Chronic pain is one of the most common conditions for which people seek medical treatment; it affects more than 85 million Americans. 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.

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

John F. Manfredonia, DO

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 overdosage, 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.

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. Unlike morphine sulfate, methadone has no active metabolites and hepatic metabolism has no significant effect on methadone concentrations, clearance, or clinical disposition. 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.

The mean plasma half-life of methadone is probably 15 to 60 hours, though even this range is extremely variable and dependent on single versus multiple dosing, individual adipose stores, and protein binding. This wide range of half-lives is due to the large interpatient variability in the disposition of methadone hydrochloride.
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.

**Drug Interaction**

Cytochrome P450 is the main isoenzyme involved in methadone biotransformation. Physicians must be sensitive to coadministration of other drugs that could result in either an increase or a reduction of methadone levels. Table 1 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 attractive 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.

Whereas methadone and fentanyl have been shown to be safe in patients with renal failure, 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. Figure 2 summarizes the advan-

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**Table 1**

<table>
<thead>
<tr>
<th>Decrease Level</th>
<th>Increase Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td></td>
</tr>
<tr>
<td>Ketoconazole</td>
<td></td>
</tr>
<tr>
<td>Macrolide antibiotics</td>
<td></td>
</tr>
<tr>
<td>Nifedipine</td>
<td></td>
</tr>
<tr>
<td>Sertraline hydrochloride</td>
<td></td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td></td>
</tr>
<tr>
<td>Zidovudine</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2**

<table>
<thead>
<tr>
<th>Morphine Sulfate</th>
<th>Ratio</th>
<th>Methadone Hydrochloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 100 mg</td>
<td>3:1</td>
<td>22 mg–33 mg</td>
</tr>
<tr>
<td>101 mg–300 mg</td>
<td>5:1</td>
<td>20 mg–60 mg</td>
</tr>
<tr>
<td>301 mg–600 mg</td>
<td>10:1</td>
<td>30 mg–60 mg</td>
</tr>
<tr>
<td>601 mg–800 mg</td>
<td>12:1</td>
<td>50 mg–67 mg</td>
</tr>
<tr>
<td>801 mg–1000 mg</td>
<td>15:1</td>
<td>53 mg–67 mg</td>
</tr>
<tr>
<td>≥ 1000 mg</td>
<td>20:1</td>
<td>50 mg–__ mg</td>
</tr>
</tbody>
</table>


Advantages

- Very inexpensive (see Table 3)
- Very effective in relieving chronic pain
- Long acting
- Available in tablet and liquid form
- Safe in renal failure and stable liver disease
- Treatment of neuropathic pain
- No active metabolites
- Lower incidence of constipation†
- N-methyl-D-aspartate (NMDA) receptor antagonist (helps prevent tolerance)

Disadvantages

- Reluctance of clinicians to prescribe; stigma of use in heroin addicts
- Patients’ perception of methadone as a drug used for heroin addiction
- Individual wide dosing variations
- Long half-life
  - Average of 3 to 5 days
  - May lead to accumulation and overdosage
  - Difficult to titrate quickly
- Equianalgesic conversion more complex than for other opioids
- Inadequate promotion of its use consequential to its low cost as compared with other opioids (see Table 3)

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* 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.*,† 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.* †
- 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-
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.9,10

Table 3 provides a cost comparison of methadone with equivalent medication doses of other opioids.11

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


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.

References

Table 3

<table>
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Resources

BOOKS

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.