

# Methadone Analgesia: Balancing the Risks and Benefits

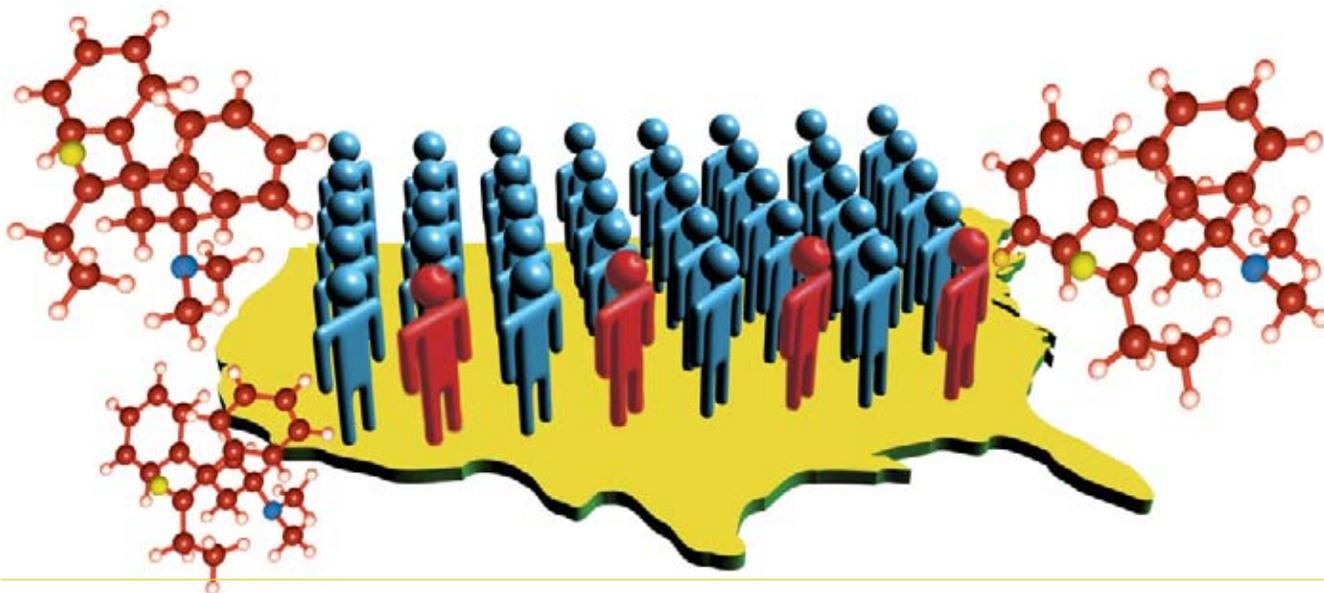
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**P**ain continues to be a major concern for health care providers and their patients. Chronic daily regional pain is estimated to afflict approximately 10% of the population in the United States.<sup>1</sup> Common pain conditions result in substantial costs to society, both directly by necessitating health care expenditures and indirectly by causing lost productivity in the workplace.<sup>2</sup>

Physicians are constantly striving to provide needed pain relief to and restore function for patients with chronic pain while avoiding harmful consequences, such as analgesic toxicity and debilitating side effects. Data from the Centers for Disease Control and Prevention reveal that analgesics, including both opioid and nonopioid agents, are the most frequently prescribed class of medication in the United States today.<sup>3</sup> In a recent national survey, 2% of those queried indicated that they had used opioids at least 5 days per week for a period longer than 4 weeks.<sup>4</sup> Another 2.9% reported less frequent use. Based on these data, more than 4.3

million adults in the United States regularly consume opioid medication. In an era of increasing health care costs and declining insurance coverage for prescription medication, many physicians have had to resort to prescribing methadone as a less expensive alternative to many of the more costly continuous-release opioid products for managing chronic pain.

## Pharmacokinetics

Methadone is unique among the available long-acting opioid preparations in that its sustained duration of action is due to slow elimination, so that blood levels

are maintained. Methadone is a lipid-soluble compound with excellent bioavailability, achieving peak blood levels within approximately 3 hours. It has a large volume of distribution, a prolonged elimination phase, and a  $\beta$ -elimination half-life of approximately 30 to 60 hours, although this varies considerably among patients and may be particularly extended in the elderly.<sup>5</sup> This half-life makes it possible to administer methadone as a single daily dose in addiction maintenance therapy. However, when methadone is used for analgesic therapy, dosing at 8-hour intervals is necessary to maintain the necessary analgesic blood level.

