

NEWFOUNDLAND AND LABRADOR PHARMACY BOARD

Standards of Pharmacy Practice



The Newfoundland and Labrador Methadone Maintenance Program

Approved as Guidelines by the NLPB Board March 5, 2005
Updated: June 16, 2005
Approved as Standards of Pharmacy Practice: January 20, 2007
Updated: October 6, 2008

Table of Contents

Introduction	3
Pharmacist's Role in Pharmaceutical Care.....	4
Care of the Methadone Patient.....	4
General Guidelines	5
What is Methadone?.....	5
Authority to Prescribe and to Dispense Methadone	5
Patient Orientation to Pharmacy Service and the Methadone Maintenance Program.....	7
Methadone Dosing Issues	8
Initial Dosing.....	8
General Dosing.....	8
Missed Doses	9
Split Dosing	9
Preparing Oral Dosages of Methadone	10
Dispensing Methadone to the Patient.....	10
Inappropriate Behaviour	11
Refusal to Fill a Prescription.....	12
Patient's Choice to Move to Another Pharmacy.....	12
Costs and Payments	12
Methadone use in Hospitals or Correctional Settings.....	12
Take-Home Doses or Carry Medication.....	13
Criteria for Carries	14
Appendix A - Methadone Program Agreement Form.....	16
Appendix B - Part Fill Documentation.....	18
Appendix D - Daily Dose Log.....	21
Appendix E - Take Home/Carry Dosage Log.....	22
Appendix F - Incident Report Form.....	23
Appendix G – Methadone Compounding Log.....	24
Appendix H - Background Information	25
Appendix I - Methadone Dosing Recommendations for Treatment of Chronic Pain	30
Appendix J - References.....	36

Introduction

Methadone is a synthetic pure opioid agonist with good oral bioavailability, and a long duration of action. Methadone prevents withdrawal symptoms and helps reduce drug cravings in opioid dependent individuals. It also blocks the euphoria produced by short acting opioids. This collection of attributes makes this drug an appropriate choice for opioid maintenance therapy.

Over the past few years, there has been a significant increase in the number of pharmacies providing methadone to patients, in particular, those patients on methadone maintenance therapy for opioid dependence. At this time in Canada methadone remains the only opioid approved for long-term (greater than 180 days) treatment of opioid dependence.

The philosophy of methadone maintenance therapy is based on harm reduction; it attempts to nurture an attitude of tolerance and understanding towards opioid dependent individuals in our community. It typically involves the daily oral administration to opioid dependent individuals of methadone over extended periods of time as a substitute for heroin or other short acting opioids. Once an individual has been stabilized on a dose of methadone subsequent daily doses should not cause sedation, analgesia, or euphoria. Methadone is long acting; it can prevent the occurrence of withdrawal symptoms or cravings when a patient receives an optimal dose. This enables individuals to function normally and to perform mental and physical task without impairment. In sufficient doses, cross-tolerance to other opioids develops i.e. methadone "blocks" the euphoric effects of self-administered illicit opioids.

Methadone maintenance therapy has been shown to improve the health status of patients, decrease the transmission of HIV, increase employment, decrease associated costs to society and decrease mortality. Methadone is primarily intended for i.v. opioid users because of the significant morbidity and mortality issues associated with i.v. drug use. Methadone maintenance treatment may be considered for non-i.v. opiate users who experience adverse consequences, and have poor support systems

Generally, the goals of the Methadone Maintenance Program are to:

- Reduce illicit opiate use and other i.v. drug use and ideally become drug free
- Reduce use of other mood-altering substances
- Reduce morbidity and mortality
- Reduce criminal activity associated with addiction
- Improve physical and psychological health
- Maintain and improve quality of family life and personal productivity
- Facilitated reintegration into the workplace and education systems

This document is intended to provide information and guidance to pharmacists involved in the dispensing of methadone for opioid dependence, and to promote consistency in the dispensing of methadone for opioid dependence. These standards are not intended to apply to the dispensing of methadone for chronic pain.

While dosing recommendations on the use of methadone for the treatment of chronic pain are attached for information purposes as Appendix I, the recommendations in Appendix I are not a part of these Standards.

Success of a methadone maintenance program can only be achieved when patients understand the requirements of their continued participation and pharmacists apply the requirements in a fair and consistent manner. These standards lay the framework for those requirements.

These Standards were developed after review of guidelines published by Health Canada as "*Best Practices: Methadone Maintenance Treatment*" and after review of guidelines for pharmacists adopted in British Columbia, Alberta, Saskatchewan, New Brunswick and Nova Scotia. Also considered were the final report of the Newfoundland

and Labrador OxyContin Task Force and the work of the Newfoundland and Labrador Working Group on a Methadone Maintenance Program. The inclusion of aspects of each of these documents into these Standards is gratefully acknowledged.

These Standards are also intended to be complementary to the Methadone Maintenance Treatment Guidelines adopted by the College of Physicians and Surgeons of Newfoundland and Labrador for the guidance of physicians. Any perceived inconsistencies between these Standards and those of the College of Physicians and Surgeons of Newfoundland and Labrador, or any other comments and suggestions for improvements should be forwarded to the Newfoundland and Labrador Pharmacy Board office.

It is recognized that there may be particular situations, or extenuating circumstances, in which some of the provisions of these Standards of Practice may not be appropriate. In such situations where these Standards are not followed it is expected that the pharmacist will document such situations or circumstances.

Research and evaluation of methadone maintenance treatment is ongoing. Evaluation of MMT programs is essential in order to determine the extent to which programs meet their objectives and the needs of the patients. This evaluation requires the commitment of the physicians and pharmacists who are delivering treatment, patients, counsellors and the support of policy makers. This document will be reviewed as new treatment protocols are revised.

Pharmacist's Role in Pharmaceutical Care

Care of the Methadone Patient

A non-judgmental and respectful approach, which builds a good rapport with the patient, will encourage them to stay motivated to continue treatment. Substance dependence is a chronic and relapsing disorder, not an acute condition that can be rapidly cured upon detoxification. Relapses are a common part of recovery. As the pharmacist will see the patient on a daily basis at the beginning of treatment, they are in a good position to assess the patient's progress and provide information to other members of the treatment team. The pharmacist must be aware of the treatment goal of the patient (reduction of harmful use vs. abstinence). Good communication with the physician, addictions counselor and other members of the treatment team is essential. The pharmacist may access information about the patient's drug use from other pharmacies.

Patient confidentiality is paramount. To ensure patient safety however, and with the patient's written consent, pharmacists may exchange relevant information, such as the use of other drugs, urine testing results, the use of alcohol, etc., with the other professionals on the treatment team.

It is required that the pharmacy establish individual agreements with their methadone maintenance patients.

Examples of issues to be addressed in such an agreement (**Appendix A**) include:

- I understand that the pharmacist may share patient information/prescription records with other health professionals involved with my care.
- I understand that methadone is an opioid that I will become physically dependent on, and abrupt discontinuation will cause withdrawal symptoms.
- Illicit drug or alcohol use with methadone may be life threatening. For safety reasons, the methadone dose may be withheld if I appear to be intoxicated or under the influence of other substances.
- I agree to provide ID when required for the pick-up of my medication.
- I understand that missed, lost, stolen or wasted doses will not be replaced without a new prescription.

- I understand that inappropriate behaviour on my part, including threats, disruptive or violent behaviour or illegal activity, may result in a refusal to continue filling my prescription.

This agreement shall be signed by the patient and kept on file in the dispensary.

Ethics of confidentiality must be maintained for methadone as it is for other medication orders, to ensure patient's safety. The professionals involved with treatment may exchange information regarding:

- Prescriptions for mood altering drugs obtained from other doctors;
- Use of other drugs, whether pharmaceutical, street drugs or alcohol, especially if they appear to be under the influence; and/or
- Urine testing results or other information relevant to the patient's medical well being.

The pharmacist should be aware that many patients receiving methadone have other co-morbid conditions such as HIV, Hepatitis C, endocarditis, depression and other mental illnesses. Universal precautions in dealing with these patients should be practiced.

As patients often have engaged in criminal activities, they have more involvement with the justice system than the health care system. Continuity of care between correctional services and community pharmacies is required. It is advisable to maintain contacts within the correction, probation and justice services systems.

General Guidelines

What is Methadone?

- Methadone is a synthetic diphenylheptane-derivative opioid agonist with properties similar to morphine.
- Methadone has a relatively long duration of action, with a half-life of about 24 hours. It prevents withdrawal symptoms and helps reduce drug cravings in opioid dependent individuals. It also blocks the euphoria produced by short-acting opioids.
- Methadone maintenance therapy typically involves the daily oral administration of methadone over an extended period of time as a substitute for heroin or other opioids to a heroin/opioid dependent individual.
- Methadone is an opioid that the patient will become physically dependent on and if the patient abruptly discontinues the medication, withdrawal symptoms result.
- Methadone may, in some instances, be used for the relief of severe chronic pain. It is generally reserved for situations in which other opioid pain relievers have proven ineffective. Because analgesia is not related to serum half-life, multiple dosing daily is usually needed for pain management.
- Methadone maintenance is generally a long term or lifetime treatment option
- Methadone is supplied as a white crystalline powder that is water-soluble. It is also supplied as a clear unflavoured 10 mg/ml liquid (Metadol) in 100 ml sizes.
- More detailed information about methadone is found in **Appendix H**.

Authority to Prescribe and to Dispense Methadone

The *Controlled Drugs and Substances Act* (Canada) and *Narcotic Control Regulations* (Canada) provide that methadone may only be supplied to certain health professionals or dispensed to a person from whom the pharmacist has received a written prescription, signed and dated by a practitioner of medicine who is authorized to prescribe methadone.

