symptoms will develop.

During the stabilization period, sedation and/or withdrawal symptoms may be present. Driving an automobile or operating machinery during the stabilization period of methadone maintenance may be dangerous. Such dangers can also arise again during dose adjustment or periods of instability.

Illicit drug or alcohol use with methadone can be dangerous. The use of other substances including prescribed or non-prescribed medications while taking methadone should be discussed with the patient’s physician and pharmacist as drug interactions may occur.

For reasons of safety the methadone dose may be withheld if the patient appears to be sedated or intoxicated. (Methadone Maintenance Treatment: Cautions-Methadone Intoxication and Overdose pg. 37)

Signs of methadone toxicity and of the need to seek medical attention should they occur (Appropriate Action for Administration Errors –Appendix H).

Because a single dose of methadone is effective for 24 hours, methadone patients should attend the pharmacy at the same time every day, preferably in the morning to receive their methadone. This will result in more consistent blood levels, fewer adverse effects and allow patients to be monitored for signs of methadone toxicity. (NLPB 2007)(CPSO 2011)

All missed doses of methadone will be reported to the physician. After two missed doses the patient will have to be reassessed by the physician before methadone is given again to ensure the patient’s dose is still safe.

It must be stressed by the pharmacist that the average daily dose of methadone may result in death if taken by a person not dependent on an opioid.

Side effects from methadone maintenance can include constipation, sweating, fatigue, decreased libido and weight gain. (Methadone Maintenance Treatment: Cautions-Adverse Effects pg. 35)

Fertility improves with stabilization on methadone, so patients should consider this factor during family planning.

The law of Canada places a duty on patients to inform any physician if they have received a narcotic from another physician within the preceding thirty-day period; otherwise the patient will have committed the offence of double doctoring.

It is preferable that the patient receives methadone from only one pharmacy. There is a risk to the patient if methadone is split between pharmacies. (NFLD, 2007)
The patient will be given an opportunity to ask questions about methadone or any other currently prescribed drugs. Relevant written information will be made available about the pharmacy, including hours of operation. (NLPB, 2007)

A treatment agreement can help the pharmacist explain to their patients the goals of the program, their responsibility as the pharmacist and the responsibilities of the patient (Pharmacist-Patient Agreement Appendix C). The pharmacist will review the treatment agreement with the patient and keep a copy signed by both the pharmacist and patient in the patient’s record.

A pharmacist may decide, during initial consultation with the patient and in compliance with the Code of Ethics, they do not wish to accept the patient in their MMT program. In such situations, the pharmacist is expected to take reasonable steps to ensure this service is provided and the patient’s care is not jeopardized.
Methadone Maintenance Treatment: Dosing

Introduction

Methadone’s long half-life allows it to be dosed once daily and is generally the optimal dosing regimen for MMT.

Dosing of methadone must be undertaken carefully, individually titrating the optimal dose for each patient. An effective dose for one patient can be a lethal dose for another. Methadone overdose cases resulting in death have been reported with single methadone doses as low as 40 mg in non-tolerant patients. Many factors impact an individual’s optimal vs. toxic dose including their opioid tolerance, physiologic and metabolic response, concurrent drug therapy; and methadone’s pharmacokinetic activity. (CPSO, 2011)

Methadone reaches steady state in 5 to 7 days. Therefore blood levels of methadone continue to rise for 5 to 7 days after starting therapy or increasing a dose. Toxicity or death may result from increasing a dose before the full effect of the current dose is known. A dose that is barely adequate on day one can be toxic by day 3 to 5. (CPSO, 2011)

There is wide variability in plasma methadone levels among people prescribed the same dose. There is no consensus regarding interpretation of blood levels in clinical practice.

Initial Dosing (low and slow)

- Patients are most at risk of death from MMT during the initial stabilization period, due largely to lack of consideration for methadone accumulation and overestimation of dose required
- Cross tolerance from other opioids to methadone is unpredictable and —dose equivalency reference tables should not be used to convert opioid intake to methadone.
- The range for the initial dose is usually between 10 mg to 30 mg per day for the first three days. Those at higher risk for toxicity, such as those who have been recently abstinent, the elderly, patients with respiratory or hepatic disease, and patients on interacting drug therapy, should begin at the lower range. (CPSO, 2011)
- A single oral dose is effective for at least 24 hours. (CPSO, 2011)
• Dose adjustments during the stabilization period are typically in the range of 5 mg to 15 mg increments, and only at the lower end of this range for those at higher risk for toxicity, and should not be made more frequently than every 3 to 5 days. (CPSO, 2011)
• A patient’s dose is titrated until the minimum effective dose is obtained, providing a 24 hour period free from withdrawal symptoms with minimal adverse effects.
• During dosage titration/stabilization the patient is likely to crave their drug of choice as methadone will likely wear off before their next dose.
• There is no minimum or maximum dose of methadone to provide maintenance treatment; however, the optimal dosage range for most patients is from 60-120 mg per day. (CPSO, 2011)
• Subtle effects of overmedication can include mild euphoria and extra energy, which patients may perceive as falsely beneficial. When these effects wear off patients may seek unnecessary and possibly harmful dose increases. (Payte 2002)
• Potential drug interactions should be taken into account when considering a patient’s methadone dose. Given that methadone is metabolized by the CYP450 system (primarily CYP 3A4), physicians and pharmacists should be aware of the drugs that can inhibit or induce methadone’s metabolism, resulting in increased or decreased blood levels respectively. (Methadone Maintenance Treatment: Cautions-Drug Interactions pg. 38)
• Potential pharmacodynamic interactions can occur when drugs that have similar pharmacologic profiles are combined with methadone. Examples include an increase in CNS depression and sedation when methadone is combined with alcohol and/or benzodiazepines and an increased risk of constipation and urinary retention with the use of anticholinergic medications such as dimenhydrinate.
• High methadone doses have been associated with QT interval prolongation. (Appendix H Risk Factors for QTc Prolongation in Patients on Methadone pg. 49)

A patient’s optimal dose is usually not achieved for two to eight weeks, or longer. The optimal methadone dose for a patient will:

• relieve all withdrawal symptoms
• reduce opioid cravings for 24 hr
• block euphoria from opioid use
• not cause sedation or other significant side effects. (CPSO, 2011)

“Tolerance” to methadone such that a stabilized patient requires an increased dose of methadone to once again achieve optimal effect rarely occurs and most people can be maintained on the same optimal dose for years. (ACCA, 2007)
In situations where a stabilized patient indicates that their dose is no longer adequately “holding them”, the physician should be advised for exploration of possible causes including:

- Ingestion of other substances that accelerate methadone metabolism (e.g. chronic alcohol, barbiturates, sedative hypnotics, etc.) or opioid antagonists (e.g. pentazocine, butorphanol, nalbuphine, naltrexone).
- Environmental stresses and other changes that increase the availability of illicit drugs resulting in increased cravings (Payte, 2005)

**Take Home Doses (“Carries”)**
The dispensing and administration of witnessed ingestion of methadone to patients must be done on a daily basis until such time as the prescriber authorizes carry privileges. The overarching considerations for granting carries are patient safety, public safety and risk of diversion. (Isaac, 2004)

Based on certain criteria, carry privileges may be granted by physicians to stable patients in order to improve the quality of the patient’s daily life.

