

Methadone for Analgesia Guidelines

Table of Contents

Introduction	2
Prescribing Methadone	3
Patient Assessment	4
Opioid Use Disorder and Chronic Pain	6
Pharmacology of Methadone	8
Side Effects	9
Drug Interactions	12
Available Strengths and Forms of Methadone	14
Switching Opioids	15
Indications for Switching Opioids	15
Methods for Switching to Methadone	18
"Start Low, Go Slow"	18
Slow-Switch Method: 33 Per Cent Steps at Three-Day Intervals	20
Rapid-Switch ("Stop-Start") Method	22
PRN Methadone Switch	23
Using Methadone Safely: What Can Go Wrong	24
Urine Drug Testing	25
Appendices	26
Appendix A: Links to application forms and relevant documents	26
Appendix B: Equianalgesic conversion guides	27
Appendix C: Equianalgesic potency of opioids for chronic pain	28
Revision History	30

Methadone for Analgesia Guidelines

Introduction

Although methadone is most commonly used in the treatment of opioid use disorder, it is also used for the treatment of chronic pain. The Prescription Review Panel of the College of Physicians and Surgeons of British Columbia (hereafter known as the College), in consultation with several experienced prescribers and pharmacists, has developed these guidelines, based on best clinical evidence and experience, as a resource for physicians who wish to prescribe methadone in the management of pain.

Methadone is an oral long-acting synthetic opioid which is often effective in treating chronic pain. Due to the unique pharmacokinetics of methadone, which has a long and variable half-life and a large volume of distribution, there is a risk of accumulation leading to sedation, respiratory depression and even death. It is a drug that must be used cautiously and doses must be tailored to each patient. It is important that physicians be familiar with methadone's unique attributes and aware of the complexity of prescribing methadone before initiating patients on therapy. Inexperienced physicians are encouraged to consult with colleagues who are familiar with the use of methadone for chronic pain.

Physicians should carefully assess and reassess patients, particularly when initiating methadone therapy, as the risk and onset of respiratory depression is somewhat unpredictable. Particular caution should be exercised when using methadone in patients who are opioid-naïve, elderly patients, and patients with liver disease. It is important to give consideration to the drug interactions between methadone and other drugs that are metabolized through, or affect the cytochrome P450 pathway. Regular review of PharmaNet facilitates this by enabling the prescriber to have a comprehensive appreciation of the patient's medication regimen.

In addition to individualizing treatment, physicians should be careful when switching patients from other opioids to methadone. When compared to other opioids, methadone has more potential drug interactions. The values found in published equianalgesic charts indicate a wide range of possible methadone doses, and it is important to remember that **the equianalgesic dose quoted is an expected end point and not a starting point for a switch**. Again, individual patient responses may vary from those predicted by equianalgesic guidelines.

As with all controlled drugs, physicians should be alert for diversion of their prescriptions of methadone and potentially fraudulent requests for this drug, as this remains a significant concern in the community. Methadone-related deaths are commonly associated with illegal or unauthorized use, or with patients receiving methadone for analgesia.

Methadone for Analgesia Guidelines

Prescribing Methadone

On May 19, 2018, Health Canada removed the requirement for physicians to obtain an exemption to prescribe methadone under section 56(1) of the *Controlled Drugs and Substances Act*. There is no longer an application and approval process, and the College no longer maintains a list of methadone prescribers. The College of Pharmacists of British Columbia no longer maintains information on which pharmacies dispense methadone. All BC pharmacies have the option of providing methadone services, but some may choose not to do so.

Physicians wishing to prescribe methadone for analgesia must read and adhere to the College standard *Prescribing Methadone*, and complete the Canadian Virtual Hospice's free, one-hour accredited online course on methadone for pain in palliative care (<http://www.methadone4pain.ca/>). Prescribers are also required to familiarize themselves with the College standard *Safe Prescribing of Opioids and Sedatives*, and to regularly review each patient's PharmaNet profile, to ensure safe prescribing of methadone and to encourage communication with the patient's other health professionals, where necessary.

Physicians looking for resource articles are encouraged to contact College [library](#). Most articles are provided free of charge to registrants, and monthly automated searches can be customized for the registrant.

Prescriptions for analgesic methadone should be written on a regular controlled prescription form (also known as a duplicate form). Physicians' copies of the controlled prescription forms should be retained with the patient record (not in the prescription pad) and must be identical to the copies issued to the patients.

Methadone for Analgesia Guidelines

Patient Assessment

Methadone may be indicated for management of cancer pain or chronic non-cancer pain (CNCP). It is not a first-line analgesic, nor is it appropriate for acute or unstable pain. It is important to determine and document the patient's diagnosis before establishing a treatment plan which addresses the chronic pain and also takes into account concurrent problems. Clearly, a patient with metastatic cancer will have a vastly different treatment plan than that of a patient with CNCP and/or substance use disorder.

An assessment comprises the following:

1. Pain history and physical examination – to establish physical function and degree of disability
2. Medical history – review all documentation and previous diagnoses
3. Surgical history – review all documentation and previous diagnoses
4. Psychiatric history – screen for mood disorders, sleep disturbance, personality disorders, lack of coping skills and psychosocial supports
5. Family history – including any history of sudden death, which could be from a hereditary long QT syndrome
6. Laboratory tests and X-rays if required
7. Structured screening for substances of misuse—this is recommended, especially with patients presenting with chronic non-cancer pain. This should include but is not limited to the following:
 - a. Questions pertaining to current and past quantity and frequency of substance use—examples:
 - i. “In the last year, how many times have you had five or more drinks (or, for women, four or more drinks) on one occasion?”
 - ii. “In the last year, have you used substances such as cocaine, heroin, fentanyl or methamphetamine?”
 - iii. “Have you or your family ever felt that you were falling in trouble with use of recreational drugs, including alcohol?”
 - b. Questions pertaining to past history of treatment—example:
 - i. “Have you ever received treatment for substance misuse, such as attending a treatment centre, 12-step meeting or counselling?”
 - c. Questions pertaining to family or patient history of substance misuse—example:
 - i. “Have you or any of your family members ever been diagnosed with substance use problems?”
8. Urine drug testing (UDT)

The literature concerning substance misuse demonstrates that self-reports by patients who misuse substances are variable and of questionable validity. Therefore, most experts recommend a urine drug test prior to prescribing opioids. Routine use of UDT on all patients being prescribed opioids will destigmatize the test. Ensure that if a patient is already being

Methadone for Analgesia Guidelines

prescribed an opioid that this information is provided in the request for analysis of the urine specimen, as some synthetic opioids do not show up on routine screening and must be specifically requested.

Counselling prior to administration of the test is recommended. Random urine drug testing for other indications, such as aberrant behaviour, may also be indicated.

9. Pill counts

If methadone is being considered for treatment of CNCP in pill form, the assessing physician should consider undertaking a pill count of the current medication to assess whether it correlates with the last dispense and the way the patient describes taking it. Any discrepancies should be discussed. This principle applies to all controlled medication, whether in pill or patch form.