A physician who wishes to prescribe or administer methadone must first obtain authorization from the Federal Minister of Health. An authorization is issued for a specific time period. There are currently no restrictions on pharmacists as to who may dispense methadone.

The pharmacist is responsible for ensuring that the practitioner is authorized to prescribe methadone prior to dispensing it to the patient. To confirm physician status, the pharmacists can call the Office of Controlled Substances at (613) 946-5139.

A Pharmacist-In-Charge of a pharmacy that wishes to dispense methadone must:

- **register with the Newfoundland and Labrador Pharmacy Board**
- **notify the Board of the hours of operation.**
- **have a copy of these guidelines and the latest edition of "Methadone Maintenance: A Pharmacist's Guide to Treatment" (published by Centre for Addiction and Mental Health) on hand for pharmacists' reference. To order please refer to: <http://www.camh.net/publications/methadonemaintenance.html>.**
- **ensure any pharmacist dispensing methadone has studied these guidelines and is knowledgeable in Methadone Maintenance Treatment.**

A prescription for any narcotic, including methadone, must have a specified total quantity stated on the prescription for it to be valid and legally filled by a pharmacist. **A physician must state a specific total quantity to be dispensed.**

In the *Narcotic Control Regulations* the definition of a prescription is as follows:

"Prescription" means, in respect of a narcotic an authorization given by a practitioner, that a stated amount of a narcotic be dispensed for the person named in the prescription."

It is the responsibility of the pharmacist to ensure all orders or prescriptions are written in accordance with section 31 of the *Narcotic Control Regulations*, which states:

"31. (1) No pharmacist shall supply narcotics except in accordance with subsections (2) and (3) and sections 34 to 36.

(2) A pharmacist may supply a narcotic other than methadone to a person

(a) If the person is exempted under section 56 of the Act with respect to the possession of that narcotic; or

(b) If the pharmacist has first received a written order or prescription therefore signed and dated by the practitioner and the signature of the practitioner, where not known to the pharmacist, has been verified by him.

(3) A pharmacist may supply methadone to:

(a) A licensed dealer

(b) Another pharmacist

(c) A hospital employee or a practitioner in a hospital

(d) A person exempted under section 56 of the Act with respect to methadone; or

(e) A person from whom the pharmacist has received a written order or prescription signed and dated by a practitioner of medicine who is exempted under section 56 of the Act with respect to methadone."

A prescription for methadone indicating that it be continued until there is a dosage change, without indicating the total amount to be dispensed, would violate Section 31 of the *Narcotic Control Regulations*, and would not be an acceptable prescription.

The written prescription must be in the pharmacist's possession BEFORE the methadone is given to the patient. A new prescription is required for any changes in dosage, except when the dosage is being tapered up or down by the physician. A tapered dosage regimen may be written on one prescription. (e.g., patients will be started on 30mg for two days, 40mg for two days and 50mg for three days on the first prescription)

Part-fills must not be confused with refills. Refills are not permitted for narcotics.

Part-fills for methadone are permitted if the total quantity dispensed does not exceed that originally authorized. The principal requirement is that the physician **MUST** authorize the total quantity as a single figure and not as a smaller figure multiplied by the number of times the medication is to be dispensed. The physician must be conscious of the total, which s/he is prescribing. (Please see attached example of appropriate part fill documentation – **Appendix B**)

Faxed prescriptions for methadone are acceptable as long as the prescriber follows approved Standards of Practice for faxing a prescription. If the pharmacist suspects that the prescription has been tampered with in any way, the prescribing physician must be consulted prior to filling.

Summary:

- Physicians must have special authorization issued by the Office of Controlled Substances, Health Canada to prescribe methadone for maintenance therapy, detoxification or analgesia. Pharmacists may call the federal Methadone Line at (613) 946-5139 or email: exemption@hc_sc.gc.ca for verification.
- Any licensed pharmacist may order methadone from a wholesale. There is currently no special authorization required for pharmacists to order or dispense methadone.
- 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. The prescription must be written on the tamper resistant prescription form approved by the Newfoundland and Labrador Pharmacy Board and the College of Physicians and Surgeons.
- Prescriptions may be written as part-fills. A hard copy of the original prescription must be generated for each part-fill, referenced back to the original prescription, initialled by the pharmacist filling the part-fill and filed with the N/C prescriptions filled that day.
- Prescriptions for methadone must be clear and complete. The prescription must include the total amount of methadone to be provided, the required daily dose and the dispensing schedule. The dispensing schedule should include the dosage frequency and indicate if the doses must be administered as supervised ingestions. It should also specify if "carries" (take-home dosages) are permitted and, if so, the carry schedule.
- A record (dosage chart) must be kept for each daily dose administered to each patient. The patient must sign for each dosage administered. If "carries" are provided to the patient, these must also be signed for.
- Records must be kept for methadone purchases and sales. If stock solutions are prepared, compounding records should be maintained. The records should include the name, lot number, manufacturer and quantity of methadone used along with the total volume and date prepared. The initials of the pharmacist preparing and/or checking the prescription should be included.
- **A Methadone Compounding Log must be kept to document the preparation of stock solutions (Appendix G)**

Patient Orientation to Pharmacy Service and the Methadone Maintenance Program

The patient should receive an orientation to the pharmacy, including information about methadone. The patient should be given an opportunity to ask questions about methadone or any other currently prescribed drug. Relevant written information should be made available about the pharmacy, hours of operation, and any treatment agreements you may wish the patient to sign.

Patients are enrolled in the program voluntarily and are required to sign an agreement acknowledging their responsibilities and requirements for remaining in the program. (Appendix A)

If a pharmacy decides after consultation with the patient they do not wish to dispense methadone to a specific patient the patient will have the option of addressing the decision through the complaints process of the Pharmacy Board.

Certain points have to be communicated to the patient upon orientation:

- Methadone is an opioid the patient will become physically dependent on 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 the 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 your physician as drug interactions may occur
- For reasons of safety the methadone dose may be withheld upon consultation with the physician if the patient appears to be intoxicated.
- Any missed doses of methadone will be reported to the physician. After three missed doses the patient will have to be reassessed by the physician before methadone is given again.
- 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.
- Fertility frequency 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.

Methadone Dosing Issues

Initial Dosing

The initial dose for methadone maintenance therapy is 15mg to 30mg per day for the first three days. A single oral dose is effective for at least 24 hours Dose adjustments during the stabilization period are typically in the range of 5 mg to 15 mg increments. Dose adjustments should not be made more frequently than every 3 to 4 days. Three days represents the average time for an individual, being dosed daily, to reach 87% of steady state for a drug with a half-life of 24 hours. Remember that it requires 4 doses to achieve a steady state due to the long half-life of methadone.

General Dosing

Methadone must be dispensed in a vehicle (such as Tang) and made up to a volume of at least 100 ml so that the possibility of injection is minimized.

Single dose overdose cases resulting in death have been reported with methadone doses as low as 40mg in non-tolerant patients. Methadone blood levels continue to rise for five days after starting or raising a dose. Death by accumulated toxicity may result from increasing a dose before the full effect of the current dose is known.

Because a single dose of Methadone is effective for 24 hours, Methadone patients should be counseled to attend the pharmacy at the same time every day to receive their Methadone. This will result in more consistent blood levels and fewer adverse effects.

The optimal methadone dose for maintenance therapy is the dose which relieves withdrawal symptoms and blocks euphoric and drug cravings; without causing sedation or other significant side effects. The usual maintenance dose ranges from 50 mg to 120 mg daily. A dose above 120 mg per day is considered to be in the high range. It is recommended that a physician knowledgeable in addiction medicine be involved with patients receiving doses above 120 mg daily.

The usual dose for pain management (analgesia) is 5-20 mg every 4-8 hours.

Missed Doses

All missed doses should be reported to the physician especially if the patient has not yet been stabilized or of there is an apparent pattern of missing doses that the physician should be made aware of.

Patients who miss their methadone treatment for two or more consecutive days must be reported to their physicians. If three consecutive doses are missed, no further doses are to be dispensed without the physician's authorization. Due to the variability and unpredictable loss of tolerance experience with opioids, the physician must be contacted for a new prescription at a lower dose. After missing five or more days of methadone the body has eliminated the drug, the physician should be contacted and the patient should be restarted at 30mg or less.

Patients who have missed doses may show withdrawal symptoms including nausea, vomiting, pupil dilation, tremor, runny nose, teary eyes, and sweating. If withdrawal is expected contact the physician.

Split Dosing

Once stable, fast metabolizers (such as pregnant patients, patients taking anti-epileptics, etc.) may need split dosing even at relatively high doses. Splitting the daily dose 50/50 a.m. and p.m. is often effective. Split doses are not recommended for new patients.

Preparing Oral Dosages of Methadone

A stock solution of methadone may be prepared by dissolving methadone crystals in bacteriostatic water at the strength of 10mg per ml. but bear in mind, there are patients with sensitivity to preservatives. An aqueous stock solution using bacteriostatic water would be expected to have an expiry date of 30 days. An aqueous stock solution using distilled water will be stable at least 1-2 weeks when kept refrigerated (see Appendix C). Since stability is influenced by diluents reference to Appendix C must be made in determining a suitable storage period.

The major concern is bacterial growth, as opposed to stability. Therefore, check the stock solution regularly for signs of bacterial growth.

The stock solution should be stored in a glass, light resistant bottle in the fridge, in a secure location. The stock bottle must be **CLEARLY LABELED** as to the drug, strength and preparation date.

The diluent used to prepare the final solution is usually TANG. TANG does not lend itself to injection (can't be boiled down). Methadone may also be dispensed in other flavoured diluents such as grape Kool-Aid, grape Crystal Light, Apple Juice or high quality lemonade. Orange drinks or other juices used for dilution are also susceptible to bacterial growth and some go rancid in just a few days. A stability chart is provided for your information in **Appendix C**.

