



## Prescribing Methadone for Pain Management in End-of-Life Care

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Methadone hydrochloride is an effective, inexpensive, and relatively safe opioid to use in the treatment of patients with chronic pain. It is especially effective in management of pain during the final stages of life, as it is the only long-acting analgesic available in liquid form. However, because methadone has a long half-life, individual wide variations, and potential for accumulation and overdose, physicians must judiciously and conscientiously prescribe it. Also, they should closely monitor patients during the titration phase and educate them with regard to basic pharmacologic properties and potential side effects. A plan to start at low doses and proceed slowly is applicable to methadone.

Chronic pain is one of the most common conditions for which people seek medical treatment; it affects more than 85 million Americans.<sup>1</sup> In end-of-life care, in which the primary focus is the reduction or elimination of suffering, a significant number of patients still suffer with uncontrolled pain. In recent years, healthcare consumers have become more sophisticated, demanding better pain control. Therefore, physicians need to be familiar and competent with the various treatment options and pharmacologic management of their patients with chronic pain.

Although the primary responsibility of physicians is to nurture the physical

and psychological well-being of their patients, it is also important that they serve as stewards of financial resources. In the past several years, there has been resurgence in the understanding of the pharmacologic and pharmacokinetic properties of methadone hydrochloride. This resurgence, coupled with methadone's low cost, has led to increased use of this agent in the treatment of chronic pain.

Methadone is a synthetic opioid agonist developed in the late 1940s. Historically, it has been used in the treatment of patients with narcotic addiction and heroin maintenance since the 1960s. Although substantial information exists regarding such use of methadone, only limited data are available with respect to pain management. It is only within

the past decade that there has been a renewed focus on its use in the treatment of patients with chronic pain.

Initial interest in methadone for pain management emerged in the care of terminally ill patients with cancer, but methadone recently has been gaining recognition in management of nonmalignant pain. Methadone is achieving greater acceptance in end-of-life care because of its unique characteristic as the sole long-acting opioid in liquid form. Its wide spectrum of absorption and formulations allows administration using every route available: oral, sublingual, rectal, subcutaneous, intramuscular, intravenous, epidural, intrathecal, and percutaneous endoscopic gastrostomy (PEG) tube.

### Formulations

Methadone hydrochloride is available in the United States as Dolophine or Methadose in multiple formulations, including 5-mg, 10-mg, and 40-mg scored tablets; solution in concentrations of 5 mg/5 mL, 10 mg/5 mL, and 10 mg/mL for oral administration, and a 10-mg/mL solution for parenteral administration.

### Pharmacokinetics

Methadone is a highly lipophilic drug that is rapidly absorbed with extensive tissue distribution.<sup>2</sup> Unlike morphine sulfate, methadone has no active metabolites and hepatic metabolism has no significant effect on methadone concentrations, clearance, or clinical disposition.<sup>3</sup> It is predominantly excreted in the feces; however, acidification of the urine will increase renal excretion. It has a prolonged and variable elimination phase with a plasma half-life that ranges between 4.2 hours and 190.0 hours, depending on the literature that is reviewed.<sup>2,4-6</sup>

The mean plasma half-life of methadone is probably 15 to 60 hours,<sup>4</sup> though even this range is extremely variable and dependent on single versus multiple dosing, individual adipose stores, and protein binding. This wide

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## Checklist

### ■ Phenanthrene Derivatives

- Codeine
- Hydrocodone
- Oxycodone
- Morphine sulfate
- Hydromorphone hydrochloride

### ■ Phenylpiperidine Derivatives

- Meperidine hydrochloride
- Fentanyl

### ■ Diphenylheptane Derivatives

- Methadone hydrochloride
- Propoxyphene

**Figure 1.** Opioid family categories. (Source: Killian K, ed. Drug Facts and Comparisons. 54th ed. St Louis, Mo: Facts and Comparisons; 2000:784-797.)

variation in half-life contributes to methadone's potential for toxic accumulation and has created difficulty with appropriately and easily dosing this medication.

