Methadone for Analgesia Practice Standards and Guidelines

ACKNOWLEDGEMENTS

The information contained in this publication is based heavily upon the College of Physicians and Surgeons of British Columbia's documents ***Methadone for Analgesia Guidelines*** and ***Prescribing Methadone Practice Standard*** and has been liberally adapted with permission to provide support to methadone-prescribing physicians in Saskatchewan.

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Introduction

Methadone is most commonly used for the treatment of opioid use disorder but can also be used for the treatment of severe pain associated with chronic conditions or cancer. The College of Physicians and Surgeons of Saskatchewan (the College) has adapted the following guidelines from those developed by the College of Physicians and Surgeons of British Columbia as a resource for physicians who prescribe methadone for the management of pain.

Methadone is an oral long-acting synthetic opioid with unique pharmacokinetic properties. Its long, variable half-life and large volume of distribution provides potent and sustained analgesia. The pharmacokinetic properties may also cause accumulation leading to risks such as sedation, respiratory depression and even death if dosed inappropriately high. Methadone is a drug that must be prescribed and used cautiously; doses must be tailored to each patient. It is important that prescribers are familiar with methadone's unique attributes before initiating and maintaining therapy.

Physicians should carefully assess and closely monitor patients, particularly when initiating methadone therapy, as the risk and onset of respiratory depression can be unpredictable. Caution should be exercised in patients who are elderly and patients with liver disease. It is important to consider the drug interactions between methadone and other drugs which are metabolized through or affect the cytochrome P450 pathway. Methadone has many potential drug interactions and a full medication review, including consultation with a pharmacist is recommended. Prescribers need to be careful when switching patients from other opioids to methadone; this type of rotation is best left to experienced prescribers. **Published equivalent analgesia opioid conversion values indicate a wide range of possible methadone doses, with the equivalent dose quoted as an expected end point opposed to a starting point for a switch**.

As with all controlled drugs, physicians should be cognizant of diversion potential and be mindful of potentially fraudulent requests for this drug. Accidental and intentional methadone-related deaths are commonly associated with illegal or unauthorized use [(1)].

Not all pain responds beneficially to opioids. There is evidence to suggest that some patients with chronic pain may experience worsening pain by taking high-dosed opioids because of opioid-induced hyperalgesia (OIH). OIH is manifested by spread of pain outside the localized area of presentation and increase in pain sensitivity, often encompassing the whole body and potentially worsened by opioid dose increases. Allodynia may also be present, where a normally non-painful sensory stimulus (e.g. light touch) is perceived as painful. When OIH or allodynia are identified in a patient already taking a non-methadone opioid, a switch to methadone may help relieve the allodynia, start to reverse the hyperalgesia and facilitate a slow taper off opioids altogether. In doing so, more appropriate non-opioid and non-pharmacological treatments can be implemented [(2,3)]

Definitions: Standard vs. Guideline

Standards define a minimum acceptable level of care to ensure patient safety. Standards are a mandatory requirement.

Guidelines provide clinical direction that "should" be followed for effective and optimal patient care. Guidelines assist prescribers in making clinical decisions and may be adopted, modified, or rejected according to clinical needs, individual patient considerations, local resources and physician discretion. A physician must exercise reasonable discretion and have justifiable reasons when there is a decision to not follow a guideline. In every instance, the reasons of not following a guideline must be thoroughly documented.

Practice Standards

1. Before initiating methadone treatment, registrants must ensure that a comprehensive, biopsychosocial evaluation of their patient including history, physical, and relevant investigations has been completed and documented. Frequent reassessments must be performed.
2. Patient safety is paramount. Methadone must only be initiated once the risks and benefits of treatment have been weighed and a clear rationale for its use is derived.
3. Registrants must develop a treatment plan that takes into account any risks identified during the patient's assessment.
4. Decisions to prescribe methadone with other long-acting opioid agonists, or with benzodiazepine receptor agonists must be guided by a thoughtful and well-documented process including input by addictions specialists, psychiatrists, or pain specialists where needed and when available.
5. Registrants must review a patient's medication profile, inquire about over-the-counter medication use, and consult the Pharmaceutical Information Program (PIP) or electronic Health Record (eHR) Viewer before prescribing methadone.
6. Registrants must ensure continuity of care when patients transition between institutional environments and community.
7. Naloxone kits (e.g. take-home naloxone) must be discussed with and offered to the patient, and (where relevant) naloxone training discussed with friends, family, or other care providers. Naloxone is particularly important for patients on doses of any opioid >50 morphine equivalent dose [MED]/day, and those with a history of overdose or concurrent benzodiazepine/gabapentinoid use [18]. Patients in Saskatchewan may be referred to Take Home Naloxone Program Sites.

Prescribing Methadone in Saskatchewan

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*.

Pursuant to Regulatory Bylaw 19.1(e), a physician is not required to obtain approval from the Registrar to prescribe buprenorphine in its transdermal form, nor is a physician required to obtain approval from the Registrar to prescribe methadone or buprenorphine **solely for the purpose of pain control**.

Alternatively, in accordance with Regulatory Bylaw 19.1(d), no physician shall prescribe methadone or buprenorphine for the treatment of **addiction** unless the Registrar has approved the physician to do so. For more information, on the prescribing requirements for the treatment of opioid use disorder, please contact the *Opioid Agonist Therapy Program* at (306) 244-7355.