The final dosage volume for each individual dose must be not less than 100 ml, both for on site consumption and for take home carries, i.e. sufficiently large enough 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.) For example, a dosage of 80 mg requires 8ml of a 10mg/ml stock solution, then qs to 100ml with liquid Tang or another flavoured diluent. For lower doses, a more dilute stock solution may be prepared. You may wish to adjust the amount of water when preparing Tang to allow for the water in the stock solution.

Each 100 ml dose should be bottled separately (one bottle per dose). "Carries" should be dispensed in separate 100 ml doses, clearly labelled in childproof, amber, bottles. The dilute solutions (in juice or flavour crystals) are generally stable for at least one month in the fridge.

To improve patient service and accommodate workflow, doses should be prepared ahead of time. Label each dose appropriately and store in refrigerator until dispensed and administered to the patient.

Cases of accidental poisoning have occurred in a pharmacy when a stock solution of methadone was mistaken for distilled water. **All methadone solutions should be labelled clearly and stored separately from the distilled water in a distinctive container. Colouring the stock solution is an acceptable option.** Although it may not always be possible or practical for security reasons, it is recommended that the methadone, both as stock solution and as doses prepared for administration, be stored in a separate refrigerator away from the high traffic area in the dispensary.

Dispensing Methadone to the Patient

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

Carry doses may be dispensed only as specifically authorized on the prescription.

To ensure that the patients consume their dosages on site and to prevent diversion to the street, the medication must generally be consumed under the direct supervision of the pharmacist. The pharmacist must ensure that the

methadone has been swallowed, for example, by having the patient talk after taking their dose, or having them drink water after their dose. This is an ideal time to do patient counselling and follow up monitoring. Ask the patient to return the bottle or cup they have used.

A single dose of methadone is effective for 24 hours. Therefore, patients should be counselled to attend the pharmacy at the same time each day to ensure consistent blood levels.

The pharmacist is responsible to ensure that patients receive their methadone in person. Doses are not to be released to spouses, friends or relatives. **If a pharmacist is observing the patient consume methadone outside a pharmacy setting, a log sheet must be maintained at the pharmacy, signed by the patient and the administering pharmacist.**

Spilled, lost or stolen doses may not be replaced without a new prescription from the physician. Patients are responsible for protecting their "carry" doses.

It may be appropriate to replace a dose if the patient actually vomits it up in front of the pharmacist immediately after taking the dose and the pharmacist knows, beyond a doubt, that emesis occurred. Notify the physician if this occurs. Document in the patient's chart. Further discussions regarding lost or vomited doses should take place with the physician and addictions counsellor. Note that, because it is difficult to completely empty the stomach by emesis, repeated dose replacement can lead to overdose.

The following guideline¹ is offered should it be agreed that a prescription for a replacement dose be issued:

- *Emesis < 15 minutes after consumption – replace the full dose*
- *Emesis between 15 - 30 minutes after consumption - replace 50% of the dose*
- *Emesis > 30 minutes after consumption – no replacement*

Patients who miss their methadone treatment for **two** or more consecutive days **must** be reported to their physician. **If three or more consecutive doses are missed** no further doses are to be dispensed without the physician's authorization. A clinically significant loss of tolerance to methadone may occur with as little as three days without medication. Therefore the physician may consider reducing the dose temporarily to prevent an overdose situation.

Long acting morphine may be prescribed concurrently until the patient's methadone dose reaches a level that controls withdrawal symptoms and cravings. In such cases the morphine is administered daily along with the methadone in a manner which does not allow for diversion, such as splitting the capsules and placing the granules on a teaspoon or in the methadone solution. (Note: these preparations are not soluble in solution and will clump at the bottom of the bottle requiring several rinses of the bottle with water to obtain the total dose.)

Records must be kept for each daily dose administered to the patient and the patient must sign for each dose administered, including carries authorized by the physician. **(Appendix D).** Have the patient sign the log record indicating receipt of the dose.

Inappropriate Behaviour

Physicians and pharmacists should have an agreement and a plan of action in place to manage problematic situations which may arise, such as missed/lost/stolen doses, impairment with alcohol and other drugs, violence, selling or diversion of carries, shoplifting, and other inappropriate behaviour, **before** the behaviour occurs.

If the patient appears to be intoxicated with alcohol or other drugs they should not receive their dose of methadone as the use of methadone in combination with alcohol may lead to serious adverse events. The physician should be contacted, and the patient may be advised that s/he would be reassessed and asked to come back later.

¹ Methadone Maintenance Guidelines, Ontario, 2004

Refusal to Fill a Prescription

At any time the pharmacist may refuse to dispense methadone for any of the following reasons:

- **Threats** – the patient, family member or friend has threatened the safety or well being of any staff member or another patient or pharmacy customer by oral or written action
- **Disruptive Behaviour** – the patient, family member or friend has engaged in disruptive behaviour on the premises
- **Violent Behaviour** – the patient, family member or friend has engaged in violent behaviour towards a staff member, a patient or another person
- **Illegal Activity** – the patient, family member or friend has engaged in an illegal act on the premises
- **Diversion of Methadone** – the patient has diverted, or allowed to be diverted, any part of their methadone
- **Contraindication of Methadone** – In the opinion of the prescriber, methadone has become contraindicated for the patient
- **Missed Doses** – The patient has failed to pick up doses of methadone for 3 consecutive days (unless alternative arrangements for pick-up have been made or there is convincing evidence that the failure to pick-up was beyond their control).

In such instances, the physician should be notified of any refusal to dispense methadone.

Patient's Choice to Move to Another Pharmacy

If the pharmacist is aware that the methadone patient has come from another pharmacy or institution, the pharmacist must check with them before administering the first dose to verify when they had their last dose administered and to determine the reason for the patient's choice to move to another pharmacy. Narcotic prescriptions may **not** be transferred. A new prescription is required.

Ideally, the physician would indicate on the prescription whether the patient is starting therapy or is continuing treatment.

Costs and Payments

The patient is responsible for payments as with any other prescription.

Methadone use in Hospitals or Correctional Settings

During an inpatient stay, or the confinement of a patient to a correctional setting, the institutional staff should ensure the continuity of methadone pharmacotherapy through its own pharmacy or by arrangement with the patient's community pharmacy. Should a patient present at the Emergency Room for admission, or observation, require a daily dose, the hospital pharmacy should contact the patients' pharmacy to determine the dose and in collaboration with the patients' pharmacy make arrangements for the patient to receive their dose. It is important that both pharmacies maintain contact and keep the other informed of any changes in the patient's therapy.

If the physician ordering the patient's methadone is not the admitting physician, and there is no physician on staff authorized to prescribe methadone, the physician responsible for the patient in the institution may obtain a temporary exemption (for dependency or analgesia) to prescribe methadone for a patient already stabilized on methadone.

A temporary exemption is issued to the physician responsible for the patient's treatment at the hospital or other institution. It must be noted that only practitioners are eligible to receive a temporary exemption (e.g. medical residents may not receive an exemption). The exemption is granted for the period of the patient's hospitalization (up to 60 days) and expires on the earlier of the date on which the patient is discharged from the hospital or a maximum of 60 days. Should the patient be hospitalized longer than 60 days, the authorization may be extended. A physician with a temporary exemption may not start new patients on methadone. A temporary exemption is only for patients who are already on methadone before hospitalization.

The attending physician may obtain a temporary exemption by contacting the Office of Controlled Substances

Phone: (613) 946-5139

1-866-358-0453 (toll free)

Fax: (613) 952-2196

e-mail: exemption@hc-sc.gc.ca

The following information is required to be provided:

- Full name and Licence number of physician
- Telephone number of physician
- Name and address of hospital
- Telephone number of hospital pharmacy
- Name of patient
- Indication for methadone (dependency or analgesia)
- Daily dose of methadone
- Date of first dispensing dose

Methadone should be administered in a correctional facility in accordance with MMT Policy and Procedure Statement of that facility.

Before discharge, the institutional pharmacist should notify the patient's community pharmacy of the time of discharge and the time and amount of last dose of methadone to ensure resumption of outpatient pharmacotherapy without interruption. If the patient is discharged to continuing care facilities, arrangements for continued provision of methadone should be part of the discharge plan.

Take-Home Doses or Carry Medication

Based on certain criteria, "carry" privileges may be granted by physicians to stable individual patients to reduce disruption in and improve the quality of the patient's daily life.

Patients should drink the first dose under pharmacist observation and are then permitted to take the remaining carry medications home.

Carries must always be diluted to 100 ml with TANG or another suitable diluent.

A dose as small as 10 mg can be fatal to a child, therefore carries must be dispensed in childproof bottles and patients must be counselled to keep doses out of the reach of children.

Carries must be labelled according to federal and provincial requirements and must include **a warning that the amount of drug contained could cause serious harm or toxicity if taken by someone other than for which it was prescribed.**

Carries should be refrigerated and taken on the day of the week indicated on the label.

Patients should be advised that they might be asked at any time to appear at the pharmacy with the balance of their carry medications. This is to deter patients from diverting their methadone.

Patients should be informed that a locked container for their carries is advisable in situations where other individuals (especially children) may have access to the carries or in the circumstances of shared accommodation with other drug users.

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 should notify the physician.

Since some pharmacies may not be open on weekends or holidays, the patient may need to use an alternate pharmacy on weekends or holidays. It may, or may not, be appropriate for the patient to receive carries because a pharmacy is not open to dispense methadone. The physician has been guided to call the NLPB for a list of pharmacies dispensing methadone on weekends and holidays. If more than one pharmacy is treating the same patient, both pharmacies should be aware of the arrangements.