- Once a patient is assessed to be functionally stable on methadone not all doses may have to be witnessed by a pharmacist, and the physician may grant carries.
- The first dose of each dispensing of carries will be witnessed by the pharmacist.

The practice of dispensing continuous carries without witnessed ingestions is strongly discouraged because:

- It is inconsistent with current best practices.
- It places the patient at risk of overdose or toxicity.
- It places the public at risk of diversion.
- Carries are not recommended during the first two to three months of treatment.
- Carries are a progression of treatment. A decision to grant carries by the physician should ideally be made in consultation with other professionals involved, including counselors and pharmacists. Therefore, it is important that pharmacists understand the general criteria for carries.

**Criteria for Carries**
1. Program participation including:
   a) Attendance at the pharmacy on schedule for their methadone dose;
   b) Attendance at scheduled appointments with the physician, nurse or counselor; and
   c) Compliance with the treatment agreement.

2. Demonstration of cognitive stability to assume responsibility for the care and use of the medication.

3. Use of drugs improves (as evidenced by acceptable urines for 3 months), either from abstinence or non-harmful use of drugs (harm can be seen as a continuum and can result from a single use or from long term use of drugs).

4. Social integration via employment, school attendance, child-care responsibilities, and volunteer work.

5. Patients with carries must be able to accept responsibility for the carried doses, which includes proper security and use of the methadone.

   a) Patients with unstable living arrangements such as those living on the street or in hostels without storage facilities may not be appropriate candidates to receive carries. If the pharmacist is aware of such circumstances, they will notify the physician.

   b) It is strongly recommended that patients bring a locked box with them in which to place the dispensed carries. Patients should be counselled to store the locked box containing carries in the refrigerator.

**Discontinuation of /Refusal to fill Carries**

A pharmacist may refuse to fill a prescription for a carry if there is concern for the safety of the patient, or the safety of others. This decision must be communicated to the physician.

Carries may be discontinued or decreased by the physician or pharmacist for one of many possible reasons including:

- the patient has failed to meet the terms of the treatment agreement.
- the patient has a sustained use of unauthorized drugs.
- the patient has produced an unacceptable urine sample or has tampered with the collection of the urine sample.
- the patient has approached another methadone treated patient suggesting or proposing to sell, buy or share any urine sample or tamper with any urine sample.
• the patient has diverted, or permitted to be diverted any part of the methadone.
• the patient has approached another methadone treated patient suggesting or proposing to sell, buy or share methadone.
• the patient shows disruptive behavior.
Dosing in Special Circumstances: Divided Dosing

Prescribers may authorize “split doses” for the following reasons:

1. A small proportion of patients may metabolize methadone rapidly.

2. Spilt dosing is generally recommended in the 3rd trimester of pregnancy in opioid dependent women and occasionally in the initiation phase of their treatment, after which the doses can be combined into a single daily dose.

Dosing in Special Circumstances: Missed Doses

A clinically significant loss of this tolerance may occur with as little as three days without methadone. (CPSO, 2011)

All missed doses will be:

1. reported to the physician and noted on the patient’s profile;
2. noted on the Patients Daily Methadone Witnessed Ingestion and Carry Log, Appendix D);
3. documented in the patient’s electronic record.

Patients who miss one dose:

- Can be administered the original prescribed dose provided they are not intoxicated. (CPSO, 2011)

Patients who miss their methadone treatment for two consecutive doses:

- must be reported to their physician.
- will not be dispensed further methadone without the physician’s authorization.
- should be reassessed by their prescriber because the prescribed dose may carry a risk of toxicity.
- should have their dose decreased to 50% of the current dose or 30mg. (CPSO, 2011)
After missing four or more days of methadone: (CPSO, 2011)

- the body has eliminated the drug.
- the remainder of the patient’s current prescription will be cancelled.
- the physician will be contacted, and the patient should be restarted at 30 mg or less.

Patients who have missed doses may show withdrawal symptoms including nausea, vomiting, pupil dilation, tremor, runny nose, teary eyes, goose bumps and sweating. If withdrawal is suspected, contact the physician. (Isaac 2004)

**Dosing in Special Circumstances: Vomited Doses**

Methadone is rapidly absorbed when given orally. Consuming methadone slowly in small sips may decrease the risk of vomiting. (CPBC, 2007)

When a patient reports that they have vomited their dose:

- The patient should contact the physician. Alternatively the pharmacist may do so if they have witnessed the incident and provide him or her with as much information as possible (time the dose was taken, time of vomiting, etc.). (CPBC, 2007)
- Physicians can authorize replacement doses by faxing a prescription to the pharmacy. This authorization must be referenced to the original methadone prescription.

Note that, because it is difficult to completely empty the stomach by emesis, repeated dose replacement can lead to overdose. The following guideline is offered should it be agreed that a prescription for a replacement dose be issued:

- emesis < 15 minutes after consumption – replace not more than 50% of the full dose
- emesis between 15 - 30 minutes after consumption - replace 25 to 50% of the dose.
- emesis> 30 minutes after consumption – no replacement. (CPSO, 2011)

**Methadone Discontinuation**

Methadone maintenance programs focus on maintaining patients on methadone for as long as they continue to benefit from treatment. While some patients may want to reduce their
methadone dose or stop using methadone entirely; these outcomes are not the exclusive emphasis of most programs. (Health Canada, 2002)

Although achieving a sustained drug-free state is an optimal treatment goal most individuals who are dependent on opioids cannot achieve this. Programs with a long-term maintenance philosophy have better retention rates than programs with a short-term maintenance philosophy. (Health Canada, 2002)

Patients may express an interest in tapering off methadone and leaving the program. The wish to taper off methadone may be influenced by several factors (Health Canada 2002):

- the patient’s unrealistic expectations for recovery
- pressure from family and friends who may not recognize that recovery is a long-term process
- the patient’s sense of stigma in being associated with the program
- their concern over the cost of the treatment
- the inconvenience of regular attendance at appointments

