Oral Methadone Dosing Recommendations for the Treatment of Chronic Pain

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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

Summary

- Methadone is not a first line agent for the treatment of chronic pain[1]. It is an alternative long-acting opioid analgesic that may be useful in managing chronic pain in select patients.
- 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;* [1] 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 to 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 the following clinical scenarios:
  - *With risk factors for QTc prolongation:* Obtain a pretreatment ECG for patients with risk factors for QTc prolongation and a follow-up ECG 2-4 weeks after initiation.
  - *In patients with unknown risk for QTc prolongation:* Consider obtaining a pretreatment ECG.
  - *Escalating dose or new risk factor:* Obtain a follow-up ECG when methadone reaches 30-40mg/day, then again if it reaches 100mg/day and when new risk factors arise or signs or symptoms suggestive arrhythmia for all patients.
  - *Stable dosing:* Consider obtaining yearly ECGs once a stable dose is reached.

Overview

Methadone is a potent synthetic opioid agonist with a diphenylheptane structure similar to propoxyphene (Darvon®, withdrawn from the US market in 2010 due to risk of cardiotoxicity). Methadone's mu receptor affinity is similar to that of morphine, but its ability to inhibit the N-methyl-D-aspartate (NMDA) receptor, inhibit monoamine-reuptake, and other minor differences make it a unique opioid.[2-4] Methadone is indicated for persistent, moderate to severe chronic non-cancer and cancer pain in patients requiring continuous, around-the-clock opioid administration over an extended time. Some experts believe that methadone may be more effective than other opioids in the treatment of neuropathic pain due to its NMDA antagonistic effects; however, further studies are needed to verify this property.[3, 5]

Methadone's pharmacokinetic properties are complex and incompletely documented.[6, 7] It has a long elimination half-life which has wide inter-patient variability (mean or median half-life, depending on subject

type, ranges from 3 to 128 hours) [8-21] and does not reflect duration of analgesia.[18, 22] Initially, methadone duration of analgesia ranges from 4-6 hours; however, with repeated dosing, duration of analgesia can extend to 8-12 hours. Accordingly, while initial dosing may require more frequent administration (TID) to achieve adequate analgesia, [23, 24] once steady-state levels are established, reducing dosing frequency to 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 10 days for plasma levels to stabilize; thus, as a general rule, dose titration should not be more frequent than every 5-7 days.[3] Patients should be reassessed more frequently (e.g., every few days) when methadone is initiated and when the dose is increased.[1] Once stable dosing is established, follow-up can be as clinically warranted. Methadone's long-duration of effect is not dependent upon a specialized delivery system, as is the case with transdermal fentanyl or sustained release formulations of morphine, hydromorphone or oxycodone. Therefore, as opposed to these extended-release agents, methadone is the only long-duration opioid that is available in an oral solution and can be crushed to add to a gastrostomy tube (of note: the contents of Kadian® capsules, containing sustained-release morphine pellets, may also be administered through a 16-French gastric tube[58]).

While methadone is an alternative to morphine 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.[1, 25-31] **Significant toxicity has occurred particularly when doses were increased too frequently, conversion doses were too high, or dosing intervals too close**.[28,32-34] Furthermore, in November of 2006 the FDA issued a public health advisory *"Methadone Use for Pain Control May Result in Death and Life-Threatening Changes in Breathing and Heart Beat"*.[35] Shortly thereafter, a multidisciplinary panel of experts met to review the cardiac effects of methadone and to develop cardiac safety recommendations for methadone prescribers.[36] 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.[37] Table 1 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 1: Baseline and monitoring recommendations based on categorization of patients for risk of QTc prolongation [37]

Category	Baseline ECG	Follow Up ECGs†	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 30-40mg/d • When methadone dose reaches 100mg/day • When new risk factors arise or s/sx suggestive arrhythmia	• Avoid use if QTc > 500 ms* • Consider alternative to methadone for QTc 450-500* • 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 30-40mg/d • When dose reaches 100mg/d • When new risk factors arise or s/sx suggestive arrhythmia	• Avoid use if QTc > 500 ms* • Consider alternative to methadone for QTc 450-500* • Evaluate and correct reversible causes of QTc prolongation

* For patients on stable doses of methadone in whom a prolonged QTc has been noted (QTc >450ms), 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.

† Consider obtaining yearly ECGs once a stable dose is reached.

Special caution is recommended with concurrent benzodiazepines and drugs that prolong the QT interval.[38]

It had been believed that methadone is metabolized by cytochrome P450 3A; however, in several studies conducted from 2004 through 2013, Kharasch et al. found that methadone is primarily metabolized by CYP450 2B6 to inactive/nontoxic metabolites.[39-45] CYP2B6 is a highly polymorphic gene[47] 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.

