

## Methadone Dose Conversion Guidelines

Adapted from AAHPM Palliative Care Primer, 2010 edition with permission from Timothy Quill M.D.

### Background

Methadone is a potent opioid with several favorable characteristics, including oral bioavailability of 80%, no active metabolites requiring dose adjustments in renal impairment, low cost, steady analgesic effect, and (possibly) more efficacy when used for neuropathic pain than other opioids. However, methadone has a long, variable half-life (ranging from 6 to 190 hours depending on the dosage). The rapid titration guidelines used for other opioids do not apply to methadone; in general, do not increase dosage more frequently than every 4 days in lower doses and 1 to 2 weeks in higher doses. Small changes in total daily dosage may slowly and progressively have a larger effect on blood level when patients are on dosages greater than 30 mg per day. Dose-conversion ratios are complex and vary based on current opioid dosage and individual factors (see table below).

**Conversion table from morphine to methadone (most commonly used in the USA)**

<b>24 hour total dose of oral morphine</b>	<b>Conversion ratio (oral morphine: oral methadone)</b>
<30mg	2:1 (2mg morphine to 1mg methadone)
31-99mg	4:1
100-299mg	8:1
300-499mg	12:1
500-999mg	15:1
1000-1200mg	20:1
>1200mg	Consider consult with palliative care or pain specialist

Because of the potential for drug accumulation from the long half-life, always write “hold for sedation” when initially prescribing or changing dosages of methadone.

Converting from methadone back to morphine or other opioids is especially complex, because methadone affects more opioid receptors than other opioid analgesics; assistance from palliative care or pain management experts is generally advisable for this transition if patients have been on more than 30 mg for more than a few weeks.

Because of its long half-life, methadone is better used as a baseline, scheduled analgesic, with shorter-acting opioids such as morphine or hydromorphone used prn. In relatively stable situations, however, small doses of methadone can be given prn in addition to the scheduled regimen. In general, no matter how high the regular standing methadone dosage, the prn should be no more than 2.5 to 5 mg two or three times daily. Because of the progressively long half-life, small incremental doses for patients receiving a large baseline dose may have a major effect on blood level if taken regularly.

Although the ratio of oral methadone to intravenous methadone may vary from 1:1 to 2:1, when converting to oral to intravenous methadone it is prudent to reduce the total daily dose of methadone by 50%. On the other hand, when converting from intravenous methadone to oral methadone, it is recommended to use the most conservative 1:1 conversion to avoid over-medicating the patient. In these transitions, the patient should be carefully observed for under- and over-dosing.

Under most circumstances, unless the prescriber is very familiar with methadone pharmacokinetics, it is safer to use a different opioid with a much shorter half-life as a prn when using methadone as the baseline opioid. The usual calculation ratios and intervals used for determining breakthrough doses of other opioids do not apply to methadone (and fentanyl).

### Cautions about Methadone

(\*) The long half-life can lead to drug accumulation, sedation, confusion, and respiratory depression, especially in the elderly or with rapid dose adjustments.

(\*) Methadone in moderate to high dosages can prolong the QTc interval and increase the risk of the potentially lethal *torsades de pointes* arrhythmia. Depending on the goals of treatment, the presence of associated heart disease, the patient’s prognosis, and the presence of other medications that might cause similar problems (eg, haloperidol), consider checking the QTc at baseline, and begin monitoring after each dosage change for patients taking over 100 mg of methadone per day. If QTc becomes significantly prolonged (QTc 450-499 milliseconds moderate risk; QTc > 500 milliseconds = high risk), consideration should be given to lowering the methadone dosage or rotating to an alternate opioid. Formal consultation with palliative care, acute pain service, cardiology, and pharmacy should be considered.

(\*) Medications that can decrease methadone levels include rifampin, phenytoin, corticosteroids, carbamazepine, bosentan, Phenobarbital, St. John's Wort, and a number of antiretroviral agents.

(\*) Medications that can increase methadone levels include tricyclic antidepressants,azole antifungals (especially voriconazole), macrolides and fluoroquinolones, amiodarone, selective serotonin reuptake inhibitors (SSRIs), and diazepam. Grapefruit juice also can increase methadone levels.

### Sample Calculation - Conversion to Methadone

A 50-year-old woman with metastatic breast cancer has good pain control with sustained-release oral morphine 200 mg, two tablets twice a day. However, she develops persistent myoclonus. A decision is made to rotate opioids to methadone. (Our conversion table [Table 2.1] always requires that the equianalgesic amount of oral morphine be determined to calculate a daily dosage of methadone.)

Step 1. Calculate the total daily oral morphine dosage.

(\*) Two tablets of 200 mg each, taken twice daily = 800 mg total oral morphine per day

Step 2. Convert to methadone.

(\*) For a dosage of 800 mg per day, the conversion ratio of morphine to methadone is 15 : 1 (see Table 2.1).

(\*)  $800 \text{ mg per day oral morphine} \times 1 \text{ mg methadone}/15 \text{ mg oral morphine} = 53 \text{ mg methadone per day}$

Step 3. Reduce the dosage because of incomplete cross-tolerance.

(\*) Reduce the equianalgesic dose by 1/3 to 1/2 when switching opioids because of incomplete cross-tolerance.

(\*)  $53 \text{ mg} \times 2/3$  equals about 35 mg methadone; alternatively,  $53 \text{ mg} \times 1/2$  equals about 26 mg methadone

(\*) Total daily dosage should be between 26 mg and 35 mg methadone per day.

(\*) The baseline methadone dosage would be increased no more frequently than every 4 days because of the danger of gradual accumulation.

Step 4. Determine dosing schedule.

(\*) Methadone is initially dosed in divided doses three times per day (higher doses can be given twice daily, given its long half-life).

(\*) A dosage of 30 mg per day of methadone (between 26 mg and 35 mg) can be given as 10 mg three times per day.

(\*) When ordering methadone, because of its long and variable half-life, always write "hold for sedation."

Step 5. Choose a prn medication.

(\*) Because of its potentially long half-life, prn doses of methadone can be difficult to manage correctly.

Therefore, an opioid with a short half-life is generally preferable for prn dosing.

Step 6. Determine the prn dose (morphine).

(\*) The prn dose should be 10% of the total daily opioid dosage.

(\*) Because the patient was already on 800 mg per day of oral morphine, the prn dose based on the prior total daily dosage of morphine would be:  $800 \text{ mg oral morphine} \times 10\% = 80 \text{ mg oral morphine every 1 to 2 hours as needed}$ .

(\*) This could be given as 4 cc of 20 mg/cc morphine concentrate or equivalent every 1 to 2 hours as needed.

### Practical facts

Pills 5, 10mg; Liquid 1mg/mL, 2mg/mL, 10mg/mL; Parenteral 10mg/mL

Cost of methadone: 1/10 morphine sulfate ER, 1/75 oxycodone ER, 1/15 of transdermal fentanyl.

Any physician with a Schedule II DEA license can prescribe methadone for pain. A special license is only required when using for the treatment of addiction. **(N.B. must write "for pain" on the prescription when used for pain)**

Get help if converting from large doses of other opioids, converting to IV, or if inexperienced

### References

Morley JS, Bridson J, Nash TP, Miles JB, White S, Makin MK. Low-dose methadone has an analgesic effect in neuropathic pain: a double-blind randomized controlled crossover trial. Palliat Med. 2003 Oct;17(7):576-87.

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