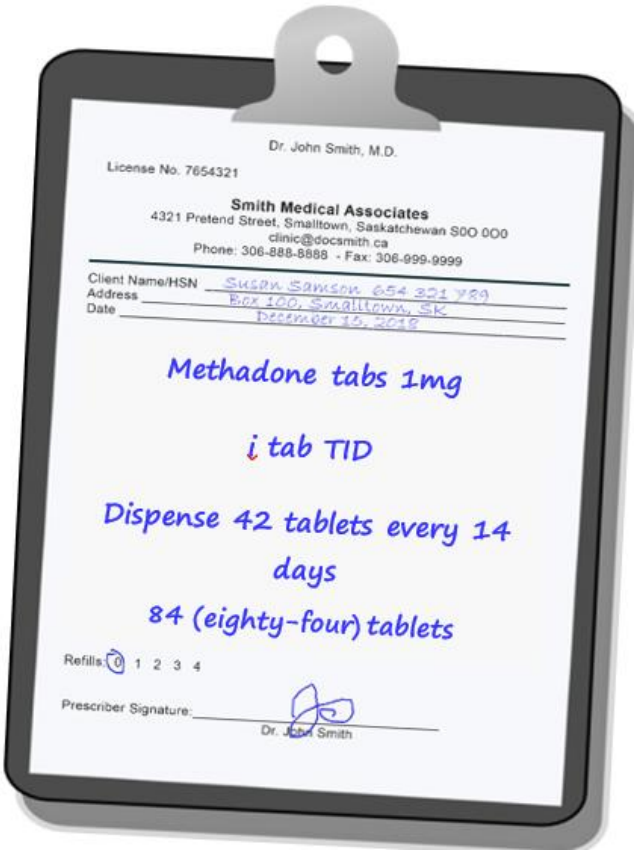
As methadone is listed in the Panel of Monitored Drugs (Regulatory Bylaw 18.1), any prescription must meet federal and provincial legal requirements and include the following:

(i) The patient's date of birth;
(ii) The patient's address;
(iii) The total quantity of medication prescribed, both numerically and in written form;
(iv) The patient's health services number; and,
(v) The prescriber's name and address.

Part-fills of medications to which the Prescription Review Program apply if the following information is specified on the prescription:

(i) The total quantity;
(ii) The amount to be dispensed each time; and
(iii) The time interval between fills.

For more information, please refer to the CPSS Regulatory Bylaws.



Prescribers are strongly encouraged to provide the indication for prescribing (e.g. chronic pain) on methadone prescriptions to enhance communication with the pharmacist, and assist the pharmacist with accurate transmission to the Pharmaceutical Information Program (PIP). Billing for methadone solution depends on the indication (pain vs. addiction).

Practice Guideline: Patient Assessment

Methadone may be indicated for the 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. A comprehensive assessment, with documentation of the diagnosis, is important before establishing a treatment plan to address the pain.

When considering methadone, assess the following:

1. **Pain history** – this assessment should include (but is not limited to):
    a. Previous trials of non-pharmacologic treatments.
    b. Review of past medication trials, detailed with medication effectiveness in terms of pain and function. Confirm adequate doses were attempted (in the absence of adverse effects).
    c. A brief systems review with particular attention to gastrointestinal, hormonal, and sleep-related symptoms. For example, prior to initiating methadone, it is important to consider whether the patient has constipation or symptoms of sleep-disordered breathing.
2. **Medical history** – review all documentation and previous diagnoses with specific attention to any history of heart disease, arrhythmia, and syncope.
3. **Current medication review** – watch for interactions and other medications that may prolong the QT interval and/or have the potential for CNS depression.
4. **Surgical history** – review all documentation and previous diagnoses.
5. **Psychiatric history** – screen for mood disorders, sleep disturbance, trauma history (particularly childhood sexual trauma), personality disorders, limited coping skills.
6. **Substance use history** – screen for past and current substance use including nicotine, alcohol, over-the-counter medication, medical cannabis, and illicit substances. See Appendix D for Screening for and Diagnosing OUD.
7. **Family history** – include any history of sudden death, which may be attributed to a hereditary long QT syndrome.
8. **Social history** – specific attention to social supports, the presence of children or young adults.
9. **Physical examination** – to establish physical function and degree of disability.
10. **Laboratory tests and imaging results** if required — pay special attention to hepatic function and electrolyte disturbances that can lead to a prolonged QT interval.
11. **ECG** – before initiating methadone, the prescribing physician must be aware of arrhythmia risk at high doses (over 120mg/day) and consider requiring a baseline ECG with history of arrhythmia or if the patient is concurrently treated with other QT prolonging drugs or has an electrolyte disturbance. In patients with no other risk factors for cardiac arrhythmia, the threshold for recommending recording an ECG is unclear and there is limited universal agreement in the literature.
12. **Red Flags** – 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, over sedation, and sleep apnea**.

Once a thorough patient assessment has been undertaken, a full diagnosis can be made. This should typically identify the source and type of pain (e.g. peripheral nociceptive, neuropathic, mixed nociceptive-neuropathic, nociplastic, opioid-induced hyperalgesia, opioid-induced allodynia), as well as, any potential allied clinical considerations and patient goals of treatment (typically based on function and disability reduction). It is important to communicate with all other prescribers to ensure that all involved support the goals of care and maintain clarified prescribing responsibilities.

Ideally, the prescriber of opioids is the sole prescriber of pain medication for the patient. With specialist-initiated treatments, once a patient is stable, **the family physician assumes ongoing prescribing for the patient.** Family

physicians of patients who require methadone for pain are strongly encouraged to obtain adequate education and training in prescribing methadone for analgesia to maintain continuity of care. This will help free up specialist clinics to be able to provide consultations for new patients more quickly.

Recommended online course: *methadone4pain.ca*.

Practice Guideline: Opioid Use Disorder and Chronic Pain

Chronic non-cancer pain (CNCP) is a very common condition affecting up to one 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 verify diagnostic consistency and to prevent misdiagnosis of treatable conditions. Though many patients have identifiable pain generators such as arthritis or spinal degeneration, it can be difficult to identify the actual cause(s) of pain for some patients.

Pain can also exist as a presenting symptom of psychiatric illnesses such as depression, or social issues ("total pain"). Examples include sleep deprivation, victimization of domestic violence, or post-traumatic stress disorder. These issues should be identified and treated by thorough patient assessment with ongoing review as untreated psychiatric illnesses can confound optimal pain management.

