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MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

3.1 Introduction: The Pharmacology of Methadone & Management of Adverse Effects

GENERAL CONSIDERATIONS

Methadone is a long-acting synthetic opioid. It is a full agonist, with actions predominantly at the mu-opioid receptor. The unique pharmacologic properties of methadone make it an effective medication for the treatment of opioid use disorder. However, it is this same unique pharmacology that poses a significant safety risk to patients when prescribed inappropriately. Therefore, a thorough understanding of the pharmacology of methadone is crucial for all team members involved in clinical decision making.

Providers and team members must ensure that patients receive adequate education regarding the risks involved with methadone treatment, as care plans are negotiated and adjusted over time. This education must be provided in a manner that is easy to understand and relevant to the patient's circumstances and literacy level. Handouts that patients can share with family, friends, and roommates, may be especially useful. See **Appendix Y**, "A Patient Guide: Avoiding Overdose in the First Two Weeks of Opioid Agonist Therapy (OAT)", as an example to facilitate this teaching.

PHARMACOLOGY

Methadone – The Full Agonist

The full agonist activity of methadone is predominantly at the mu-opioid receptor, with some additional agonist activity at the κ and σ opioid receptors[1]. These pharmacologic actions produce effects common to all mu-opioid receptor *agonists*, which will reduce cravings and alleviate opioid withdrawal in a patient with an opioid use disorder.

Dissimilar to other opioids, methadone has also been shown to have some *antagonist* activity at the N-methyl-D-aspartate (NMDA) receptors. While these effects are not fully understood, this activity may make methadone more effective in treating neuropathic pain when compared to other opioids[2].

Peak plasma levels of methadone occur on average between 2.5 and 4 hours. Opioid agonist effects associated with this peak are sometimes noticed by the patient, particularly during the initiation phase and with sizable dose increases. Patients should be cautioned about sedative effects during this peak which will usually dissipate once the patient is on a stable dose. This is especially relevant to patients who drive or who engage in safety sensitive activities in their personal or professional lives.

Oral Administration & Metabolism

Methadone has a long duration of action and a high oral bioavailability which allows for once-daily oral dosing and a convenient method for health professionals to witness and monitor ingestion.

However, since methadone has a highly variable elimination half-life of 22 to 48 hours and time to reach steady state (i.e., 3 to 7 days) with a resultant variable response[2], the clinical response can be difficult to predict. Individuals who metabolize methadone slowly might experience a rapid accumulation of methadone blood levels, particularly during the induction phase and with dose increases. Since methadone is a full agonist and has **no ceiling effect** (see FIGURE 1), this accumulation may lead to toxicity and serious harm if the induction dose is too high, or the dose is increased too quickly. Figure 1 compares a full agonist, like methadone, to the partial agonist activity inherent to buprenorphine.