10. The assessing physician should obtain collateral information from the patient's usual prescriber/family physician. Any red flags in the patient's care should be considered including running out of medication early, lost medication, stolen medication, oversedation, and sleep apnea.

A review of patients' PharmaNet profiles can confirm their reported history of prescription drug use. This also provides an opportunity to contact all other prescribers to ensure that all involved agree on the goals of care and prescribing responsibilities. Ideally, the prescriber of methadone would be the sole prescriber of pain medication for the patient. With most specialist-initiated treatments, once a patient is stable, the family physician assumes ongoing prescribing for the patient. Similarly, family physicians of methadone patients are strongly encouraged to obtain adequate education and training in prescribing methadone for analgesia, to maintain continuity of care. This will also free up specialist clinics to take on new patients more quickly.

Methadone for Analgesia Guidelines

Opioid Use Disorder and Chronic Pain

Chronic non-cancer pain (CNCP) is a very common condition affecting up to a third of the population, and causes tremendous costs to society, both financially and socially. All patients with CNCP should undergo a thorough evaluation and regular review to make sure that a potentially treatable condition is not missed. Though many patients have identifiable pain generators such as arthritis, spinal degeneration or musculoskeletal injuries, it can be difficult to identify a cause in some patients; in fact, it may only become apparent after months or years of pain. Improvement in clinical examination techniques, investigations and treatments for these conditions is urgently needed.

There are also patients in whom pain is the presenting symptom of psychiatric illnesses such as depression, or social issues (“total pain”). Examples include sleep deprivation, being a victim of domestic violence, or post-traumatic stress disorder. These issues should be identified by thorough patient assessment and ongoing review.

The 2012 Canadian Community Health Survey found that approximately 21.6% of Canadians (about 6 million people) met the criteria for a [substance use disorder](#) during their lifetime (Table 1). [Alcohol](#) was the most common substance for which people met the criteria for abuse or use disorder at 18.1%. More Canadians had symptoms of cannabis abuse or use disorder in their lifetime (6.8%) compared with [other drugs](#) (4.0%). However, the literature for rational pharmacotherapy leading to iatrogenic addiction is sparse. It is therefore important that all patients who are being considered for opioid therapy, and especially those with CNCP, be evaluated for substance use disorder, including alcohol, prescription medication, or street drugs.

Table 1: Rates of selected mental or substance use disorders, lifetime and 12 month, Canada, household population 15 and older, 2012

Mental or substance use disorders ¹	Lifetime	12-month
	percent	
Substance use disorder ²	33.1	10.1
Alcohol abuse or dependence	21.6	4.4
Cannabis abuse or dependence	18.1	3.2
Other drug abuse or dependence (excluding Cannabis)	6.8	1.3
Mood disorder ³	4.0	0.7
Major Depressive Episode	12.6	5.4
Bipolar Disorder	11.3	4.7
Generalized Anxiety Disorder	2.6	1.5
	8.7	2.6

1. Mental or substance use disorders is comprised of: substance use disorders, mood disorders and general anxiety disorder. However, these three disorders cannot be added to create this rate because these three categories are not mutually exclusive, meaning that people may have a profile consistent with one or more of these disorders.

2. Substance use disorder includes alcohol abuse or dependence, cannabis abuse or dependence and other drug abuse or dependence.

3. Mood disorder includes depression (major depressive episode) and bipolar disorder.

Source: Statistics Canada, Canadian Community Health Survey – Mental Health, 2012.

Treatment with an opioid analgesic is not contraindicated in a patient with a history of substance use disorder (SUD), but a comprehensive treatment plan with firm boundaries, which addresses both the chronic pain and SUD, must be developed before medication is provided. Patients who are already addicted to other substances may experience further loss of control if they are provided with opioids. An appropriate recovery program is an essential component of the treatment plan for such patients. It is recommended that a physician experienced in addictions assessment and treatment be consulted and that a shared-care treatment and monitoring plan be developed for these patients. Addiction specialist

Methadone for Analgesia Guidelines

support can be invaluable in this situation. If an addictions specialist is not present in your community, support may be obtained by contacting the RACE line (<http://www.raceconnect.ca>).

It should also be clearly understood that not all pain responds to opioids. There is evidence to suggest that some patients with chronic pain may have their pain made worse by taking opioids other than methadone, because of opioid-induced hyperalgesia. This is manifested by spread of pain outside the localized area of presentation, and increased sensitivity to pain (hyperalgesia) over the whole body. Allodynia may also be present, where normally non-painful sensory stimulus (e.g. light touch) is perceived as painful. When this is identified in a patient already taking a non-methadone opioid, a switch to methadone can relieve the allodynia, start to reverse the hyperalgesia, and facilitate a slow taper off opioids altogether, whilst more appropriate non-opioid and non-pharmacological treatments can be implemented.

Methadone for Analgesia Guidelines

Pharmacology of Methadone

Methadone has many characteristics which make it useful for the treatment of chronic pain, particularly its pharmacologic activity in chronic pain syndromes. It is a potent mu (μ) opioid receptor agonist and an NMDA (N-methyl-D-aspartic acid) receptor antagonist. The NMDA mechanism is thought to play an important role in the prevention of opioid tolerance, potentiation of analgesic effects and for neuropathic pain syndromes.

Methadone is highly lipophilic with rapid absorption in the upper gastrointestinal tract and an onset of action within approximately 30 minutes. It has a large initial volume of distribution followed by slow tissue release, as well as a high bioavailability of around 80%. Methadone has no active metabolites and biotransformation is not required for analgesic effect. It is metabolized primarily through the cytochrome P450 3A4 enzyme, which is a major metabolic enzyme for many other drugs. Careful review of concurrent medications is important when considering methadone as a treatment option.

Methadone is useful in the presence of renal disease, as it is metabolized in liver and predominantly excreted in feces.¹ No dose adjustment is needed in mild to moderate renal failure, but when switching to methadone from another opioid in the presence of severe renal impairment, a slow switch and conservative dosing is usually recommended, and the dose then increased according to patient tolerability. Methadone is not removed by dialysis.

Methadone metabolism does not appear to be affected by mild to moderate hepatic disease, but caution should be exercised in patients with severe or unstable hepatic failure, hepatitis, or HIV.² Methadone has an extremely long half-life (up to 190 hours), which does not correlate with the observed duration of analgesia (six to 12 hours). This can lead to accumulation and increased risk of sedation and respiratory depression if the dose is increased too rapidly. Rapid titration methods for other opioids, such as morphine and hydromorphone, do not apply to methadone. Methadone dosages should not be increased more frequently than every three to five days except under close supervision, such as on an inpatient or palliative care unit. Methadone is not effective for chronic pain as a single daily dose and is usually prescribed one dose every eight hours. A small proportion of patients may require a dose every six hours and occasionally patients may find a 12-hour schedule adequate.