All patients who are considered for opioid therapy should be screened for underlying substance use disorder, including alcohol, prescription medication, and illicit use. **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 clear boundaries, which address both the chronic pain and SUD, must be developed before medication is provided**. Patients who are using other substances in a problematic manner may experience further loss of control if provided with large dispenses of potent opioids. Engagement in a recovery program is not prerequisite, but strongly recommended for such patients. It is also recommended that a physician experienced in addiction assessment and treatment be consulted and that a shared-care treatment and monitoring plan be developed. At a minimum, the treating physician should frequently follow-up with the patient and require periodic objective measurements of compliance (e.g. random urine screening, pill counts, etc.).

For further guidance, refer to the Canadian Guideline for Opioids for Chronic Non-Cancer Pain.

Practice Guideline: Methadone Pharmacology and Dosing

Methadone has many pharmacological characteristics, making it useful for the treatment of chronic pain and 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, utilization for neuropathic pain syndromes, and treatment of hyperalgesia and allodynia.

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%. Initial extensive and rapid distribution into body fat occurs within 2 to 3 hours of ingestion and a subsequent slower elimination phase lasts for 15 to 60 hours [4-6]. Methadone has no active metabolites and biotransformation is not required for analgesic effect. It is metabolized in the liver primarily through the cytochrome P450 3A4 enzyme, which is a major metabolic enzyme for many other medications and substances and is predominantly excreted in feces [5]. Accordingly, careful review of concurrent medications is important when considering

methadone as a treatment option to avoid alterations in the metabolism of methadone that can occur when combined with medications that induce or inhibit CYP3A4.

Methadone's analgesic potency as compared with other opioids can be unpredictable. Its 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 people on antiretrovirals for HIV [7]. Methadone has an extremely long and variable half-life (24 to 190 hours depending on the individual), which does not correlate with the observed duration of analgesia (6 to 12 hours). The long half-life can lead to accumulation, with an increased risk of sedation and respiratory depression if the dose is increased too rapidly. Rapid titration methods used for other opioids, such as morphine and hydromorphone, should not be applied 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.

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 should be increased according to patient tolerability. Methadone is not removed by dialysis.

Methadone is not effective for chronic pain as a single daily dose (e.g. O.D.) and is usually prescribed every eight hours (e.g. T.I.D.). A small proportion of patients may require a dose every six hours and occasionally patients may find a 12-24 hour schedule adequate.

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 by direct comparison, and the method chosen should be appropriate for the circumstances. It is recommended that conversions be undertaken by or in collaboration with an experienced methadone prescriber.

Practice Guideline: Methadone Side Effects

Central Nervous System

CNS side effects include sedation, dysphoria, disorientation, and more rarely, myoclonus, delirium and headache. 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 or in the chronic non-cancer pain setting because of the high rate of development of tolerance and the potential for misuse. Patients should be instructed not to drive or operate machinery during the initiation and stabilization phases; during dose increases; or during introductions of additional CNS depressants. 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.

Gastrointestinal System

As with any opioid, methadone can cause gastrointestinal side effects such as nausea, constipation, dry mouth, anorexia and (rarely) biliary spasm. Methadone may be less constipating than other oral opioids. As a preventative measure, it is advised that bowel regimens are discussed with all patients treated with opioids.

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 usually 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, as with COPD or severe sleep apnea, should be observed cautiously when initiating any opioid, and the dose should be titrated slowly with close monitoring. 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 experienced but can occur with any opioid, including methadone. For patients with a history of 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 also occur. Peripheral edema has been reported, more likely with high doses, and can occur months after commencing methadone [7,8].

Unlike other opioids, methadone can cause QT prolongation through interaction with the voltage-gated potassium channels of the myocardium. There have been some reports of *torsades de pointes* in patients taking high-dose methadone (more common with doses in excess of 150 mg/day); these doses are rarely required, especially for pain management. Most TdP cases involve concurrent risk factors for cardiac arrhythmia such as pre-existing cardiac disease, metabolic concerns (e.g. 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, are taking other medications or have metabolic concerns known to cause QT interval prolongation have an electrocardiogram prior to initiating methadone (see Drug Interactions).

If the QTc interval is prolonged to 450-500 ms, then the risks and benefits of methadone (in the context of the patient's goals of care) must be evaluated. The QT interval may fluctuate over time, so periodic repeat ECGs are recommended if there are concerns such as high methadone dosing (e.g. ≥120mg in the absence of risk factors), other risk factors for arrhythmia, or potential interactions. If QTc >500 ms, re-evaluate the dose, consider other contributory factors (e.g. other QTc prolonging drugs, drugs that slow methadone metabolism[9]) and seek expert consultation, as required.

Genitourinary System

Urinary hesitancy or retention may occur with any opioid and is often less of an issue with methadone [10]. Chronic use of any opioid can result in hypogonadism, due to central suppression of hypothalamic release of gonadotrophin-releasing hormone (GnRH). GnRH suppression can lead to fatigue, depression, anxiety, decreased muscle mass and reduced libido. Testosterone replacement may be necessary if testosterone levels are low and patients are symptomatic.

Dermatologic System

Sweating can be problematic with any opioid, and is common with methadone. Oxybutynin or clonidine may be trialed for management of methadone induced hyperhidrosis (**off-label use**) but must be prescribed cautiously given the potential for misuse. Pruritus and rashes are experienced less frequently with methadone than with other opioids, and methadone may be well tolerated by patients who have allergic reactions to other opioids.

Practice Guideline: Drug Interactions

Drugs interacting with methadone generally involve inducers or inhibitors of the cytochrome P450 (CYP) system—mainly CYP3A4 and, to a lesser extent, 1A2 and 2D6. Some genetic polymorphism can influence enzyme distribution and close monitoring may be warranted. Consult with an experienced provider and/or a pharmacy colleague if there are concerns about interactions.