Since the likelihood of relapse is high, patients should be advised that tapering off methadone is an option, but that it is possible to continue on methadone maintenance and lead a fulfilling life. (Health Canada, 2002)

If a patient starts a “self-taper” by drinking only a portion of their daily methadone, this will be recorded on the prescription with a note of the estimated dose consumed. The pharmacist must discuss the taper with the prescribing physician. This discussion provides a chance to work together to determine a strategy for future prescribed doses. Slower tapering has shown to be more successful, with a maximum taper of 5 mg per week being suggested. (ACP, 2007) (CPBC, 2007)

The last part of the taper process is the most difficult, and therefore should be done slowly and cautiously. Many patients can only tolerate decreases of 1 mg every one to two weeks at this point. Abrupt discontinuation is discouraged as withdrawal symptoms can be severe and long-lasting. (ACP, 2007)
If the patient is insistent on discontinuing their methadone treatment, the patient should be made aware of the consequences and risk of relapse to illicit drug use. Other members of the health care team should be informed of the patient’s decision and status. (ACP, 2007)

Medication for the symptoms of withdrawal should be considered (clonidine, loperamide, NSAIDs, dimenhydrinate), and counselling on other appropriate resources should be made available. (ACP, 2007)

**Methadone Maintenance Treatment: Preparation and Administration of Doses**

It is the position of the PEICP that the public would be better served if pharmacists used a commercially available 10mg/mL methadone solution when preparing individual patient doses because of:

- enhanced patient safety (fewer steps to be potentially impacted by human error);
- enhanced stability of commercial product;
- general expectation that large volume production is undertaken under the requirements of federal legislation governing manufacturing.

However, recognizing that pharmacists have the knowledge and skills to compound drugs, it is permissible for pharmacists to prepare a methadone stock solution from methadone powder when the concentration required is not available in a commercially prepared product.

In addition to the processes directed in this document, pharmacy compounded methadone solutions will be prepared in compliance with standard compounding techniques described in NAPRA’s *Guidelines to Pharmacy Compounding* and adopted by the PEICP.

**Preparing Stock Solution**

1. All containers used in the preparation and storage of methadone solutions must be used for methadone only and labelled accordingly.

2. Calculations for the preparation of the compound must be completed by a pharmacist. It is preferable if these calculations are verified using an independent calculation performed by another pharmacist or pharmacy staff member.

3. A compounding log must be retained to record the specifics of solutions prepared, including how much was prepared and who prepared the product (see *Methadone Stock Solution Compounding Log* Appendix F). Noting the date of preparation and the use-by-date on the...
container assists dispensary staff in ensuring that all methadone is dispensed within a reasonable amount of time.

4. Procedure

- Weigh the correct amount of methadone powder to prepare a 10 mg/mL solution and place it into a calibrated container.
  *(Note: you must first calibrate the container with a known volume of water, measured in a scientifically approved graduated device. Mark the calibrated volume with a permanent marker so you do not have to recalibrate the measuring device each time you use it.)*

5. Dissolve the methadone crystals in distilled water to a 10 mg/mL concentration. The stock solution must be stored in a light resistant bottle in the fridge, in a secure location.

6. The stock bottle must be CLEARLY LABELLED as to the:
   a. drug
   b. strength
   c. preparation date
   d. expiry date of 14 days from the date of preparation (under refrigeration)
   e. unique batch number (as assigned and subsequently recorded in compounding log)
   f. auxiliary label —Keep Refrigerated

7. All methadone solution must be stored in distinctive containers unlike those for water, juice, etc. (accidental poisoning may occur if a solution of methadone is mistaken for distilled water).

**Individual Dose Preparation**

1. Calculations for the preparation of the patient’s dose must be completed by a pharmacist. It is preferable if these calculations are checked using an independent calculation performed by another pharmacist or pharmacy staff member.

2. Procedure:
   i. Measure the amount of 10mg/mL methadone solution required to obtain the individual dose using an appropriately sized syringe.
   ii. Perform independent double-check of quantity of methadone in syringe.
iii. Put measured stock solution in a child proof, amber, calibrated bottle.
iv. Add sufficient quantity of Tang*** to bring the final volume of the dose to 100mL

3. The final dosage volume for each individual dose must not be less than 100 ml, both for on-site consumption and for take home carries (e.g. a dosage of 80 mg requires 8ml of a 10 mg/ml stock solution, then qs to 100ml with liquid Tang®). A consistent volume enables patients to more easily identify unanticipated changes in the taste of their solution [i.e. in the event of an error]). This volume is sufficiently large to ensure the dose is not retained in the mouth. Patients have been known to “cheek” their dose, spit it out later and then inject or divert it.

4. All individual patient doses will be bottled separately in 100 mL amber, childproof bottles. The dilute solutions are generally stable for at least one month in the fridge.

5. When periodic auditing of unconsumed carry bottles is being considered, the use of tamper evident seals is recommended.

6. If individual patient doses are prepared in advance of being processed for dispensing, they must be clearly labeled with at least: (1) strength and quantity of methadone (i.e. methadone 8 mg in 100 mL) (2) prepared date/expiry date and (3) initials of preparing pharmacist (4) the unique batch number assigned if using a compounded stock solution.
These doses must be stored securely with the stability of the solution taken into consideration when deciding where to store prepared doses.

7. All doses provided to the patient (i.e. by witnessed ingestion or by witnessed ingestion + carries) must be labelled in accordance with the provincial labelling requirements. In addition, the label of each all dispensed doses must include the total dose of mg of methadone contained in the bottle.

8. Individual patient doses dispensed as carries must also be labelled with:
   - The date of ingestion of carries
   - The auxiliary label “Keep in Refrigerator”
   - The auxiliary label “ Keep Away From Children”
   - A notation “Drink entire contents of bottle” and one of the following auxiliary labels:
     - Methadone can be fatal when taken by individuals for whom it is not prescribed or,
ii. 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.

9. For security and safety reasons, it is recommended that the preparation of methadone occurs away from the high traffic area in the dispensary.

**Note: Orange flavored Tang® is the preferred diluent because:**

- it frustrates extraction of the methadone from solution
- it is consistent with the practice of the majority of MMT programs (a consistent product enables patients to more easily identify unanticipated changes in the taste of their solution [i.e. in the event of an error]).