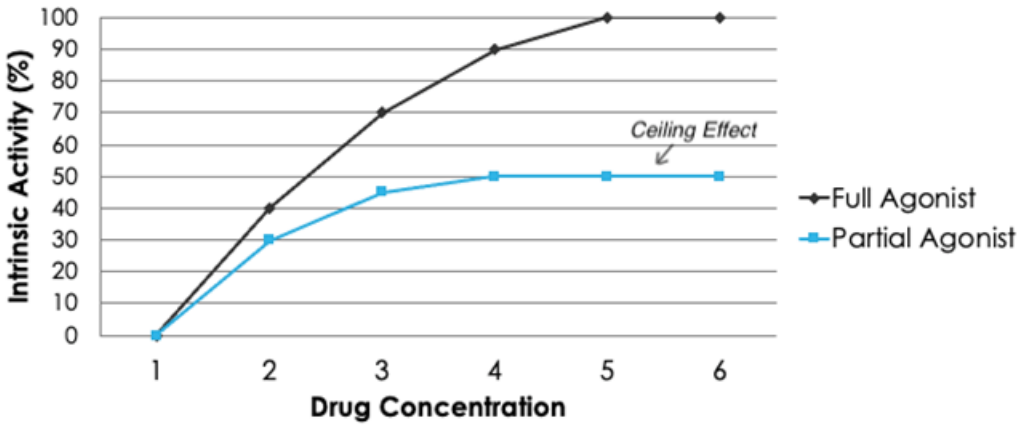

FIGURE 1: FULL AGONIST VS. PARTIAL AGONIST

Conversely, when metabolism of methadone occurs rapidly, once-daily dosing may elicit some withdrawal near the end of a 24-hour interval in a very small portion of patients who one would otherwise expect to be stabilized. While most patients may tolerate and adjust to this mild withdrawal, some cases may necessitate clinical intervention such as split dosing or switching to other treatments if suitable (e.g., buprenorphine). See Ongoing Care for further guidance around assessment of rapid metabolism and management of split dosing (specifically, *Rapid Metabolism & Serum Levels* and *Methadone Split Doses*).

Methadone Elimination

Methadone undergoes urinary and fecal excretion. The major metabolite of methadone is EDDP (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine) which can be detected in the urine of patients who are metabolising methadone. EDDP is a useful marker to corroborate the authenticity of a urine sample. Patients who are on very low doses (e.g., below 5 mg/day) may not test positive for EDDP on a standard urine drug test, especially if they metabolize methadone quickly.

Drug Interactions – Hepatic Inhibitors & Inducers

Hepatic metabolism of methadone occurs principally at CYP3A4, and to a lesser extent CYP2B6, 2C19, 2D6, 2C9, and 2C8[2,3]. Inhibitors and inducers of these enzymes may lead to clinically significant drug interactions.

Hepatic inhibitors will typically increase methadone levels noticeably in as little as one to two days[2]. Studies have shown that pharmacodynamic outcomes with hepatic inhibitors have been associated with little to no reported adverse effects in stabilized patients[3], however monitoring may still be warranted. Caution is advised in patients who would have an increased risk of additive central nervous system (CNS) depressant effects such as during the induction phase, after dose increases, in unstable patients, and/or patients taking other CNS depressants, such as benzodiazepines/Z-drugs.

Hepatic inducers typically cause effects to methadone plasma levels more slowly (i.e., one to two weeks[2]), and there have been reports of withdrawal effects from the reduction in methadone exposure. Some antiretroviral drugs, such as efavirenz and nevirapine, have led to significant reductions in C_{max} and AUC requiring methadone dose increases to treat resultant withdrawal effects[3]. Rifampin (commonly used for tuberculosis) and the anticonvulsants carbamazepine and phenytoin have also been shown to cause opioid withdrawal effects[4].

Clinicians may need to increase and/or split the methadone dose because of the effects of a hepatic inducer. If this is the case, the original dose should be gradually resumed after the interacting medication is stopped. **If it is necessary to use a hepatic inducer for a patient on methadone, prescribers should consult with a specialist to manage this drug-drug interaction.**

Drug Interactions – CNS Depressants

Central nervous system depressants combined with methadone can produce additive CNS-depression effects, and this can lead to an increased risk of sedation and respiratory depression. Of note, benzodiazepines/Z-drugs have been associated with an increased risk of overdose and death in patients who are taking OAT[5].

Starting methadone at low doses and titrating slowly is warranted in patients who are prescribed or suspected to be taking CNS depressants. This includes prescribed medications, prescription medications obtained from illicit sources, and over-the-counter medications with sedating properties. If such concerns are identified upon intake assessment or clinical suspicion is high, a comprehensive urine drug screen may be warranted to further evaluate this risk. The chapter Methadone Induction, Titration, & Stabilization provides detailed recommendations for different patient contexts, including induction and titration in higher-risk situations (see *Patients at Higher Risk for Methadone Toxicity*).

Combining medications that cause QTc interval prolongation with methadone, a well-established risk factor for QTc prolongation, increases the overall risk of developing torsade de pointes. Further discussion about this can be found in a subsequent section of this chapter under *QTc Interval Prolongation*.