Dosing Strategies

The dosing recommendations listed below are provided to offer guidance on using methadone in the treatment of patients with chronic non-cancer pain (CNCP) or chronic cancer 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 health care 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 SA, oxycodone SA, or fentanyl patch).***

Various methadone dosing strategies have been employed [30, 48, 49] and methods are still evolving. Older, prospective studies found no evidence to support the superiority of one dosing strategy over another. [26,50,52] A more recent review performed by the Evidence-Based Clinical Practice Guideline Working Group for the VA/DoD, Management of Opioid Therapy for Chronic Pain, failed to identify any large scale comparative studies that could provide additional guidance.[38] The lack of prospective and comparative studies concerning dosing strategies highlights the need to carefully individualize the dosing regimen of methadone.

When initiating methadone, the first step is to determine whether the patient is opioid naïve; for opioid naïve patients, the rapidity of dose escalation is the differentiating factor in a given clinical situation. [3] The dosing strategies detailed in Table 2 are categorized by rapidity of titration. Faster titration should be reserved only for severe pain where frequent monitoring is possible (e.g. hospital setting).

For opioid tolerant patients, a number of different equianalgesic dose ratio (EDR) tables can be used to determine the dose of methadone.[53-58] This VA PBM-MAP-VPE guidance document includes one of the more conservative EDR tables as a reference for providers to discuss and/or consider (Table 3). [58] Local subject matter experts (SMEs) may prefer, or be more familiar with, other accepted (evidence-based) EDR tables. No EDR table is

considered superior and all have similar limitations (Table 4). When converting to methadone, lower morphine equivalent daily doses (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, 60mg MEDD would be ~15mg of methadone/day (a ratio of ~4:1); whereas 180mg MEDD would be ~22.5mg/day (a ratio of ~8:1). Methadone dose conversion is not a linear process. *Furthermore, while the EDR tables account for cross-tolerance[3], some SMEs feel the calculated methadone dose should be further decreased for incomplete cross-tolerance [59] especially for patients on higher MEDDs.*[37]

Table 2: Dosing recommendations for patients receiving codeine preparations or no previous opioids

Dosing strategy	Initial METHADONE dose	Increments	Comments
Gradual titration (For CNCP and situations necessitating less frequent monitoring)[60]	2.5 mg q12h or q8h	2.5 mg q12h or q8h every 5 to 7d	As a general rule, *start low and go slow.*
Faster titration (For cancer pain and situations where frequent monitoring is possible)	2.5-5mg q8h	2.5-5mg q8h as often as every third day	

The dosing recommendations for gradual titration were modified with permission from *Evidence-Based Recommendations for Medical Management of Chronic Non-Malignant Pain*, College of Physicians and Surgeons of Ontario, November 2000. **All doses refer to oral administration.** CNCP = Chronic noncancer pain; MET = Methadone

Table 3: Equianalgesic Dose Ratios (EDR).[59]

Morphine Dose (mg/d)	<30	31-99	100-299	300-499	500-999	1000-1200	>1200
Morphine: Methadone	2:1	4:1	8:1	12:1	15:1	20:1	Consult

Source: adapted from Quill TE, Bower KA, Holloway RG, et al. (2014). Primer of Palliative Care, 6th Edition. Chicago, IL: American Academy of Hospice and Palliative Medicine.

Table 4: Points to consider/limitations of EDR tables

The conversion ratio increases as the ME dose increases.[1, 26-28, 65] Hence, the oral morphine to oral methadone conversion ratio can be very high, and the methadone dose unexpectedly low, for patients that previously received very high doses of morphine.
While the above EDR table is conservative, an overdose of methadone may still occur for many reasons, a few of which are listed below. Therefore, monitoring patients closely when initiating/titrating methadone is suggested. ▪ A number of EDR tables underestimate the potency of methadone.[61-65] ▪ Dose ratios in many EDR tables do not apply to repeated doses of opioids. As with all opioids, much of the data in EDR tables are obtained from single-dose cross-over studies in opioid-naïve patients with acute pain. ▪ There may be large inter-patient variability in the EDR; a single ratio may not be applicable to all patients.[67] ▪ The use of high but ineffective doses of previous opioid may results in overestimation of the equivalent dose of methadone. For a very conservative dosing strategy refer to Chou and colleagues' Methadone Safety Guidelines.[37]
While the EDR tables take into account cross-tolerance,[3] some SMEs feel the calculated methadone

dose should be further decreased for incomplete cross-tolerance.[37]
The EDR tables are not bi-directional. They cannot be used in reverse (i.e. the morphine to methadone conversion ratio may not be the same as the methadone to morphine ratio).[66]

The EDR is only one component of the process for appropriate dosing of methadone and other opioids. Once the dose is determined, there are two different methods to make the switch, a rapid conversion method and a stepwise/phased conversion. Again, no one conversion method has been determined to be superior to the others.