However, an exception to Tang can be made in special circumstances. When deemed appropriate by the pharmacist, and in collaboration with the patient and the MMT team, alternative diluents may used including: Grape Kool Aid, Grape Crystal Light, Grape Crystal Light with 0.1% Sodium Benzoate, Allen’s Apple Juice (NLPB 2007)

**Storage and Stability**

When storing individual doses of methadone pharmacists must consider the following:

- The stability of commercially available methadone solution versus compounded methadone solution,
- Whether the individual doses have been diluted,
- The date the individual dose was prepared.

**Stock Solutions**

An aqueous stock solution using distilled water has an expiry date of 14 days under refrigeration.

An aqueous stock solution using bacteriostatic water is expected to have an expiry date of 30 days.

(NLPB, 2007)
Individual Patient Doses

The following chart identifies the stability of methadone solutions according to the diluents used and storage conditions:

<table>
<thead>
<tr>
<th>Diluent</th>
<th>Period of Stability Room Temperature 20-25°C</th>
<th>Period of Stability Refrigerated 5°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grape Flavoured Kool Aid®</td>
<td>17 days</td>
<td>55 days</td>
</tr>
<tr>
<td>Orange Flavoured Tang®</td>
<td>11 days</td>
<td>49 days</td>
</tr>
<tr>
<td>Allen’s® Apple Juice</td>
<td>9 days</td>
<td>47 days</td>
</tr>
<tr>
<td>Grape Flavoured Crystal Light®</td>
<td>8 days</td>
<td>54 days</td>
</tr>
<tr>
<td>Grape Flavoured Crystal Light® with 0.1% Sodium Benzoate</td>
<td>29 days</td>
<td>--</td>
</tr>
</tbody>
</table>


Administration of doses

The dispensing and administration of methadone to patients must be done on a daily, witnessed ingestion basis until such time as the prescriber authorizes carry privileges.

Prior to dispensing, the pharmacist must ensure that it is safe for the patient to ingest methadone, including assessing whether or not the patient:

- appears intoxicated (see Special Circumstances- Intoxicated Patients, pg 31)
- has two or more missed doses (see Dosing – Dosing in Special Situations: Missed Dose, pg 20)
- shows signs of withdrawal *(see exception below) (see Cautions – Withdrawal and Methadone Underdose, pg 37).
- exhibits significant changes in appearance and behaviour

In such situations the dose must be withheld until the physician is contacted. Opioid withdrawal, while uncomfortable, is not life threatening - but methadone toxicity can be fatal. (Isaac, 2004)
*Note: Exception - Patients may exhibit signs of mild withdrawal during initial stabilization and tapering periods. In such situations, the dose should not be withheld.

**Administration Area**
A respectful environment within the pharmacy will be provided to methadone clients. Pharmacies will set aside a private area for dispensing and observing the ingestion of methadone.

Some patients may be comfortable taking their dose at the pharmacy counter in full view of other customers, while some may prefer more privacy. It is important to respect the patient’s wishes. Making a note in the patient’s profile as to their preference is suggested.

**Patient Verification**
Positive identification is required for all patients presenting at the pharmacy for the first time. Due to potential staff changes, clients should be prepared to present a form of identification at time during their MMT. If a patient cannot provide the required identification, as determined by the pharmacy, the prescribing physician may be contacted to assist in verifying the patient’s identity. (CPBC, 2007)

**Supervised Ingestion**
The directions on the prescription will indicate that the dose is to be dispensed daily and that the consumption will be witnessed by a pharmacist. (CPBC, 2007) This is to ensure that the patient consumes their dose on site and prevents diversion. (NLPB, 2007) If the physician has not clearly indicated his or her intentions, the pharmacist must assume daily witnessed ingestion and witness every dose.

**Administration Errors**
In the event of a medication dosing error, confirmed or suspected, the pharmacist must take appropriate and necessary action to minimize harm to the patient, ensuring transparency throughout the entire process. This includes prompt consultation with the patient’s other health care provider(s) for determination of appropriate action. The resource [Appropriate Action in Administration Errors](#), Appendix G, is a readily retrievable reference for these situations.

In addition to the following standards specific to methadone, it is expected that pharmacists will manage the error in accordance with the NAPRA [Model Standards of Practice for Canadian Pharmacists (2009)](https://www.napra.org) and the individual pharmacy’s medication error management policy.
Methadone Maintenance Treatment: Special Circumstances

Intoxicated Patients

In most methadone related deaths, concurrent use of sedatives such as benzodiazepines and alcohol were found to have contributed to the cause of death. (CPBC, 2007)

Prior to dispensing methadone pharmacists must assess all patients for signs of intoxication methadone including:

- slurred speech
- incoordination
- smelling of alcohol
- unusual behavior
- ataxia

If an intoxicated patient presents at the pharmacy asking for their methadone dose, their physician will be contacted to discuss whether or not the dose should be administered that day. If the physician is unavailable, the dose will be withheld and the pharmacist will inform the physician at the next convenient time.

It is safer to refuse to dispense a patient’s methadone than to medicate an intoxicated patient. Opioid withdrawal, while uncomfortable, is not life threatening - but adding methadone to the other drugs already consumed by an intoxicated patient may be.

The handling of such situations will have been made clear to the patient well in advance, by means of a pharmacist-patient agreement. In such a situation, the pharmacist will:

- Try to avoid confrontation with the patient by explaining that it would be dangerous to medicate at this time.
- Warn the patient against driving a car.
- Inform the prescriber that the patient appeared intoxicated in your pharmacy.
- Clearly document their actions. (Isaac, 2004)
Pregnancy

Pregnancy in opioid-dependent women is an urgent indication for inclusion into a methadone maintenance program. As in the case of HIV/AIDS, expectant mothers should be accepted into treatment immediately. (ACP, 2007)

Compared to the risks associated with continued opioid use, the use of methadone during pregnancy is preferred for both the mother and the fetus. Studies have shown that MMT improves both maternal and neonatal outcomes in pregnant opioid-dependent women. (CPSO, 2011)

Some of the advantages of methadone treatment in pregnant, opioid-dependent women include:

- better prenatal care and nutrition
- improved birth weight
- decreased infant mortality (Isaac, 2004)

Special care is required and initiation of methadone during pregnancy is often done in hospital or in close association with a hospital. (ACP, 2007)

Split dosing is suggested in the third trimester due to changes in the woman’s body composition. Pregnancy may cause the effects of methadone to abruptly change and therefore close monitoring is required. (ACP, 2007)

Pregnant women should not miss a dose of methadone, as the withdrawal symptoms associated with missing a dose may cause fetal distress. (NLPB, 2007)

Take-home Carries released to patient’s agent (Exceptional Circumstance)

In rare, exceptional circumstances (e.g. patient is physically incapable of attending the pharmacy), patients may request that an agent pick up their authorized carries. In this situation, the patient must provide their pharmacist with written authorization from their prescribing physician. This authorization must be date specific and the agent and circumstances must be clearly defined. (CPBC, 2007)

If a patient is in police custody, methadone will not be given to a police officer. A health care provider is the only one who can assess and supervise methadone ingestion. (Isaac, 2004)
Home Delivery

The PEICP does not recommend home delivery of methadone.