Alcohol & Methadone

Patients on methadone who use alcohol can be difficult to manage due to the **dual effects of alcohol on hepatic metabolism and CNS depression**. *Acute* alcohol use has been shown to decrease methadone metabolism by competing for metabolic enzyme activity[6]. This may lead to accumulation of methadone levels, and when combined with the CNS depressant effects of alcohol can pose a serious risk of harm to the patient. Due to this heightened risk, it is imperative to assess the patient for intoxication prior to administering the dose.

Conversely, *chronic* alcohol use has been shown to induce hepatic metabolism of methadone[6], which may lead to opioid withdrawal symptoms and can pose a challenge when trying to stabilize a patient on daily methadone. In the interest of optimizing safety, patients should be cautioned on the risks of both acute and chronic alcohol use when they are prescribed methadone.

Please refer to the chapter, Managing Polypharmacy, Benzodiazepines, Alcohol, & Polysubstance Use in OAT, for further recommendations around managing the risks of methadone treatment and other substances.

ADVERSE EFFECTS & MANAGEMENT

While methadone is typically well tolerated in most patients, it may cause adverse effects which are consistent with opioid agonist effects.

Due to the full agonist effect of methadone, adverse effects tend to be more pronounced than partial agonists used for OAT (e.g., buprenorphine).

With repeated use, patients usually develop tolerance to adverse effects caused by methadone. These transient adverse effects include sedation, nausea, vomiting, light-headedness, and dizziness[1,2]. Methadone may also cause adverse effects that persist and require clinical management, such as constipation, sweating, and sexual dysfunction[1,2].

Constipation

Patients on methadone often endure constipation as an adverse effect with varying levels of severity. Approximately two-thirds of patients report some level of constipation, with approximately one-fifth of patients reporting severe to very severe constipation[7,8].

Methadone-induced constipation often goes unrecognized in this patient population and may adversely affect quality of life. OAT prescribers are encouraged to ask about and treat constipation aggressively. This approach may improve long-term adherence to agonist therapy.

The treatment regimen should include both pharmacological and non-pharmacological methods such as:

- Daily administration of an osmotic laxative (e.g., polyethylene glycol 3350),
- Use of a stimulant laxative, as needed (e.g., senna or bisacodyl),
- The above can be used with or without a stool softener (e.g., docusate), and
- Non-pharmacological methods such as increased fiber intake and fluid consumption should always be endorsed for the prevention of opioid-induced constipation[9].
- While most laxatives can be helpful, bulk-forming laxatives (e.g., psyllium) are typically not effective for opioid-induced constipation and should be avoided.

Hyperhidrosis

Methadone-induced hyperhidrosis has been reported in up to 45% of patients, however this complaint is not often reported as patients may become accustomed to the side effect and prescribers may not inquire about this adverse effect[10]. It is important to differentiate excessive sweating as an adverse effect of methadone, since it may also be a symptom of opioid withdrawal which often presents at the end of the 24-hour dosing interval and will usually resolve independently as the patient approaches a stable dose.

Hyperhidrosis can often be tolerated without treatment, but medical intervention may be warranted in some cases. Clonidine, an inhibitor of sympathetic stimulation, has been used off-label with some success to treat excessive sweating[11], although it should be noted that research analyzing its use in this patient population is lacking. Misuse of clonidine has been reported[12], and consideration should be made to control the dispensing frequency.

Clonidine should, in most patients, be dispensed on the same schedule as methadone. Oxybutynin and desloratadine have been shown to have some success off-label as well[10,13], however the evidence is very limited.

Most patients with hyperhidrosis, who benefit from treatment with clonidine, will experience effective relief with no more than clonidine 0.1 mg po BID. In severe cases, where sweating interferes with social function, up to clonidine 0.2 mg po BID may be trialled.

In cases where a trial of clonidine is not effective in reducing sweating, it should be discontinued to avoid unwanted side-effects and prevent diversion. Clonidine has sedating properties and may cause fatigue that not all patients tolerate. Clonidine is also centrally acting and reduces blood pressure. A baseline blood pressure check, repeated after starting clonidine, may be warranted. The use of clonidine can also exacerbate postural hypotension, especially is older patients. Educating patients about this risk is important, especially if they are already at risk of falls.

