

Massachusetts General Hospital  
Clinical Practice Recommendations  
Methadone for Pain Management

**BACKGROUND:**

1. Methadone is increasingly used as a second-line treatment for managing pain. A patient with an allergy to other opioids may not be allergic to methadone, because it is chemically different.
2. In addition to broad spectrum opioid receptor activity, methadone affects other receptors that may explain its analgesic efficacy and relatively lower dose requirement for refractory pain.
3. Knowledge of methadone's unique pharmacology (bioavailability, long half-life, and incomplete cross-tolerance) is important to consider when switching patients from other opioids to methadone.

**CRITICAL ELEMENTS:**

1. Initiation of methadone therapy for pain is restricted to physicians in the Pain or Palliative Care Services because of unique safety and efficacy considerations.
2. Dosing and administration errors are well documented and potentially serious. For these reasons, safety precautions and vigilance are needed. All professionals (doctors, nurses, and pharmacists) need to check the order carefully whenever methadone is prescribed, dispensed and administered at initiation of therapy; and whenever doses, medication source, or pump settings are changed.
3. Methadone can cause serious sedation, respiratory depression and even death. Accumulation occurs before steady-state (which may take several days) is reached, requiring close monitoring.
4. The risk of QT prolongation or Torsade de Pointes with IV methadone is low, but more common with doses > 200mg/day; use of QT interval-prolonging drugs; or conduction abnormality history. ECG monitoring is recommended at baseline and periodically in at-risk patients.
5. Methadone's analgesic effect may begin within 20 minutes of an IV administration, with analgesia lasting 4-8 hours. Respiratory depression may occur even after analgesic effects have worn off.
6. For both intermittent dosing and continuous infusions, the greatest risk of respiratory depression may not become apparent for several days, requiring supervision during this period.
7. With Patient Controlled Analgesia (PCA), only the patient activates the patient-controlled pendant and orders should be rewritten every 72 hours.

**INDICATION:** Management of moderate to severe pain

**PATIENT MONITORING:**

- 1) Vital signs and sedation checks
  - a. Done at initiation of IV therapy and repeated at 30 minutes, and 1 hour,
  - b. Checked every 4 hours when stable on steady doses
  - c. After each dose increase, VS are rechecked in 1 hour.
- 2) Verify IV patency & pump settings against the order when therapy is initiated; new bags are hung; doses are changed; at change of shift or transfer; and as indicated by changes in clinical condition.
- 3) ECG (12 lead) evaluation is done as ordered.
- 4) The nurse monitors reportable conditions and teaches patients/family to recognize/report them:
  - a. CNS effects: dysphoria, insomnia, agitation, disorientation, drowsiness
  - b. Dysrhythmias, palpitations or chest pain. Prolongation of QT interval on ECG
  - c. Pruritus, or rash

- d. GI upset: anorexia, nausea, vomiting, constipation (implement a bowel regimen)
- e. GU: urinary retention, antidiuretic effect, impotence, lower libido
- f. Other: weakness, myoclonus, visual disturbances, breathing difficulty

### **PHARMACOKINETICS AND DYNAMICS:**

1. Methadone has excellent bioavailability (80%) when administered orally.
2. Methadone is highly lipophilic, which leads to drug accumulation in body tissues.
3. Analgesia onset is 20 minutes with intravenous, and one hour with oral administration.
4. The half-life of methadone is variable and biphasic at 14 hours (primary) and 55 (secondary) hours.
5. Approximately 90% is protein bound to the  $\alpha_1$  acid glycoprotein
6. Methadone is metabolized (N-demethylation process) by the liver without active/toxic metabolites.
7. The Cytochrome P450 metabolic pathways are involved, including CYP3A4, CYP2B6, CYP2C19 and CYP2D6. See Table 1 of drug interactions.
8. Excretion is primarily (90%) fecal with some pH-dependant renal excretion (10%)

### **CONTRAINDICATIONS:** Methadone is contraindicated in patients with:

- Hypersensitivity to methadone hydrochloride
- Respiratory depression, acute bronchial asthma or hypercarbia
- Paralytic ileus