For methadone prescriptions that require witnessed ingestion, the pharmacist must be present to witness the dose at the pharmacy. **Witnessing ingestion cannot be delegated to a technician or other pharmacy staff member.**

Guest Dosing

There are occasions, such as a vacation or business travel, when a methadone patient might ask to be medicated on a temporary basis at another pharmacy. Guest dosing generally involves situations in which the patient cannot be provided with sufficient take-home doses for the period of absence. Such situations may arise when the patient:

- is not considered functionally stable enough to be given take-home doses for the time period.
- may be away for a long period that prevents issuing sufficient take-home doses. For example, juice will spoil, it is not practical to travel with a large number of containers, or concern exists about loss or theft of a large number of containers.

With the patient’s consent, the pharmacist can facilitate identifying a conveniently located pharmacy that would be willing to dispense methadone on a temporary basis. Health care professionals may contact the PEICP to identify pharmacies dispensing methadone in PEI. Addiction Treatment Centers in other provinces can often facilitate identification of MMT physicians and pharmacies in their province. The name of a methadone-dispensing pharmacy will not be provided to a patient without the prior consent of that pharmacy.

The patient or pharmacist will inform the methadone prescriber of the name and address of the temporary pharmacy. If the prescription at the usual pharmacy is still valid for the time the patient will be away, the physician should cancel the remainder of that prescription and write a new one for the temporary pharmacy.

The pharmacists at both pharmacies must communicate clearly with one another at the beginning and end of the guest-dosing period, so that everyone understands where and when
the patient is receiving the methadone. This communication is imperative to prevent double-dosing or missed dosing. (Isaac, 2004)

HIV/AIDS Treatment Concurrent with Methadone Maintenance

High priority is given to patients with HIV/AIDS in order to help decrease the risk of transmission of HIV infection in the community. The frequent contact with health care providers associated with methadone maintenance treatment may also increase the benefit of HIV/AIDS treatments. (ACP, 2007)

Many medications used for the treatment of HIV/AIDS interact with methadone, but these interactions can generally be managed by monitoring side effects and adjusting the dose accordingly. (Isaac, 2004)
Methadone Maintenance Treatment: Cautions

Adverse Effects

Methadone is generally well tolerated. Table 1 lists common adverse effects.

Table 1: Common Adverse Effects

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>• May occur at the start of treatment and when doses are increased</td>
</tr>
<tr>
<td></td>
<td>• Patients generally become tolerant to this effect</td>
</tr>
<tr>
<td></td>
<td>• Caution should be exercised when performing activities that require alertness</td>
</tr>
<tr>
<td></td>
<td>• Avoid other substances that may contribute to sedation</td>
</tr>
<tr>
<td>Sweating</td>
<td>• Commonly reported (up to 50% of high dose patients)</td>
</tr>
<tr>
<td></td>
<td>• May be related to inappropriate dose (too)</td>
</tr>
<tr>
<td></td>
<td>• Reassure patient that it causes no medical problems</td>
</tr>
<tr>
<td></td>
<td>• Balance reduction of dose to address sweating with risk of opioid use relapse</td>
</tr>
<tr>
<td>Constipation</td>
<td>• Common to all opioids</td>
</tr>
<tr>
<td></td>
<td>• Reported to be less with methadone</td>
</tr>
<tr>
<td></td>
<td>• Results from interference with bowel</td>
</tr>
<tr>
<td></td>
<td>• Recommend regular exercise and increased fluid intake</td>
</tr>
<tr>
<td></td>
<td>• Occasional osmotic laxative use may be recommended</td>
</tr>
<tr>
<td></td>
<td>• Regular use of stimulant laxative should be discouraged</td>
</tr>
<tr>
<td>Weight Gain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• May be due to decrease drug use and improved nutrition as a result of methadone treatment</td>
</tr>
<tr>
<td>Sexual Problems (libido)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• May increase or decrease</td>
</tr>
<tr>
<td>Psychoactive Effects</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Mild euphoria can occur in those given a dose slightly higher than their tolerance</td>
</tr>
<tr>
<td></td>
<td>• Patient may complain of withdrawal when effect wears off</td>
</tr>
<tr>
<td>Insomnia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Tends to improve as patients are stabilized</td>
</tr>
<tr>
<td></td>
<td>• Educate patient with regard to good sleep hygiene techniques</td>
</tr>
</tbody>
</table>
Less common adverse effects include muscle and bone aches, peripheral edema, change in menstruation, flushing and itching. (Isaac, 2004)

**QT Interval Prolongation**

Administration of methadone is associated with QTc interval prolongation and torsades de pointes. The rate of this occurrence is not clear and while it seems to be dose-dependent, it is important to note that sudden cardiac death associated with methadone has been seen at dosages as low as 29 mg/day. This means that arrhythmia can occur in dosages commonly used in both analgesia and addiction treatment, and that dosage is just one consideration with regard to limiting arrhythmia risk. (Stringer, 2009) (Pearson 2005)

More information about QT prolongation including drugs known to cause QT prolongation can be found at [www.azcert.org](http://www.azcert.org)

*See Risk Factors for QTc Prolongation in Patients on Methadone, Appendix G*

**Methadone Intoxication and Overdose**

Assessing a patient’s clinical signs, and considering the feedback a patient provides on their symptoms, are important indicators in assessing the adequacy of their dose and the safety of continuing with their current methadone dosing schedule.

Overdose may occur as a result of:

- Too high a dose being prescribed
- Increasing the dose too quickly
- Drug interactions (especially alcohol, benzodiazepines and other opioids
- Impaired metabolism due to hepatic/renal insufficiency
- Misuse of prescribed methadone therapy ie. patients not taking carry doses as intended
- Accidental ingestion in a non-tolerant person*
- Intentional ingestion in a non-tolerant person*

(*Note: non-tolerant person includes a patient who has missed 3 or more doses of their daily methadone)
Other risk factors include age, cardio-respiratory illness, use before onset of sleep, and concurrent use of sedative drugs. (CPSO, 2005)

Symptoms of Methadone Intoxication and Overdose: Euphoria, sedation, dysphoria, motor retardation, pinpoint pupils, slowed speech, respiratory depression, circulatory collapse, bradycardia, cardiac arrest, death.