Methadone has a rapid onset of action, with analgesic effects occurring within 30 to 60 minutes and an analgesic peak between 2.5 and 4.0 hours. Its oral bioavailability, though variable, generally exceeds 80%. It binds with mu, delta and to a lesser extent kappa opioid receptor sites. Figure 1<sup>7</sup> categorizes the opioid family.

### Drug Interaction

Cytochrome P450 is the main isoenzyme involved in methadone biotransformation.<sup>2</sup> Physicians must be sensitive to co-administration of other drugs that could result in either an increase or a reduction of methadone levels. Table 1<sup>2</sup> reflects examples of some of those medications.

### Clinical Advantages

Although initially used in cancer patients, methadone is being increasingly used in the end-of-life care setting for patients with nonmalignant pain syndromes. As the only long-acting opioid liquid formulation, methadone provides an attrac-

Decrease Level	Increase Level
<b>Antibiotics</b> Rifampin	Cimetidine Ciprofloxacin Fluconazole Fluoxetine Ketoconazole Macrolide antibiotics Nifedipine Sertraline hydrochloride Tricyclic antidepressants Zidovudine
<b>Anticonvulsants</b> Phenytoin Phenobarbital Carbamazepine	
<b>Antipsychotics</b> Risperidone	
<b>Antiretrovirals</b> Ritonavir Nevirapine	

**Source:** Ripamonti C, Bianchi M. The use of methadone for cancer pain. *Hematol Oncol Clin North Am.* 2002;16:543-555.

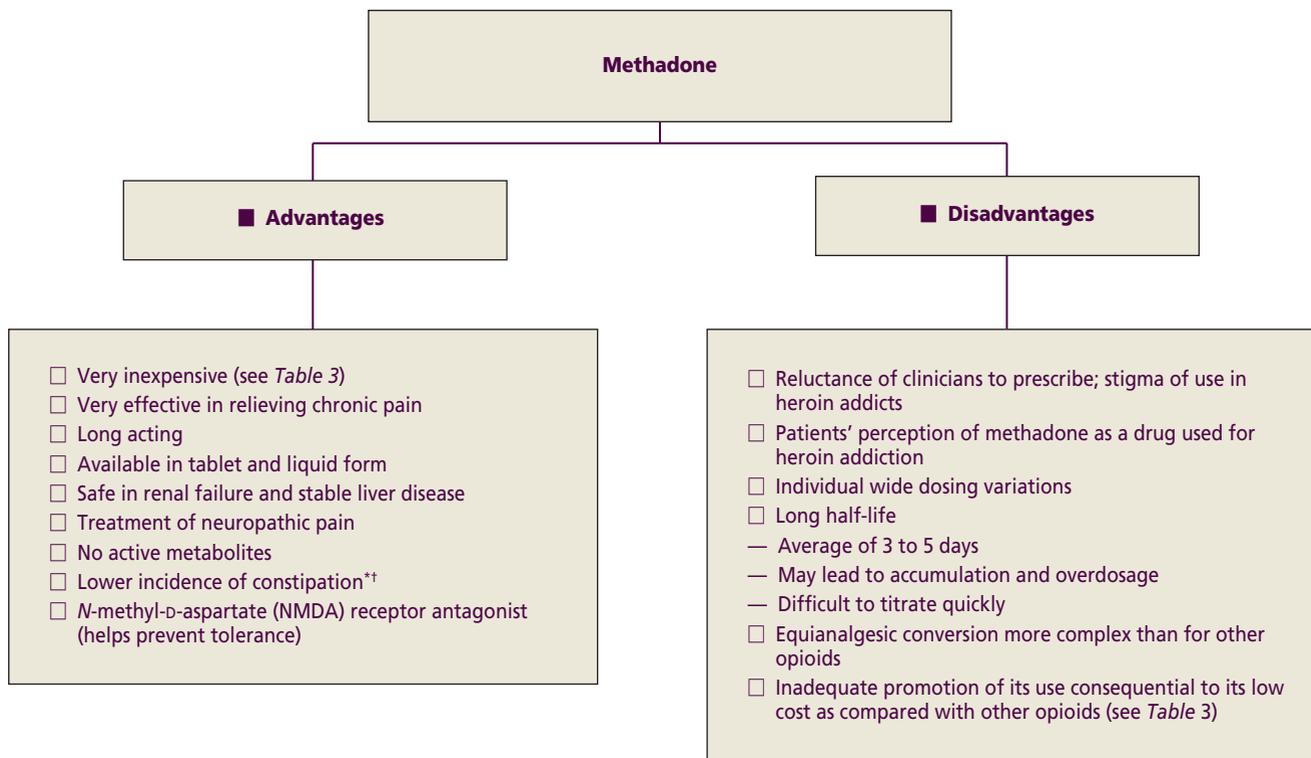
Morphine Sulfate	Ratio	Methadone Hydrochloride
≤100 mg	3:1	?? mg–33 mg
101 mg–300 mg	5:1	20 mg–60 mg
301 mg–600 mg	10:1	30 mg–60 mg
601 mg–800 mg	12:1	50 mg–67 mg
801 mg–1000 mg	15:1	53 mg–67 mg
≥1000 mg	20:1	50 mg–__ mg