### **DOSAGE AND ADMINISTRATION:**

1. Methadone can be administered by a variety of routes of administration, including: oral, intravenous, subcutaneous, and intramuscular.
2. Responses to methadone are highly individualized, thus doses need to be tailored to responses
  - A. Opioid-Naïve: Methadone is generally not used in opioid-naïve patients but may be indicated in certain circumstances. Suggested initial dosing is as follows:
    - 5mg PO or 2.5 - 5mg IV every 8 hours, slowly titrated to effect; more frequent administration may be required during methadone initiation.
    - Methadone is titrated more slowly than other opioids used to control pain.
    - Breakthrough pain should be managed with a short-acting opioid and made available every 3 or 4 hours prn; methadone is occasionally used for breakthrough pain at the discretion of a prescriber familiar with the drug.
  - B. Opioid-Tolerant: Converting to methadone from another opioid involves a multi-step process (see Appendix A for one method). Up to 10mg IV push may be administered to an opioid tolerant patient, with higher doses administered using an infusion pump.
  - C. Weight-based dosing is used for children under 40kg.
  - D. If converting from oral methadone to IV methadone a 2:1 ratio is used.
3. A 25-50% dose reduction is indicated for patients with renal impairment ( $Cl_{cr} < 10$  mL/min)
4. Patients with mild or moderate hepatic impairment can be treated with methadone, however, it should be avoided in severe liver disease.

**Available Strengths/Dosage forms at MGH:**

Tablets: 5mg, 10mg

Oral Solution: 1mg/ml (5ml container), 10mg/ml Concentrated Solution

IV: 1mg/ml (5ml vial); 1mg/ml (50ml bag), 10mg/ml (50ml bag)

10mg/ml (20ml vial – pharmacy use only – to provide ordered bolus doses in 100mL bag)

**Preparation of IV Methadone Admixtures:****A. Outpatient Preparation: Yawkey 8 and Cox 1 areas**

Boluses are individually prepared by pharmacy

If continuous infusions are required, a 5-hour mix is typically prepared

**B. Inpatient Preparation:** Restricted: Pain Service or Palliative Care Ordering Required

Route	Dose	Volume	Administration
IV Bolus	Per MD	Add to 100ml NS bag pharmacy prepared	Entire bag infused over 15 minutes
IV Continuous Infusion	Per MD Order using a standard concentration	50mL bag (inpatient) 250 mL bag (outpatient)	Hourly rate (in mg/hr) per MD order using an infusion pump
IV PCA (where PCA is available)	Per MD Order using an available dosage form (above)	50mL bag for loading to PCA pump	Per order (may include) <ul style="list-style-type: none"> <li>• PCA dose range</li> <li>• Starting dose</li> <li>• Lockout time</li> <li>• Continuous dose rate</li> <li>• 1 hour limit</li> <li>• Loading dose</li> </ul>
IV Push	<p>Opioid Naïve Patients: Nurses may IVP doses up to 5 mg over 2 minutes supplied in 1mg/1mL (5mL vial)</p> <p>Opioid Tolerant Patients: Nurses may IVP doses up to 10 mg over 2 minutes supplied in 1mg/1mL (5 mL vials)</p> <p>Doses &gt; 10 mg will be mixed in 100 mL bag and delivered via an infusion device</p>		

**PRECAUTIONS:**

1. Rapid dose escalation of methadone in the first 24-48 hours of initiation has resulted in over-sedation and respiratory depression due to accumulation of methadone. Increasing the continuous infusion rate of methadone during this period is not recommended.
2. Respiratory effects of methadone last longer than analgesic effects. Slow titration is recommended.
3. Methadone has been associated with QT prolongation. Use with caution in patients who are at risk for QT prolongation. Use with caution in patients receiving medications known to prolong the QT interval as well as patients with a history of conduction abnormalities. Electrolyte abnormalities may predispose any patient to QT interval abnormalities.