Note: Definite signs of methadone toxicity may not become apparent for 5-9 after the overdose. (CPSO, 2011)

**Withdrawal and Methadone Underdose**

With abrupt discontinuation of methadone, signs and symptoms of withdrawal are not usually observed until 36 to 48 hours after the last dose. They appear gradually and peak at about 72 hours after the last methadone dose. They may continue at this peak level for about two weeks. The withdrawal syndrome then declines very gradually. Symptoms may be experienced for months. Therefore, patients who are doing well and want to discontinue methadone treatment are generally encouraged to taper slowly. The rate of taper is usually guided by the patient. (Isaac, 2004)

Alternative explanations for the withdrawal symptoms should be sought if the patient:

- gives an inconsistent history of withdrawal symptoms;
- has one isolated symptom (such as insomnia or nausea);
- advises the onset of symptoms is not related to the time of the dose; or
- has been taking a stable dose and suddenly complains of withdrawal (see below).

A dose might be considered acceptable if the patient sleeps comfortably at night and only has mild withdrawal symptoms on awakening. (CPSO, 2007)
Drug Interactions

Pharmacodynamic interactions can occur when drugs that have similar pharmacologic profiles are combined with methadone. Examples include an increase in CNS depression and sedation when methadone is combined with alcohol and/or benzodiazepines and an increased risk of constipation and urinary retention with the use of anticholinergic medications such as dimenhydrinate.

Methadone is metabolized mainly via the CYP 450 3A4 enzyme system and as a result, may interact with medications that either induce or inhibit these enzymes. (CPSO, 2011)

The sequence of administration 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 first drug is discontinued. It is only if a patient is stabilized on methadone and an interacting drug is initiated or discontinued that an interaction may occur.

*Note: The following table contains examples of drug interactions affecting/affected by methadone. Pharmacists must refer to a current reputable drug interaction reference for a comprehensive list.*

| Drugs that may decrease methadone levels | Barbiturates  
|                                         | Carbamazepine  
|                                         | Various antiretroviral medications  
|                                         | Chronic alcohol use  
|                                         | Phenytoin  
|                                         | Primidone  
|                                         | Rifampin  
|                                         | Urinary acidifiers  
|                                         | St. Johns Wort  
| Drugs that may increase methadone levels | Ciprofloxacin  
|                                         | Fluconazole/ketoconazole  
|                                         | Cimetidine  
|                                         | Various antiretroviral medications  
|                                         | Diazepam  
|                                         | Acute alcohol use  
|                                         | Fluvoxamine  
|                                         | Urinary alkalinizers  
| Drugs whose levels may be affected by | Desipramine  

Methadone Maintenance Treatment Services- Practice Directives for Community Pharmacies, 2014
<table>
<thead>
<tr>
<th>methadone</th>
<th>Zidovudine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interactions with food</td>
<td>Grapefruit juice may inhibit metabolism</td>
</tr>
</tbody>
</table>

Medications that might precipitate withdrawal syndrome for patients on methadone must be avoided. These are mainly opioid antagonists such as Naltrexone and partial agonist such as pentazocine, butorphanol, nalbuphine.

Appendix A- Pharmacokinetics and Actions of Methadone

Dosing of methadone must be undertaken carefully, individually titrating the optimal dose for each patient. An effective dose for one patient can be a lethal dose for another. Many factors impact an individual’s optimal vs. toxic dose including the individual’s opioid tolerance, physiologic and metabolic response, and concurrent drug therapy; and the drug’s pharmacokinetic activity.

Absorption

- When given orally, methadone is effectively absorbed from the gastrointestinal tract within approximately 30 minutes.
- Oral bioavailability is approximately 90 per cent.
- Peak plasma levels occur about two to four hours after oral ingestion.
- Blood levels of methadone continue to rise for five days after starting therapy or increasing a dose. Death from accumulated toxicity may be the result of increasing a dose before the full effect of the current dose is known (i.e. a dose that is barely adequate on day one can be toxic by day three to five). (CPSO, 2011) (Kleber, 2008)
- A dose as low as 40mg can be lethal by day three in a methadone naïve adult and single doses as low as 30mg have been fatal in children. (CPSO, 2005)

Distribution

- Methadone is extensively bound to plasma proteins.
- Volume of distribution is 4 – 5 L/kg of body weight.
- Elimination half-life (t1/2) of methadone averages 24 to 36 hours, with a range of 13 to 56 hours. (Kleber, 2008) This long half-life permits once-daily dosing for methadone maintenance. Its analgesic effects are not as long lasting, and dosing in pain is usually every six to eight hours. The long half-life also results in it taking longer (i.e. five to seven days) for plasma levels to reach steady state than most other opioids, and therefore doses must be titrated slowly.
- There is wide variability in plasma methadone levels among people prescribed the same dose. There is no consensus regarding interpretation of blood levels in clinical practice.
- In pregnancy, methadone passes through the placenta to the fetus.
- Methadone is excreted into breast milk in small amounts.
Metabolism

- Methadone is metabolized in the liver through demethylation and glucuronidation.
- It is predominantly metabolized through the cytochrome P450 system, mainly by CYP 3A4.
- Active metabolites are produced in small amounts. The primary metabolite has no significant pharmacological activity.
- Metabolism by CYP3A4 is subject to induction and inhibition effects by many other drugs.

Excretion

- Methadone is excreted in the urine and feces, both as unchanged methadone and as metabolites.
- Urinary excretion of methadone and metabolites is dose dependent. It becomes the major route of excretion when doses exceed 55 mg/day.
- Renal absorption of the parent compound increases as urine pH increases.

Physiological Effect

- As a synthetic opioid agonist, methadone affects similar physiological functions as morphine and other opioids, although to varying degrees.
- Patients develop a tolerance for some of the physiological effects of methadone once stabilized on a dose, at which time cognitive skills and attention are not impaired.
- Physiological tolerance to methadone is lost very quickly. A patient who has missed 3 days of methadone doses may no longer be able to safely tolerate the dose to which they had been titrated, and therefore will not be given their current maintenance dose. (CPSO 2011)
Table 2. Physiologic Effects of Methadone