- For rapid conversion, the previous opioid is discontinued and the calculated methadone dose is started on day one.
- For the stepwise/phased conversion, the dose of the previous opioid is decreased by 1/3 and replaced with 1/3 of the calculated methadone dose (given in 3 divided doses). Then the previous opioid dose is decreased by an additional 1/3 and the methadone dose is increased by 1/3. Finally, the remaining 1/3 of the previous opioid dose is discontinued and the methadone dose is increased to the initial calculated dose. This can be done over several days or weeks. [3, 51]

There are two titrating strategies:

- Dose titration can be done by increasing the methadone regimen by an absolute mg amount (e.g., 2.5mg q8h)[47] or
- By calculating how much opioid has been used for breakthrough pain and adjusting the standing methadone regimen accordingly. For this approach, determine how much "PRN" opioid the patient used on days 5, 6 and 7. Average that amount and convert to methadone.

With either method, dose titration should not occur more frequently than every 5-7 days.[3]

For breakthrough pain (BTP), a short-acting opioid preparation (e.g., acetaminophen with hydrocodone, oxycodone with or without acetaminophen, or immediate-release morphine) may be used until steady state is achieved (i.e. 5-7 days). *As needed* methadone has also been used [30, 48, 50] in a palliative care setting; however, it is generally discouraged to avoid drug accumulation. It is important to note that use of BTP medications in patients with CNCP is controversial; if opioid medications for BTP are indicated, following titration to a stable methadone dose in CNCP, they should be used sparingly.[52]

Converting FROM methadone to oral morphine

Switching from methadone to another opioid is ***NOT*** simply the reverse process; the EDR tables previously mentioned are not bi-directional and cannot be used in reverse (i.e. the morphine to methadone conversion ratio may not be the same as the methadone to morphine ratio).[66] There is no widely accepted conversion strategy for switching from methadone to another opioid. A proposed safe and conservative approach is a 1:3 methadone to morphine ratio (10mg methadone/day = 30mg oral morphine/day).[3] However, literature suggests patients may end up on as high as 1:4.7 methadone to morphine ratio (10mg methadone = 47mg morphine).[67]

Special patient populations

Patients 65 years and older may have decreased clearance of methadone.[20] Dosage adjustments do not appear necessary in patients with stable chronic liver disease; in addition, methadone and its metabolites do not accumulate in patients with renal failure.[69] However, two prospective studies on methadone dosing strategies excluded patients with liver or renal disease,[26, 50] thus caution should be observed when dosing methadone in these populations. Dosage adjustments may be necessary in patients with end-stage liver or renal disease.

General principles for dosing methadone

- Methadone should only be used for persistent chronic pain.
- Individualize doses and slowly titrate to response, usually no more frequently than every 5-7 days.
- If a patient develops sedation (which may be a precursor to respiratory depression), hold or decrease the following dose of previous opioid or methadone (depending on dosing strategy) and decrease subsequent doses and/or make dosage increments less frequent. Do not increase the dose of methadone.
- Short-acting opioids may be used for the treatment of BTP after initiation of methadone and while methadone dose is not yet stable.
- The use of medications for BTP in the treatment of CNCP is controversial. If medications for BTP are indicated after titration to a stable methadone dose, they should be used sparingly.[53]
- Reassess patients at appropriate intervals; at least once weekly during titration (preferably within 3 days of initiation/dosage increase[1]) and at least once monthly after the daily dosage is stabilized. Providers who do not have the resources to adequately monitor patients on methadone therapy should consider using alternative therapies.
- Use additional caution with elderly patients (≥ 65 years), patients with liver, renal, or pulmonary disease, debilitated patients, and patients previously receiving high doses of opioid. Patients who cannot be adequately monitored at home may be considered for inpatient titration of methadone.
- Obtain a pretreatment ECG for patients with risk factors for QTc prolongation and a follow-up ECG 2-4 weeks after initiation. In those patients with unknown risk for QTc prolongation, consider obtaining a pretreatment ECG. Obtain a follow-up ECG when methadone reaches 30-40mg/day, then again if it reaches 100mg/day and when new risk factors arise or s/sx suggestive arrhythmia for all patients. Consider obtaining yearly ECGs once a stable dose is reached.