Newborns of mothers on methadone treatment for substance use disorder have better perinatal perimeters such as birth weight and head circumference than those of untreated patients with active addictions, however the balance between risks and benefits of methadone treatment for analgesia are different. Patients receiving methadone for analgesia who plan on becoming pregnant should be made aware that the risks to fetus appear small but are probably not zero, and abstinence from opioids would be preferred. If this is not possible, the prescriber should be aware of the physiologic changes in methadone metabolism that occur in pregnancy. These include- changes in protein binding, changes in total body fluid, volume and fat, longer gastrointestinal transit time, and induction of CYP3A4, which will affect methadone absorption and distribution. Methadone metabolism increases from the first to the third trimesters, so doses may need to be adjusted to prevent over- or under-medication. It is important

¹ Kreek MJ, Schechter AJ, Gutjahr CL, Hecht M. Methadone use in patients with chronic renal disease. *Drug Alcohol Depend.* 1980 Mar;5(3):197-205.

² Layson-Wolf, C, Goode JV, Small RE. Clinical use of methadone. *Journal of Pain & Palliative Care Pharmacotherapy.* 2002;16(1):29-59.

Methadone for Analgesia Guidelines

to monitor for neonatal withdrawal in the postpartum period, and to be aware of potential for toxicity as excess fat gained throughout pregnancy is metabolized and releases the stored methadone.

Methadone is present in breast milk in only very small amounts, and maternal methadone therapy should not be considered a contraindication to breastfeeding, especially at low doses.³

When switching from other opioids, such as morphine, the equianalgesic ratio is quite variable. Extreme caution must be exercised, particularly when the patient is on high doses of the previous opioid. In highly opioid-tolerant patients, the ratio can vary from 25:1 to as high as 200:1. There are a number of published guidelines for conversion from morphine to methadone. No method has been shown to be superior to another by direct comparison, and the method chosen should be appropriate for the circumstances.

See appendix B for a table of conversion ratios for oral morphine to oral methadone. Remember that these conversion guides refer to the maintenance dosage. **The starting dose should be much lower and gradually increased until analgesia is achieved.** Also see [Switching Opioids](#) for suggested protocols. In an outpatient setting, the preferred method is “start low, go slow.”

Side Effects

Central Nervous System

CNS side effects include sedation, dysphoria, disorientation, and more rarely, myoclonus, delirium and headache. Headaches may occur with all opioids, but are more commonly seen with short-acting opioids. Sedation tends to resolve within a few days of a dose increase, but may be dose-limiting. Stimulants may be helpful to counteract opioid-induced sedation in patients with a short life expectancy (i.e. in palliative care), but are not recommended for long-term treatment because of the high rate of development of tolerance and the potential for abuse. Patients should be instructed not to drive or operate machinery during the initiation and stabilization phases. Once patients are on a stable dose, however, the use of methadone (or any other long-acting opioid) should not be a barrier to driving. Delirium can be caused by opioid toxicity and is a frequent indication for a switch to methadone, which has a lower potential to cause delirium (see [Switching Opioids](#)).

Gastrointestinal System

Gastrointestinal side effects include nausea, constipation, dry mouth, anorexia and (rarely) biliary spasm. Methadone tends to be less constipating than other oral opioids. When switching from other oral opioids to methadone (or to transdermal fentanyl), patients may experience temporary diarrhea and so may need fewer laxatives. Constipation is easier to prevent than to treat so it is advised to discuss bowel regimens with all patients.

Respiratory System

Respiratory depression may occur in patients whose initial dose of methadone is too high or whose dose is increased too quickly. Respiratory depression is not a concern with chronic stable dosing. Patients with decreased respiratory drive, such as COPD patients with CO₂ retention or those with severe sleep

³ Glatstein MM, Garcia-Bournissen F, Finkelstein Y, Koren G. Methadone exposure during lactation. *Can Fam Physician*. 2008 Dec;54(12):1689–1690.

Methadone for Analgesia Guidelines

apnea, should be observed cautiously when initiating an opioid, and the dose should be titrated slowly. This concern should not preclude the use of long-acting opioids for dyspnea due to cancer, end-stage COPD, heart failure or other chronic lung diseases, as opioids may offer much relief in these situations. Transient pulmonary edema and bronchospasm are rarely seen but can occur with any opioid, including methadone. If patients have a history of true opioid allergy (e.g. anaphylaxis or urticaria), the initial doses of methadone should be administered under close medical supervision.

Cardiovascular System

Hypotension and bradycardia occur rarely and may lead to faintness or syncope. Flushing may occur. Peripheral edema has also been anecdotally reported, usually when high doses are used, but can occur months after commencing methadone.⁴ Methadone can cause QT prolongation. Patients treated with methadone for pain do not usually require doses over 150 mg/day, but there have been some reports of torsades de pointes in patients taking high-dose methadone (doses well in excess of 150 mg/day). Most of these cases also had other risk factors for cardiac arrhythmia such as pre-existing cardiac disease, metabolic concerns (such as hypomagnesemia from prior use of platin-based chemotherapy), or the use of drugs known to cause QT prolongation. Severe malnutrition due to eating disorders, alcoholism or general debility can cause severe bradycardia and QT prolongation, which increases the risk of arrhythmia, especially in the presence of electrolyte abnormalities, particularly hypomagnesemia. It is recommended that patients who have cardiac disease, other medications or metabolic concerns known to cause QT interval prolongation should have an electrocardiogram prior to starting on methadone (see [Drug Interactions](#)). If the QT interval is prolonged despite correction of reversible causes, a risk-benefit analysis regarding methadone prescribing should be undertaken by the physician. In patients with no other risk factors for cardiac arrhythmia, the threshold for recommending recording an ECG is unclear and there is no universal agreement in the recent literature.^{5,6,7,8}

Physicians should apply their clinical judgment when treating patients for pain, bearing in mind the above cautions. A level of 150 mg/day is a conservative recommendation for a screening ECG in a patient with no risk factors for arrhythmia. The ECG should be repeated as clinically indicated. It has recently been reported that the QT interval may fluctuate over time, so periodic repeat ECGs are recommended if there is concern about high methadone dosing, other risk factors for arrhythmia or potential interactions.

Genitourinary System

Urinary hesitancy or retention may occur with any opioid, but may be less so with methadone.⁹ Chronic use of any opioid can result in hypogonadism, due to central suppression of hypothalamic release of

⁴ Mahe I, Chassany O, Grenard AS, Caulin C, Bergmann JF. Methadone and edema: a case report and literature review. *Eur J Clin Pharmacol.* 2004 Feb;59(12):923-4.

⁵ Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MC. QTc interval screening in methadone treatment: the CSAT consensus guideline. *Ann Intern Med* 2009 Mar 17;150(6):387-95.

⁶ Byrne A. Close examination finds flaws with Annals article on QT effects from methadone [Internet]. Redfern (NSW), Australia: Redfern Clinic; 2009 [updated 2009 Mar 6; cited 2009 Dec 9]. Available from: <http://www.redfermclinic.com/c/2009/03/close-examination-finds-flaws-with-4855.php4>.