**ADVERSE EFFECTS:**

**Common:** lightheadedness, dizziness, sedation, nausea, vomiting, sweating

**Serious, rare effects:** QT prolongation, Torsade de Pointes

**ADVERSE EFFECTS BY SYSTEM:**

**Body as a whole:** edema, headache

**Cardiovascular:** bradycardia, peripheral vasodilation, cardiac arrest, syncope, faintness, orthostatic hypotension, tachycardia, T wave inversion, ECG abnormalities, ventricular fibrillation/tachycardia

**CNS:** euphoria, dysphoria, insomnia, agitation, disorientation, seizures, hallucinations, visual disturbances

**Dermatologic:** pruritus, urticaria, rash

**Endocrine/Metabolic:** hypokalemia, hypomagnesemia, weight gain

**GI:** constipation, anorexia, stomach cramps, xerostomia, biliary tract spasm, glossitis

**GU:** urinary retention hesitancy, antidiuretic effect, impotence

**Neuromuscular/skeletal:** weakness, myoclonus

**Respiratory:** pulmonary edema, depression

**DRUG INTERACTIONS:**

Methadone is a major substrate of CYP3A4 and is subject to drug interactions involving inducers or inhibitors of this enzyme pathway. Methadone is also a moderate inhibitor of CYP2D6 and may increase serum concentrations of drugs that are metabolized through this pathway. See Appendix B

**APPENDIX A: Sample: Conversion to IV methadone from another opioid**

CJ is a 48 year old male with metastatic esophageal cancer. He has been on escalating doses of oxycodone extended-release (ER) for 6 months with occasional pain control that is short-lived. His current dose is 280mg PO q8hrs. He also takes oxycodone immediate-release (IR) 5mg PO q4hrs prn. In the last 24 hours, CJ has taken 4 prn doses. Today is reporting 8 out of 10 pain. The attending would like to discontinue oxycodone ER and start methadone.

Calculation to determine an equivalent amount of oxycodone based on actual oral morphine use

Step 1: Determine the total current 24-hour opioid requirement of current medication:

Extended release (Oxycodone-ER):  $280 \text{ mg} \times 3 = 840 \text{ mg}/24 \text{ hrs}$   
 Short-acting (Oxycodone -IR):  $5 \text{ mg} \times 4 = +20 \text{ mg}/24 \text{ hrs}$   
 $840 + 20 = 860_{\text{mg}} \text{ oxycodone}/\text{day}$

Table 2		
Opioid Equianalgesic Doses		
Drug	PO/PR (mg)	SQ/IV (mg)
Morphine	30	10
Oxycodone	20	--
Hydrocodone	20	--
Hydromorphone	7.5	1.5
Fentanyl	N/a	0.1 (100 mcg)

Note: 25 mcg fentanyl patch  $\approx$  50 mg oral morphine/24 hrs

Step 2: Set up an equianalgesic equation See Table 2:

$$\frac{\text{Equianalgesic Table dose of current drug}}{\text{Equianalgesic Table dose of new drug}} = \frac{24^{\circ} \text{ dose current drug}}{X (24^{\circ} \text{ dose new drug})}$$

$$\frac{20\text{mg oral oxycodone}}{30\text{mg oral morphine}} = \frac{860 \text{ mg}/\text{day oxycodone}}{X\text{mg}/\text{day oral morphine}}$$

Step 3: Solve for X

$$\frac{20\text{mg oral oxycodone}}{30\text{mg oral morphine}} = \frac{860\text{mg}/\text{day oxycodone}}{X\text{mg}/\text{day oral morphine}}$$

- a)  $860 \times 30 = 20X$
- b)  $25,800/20 = X$
- c)  $1290\text{mg} = X$

Thus CJ requires 1,290mg of oral morphine equivalents per day to control his cancer pain

Step 4: Calculate starting dose of oral methadone at over 1,000mg of oral morphine per day requirement, a 20:1 ratio is used (See Table 3).  $1,290\text{mg}/20 = 64.5\text{mg}$  of oral methadone.

**Table 3: Equianalgesic Conversion Oral Morphine to Oral Methadone**

Calculated 24 hour oral morphine requirement (mg/day)	Equianalgesic Ratio Oral Morphine to Oral Methadone	Example: morphine / methadone (oral mg/day)
<90	4:1	80mg morphine / 20mg methadone
90-300	8:1	320mg morphine / 40mg methadone
>300	12:1	600mg morphine / 50mg methadone

Adopted from American Pain Society (2008) Principles of Analgesic Use in the Treatment of Acute and Cancer Pain (6<sup>th</sup> Ed)

\*Step 5: Decrease starting dose by 25% to account for incomplete cross-tolerance.  
 $64.5\text{mg} \times 0.75 = 48.4\text{mg}$  of oral methadone per day

Step 6: Given greater bioavailability by the Intravenous route, decrease starting dose by 50%.  
 $48.4\text{mg} \times 0.5 = 24\text{mg}$  of IV methadone per day

Step 7: Determine starting dose by considering desired pattern of administration

24mg/day = continuous IV drip at rate of 1mg/hour

or

6mg IV Q6H

Step 8: Add *PRN* rescue dosing 10-20% of daily opioid requirement available every 2 or 3 hours for short-acting opioids. If methadone is used for breakthrough pain, dose every 4 or 6 hours.

