Methadone Dosing Recommendations for Treatment of Chronic Pain

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Summary

- Methadone is a safe and effective long-acting opioid analgesic that is useful in managing chronic pain.
- Although it has unique pharmacokinetic and pharmacodynamic properties, the general principles of dosing methadone are similar to those of other opioids.
- 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 is most easily titrated by using small initial doses or adjusting the initial dose according to the previous opioid dose.
- A number of methods are available for titrating methadone using conversion ratios, as detailed below. However, titration should be based on patient response and not solely based on equianalgesic dosing tables.
- **Methadone should be initiated by or in consultation with a practitioner who has the relevant knowledge.** If a practitioner or consultant with experience in using methadone for chronic pain is not available, then another long-duration opioid may be used until such consultation can be obtained.[a]

Background

Methadone should be used when a strong opioid is needed and the patient has not achieved adequate pain relief on escalating doses of controlled-release morphine or has experienced intolerable adverse effects on controlled-release morphine. Commonly, nonsteroidal anti-inflammatory drugs and adjuvant agents (e.g., tricyclic antidepressants) should be used in combination with methadone. Methadone's duration of effect is not dependent upon a specialized delivery system, as is the case with transdermal fentanyl or sustained release formulations of morphine or oxycodone. It is the only long-duration opioid available as an oral solution.

While methadone has gained increasing acceptance as an alternative to morphine for treatment of moderate to severe pain, a number of authors have cautioned clinicians about the complexities of dosing methadone or have suggested the drug be prescribed by practitioners with relevant experience in an adequately monitored setting.[1-7] Significant toxicity has occurred particularly when dosage increments were made too frequently, conversion doses were too high, or dosing intervals were too close.[5,8-10] Accruing experience, however, suggests that methadone can be safely used when initial doses are small, conversion ratios are adjusted to the previous opioid dose, and dosage is slowly titrated to patient response.[2,3,5,6,9,11-15] The general principles of dosing methadone are similar to those of other opioids.

The pharmacokinetic and pharmacodynamic properties of methadone are complex and incompletely documented.[16,17] Although methadone may have a long elimination half-life (range of mean/medians among studies: 3 to 128 h in healthy volunteers, opiate addicts, patients with chronic pain, and patients with acute pain),[18-31] the elimination half-life does not necessarily reflect duration of analgesia.[28,32] Patients may require dosing intervals of 6 hours to achieve adequate pain relief, although repeated oral administration of methadone for cancer pain may lead to progressively longer dosing intervals.[33,34] As a result of the dissociation between half-life and analgesic duration, tissue accumulation of methadone can occur. Patients need to be reassessed more frequently (e.g., every few days) when methadone is initiated and when the dose is increased. However, once a stable dosing is established, follow-up can be as clinically indicated. With a 3-day phased conversion from morphine to methadone, the analgesic effects have taken a median of 5 days (range: 4 to 13 days) to stabilize.[3]

It is important to note that the equianalgesic conversion ratios between methadone and other opioids are imprecise (Table 1).

Table 1 Points to consider about equianalgesic conversion ratios

A number of equianalgesic dosing tables underestimate the potency of methadone.[†]
Conversion ratios in many equianalgesic dosing tables do not apply to repeated doses of opioids.
The morphine- or hydromorphone-to-methadone conversion ratio increases (i.e., the potency of methadone increases) as the previous dose of morphine or hydromorphone increases.[‡]
Conversion ratios may not be bi-directional (i.e., the morphine-to-methadone conversion ratio may not be the same as the methadone-to-morphine ratio).[§]
There may be large interpatient variability in the equianalgesic conversion ratio; a single ratio may not be applicable to all patients.[§]
The use of high but ineffective doses of previous opioid may result in overestimation of the equivalent dose of methadone.
The relative analgesic potency ratio of oral to parenteral methadone is 2:1; however, confidence intervals are wide.[‖]

† Management of Cancer Pain, Clinical Practice Guidelines, AHCPR (1994)[35]; Cancer pain: a monograph on the management of cancer pain, Health & Welfare Canada (1984)[36]; Twycross (1990)[37]; Levy (1985)[38]

‡ The oral morphine to oral methadone conversion ratio may be unexpectedly much higher in patients who previously received very high doses of morphine.[2-4,39]

§ Bruera (1999)[40]

‖ Estimated ratio based on single-dose, double-blind, double-dummy, cross-over studies in patients with moderate to severe cancer pain.[1]

a For more information on identifying patients who should be referred to a pain specialist or pain clinic and on dosing methadone, 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/).

Certain drug interactions may also potentially affect methadone dosage requirements (Table 2).