⁷ Martin J. President's column. *CSAM News*. San Francisco: California Society of Addiction Medicine. 2008;35(1):3,8. Available from: http://www.csam-asam.org/pdf/misc/CSAM_Winter_2008.pdf.

⁸ ECG screening in methadone patients challenged. In "Misguided pain guidelines? When strong claims follow from weak evidence." *Pain Treatment Topics e-Briefing.* 2009;4(1):4-6. Available from: <http://pain-topics.org/pdf/e-Briefing-Vol4-No1-2009.pdf>.

⁹ Gedney JA, Liu EHC. Side-effects of epidural infusions of opioid bupivacaine mixtures. *Anaesthesia*; 1998;53(1148-1155).

Methadone for Analgesia Guidelines

gonadotrophin-releasing hormone (GnRH). GnRH suppression can lead to fatigue, depression, anxiety, decreased muscle mass and reduced libido. Testosterone replacement may be appropriate if testosterone levels are low and patients are symptomatic.

Dermatologic System

Sweating can be a problem with all opioids, and is very common with methadone. Pruritus and rashes are seen less frequently with methadone than with other opioids, and methadone can be well tolerated by patients who have allergic reactions to other opioids. If patients have a history of true opioid allergy (e.g. anaphylaxis or urticaria), the initial doses of methadone should be administered under close medical supervision.

Methadone for Analgesia Guidelines

Drug Interactions

Drugs which interact with methadone generally involve inducers or inhibitors of the cytochrome P450 (CYP) system—mainly CYP3A4 and, to a lesser extent, 1A2 and 2D6. Note that some genetic polymorphism can influence enzyme distribution.

[Appendix A](#) contains a complete list of medications metabolized by cytochrome P450 3A4. This list is divided into inducers, substrates and inhibitors, and should be referred to whenever a new drug is started or when a drug which has been in chronic use is discontinued. Commonly used drugs in each class of interaction are described here.

Inducers of P450 3A4	These drugs will reduce methadone levels—for example, rifampin/rifampicin, phenytoin, phenobarbital, carbamazepine. When patients on methadone are initiated on a P450 3A4 inducer, a minor dose increase in methadone may be required.
Inhibitors of P450 3A4	These drugs will raise methadone levels—for example, ketoconazole, fluconazole, fluvoxamine, fluoxetine, cimetidine, ciprofloxacin and erythromycin. When methadone patients are initiated on a P450 3A4 inhibitor, careful observation is required and, in some instances, the methadone dose may need to be reduced.
Substrates	These drugs compete for metabolism with methadone—for example, imipramine, nortriptyline, alprazolam. They may or may not also inhibit or induce the enzyme, and changes in dosing should be made if an interaction is suspected.

A link to a list of drugs associated with QT interval prolongation can be found in [appendix A](#). These are some common examples:

Drugs	Examples
antidepressants	amitriptyline, imipramine, nortriptyline, desipramine, doxepin, maprotiline
antipsychotics	haloperidol, pimozide, ziprasidone, quetiapine
antibiotics	erythromycin, clarithromycin
antimalarials	chloroquine
antihistamines	diphenhydramine
antiarrhythmics	quinidine,* amiodarone,* disopyramide, flecainide, ibutilide, procainamide, propafenone, sotalol

Methadone for Analgesia Guidelines

Drugs	Examples
others	probucol, tacrolimus, arsenic trioxide, droperidol

*Quinidine and amiodarone also inhibit 3A4, which may lead to increased methadone levels.

Patients with impaired liver function need to be monitored carefully and methadone doses may need to be reduced as liver function deteriorates. These patients require frequent reassessment.

Alcohol will potentiate the sedative and respiratory depressant effects of methadone. Chronic alcohol use will initially induce enzymes and tend to reduce methadone levels, but as liver function deteriorates due to chronic disease and/or alcohol abuse, methadone will tend to accumulate. It is recommended that alcohol be avoided by patients maintained on methadone for chronic pain.

Benzodiazepines and methadone have additive toxicity and, when used in combination, enhance respiratory depression and sedative effects. In particular, benzodiazepines with active metabolites and a long half-life (such as diazepam, which is also metabolized by P450 3A4) should be avoided. Patients using both methadone and a benzodiazepine require careful monitoring (in general, this combination should be avoided in the CNCP setting).

When accessing walk-in clinics and emergency rooms for conditions such as cold and flu symptoms, patients should always inform new prescribers of all current medications, particularly methadone, so that drug interactions can be prevented.

Methadone for Analgesia Guidelines

Available Strengths and Forms of Methadone

Liquid methadone is most commonly available as Methadose® flavoured oral solution. It can be further diluted in water or any juice (except grapefruit) for enhanced palatability. The usual solution strength is 10 mg/mL, though other strengths may be made available when necessary. When switching to a higher strength, physicians should exercise extra caution, as inadvertent overdose may occur if the higher concentration is not recognized.

The bottle containing the liquid methadone preparation should always be shaken before use. Patients should use a syringe to measure the liquid methadone preparation, rather than a spoon or measuring cup, to ensure the accuracy of the volume ingested. Depending on the dose, or container provided, the patient may need to first pour some into a measuring cup in order to use the syringe. Any remaining liquid should be poured back into the bottle. If a measuring cup is used to administer the dose, rinse the cup with water and ingest that as well, to ensure accuracy of the complete dose.

Methadone is also available in tablet form, in 1 mg, 5 mg, 10 mg and 25 mg strengths. These are more expensive than the liquid methadone preparation and are covered by PharmaCare only through the BC Palliative Care Drug Program. Many extended health plans may cover the oral preparations. The use of methadone tablets rather than liquid reduces the likelihood of dosing errors and may be preferred if patients' measuring skills are in doubt or if the liquid methadone preparation is too small to be safely measured. Some patients choose to use the liquid when at home but keep tablets for use when away from home or travelling. It may be more practical for patients being started on methadone to first use the tablets, then switch to liquid to save money if appropriate, once dosing is stable.

Pharmacies can prepare custom-made methadone capsules or suppositories if standard preparations are not satisfactory, such as when patients are unable to swallow or if doses are too high to allow buccal or sublingual administration (usually used in the palliative care setting but not for CNCP). It should however be noted that methadone suppositories are not absorbed as well as the oral solution administered rectally, and dose adjustments would need to be made accordingly if using custom suppositories. Monitor dose and side effects if changing administration to the rectal route and be prepared to make dose adjustments.

Secure storage of methadone is of utmost importance, particularly in households with children who may find its coloring particularly tempting. One teaspoon ingested by a toddler can be lethal. Secure storage can also prevent diversion by others.

Methadone for parenteral injection is no longer available in Canada except by compounding in some specialist centres.