Sexual Dysfunction

The prevalence of sexual dysfunction has been reported to be as high as 52% in patients who take methadone and was significantly higher when compared to patients who take buprenorphine for opioid use disorder[14]. Men are more commonly affected and may experience a decrease in libido, erectile dysfunction (ED), and orgasm dysfunction, while reports show that women may experience decreases in libido and menstrual irregularity[15].

Low testosterone levels, along with elevation of prolactin levels and interference with the normal production of LH, FSH, and GnRH, are suspected causes of sexual dysfunction in men, while interference of the normal cyclic production of LH and FSH are suspected to be the cause of sexual dysfunction in women[15].

Sexual dysfunction can have a major impact on treatment adherence, so addressing this adverse effect may improve patient outcomes. Treating the specific symptoms, for example, by using PDE-5 inhibitors for ED, or managing low testosterone levels in men, can be a suitable approach to managing this condition. Bupropion has been shown in methadone patients to improve sexual desire, erectile function, and intercourse satisfaction, with more evidence in the male population[16].

QTc Interval Prolongation

Methadone is known to cause QTc interval prolongation, a well-known risk factor to develop torsade de pointes which may lead to potentially fatal ventricular fibrillation. The prevalence of QT prolongation is not clearly established, but some reports showed that approximately 2% of methadone patients (all receiving doses over 100 mg/day) exhibited a QTc interval above 500ms, which is associated with a two-fold to three-fold increase in risk for torsade de pointes[17,18].

The effects of methadone on QTc prolongation are dose dependent. Doses above 100 mg/day are frequently reported in cases of torsade de pointes, and some case reports show that the QTc interval normalizes when methadone is discontinued or reduced in dose[17].

The risk of torsade de pointes is often increased when other risk factors for QTc prolongation are present. In addition to a higher dose of methadone, other risk factors for QTc prolongation include:

- The presence of other drugs that prolong QTc interval,
- Hypokalemia,
- Female sex,
- Advancing age,
- Genetic predisposition,
- Hypomagnesemia,
- Heart failure, and
- Bradycardia[19].

Whenever possible, modifiable risk factors like drug-drug interactions and hypokalemia should be rectified first. See Ongoing Care for further recommendations around clinical management of the QTc prolongation, specifically, ECG MONITORING FOR PROLONGED QTc.

Other Adverse Effects

Weight gain has been reported with methadone treatment; however, a causal link has not been firmly established. Some reports suggest that negative changes in diet habits and an increased preference for sweet foods when methadone is started may be contributory to weight gain, and for this reason education about nutritional habits may be beneficial[20]. Documenting baseline weight at intake is a useful strategy and presents an opportunity to discuss healthy eating resources.

Patients on methadone tend to report poor dental health, including a high level of dental caries, however a direct causal link has not been established[21,22]. It is thought that a variety of factors commonly affiliated with all opioid users might contribute to this issue, including dry mouth, poor dental hygiene, a higher intake of sweet foods, masking of dental pain, bruxism, and the high prevalence of alcohol and tobacco use in this population[22]. When treatment is initiated, it is recommended to inform patients about potential dental issues and encourage good dental hygiene, regular visits to the dentist, and limited intake of sugar-containing foods. Additional monitoring may be required in patients who experience a severe case of dry mouth (xerostomia), such as in patients who are taking antidepressants.

Peripheral edema in the extremities has been reported on rare occasions in patients on methadone and may occur even after three to six months of treatment[23].

Sometimes edema is self-limiting and will resolve on its own, but if edema persists, the only way to resolve it may be to taper off methadone and/or consider an alternative form of OAT (e.g., buprenorphine). However, the risk of reverting back to illicit opioid use must be considered and discussed with the patient if an adjustment to methadone treatment is considered[2].