Methadone is a chiral molecule, available as a racemic mixture in the United States. The *R*-isomer has potent  $\mu$ - and  $\delta$ -opioid receptor agonist activity. The *S*-isomer displays no  $\mu$ -opioid receptor agonist activity but may offer valuable analgesic benefit by virtue of its *N*-methyl-D-aspartate (NMDA) antagonist activity. *S*-methadone also is reported to inhibit the reuptake of both norepinephrine and serotonin, providing another mechanism for adjuvant analgesia. The combined analgesic effects of NMDA antagonism, potent  $\mu$ -opioid receptor agonism, and inhibition of neurotransmitter reuptake probably account for the dramatic efficacy noted when

patients with pain refractory to treatment with other opioid preparations are rotated to methadone.

Methadone is eliminated predominantly through metabolic activity in the liver. Cytochrome P-450 (CYP) isozymes are the primary pathway for inactivation of the drug. Originally, the CYP3A4 isozyme was believed to be the predominant pathway for the elimination of methadone. However, recent evidence supports an important role for CYP2B6 *N*-demethylation.<sup>6</sup> A recent *in vitro* study demonstrated a stereoselective inhibitory effect of clopidogrel (Plavix, Sanofi-Aventis/Bristol-Myers Squibb) on methadone metabolism by the CYP2B6 isozyme pathway. CYP3A4 contributes approximately 20% to 30% of *S*-methadone metabolism, with CYP2B6 contributing 50% to 60%. CYP2B6 displays a greater stereo-selectivity for the *S*-enantiomer. A major concern relates to the potential for drug interactions. Given the prolonged elimination half-life of methadone, drug interactions can result in substantial alterations in blood levels, creating the potential for toxicity (Table 1).

## Toxicity

### NARROW THERAPEUTIC INDEX

All opioids share a pattern of adverse reactions that

**Table 1. Drug Interactions With Methadone Resulting in Elevated Blood Levels and/or the Potential for Cardiac Toxicity<sup>a</sup>**

Agent	Interaction
<b>Antibiotics</b>	
Fluoroquinolones (eg, ciprofloxacin, moxifloxacin)	Inhibition of CYP enzymes, direct potentiation of QT-interval prolongation
Macrolides (eg, clarithromycin, erythromycin)	
<b>Antidepressants</b>	
Tricyclic antidepressants	May directly contribute to QT-interval prolongation
Selective serotonin reuptake inhibitors (fluvoxamine, fluoxetine, sertraline)	Inhibition of CYP enzymes
<b>Antifungals</b>	
Fluconazole, itraconazole, ketoconazole, voriconazole (Vfend, Pfizer),	Inhibition of CYP enzymes
<b>Antipsychotic agents</b>	
Chlorpromazine, droperidol, haloperidol, mesoridazine, pimozide, thioridazine, ziprasidone	Directly contribute to QT prolongation
<b>HIV Protease Inhibitors</b>	
Atazanavir (Reyataz, Bristol-Myers Squibb), ritonavir (Norvir, Abbott)	Inhibition of CYP enzymes (mixed effects reported, may induce and inhibit methadone metabolism)

CYP, cytochrome P-450

<sup>a</sup> This table is a general summary and does not list all potential interactions.

include respiratory depression, sedation, nausea and vomiting, pruritus, and constipation. Most of these adverse effects are mediated by the  $\mu$ -opioid receptor and appear to be inseparable from the analgesic activity of all opioids. Recently, 2 peripherally acting opioid antagonists, alvimopan (Entereg, Adolor) and 5-methylnaltrexone (Relistor, Progenics/Wyeth), were introduced into the US market. These agents may have a role in managing many of the bothersome side effects of opioids, such as constipation, pruritus, and nausea.