Methadone for Analgesia Guidelines

Switching Opioids

Not only do opioids differ in their effects on opioid receptors, but individuals vary in their ability to metabolize the different opioids. These differences are largely genetically based, through hepatic and renal enzymes or transporter proteins. At present, it is not possible to determine which opioid will best suit an individual other than by trial and error. When initiating a trial of opioid therapy, it is important that physicians be prepared to try more than one opioid and are comfortable rotating from one to another until either satisfactory analgesia is achieved or the trial is abandoned. Monotherapy with one opioid (including methadone) is ideal, and one can incorporate other treatment modalities such as neuropathic agents, physical/occupational therapy, psychological approaches, and adjunctive therapies.

Morphine is the usual first-line opioid for the treatment of chronic pain. The other long-acting opioids (oxycodone, hydromorphone and codeine) may be better tolerated and/or more effective in some individuals but are more expensive and may require PharmaCare authorization. The NMDA-receptor-blocking effect of methadone precludes development of tolerance as compared with other opioids, suggesting that it may be the preferred opioid for long-term use. Methadone may also be considered for morphine-intolerant patients, especially when long-term treatment is anticipated. Methadone and fentanyl are not considered first-line treatments for CNCP (especially in opioid-naïve patients), and should be considered only after trials of other agents have been unsuccessful.

Indications for Switching Opioids

1. Inadequate pain control with dose-limiting side effects

This may occur especially with neuropathic pain. Before switching opioids, physicians should perform a detailed pain assessment and consider the use of adjuvant analgesics and other treatments. For example, constipation can usually be well controlled with a good bowel protocol.

2. Confusion, hallucinations or delirium

Although these are often attributable to opioid toxicity, there are many potential causes for delirium in patients with advanced cancer. A clinical assessment and investigation is imperative to exclude other causes before assuming that opioids are responsible. Until these have been excluded, it may be more appropriate to reduce the dose of the opioid. Parenteral administration should be used cautiously, as it may actually worsen delirium, especially in the elderly.

3. Non-compliance

Patients' compliance may be enhanced by switching to a different delivery method, such as from an oral to a transdermal opioid. Fentanyl transdermal patches, for example, need to be changed only every three days. Although these patches are expensive, such switches may be considered cost-effective if other expenses incurred in the daily administration of medication (such as a home care nurse) can thereby be eliminated. Children taking opioids for chronic pain from severe medical conditions may dislike taking tablets but may find flavored juices acceptable.

4. Problems with the route of administration

Methadone for Analgesia Guidelines

When an oral route is not available, use of a topical opioid may circumvent the need for injections. Specialty pharmacies can compound pain creams with a variety of ingredients, including methadone. Suppositories can also be compounded for rectal use, if faster absorption is needed, but should be avoided in patients with anal or rectal lesions.¹⁰

Methadone may easily be administered via a gastrostomy or jejunostomy tube, whereas other long-acting opioid preparations may cause blockages or get stuck in such tubes. Short-acting opioids, which require frequent administration, may be impractical.

5. Cost

The high cost and (potential lack of) coverage of many long-acting opioids may be a factor in switching to methadone, which is considerably cheaper, especially when high-dose opioid therapy is required.

When switching to a new opioid other than methadone, an up-to-date equianalgesic table should be used, such as the one in [appendix C](#). The patient's total opioid dose should be converted to an oral morphine equivalent using the table. Once the equianalgesic dose has been calculated, a 30 to 50% dose decrease should be incorporated, to allow for incomplete cross-tolerance; then the patient can be started at the newly calculated dose.¹¹

Physicians should ensure that an adequate dose of a short-acting opioid is available when switching opioids, as the equianalgesic ratios can vary between individuals. The dose of the new opioid often needs to be adjusted even when using the ratios suggested. Physicians should also consider the onset of action and clearance of an opioid preparation, so that there is no gap in therapy when switching opioids. This is particularly important with fentanyl patches, which may take up to 24 hours to reach full effect. Methadone usually takes at least three days to reach steady state, and toxicity from methadone most commonly occurs on days three to five following a switch. This is why the “start low, go slow” method is recommended unless there is clinical urgency, such as severe opioid toxicity, for example seizures. In this type of situation hospitalization is usually unavoidable.

Although the usual dosing for methadone for analgesic purposes is at eight-hour intervals, individual needs may range from every six hours up to every 12 hours. Patients should be assessed on an individual basis. Short-acting opioids such as morphine, hydromorphone, oxycodone or transmucosal fentanyl or sufentanil (in-patient setting) would be more suitable for these situations.

If possible, patients on high-dose opioid therapy should be admitted to hospital while opioids are being rotated. However, switching can be done as an outpatient procedure if **excellent** supervision is available and if the situation is not acute. A stepped switch method as described below for methadone would be entirely appropriate for other opioids as well if admission to hospital is not otherwise needed. The prescribing physician is responsible for ensuring such supervision. Methadone should be started only if the physician is prepared to provide the required supervision, especially in the first two weeks. Communication about new doses can be complex and confusing for many people, with great potential for errors. Safety parameters that can be employed for outpatient rotation include: family member presence at physician appointments and during first few days of rotation; home care nursing visits; and

¹⁰ Fraser Health Authority, Hospice Palliative Care Program. Principles of opioid management. Surrey, BC; 2006 [cited October 4, 2016]. 45p. Available from: <https://www.fraserhealth.ca/media/16FHSymptomGuidelinesOpioid.pdf>

¹¹ Perry GF, Portenoy RK. Establishing “best practices” for opioid rotation: conclusions of an expert panel. *J Pain Symptom Manage*. 2009; 38(3): 418-425.

Methadone for Analgesia Guidelines

advice to avoid driving/operating heavy machinery until stable. Use of daily dispensed medication may be appropriate in some circumstances so the pharmacist can review the patient daily until stable dosing is achieved.

Methadone for Analgesia Guidelines

Methods for Switching to Methadone

The schedules for switching to methadone described in this chapter represent only a few of the many available. Most experienced prescribers prefer to switch gradually, over a period of two to three weeks, as this is the safest method. It is important to remember that the equivalence to morphine may vary considerably from one individual to another. In general, the higher the dose of the previous opioid, the more potent methadone appears to be. The switching method chosen will depend on the circumstances of the individual case. Refer to [appendix B](#) for conversion ratios for oral morphine to oral methadone, and to the equianalgesic chart in [appendix C](#) for conversion between opioids.

"Start Low, Go Slow"

In an outpatient or non-urgent setting where the reason for switching is not due to toxicity of the prior opioid, the **preferred method** for initiating methadone is the "start low, go slow" method. Methadone is started at a low dose and gradually increased at intervals of no less than three days until good analgesia is achieved. For elderly patients or patients with impaired liver function, this adjustment period should be increased. Doses of 1 mg to 2 mg every eight hours can be highly effective. Once patients are comfortable, the prior opioid can be slowly tapered to discontinuation. During this taper the dose of methadone may require further increase, but again should be increased at no less than three-day intervals, and no more than 20% at a time; longer in the elderly or if liver function is impaired, and with smaller increments if the patient is not opioid-tolerant.