Table 2 Potential clinically relevant drug interactions with methadone

Agents that may DECREASE methadone concentrations	Agents that may INCREASE methadone concentrations	Agents that may increase the adverse effects of methadone
Antiepileptics: carbamazepine, phenobarbital, phenytoin (no interaction with valproic acid and gabapentin)	*Antidepressants*: selective serotonin reuptake inhibitors (venlafaxine least likely to interact); amitriptyline	Benzodiazepines St. John's Wort
Antipsychotics: risperidone	*Antifungals*: fluconazole, ketoconazole	
Antiretrovirals: nevirapine, ritonavir		
Antitubercular: rifampin (no interaction with rifabutin)		

Sources: Davis (2001)[41]; Natural Medicines Comprehensive Database[42]; Plummer (1988)[30,43]

The present dosing recommendations are provided to offer guidance on dosing methadone in the treatment of patients with chronic noncancer pain (CNCP) or chronic cancer pain, particularly when converting from another opioid to methadone. If in doubt, a practitioner should consult a pain management specialist, clinical pharmacist, or another practitioner who has the relevant knowledge.[b] *The use of methadone for pain should be done in the context of an organized pain clinic or with assistance of local pain management experts, including health care providers or pharmacists, who have experience with methadone use. If such resources are not readily available, oxycodone CR or fentanyl would generally be the alternative long-acting opioid to morphine.*

Dosing Strategies

The best titration strategy has not been determined. Any methadone dosing strategy could be used for treating either CNCP or chronic cancer pain. The rapidity of conversion may be more important than type of pain in determining which method is useful in a given clinical situation. Therefore, the dosing strategies have been categorized by previous opioid exposure and rapidity of titration or conversion (Table 3 and Table 4). The dosing recommendations shown here represent a conservative approach to titrating methadone.

Table 3 Dosing recommendations for patients receiving codeine preparations or no previous opioids

Dosing strategy	Initial MET dose	Increments	Comments
Gradual titration (For CNCP and situations necessitating less frequent monitoring)[44]	2.5 mg q 8 h	2.5 mg q 8 h 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 mg q 6 or 8 h	2.5 mg q 6 or 8 h as often as every day over about 4 d	

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 4 Dosing recommendations for patients previously receiving other opioids: GRADUAL CONVERSION (for CNCP and patients monitored less frequently)

MOR-E (mg/d)	Calculated MET dose (mg /d)	Initial MET dose	Increment[†]	Example
< 200[‡]	15 mg	5 mg q 8 h	Increase by calculated MET dose every 5–7 d as needed.	90 mg/d MOR. Switch to MET 5 mg q 8 h.
200 – 500	~ 7% of MOR-E[§]	Calculated MET dose given in divided doses q 8 h	Increase by calculated MET dose every 5–7 d as needed.	300 mg/d MOR = 300 x 7% = 21 mg/d MET. Rounding to nearest tablet size, give 7.5 mg q 8 h (22.5 mg/d).
>500	~ 7% of MOR-E[§]	1/3rd of calculated MET dose given in divided doses q 8 h	Add 1/3rd of calculated MET dose every 5 d. Decrease previous opioid by 1/3rd every 5 d. (Complete conversion period = 15 days).	600 mg/d MOR = 600 x 7% = 42 mg/d MET 1/3rd of 42 mg/d = 14 mg/d or about 15 mg/d Give: MET 5 mg q 8 h + MOR 400 mg/d (in divided doses) x 5 d MET 10 mg q 8 h + MOR 200 mg/d (in divided doses) x 5 d MET 15 mg q 8 h + discontinue MOR

Source: The dosing recommendations for gradual conversion 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.{CPSO Task Force on CNMP, 2000 #2017}

All doses refer to oral administration.

CNCP = Chronic noncancer pain; HMO = Hydromorphone; MET = Methadone; MOR = Morphine; MOR-E = Morphine-equivalent; OXY = Oxycodone

† In patients with CNCP, look for a graded analgesic response to dosage increments; if absent, the patient may have opioid-nonresponsive pain.

‡ Previous MOR-E dose < 200 mg/d includes patients already on a major opioid analgesic like oxycodone with or without acetaminophen.

§ For patients with CNCP who have received repeated doses of > 200 mg/d MOR-E, calculate MET dose using the table below.

Drug	Oral dose	Drug/MOR	Example
Methadone (MET)	2 mg	7%	—
Morphine (MOR)	30 mg	100%	250 mg/d MOR = 250 x 2 /30 = 17 mg/d MET ~ 5 mg q 8 h MET
Hydromorphone (HMO)	8 mg	27%	60 mg/d HMO = 60 x 2 / 8 = 15 mg/d MET = 5 mg q 8 h MET
Oxycodone (OXY)	15 mg	50%	120 mg/d OXY = 120 x 2 /15 = 16 mg/d MET ~ 5 mg q 8 h MET

[b] See footnote "a" on page 1.

