

Methadone Key Facts For Prescribing

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1. Availability

Scored Tablets 5mg and 10mg

Wafers (40mg) only available for methadone maintenance programs

Any prescriber with a DEA number can prescribe it for chronic pain. Only those with added qualifications for chemical dependency can prescribe it for maintenance program for opioid addicts

2. Diversion

Although methadone does not give a sense of euphoria it still has a black street market value of about \$1 per mg as it is used to decrease the withdrawal effects when an addict cannot get heroin or prescription opioids. Because of its potency and accumulation in the body if taken incorrectly and in association with sedatives and alcohol by opioid naïve subjects, there is a significant risk of excessive respiratory depression and death.

It is important to discuss safe keeping of this and other medications to avoid diversion or theft.

3. Prior to starting:

- Risk Assessment for addiction-consult if necessary. COMM questionnaire also helpful.
- Opioid Agreement (New term by FDA is Provider Patient Agreement) for informed consent is also recommended.
- Asses for contraindications: significant sleep apnea / severe COPD / acute asthma or other clinically relevant states of respiratory depression / other medications - see the list below
- Methadone does not produce complete tolerance to respiratory depression, even over time. Sleep oximetry is recommended looking for central sleep apnea for doses of methadone >40mg/day even in patients without any sleep apnea symptoms.
- Baseline ECG to asses QTc interval. (QTc is QT corrected for heart rate – always refer to this measure).
- Goal is to ensure it stays below 500msec. Normal in females is up to 460 msec, in males 440msec.
- A change of 40-60msec from baseline is considered significant. You will need to do an ECG before you start so you know what baseline is.
- If baseline QST is between 450-500mg increase methadone with caution and reassess ECG as you go. Most reported cases of QT prolongation were at doses >80mg per day

- Prolonged QT presents as polymorphic V Tach then V fib and sudden death. Symptoms include presyncopal/syncopal episodes and shortness of breath.
- Consider checking magnesium and potassium as low levels of these will increase risk of arrhythmia.
- Clopidogrel (Plavix) is an effective blocker of 3A4 therefore patients on Plavix may experience increased levels of the S form of methadone which is the isomer thought to cause QT prolongation, hence they may be at increased risk of QT prolongation and torsades de pointes
- One website with information is <http://emedicine.medscape.com/article/1950863-overview-aw2aab6b6>
- No dose adjustments are necessary for renal or hepatic failure. Methadone is poorly removed by dialysis.

4. Dosing:

- a) Opioid Naïve or if on less than 200mg/day Morphine equivalent: start at 2.5 mg bid and titrate up to 2.5 mg tid after a week with small increases weekly as needed.
 - i. There are some patients who are very slow metabolisers and will develop severe drowsiness and respiratory depression on doses of 15 mg a day or even less so go slow.
- b) On Morphine equivalent of 200mg/day or more: start at 5mg tid. Usual increase is 2.5-5mg increments: i.e. 10mg tid X 7 days then 12.5mg tid X 7 days

Do not titrate up faster (ever unless Palliative) than q 3 days and preferably q 7 days

For opioid tolerant patients who are being switched also Rx a short acting opioid (morphine, oxycodone or hydromorphone) for BTP or withdrawal symptoms. Give approx 10% of previous opioid dose, e.g. patient on 200mg oxycodone = 400 mg morphine equivalence. Rx methadone 5mg tid for 1st week and provide oxycodone 20mg q 3-4 h prn pain or withdrawal symptoms max 6 doses per day.

5. During Treatment:

Recheck ECG- when depends on their initial QTc interval and the dose. It may be prudent to recheck it with each dose increase over 80 mg/day although doses this high are very unusual. Ensure ongoing documentation of the 6A's:

- 1) Analgesia (pain relief)
- 2) Activities (physical and psychosocial functioning)
- 3) Adverse Effects (and your advice)
- 4) Ambiguous Drug Taking Behavior (and your response)
- 5) Affect
- 6) Accurate medication record

If a patient runs out or stops methadone for > 5 days and wished to restart then begin at a lower dose (25%-50% less) and gradually titrate back to the previous dose.

6. Stopping methadone:

Reassure the patient that withdrawal from opioids is uncomfortable but not life-threatening. Each dosage reduction may result in symptoms similar to a severe, flu-like illness beginning within 12-36 hours and peaking at 48-72 hours and then tapering off after 1 week. Some people experience a period of vague dysphoria for 1-2 weeks after withdrawal. Methadone withdrawal may peak later with less intensity but can go on for 4-6 weeks in some people and for months in a few.