Specific instructions regarding the dispensing carries must be clearly indicated on the prescription by the physician. The prescription should indicate the number of carries to be dispensed per week, or the days of the week the patient receives carries, or the specific dates the patient is to receive carries.

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

Physicians generally **will not authorize more than six consecutive carry doses**. An exemption to this restriction may be given for the following reasons:

- The patient is going on vacation to an area where methadone is not readily available
- The patient has employment opportunities in an area where methadone is not readily available
- Compassionate reasons
- The client has been in the program for a reasonable length of time, has been well controlled, and is progressing in the program.

If the number of carries authorized by the prescription exceeds the guidelines established by the College of Physicians and Surgeons, the pharmacist should obtain documentation of the reason carries were authorized from the physician before the carries are dispensed.

The dispensing of carries must be recorded in a similar manner as the daily administration records. (Appendix E)

Criteria for Carries

As a pharmacist and member of the care team you may be contacted by the physician, addictions counsellor or other member of the treatment team to offer your assessment of the patient's progress in treatment and their compliance with the use of carry medications. It is therefore important that you understand the general criteria for carries.

Carries are a progression of treatment. Once a patient has been stabilized on methadone not all doses may have to be witnessed by a pharmacist and the physician may grant carries. A decision to grant carries by the physician should ideally be made in consultation with other professionals involved, such as counsellors and pharmacists.

Carries may be issued to patients who are considered to be functionally stable (carries are not recommended during the first two months of treatment) and are assessed by the care team and physician for the following:

- Program participation including:
 - Attendance at the pharmacy on schedule for their methadone dose
 - Attendance at scheduled appointments with the physician, nurse or counsellor; and
 - Compliance with the treatment agreement;
- Demonstration of cognitive stability to assume responsibility for the care and use of the medication;
- 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).
- Social integration via employment, school attendance, child-care responsibilities, and volunteer work.

Patients with carries must be able to accept responsibility for the carried doses, which includes proper security and use of the methadone. 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 and addictions counsellor. (See attached incident report - **Appendix F**).

Carries may be discontinued by the physician or pharmacist for any of the following reasons:

- Evidence the patient has failed to meet the terms of the treatment agreement;
- 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;
- Disruptive behaviour by the client, the client's family or friends.

Appendix A - Methadone Program Agreement Form

Full Name:

Last Name

First Name & Initial

MCP #:

Date of Birth:

Home Address:

Street Address (or P.O. Box)

City/Town & Province

Postal Code

Phone Numbers:

() _____

Home Phone Number

() _____

Other Phone Number

Physician

Physician Name

Physician Phone Number

Methadone Program Agreement

1. I realize I may not be given a methadone prescription if I am under the influence of other substances.
2. I will not participate in any illegal activity at the clinic/office/pharmacy etc.
3. I will not abuse any staff person verbally or otherwise.
4. 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.
5. I realize any drug abuse will be reported to the prescribing physician.
6. If I see a doctor other than the methadone-prescribing doctor, I will inform them that I am on the methadone program.
7. I agree to undergo supervised urine samples on a periodic basis, as ordered by the physician.
8. I realize I may not request a carry privileges unless I have tested "clean" in the immediate previous six-week period.
9. I acknowledge that a total of five (5) positive urine tests may result in expulsion from the program, and that failure to supply a test will count as a positive test.
10. I agree that I will not stockpile my methadone doses.
11. I will be observed swallowing my methadone dose and that this will be confirmed by speaking to the pharmacist staff after swallowing the dose.
12. I will return the container used to drink my methadone dose in the pharmacy.
13. I will pick up my daily dose between the hours of 00:00 and 00:00 daily (may be AM or PM and should be a consistent time each day).
14. I realize it is best to spread the time between methadone doses by at least 16 hours. There will be no twice daily dosing.

15. 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 children.
16. I will confirm I have received the appropriate number of doses and sign for the same.
17. I realize no one else may pick up my doses for me.
18. 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.
19. I realize that any doses vomited or any carries lost will not be replaced without a written prescription from the prescribing physician.
20. I realize that a missed day means a missed dose, which will not be made up.
21. 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.
22. The pharmacist may obtain information about my medication use from other pharmacies.
23. At any time the pharmacist may refuse to dispense methadone for any of the following reasons:
 - **Threats** – the patient, family member or friend has threatened the safety or well being of any staff member or another patient or pharmacy customer by oral or written action
 - **Disruptive Behaviour** – the patient, family member or friend has engaged in disruptive behaviour on the premises
 - **Violent Behaviour** – the patient, family member or friend has engaged in violent behaviour towards a staff member, a patient or another person
 - **Illegal Activity** – the patient, family member or friend has engaged in an illegal act on the premises
 - **Diversion of Methadone** – the patient has diverted, or allowed to be diverted, any part of their methadone
 - **Contraindication of Methadone** – In the opinion of the prescriber, methadone has become contraindicated for the patient
 - **Missed Doses** – The patient has failed to pick up doses of methadone for 3 consecutive days (unless alternative arrangements for pick-up have been made or there is convincing evidence that the failure to pick-up was beyond their control).

I understand and agree to comply with these guidelines.

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

Patient Signature	Date	Witness Signature	Date
Pharmacist Signature	Date	Witness Signature	Date


DR. K. SMITH
 1234 Campbell Road
 St. Johns Hill
 A/C 952
 Tel: (709) 739-1234
 00001

Mr. John Doe 03 / 02 / 2001
Patient's Full Name Date DD MM YY
 123 Smith Road
Address

111 222 333 444

MCP #

R Methadone 2400mg
 (twenty-four hundred)
 dispense in lots of 80mg
 (eighty) daily for 30 days

Dr. K. Smith
Signature of Prescriber
 FO1111

Name of Pharmacy to dispense License #
 Valid For: 03/01/2001 to 03/31/2004

This prescription is correctly written for part-fills. It is valid for a total of 30 fills – the original plus 29 part fills.


DR. K. SMITH
 1234 Campbell Road
 St. Johns Hill
 A/C 952
 Tel: (709) 739-1234
 00001

Mr. John Doe 03 / 02 / 2001
Patient's Full Name Date DD MM YY
 123 Smith Road
Address

111 222 333 444

MCP #

R 2400mg (twenty-four hundred) Methadone
 Dispense in 80mg (eighty) lots
 Take 80mg (eighty) daily

Dr. K. Smith
Signature of Prescriber
 FO1111

Name of Pharmacy to dispense License #
 Valid For: 03/01/2001 to 03/31/2004

This prescription is correctly written for part-fills. It is valid for a total of 30 fills – the original plus 29 part fills.

Appendix C - Stability of Methadone

Stability of Methadone According to the Diluent used and Conditions of Storage

Diluent <i>(Prepared according to product instructions with deionized water)</i>	Stock Solution	Final Concentration	Container	Stability at Room Temp <i>(20-25°C; unprotected from light)</i>	Sterility at Room Temp <i>(20-25°C; unprotected from light)</i>	Stability Refrigerated <i>(5°C)</i>	Sterility Refrigerated <i>(5°C)</i>
Grape flavoured Kool-Aid	Methadone hydrochloride in distilled water (10 mg/mL)	0.2, 0.8 and 1.5 mg/mL	Stoppered glass volumetric flasks	17 days	Visible signs of biological growth after ~ 2weeks	55 days	No visible signs of biological growth after 30 days
Orange flavoured Tang				11 days		49 days	
Allen's Apple Juice <i>(not diluted)</i>				9 days		47 days	
Grape flavoured Crystal Light				8 days		34 days	
Grape flavoured Crystal Light with 0.1% Sodium Benzoate*				29 days	No visible signs of biological growth after 30 days	Not studied	Not studied

*6.47 g of grape-flavoured Crystal Light mix and 1.01 g of 0.1% sodium benzoate in 1 L of deionized water.

Lauriault G, LeBelle MJ, Lodge BA, Savard C. Stability of methadone in four vehicles for oral administration. *A J Hosp Pharm.* 1991 Jun; 48: 1252-6

Appendix E - Take Home/Carry Dosage Log

Pharmacy Name: _____

Patient Name: _____

Physician Name: _____

Month: _____

Day	Dose	Number of Carry Bottles Taken	Pharmacist Signature	Patient Signature
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				
29				
30				
31				

Appendix H - Background Information

Introduction

According to the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) addiction involves substance tolerance, symptoms secondary to substance withdrawal, escalating substance use, reduction in social and recreational activities because of substance use and increased expenditure of time to obtain and use the substance.

Opiate addiction has become a serious problem in society causing unemployment and family disruption, leading to criminal activities such as prostitution, vandalism, drug dealing and theft. Most break and enters/robberies of homes and cars are used to finance drug abuse.

Addiction may also lead to HIV, Hepatitis B&C, TB, STDs and death. Pharmacotherapy may assist the opioid abuser in re-establishing life along more constructive lines by promoting rehabilitation, reducing health risks and costs to the community. Support services addressing the psychological, social and physical health issues in an abuser's life must be available to support pharmacotherapy.

Opiate addiction is a medical illness, a recognized chronic progressive disease. Long standing opiate addiction can be permanent and require permanent treatment. Withdrawing from opiate addiction is very distressing and painful (dope sickness).

Some pharmacists find it very rewarding to watch patients transform from someone whose language of medical commerce includes lies, deceit, manipulation and mistrust to a person capable of being in the mainstream with responsibilities to themselves and their communities.

Not all patients are a success story, but it is well worth participating in the program for those who do succeed.

Methadone

Methadone is a synthetic opioid (mu receptor) agonist with actions similar to morphine, which has good oral bioavailability and three important functions:

- Analgesia for about 6 hours,
- Suppression of opioid withdrawal and craving for about 24 hours, and
- A mood stabilizing effect for longer periods.