Most opioids share side effects and adverse reactions, yet mounting data suggest that methadone may have a narrower therapeutic index than those of other medications in its class. Evidence for this has come from several sources, most notably from recent concerns surrounding the dramatic escalation in the number of unintentional overdose deaths involving prescription opioids.<sup>7</sup> Although methadone is prescribed an order of magnitude less frequently than hydrocodone or oxycodone, it accounts for an inordinate number of accidental overdose deaths.<sup>7</sup> The disparity may be explained in part by the tendency for substance abusers to be treated with methadone, hence the likelihood of finding methadone along with other opioids and illicit substances in the blood of overdose death victims. Investigation of most accidental overdose deaths involving methadone typically reveals the presence of other prescription medications, including opioids and benzodiazepines.

Another aspect unique to methadone is the lack of familiarity among physicians and patients with the normal dosing range of the drug. Many physicians encounter patients taking a single daily 80- to 120-mg dose of methadone as maintenance therapy for opioid addiction. This experience with patients who have established a tolerance to opioids contributes to confusion among clinicians and may lead to inappropriate dosing. Patients without tolerance to opioids must be started on substantially lower doses of methadone. Doses in the range of 50 mg or more can be lethal in opioid-naïve patients. Furthermore, the prolonged time required to attain steady-state blood levels of methadone can be confusing for patients who have taken other, shorter-acting opioids. Steady-state blood levels will not be reached for 5 half-lives, a period of more than 1 week in some cases. Inpatient persons may double their early doses—resulting in toxicity 2 to 3 days later. All patients should be carefully counseled about the need to adhere to the prescribed doses and intervals, and why they should do so.

### **CARDIAC RISKS**

A new concern surrounding the use of methadone for analgesia is the potential for lethal cardiac arrhythmias.<sup>8</sup> Sudden death associated with methadone was occasionally noted among patients receiving the drug as maintenance therapy. The etiology of these events was difficult to elucidate because of their often-unwitnessed nature and the existence of complicating circumstances involving concomitant substance abuse.

Krantz et al reported on the development of torsades de pointes arrhythmia among patients receiving high-dose methadone, suggesting that methadone may directly contribute to some cases of sudden cardiac death.<sup>8</sup> The *S*-isomer of methadone inhibits the *HERG* (human ether-à-go-go related gene) potassium rectifier channel in myocardial tissue, which in turn can prolong the QT interval, a contributing factor in the development of polymorphic ventricular tachycardia. The significance of this effect may vary depending on a confluence of several predisposing factors.<sup>9</sup>

A clear dose-response relationship between methadone and cardiac complications has not been shown. However, data suggest that doses greater than 120 mg are likely to carry an increased risk for polymorphic ventricular tachycardia.<sup>10</sup> Certain medical conditions, including asthma, diabetes mellitus, and cardiac diseases, are associated with a higher incidence of in-hospital cardiac arrests in patients receiving QTc-prolonging drugs.<sup>11</sup> Additional risk factors include the following: congenital prolonged QT syndromes, concomitant ingestion of other pharmacologic agents capable of producing QT-interval prolongation, concomitant use of drugs contributing to hypokalemia or hypomagnesemia, IV administration of methadone, use in elderly patients, and the introduction of pharmacologic agents capable of inhibiting methadone elimination (Table 1). Medications known to prolong the QT interval include several agents frequently used to treat pain, such as the antidepressants and anti-convulsant classes of drugs (Table 2).<sup>12</sup>

Whenever a new medication is added to the treatment plan of a patient receiving methadone, the physician must perform a careful assessment, possibly including serial electrocardiograms. At present, data are insufficient to support the recommendation that all patients being considered for methadone treatment undergo electrocardiography before the initiation of therapy. However, it may be helpful to inquire for a family history of sudden cardiac death and to consider obtaining electrocardiograms when a patient is taking a dose exceeding 120 mg per day or receiving treatment with IV methadone.<sup>13</sup> Prolongation of the QT interval does not necessarily preclude the use of methadone, but it warrants closer monitoring, especially in the setting of coexisting risk factors.

