

## **Methadone – Continuing Safety Concerns**

### **Introduction**

Fatal drug overdoses in the United States involving opioid analgesics have more than tripled since 1999, with higher rates among men, individuals aged 35 to 54 years, and non-Hispanic whites. A recent report (September 2009) from the Centers for Disease Control and Prevention (CDC) shows that the number of fatal poisonings caused by opioid overdose increased from 4,000 in 1999 to 13,800 in 2006 and represented almost 40 percent of all poisoning deaths in 2006. Among these opioid analgesic related deaths, those involving methadone increased the most during the study period. In fact, the number of deaths involving methadone (30 percent of the total) increased nearly seven times (i.e., 790 to 5,420)! What has caused methadone to become one of the deadliest drugs around?

Methadone, a synthetic, long acting opioid has been available as an analgesic for more than 50 years although for most of its history it has been used primarily for treatment of opioid addiction. Starting in 1999, with increased concerns about the abuse potential of the pain-reliever OXYCONTIN and the desire for a relatively inexpensive, long-acting opioid analgesic, the use of methadone began to increase significantly. In fact, the number of methadone prescriptions increased by nearly 700 percent between 1998 and 2006, with nearly 4 million prescriptions written for chronic pain relief in 2008.

### **What are the potential problems with methadone?**

**Tricky pharmacokinetics:** Methadone is indicated for the treatment of moderate to severe pain not responsive to non-narcotic analgesics. Methadone differs from many other opioid agonists in several important ways. Methadone's pharmacokinetic properties, coupled with high inter-patient variability in its absorption, metabolism, and relative analgesic potency, potential for significant drug-drug interactions, and dose dependent cardiac conduction effects necessitate a cautious and highly individualized approach to prescribing. Particular vigilance is necessary during treatment initiation, conversion from one opioid to another, and dose titration. Patients known to be at high risk for adverse effects include: a.) age greater than 65 years, b.) debilitated, and c.) significant pulmonary disease.

While methadone's duration of analgesic action (typically four to eight hours) in the setting of single-dose studies approximates that of morphine, methadone's plasma elimination half-life is substantially longer than morphine (typically eight to 59 hours vs. one to five hours, respectively). Methadone's peak respiratory depressant effects typically occur later and persist longer than its peak analgesic effects. Therefore, when initiating therapy with methadone, repeated doses every three to four hours are necessary to obtain plasma levels capable of providing sufficient pain relief. Also, with repeated dosing, methadone may be retained in the liver and then slowly released, prolonging the duration of action despite low plasma concentrations. For these reasons, steady-state plasma concentrations and full analgesic effects are usually not attained until three to five days of dosing. When pain control is finally achieved, the dosing schedule must then be reduced to every six to 12 hours to avoid accumulation. In other words, patients can experience toxic levels of methadone while at the same time complaining of poor pain control. Unfortunately, symptoms of overdose (e.g., respiratory depression) may develop slowly, sometimes up to a week after initiation of therapy or change in dosing, increasing the risk that an overdose will go unrecognized until it is too late.

**Cross tolerance and/or conversion with other opioid pain relievers:** Additionally, cross tolerance between methadone and other opioids is incomplete. This incomplete cross-tolerance makes the conversion of patients on other opioids to methadone complex and does not eliminate the possibility of methadone overdose, even in patients tolerant to other opioids. In addition, the conversion ratio of 20mg methadone for each 30mg of morphine equivalent, utilized in some conversion tables, should not be used.

**Drug-drug interactions:** Methadone's respiratory depression can be additive with other respiratory depressants (e.g., benzodiazepines, opioids, etc.). In addition, acute alcohol ingestion can slow methadone metabolism, resulting in an increased risk of methadone toxicity. Inhibitors of the P450 enzyme CYP3A4 (e.g., fluoxetine, fluconazole, etc.) have been shown to increase methadone levels. Serum levels of tricyclic antidepressants (e.g., desipramine) have been shown to increase through inhibition of the CYP2D6 enzyme system when co-administered with methadone. This may be significant since both methadone and tricyclic antidepressants can prolong the QT interval and perhaps increase the risk of arrhythmias.

**Cardiac Arrhythmias:** Methadone can cause dose-dependent QT prolongation. This can lead to torsades de pointes, a potentially lethal cardiac arrhythmia. Risk factors include: heart failure, structural heart disease, hypokalemia, long QT syndrome, and family history of sudden cardiac death. Recent dosage increase, high methadone dose, liver dysfunction, and use of other QT prolonging drugs (e.g., antipsychotics) may increase this risk.

### Information for Health Care Professionals

In its November 2006 Alert and Public Health Advisory, the U.S. Food and Drug Administration (FDA) recommended the following information be communicated to all patients taking methadone for relief of moderate to severe pain:

- Pain relief from methadone does not last as long as methadone stays in your body. Therefore, do not take more methadone than prescribed because methadone could accumulate in your body and cause death.
- Methadone can cause life-threatening changes in breathing.
- Methadone may cause life-threatening changes to the heart beat that may not be felt.
- Seek medical attention right away if you experience symptoms suggestive of an arrhythmia such as palpitations, dizziness, lightheadedness, or fainting, or if you experience symptoms suggestive of a methadone overdose such as slow or shallow breathing, extreme tiredness or sleepiness, blurred vision, inability to think, talk or walk normally, feeling faint, dizzy or confused.
- Follow your doctor's directions if your pain is not well controlled after taking the prescribed amount of methadone.
- Tell your doctor if you stop or start other medications because they can interact with methadone and possibly cause death or life threatening side effects.
- Tell your doctor if you are breastfeeding because methadone is secreted into human milk and therefore babies can experience the same serious side effects from methadone as the mother.

### Conclusion:

Methadone can be a safe and effective pain reliever when used correctly. The keys to safe methadone use include proper titration to the lowest effective dose, and careful patient selection, education and monitoring. Drowsiness often heralds respiratory depression and patients should be alerted to contact the prescriber in the event of drowsiness. Close monitoring is especially important during titration or a dosage increase for a minimum of one week. Patients should be screened for concomitant use of interacting medications with additive respiratory depression or QT prolongation. Lastly, advise patients to never take extra doses without instructions from their prescriber.

Patients or practitioners who encounter problems (e.g., adverse drug events, etc.) with methadone are asked to file a MedWatch report with the FDA via telephone at (800) 332-1088; via fax at (800) FDA-0178 (332-0178); via mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787; or online at [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

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