Its major short-term effect is to prevent withdrawal symptoms and help reduce drug and needle cravings in opiate-dependent/addicted individuals. It slowly accumulates in the liver giving it a long duration of action (24 to 36 hours). It is available in Canada as a white, odourless, crystalline powder. The correct dose in a stabilized patient should prevent cravings for about 24 hours without causing euphoria or sedation. It is chemically unrelated to opiates, therefore, when required, other opiates may also be prescribed (i.e. post-op pain, chronic pain).

Methadone is commonly prescribed as maintenance therapy for opiate addicts because its long half-life delays the withdrawal syndrome, making its effects less severe. Over time, methadone eventually replaces and blocks all other opiates at the mu receptor site. In sufficient doses, cross-tolerance to other opioids develops (i.e. methadone "blocks" the euphoric effects of self-administered opioids).

Initially, methadone and morphine may both be prescribed. The morphine (or other opiate) is prescribed orally for detoxification purposes. Over the stabilization or transition period methadone is increased and opiates are decreased to zero. During this transition, no other doctor should prescribe drugs of dependency. For patients with a dual diagnosis the use of other medications to treat their psychiatric conditions is appropriate.

The dose of methadone is adjusted depending on the withdrawal and craving symptoms. This must be done gradually as methadone can be fatal for anyone not used to it (even for heavy opiate addicts). There is no simple mg

for mg dose and the adjusted dose usually ends up in the range of 60 to 100 mg administered orally once daily. Increase in dosing may cause drowsiness; therefore patients should be cautioned about driving. They should also be counselled regarding nausea.

Pharmacology and Drug Interactions

Methadone is extensively metabolized by cytochrome CYP3A4 in human liver microsomes (Chem Res Toxicology 1996;9:3 65-73). Patients may experience withdrawal symptoms when started on other medications that are known inducers of the cytochrome P450 enzymes, including CYP3A4 and CYP2B6. A "Dear Doctor" letter was issued by the fabricators of the antiretroviral therapy, VIRAMUNE (nevirapine), Boehringer Ingelheim on July 30, 1999 discussing this interaction.

Drugs that are contraindicated and may precipitate a withdrawal syndrome include preparations with opioid antagonist's activity such as pentazocine, butorphanol, nalbuphine and naltrexone.

Drugs, which may lower the plasma level and effectiveness of methadone, include rifampin, barbiturates, phenytoin, carbamazepine and urinary acidifiers. Chronic alcohol use may also lower plasma levels.

Drugs, which may increase plasma levels and increase the effect of methadone, include disulfiram, cimetidine, fluvoxamine, diazepam, amitriptyline and urinary alkalinizers. The acute use of alcohol may also increase plasma levels. The pharmacokinetics of desipramine and zidovudine (AZT) may be altered by methadone.

Side Effects and Adverse Events

Some of the more common side effects include sweating, constipation, sexual difficulties, sleepiness or drowsiness, and weight gain. Adverse effects such as respiratory depression, decreased bowel motility, miotic pupils, nausea and hypotension can occur. After abrupt discontinuation or administration of an antagonist such as naloxone, an abstinence syndrome can develop, consisting of lacrimation, rhinorrhea, sneezing, nausea, vomiting, fever, chills, tremor and tachycardia.

The most serious adverse effect is the potential for apnea, respiratory failure and hypoxia, leading to coma or death.

Other adverse effects associated with long-term use of methadone can include appetite disturbance, abnormal menses, urinary retention, blurred vision, biliary pain, insomnia, gynecomastia and hepatotoxicity.

A patient presenting to an emergency room may appear to recover when given a dose of naloxone, however, due to the long half-life of methadone, the potential for serious adverse events can persist for up to 24 hours and a naloxone drip is advised.

Overdose Information

With typical maintenance dosing, methadone has a half-life of about 24 hours. As with all opiates, toxicity is thought to be the result of respiratory depression due to decreased sensitivity of the brain's respiratory centre to the stimulatory effect of carbon dioxide. There is, however, no clear definition of what constitutes a toxic or fatal blood methadone level. One reason for the difficulty of determining a toxic blood methadone level is drug interaction. A given blood methadone level may or may not be toxic depending on the presence of other drugs, which may augment or counteract any toxic effects of methadone.

Use in Pregnancy

Methadone crosses the placenta and can cause fetal dependence; therefore, its use in pregnant women should be limited to those with opioid dependence. The primary intent of methadone use is to create a stable environment for the pregnancy and to improve outcomes. Methadone has no teratogenic effects. Detoxification is not recommended during pregnancy because fetal distress can occur. However, women who are dependent on opioids do better with methadone than with no treatment. The advantages include longer gestational periods and higher birth weights, as well as a more moderate abstinence syndrome in the neonate. The newborn infant will need close monitoring for signs of withdrawal, and treatment if it occurs. Methadone will pass into the breast milk.

Use in Pain Management

Methadone is a good alternative to morphine sulfate for pain management, particularly parenteral methadone, which is about twice as potent as oral methadone. Because analgesia is not related to serum half-life, multiple dosing daily is usually needed for pain management. When methadone is used as an analgesic, different dosing schedules are used. The normal adult dosage for acute severe pain is 2.5mg-10mg every three to four hours as needed and 5-20mg every six to eight hours for severe chronic pain. For the treatment of severe, chronic pain (eg terminally ill patient), doses of 5mg - 20mg every 6-8 hours may be used. Dosing should be individualized to meet the needs of the patient.

Further information on use in treating chronic pain is detailed in **Appendix I**.

About Substance Use and Harm Reduction

Substance use involves three elements – the properties of the substance, the characteristics of the user and the environment in which the use occurs. Although a drug produces a psychoactive effect on the body, the harm varies according to the user. Patterns of use, perceptions of pleasure and risk, demographics, socio-economic and culture characteristics of the user are all important.

Currently there is no international or nationally recognized definition of harm reduction. The World Health Organization has stressed that any country's attempts to reduce drug use should not compromise the measure to stop the spread of AIDS. Harm reduction focuses on public health principles not moral concerns. It strives to reduce the immediate harmful consequences of drug use and acknowledges the role of the user in harm reduction without insisting on abstinence. Policies and programs such as methadone maintenance needle exchange and outreach projects are all part of harm reduction.

Many substance users lack the capacity to understand the consequences of their actions. These individuals often exist on society's periphery because of such factors as mental illness, lack of safe affordable housing and societal judgment. A team approach is required, including physicians, pharmacists, nurses and other health care professionals, addiction and mental health workers, lawmakers, law enforcement agencies, community representatives, advocates, social services, justice and parole services and various outreach agencies as well as native elders and spiritual advisors. A professional response that demonstrates respect for individual differences is essential.

Most programs offer three options:

1. Withdrawal from opioids without methadone
2. Methadone maintenance for as long as needed
3. Methadone withdrawal over a period of time.

Diversion Concerns and Public Attitudes

No other medication is so highly regulated. Methadone is currently the most common drug used to treat opiate addicts. Other drugs such as hydromorphone and buprenorphine have also been used; therefore, its intended use creates a potential for abuse different from that of other controlled substances insofar as providing methadone to patients on a regular basis creates special opportunities for diversion.

Previous guidelines were written in part, to respond to real abuses and to the perceived threat of diversion of methadone into illicit channels. It is now perceived that the benefits both to the individual patient and to society at large from authorizing greater clinical discretion in methadone treatment far outweigh the risks from diversion, with recognition of the existence of both a real threat and considerable public fear of diversion.

With respect to public opinion, a substantial segment of public opinion over the years has opposed the use of methadone for the treatment of opiate addiction, and another segment is ambivalent about its use. Public attitudes

toward addiction of any type, but particularly heroin addiction, are overwhelmingly negative. The debate over the extent to which addiction is a disease or a moral failure remains unsettled in the public mind. The stereotypes of addicts are of individuals engaged in criminal activity, predatory toward others, and unable or unwilling to respect the norms of acceptable social behaviour or participate in the work force. The public's fear of opiate addicts creates a reluctance to spend "treatment" dollars on them; it also creates sympathy for a criminal justice response.

In general, members of the medical profession often share many of the negative attitudes of the general public. Many are either indifferent or hostile to its use for the treatment of heroin addiction. Ignorance about its effectiveness may stem from the fact that methadone maintenance historically has been poorly linked to the provision of primary and specialized medical care and to mental health services, both of which are often needed by patients.

Information on the Benefits of Methadone from the National Institute on Drug Abuse

The use of methadone has recently been comprehensively re-evaluated by the National Institute on Drug Abuse in the United States and found to be effective for opioid addiction. Researchers found that, in adequate dosage and with supportive therapy, methadone reduces illicit opioid use and criminal activity, improves social health and productivity, improves physical health, reduces HIV (human immunodeficiency virus) transmission, improves pregnancy outcomes in opioid addicted women, and is safe for long-term use. Cost benefit analyses indicate savings of \$4 to \$5 in health and social costs for every dollar spent on MMT. In terms of Canadian dollars, it is estimated it costs approximately \$6,000 (includes such costs as medication, urine testing and physician, nursing and counselling staff) on an annual basis to maintain a patient on methadone treatment while the untreated opiate user can cost society on average \$49,000 per year.²

Opioid Use:

The effects of any drug depend on several factors:

- The amount taken at one time
- The users past drug experience
- The manner in which the drug is taken
- The circumstances under which the drug is taken (the place, the user's psychological and emotional stability, the presence of other people, simultaneous use of alcohol or other drugs, etc.).