Patients with impaired liver function should be monitored carefully and frequently reassessed as methadone doses may need to be reduced as liver function deteriorates. Acute use of alcohol will potentiate the sedative and respiratory depressant effects of methadone, and patients should be advised to either avoid drinking alcohol or to limit consumption to non-daily use and only 1 standard unit after the initial peak in serum methadone levels (up to 3 hours post-dose). Chronic daily alcohol use outside of safe drinking guidelines will initially induce liver enzymes and tend to reduce methadone levels, but as liver function deteriorates due to chronic disease and/or ongoing alcohol use, methadone will tend to accumulate. Patients with alcohol use disorder should be treated for alcohol use disorder before methadone is initiated as uptake and bioavailability is unpredictable.

Benzodiazepine-receptor agonists (i.e. benzodiazepines, z-drugs) and methadone have cumulative toxicity and, when used in combination, enhance respiratory depression, cognitive function, and sedative effects. Such combinations should be avoided for CNCP. Gabapentinoids (e.g. gabapentin and pregabalin) also increase the risk of opioid toxicity when combined with methadone, and although concurrent use may be indicted for the management of the pain condition, caution must be taken with respect to dosing of both agents to minimize the risk of opioid toxicity.

See Appendix A for Medications that Can Prolong QT Interval.

Practice Guideline: Available Strengths and Forms of Methadone

Methadone can be administered orally, sublingually/buccally, topically, and per rectum.

For oral, buccal, and sublingual administration, liquid methadone is most commonly available as a 10 mg/mL solution. It can be further diluted in water or any juice (except grapefruit) for enhanced palatability (consult the product monograph for the individual methadone product dilution to assess stability or consult a pharmacist).

Methadone is also available in tablet form, in 1 mg, 5 mg, 10 mg and 25 mg strengths. Pharmacies can prepare custom-made methadone capsules or suppositories if standard preparations are not satisfactory, such as when patients are unable to swallow and doses are too high to allow buccal or sublingual administration at end of life. It should, however, be noted that methadone suppositories are not absorbed as effectively as the oral solution administered rectally, and dose adjustments need to be made accordingly with use of custom suppositories. The same oral solution dose can be used when switching to rectal administration. Effectiveness and side effects should be reassessed and dose adjustments made, if needed.

Methadone is easily administered via a gastrostomy or jejunostomy, as liquid formulations are available, whereas other long-acting opioid preparations may cause blockages. Similarly, short-acting opioids, requiring frequent administration, may be impractical in such cases.

When other routes are not available, use of topical methadone may circumvent the need for injections. Specialty pharmacies can compound methadone in Lipoderm®. Pain from malignant wounds may respond well to opioids administered topically. Expert consultation is advised in such circumstances.

Practice Guideline: When to Consider Methadone

Methadone is rarely considered a first line analgesic and is generally prescribed after a trial of other opioid analgesic(s). Monotherapy with one opioid (including methadone) is ideal, with incorporated multimodal 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.

Methadone's unique pharmacologic properties make it an effective analgesic. Neuropathic pain may respond better to methadone and can be considered for patients who are intolerant to other opioids. Methadone may also be appropriate where an opioid is indicated for a patient with a concurrent substance use disorder.

Practice Guideline: How to Prescribe Methadone for Pain

Monotherapy with methadone may be enough, but treatment of breakthrough pain during the conversion and dose-titration periods may be required. An NSAID, acetaminophen, and/or a short-acting opioid can be effective for treatment of breakthrough pain. Methadone may be used as a breakthrough opioid once steady state has been reached, but it is prudent to limit each PRN doses to a maximum of 10% of the total daily dose and no more than three breakthrough doses per day to avoid accumulation.

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 to five days until adequate analgesia is achieved. For elderly patients or patients with impaired liver function, the adjustment period should be increased (e.g. every seven to ten days). Doses of only 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 increases, but should be increased at no less than three-day intervals (five-day intervals for increases of ≥5mg), and no more than 10-20% (not exceeding 10mg per increase) at a time (longer in the elderly or if liver function is impaired, and with smaller increments if the patient is not opioid-tolerant).

Example – A patient with peripheral neuropathy following chemotherapy; undergoes tumor-removal surgery which results in radiculopathy. The patient is reluctant to try opioids but has had very limited success with tricyclic antidepressants, gabapentin or pregabalin. The prescriber initiates 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 reassessment every seven days and increases of 1 mg q8h until adequate pain control is achieved or side effects limit dose.

Any doses exceeding 120mg of methadone per day should involve added safety measures and for inexperienced prescribers, expert consultation is **highly recommended**.

Practice Guideline: Indications for Switching Opioids

If the patient is current treated with a different opioid, other than methadone, methadone should be initiated cautiously as part of a gradual cross taper.

1. Inadequate pain control with dose-limiting side effects +/- opioid induced hyperalgesia

- This is more common with neuropathic pain. Before switching opioids, physicians should perform a detailed pain assessment and consider the use of adjuvant analgesics and other treatments.

2. Confusion, hallucinations or delirium

- Although these are often attributable to opioid toxicity, there are many potential causes for delirium especially in patients with advanced cancer. A clinical assessment and investigation is imperative to exclude other causes before assuming that opioids are the causative agent. Until other causes have been excluded, it may be appropriate to reduce the dose of the opioid.

3. Problems with the route of administration

- For children taking opioids for chronic pain for severe medical conditions, liquid administration may be preferable and/or more practical than oral tablets. For patients with advanced cachexia and little subcutaneous fat, transdermal delivery of fentanyl may be ineffective, and methadone may be an appropriate alternative.

4. Cost

- The high cost and (potentially lack of) coverage of many long-acting opioids may be a factor in switching to methadone; methadone is often less cost prohibitive, especially when high-dose opioid therapy is required.

Methadone usually takes at least three days to reach steady state, and accordingly, toxicity from methadone most commonly occurs between three to five days following a switch (or dose increase). To avoid accumulation and subsequent toxicity, do not make additional dose increases for at least three (preferably five) days.

In situations of severe toxicity, it may be required to convert all the previous opioid to methadone quickly. It is recommended that full conversions be managed by experienced prescribers, preferably in a safe and controlled environment.