The patient can choose to withdraw abruptly and experience a more severe but shorter overall period of symptoms, or to taper over 10 to 14 days and experience milder but a more prolonged withdrawal. Simply provide a 10% reduction daily over 10 days. Use frequent (even daily) pharmacy dispensing for the tapering process in high-risk patients. Once-daily opioid formulations may make the withdrawal process simpler. A methadone taper allows for a less intense but longer period of withdrawal symptoms..

Clonidine has been used the longest to decrease some of the autonomic symptoms of opioid withdrawal. The main side effects are orthostatic hypotension and sedation. Prescribe 0.1-0.2 mg po q6h prn maximum 6 tabs per day. The dose may have to be lowered if the patient reports orthostatic symptoms or has a BP less than 90/60 mmHg, 1 hour after a dose. Continue clonidine until off of opioids for 3-5 days then taper over next 3-5 days. (what about a clonidine patch?)

One of the symptoms of opioid withdrawal is pain (usually arthralgias and myalgias) which may persist longer than other withdrawal symptoms, but will eventually settle. NSAIDs or tramadol or acetaminophen may be helpful. If attempting to re-evaluate a patient's pain off of opioids, the opioids need to be discontinued for at least 3-4 weeks to get through withdrawal pain and allow opioid receptors to "reset."

We do not know how long it takes to reset especially with opioid induced hyperalgesia probably >3 months

Diphenoxylate, (Imodium) can help decrease abdominal cramping and diarrhea if these occur.

Acupuncture or TENS have been shown in some studies to decrease symptoms of opioid withdrawal.

Short-term use of an antiepileptic such as gabapentin or pregabalin, an antipsychotic such as quetiapine or hydroxyzine for the first 1-2 weeks may help with sleep and anxiety. Warn patients that with severe withdrawal insomnia can be extremely treatment resistant and they may just have to cope with a few sleepless nights.

7. Drug Interactions: NOTE: THIS IS A SYNOPSIS OF COMMON DOCUMENTED CLINICALLY SIGNIFICANT INTERACTIONS AND DOES NOT PROVIDE COMPREHENSIVE INFORMATION. PLEASE SEE [Methadone-Drug Interactions-2010.pdf](#) FOR MORE DETAILED INFORMATION.

Present in vitro findings indicated that CYP3A4, CYP2C8, and CYP2D6 are all involved in the stereoselective metabolism of methadone (R)- and (S)-enantiomers

A drug interaction should be suspected when a patient complains of withdrawal symptoms or unusual sedation. In this case, hold the methadone until LOC returns to normal. In case of significant sedation with respiratory depression, send to the ED where dilute naloxone may be titrated in carefully to avoid severe withdrawal symptoms

Medications contraindicated in patients using methadone.

- a. *Other analgesics which can cause rapid withdrawal by displacing methadone from its receptor. buprenorphine, butorphanol, dezocine, nalbuphine, pentazocine (Buprenex, Subutex, Suboxone, Stadol, Dalgan, Nubain, Talwin). Opioid antagonists can cause the same effect. naltrexone, nalmefene, naloxone (Depade, ReVia, Revex, Narcan)*
- b. *Monoamine oxidase (MAO) inhibitors such as Nardil or Parnate have been reported to cause adverse effects.*
- c. *Concomitant use of benzodiazepines and choral hydrate can cause additive respiratory sedation and deaths have been reported.*
- d. *Caution with any other sedating medications, alcohol and cannabis due to additional sedation. Using TCA's has been reported to have increased TCA toxicity.*
- e. *Watch for effects from starting new medications that inhibit the metabolism of methadone and increase serum levels like fluoxetine or paroxetine OR effects from stopping ongoing medications that were inducing the metabolism and keeping the levels down but now stopped will cause an increase in the serum levels since they are no longer inducing the 3A4 to metabolize the methadone more quickly – such as stopping dilantin.*
- f. *The interaction and effect may be rapid (<24 hours) or delayed (up to a week)*

Starting drugs that INCREASE methadone levels by a MODERATE amount: (some of these are major competitive substrates and they have an early effect, some are 3A4 Inhibitors and their effect is delayed).

REMEMBER that if a patient was started on methadone while taking any of these medications and then one of these medications is STOPPED, it will have the opposite effect. I.e. STOPPING paroxetine will reduce methadone analgesia and may precipitate withdrawal.