Short-term effects appear soon after a single dose and disappear in a few hours or days. Opioids briefly stimulate the higher centres of the brain but then depress activity of the central nervous system. Immediately after injection of an opioid into a vein, the user feels a surge of pleasure or a "rush." This gives way to a state of gratification; hunger, pain, and sexual urges rarely intrude. The dose required to produce this effect may at first cause restlessness, nausea, and vomiting. With moderately high doses, however, the body feels warm, the extremities heavy, and the mouth dry. Soon, the user goes "on the nod," an alternately wakeful and drowsy state during which the world is forgotten. As the dose is increased, breathing becomes gradually slower. With very large doses, the user cannot be roused; the pupils contract to pinpoints; the skin is cold, moist, and bluish; and profound respiratory depression resulting in death may occur. Overdose is a particular risk on the street, where the amount of drug contained in a "hit" cannot be accurately gauged. In a treatment setting, the effects of a usual dose of morphine last three to four hours. Although pain may still be felt, the reaction to it is reduced, and the patient feels content because of the emotional detachment induced by the drug.

Long-term effects appear after repeated use over a long period. Chronic opiate users may develop endocarditis, an infection of the heart lining and valves as a result of unsterile injection techniques. Drug users who share needles are also at a high risk of acquiring AIDS (acquired immune deficiency syndrome) and HIV infection (human immunodeficiency virus). Unsterile injection techniques can also cause abscesses, cellulitis, liver disease, and even brain damage. Among users with a long history of subcutaneous injection, tetanus is common. Pulmonary

² Methadone Maintenance Treatment: A Community Planning Guide

complications, including various types of pneumonia, may also result from the unhealthy lifestyle of the user, as well as from the depressant effect of opiates on respiration. Psychological dependence exists when a drug is so central to a person's thoughts, emotions, and activities that the need to continue its use becomes a craving or compulsion. With physical dependence, the body has adapted to the presence of the drug, and withdrawal symptoms occur if use of the drug is reduced or stopped abruptly. Some users take heroin on an occasional basis, thus avoiding physical dependence. Withdrawal from opioids, which in regular users may occur as early as a few hours after the last administration, produces uneasiness, yawning, tears, diarrhea, abdominal cramps, goose bumps, and runny nose. These symptoms are accompanied by a craving for the drug. Major withdrawal symptoms peak between 48 and 72 hours after the last dose and subside after a week. Some bodily functions, however, do not return to normal levels for as long as six months. Sudden withdrawal by heavily dependent users who are in poor health has occasionally been fatal. Opioid withdrawal, however, is much less dangerous to life than alcohol and barbiturate withdrawal.

Appendix I - Methadone Dosing Recommendations for Treatment of Chronic Pain

Prepared by Francine Goodman, PharmD, BCPS; William N. Jones, BSc, MSc; and Peter Glassman, MBBS, MSc December 2001
Updated versions may be found at <http://www.vapbm.org> or <http://vawww.pbm.med.va.gov>

Summary

- Methadone is a safe and effective long-acting opioid analgesic that is useful in managing chronic pain.
- Although it has unique pharmacokinetic and pharmacodynamic properties, the general principles of dosing methadone are similar to those of other opioids.
- In general, as with other opioids, methadone should be used as one aspect of a comprehensive pain management plan, as agreed upon by the practitioner and the patient.
- Methadone is most easily titrated by using small initial doses or adjusting the initial dose according to the previous opioid dose.
- A number of methods are available for titrating methadone using conversion ratios, as detailed below. However, titration should be based on patient response and not solely based on equianalgesic dosing tables.
- Consultation with a pain specialist, clinical pharmacist, or other practitioner who has experience with using methadone for chronic pain is recommended if questions arise about dosing or titrating methadone. For more information on identifying patients who should be referred to a pain specialist or pain clinic and on dosing methadone, see the Web-based educational program for VA employees entitled *Opioids in the Management of Acute and Chronic Pain*, available at: <http://vawww.sites.lrn.va.gov/pain/opioids/>.

Background

Methadone should be used when a strong opioid is needed and the patient has not achieved adequate pain relief on escalating doses of controlled-release morphine or has experienced intolerable adverse effects on controlled-release morphine. Commonly, non-steroidal anti-inflammatory drugs and adjuvant agents (e.g., tricyclic antidepressants) should be used in combination with methadone. Methadone's duration of effect is not dependent upon a specialized delivery system, as is the case with transdermal fentanyl or sustained release formulations of morphine or oxycodone. It is the only long-duration opioid available as an oral solution.

While methadone has gained increasing acceptance as an alternative to morphine for treatment of moderate to severe pain, a number of authors have cautioned clinicians about the complexities of dosing methadone or have suggested the drug be prescribed by practitioners with relevant experience in an adequately monitored setting.¹⁻⁷ Significant toxicity has occurred particularly when dosage increments were made too frequently, conversion doses were too high, or dosing intervals were too close.^{5,8-10} Accruing experience, however, suggests that methadone can be safely used when initial doses are small, conversion ratios are adjusted to the previous opioid dose, and dosage is slowly titrated to patient response.^{2,3,5,6,9,11-15} The general principles of dosing methadone are similar to those of other opioids.

The pharmacokinetic and pharmacodynamic properties of methadone are complex and incompletely documented.^{16,17} Although methadone may have a long elimination half-life (up to a mean/median of 128 h),¹⁸⁻³¹ the elimination half-life does not necessarily reflect duration of analgesia.^{28,32} Patients may require dosing intervals of 6 hours to achieve adequate pain relief, although repeated oral administration of methadone for cancer pain may lead to progressively longer dosing intervals.^{33,34} As a result of the dissociation between half-life and analgesic duration, tissue accumulation of methadone can occur. Patients need to be reassessed more frequently (e.g., every few days) when methadone is initiated and when the dose is increased. However, once a stable dosing is established, follow-up can be as clinically indicated. With a 3-day phased conversion from morphine to methadone, the analgesic effects have taken a median of 5 days (range: 4 to 13 days) to stabilize.³

The present dosing recommendations are provided to offer guidance on dosing methadone in the treatment of patients with chronic nonmalignant pain (CNMP) or chronic cancer pain, particularly when converting from another opioid to methadone. If in doubt, a practitioner should consult a pain management specialist, clinical pharmacist, or another practitioner who has the relevant knowledge.

It is important to note that the equianalgesic conversion ratios between methadone and other opioids are imprecise (Table 1).

Table 1: Points to consider about equianalgesic conversion ratios

<ul style="list-style-type: none"> • A number of equianalgesic dosing tables underestimate the potency of methadone.[†] • Conversion ratios in many equianalgesic dosing tables do not apply to repeated doses of opioids. The morphine- or hydromorphone-to-methadone conversion ratio increases (i.e., the potency of methadone increases) as the previous dose of morphine or hydromorphone increases.[‡] • Conversion ratios may not be bi-directional (i.e., the morphine-to-methadone conversion ratio may not be the same as the methadone-to-morphine ratio).[§] • There may be large interpatient variability in the equianalgesic conversion ratio; a single ratio may not be applicable to all patients.[§] • The use of high but ineffective doses of previous opioid may result in overestimation of the equivalent dose of methadone. The relative analgesic potency ratio of oral to parenteral methadone is 2:1; however, confidence intervals are wide.
--

[†] Management of Cancer Pain, Clinical Practice Guidelines, AHCPR (1994)35; Cancer pain: a monograph on the management of cancer pain, Health & Welfare Canada (1984)36; Twycross (1990)37; Levy (1985)38

[‡] The oral morphine to oral methadone conversion ratio may be unexpectedly much higher in patients who previously received very high doses of morphine.2-4,39

[§] Bruera (1999)⁴⁰

^{||} Estimated ratio based on single-dose, double-blind, double-dummy, cross-over studies in patients with moderate to severe cancer pain.¹

Certain drug interactions may also potentially affect methadone dosage requirements (Table 2).

Table 2: Potential clinically relevant drug interactions with methadone

Agents that may DECREASE methadone concentrations	Agents that may INCREASE methadone concentrations	Agents that may increase the adverse effects of methadone
<i>Antiepileptics:</i> carbamazepine, phenobarbital, phenytoin (no interaction with valproic acid and gabapentin) <i>Antipsychotics:</i> risperidone <i>Antiretrovirals:</i> nevirapine, ritonavir <i>Antitubercular:</i> rifampin (no interaction with rifabutin)	<i>Antidepressants:</i> selective serotonin reuptake inhibitors (venlafaxine least likely to interact); amitriptyline <i>Antifungals:</i> fluconazole, ketoconazole	Benzodiazepines; St. John's Wort

Sources: Davis (2001)⁴¹; Natural Medicines Comprehensive Database⁴²; Plummer (1988)^{30, 43}

Dosing Strategies

The best titration strategy has not been determined. Any methadone dosing strategy could be used for treating either CNMP or chronic cancer pain. The rapidity of conversion may be more important than type of pain in determining which method is useful in a given clinical situation. Therefore, the dosing strategies have been categorized by previous opioid exposure and rapidity of titration or conversion (Table 3 and Table 4). The dosing recommendations shown here represent a conservative approach to titrating methadone.