Practice Guideline: Prescribing Methadone Safely

Communication errors are the most frequent causes of problems in the initial switching period, especially in the home environment. Clearly write the instructions and request assistance of home care nurses and pharmacists for ensuring adherence, as required.

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 if adverse effects occur.
Even at stabilized doses, interactions with other medications can have a significant effect on methadone metabolism; always check for medications metabolized by cytochrome P450 3A4, as toxicity can occur without methadone dose adjustments**.**

As with all controlled drugs, diversion and theft can occur if the patient does not live in a safe environment. Patients should be educated on the risks associated with diversion and theft and take adequate precautions to ensure safe storage. Locked boxes are a useful means of storing medication, particularly if there are children/young adults or people with a substance use history in the home. If tablets are compliance or blister packaged, packaging is not child-resistant so storage in a locked box is strongly advised. A very small dose can be lethal to a child or non-tolerant individual.

Chronic pain and depression often coexist. Deliberate methadone overdoses have occurred [1], especially when large amounts have been prescribed and dispensed for non-cancer pain with associated severe depression. If methadone is to be used for analgesia in these circumstances, limited dispensing and ensure appropriate supervision/support is arranged. Consider referral to psychiatry for assessment before initiating methadone in someone with active/recent suicidality. Additionally, it is imperative to ensure there is a take-home naloxone kit available in the home.

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

Practice Guideline: Random Urine Drug Screening (RUDS)

Random Urine Drug Screening (RUDS) is the analysis of urine for the presence of prescribed medications and illicit drugs or the associated drug metabolites. RUDS may not be appropriate in situations where end of life is imminent and/or risk of abuse/diversion is assessed as very low (e.g. supervised long-term care or hospice). There is, however, evidence that RUDS is a useful tool in the clinical management of patients receiving chronic opioid therapy for any indication, including cancer-related pain. Repeated qualitative RUDS has been shown to improve patient compliance with opioid therapy [9]. Self-reporting of drug use may be unreliable, and the detection of inappropriate or illicit medication use is important for the early identification of concurrent disorders or misuse of medication.

Prior to initiating an opioid trial, RUDS is a useful tool to increase safety. Contingency plans need to be in place for management of issues related to addiction, misuse or diversion, should any occur. RUDS should be used as an objective, non-discriminatory tool for appropriate longitudinal assessment and management of patients' pain and chronic condition, rather than a test where the primary function is to allow or deny opioids.

RUDS should be analyzed by the provincial lab (gas chromatography/mass spectrometry). Urine specimens are retained in the laboratory for a short duration post-collection so the ordering physician can review the results with the toxicologist and requires confirmatory tests when required. Confirmatory tests may be helpful when results present as unexpected.

When interpreting laboratory results, it is important to be aware of drug metabolites. Please refer to Appendix A for an overview and/or contact the provincial laboratory for assistance. Methadone's primary metabolite is EDDP. For patients prescribed methadone, samples must include EDDP (low doses of methadone may only show as EDDP); samples may include both methadone + EDDP.

UDS should be used as a tool, part of a comprehensive risk assessment and facilitates non-punitive conversations with patients regarding medication safety and compliance.

See Appendix B for Drug Metabolism Charts.

Practice Guideline: Patient Agreement

It is recommended that physicians establish treatment agreements with all patients prescribed long-term opioids. The current CNCP guidelines state: *The benefits of treatment agreements are limited by low-quality evidence with equivocal effects on opioid misuse. A written treatment agreement may, however, be useful in structuring a*

process of informed consent around opioid use, clarifying expectations for both patient and physician, and providing clarity regarding the nature of an opioid trial with endpoints, goals, and strategies in the event of a failed trial [12].

See Appendix C for a Sample Patient Agreement for Long-Term Opioid Therapy.

Summary: Clinical Pearls

- Treat pain holistically, considering biological, psychological, and social aspects of pain
- Methadone, as an analgesic, is indicated for the relief of severe pain; in general, it should NOT be prescribed for patients who are opioid naïve [19]
- Concomitant use with benzodiazepines or other central nervous system depressants may result in profound sedation, respiratory depression, coma and death [19]
- Limit doses and duration of treatment to the minimum required [19]
- Methadone dosing is usually T.I.D. due to the shortened analgesic effect compared to opioid withdrawal suppressive effect
- Patient education regarding risks vs. benefits; side effects; and drug interactions are essential
- Methadone, like any opioid, should not be discontinued abruptly

Appendix A: Medications that Can Prolong QT Interval [11]

Comments:

1. **No list is all inclusive and it is conceivable a medication that interacts with methadone or causes QTc prolongation may not appear on the list.** CredibleMeds is an online resource for checking the QTc prolongation potential of medications.

2. Management of potential drug interactions requires clinical judgment with consideration of drug and patient specific factors. In some cases, no specific action may be required, while in other cases close monitoring and/or changes in drug therapy might be warranted when an interaction is noted.

Practitioners interested in more information on the nature of these drug interactions are encouraged to:

Contact **MedSask** for any medication-related queries at:

medSask
YOUR MEDICATION INFORMATION SERVICE

1-800-667-3425
(within Saskatchewan)

OR

http://medsask.usask.ca/index.php

Call **PADIS** (Poison and Drug Information Services) at:

1-866-454-1212 (within Saskatchewan)

Medications That Can Prolong QT Interval

www.torsades.org

Cardiovascular

Anti-arrhythmics

- Amiodarone (low risk of TdP compared to other class III agents such as sotalol; however potential for DIs)
- Bepridil
- Bretylium
- Disopyramide
- Dofetilide
- Dronedarone
- Flecainide
- Ibutilide
- Mexiletine
- Procainamide
- Propafenone
- Quinidine less at ↑ dose
- Sotalol
- Dobutamine
- Dopamine
- Isradipine
- Moexipril/HCTZ
- Nicardipine
- Norepinephrine
- Ranolazine

ADHD agents

- Amphetamine
- Atomoxetine
- Dexmethylphenidate
- Dextroamphetamine
- Guanfacine
- Lisdexamfetamine
- Methylphenidate