**Source:** Gazelle G, Fine P. Fast Facts and Concepts #075. Methadone for the treatment of pain. September 2002. End-of-Life Physician Education Resource Center. Available at: <http://www.eperc.mcw.edu>. Accessed January 15, 2005.

tive alternative to the expensive transdermal fentanyl patch in patients with debilitating states of advanced dementia, in patients with arthritis, and in deconditioned bedridden individuals with adult failure to thrive who have generalized pain or allodynia and when patients can no longer swallow pills. Methadone's high bioavailability and long duration of action with rectal administration make it a potential alternative to intravenous administration.<sup>7</sup>

Whereas methadone and fentanyl

have been shown to be safe in patients with renal failure,<sup>3</sup> morphine and codeine with their active metabolites should be avoided and hydromorphone and oxycodone should be used with caution. An additional advantage of methadone is its property as an N-methyl-D-aspartate (NMDA) receptor antagonist. This property contributes to a reduced propensity to develop opioid tolerance as compared with morphine and a greater efficacy in treating patients with neuropathic pain.<sup>2,3,5</sup> Figure 2 summarizes the advan-



**Figure 2.** Advantages and disadvantages associated with the use of methadone. (\*Ripamonti C, Bianchi M. The use of methadone for cancer pain. *Hematol Oncol Clin North Am.* 2002;16:543-555. †Bruera E, Sweeney C. Methadone use in cancer patients with pain: a review. *J Palliat Med.* 2002;(1):127-138.)

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### Prescribing Methadone

Equianalgesic dosing of methadone is more complex than it is for other opioids. Unlike morphine, methadone exhibits wide variations in half-life among patients and must be cautiously prescribed, especially in individuals currently medicated with an opioid.

There are several approaches to prescribing methadone. In end-of-life care where some patients have noncancer pain syndromes and debilitated elderly have moderate pain, a reasonable approach is to start at 5 mg every 12 hours. Additional increases are determined based on the frequency and amount of short-acting opioid used for breakthrough or incidental pain and titrated accordingly every 3 to 5 days. The following examples demonstrate some of the established protocols<sup>8</sup> for both initiating and converting to methadone.

### New Start: Opioid-Naïve Patients

This is the easiest method for initiating treatment with methadone in opioid-naïve patients:

- Start methadone 5 mg every 6 to 12 hours.
- Titrate every 3 to 5 days until adequate analgesia is achieved.
- When steady state is achieved, switch to every 8- to 12-hour dosing schedule.
- Use methadone or a short-acting opioid as needed for breakthrough or incidental pain. Provide 10% to 15% of the total 24-hour dose every 2 hours as needed.

