

Rethinking methadone for the management of chronic pain

Gary M. Reisfield, MD
Paul A. Sloan, MD

The use of long-term opioid therapy in the management of chronic nonmalignant pain has increased dramatically over the past decade and a half.¹ Methadone is one of several opioids used by physicians in the management of severe pain. A recent report by the Centers for Disease Control and Prevention, however, highlighted the disproportionate role of methadone in prescription opioid-related morbidity and mortality.² For example, in 2009, methadone accounted for 1.7 percent of opioid prescriptions, but was involved in 31.4 percent of opioid deaths.² A major part of the appeal of methadone is its low cost. As many states are contemplating expanding their Medicaid programs to cover the uninsured poor under President Obama's Affordable Care Act, we believe it is worth revisiting this Medicaid-preferred medication. Data indicates that this population is at increased risk of opioid-related morbidity and mortality.^{3,4}

WHY HAS METHADONE BECOME A POPULAR ANALGESIC?

There are several reasons for the increasing popularity of methadone as an analgesic in recent years. First, methadone is an inexpensive, generic medication. Its low cost has made it a preferred drug for third party payers, including Medicaid.⁴ Second, it is a potent opioid, and thus an appealing choice when less potent opioids, such as hydrocodone/acetaminophen combination products are ineffective. Third, it has a relatively long analgesic duration of action; it can often be dosed thrice daily for pain control. Fourth, it produces no clinically significant active metabolites, making it relatively safe in the face of renal insufficiency. Fifth, it has excellent oral bioavailability. Sixth, it is available in oral and parenteral formulations, and it can be crushed and administered via feedings tubes, making it practical across treatment settings. Finally, in addition to acting as a mu-opioid receptor agonist, it has other

potentially beneficial mechanisms of actions, including noncompetitive NMDA receptor antagonist activity and serotonin and norepinephrine reuptake blockade.

WHY IS METHADONE POTENTIALLY DANGEROUS?

Notwithstanding its benefits, methadone also offers potential risks. It is involved in more single-drug deaths than any other opioid, although it accounts for a small proportion of opioid prescriptions.³ The primary danger is ventilatory depression. There are several, non-exclusive reasons for this. First, methadone has a delayed onset of analgesic action. This may compel some patients to administer extra doses in an attempt to achieve rapid pain relief (and possibly anxiolysis or euphoria). Second, its analgesic duration of action of 6 to 8 hours is considerably shorter than its long and highly variable elimination half-life—30 to 60 hours or greater—thus allowing for drug accumulation. Third, methadone is metabolized by several cytochromes (CYPs), including, importantly, CYP3A4 which is both highly inducible and highly repressible by scores of common medications.⁵ The consequence of methadone co-administration with CYP3A4 inhibitors is potentially dangerous opioid accumulation. A related concern is a high degree of interindividual variability in hepatic CYP 3A4 activity.⁵ Finally, methadone has non-linear conversions to and from other opioids, making opioid rotation an inherently risky activity, even—or especially—when using standard conversion tables.

A more recently appreciated danger of methadone is the risk of cardiotoxicity. It has been associated with prolonged QTc interval, which can lead to the potentially lethal dysrhythmia, *Torsades de Pointes (TdP)*. The risk of developing *TdP* is increased by co-administration of CYP3A4 inhibitors, which may increase plasma methadone concentrations.⁵

THE WAY FORWARD

Methadone is a valuable member of the opioid pharmacopoeia for the treatment of chronic pain. It is also, however, disproportionately associated with opioid morbidity and mortality. The safe and effective use of methadone as an analgesic requires knowledge and experience in safe and appropriate opioid prescribing in general, and thorough familiarity with, and respect for, methadone in particular.

Patients should be properly selected. Methadone is inappropriate for the treatment of mild or mild-moderate pain; for opioid naïve patients; and for patients with active substance use disorders. Dosing should begin low, and it should be titrated slowly and monitored carefully. The United States Food and Drug Administration has advised a conservative rotation from other opioids, reflecting nonlinear conversions.⁶

Prescribers must be cognizant of drug-drug interactions. This includes pharmacokinetic interactions, especially with co-administered drugs that inhibit or compete with CYP3A4. It also includes pharmacodynamic interactions; great caution should be taken when co-prescribing other central nervous system depressants such as benzodiazepines and barbiturates. Alcohol should be proscribed in patients on methadone therapy.

While it is clear that methadone is associated with prolonged QTc and TdP, there is controversy surrounding the necessity, frequency, and indications for EKG screening with methadone therapy. An expert panel has recommended 1) informing patients of dysrhythmia risk, 2) asking patients about a history of heart disease, 3) obtaining pre-treatment screening EKG, follow-up EKG within 30 days of treatment initiation, annually, and when dosage exceeds 100 mg/d, 4) stratifying risk based on QTc, and 5) being aware of pharmacokinetic interactions that may increase serum methadone concentrations.⁷

With potentially tens of millions of Americans gaining access to Medicaid through new federal healthcare legislation, there will likely be pressure

on physicians to prescribe methadone for patients requiring opioid therapy for chronic pain. Methadone should not be considered a first line drug for chronic pain management. Physicians who prescribe methadone must be educated concerning the distinctive risks that the drug poses. Those who are uncertain about prescribing—either before initiating or during chronic therapy—should seek expert consultation.

Gary M. Reisfield, MD, Assistant Professor and Director, Pain Management Services, Division of Addiction Medicine, Department of Psychiatry, University of Florida College of Medicine, Gainesville, Florida.

Paul A. Sloan, MD, Professor and Vice Chair for Research, Department of Anesthesiology, University of Kentucky, Lexington, Kentucky.

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