Finally, any patient with a history of obstructive sleep apnea should be managed cautiously, if at all, with methadone. Opioids are known to depress ventilatory drive, but long-term use was thought to lead to some degree of tolerance. However, data published by Mogri and colleagues suggest that long-term opioid use can contribute to significant sleep-disordered ventilation, even in the absence of overt patient complaints.<sup>14</sup> In their study population of stable long-term users of opioids, these investigators found a high incidence of sleep apnea, and of hypoxemic episodes when the patients were awake. In a related study, Webster et al used polysomnography to study 146 patients with chronic pain who had been stabilized on daily

**Table 2. Selected Noncardiac Pharmacologic Agents With the Potential To Produce Arrhythmia and/or QTc Prolongation<sup>14</sup>**

<p><b>α-Adrenoreceptor Agonists</b> Alfuzosin (Uroxatral, Sanofi-Aventis)</p> <p><b>α-Agonists/Vasoconstrictors</b> Epinephrine Norepinephrine Phenylephrine Phenylpropanolamine Pseudoephedrine</p> <p><b>Alzheimer Agents/ Cholinesterase Inhibitors</b> Donepezil (Aricept, Eisai Inc/Pfizer) Galantamine (Razadyne, Ortho-McNeil Neurologics) Memantine (Namenda, Forest Laboratories) Rivastigmine (Exelon, Novartis) Tacrine (Cognex, Sciele Pharma)</p> <p><b>Anesthetic</b> Cocaine</p> <p><b>Anorexiants</b> Benzphetamine (Didrex, Pfizer) Diethylpropion Fenfluramine Phendimetrazine Phentermine Sibutramine (Meridia, Abbott)</p> <p><b>Antibiotics</b> Alatrofloxacin (discontinued) Ampicillin Ciprofloxacin Clarithromycin Erythromycin Gatifloxacin Gemifloxacin (Factive, Oscient Pharmaceuticals) Levofloxacin Lomefloxacin (Maxaquin, Pfizer) Moxifloxacin Norfloxacin (Noroxin, Merck) Ofloxacin Sparfloxacin (Zagam, Mylan) Telithromycin (Ketek, Sanofi-Aventis) Trimethoprim-sulfamethoxazole Trovafoxacin (Trovan, Pfizer)</p> <p><b>Anticonvulsants</b> Felbamate (Felbatol, MedPointe)</p>	<p>Fosphenytoin (Cerebyx, Pfizer/Eisai Inc) Gabapentin Phenytoin Pregabalin (Lyrica, Pfizer)</p> <p><b>Antidepressants</b> <i>Selective Serotonin Reuptake Inhibitors</i> Citalopram Escitalopram (Lexapro, Forest) Fluoxetine Fluvoxamine Paroxetine Sertraline (Zoloft, Pfizer)</p> <p><i>Tricyclics and Tetracyclics</i> Amitriptyline Amoxapine Clomipramine Desipramine Doxepin Imipramine Maprotiline Mirtazapine Nortriptyline Protriptyline (Vivactil, Odyssey) Trimipramine</p> <p><i>Other</i> Bupropion Duloxetine (Cymbalta, Lilly) Trazodone Nefazodone Venlafaxine (Effexor, Wyeth)</p> <p><b>Antiemetics</b> Alosetron (Lotronex, GlaxoSmithKline) Dolasetron (Anzemet/Sanofi-Aventis) Domperidone Droperidol Granisetron (Kytril, Roche) Ondansetron</p> <p><b>Antifungals</b> Fluconazole Itraconazole Ketoconazole Voriconazole (Vfend, Pfizer)</p> <p><b>Anti-infectives</b> Pentamidine</p> <p><b>Antimalarial Agents</b> Chloroquine Halofantrine (discontinued)</p> <p><b>Antimanic Agent</b> Lithium</p> <p><b>Anti-Parkinson Agents</b> Amantadine Pergolide</p>	<p><b>Antipsychotic Agents</b> Aripiprazole (Abilify, Bristol-Myers Squibb/Otsuka America) Chlorpromazine Clozapine Fluphenazine Haloperidol Loxapine Mesoridazine (Serentil, Boehringer Ingelheim) Molindone (Moban, Endo) Olanzapine (Zyprexa, Lilly) Paliperidone (Invega, Janssen) Perphenazine Pimozide (Orap, Teva) Prochlorperazine Quetiapine (Seroquel, AstraZeneca) Risperidone (Risperdal, Janssen) Thioridazine Thiothixene Trifluoperazine Ziprasidone (Geodon, Pfizer)</p> <p><b>Antiviral Agents</b> Foscarnet Rimantadine</p> <p><b>Bronchodilators</b> Albuterol Ephedrine Isoproterenol Levalbuterol (Xopenex, Sepracor) Salmeterol (Serevent, GlaxoSmithKline) Terbutaline</p> <p><b>CNS Stimulants/ ADHD Agents</b> Amphetamine Atomoxetine (Strattera, Lilly) Dextroamphetamine Methamphetamine Methylphenidate</p> <p><b>Diuretic</b> Indapamide</p> <p><b>Endocrine Agents</b> Levothyroxine Liothyronine Octreotide (Sandostatin, Novartis) Thyroid desiccated</p> <p><b>Gastrointestinal Stimulant</b> Cisapride (Propulsid, Janssen) Tegaserod maleate (Zelnorm, Novartis)</p>	<p><b>Immunosuppressant</b> Tacrolimus (Prograf, Astellas)</p> <p><b>Muscle Relaxants</b> Cyclobenzaprine Tizanidine</p> <p><b>NSAIDs</b> Celecoxib (Celebrex, Pfizer) Diclofenac Etodolac Etoricoxib Fenoprofen Flurbiprofen Ibuprofen Indomethacin Ketoprofen Lumiracoxib Mefenamic (Ponstel, Sciele Pharma) Meloxicam Nabumetone Rofecoxib (discontinued) Sulindac Valdecoxib (discontinued)</p> <p><b>Oncology Agents</b> Abarelix (Plenaxis, Praecis Pharmaceuticals) Arsenic trioxide (Trisenox, Cephalon) Daunorubicin Idarubicin Sunitinib malate (Sutent, Pfizer) Tamoxifen Toremifene (Fareston, GTx, Inc)</p> <p><b>Opioids</b> Alfentanil Fentanyl Hydromorphone Ketamine Levomethadyl Levorphanol Methadone Propoxyphene (dextropropoxyphene) Sufentanil</p> <p><b>Phosphodiesterase Type 5 Inhibitors</b> Sildenafil (Viagra/Revatio, Pfizer) Tadalafil (Cialis, Lilly) Vardenafil (Levitra, GlaxoSmithKline/Schering)</p> <p><b>Sedative-Hypnotic</b> Choral hydrate</p> <p><b>Uterine Relaxant</b> Ritodrine</p>
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ADHD, attention-deficit/hyperactivity disorder; CNS, central nervous system; NSAIDs, nonsteroidal anti-inflammatory drugs