Table 3: Dosing recommendations for patients receiving codeine preparations or no previous opioids

Dosing strategy	Initial MET dose	Increments	Comments
Gradual titration (For CNMP and situations necessitating less frequent monitoring) ⁴⁴	2.5 mg q 8 h	2.5 mg q 8 h every 5 to 7 days	As a general rule, <i>start low and go slow.</i>
Faster titration (For cancer pain and situations where frequent monitoring is possible)	2.5 mg q 6 or 8 h	2.5 mg q 6 or 8 h as often as every day over about 4 days	

The dosing recommendations for gradual titration were modified with permission from *Evidence-Based Recommendations for Medical Management of Chronic Non-Malignant Pain*, College of Physicians and Surgeons of Ontario, November 2000. All doses refer to oral administration. CNMP = Chronic nonmalignant pain; MET = Methadone

Table 4: Dosing recommendations for patients previously receiving other opioids

Dosing strategy	Initial MET dose	Increments	Comments
Gradual conversion (For CNMP and situations necessitating less frequent monitoring) ⁴⁴	MOR-E Dose MET Dose < 200 mg/d 5 mg q 8 h 200 to 500 mg/d ~7% of MOR-E dose, given in divided doses q 8 h (see below) > 500 mg/d ~7% of MOR-E dose; give 1/3rd of MET dose (2.3% of MOR-E dose) in divided doses q 8 h (see below) For patients with CNMP who have received repeated doses of > 200 mg/d MOR-E, calculate MET dose using the table below. <u>Drug Oral Drug/MOR MET</u> 2 mg 7% MOR 30 mg 100% HMO 8 mg 27% OXY 15 mg 50%	Increase by the calculated MET dose every 5 to 7 d as needed. <i>For patients switched from greater than 500 mg/d MOR-E:</i> add 1/3rd of MET dose (2.3% of daily MOR-E dose) every 5 d (total conversion dose [period]: ~7% of MOR-E dose [15 d]). Reduce dose of previous opioid by 1/3rd every 5 days	Previous MOR-E dose < 200 mg/d includes patients already on a major opioid analgesic like oxycodone with or without acetaminophen. In patients with CNMP, look for a graded analgesic response to dosage increments; if absent, the patient may have opioid-nonresponsive pain.
Faster conversion (For cancer pain and situations where frequent monitoring is possible) ^{2,3,5,11,12,45,46}	MOR-E Dose MET/MOR-E < 200 mg/d 10% to 30% 200 to 500 mg/d 10% to 20% 501 to 1000 mg/d 5% to 10% > 1000 mg/d 5% or less For the most conservative approach, use 5% MET/MOR-E (or less with very high MOR-E doses) to calculate the initial MET dose irrespective of the previous MOR-E dose. Give starting dose of MET in divided doses q 8 h (up to a maximum 50 mg q 8 h).	Two methods may be used: (1) <i>Phased conversion.</i> Replace 1/3 of MOR-E dose with the calculated equivalent dose of MET daily for 3 days. (2) <i>Rapid ("stop-and-go") conversion.</i> Discontinue MOR-E and start MET on day 1.	Titrate MET day by day according to patient's symptoms and the number of BTP doses administered. Smaller MET-to-MOR-E conversion proportions (%) should be used the larger the previous MOR-E dose.

The dosing recommendations for gradual conversion were modified with permission from *Evidence-Based Recommendations for Medical Management of Chronic Non-Malignant Pain*, College of Physicians and Surgeons of Ontario, November 2000. The dosing strategy for faster conversion is based on a synthesis of the most recent versions of the more notable dosing strategies used in opioid-tolerant patients with mostly cancer-related pain. **All doses refer to oral administration.** BTP = Breakthrough pain; CNMP = Chronic nonmalignant pain; HMO = Hydromorphone; MET = Methadone; MOR = Morphine; MOR-E = Morphine-equivalent; OXY = Oxycodone

It is important to note that various dosing methods have been used (including a patient-controlled regimen^{6,47}) and are still evolving. Two dosing strategies^{2,11} have been prospectively studied, but no clinical trials comparing systematic dosing methods have been performed. A literature search (PubMed 1966 to 2001) identified only a small case series that discussed methadone dosing during the treatment of CNMP.⁴⁸ The lack of prospective and comparative studies highlights the need to carefully individualize the dosing regimen of methadone, as is done with other opioids.

As a general rule, smaller methadone-to-morphine conversion proportions (%) should be used the larger the previous morphine-equivalent dose, remembering that precise conversions from another opioid to methadone are impossible. Disproportionately smaller methadone doses may be required with the larger morphine doses. However, it is important to remember that the equianalgesic conversion ratio is only one part of the process of properly dosing methadone and other opioids.

For breakthrough pain (BTP), a short-acting opioid preparation (such as acetaminophen with codeine, oxycodone with or without acetaminophen, or immediate-release morphine) may be used as necessary. Keep in mind that the use of BTP medications in patients with CNMP is controversial. If opioid medications for BTP are indicated following titration to a stable methadone dose in a patient with CNMP, they should be used sparingly.⁴⁴ Methadone has also been used (in doses 10% to 30% of the calculated daily methadone dose up to 3 to 8 doses per day as needed)^{6,11,46,47}; however, the short-acting opioids are generally preferred to avoid drug accumulation.

Special patient populations

Patients 65 years and older may have a decreased clearance of methadone³⁰. In patients with stable chronic liver disease, no dosage adjustments appear to be necessary.⁴⁹ Methadone and its metabolites do not accumulate in patients with renal failure.⁵⁰ The two prospective studies on methadone dosing strategies excluded patients with liver or renal disease.^{2,11} Use extra caution when dosing any opioid in all of these patient populations. For patients with liver or renal disease, special consideration can be given locally to use an alternative opioid at the discretion of the care team or provider.

General principles for dosing methadone

- Use methadone for treatment of patients with chronic pain.
- Individualize doses and slowly titrate to response.
- An acceptable balance between analgesic effects and tolerable and manageable adverse effects generally indicates a favourable response to pain medication. In the treatment of CNMP, the main goals are to improve the patient's ability to function and to increase the patient's quality of life.
- Once the daily dosage for adequate analgesia has been determined, a trial of longer dosing intervals may be attempted. Many patients can take the same total daily dose divided every 8 hours. Intervals of 12 hours may be attempted when patients are stable at 8-hour intervals.
- If a patient develops sedation (which may be a precursor to respiratory depression), hold or decrease the following dose of previous opioid or methadone (depending on the dosing strategy) and decrease subsequent doses and/or make dosage increments less frequently. Do not increase the dose of methadone.
- Short-acting opioids may be used for treatment of BTP, at least initially and when pain is severe and escalating.
- The use of medications for BTP in the treatment of CNMP is controversial. If medications for BTP are indicated after titration to a stable methadone dose, they should be used sparingly.⁴⁴
- Reassess patients at appropriate intervals; at least once weekly during titration and at least once monthly after the daily dosage is stabilized.
- Use additional caution with elderly patients (65 years), patients with liver, renal, or pulmonary disease, debilitated patients, and patients previously receiving high doses of opioid. Patients who cannot be adequately monitored at home may be considered for inpatient titration of methadone.

Patient education

- Explain to patients that the initial dose will often be inadequate for pain relief. BTP medication should be used during the dose titration period. A pain and pain medicine diary should be kept.
- Reassure patients that the dose will be titrated to achieve adequate analgesia.
- Advise patients that the effects of methadone will increase over at least one week following a dosage increment. Pain relief during the last few days of that week will be greater than at the first few days of the week.
- Remind patients about the need for and the frequency of monitoring during the titration and maintenance periods. Provide patients with instructions on what to do if they develop increasing or intolerable adverse effects.
- Advise patients to avoid abrupt discontinuation of their opioid medication without first consulting their physician. Educate patients about withdrawal symptoms.
- Since patients may become concerned about the social stigma associated with the use of methadone for treatment of opioid dependence, reassure them that methadone is also an accepted pain medication and that they are not "addicts" because they are taking methadone for pain control. Explain the difference between addiction and dependence.

- For more information on the definitions of addiction and dependence, see the Web-based educational program for VA employees entitled *Opioids in the Management of Acute and Chronic Pain*, available at: <http://vaww.sites.lrn.va.gov/pain/opioids/> or reference 51.