Methadone Mortality and Overdose risk

The potential for all LA/ER opioids to influence mortality and risk for overdose underscores the importance of appropriate patient selection, dosing, and monitoring as well as supports the recommendation that LA/ER opioids should not be considered first-line agents for CNCP.[1] In an analysis of 319 unintentional overdoses that occurred in 'new opioid user' Veterans with CNCP, patients prescribed LA opioids had a significantly higher rate of overdose injury than those receiving equianalgesic doses of short-acting agents (HR 2.33, 95% CI 1.26-4.32).[70] Methadone accounted for only 18% of LA opioid use and was not identified as having a higher risk than other LA agents. Risk for overdose was particularly marked during the first 2 weeks following initiation of LA opioid treatment (HR 5.25; 1.88-14.72).[70]

The estimates of risk of methadone-related overdose deaths vary by region across the US, data sources (e.g., death certificates and medical examiner data versus administrative claims data) and health care organization. In 2012, the CDC published an analysis of 2009 data collected in 13 states indicating that the rate of opioid-related overdose deaths was disproportionately higher among patients receiving methadone for pain (type not specified) compared with rates for other major opioids.[71] Specifically, methadone accounted for 9.8% of the morphine milligram equivalents prescribed but was involved in 31.4% of opioid-related overdose deaths and 39.8% of single-drug opioid deaths (twice as many as any other opioid).[71] Similarly, a 2015 review of Tennessee Medicaid records from 1997 through 2009 indicated that the relative risk of out-of-hospital death in patients receiving methadone for CNCP was 46% greater compared to those receiving morphine SR and, of the study deaths that met the definition for opioid overdose death, the risk for patients receiving methadone was more than twice that of those receiving morphine SR.[72] Methadone did not significantly influence risk of sudden cardiac death.[72]

Other data challenge the view that methadone has a higher risk of opioid-related deaths than other LA opioids. A 2011 retrospective large administrative database cohort study of over 100,000 US Veteran patients with CNCP (but including patients with non-terminal malignancies or other serious illnesses) over a 7 year period showed that methadone had almost half the risk of opioid overdose death than long-acting morphine (hazard ratio [HR] = 0.56, 95% confidence interval [CI] = 0.51, 0.62).[73] Also, in a retrospective cohort study of Oregon Medicaid administrative data, there was no significant difference between methadone and LA morphine in mortality rates and a significantly lower rate of hospitalizations with methadone than LA morphine, despite methadone patients receiving a 3.3-fold higher morphine-equivalent dose than LA morphine patients.[74]

On July 8, 2016, the CDC published an update on US trends in methadone distribution for pain treatment, methadone diversion and overdose deaths; during 2002–2014, a strong positive association was noted between rates of methadone distribution for use in pain treatment and methadone diversion and overdose deaths.[75] Methadone overdose deaths peaked during 2005–2007 but declined in subsequent years; the 3,400 reported methadone overdose deaths in 2014 is the lowest number since 2003. Declines in overdose deaths coincide with actions aimed at reducing methadone use for pain, including a 2006 FDA warning regarding risk when used for pain, restrictions on distribution of 40mg tablets, and changes in professional practice guidelines/governmental regulations. The overall decrease in incidence of methadone overdose is encouraging; however, through 2014, the decline in overdose deaths among women has been more moderate and methadone overdose rates among persons aged ≥55 have continued to increase.

Patients with CNCP who take an ER/LA opioid and/or take an opioid dose ≥ 50 OME/day are likely candidates for provision of a naloxone rescue kit; other risk factors for overdose or serious opioid-related adverse events should be considered as part of an overall opioid risk mitigation strategy.

Patient education[56]

- Methadone must be taken only as directed. Never take extra doses without getting approval from your prescriber.
- Taking methadone as frequently as other opioids may produce a fatal overdose.
- Use other CNS depressants (especially benzodiazepines) with caution and only as directed by your health care provider.
- Methadone in combination with other opioids should only be used as prescribed by your health care provider.
- The use of illicit drugs and/or alcohol with methadone may be fatal.
- Pain relief builds gradually and usually takes 5-7 days to see the full effects of a particular dose.
- Tell all of your medical providers that you are taking methadone. Adding medications or changing dosing of other medications can affect methadone and should be coordinated with the methadone prescriber.
- Avoid activities requiring mental alertness or coordination (such as driving or using machinery) until the effects of methadone are realized, typically a week or longer.
- Rise slowly from a sitting/supine position, as methadone may cause dizziness.
- Methadone, like other opioids, can cause significant constipation. Take your prescribed laxative as directed.
- Report any of the following symptoms immediately and/or seek urgent/emergent care: dizziness or lightheadedness, irregular heartbeat (palpitations), falls or near falls, chest pain/pressure, shortness of breath.

- Avoid abrupt discontinuation of methadone without first consulting your health care provider.
- **Providers:** If there is concern about the social stigma associated with the use of methadone for treatment of opioid use disorder, provide assurance that methadone is also an accepted pain medication and that your patient is not an "addict" because they are taking methadone for pain control. Explain the difference between addiction and physical dependence. For more information on the definitions of addiction and physical dependence, see the Web-based educational program for VA employees entitled *Opioids in the Management of Acute and Chronic Pain*; available at: http://vaww.sites.lrn.va.gov/pain/opioids/ or reference.[76]

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