opioid analgesics for 6 months.<sup>15</sup> The results showed that the studies of 75% of the patients were positive for sleep apnea. A greater daily dose of methadone, but not other opioids, was associated with more severe apnea-hypopnea. The authors concluded that sleep-disordered breathing is common in patients with pain that is being managed with long-term opioids, and that increased vigilance is required for patients taking methadone for analgesia.

### Prescribing Recommendations

Methadone is available in several formulations, including injectable, oral liquid, oral concentrate, dispersible diskette, and tablet preparations (Table 3). The tablet has been used primarily for pain management; the liquid and dispersible diskette are used primarily by methadone maintenance clinics.

During the past several years, use of the 40-mg diskettes for the treatment of pain has become more widespread. The Drug Enforcement Administration (DEA) recently requested a voluntary embargo on the diskettes, restricting manufacturers' distribution of this product to methadone maintenance programs and hospitals. The action of the DEA stemmed from its concern over the rapid escalation in deaths from methadone overdose, and the belief that the 40-mg diskettes may be contributing to the problem. The large amount of drug contained in the diskettes increases the likelihood of death after accidental ingestion by a child or teenager experimenting with substance abuse.

The liquid preparations come in a range of concentrations, ranging from 1 to 10 mg/mL. Care should be taken during switches between preparations to avoid inadvertent errors.