Antiemetics

- Dolasetron especially if IV
- Domperidone especially if IV, >30mg orally/day, or with ketoconazole/3A4 inhibitors
- Droperidol <1.25mg less QT concern
- Granisetron
- Metoclopramide
- Ondansetron especially ≥ 32mg IV, not over 8mg if ≥75 yrs; >16mg if <75yrs
- Palonosetron
- Promethazine
- Tropisetron

CNS / Psychotropic

Anticonvulsants

- Felbamate
- Lithium

Antipsychotics

- Amisulpride
- Asenapine
- Aripiprazole
- Butyrophenones
- Haloperidol esp. with ↑ dose or IV
- Clozapine
- Phenothiazines
  - Chlorpromazine
  - Mesoridazine
  - Perphenazine
  - Thioridazine
- Iloperidone
- Paliperidone
- Pimozide
- Quetiapine
- *Risperidone*
- Thioxanthines
- Ziprasidone

SSRIs

- Citalopram if >40mg/day, or elderly
- Escitalopram in high-/over-dose
- Fluoxetine
- Paroxetine especially ↑ pimozide
- *Sertraline*
- *Trazodone*

SNRIs

- Desvenlafaxine
- Mirtazapine
- Venlafaxine

TCAs

- Amitriptyline
- Amoxapine – seems okay
- Clomipramine
- Desipramine
- Doxepin
- Imipramine
- Maprotiline
- *Nortriptyline*
- Protripyline – seems okay
- Trimipramine

Other

- *Chloral Hydrate*
- Moclobemide

Anti-Infective

Antibiotics

- Cotrimoxazole
- Fluoroquinolones
  - Ciprofloxacin –mainly if DI on a ↑ QT drug, but some direct QT effect
  - Gatifloxacin
  - Gemifloxacin
  - Levofloxacin
  - Moxifloxacin
  - Norfloxacin
  - Ofloxacin
  - Sparfloxacin
- Macrolides
  - Azithromycin
  - Clarithromycin
  - Erythromycin
  - Roxithromycin
- Telavancin
- Telithromycin

Azole Antifungals

- Fluconazole
- Itraconazole
- Ketoconazole
- Posaconazole
- Voriconazole

Antimalarials

- Artemether-lumefantrine
- Chloroquine
- Halofantrine
- Hydroxychloroquine
- Mefloquine
- Piperaquine
- Primaquine
- Quinine

Other

- Pentamidine

Miscellaneous

- Abiraterone acetate
- Alfuzosin
- Amantidine
- Anagrelide
- Arsenic trioxide
- Atazanavir
- Bedaquiline
- Bosutinib
- Buprenorphine
- Ceritinib
- Cilostazol
- Cinacalcet
- Cisapride (Special Access)
- Cocaine
- Crizotinib
- Cyclosporine
- Dasatinib
- Degarelix
- Donepezil
- Enzalutamide
- Eribulin
- Fingolimod
- Foscarnet
- Galantamine
- Ginseng
- Goserelin
- Histrelin
- Hydroxyzine
- Indapamide
- Kaletra
- Lapatinib
- Lenvatinib
- Leuprolide
- Levomethadyl
- Lopinavir
- Methadone
- Midodrine
- Mifepristone
- Mirabegron
- Nilotinib
- Octreotide
- Orphenadrine
- Oxytocin
- Oxycodone
- Panobinostat
- Pasireotide
- Pazopanib
- Phenylephrine
- Probucol
- Propofol
- Propoxyphene
- Pseudoephedrine
- Rilpivirine ≥ 75mg/day
- Ritodrine
- Ritonavir
- Romidepsin
- Saquinavir
- Sevoflurane
- Sibutramine
- Solifenacin
- Sorafenib
- Sunitinib
- Tacrolimus
- Tamoxifen
- Telaprevir
- Tizanidine
- Tolterodine
- Torsemide
- Triptorelin
- Vandetanib
- Vardenafil
- Vemurafenib

Antihistamines

- *Diphenhydramine*
- *Clemastine*
- *Loratidine* (but no reports)

Appetite Suppressant

- Ephedrine
- Fenfluramine
- Phentermine
- Sibutramine

Bronchodilators

- Epinephrine
- Indacaterol
- Isoproterenol
- Levalbuterol
- Metaproterenol
- Olodaterol
- Salbutamol/Albuterol
- Salmeterol
- Terbutaline
- Vilanterol minimal at 100mcg

AVOID combinations of phenothiazines with TCAs, βBs, & anticonvulsants

Some drugs (e.g. erythromycin & amiodarone) prolong the QT interval AND act as inhibitors to potentially increase levels or QT effects of concomitant medications.

Drug Interactions
Cytochrome P450 Inhibitors

CYP3A4

- Amiodarone

Azole antifungals:

- Fluconazole
- Itraconazole
- Ketoconazole

Calcium channel blocker:

- Diltiazem
- Verapamil

- Cimetidine
- Ciprofloxacin
- Grapefruit juice

HIV: protease inhibitors

Macrolides:

- Erythromycin
- Clarithromycin
- Troleandomycin (not with Azithromycin)

- Methadone
- Telithromycin

SSRIs:

- Fluoxetine
- Fluvoxamine
- Nefazodone
- Paroxetine

- Trazodone

CYP2D6

- Beta-Blockers (βBs)
- Haloperidol
- Phenothiazines
- Quinidine
- SSRIs (does not interact with citalopram)
- Terbinafine
- TCAs