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Appendix Y

A PATIENT GUIDE: AVOIDING OVERDOSE IN THE FIRST TWO WEEKS OF OPIOID AGONIST THERAPY

This clinic provides opioid agonist therapy (OAT) care *as safely as possible*, but accidental overdoses sometimes happen in the first two weeks of treatment. This is especially important when starting methadone treatment, but many of the same safety ideas should also be applied when starting buprenorphine/naloxone (Suboxone).

The questions and answers below will help you to get through this period safely. Share this information sheet with a friend or family member.

Why can't my doctor increase my dose more quickly?

When you first start taking methadone or buprenorphine/naloxone, you want to get on the right dose as soon as possible. With buprenorphine/naloxone your doctor may only need a few days to get you to the right dose while making sure you can safely tolerate the medication. With methadone, however, your doctor must increase your dose slowly over several weeks, because your body takes time to adjust to the methadone and (unlike other opiates), methadone builds up slowly in your bloodstream over several days. A dose that may feel like too little on a Monday could put you in hospital by Thursday.

What can I take to relieve withdrawal and help me sleep until the OAT medication begins to work?

Your doctor may discuss taking certain medications to assist with your symptoms. These medications may include plain Tylenol® (acetaminophen) and Advil® (ibuprofen). Drinking lots of water is important to stay hydrated. Occasionally, your doctor may prescribe other medications to help with specific symptoms – **only take medications that are approved by your OAT doctor**. If you're on a medication prescribed by another doctor, your OAT doctor needs to approve it because it could interact with the buprenorphine/naloxone or methadone.

Substances that make you relaxed or sleepy can be dangerous. This includes:

- Alcohol, opioids, and benzodiazepines (e.g., Ativan®, Valium®, Xanax®, Restoril®, etc.).
- Antihistamines, cold medications, and sleeping pills (such as, but not limited to, Gravol™, Benadryl®, Nyquil™, Benylin®, or Tylenol® PM, zopilcone).
- Certain types of antidepressants and tranquilizers.

Even certain antibiotics can be dangerous as they block the breakdown of methadone in the body. **Make sure to check all your medications with your OAT doctor**.

What if I feel like I still need to use other opioids while starting OAT?

If you feel like you need to use other opioids in addition to the OAT medication, particularly while at a lower methadone dose, talk to your doctor about this honestly at every visit. Your doctor understands that your buprenorphine/naloxone or methadone dose may not last 24 hours in early treatment. Knowing that you are using other opioids and how much, will help your doctor to increase your OAT medication dose as needed, while being safe. Your doctor can also help you to determine the safest way to use additional opioids if this is needed. **However, if you can cope with your OAT dose only, that is the safest option**.

Isn't OAT, especially methadone, supposed to make you sleepy?

No. You are supposed to feel normal on your OAT medication, not high or sleepy. This applies to both buprenorphine/naloxone and methadone. When taken as prescribed by your doctor, OAT medications build up slowly in your system and should not make you feel drowsy. You should take the following precautions to help the clinic staff keep you safe:

- Take your OAT at the same time each day.
- See your doctor or case manager at least once a week for the first two weeks. (Many clinics will require visits that are more frequent.)
- Discuss your OAT treatment with a close friend or family member. If they see that you are drowsy, they must call your OAT doctor or 911.
- Discuss naloxone kits with your doctor and with a close friend or family member. Make sure you and your friend/family know how and when to use naloxone (your doctor or trained clinic staff can teach you this).

I'm starting methadone…What are some of the symptoms if my dose is too high?

- You may feel sleepy and nod off several times during the day.
- You may be forgetful.
- You may be difficult to wake up from your sleep.
- You may experience slurred speech, stumbling walk, or appear drunk.

If these things are occurring, you must call your doctor immediately and call 911 for help.

I've been offered a small amount of methadone by a methadone patient at the pharmacy. This can't hurt – I know I need 80 mg?

Above all, don't take any extra methadone! What is safe for your friend could be lethal for you. It may be true that you took 80 mg **once** and were okay. If you had taken 80 mg every day for three or four days, you might have overdosed. Remember, it takes *five or more days* for a certain dose to build up in your blood.