### Conversion From Morphine to Methadone

Table 2<sup>8</sup> provides the conversion ratio of oral morphine to methadone.

- Start dosing every 6 hours for four to six doses; then, decrease frequency to every 8 to 12 hours.
- Use an immediate-release opioid as rescue dosing.

### Switching From Another Opioid to Methadone

The process of switching from another opioid to methadone, especially when high doses are being used, is much more complex. Several conversion protocols are available.<sup>8-10</sup> One example follows:

- Discontinue current opioid.
- Start methadone at a fixed oral dose every 3 hours as needed: Administer a fixed dose of methadone that equals 10% of prior daily oral morphine sulfate equivalent with a maximum dose of 30 mg.<sup>9,10</sup>
- **Example**—If prior daily opioid dose equals 150 mg of oral morphine sulfate equivalent per day; then, use 15 mg of methadone hydrochloride every 3 hours as needed.

(Note: This is not a 1:10 ratio, unless only one dose is given in 24 hours: 1:10 ratio would be 15 mg/d, not 15 mg per dose.)

On day 6, calculate total amount of methadone taken during previous 48 hours and convert to twice-daily methadone dose. If the patient actually took the 15 mg dose every 3 hours on days 4 and 5, then the correct dosing would be 60 g every 12 hours.

- **Example**—Patient is taking 600 mg of oral morphine sulfate equivalent per day. Because the oral morphine equiva-

**Table 3**  
**Monthly Cost of Equivalent Medication Dose: Methadone Versus Other Opioids**

Medication	Strength	Dosing Interval (h)	Cost (Average Wholesale Price*)
■ Fentanyl transdermal system (Duragesic)	100 µg/h	72	\$570
■ Morphine sulfate extended-release capsules (Avinza)	210 mg	24	\$516
■ Oxycodone hydrochloride controlled-release tablets (OxyContin)	80 mg	12	\$589
■ Morphine sulfate controlled-release tablets (MS Contin)	100 mg	12	\$328
■ Methadone hydrochloride (Methadose)	40 mg	12	\$ 17

\*Source: Fleming T, ed. 2004 Drug Topic Red Book. 108th ed. Montvale, NJ: Thomson Healthcare; 2004.

## Resources

### BOOKS

- **Drug Information Handbook.** 13th ed. Hudson, Ohio: Lexi-Comp Inc; 2005
- **Goodman & Gilman's The Pharmacological Basis of Therapeutics.** 10th ed. New York, NY: McGraw Hill; 2002

### WEB SITES

- **American Pain Foundation**  
<http://www.painfoundation.org>
- **American Association for Cancer Pain Initiative**  
<http://www.aacpi.org>
- **American Chronic Pain Association**  
<http://www.theacpa.org>
- **Partners Against Pain**  
<http://www.partnersagainstpain.org>
- **American Academy of Pain Medicine**

**Figure 3.** Print and Web site resources.

lent is greater than 300 mg/d, use 30 mg of methadone hydrochloride as initial fixed dose and give 30 mg of methadone hydrochloride every 3 hours as needed. If patient has taken eight doses of 30 mg over 2 days on days 4 and 5, for a total of 240 mg in 48 hours, or 120 mg of oral methadone hydrochloride per day, then, on day 6, adjust methadone dose to 40 mg taken orally every 8 hours or 60 mg every 12 hours.<sup>9,10</sup>

Table 3 provides a cost comparison of methadone with equivalent medication doses of other opioids.<sup>11</sup> Figure 3 provides a list of additional print and Web site resources.

### Comment

Methadone is gaining recognition in the arsenal of pain management. With knowledge and initial cautious titration, physicians can readily manage and consider methadone with the other extended-release opioids of morphine, oxycodone, hydromorphone, and fentanyl. Methadone's efficacy, long-acting liquid formulations, multiple routes of administration, and low cost make it a noteworthy contender in the treatment of patients with chronic pain.

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