Monotherapy with methadone may be enough, but be prepared to provide an agent for adequate treatment of breakthrough pain during the conversion and dose-titration period. This can be an NSAID or acetaminophen, or a short-acting opioid such as morphine, hydromorphone or oxycodone. Methadone is not advised for both baseline therapy and incident pain because of the potential for accumulation and inadvertent methadone overdose. When other opioids are contraindicated, however, methadone may be used as a breakthrough opioid, but it is prudent to limit daily PRN doses to a maximum of 10% of the total daily dose and to no more than three breakthrough doses per day to avoid accumulation. In daily doses of less than 55 mg, methadone is excreted mainly through the liver into the feces.¹² However, urinary excretion of methadone and its metabolites is dose-dependent and may comprise a more significant route of excretion at high dosages. If renal function in patients on a stable dose of methadone deteriorates, and it becomes apparent that there are more side effects consistent with an increasing methadone blood level, it may be necessary to reduce the dose of methadone. Methadone is poorly dialyzed and is the preferred opioid analgesic for patients with pain and renal failure.

This method is appropriate for patients who are extremely intolerant of other opioids or are at high risk for adverse effects (such as those who have had previous anaphylaxis to morphine or COPD patients with a CO₂ retention history from chronic lung disease). It is also the preferred method for opioid-naïve patients and for chronic non-cancer pain patients.

¹² Opioid Agonist Maintenance Treatment: a pharmacist's guide to methadone and buprenorphine for opioid use disorder. Isaac, P. et al. Toronto: Centre for Addiction and Mental Health (CAMH). 2015.

Methadone for Analgesia Guidelines

Examples

1. Mesothelioma patient with nociceptive and neuropathic pain, and difficulty tolerating opioids. Agrees to try methadone after failure to achieve adequate analgesia with other opioids, and side effects of dizziness and agitation on low-dose fentanyl:

Day 1	0.5 mg q8h
Day 3	1 mg q8h (sleep has improved)
Day 6	2 mg q8h
Day 9	3 mg q8h

Dose reassessed every 3 days and increases of 1 mg q8h made until adequate pain control achieved or side effects limit dose. Patient maintains comfort at dose of 3 mg q8h for six months and slowly increases dose as needed due to disease progression. Dose of 10 mg q8h reached after one year and switched to liquid when swallowing becomes difficult. This regimen allows him to pass away peacefully at home.

2. Patient with spinal stenosis:

Week 1	1 mg q8h
Week 2	2 mg q8h
Week 3	3 mg q8h
Week 4	5 mg q8h
Week 5	7 mg q8h
Week 6	9 mg q8h
Week 7	11 mg q8h

Dose reassessed every seven days due to patient frailty and increases (ranging from 1 mg to 2 mg q8h) made until adequate pain control achieved or side effects limit dose. Patient stable on maintenance dose of 11 mg q8h, with occasional use of hydromorphone 1 mg prn, used between one and three times daily for breakthrough pain, depending on activity.

3. Patient with peripheral neuropathy following chemotherapy; undergoes tumor-removal surgery which results in radiculopathy. Patient is reluctant to try opioids but has had very limited success with tricyclic antidepressant, gabapentin or pregabalin. Specialist starts methadone:

Day 1	1 mg q8h (no significant analgesia but tolerating well)
Day 8	2 mg q8h
Day 15	3 mg q8h
Day 22	4 mg q8h (pain almost completely controlled)

Dose reassessed every seven days and increases of 1 mg q8h made until adequate pain control achieved or side effects limit dose. Patient is able to decrease dose to 3 mg q8h after six weeks; pain is nearly gone and numbness is bearable. Maintenance dose of 2.5 mg to 3 mg q8h reached

Methadone for Analgesia Guidelines

and patient is transferred to family physician with methadone analgesia authorization for ongoing care.

Children living with chronic pain from a variety of medical conditions may benefit from long-term opioid therapy, with or without an immediately life-limiting condition. The relatively infrequent dosing schedule of methadone, plus its suitability for administration in flavoured drinks or via enteral feeding tubes make methadone a useful choice of opioid in children as well as in some adults. The "start low, go slow" method of introduction would be important to follow in children, starting with lower doses than in adults, according to body size.

Slow-Switch Method: 33 Per Cent Steps at Three-Day Intervals

This method is suitable for patients in whom there is greater urgency for a switch, such as in the context of toxicity from the prior opioid, but the patient is otherwise coping and prefers to avoid admission to hospital. A short-acting form of the previous opioid should be available for breakthrough pain or for rescue dosing in case the anticipated methadone dose proves to be inadequate.

To calculate the starting dose of methadone, first use [appendix C](#) to determine the patient's current oral morphine equivalent dose per 24 hours. Divide this number by the ratio appropriate for that dose range, using the conversion ratio table in [appendix B](#) to give an estimate of the final total daily dose of methadone. Divide the total daily dose by three to give the estimated final q8h dose. This dose is then further divided by three to provide the suggested starting dose.

Example

For 600 mg morphine/24 hours, use a 10:1 conversion ratio	→ 60 mg methadone/24 hours = 20 mg methadone/8 hours final dose
For 120 mg morphine/24 hours, use a 5:1 conversion ratio	→ 24 mg methadone/24 hours = 8 mg methadone/8 hours final dose

Day 1

Calculate the starting equianalgesic dose of methadone using the instructions above, but give only a third of that dose while reducing the dose of previous opioid by a third.

In the first example 20 mg doesn't divide exactly by three, so go with the closest measurable dose (i.e. 6.5 mg q8h). The morphine would be reduced to 400 mg spread over 24 hours (i.e. 200 mg long-acting q12h or 65 mg short-acting q8h).

In the second example, 8 mg divided by three would suggest a starting dose of 2.5 mg q8h, the morphine being reduced to 80 mg long-acting q12h or 25mg short-acting q4h.

Methadone for Analgesia Guidelines

- Day 4** Increase the methadone dose to two thirds of the calculated equianalgesic dose and reduce the previous opioid to a third of the pre-switch dose.
- In the first example above the methadone would be increased to 13 mg q8h and the morphine to 100 mg long-acting q12h or 30mg q4h.
- In the second example above the methadone would be increased to 5mg q8h and the morphine decreased to 40 mg long-acting q12h or 15 mg short-acting q8h.
- Day 7** Increase the methadone to the full equianalgesic dose and discontinue regular administration of the previous opioid, allowing adequate breakthrough of a short-acting opioid as previously described.
- Day 10 onward** Adjust the dose of methadone by increments of approximately 20 percent every three to five days until an optimal balance is achieved between analgesia and side effects. Smaller incremental changes may be needed to fine-tune the dosing in very sensitive patients. Methadone dosage should not be increased to control short-lived pain episodes (such as movement-related bone pain in metastatic cancer, or dressing changes), as this may lead to excessive dosing and accumulation. Use a short-acting opioid for these episodes if needed.

