Methadone Dose Conversion Guidelines
Adapted from AAHPM Palliative Care Primer, 2019 edition with permission from Timothy Quill M.D.

Methadone is not a first line pain medication and should be used primarily by those with pain and palliative expertise. Despite representing only 2% of opioid prescriptions, methadone has been involved in 30% of opioid related deaths in recent years. Inexperienced prescribers should seek consultation.

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. The dose should not be increased more frequently than every 4 days in lower doses and 1 to 2 weeks in higher doses. Small changes in total daily dosage may progressively have a larger effect on blood levels when patients are on dosages greater than 30 mg per day. Dose-conversion ratios are complex, non-linear, 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)

24 hour total dose of oral morphine	Conversion ratio (oral morphine: oral methadone)
<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	Consult with palliative care or pain specialist prior to prescribing

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 highly recommended for such a transition if patients have been 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. There is some literature suggesting methadone can be used as a prn, however the risks if overused are much greater with methadone. Under most circumstances, unless the prescriber is very familiar with methadone pharmacokinetics and the patient is very reliable, it is safer to use an immediate release opioid 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).

Although the ratio of oral methadone to intravenous methadone may vary from 1:1 to 2:1, when converting from 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. Closely monitor for under- and over-dosing in all transitions. (See Table 1 Patient Selection for Methadone Therapy in McPherson et al)

Cautions about Methadone
- The long half-life causes drug accumulation, and can lead to possible sedation, confusion, and respiratory depression, especially in the elderly or with rapid dose adjustments. Respiratory depression must be treated with naloxone infusion due to methadone’s long half-life.
- Methadone in moderate to high dosages can prolong the QTc interval and increase the risk of the potentially lethal *torsades de pointes* arrhythmia. (See below for greater detail)
- Medications that can decrease methadone levels include rifampin, phenytoin, dexamethasone, carbamazepine, bosentan, phenobarbital, St. John’s Wort, modafinil, and a number of antiretroviral agents.
- Medications that can increase methadone levels include tricyclic antidepressants, azole antifungals (especially voriconazole), isavuconazonium, bupropion, chlorpromazine, duloxetine, haloperidol, omeprazole clarithromycin, erythromycin, and fluoroquinolones, amiodarone, selective serotonin reuptake inhibitors (SSRIs), and diazepam. Grapefruit juice and acute ETOH use also can increase methadone levels.
- Methadone has some serotonin activity and can contribute to serotonin syndrome.

- Careful patient selection and counseling should be undertaken to outline risks and benefits when using methadone.

Sample Calculation – Complete 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 "Conversion table from morphine to methadone" on previous page).
- 800 mg per day oral morphine × 1 mg methadone/15 mg oral morphine = 53 mg methadone per day

Step 3. Reduce the dosage because of incomplete cross-tolerance.
- Reduce the equianalgesic dose by 1/2 when switching opioids because of incomplete cross-tolerance.
- 53 mg × 1/2 equals about 26 mg methadone
- Total daily dosage should be about 26 mg methadone per day (general consensus that starting doses should not exceed 30-40 mg per day – see McPherson et al and Chou et al.).

Step 4. Determine dosing schedule.
- Methadone is initially dosed in divided doses three times per day (the analgesic effect is shorter than the half-life, so methadone should be generally given three times per day for pain, even though for methadone maintenance it can be given daily or even less frequently).
- A dosage of about 26 mg per day of methadone can be given as 7.5 mg to 10 mg of methadone three times per day (total daily dose of methadone being either 22.5mg or 30mg respectively).
- 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 are difficult to manage correctly and are subject to completely different rules than other prn opioids. Therefore, *unless you are a very experienced methadone prescriber*, an opioid with a short half-life is highly 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 mg oral morphine × 10% = 80 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.

Step 7. Adjustments to regimen
- Due to the variable and often long half life, changes in dosing should be made no more frequently than 5-7 days. In cases like this where higher doses of methadone are being used, 7-14 days is advised.
- Due to multiple drug interactions, close monitoring of the complete medication list of methadone patients is critical

Practical facts
- Tablets 5, 10mg; Liquid 1mg/mL, 2mg/mL; 10mg/ml. The 40mg tablets are approved for detox and addiction tx only.
- Tablets can be crushed and are reasonably well absorbed sublingually, buccally or rectally if necessary.
- 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.)**
- Seek consultation if converting from large doses of other opioids, converting to IV, or if inexperienced.

QTc Prolongation

- Depending on the goals of treatment, the presence of associated heart disease, the patient's prognosis, and the presence of other medications that prolong QTc, ECG monitoring may be indicated.

- If risk factors present, get baseline QTc.
    - Previous QTc > 450ms or known congenital long QTc syndrome
    - Underlying cardiac abnormalities, especially hx of ventricular arrhythmias, congestive heart failure
    - Use of other medications that prolong QTc and have a known risk of TdP (see https://www.crediblemeds.org/ for additional information))
    - Electrolyte abnormalities (especially low K, Ca, and Mg)
    - Hypothyroidism
- Begin monitoring after each dosage change if their baseline QTc exceeds 450ms and for all patients if and when their daily dose exceeds 30mg mg of methadone per day.
- For high-risk patients, monitor after initiation and each increase.
- Once a new steady state has been achieved, repeat ECG; generally about 4-7 days.
- There is no need for repeated checking unless dose is changed or another drug is added that would raise the blood level or affect the QTc.
- If QTc becomes significantly prolonged (QTc 450-499 milliseconds = moderate risk; QTc > 500 milliseconds = high risk), consider lowering the methadone dosage or rotating to an alternate opioid. Formal or informal consultation with palliative care, acute pain service, cardiology, and pharmacy should be considered. (see McPherson et al. and Chou R et al. for additional monitoring details)

References

McPherson ML, Walker KA, Davis MP, Bruera E, Reddy A, Paice J, et al. Safe and Appropriate Use of Methadone in Hospice and Palliative Care: Expert Consensus White Paper. J Pain Symptom Mange 2019;57(3): 635-645.

Chou R, Cruciani RA, Fiellin DA, et al. Methadone safety: a clinical practice guideline from the American Pain Society and College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society. J Pain 2014;15:e321-337.

Morley JS, Bridson J, Nash TP, Miles JB, White S, Makin MK. 2003. Low-dose Methadone Has An Analgesic Effect In Neuropathic Pain: A Double-blind Randomized Controlled Crossover Trial. *Palliative Medicine 17*(7): 576-87.

Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MC. 2009. QTc Interval Screening In Methadone Treatment. *Annals of Internal Medicine 150*(6): 387-95.

UptoDate 5/19. Methadone: Drug Information and Cancer Pain Management with Opioids

Woosley RL, Heise CW , Gallo T, Tate J, Woosley D and Romero KA, www.CredibleMeds.org, QTdrugs List, [Accession Date], AZCERT, Inc. 1822 Innovation Park Dr., Oro Valley, AZ 85755