Table 5 Dosing recommendations for patients previously receiving other opioids: RAPID CONVERSION (for cancer pain and situations where frequent monitoring is possible)

MOR-E (mg/d)	MET-to-MOR-E Ratio (%)†	Initial MET Dose	Increment
< 200	10% – 30%	Calculated daily MET dose in divided doses q 8 h (up to a maximum of 50 mg q 8 h). For the most conservative approach, use 5% MET/MOR-E (or less with very high MOR-E doses) to calculate the initial MET dose irrespective of the previous MOR-E dose.	Two methods may be used: (1) *Phased conversion*. Replace 1/3 of MOR-E dose with the calculated equivalent dose of MET daily for 3 days. Example: 600 mg/d MOR = 300 x 7.5% = 45 mg/d MET. Day 1: MET 5 mg q 8 h + MOR 400 mg/d (in divided doses); Day 2: MET 10 mg q 8 h + MOR 200 mg/d (in divided doses); Day 3: MET 15 mg q 8 h + discontinue MOR. *Rapid ("stop-and-go") conversion*. Discontinue MOR-E and start MET on day 1.
200 – 500	10% – 20%		
500 – 1000	5% – 10%		
> 1000	5% or less		

Sources: The dosing strategy for faster conversion is based on a synthesis of the most recent versions of the more notable dosing strategies used in opioid-tolerant patients with mostly cancer-related pain.[2,3,5,11,12,45,46]

All doses refer to oral administration.

CNCP = Chronic noncancer pain; HMO = Hydromorphone; MET = Methadone; MOR = Morphine; MOR-E = Morphine-equivalent; OXY = Oxycodone

† Smaller MET-to-MOR-E conversion proportions (%) should be used the larger the previous MOR-E dose.

It is important to note that various dosing methods have been used (including a patient-controlled regimen[6,47]) and are still evolving. Two dosing strategies[2,11] have been prospectively studied, but no clinical trials comparing systematic dosing methods have been performed. A literature search (PubMed 1966 to 2003) identified only a case report and small case series that discussed methadone dosing during the treatment of CNCP.[48,49] The lack of prospective and comparative studies highlights the need to carefully individualize the dosing regimen of methadone, as is done with other opioids.

As a general rule, smaller methadone-to-morphine conversion proportions (%) should be used the larger the previous morphine-equivalent dose, remembering that precise conversions from another opioid to methadone are impossible. Disproportionately smaller methadone doses may be required with the larger morphine doses. However, it is important to remember that the equianalgesic conversion ratio is only one part of the process of properly dosing methadone and other opioids.

For breakthrough pain (BTP), a short-acting opioid preparation (such as acetaminophen with codeine, oxycodone with or without acetaminophen, or immediate-release morphine) may be used as necessary. Keep in mind that the 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 a patient with CNCP, they should be used sparingly.[44] Methadone has also been used (in doses 10% to 30% of the calculated daily methadone dose up to 3 to 8 doses per day as needed)[6,11,46,47]; however, the short-acting opioids are generally preferred to avoid drug accumulation.

Special patient populations

Patients 65 years and older may have a decreased clearance of methadone.[30] In patients with stable chronic liver disease, no dosage adjustments appear to be necessary.[50] Methadone and its metabolites do not accumulate in patients with renal failure.[51] The two prospective studies on methadone dosing strategies excluded patients with liver or renal disease.[2,11] Use extra caution when dosing any opioid in all of these patient populations.[c]

General principles for dosing methadone

- Use methadone for treatment of patients with chronic pain.
- Individualize doses and slowly titrate to response.
- An acceptable balance between analgesic effects and tolerable and manageable adverse effects generally indicates a favorable response to pain medication. In the treatment of CNCP, the main goals are to improve the patient's ability to function and to increase the patient's quality of life.
- Once the daily dosage for adequate analgesia has been determined, a trial of longer dosing intervals may be attempted. Many patients can take the same total daily dose divided every 8 hours. Intervals of 12 hours may be attempted when patients are stable at 8-hour intervals.
- 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 the dosing strategy) and decrease subsequent doses and/or make dosage increments less frequently. Do not increase the dose of methadone.
- Short-acting opioids may be used for treatment of BTP, at least initially and when pain is severe and escalating.
- 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.[44]
- Reassess patients at appropriate intervals; at least once weekly during titration and at least once monthly after the daily dosage is stabilized.
- 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.

[c] For patients with liver or renal disease, special consideration can be given locally to use an alternative opioid at the discretion of the care team or provider.

Patient education

- Explain to patients that the initial dose will often be inadequate for pain relief. BTP medication should be used during the dose titration period. A pain and pain medicine diary should be kept.
- Reassure patients that the dose will be titrated to achieve adequate analgesia.
- Advise patients that the effects of methadone will increase over at least one week following a dosage increment. Pain relief during the last few days of that week will be greater than at the first few days of the week.
- Remind patients about the need for and the frequency of monitoring during the titration and maintenance periods. Provide patients with instructions on what to do if they develop increasing or intolerable adverse effects.
- Advise patients to avoid abrupt discontinuation of their opioid medication without first consulting their physician. Educate patients about withdrawal symptoms.
- Since patients may become concerned about the social stigma associated with the use of methadone for treatment of opioid dependence, reassure them that methadone is also an accepted pain medication and that they are not "addicts" because they are taking methadone for pain control. Explain the difference between addiction and dependence.[d]

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[d] For more information on the definitions of addiction and 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 [52].

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