If the dosing strengths of the previous opioid do not allow for adjustments by thirds, or if there is undue anxiety about the switch and no urgency for change, a similar procedure using four or more steps, instead of three, can be applied. **For example**, when switching a patient from transdermal fentanyl at a dose of 100 mcg/hr, the fentanyl can be reduced in 25 mcg/hr increments and the methadone started at one-fourth of the estimated eventual predicted equianalgesic dose.

See below for stepwise rotation. If the effectiveness of the methadone is not exactly as predicted, the plan can safely be adjusted without risk of unexpected over-or under-dosing.

Patient switching from fentanyl 100 mcg/hr to methadone:

For 360 mg morphine/24 hours, use a 10:1 conversion ratio → 36 mg methadone/24 hours = 12 mg methadone/8 hours

Day 1	Fentanyl 75 mcg	Methadone 3 mg every 8 hours
Day 4	Fentanyl 50 mcg	Methadone 6 mg every 8 hours
Day 7	Fentanyl 25 mcg	Methadone 9 mg every 8 hours
Day 10	Fentanyl stopped	Methadone 12 mg every 8 hours

It is not recommended to start patients on more than 30 mg/day (CNCP) or more than 90 mg/day (advanced cancer) of methadone even if their previous daily oral morphine equivalent doses are very high. To allow for incomplete cross-tolerance, you may need to consider a 30% to 50% dose decrease in your calculation.

Methadone for Analgesia Guidelines

Rapid-Switch (“Stop-Start”) Method

This method is appropriate only for patients with severe side effects from previous opioids and uncontrolled pain. Stable dosing may be achieved in three to five days. Inpatient supervision is recommended.

- Day 1** Calculate the methadone starting dose using the same method as for the slow switch above. Divide the total daily dose by three to give the q8h methadone dose. Halve the total dose of the previous opioid and convert it to q4h short-acting preparation. Give this simultaneously with the methadone for the first 24 hours. If switching from fentanyl patches, use the equianalgesic dose of short-acting morphine, oxycodone or hydromorphone instead of that for fentanyl. This is to minimize the possibility of overdosage, as the fentanyl level may not decrease for more than 18 hours after the patch is removed.

Example

300 mg long-acting morphine q12h = 100 mg morphine every 4 hours
= 20mg methadone q8h.

DIVIDE morphine by 2

→ 50 mg immediate release morphine/4 hours regularly in addition to methadone 20 mg every 8 hours

Allow an adequate dose of short-acting opioid for breakthrough pain. The usual breakthrough dose is the same as the q4h dose, but allow for more frequent dosing if necessary. Using the above example, the breakthrough dose would be 50 mg q1h PRN.

- Day 2** Reassess. If the pain is poorly controlled, then increase the dose of methadone by 20% to 25%, as long as the patient is not experiencing an increase in opioid-related side effects. If possible, wait before increasing the methadone at this point. Change the oral short-acting opioid dose to PRN only.

Methadone for Analgesia Guidelines

Day 3

Assess for analgesia and side effects and adjust methadone accordingly. Accumulation of methadone is most likely to occur at this time. If the patient is excessively sedated, decrease the dose of methadone. If pain control is inadequate and a short-acting opioid is still required, increase methadone by 20% to 25%. If in doubt, wait another day. Thereafter, assess daily until stable analgesia is achieved, usually after four to five days. **As above, it is not recommended to start patients on more than 30mg/day (CNCP) or up to 90 mg/day (palliative) of methadone even if their previous daily oral morphine equivalent doses are very high. To allow for incomplete cross-tolerance, include a 30% to 50% dose decrease in your calculations.**

PRN Methadone Switch

Some protocols suggest the total cessation of the previous opioid while commencing PRN administration of methadone. Although these instructions may appear straightforward and simple for patients to apply, it is possible for patients to inadvertently overdose using this method. This switching method is not recommended unless the prescriber is very experienced with the use of methadone and is able to offer excellent medical supervision during the switching period, preferably in hospital.

Methadone for Analgesia Guidelines

Using Methadone Safely: What Can Go Wrong

Communication errors are the most frequent causes of problems in the initial switching period, especially in the home environment. Write down your instructions and ask for the assistance of the home care nurses and pharmacists in ensuring compliance.

Take great care to accurately establish current opioid dosing and use the correct conversion ratio, to avoid errors in calculating equianalgesic doses. It is useful to have someone else (such as a pharmacist) check your calculations. **Never** start with more than 30 mg q8h; ideally never start with more than 10 mg q8h (refer to [Methods for Switching to Methadone](#) for recommended starting doses). Avoid use of online opioid equianalgesic dose calculators, as they are not always correct with respect to methadone.

Increasing the methadone dose too quickly can lead to overdose. Allow at least three days (preferably five days, based on half-life calculation of steady state) between dose adjustments if possible, and be prepared to reduce the dose as soon as adverse effects occur.

Once on stable dosing, interactions with other medications can have a significant effect on methadone metabolism. If the methadone dose is not adjusted, toxicity can occur. Always check the list of medications metabolized by cytochrome P450 3A4 appendix A for possible interactions when prescribing new medications. A wallet card may be obtained from the manufacturers of Metadol (Paladin Labs) which can be provided to the patient.

Dispensing errors can occur, especially if a different strength of liquid methadone is substituted for the 10 mg/mL strength. If more than one preparation is being used on the same hospital ward, be very careful to administer the correct strength. It would be prudent to differentiate the different strengths by flavour and colour. There is less likelihood of error if tablets are used.

Diversion of methadone and theft can occur if the patient does not live in a safe environment. Patients should be made aware of the risk that their methadone may be taken by others for their own use or to be sold on the street, so they can take adequate precautions to keep their medication safe.

Chronic pain and depression often coexist. Deliberate methadone overdose has been used to achieve suicide, especially when large amounts have been prescribed for non-cancer pain and when there is severe depression. If methadone is to be used for analgesia in these circumstances, limited dispensing and good supervision are required, but should be balanced with the need to avoid unnecessary inconvenience to those with minimal or no risk of overdose. Consider referral to psychiatry for assessment before initiating methadone in someone with active/recent suicidality.

If the switch to methadone is not successful but patients have not been taking their previous opioids/ they will lose some of their previous opioid tolerance. This may also occur when there has been an interruption in methadone therapy (for example, during a hospital admission for surgery). A return to the pre-switch opioid dose may lead to overdose if breaks in continuous therapy have not been taken into account.

Patients are sometimes reluctant to try methadone for analgesia because of the common perception that methadone is only used for treatment of addiction. Prescriptions should be clearly marked “for pain” to avoid insensitive interactions at the pharmacy or confusion among family members.

Methadone for Analgesia Guidelines

Urine Drug Testing

There is increasing evidence that urine drug testing (UDT) is a useful tool in the clinical management of patients receiving chronic opioid therapy. Self-reporting of drug use may be unreliable, and the detection of inappropriate use of medications or illicit drugs is important in the early identification of concurrent disorders such as addiction or misuse of medication. Random counts of pills or liquid volumes can aid in confirming suspicion of diversion.

