D. Methadone Dosing Guidance

a. Summary

- Methadone is not a first-line agent for the treatment of chronic pain.[33] It is an alternative long-acting opioid analgesic that may be useful in managing pain severe enough to require continuous daily treatment for which alternative treatment options are inadequate.
- In general, as with other opioids, methadone should be used as one aspect of a comprehensive pain management plan, as agreed upon by the practitioner and the patient.
- Methadone should be initiated and adjusted by, or in consultation with, a practitioner who has the relevant knowledge and expertise;[33] if a provider with clinical experience is not available, then another long-acting opioid may be used until such consultation is obtained.
- The general principles utilized in the dosing of methadone are different than those of other opioids; these differences are due to methadone's unique pharmacokinetic and pharmacodynamic properties and include, but are not limited to:
  - Dose titration should occur after at least 5-7 days on a designated dose (in the large majority of cases)
  - Careful consideration must be given to potential drug interactions and to the potential for QT prolongation
- Methadone is considered to be safe in patients with renal and/or hepatic impairment but should be used with caution in end-stage disease cases of these conditions.
- There are a number of methods available that use conversion ratios to initiate or titrate methadone; no single method is considered superior to others. Titration should be based on patient response and not solely based on equianalgesic dosing tables.
- Monitoring ECG for QTc interval prolongation is recommended based upon certain clinical scenarios.

b. Overview

Methadone is indicated for persistent, moderate-to-severe chronic pain in patients requiring continuous, around-the-clock opioid administration over an extended time. Methadone's pharmacokinetic properties are complex and incompletely documented.[199,200] It has a long elimination half-life that has wide inter-patient variability (mean or median half-life, depending on subject type, ranges from 3-128 hr) [201-214] and does not reflect duration of analgesia.[210,215] Initially, methadone duration of analgesia ranges from 4-6 hr; however, with repeated dosing, duration of analgesia can extend to 8-12 hr. Accordingly, while initial dosing may require more frequent administration (three times per day [TID]) to achieve adequate analgesia,[216,217] once steady-state levels are established, reducing dosing frequency to two times per day (BID) can be considered. In elderly and frail patients, consideration may be given to starting with BID dosing. Also, as a result of the dissociation between half-life and analgesic duration, tissue accumulation of methadone can occur. It may take ten days for plasma levels to stabilize; thus, as a general rule, dose titration should not be more frequent than every 5-7 days.[218] Patients should be reassessed more frequently (e.g., every few days) when methadone is initiated and when the dose is increased.[33] Once stable dosing is established, follow-up can be as clinically warranted.

While methadone is an alternative to ER morphine or oxycodone for treatment of moderate-to-severe pain, a number of authors have cautioned about the complexities of dosing and suggested the drug be prescribed by practitioners with relevant experience, in an adequately monitored setting.[33,216,217,219-225] Significant toxicity has occurred particularly when doses were increased too frequently, conversion doses were too high, or dosing intervals too close.[222,226-228]

In 2014, a methadone safety guideline was developed by the American Pain Society and College of Problems of Drug Dependence, in collaboration with the Heart Rhythm Society, which made recommendations for safer prescribing of methadone.[169] Table D-4 outlines baseline and monitoring recommendations based on categorization of patients for risk of QTc prolongation. Palliative care patients with the goal of comfort care may require less vigilance with ECG monitoring.

Table D-4: Baseline and Monitoring Recommendations Based on Categorization of Patients for Risk of QTc Prolongation [169]

Category	Baseline ECG	Follow Up ECGs[1]	Action
Patients with risk factors for QTc prolongation, any prior QTc >450, or history of syncope	Obtain baseline ■ ECG within last 3 months is sufficient ■ Strong recommendation ■ Low quality evidence	■ 2-4 weeks after initiation ■ With significant dose increases ■ When methadone dose reaches 30-40[2] mg/d ■ When methadone dose reaches 100 mg/d[2] ■ When new risk factors arise or signs or symptoms of suggestive arrhythmia	■ Avoid use if QTc >500 ms[3] ■ Consider alternative to methadone for QTc 450-500[3] ■ Evaluate and correct reversible causes of QTc prolongation
Patients not known to be at higher risk of QTc prolongation	Consider baseline ■ ECG within the last 12 months is sufficient ■ Weak recommendation ■ Low quality evidence	■ When methadone dose reaches 30-40[2] mg/d ■ When dose reaches 100 mg/d[2] ■ When new risk factors arise or signs or symptoms of suggestive arrhythmia	■ Avoid use if QTc >500 ms[3] ■ Consider alternative to methadone for QTc 450-500[3] ■ Evaluate and correct reversible causes of QTc prolongation