References

1. Foley KM, Houde RW. Methadone in cancer pain management: individualize dose and titrate to effect. *J Clin Oncol* 1998;16:3213-5.
2. Ripamonti C, Groff L, Brunelli C, Polastri D, Slavakis A, De Conno F. Switching from morphine to oral methadone in treating cancer pain: what is the equianalgesic dose ratio? *J Clin Oncol* 1998;16:3216-21.
3. Lawlor PG, Turner KS, Hanson J, Bruera ED. Dose ratio between morphine and methadone in patients with cancer pain: a retrospective study. *Cancer* 1998;82:1167-73.
4. Bruera E, Pereira J, Watanabe S, Belzile M, Kuehn N, Hanson J. Opioid rotation in patients with cancer pain. A retrospective comparison of dose ratios between methadone, hydromorphone, and morphine. *Cancer* 1996;78:852-7.
5. Ayrnirinde OT, Bridge DT. The rediscovery of methadone for cancer pain management. *Med J Aust* 2000;173:536-40.
6. Morley JS, Makin MK. Comments on Ripamonti et al., Pain, 70 (1997) 109-115. *Pain* 1997;73:114-5.
7. Hanks GW, Conno F, Cherny N et al. Morphine and alternative opioids in cancer pain: the EAPC recommendations. *Br J Cancer* 2001;84:587-93.
8. Symonds P. Methadone and the elderly (letter). *Br Med J* 1977;1:512.
9. Bruera E, Watanabe S, Fainsinger RL, Spachynski K, Suarez-Almazor M, Inturrisi C. Custom-made capsules and suppositories of methadone for patients on high-dose opioids for cancer pain. *Pain* 1995;62:141-6.
10. Ettinger DS, Vitale PJ, Trump DL. Important clinical pharmacologic considerations in the use of methadone in cancer patients. *Cancer Treat Rep* 1979;63:457-9.
11. Mercadante S, Casuccio A, Fulfaro F et al. Switching from morphine to methadone to improve analgesia and tolerability in cancer patients: a prospective study. *J Clin Oncol* 2001;19:2898-904.
12. Gagnon B, Bruera E. Differences in the ratios of morphine to methadone in patients with neuropathic pain versus non-neuropathic pain. *J Pain Symptom Manage* 1999;18:120-5.
13. Mercadante S, Casuccio A, Calderone L. Rapid switching from morphine to methadone in cancer patients with poor response to morphine. *J Clin Oncol* 1999;17:3307-12.
14. Hagen NA, Wasylenko E. Methadone: outpatient titration and monitoring strategies in cancer patients. *J Pain Symptom Manage* 1999;18:369-75.
15. Krames E. The Bruera/Neumann article reviewed. Discussion of Bruera E, Neumann CM. Role of methadone in the management of pain in cancer patients. *Oncology* 1999;13:1275-1282. *Oncology* 1999;13:1288-1289.
16. Ripamonti C, Zecca E, Bruera E. An update on the clinical use of methadone for cancer pain. *Pain* 1997;70:109-15.
17. Garrido MJ, Troconiz IF. Methadone: a review of its pharmacokinetic/pharmacodynamic properties. *J Pharmacol Toxicol Methods* 1999;42:61-6.
18. Wolff K, Rostami-Hodjegan A, Shires S et al. The pharmacokinetics of methadone in healthy subjects and opiate users. *Br J Clin Pharmacol* 1997;44:325-34.
19. Olsen GD, Wendel HA, Livermore JD, Leger RM, Lynn RK, Gerber N. Clinical effects and pharmacokinetics of racemic methadone and its optical isomers. *Clin Pharmacol Ther* 1977;21:147-57.
20. Verebely K, Volavka J, Mule S, Resnick R. Methadone in man: pharmacokinetic and excretion studies in acute and chronic treatment. *Clin Pharmacol Ther* 1975;18:180-90.
21. Inturrisi CE, Verebely K. Disposition of methadone in man after a single oral dose. *Clin Pharmacol Ther* 1972;13:923-30.
22. Wolff K, Rostami-Hodjegan A, Hay AW, Raistrick D, Tucker G. Population-based pharmacokinetic approach for methadone monitoring of opiate addicts: potential clinical utility. *Addiction* 2000;95:1771-83.
23. de Vos JW, Geerlings PJ, van den Brink W, Ufkes JG, van Wilgenburg H. Pharmacokinetics of methadone and its primary metabolite in 20 opiate addicts. *Eur J Clin Pharmacol* 1995;48:361-6.
24. Wolff K, Hay AW, Raistrick D, Calvert R. Steady-state pharmacokinetics of methadone in opioid addicts. *Eur J Clin Pharmacol* 1993;44:189-94.
25. Nilsson MI, Gronbladh L, Widerlov E, Anggard E. Pharmacokinetics of methadone in methadone maintenance treatment: characterization of therapeutic failures. *Eur J Clin Pharmacol* 1983;25:497-501.
26. Anggard E, Nilsson MI, Holmstrand J, Gunne LM. Pharmacokinetics of methadone during maintenance therapy: pulse labeling with deuterated methadone in the steady state. *Eur J Clin Pharmacol* 1979;16:53-7.
27. Nilsson MI, Anggard E, Holmstrand J, Gunne LM. Pharmacokinetics of methadone during maintenance treatment: adaptive changes during the induction phase. *Eur J Clin Pharmacol* 1982;22:343-9.
28. Inturrisi CE, Colburn WA, Kaiko RF, Houde RW, Foley KM. Pharmacokinetics and pharmacodynamics of methadone in patients with chronic pain. *Clin Pharmacol Ther* 1987;41:392-401.
29. Gourlay GK, Cherry DA, Cousins MJ. A comparative study of the efficacy and pharmacokinetics of oral methadone and morphine in the treatment of severe pain in patients with cancer. *Pain* 1986;25:297-312.
30. Plummer JL, Gourlay GK, Cherry DA, Cousins MJ. Estimation of methadone clearance: application in the management of cancer pain. *Pain* 1988;33:313-22.
31. Denson DD, Concius RR, Warden G, Raj PP. Pharmacokinetics of continuous intravenous infusion of methadone in the early post-burn period. *J Clin Pharmacol* 1990;30:70-5.
32. Grochow L, Sheidler V, Grossman S, Green L, Enterline J. Does intravenous methadone provide longer lasting analgesia than intravenous morphine? A randomized, double-blind study. *Pain* 1989;38:151-7.
33. Hanson J, Ginman C, Hartvig P, et al. Clinical evaluation of oral methadone in treatment of cancer pain. *Acta Anaesthesiol Scand* 1982;74:124-127.
34. Sawe J, Hansen J, Ginman C et al. Patient-controlled dose regimen of methadone for chronic cancer pain. *Br Med J (Clin Res Ed)* 1981;282:771-3.
35. AHCPR. Management of Cancer Pain, Clinical Practice Guidelines. Rockville, MD: Agency for Health Care Policy and Research; U.S. Department of Health and Human Services; 1994. AHCPR Pub. No. 94-0592.
36. Health & Welfare Canada. Cancer pain: a monograph on the management of cancer pain. Ottawa, Canada: Health & Welfare Canada, Minister of Supply and Services; 1984. H42-2/5.
37. Twycross R, Lack S. Pain relief. In: Twycross R, Lack S, eds. *Therapeutics in terminal cancer, 2nd edition*. Edinburgh: Churchill Livingstone; 1990:2:11-39.
38. Levy MH. Pain management in advanced cancer. *Semin Oncol* 1985;12:394-410.
39. Ripamonti C, De Conno F, Groff L et al. Equianalgesic dose/ratio between methadone and other opioid agonists in cancer pain: comparison of two clinical experiences. *Ann Oncol* 1998;9:79-83.
40. Bruera E, Neumann CM. Role of methadone in the management of pain in cancer patients. *Oncology (Huntingt)* 1999;13:1275-82; discussion 1285-8, 1291.
41. Davis MP, Walsh D. Methadone for relief of cancer pain: a review of pharmacokinetics, pharmacodynamics, drug interactions and protocols of administration. *Support Care Cancer* 2001;9:73-83.
42. Jellin JM, Gregory P, Batz F, Hitchens K, et al. Pharmacist's Letter/Prescriber's Letter Natural Medicines Comprehensive Database, 3rd ed. Stockton, CA: Therapeutic Research Faculty; 2000.
43. Brown LS, Sawyer RC, Li R, Cobb MN, Colborn DC, Narang PK. Lack of a pharmacologic interaction between rifabutin and methadone in HIV-infected former injecting drug users. *Drug Alcohol Depend* 1996;43:71-7.
44. CPSO Task Force on CNMP. Evidence-based recommendations for medical management of chronic non-malignant pain: College of Physicians and Surgeons of Ontario (CPSO); Nov 2000.
45. De Conno F, Groff L, Brunelli C, Zecca E, Ventafredda V, Ripamonti C. Clinical experience with oral methadone administration in the treatment of pain in 196 advanced cancer patients. *J Clin Oncol* 1996;14:2836-42.
46. Friedman LL. Using Methadone. Lecture presented at: American Academy of Hospice and Palliative Medicine, 13th Annual Assembly; 22 June 2001; Phoenix, AZ.
47. Morley J, Makin M. The use of methadone in cancer pain poorly responsive to other opioids. *Pain Rev* 1998;5:51-58.
48. Gardner-Nix JS. Oral methadone for managing chronic nonmalignant pain. *J Pain Symptom Manage* 1996;11:321-8.
49. Novick DM, Kreek MJ, Fanizza AM, Yancovitz SR, Gelb AM, Stenger RJ. Methadone disposition in patients with chronic liver disease. *Clin Pharmacol Ther* 1981;30:353-62.
50. Kreek MJ, Schecter AJ, Gutjahr CL, Hecht M. Methadone use in patients with chronic renal disease. *Drug Alcohol Depend* 1980;5:197-205.

51. Portenoy RK. Pain specialists and addiction medicine specialists unite to address critical issues. American Pain Society Web site. APS bulletin (online). 1999;9(2). Available at: <http://www.ampainsoc.org/pub/bulletin/mar99/president.htm>. Accessed 5 October 2001.

Methadone Dosing Final (20Dec01).doc Updated versions may be found at <http://www.vapbm.org> or <http://vaww.pbm.med.va.gov> 4 of 4

Appendix J - References

1. Best Practices: Methadone Maintenance Treatment, Health Canada, www.cds-sca.com
2. Centre for Addictions and Mental Health Web site: www.camh.net
3. The Lindsmith Centre - Drug Policy foundation Web site: www.lindesmith.org
4. Addictions Foundation of Manitoba Web site: www.afm.mb.ca
5. National Institute on Drug Abuse Web site: www.nida.nih.gov
6. Medical Methadone Maintenance: The Further Concealment of a Stigmatized Condition, by Herman Joseph, PhD. www.tir.com/~yourtype/dole_nys.htm
7. Methadone Maintenance, A Pharmacist's Guide to Treatment (2nd edition), Centre for Addiction and Mental Health, 2004 www.camh.net
8. Help for Heroin Dependence, Pharmacy Practice, October 1996, Vol. 12, No 10, Kalvik, Isaac, Janecek.
9. Dispensing Methadone for the Treatment of Opioid Dependence, Health Canada, 1994.
10. Draft Guideline, Opioid Dependency and Addiction, Therapy Guidelines Including Methadone, Saskatchewan Health, College of Physicians and Surgeons of Saskatchewan, October 2000.
11. Methadone Program for Saskatchewan Pharmacists. Saskatchewan Pharmaceutical Association, July 2002
12. Guidelines for Methadone Maintenance Programs. Shoppers Drug Mart, Sept. 1998
13. What British Columbia Pharmacists Need to Know About the Methadone Maintenance Program, College of Pharmacists of British Columbia, 1997
14. Methadone Distribution Guidelines for a Methadone Maintenance Program, New Brunswick Pharmaceutical Society, 2004
15. Methadone, Information for the Pharmacist providing Methadone Maintenance Therapy, Nova Scotia College of Pharmacists, 2003
16. Methadone Maintenance Treatment Guidelines, College of Physicians and Surgeons of Newfoundland and Labrador, 2005