
GUIDELIN

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 (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 for the management of chronic pain.

Methadone is an oral long-acting synthetic opioid. Due to the unique pharmacokinetics of methadone, which has a long and variable half-

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.

An assessment of any patient with chronic pain comprises the following:

1. Pain history – this assessment should include:
    a. Previous trials of analgesia and non-pharmacologic treatments.
    b. What the patient is currently taking and its effectiveness in terms of pain and function.
    c. A brief systems review with particular attention to gastrointestinal, hormonal, and sleep-related symptoms. For example, prior to starting methadone it is important to know if the patient has constipation or symptoms of sleep-disordered breathing.
2. Medical history – review all documentation and previous diagnoses; specific attention to any history of heart disease, arrhythmia, and syncope.
3. Surgical history – review all documentation and previous diagnoses.
4. Psychiatric history – screen for mood disorders, sleep disturbance, trauma history (particularly childhood sexual trauma), personality disorders, limited coping skills.
5. Substance use history – screen for past and current substance use including nicotine, alcohol, over-the-counter medication, medical cannabis, and illicit substances. Structured screening for substances of misuse 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?"
6. Family history – including any history of sudden death, which could be from a hereditary long QT syndrome.

Opioid use disorder and chronic pain[3]

Chronic non-cancer pain (CNCP) is a very common condition affecting up to a third of the population. It 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 or spinal degeneration, it can be difficult to identify a cause in some patients.

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.

It is important that all patients who are being considered for opioid therapy, and especially those with CNCP, be screened for underlying substance use disorder, including alcohol, prescription medication, or street drugs. Treatment with an opioid analgesic is not contraindicated in a patient with a history of substance use disorder (SUD), but a

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-aspartate) 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. It has a large initial volume of distribution followed by slow tissue release, as well as a high bioavailability of around 80%. Although its onset of action can be as short as 30 minutes, it should be avoided as a breakthrough or PRN medication due to its long duration of action and potential for dose accumulation.

Gastrointestinal system

As with any opioid, methadone can cause gastrointestinal side effects such as 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, 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, unless new medication with the potential to interact has been added (for example, zopiclone for insomnia). Patients with decreased respiratory drive, such as COPD patients with CO_2 retention or those with severe sleep apnea, should be observed cautiously when initiating any 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 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 hypersensitivity (e.g. anaphylaxis or urticaria), the initial doses of methadone should be administered under close medical supervision.

Cardiovascular system

Hypotension and bradycardia can occur and may lead to faintness or syncope. Flushing may occur. Peripheral edema has been reported, usually when high doses are used, and can occur months after commencing methadone.[8]

Unlike other opioids, methadone can cause QT prolongation through interaction with the voltage-gated potassium channels of the myocardium. Patients treated with methadone for pain do not usually require doses over 150 mg/day. There have been some reports of *torsades de pointes* in patients taking high-dose methadone (doses 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 and/or malnutrition), or the use of other 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. It is recommended that patients who have cardiac disease, other medications or metabolic concerns known to cause QT inte8h3l4(p)5 TJETQq0.00000912 0 612 792 reW* nBT/F1 11.04 Tf1 0 0 1 286

dose, other contributory factors (e.g. other QTc prolonging drugs, drugs that slow methadone metabolism[9]), and consider specialist consultation.

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

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 individual opioid trial. When initiating a trial, 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 non-opioid pharmacotherapy (e.g. neuropathic agents, anti-inflammatories), physical treatments (e.g. physiotherapy, occupational therapy, heat-ice therapy, and intramuscular stimulation), exercise, and psychological treatment.

Morphine is the u 1 195.86 553.06 Tm0 g2(iti)]TJETQq0.000 reW*iheat

Methods for switching to methadone

The schedules for switching to methadone described in this chapter represent only a few of the many available. Experienced prescribers generally 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. For example a person on a high dose of another opioid might need less methadone than expected upon making the switch. The switching method chosen will depend on the circumstances of the individual case. Refer to appendix B for conversion ratios from oral morphine to oral methadone, and to the equianalgesic chart in appendix C for conversion between opioids.

"Start low, go slow"

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, including transdermal fentanyl:

   Day 1 0.5 mg q8h

   Day 4 1 mg q8h (sleep has improved)

   Day 7 2 mg q8h

   Day 10 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.

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:

Week 1	1 mg q8h (no significant analgesia but tolerating well)
Week 2	2 mg q8h
Week 3	3 mg q8h
Week 4	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 and patient is transferred to family physician for ongoing care.

Children living with chronic pain from a variety of chronic 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. If there is no local pediatric specialist available, the physician should consult an appropriate regional specialist.

Slow-switch method

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. The advantage of a slow switch method is that the dose of methadone can be adjusted from the planned dose if it appears to be more effective than predicted.

1. Calculate the oral morphine equivalent 24hr total dose using appendix C

Suppose you choose a 3-step switch:

Example of a patient switching from fentanyl 100 mcg/hr to methadone:

1. Calculate the methadone start dose by calculating oral morphine equivalent and selecting appropriate conversion ratio
2. Divide by 3 to give the estimated final q8h methadone dose
3. Decide on how many steps you would like to take to complete the switch.
4. Provide short-acting opioid

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 home care nurses and pharmacists in ensuring compliance.

Take great care to accurately establish current opioid dosing and use an appropriate conversion ratio, to avoid errors in calculating equianalgesic doses. It is useful to have someone else (such as a pharmacist) check your calculations. 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. If the equianalgesic dose and applicable ratio suggest a higher starting dose, go with more steps.

Increasing the methadone dose too quickly can lead to overdose. Allow at least three days (preferably five days) 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 in appendix A for possible interactions when prescribing new medications.

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.

As with all controlled drugs, 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 medication 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.

should be clearly marked “for pain” to avoid insensitive interactions at the pharmacy or confusion among family members.

Urine drug testing

Urine drug testing

This conversion guide applies to the maintenance dosage. The starting dose should be much lower and gradually increased until analgesia is achieved.

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.

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	Examples	PO Dose	Schedule
Morphine	Immediate release	MOS, MSIR	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			

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