<table>
<thead>
<tr>
<th>Primary Actions</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Analgesia</td>
<td>• Sleep disturbances</td>
</tr>
<tr>
<td>• Sedation</td>
<td>• Nausea and vomiting</td>
</tr>
<tr>
<td>• Respiratory depression</td>
<td>• Constipation</td>
</tr>
<tr>
<td>• Euphoria (oral methadone causes less euphoria than intravenous heroin)</td>
<td>• Dry mouth</td>
</tr>
<tr>
<td></td>
<td>• Increased sweating</td>
</tr>
<tr>
<td></td>
<td>• Vasodilation and itching</td>
</tr>
<tr>
<td><strong>Other Actions</strong></td>
<td></td>
</tr>
<tr>
<td>• Decreased blood pressure</td>
<td></td>
</tr>
<tr>
<td>• Constriction of the pupils</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal tract actions</strong></td>
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<tr>
<td>• Reduced gastric emptying</td>
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<tr>
<td>• Reduced motility</td>
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<tr>
<td>• Elevated pyloric sphincter tone</td>
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<tr>
<td>• Elevated tone of Sphincter of Oddi can result in biliary spasms</td>
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<tr>
<td><strong>Skin actions</strong></td>
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<tr>
<td>• Histamine release</td>
<td></td>
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<tr>
<td>• Endocrine actions including</td>
<td></td>
</tr>
<tr>
<td>• Reduced Follicle Stimulating</td>
<td></td>
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<tr>
<td><strong>Hormone</strong></td>
<td></td>
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<tr>
<td>• Reduced Luteinizing Hormone</td>
<td></td>
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<tr>
<td>• Elevated Prolactin</td>
<td></td>
</tr>
<tr>
<td>• Reduced adrenocorticotropic</td>
<td></td>
</tr>
<tr>
<td>• Reduced testosterone</td>
<td></td>
</tr>
<tr>
<td>• (Endocrine function may return to normal after 2-10 months on methadone)</td>
<td></td>
</tr>
<tr>
<td>• Elevated Anti Diuretic Hormone</td>
<td></td>
</tr>
<tr>
<td>• Antitussive</td>
<td></td>
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</tbody>
</table>
## Methadone Prescription Fax Form

For Patients on Methadone Maintenance Treatment

<table>
<thead>
<tr>
<th>Pharmacy Name:</th>
<th>Fax:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Name:</td>
<td>PHN:</td>
</tr>
</tbody>
</table>

**Rx** Methadone________ mg _______________Dose in words p.o. Once Daily (each dose to be individually bottled, labeled and mixed in juice)

Start Date:________________________ End Date:________________________ Inclusive

Total Doses:______ Total Observed Doses:______ Total Take-home doses (carries):______

Drink observed doses in the pharmacy on days circled:

<table>
<thead>
<tr>
<th>Mon</th>
<th>Tues</th>
<th>Wed</th>
<th>Thurs</th>
<th>Fri</th>
<th>Sat</th>
<th>Sun</th>
</tr>
</thead>
</table>

Special instructions:

Hold prescription if two or more consecutive doses are missed and contact prescriber. Notify prescriber if a dose is missed or if there are any concerns about this prescription.

_________________________ __________________________ /

Physician Signature Print Name License #

_________________________

Date

Prescriber 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 or retained so that it cannot be re-issued.
Verification: This certifies the above prescription has been transmitted only to the pharmacy indicated.

Name of Sender: _____________________________  Date Sent: ___________________________
Appendix C- Patient Pharmacist Agreement

Patient-Pharmacist Agreement

Name: __________________ Address: ________________________________
Tel#: __________________ Postal Code: __________________________
Date of Birth: ____________ Physician: __________________________

OUR COMMITMENT TO YOU:

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

We will treat you professionally and respectfully at all times.

We are part of your health care team and will communicate with your physician when necessary. The kinds of issues we will discuss with your physician include:

- missing one or more doses,
- refusal to drink the full prescribed dose of methadone,
- being intoxicated or sedated when you arrive at the pharmacy,
- doses for replacement of lost, stolen or vomited methadone, and;
- seeing another physician and being prescribed mood-altering medications by another physician.

We will provide methadone to you exactly as your physician has prescribed it.

We are not able to give you extra doses, early doses, or methadone to take home unless your physician prescribes it.

We are required to watch you drink your dose of methadone and have a conversation with you afterward, unless your physician specifically directs otherwise on your prescription. You may also be required to drink water after swallowing your dose.

We will not dispense your methadone to anyone other than you unless directed to do so by your physician on your prescription.
We welcome any comments or suggestions you may have in regards to our services.

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

**YOUR COMMITMENT TO US:**

I will not arrive at the pharmacy before the pharmacy is open. I will arrive for my daily dose between the hours of ____ and ____ daily (preferably in the morning and should be a consistent time each day).

I will respect the pharmacy’s neighbourhood. I will ensure that all pharmacy packaging materials and litter are disposed of in the garbage containers provided.

I will be respectful of others, including staff, other patients, and neighbours of the pharmacy.

If I am prescribed take-home doses of methadone (carries), I will store them safely and securely in my home.

I realize that I may be asked to present identification before receiving my first dose of methadone from the pharmacy and when receiving methadone from any new pharmacist on staff.

I realize I may not be given a methadone prescription if I am under the influence of other substances.

I will not participate in any illegal activity at the clinic/office/pharmacy etc.

I will not abuse any staff person verbally or otherwise.

I realize that my doctor, pharmacist, nurse and other health professionals directly involved in my care may openly communicate with each other concerning any aspect of the methadone program.

I realize any drug abuse will be reported to the prescribing physician.

If I see a doctor other than the methadone prescribing doctor, I will inform them that I am in the methadone program.

I agree to undergo supervised urine samples on a periodic basis, as may be required of my program.

I will not stock-pile my methadone doses.
I will be observed swallowing my methadone dose and this will be confirmed by speaking to the pharmacist after swallowing the dose and/or drinking water.

I will dispose of the container used to drink my methadone dose in the pharmacy.

I realize it is best to spread the time between methadone doses by at least 16 hours. There will be no twice daily dosing.

I realize that all doses must be made up in Tang, unless specified otherwise by the physician on each prescription.

I will ensure that all caps on all carries are tightly secured and that the doses will be kept in a secure place away from others, especially children.

I will confirm I have received the appropriate number of doses and sign for same. I may periodically be expected to present remaining carry bottles to the pharmacy.

I realize I require a valid prescription and no methadone will be dispensed without one. It is my responsibility to make sure the prescription does not expire before a new prescription is presented to the pharmacy.

I realize that any doses vomited or any carries lost will not be replaced without a written prescription from the prescribing physician.

I realize that a missed day means a missed dose which will not be made up. If I am required to pay for my methadone, I will pay at the time I receive the dose.

Failure to pay for my doses may result in discharge from the program. The pharmacist may obtain information about my medication use from other pharmacies.

I understand that failure to honour this agreement may result in my no longer being serviced at this pharmacy.