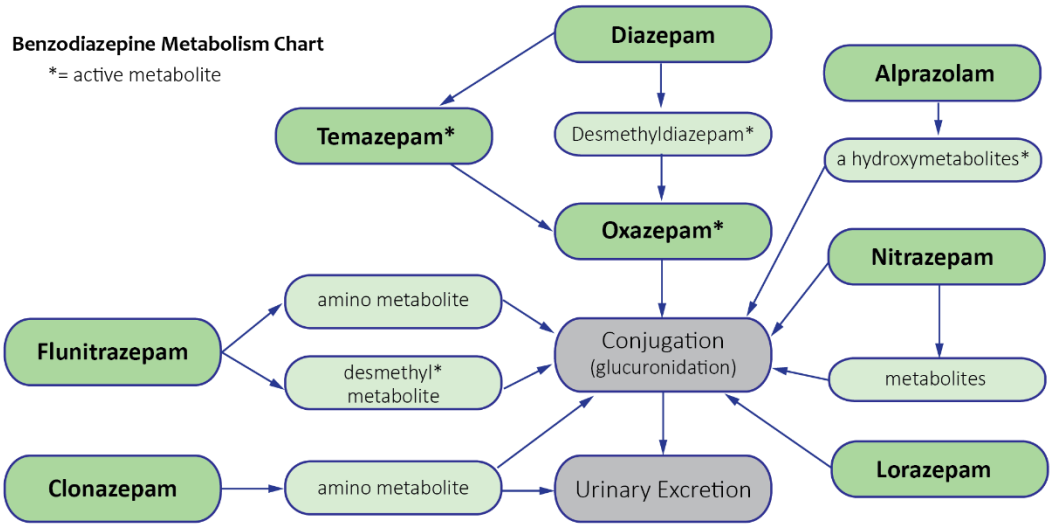
CYP1A2 (less significant)

- Fluoroquinolones
- Fluvoxamine
- Grapefruit juice

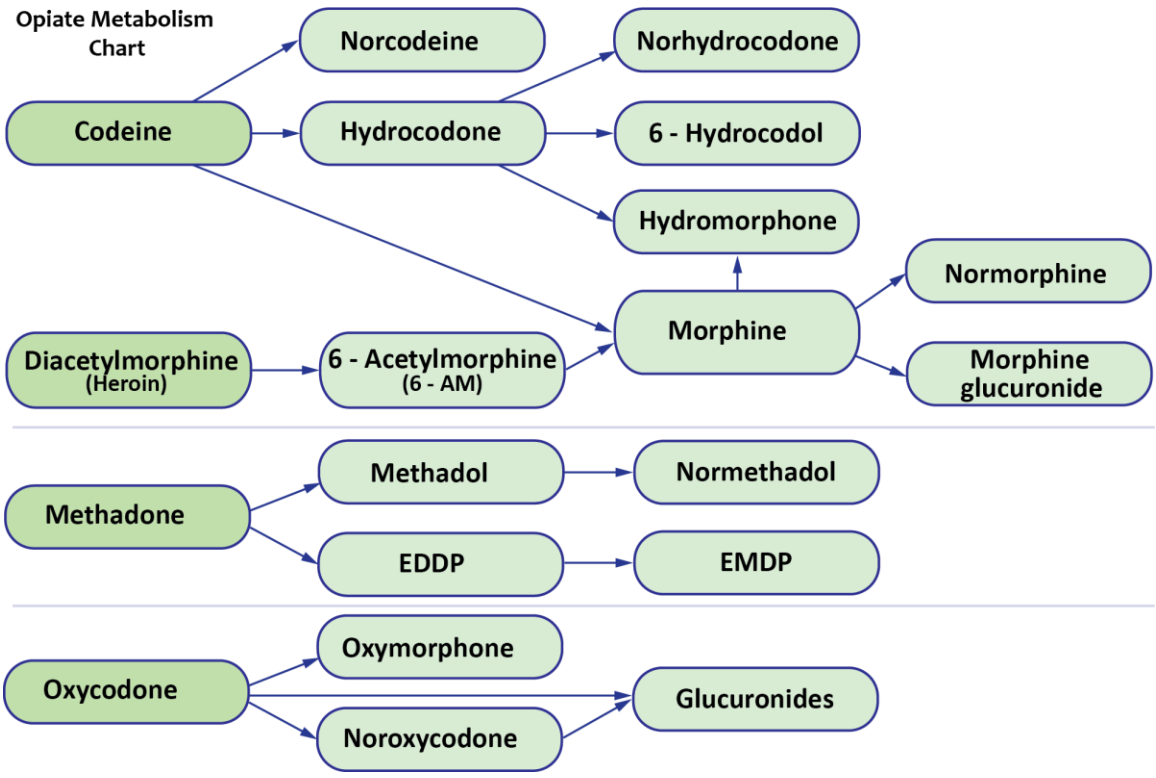
Major significance (well-documented); Low to moderate significance (fewer case reports); *Minor significance (theoretical, few if any case reports)*

Appendix B: Drug Metabolism Charts

Benzodiazepines



Opioids



Appendix C: Sample Patient Agreement for Long-Term Opioid Therapy

1. I,_____ agree that Dr. _____ will be the only physician prescribing OPIOID (also known as NARCOTIC) pain medication for me and that I will obtain all of my prescriptions for opioids at one pharmacy. The exception would be an emergency situation or in the unlikely event that I run out of medication. Should such occasions occur, I will inform my physician as soon as possible.
2. I will take the medication at the dose and frequency prescribed by my physician. I agree not to increase the dose of opioid without first discussing it with my physician. I will not request earlier prescription refills.
3. I will attend all reasonable appointments, treatments and consultations as requested by my physician. I agree to other pain consultations/management strategies as necessary.
4. I understand that the common side effects of opioid therapy include nausea, constipation, sweating and itchiness of the skin. Drowsiness may occur when starting opioid therapy or when increasing the dosage. I agree to refrain from driving a motor vehicle or operating dangerous machinery until such drowsiness disappears.
5. I understand that using long-term opioids to treat chronic pain may result in the development of a physical dependence on this medication, and that sudden decreases or discontinuation of the medication will lead to the symptoms of opioid withdrawal. I understand that opioid withdrawal is uncomfortable but not lifethreatening.
6. I understand that there is a small risk that I may become addicted to the opioids I am being prescribed. As such, my physician may require that I have blood, urine or hair testing and/or see a specialist in addiction medicine should a concern about addiction arise.
7. I understand that the use of a mood-modifying substance, such as tranquilizers, sleeping pills, alcohol or illicit drugs (such as cannabis, cocaine, heroin or hallucinogens), can cause adverse effects or interfere with opioid therapy. Therefore I agree to refrain from the use of all of these substances without prior agreement from myphysician.
8. I agree to be responsible for the secure storage of my medication at all times. I agree not to give or sell my prescribed medication to any other person. Depending on the circumstances, lost medication may not be replaced until the next regular renewal date.
9. I consent to open communication between my doctor and any other health care professionals involved in my pain management, such as pharmacists, other doctors, emergency departments, etc.
10. I understand that if I break this agreement, my physician reserves the right to stop prescribing opioid medications for me.