Rapidly: fluoxetine, fluvoxamine, moclobemide, grapefruit juice

Delayed: diazepam, midazolam, erythromycin, zidovudine

Paroxetine is a strong CYP2D6 inhibitor and patients who were extensive metabolizers did have a significant increase in methadone serum levels. (Journal of Clin Psychopharm: April 2002 - Volume 22 - Issue 2 - pp 211-215)

Other common drugs that inhibit 2D6 variably (none to minor) but could possibly increase methadone levels: Ciprofloxacin, clarithromycin, norfloxacin, ketoconazole, haloperidol, sertraline, paroxetine, venlafaxine, thioridazine, cimetidine, diltiazem, quinidine, delavirdine

Starting drugs that will DECREASE Methadone by a MODERATE amount: (most are 3A4 inducers).

REMEMBER that if a patient was started on methadone while taking any of these medications and then one of these medications is STOPPED, it will have the opposite effect.

Rapidly: none

Delayed: rifampin, carbamazepine, dilantin, respiradone, rifabutine, efavirenz (8-10 days), nelfinavir, nevirapine (4-8 days), ritonavir, zidovudine

Other common drugs that induce 3A4 with variable (none to minor) activity but possibly able to decrease methadone levels: Barbituates especially phenobarbital, amprenavir dexamethasone, St. John's Wort, oxcarbazepine, phenytoin, topiramate

8. Methadone Toxicity:

Naloxone solution: dilute 1 ml of 0.4 mg/ml naloxone in 9 ml of normal saline (0.04 mg/ml = 0.1 ml)

Give 0.004 mg naloxone q 1-2 min until respiratory rate > 8/min and O₂ saturation > 90%

Repeat q 20-30 min until patient stabilized

Because of methadone's long half life, a naloxone infusion may be required following stabilization

Start with 50 mcg naloxone (0.1 mcg/ml) per hour and titrate to effect

In an emergency if the patient is still conscious, open a 1ml vial of naloxone (0.4mg), pour it onto a cotton ball, hold it up to the patients nose and have them sniff hard.

9. Perioperative Pain Management for patients on Methadone:

For all patients:

Pre-operative anesthesia consult
Continue methadone on day of surgery
Advise patients to bring their own methadone to hospital
Pre-operative ECG

For day-surgery patients:

Resume regular dose of methadone after surgery. May need to increase 25%
Additional analgesia for pain control
In-patient surgery (NPO < 48 hrs)
While NPO, give IV methadone or alternative analgesia
(e.g., PCA/RA) to avoid opioid debt
Resume methadone PO ASAP when tolerating oral fluids well

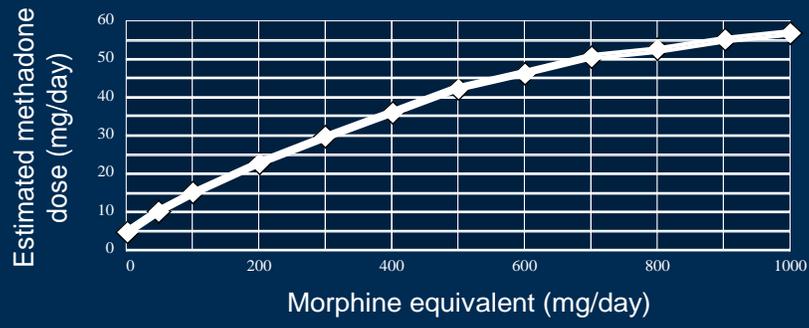
For in-patient surgery NPO > 48 hrs: (e.g., bowel resection)

While NPO give IV methadone or provide concentrated suspension at 20mg/ml and administer it buccally or provide alternative opioid by PCA or infusion to avoid opioid debt
Watch for drug interactions
Resume oral methadone ASAP when tolerating oral fluids well. If off methadone > 5 days resumption of methadone should be made with advice of an experienced methadone prescriber.

10. Travel

Methadone is legal in the USA and Canada but illegal in Mexico (at least when used for addiction) and Thailand. Patients need to check with the embassy of the country they are travelling to for up to date information. Patients will need a travel note stating they have a chronic pain disorder and listing the scheduled medications they use. For countries where it is legal, patients must carry the medication in the original prescription bottles and should take it in their carry-on luggage.

Conversion Nomogram: Estimated Dose



Toombs JD. February 2006. Available at: www.pain-topics.com