I have read the above agreement and understand and agree with its content

Patient Name: ________________________ Patient Signature: ________________________
Pharmacist Name: ____________________ Pharmacist Signature: ____________________
Date: ____________________

Methadone Maintenance Treatment Services Practice Directives for Community Pharmacies, 2014 48
Appendix D Patient Daily Methadone Log

Patient Daily Methadone Witnessed Ingestion and Carry Log

Patient: _______________________________________________
Physician: _____________________________________________

<table>
<thead>
<tr>
<th>Date</th>
<th>Rx#</th>
<th>Dose (mg/bottle consumed)</th>
<th># of carry bottles given</th>
<th># of carry bottles returned</th>
<th>Patient signature</th>
<th>Pharmacist signature</th>
</tr>
</thead>
<tbody>
<tr>
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</table>

If the patient does not arrive for their witnessed ingestion or carry doses, it must be noted on this log.
### Appendix E- Methadone Stock Solution Log

<table>
<thead>
<tr>
<th>Date Prepared</th>
<th>Manufacturer of powder</th>
<th>Manufacturer’s lot and expiry date</th>
<th>Quantity of solution prepared</th>
<th>Quantity of powder used</th>
<th>Expiry date of solution</th>
<th>Batch number assigned by Pharmacist</th>
<th>Initials of preparer (pharmacist/tech)</th>
<th>Initials of checking pharmacist</th>
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</thead>
<tbody>
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</table>
Appendix F- Appropriate Action for Administration Errors

If you become aware of a medication dosing error, you should take appropriate and necessary action to minimize harm to the patient, ensuring transparency throughout the entire process. This includes prompt consultation with the patient’s other health care provider(s) for determination of appropriate action.

In addition to the following standards specific to methadone, it is expected that pharmacists will manage the error in accordance with the NAPRA Model Standards of Practice for Canadian Pharmacists and the individual pharmacy’s medication error management policy.

**Methadone Overdose**

As soon as you realize the error:

- Tell the patient. If the patient has left the pharmacy, contact him or her by telephone. If the patient has no phone, you may need to contact the patient’s physician or MMT clinic to obtain a contact number or send police to the home.
- Advise the patient to seek medical attention immediately. If the patient refuses medical attention, document the time and details. Ask the patient to remain in the care of a friend or relative for the day;
- Advise the patient of the symptoms of overdose; including the possibility of euphoria and respiratory depression (see Symptoms of Methadone Intoxication and Overdose, pg 40. Make follow-up contact with the patient throughout the day;
- Advise the patient’s physician or MMT clinic;
- Reassess the patient's health condition before administering the next daily dose.

**Methadone Underdose**

- Advise the patient’s physician or MMT clinic and the patient as you would with an overdose.
- Once the patient is contacted, offer the patient the "difference" of methadone between the amount administered and the amount prescribed.
- Should the patient refuse to return for the methadone, advise them of the possibility of withdrawal and the symptoms related to opioid withdrawal.
• If the patient cannot be reached during business hours, advise them of the error at their next administration. (AADAC, 2007)

**Important Methadone Overdose Information for the Patient**

• Methadone overdose (receiving a larger dose of methadone than intended) is a serious medical emergency.
• Methadone is a long-acting medication and can stay in your body for many hours.
• Even if you have been on methadone for a long time, taking more methadone than your body is used to can be dangerous. Even what may seem like a small dose increase can be dangerous.
• If you are new to methadone or have not been taking your regular dose, even for a few days, you are at increased risk of overdose.
• Taking too much methadone can result in difficulty breathing (slow or shallow breathing), drowsiness, small pupils, and, in some cases, coma and death.
• For this reason **IT IS ESSENTIAL THAT YOU GO TO THE EMERGENCY DEPARTMENT** to be observed for a minimum of 10 hours, and maybe longer, depending on your symptoms.
• There is good treatment available in the emergency department that can reverse the effects that you may get from taking too much methadone. (CPSO, 2005)
Appendix G: Risk Factors for QTc Interval Prolongation

Risk Factors for QTc Prolongation in Patients on Methadone


<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older Age</td>
<td>Non-Opioid treatments</td>
</tr>
<tr>
<td>Structural heart disease</td>
<td>Myocardial infarction, congestive heart failure, valvular disease, cardiomyopathy</td>
</tr>
<tr>
<td>HIV</td>
<td></td>
</tr>
<tr>
<td>Low Potassium Levels</td>
<td>On drugs that lower potassium (e.g. diuretics)</td>
</tr>
<tr>
<td>Low Prothrombin</td>
<td></td>
</tr>
<tr>
<td>On medications that inhibit Cytochrome p450 3A4*</td>
<td>HIV antivirals eg. indinavir</td>
</tr>
<tr>
<td></td>
<td>Antifungals e.g., Fluconazole, ketoconazole</td>
</tr>
<tr>
<td></td>
<td>Calcium channel blockers e.g., Diltiazem, verapamil</td>
</tr>
<tr>
<td></td>
<td>Antimicrobials e.g., Norfloxacin</td>
</tr>
<tr>
<td></td>
<td>Antidepressants e.g., Fluvoxamine</td>
</tr>
<tr>
<td></td>
<td>Contraceptives e.g., Mifepristone</td>
</tr>
<tr>
<td></td>
<td>Food eg. Grapefruit juice</td>
</tr>
<tr>
<td>Alcohol Use</td>
<td></td>
</tr>
<tr>
<td>Cocaine Use</td>
<td></td>
</tr>
<tr>
<td>Family or past history of long QT syndrome</td>
<td>History of syncope or sudden cardiac death in the family</td>
</tr>
<tr>
<td>On medications that prolong QTc*†</td>
<td>Cardiac medications e.g., amiodarone, sotalol</td>
</tr>
<tr>
<td></td>
<td>Antipsychotics e.g., chlorpromazine, haloperidol, pimozide, thioridazine</td>
</tr>
<tr>
<td></td>
<td>Antibiotics e.g., clarithromycin, erythromycin</td>
</tr>
</tbody>
</table>

*NOTE: The drugs listed in this table are examples of drug interactions affecting / affected by methadone. Pharmacists must refer to a current reputable drug interaction reference for a comprehensive list.

†More information about QT prolongation including drugs known to cause QT prolongation can be found at www.axcert.org
References


Leavitt SB, Editor, Addiction Treatment Forum: Methadone Dosing & Safety in the Treatment of Opioid Addiction; ClincoCommunications, Inc., Mundelein, IL Sept 2003


Winstock AR, Lea T, Sheridan J. Problems experienced by community pharmacists delivering opioid substitution treatment in New South Wales and Victoria, Australia. Addiction, 2009; 105, 335–342