When methadone is prescribed, several critical issues must be addressed. Both the prescribing physician and the patient must be familiar with the unique aspects of methadone pharmacokinetics and the factors that may affect the action of this drug. The elimination of methadone can vary considerably, depending on the patient's age and the effect of multiple interacting medications that are added or removed from the patient's medication profile. As previously noted, the volume of distribution of methadone is very large and marked by the slow saturation of various tissue reservoirs. Thus, it may take 4 to 5 half-lives, in the range of 5 to 10 days, to reach peak plasma levels. The rapid adjustment of doses and the administration of supplemental doses carry the risk of overshooting the desired therapeutic level as a consequence of gradual accumulation. Another significant concern relates to the potential for drug interactions. Some medications, such as the anticonvulsants, rifampin, and various HIV protease inhibitors, can induce the metabolism of methadone, producing a fall in methadone levels with an increase in pain or the development of withdrawal symptoms. Other medications may lead to a rise in blood levels of methadone, contributing to toxicity (Table 1).

The guiding principle in prescribing methadone for

analgesia is the concept of "start low and go slow." In opioid-naïve patients, treatment should be initiated at doses of 2.5 to 5 mg taken at 8- to 12-hour intervals. Modest adjustments may be made periodically, with the patient's age and general state of health taken into account. Escalations of 2.5 to 5 mg every other day may aid titration. The patient or family caretaker should be warned to watch for evidence of drug accumulation, although such signs may not appear for several days. A wise policy is to avoid prescribing a large amount of medication initially to deter disposal and diversion should the patient not tolerate the medication.

### Conversion to Methadone

Converting an opioid-tolerant patient to methadone requires considerable caution and a knowledge of opioid rotation strategies. Although a degree of cross-tolerance exists among most opioids, much less methadone is often required than might be predicted. The conversion dose of methadone is inversely related to the total dose of the initial opioid. For example, when a patient is switched from oxycodone or morphine, the replacement dose of methadone is estimated to be approximately 20% to 30% of the daily dose of the original opioid. However, clinical studies have suggested that when high doses of morphine are used, the calculated rotation dose of methadone may need to be reduced by 90%.

Two methods of rotation have been employed.<sup>16,17</sup> In the "stop and go" approach, the original opioid is discontinued and the calculated 24-hour dose of methadone is initiated.<sup>17</sup> Supplemental doses are provided to bridge the period during the methadone equilibration phase. The second method gradually tapers the 24-hour dose of the original opioid by one-third on consecutive days.<sup>16</sup> Thus, the patient will receive two-thirds of the initial morphine equivalent dose on day 1, one-third of the original morphine equivalent dose on day 2, and will

**Table 3. Methadone Formulations**

Form	Strength or Concentration
Oral tablets	5 and 10 mg
Oral diskettes (not available for treatment of pain) <sup>a</sup>	40 mg scored
Oral solutions	5 mg/5 mL 10 mg/5 mL 10 mg/1 mL (concentrated)
Injectable formulation (Xanodyne)	10 mg/mL

<sup>a</sup> The Drug Enforcement Administration restricts the use of oral diskettes to methadone maintenance therapy.

be completely off morphine on the third day.

Methadone is simultaneously initiated at a conventional dose of 2.5 to 5 mg every 8 hours or one-tenth of the daily oral morphine equivalent dose, gradually escalating to comfort. This method is more convenient for rotating patients to methadone from an IV opioid.

Several methods have been proposed for estimating the appropriate 24-hour conversion dose for methadone. One approach, in which a linear regression model is used to analyze 5 protocols for estimating the methadone conversion dose, is a formula referred to as the “rule of 15.”<sup>18</sup> This formula estimates the oral 24-hour dose of methadone (in milligrams) by taking the oral 24-hour morphine equivalent dose (in milligrams), dividing it by 15, and adding 15 mg to the quotient. The resulting sum is divided by 3 to obtain the 8-hour dose. This formula is considered valid only for patients taking daily morphine equivalents in the range of 60 to 1,200 mg per day. It must be remembered that this is an estimate; the requirements of individual patients will vary. Constant reassessment is needed to avoid undesirable complications.

## Conclusion

Methadone is a valuable but potentially hazardous tool for managing pain conditions that are difficult to control. Physicians seeking to prescribe methadone must have a detailed knowledge of its pharmacokinetics and possible interactions with other medications to avoid putting their patients at risk for serious, and even life-threatening, adverse reactions. In addition, the patient must be made aware of the unique aspects of methadone. It is not simply another opioid. Patients at high risk for misuse or toxicity will need close monitoring. However, when properly employed, methadone can be an effective—and cost-effective—analgesic.

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