Prior to initiating a trial of methadone, patients should be aware that UDT is a routine part of treatment and must provide their consent for these tests, with a full understanding of the use of such test results. Contingency plans need to be in place to deal with issues related to addiction or diversion. UDT should be seen as an objective, non-discriminatory tool for appropriate longitudinal assessment and management of patients' pain and clinical condition, rather than a test whose primary function is to allow or deny opioids to patients. UDT may not be appropriate in situations where end of life is imminent and/or risk of abuse/diversion is assessed as very low, such as in supervised long-term care or hospice.

Urine drug testing should be conducted on a random urine sample that is freshly obtained in the office or laboratory. It is essential that a standard urine collection protocol be in place to ensure reliability of the specimen (see [appendix A](#)). Further information on UDT can be found in the BCCSU guidelines on the clinical management of opioid use disorder, or obtained through the College library. On the laboratory requisition, specify the drugs for which the sample should be screened. This decision may depend on the patient population as well as geographic location because of regional differences in drug use.

Not all drugs in a particular drug class will be detected by the enzyme immunoassay technique employed by routine drug screens (typically a five-panel screen of opiates, cocaine, amphetamines, benzodiazepines, methadone metabolite). If more thorough investigation is needed, a confirmatory GC-MS (gas chromatography-mass spectrometry) test will be required. This limitation is particularly evident when screening for opioids. The standard immunoassay will only reliably identify natural opioids such as diacetylmorphine (heroin), monoacetylmorphine (first metabolite of heroin), morphine and codeine.

The synthetic and semi-synthetic opioids require GC-MS testing for their identification. The benzodiazepine immunoassay may not identify two of the most commonly prescribed benzodiazepines (lorazepam and clonazepam).

Urine specimens for drug testing are retained in the laboratory for up to 14 days so the ordering physicians can review results with the toxicologist and order confirmatory tests when required. It is advisable to make the purpose of testing clear on the requisition to avoid delay and potential for potentially damaging miscommunication with the patient.

Methadone for Analgesia Guidelines

Appendices

Appendix A: Links to application forms and relevant documents

- [*Prescribing Methadone standard*](#)
- [*Methadone for Pain in Palliative Care online CME*](#)
- [*Safe Prescribing of Opioids and Sedatives*](#)
- [*Non-Prescription Naloxone Now Available Outside of Pharmacies*](#)
- [*Take-home naloxone kits now available at community pharmacies*](#)
- [*Medications metabolized by cytochrome P450 3A4*](#)
- [*Drugs associated with QT interval prolongation*](#)

Methadone for Analgesia Guidelines

Appendix B: Equianalgesic conversion guides

Daily oral morphine equivalent (mg)	Conversion ratio of oral morphine: oral methadone Ayonrinde
30-100	3:1
101-300	5:1
301-600	10:1
601-800	12:1
801-1000	15:1
>1000	20:1

*** Maximum starting doses = 30 mg/day (CNCP) or 90 mg/day (palliative)**

- This conversion guide contains recommendations from two different sources. Choose one and keep dose changes consistent with that same source.
- This conversion guide applies to the maintenance dosage. The starting dose should be much lower and gradually increased until analgesia is achieved. Allow 30% to 50% reduction in starting dose to account for incomplete cross-tolerance if rotating from another opioid.
- For switching protocols, refer to [Switching Opioids](#).
- In an outpatient setting, the preferred method is to "start low, go slow."
- This suggested conversion guide has no relevance in the initiation of methadone for opioid dependence and should not be used for that purpose.

Methadone for Analgesia Guidelines

Appendix C: Equianalgesic potency of opioids for chronic pain

Doses in each column are equianalgesic and interchangeable at the doses shown, with the cautions mentioned below.

Equianalgesic doses of opioids may vary considerably from those predicted and should be modified according to response.

	Drug	Example	Parenteral Dose	PO Dose	Schedule
Morphine	Immediate release	MOS, MSIR	7-10 mg*	20 mg	q4h
	Sustained release	M-Eslon, MS Contin Kadian	-	60 mg	q12h
Codeine	Immediate release		-	120 mg*	q4h
	Sustained release	Codeine Contin	-	360 mg	q12h
Oxycodone	Immediate release	Supeudol, Oxy-IR	-	15 mg	q4h
	Sustained release	OxyNeo	-	45 mg	q12h
	Combination products	Oxycocet/Percocet (+Acetaminophen)		15 mg*	q4h
Hydromorphone	Immediate release	Dilaudid	2 mg	4 mg	q4h
	Sustained release	Hydromorph Contin		12 mg	q12h
Fentanyl	Topical	Duragesic Patch	See below*		q72h
Not recommended for chronic pain (included to guide discontinuation):					
Meperidine		Demerol	75 mg	300 mg* Toxic	q2-3h
Pentazocine		Talwin	60 mg	180 mg	q3-4h

Methadone for Analgesia Guidelines

*Cautions:

- Oral: parenteral potency varies between 2:1 and 3:1.
- Doses of codeine above 300 mg/12 hrs are not recommended. Tramadol is considered approximately equivalent to codeine, so one Tramacet would be equivalent to one Tylenol #3. If higher doses are needed, a switch to a strong opioid such as morphine is recommended. The maximum recommended dose of acetaminophen is 3,900 mg/day, or 12 x Tylenol #3.
- To make 15 mg of oxycodone, these require three tablets q4h which may become toxic for the ASA or acetaminophen. Pure oxycodone or other opioids are recommended in this situation.
- Previous opioid should be tapered over first 12 hours of fentanyl as absorption is delayed.
- 300 mg oral doses of Demerol are toxic and are included for analgesic purposes only

Recommended conversion for fentanyl to oral morphine equivalent as recommended by the Fraser Health *Principles of Opioid Management* guideline:

Fentanyl Transdermal Equianalgesic Conversion Chart*

Morphine PO (mg per day)	Hydromorphone PO (mg per day)	Oxycodone PO (mg per day)	Fentanyl Patch (mcg per day)
45-134	9-26	30-89	25
135-224	27-44	90-149	50
225-314	45-62	150-209	75
315-404	63-80	210-269	100
405-494	81-98	270-329	125
495-584	99-116	330-389	150
585-674	117-134	390-449	175
675-764	135-152	450-509	200
765-854	153-170	510-569	225
855-944	171-188	570-629	250
945-1034	189-206	630-689	275
1035-1124	207-224	690-749	300

*The conversions between fentanyl and morphine are taken from the 2004 Compendium of Pharmaceuticals and Specialties.⁽¹⁶⁾ The hydromorphone and oxycodone conversion are based on a morphine to hydromorphone ratio of (5:1) and a morphine to oxycodone ratio of (1.5:1)

Methadone for Analgesia Guidelines

Revision History

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