Given the prudent approach to not adjusting continuous infusions more than once a day and slowly titrating methadone doses until steady state is reached (~ one week), the clinician can continue oxycodone for breakthrough pain during this transition.

Step 9: Monitor patient closely for balance of analgesia, function, and side effects. Adjust doses slowly and cautiously based on clinical effect.

**\*NOTE:** The American Pain Society (2008) “Analgesic Guidelines” recommend reducing the dose further after calculating the equivalent dose. Avonrinde (2000) uses a different conversion chart (with ratios up to 20:1) with no further reduction in dose needed. In fact, Avonrinde recommends an additional 25-50% loading dose be used for the first 2 days to allow saturation of body tissues unless frail, elderly, or concurrent sedating drugs are being used.

## APPENDIX B: Methadone Drug Interactions Chart\*

Significance, Key to Description, and Onset ( r = rapid; d = delayed )

■■■ Use Contraindicated ■■■		Major Significance		Moderate significance	
	Key/ onset		Key/onset		Key/ onset
cisapride	5	alcohol	2, 7 / r	abacavir	1
mesoridazine	5,7	amiodarone	5	darunavir	8
naltrexone	6,8 / r	amprenavir	1,8 / d	delavirdine	2, 8 / d
pimozide	5	arsenic trioxide	5	desipramine	5, 7 ,8 / d
ranolazine	5	buprenorphine	6, 8 / d	didanosine	4 / r
rasagiline	8	butorphanol	6, 8 / d	efavirenz	1 / d
selegiline	8 / r	chlorpromazine	7,8	erythromycin	2
thioridazine	5,7	dofetilide	5	etravirine	8
ziprasidone	5,7	droperidol	5 ,7	fluconazole	2
		fluphenazine	7, 8	fluoxetine	2, 8
		fosamprenavir	1 / d	fluvoxamine	2,8 / d
		ibutilide	5	isocarboxazid	8
		levofloxacin	5	ketoconazole	2
		nalbuphine	6,8 / d	methohexital	7, 8 / r
		nefazodone	2,7	moclobemide	8
		nilotinib	5	nelfinavir	1,8 / d
		paliperidone	5,7	nevirapine	1,8 / d
		pentazocine	8 / d	pargyline	8
		perphenazine	7,8	phenezazine	8
		prochlorperazine	7,8	phenobarbital	1, 7 / d
<b>Minor Significance</b>		quinidine	5	rifampin	1 / d
	Key/ onset	quinine	5	risperidone	7, 8 / d
ammonium chloride	8 / d	sotolol	5	ritonavir	1 / d
carbamazepine	1 / d	sunitinib	5	saquinavir	1
fosphenytoin	1,8 / d	telithromycin	5	sertraline	2,8
phenytoin	1,8 / d	thiethylperazine	7,8	stavudine	4 / r
		trifluoperazine	7,8	St. John's wort	1,8 / d
		vardenafil	5	tipranavir	1
		voriconazole	2	tranlycypromine	8
				zidovudine	3 / d

### Key to Description of Interactions

# 1 : May decrease methadone levels; potential for increased pain and/or methadone withdrawal

# 2 : May increase methadone levels; may result in oversedation and respiratory depression

# 3 : Decreases clearance of zidovudine; potential for increased zidovudine toxicity

# 4 : Decreased absorption of stavudine and didanosine; potential for reduced effect of these drugs

# 5 : Additive Q-T segment prolongation when combined; potential for serious, even fatal, cardiac arrhythmias

# 6 : Methadone should not typically be used in combination with narcotic antagonists or partial antagonists.

# 7 : Methadone used in combination with other CNS depressant medications can cause increased CNS depression

# 8 : Consult Micromedex or LexiComp for additional information r=Rapid onset interaction d : Delayed onset interaction

\* This table is based on the best information available May 2008, consult other sources for the most up to date information

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