[1]Consider obtaining yearly ECGs once a stable dose is reached.
[2]Doses this high are not recommended for chronic pain and are typically observed only for patients receiving methadone for MAT for OUD.
[3]For patients on stable doses of methadone in whom a prolonged QTc has been noted (QTc >450 ms), consider tapering the dose of methadone and repeating the ECG. Other QT prolonging medications should be evaluated and cardiology specialty care should be consulted for expert opinion.
Abbreviations: d: day(s); ECG: electrocardiogram; MAT: medication assisted treatment; ms: millisecond(s); mg: milligram(s); OUD: opioid use disorder; QTc: QTc interval (the heart rate's corrected time interval from the start of the Q wave to the end of the T wave)

Special caution is recommended with concurrent benzodiazepines and drugs that prolong the QT interval.[229]

Methadone is primarily metabolized by CYP450 2B6 to inactive/nontoxic metabolites.[230-236] CYP2B6 is a highly polymorphic gene[237] and may help to explain why the pharmacokinetics of methadone can be extremely variable from individual to individual. Currently, it is unclear whether cytochrome P450 3A has

any influence on methadone metabolism and caution is encouraged when using drugs that interact with both enzymes.

c. Dosing Strategies

The dosing recommendations listed below (in Table D-5) are provided to offer guidance on using methadone in the treatment of patients with chronic pain, particularly when converting from another opioid to methadone. The use of methadone for pain should be done in the context of a pain clinic or with assistance of local pain management experts, including healthcare providers or pharmacists, who have experience with methadone's use. If such resources are not readily available, other long-acting opioids should be considered (e.g., morphine sustained action [SA], or oxycodone SA).

Various methadone dosing strategies have been employed [224,238,239] and methods are still evolving. Older, prospective studies found no evidence to support the superiority of one dosing strategy over another.[220,240,241] The lack of prospective and comparative studies concerning methadone dosing strategies highlights the need to carefully individualize the dosing regimen of methadone.

For opioid tolerant patients, a number of different equianalgesic dose ratio tables can be used to determine the dose of methadone.[220,223,242-245] This VA/DoD OT CPG includes one of the more conservative equianalgesic dose ratio tables as a reference for providers to discuss and/or consider (Table D-3).[245] Local subject matter experts may prefer, or be more familiar with, other accepted (evidence-based) equianalgesic dose ratio tables. No equianalgesic dose ratio table is considered superior and all have similar limitations. When converting to methadone, lower MEDDs have lower conversion ratios than higher MEDDs. As compared to lower MEDDs, higher MEDDs may convert to smaller methadone doses than one might expect. For example, 60 mg MEDD would be ~15 mg of methadone/day (a ratio of ~4:1); whereas 180 mg MEDD would be ~22.5 mg/day (a ratio of ~8:1). Methadone dose conversion is not a linear process. Furthermore, while the equianalgesic dose ratio tables account for cross-tolerance,[218] some subject matter experts feel the calculated methadone dose should be further decreased for incomplete cross-tolerance, especially for patients on higher MEDDs. [169,246]

Table D-5: Dosing Recommendations for Patients Receiving Codeine Preparations or No Previous Opioids [247,248]

Dosing Strategy	Initial Methadone Dose	Increments	Comments
Gradual titration (For CNCP and situations necessitating less frequent monitoring)	2.5 mg every 12 hr or 8 hr	2.5 mg every 12 hr or 8 hr, no more often than every 5 to 7 d	As a general rule, *start low and go slow*
Faster titration (For cancer pain and situations where frequent monitoring is possible)	2.5-5 mg every 8 hr	2.5 to 5 mg every 8 hr as often as every third day	

Note: All doses refer to oral administration
Abbreviations: CNCP: chronic non-cancer pain; d: day(s); hr: hour(s); mg: milligram(s)