Date: _____

_____ (Patient)

_____ (Physician)

See www.RxFiles.ca for customizable form for your office.

Adapted from www.PainCare.ca

Appendix D: Screening for and Diagnosing Opioid Use Disorder

Prescription Opioid Misuse Index (POMI)

The POMI is a 6-point questionnaire with strong predicative abilities for OUD [13].

Questions	Response (circle one)
1. Do you ever use more of your medication, that is, take a higher dose than is prescribed for you?	YES NO
2. Do you ever use your medication more often, that is, shorten the time between doses, than is prescribed for you?	YES NO
3. Do you ever need early refills for your pain medication?	YES NO
4. Do you ever feel high or get a buzz after using your pain medication?	YES NO
5. Do you ever take your pain medication because you are upset, using the medication to relieve or cope with problems other than pain?	YES NO
6. Have you ever gone to multiple physicians, including emergency room doctors, seeking more of your pain medication?	YES NO

DSM-5 OUD Criteria

For patients who may have OUD (as determined by the POMI), the DSM-5 criteria can be used for diagnosing OUD [14,15].

The DSM-5 defines OUD as a problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the eleven criteria within a twelve-month period.

	DSM-5 OUD Criteria
□	Opioids are often taken in larger amounts or over a longer period than was intended
□	There is a persistent desire or unsuccessful efforts to cut down or control opioid use
□	A great deal of time is spent on activities necessary to obtain the opioid, use the opioid, or recover from its effects
□	Craving, or a strong desire or urge to use opioids
□	Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home
□	Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids
□	Important social, occupational, or recreational activities are given up or reduced because of opioid use
□	Recurrent opioid use in situations in which use is physically hazardous
□	Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance
□	Exhibits tolerance*: -Need for markedly increased amounts to achieve intoxication or desired effect [16] -Markedly diminished effect with continued use of the same amount [16]
□	Exhibits withdrawal*: -Characteristic opioid withdrawal syndrome [16] -Same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms [16]

*Exception: patients who are taking opioids for chronic pain

DSM-5 OUD criteria have not been validated in youth ≤ 12 years of age [17].

All patients diagnosed with OUD should be offered or referred for first-line treatment (e.g. buprenorphine/naloxone).

References:

1. Saskatchewan Coroners Service. Drug Toxicity Deaths: Saskatchewan, 2010 to 2020.
2. Hayes CJ, Painter JT. A comprehensive clinical review of opioid-induced allodynia: discussion of the current evidence and clinical implications. J Opioid Manag, 2017; 13(2):95-103.
3. Yi P, Pryzbylkowski P. Opioid induced hyperalgesia. Pain Med, 2015; 16(1):S32-6.
4. Thai V, Fainsinger RL. Pain. In: Emanuel LL, Librach LS, editors. Palliative care core skills and clinical competencies. 2nd ed. Philadelphia: Saunders; 2011; 95-114.
5. Kreek MJ, Schecter AJ, Gutjahr CL, Hecht M. Methadone use in patients with chronic renal disease. Drug Alcohol Depend, 1980; 5(3):197-205.
6. Layson-Wolf, C, Goode JV, Small RE. Clinical use of methadone. J Pain Palliat Care Pharmacother, 2002; 16(1):29-59.
7. Mahe I, Chassany O, Grenard AS, Caulin C, Bergmann JF. Methadone and edema: a case report and literature review. Eur J Clin Pharmacol, 2004; 59(12):923-4.
8. Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MCP. QTc interval screening in methadone treatment. Ann Intern Med, 2009; 150(6): I-26.
9. Knezevic NN, Khan OM, Beiranvand A, Candido KD. Repeated quantitative urine toxicology analysis may improve chronic pain patient compliance with opioid therapy. Pain Physician, 2017; 20(2S):S135-S145.
10. Gedney JA, Liu EH. Side-effects of epidural infusions of opioid bupivacaine mixtures. Anaesthesia, 1998; 53(12):1148-55.
11. Geri-RxFiles 2nd ed. QT Prolongation & Torsades de Pointes: Drugs & Sudden Death. Available from www.RxFiles.ca.
12. Busse JW, Craigie S, Juurlink DN, Buckley DN, Wang L, Couban RJ, Agoritsas T, Akl EA, Carrasco-Labra A, Cooper L, Cull C, da Costa BR, Frank JW, Grant G, Iorio A, Persaud N, Stern S, Tugwell P, Vandvik PO, Guyatt GH. Guideline for opioid therapy and chronic non-cancer pain. CMAJ, 2017;189(18):E659-E666.
13. Alberta College of Family Physicians. Tip #222 Prescription Opioid Misuse Index (POMI) [cited 2020 November 06].
14. BMJ Best Practice. Opioid use disorder. 2018.
15. British Columbia Centre on Substance Use (BCCSU). DSM-5 Clinical Diagnostic Criteria for Opioid Use Disorder.
16. Centre for Effective Practice. Opioid Tapering Template. 2018.
17. British Columbia (BC) Guidelines. Opioid Use Disorder: Diagnosis and Management in Primary Care. 2018.
18. Centre for Effective Practice. Opioid Use Disorder (OUD) Tool. 2018.
19. Metadol®. Paladin Labs Inc. 2020. Available from https://www.paladin-labs.com/our_products/PM_Metadol_EN.pdf?ver=11.