# Keeping Patients Safe From Methadone Overdoses

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**PROBLEM:** Methadone (e.g., Dolophine, Roxane), a synthetic opioid often prescribed for the detoxification of and maintenance therapy for patients with narcotic addiction, has steadily gained popularity as a therapy for moderate-to-severe chronic pain. When used for narcotic addiction, methadone must be prescribed by a practitioner who is registered with the U.S. Drug Enforcement Administration and who is participating in a narcotic treatment program. The drug must also be dispensed by an approved pharmacy or a state-approved maintenance program. However, when methadone is used as an analgesic, any health care provider licensed to prescribe Schedule II controlled substances may prescribe it and any licensed pharmacy may dispense it.

Methadone differs from other opioids in several important ways:

- Variability in the drug's absorption, metabolism, and relative analgesic potency among patients calls for a highly individualized approach to prescribing. Particular vigilance is necessary during treatment initiation and titration.[1]
- Incomplete cross-tolerance between methadone and other opioids makes dosing complex when patients are switched from one opioid to another. A high degree of tolerance to other opioids does not eliminate the possibility of a methadone overdose.[1]
- Although methadone's duration of analgesic action for single doses (four to eight hours) approximates that of morphine, methadone's half-life is substantially longer than that of morphine (eight to 59 hours vs. one to five hours).[1]
- The half-life of methadone in an opioid-tolerant patient is approximately 24 hours; its half-life in an opioid-naive patient is approximately 55 hours. Therefore, the duration of effect is extended in opioid-naive patients.[2]
- Owing to methadone's long half-life, full analgesic effects might not be attained until after three to five days of use. Therefore, the dose must be titrated more slowly than that of other opioids.[1]
- Methadone's peak respiratory depressant effects typically occur later and persist longer than its peak analgesic effects.[1]

As a result of methadone's dosing complexities and other contributing factors, the FDA, the Institute for Safe Medication Practices (ISMP), and ISMP Canada have received multiple reports of medication errors involving methadone that have resulted in serious patient harm, including fatalities. Methadone represents fewer than 5% of total opioid prescriptions dispensed but one-third of opioid-related deaths nationwide.[3]

**Dosing errors.** Prescribers who order methadone for pain, as well as patients who take this medication, may underestimate the risk of potentially harmful events associated with this drug. In November 2006, the FDA issued a Public Health Advisory (which was updated in July 2007) to warn health care practitioners and consumers about reports of death and life-threatening adverse effects (AEs) in patients taking methadone.[4] These AEs occurred in patients who were just starting to use methadone for pain control and in those who switched to methadone after using other opioids for pain.

For example, the ISMP had learned of two fatalities and a near-fatality that resulted from prescribing too large of a dose for patients who had previously taken high daily doses of oxycodone controlled release (OxyContin, Purdue Pharma) or hydrocodone/acetaminophen (Vicodin, Abbott). In these cases, the accumulation of methadone during chronic administration was not considered, consequently leading to a buildup of toxic levels.

**Confusion between mL and mg units**. ISMP Canada received several reports of dosing errors with the oral liquid form of methadone. In one report, a hospitalized patient received a large overdose of methadone. Before admission, the patient had been taking 13 mg/day, which was prepared as a 1-mg/mL concentration in his community pharmacy. Assuming that the hospital carried the same concentration, the attending physician prescribed 12 mL of methadone daily without specifying the dose in milligrams.

The order was entered into the hospital pharmacy computer system and was then filled by a technician who used a 10-mg/mL stock solution of methadone. The checking pharmacist did not detect the error. The hospital carried only the 10-mg/mL concentration, and the patient's methadone dose did not signal a problem (doses can be quite variable).

The drug was sent to the nursing unit, and the patient received 120 mg—approximately nine times more than his usual dose. Fortunately, most of the medication was eliminated by emesis. Later that day, the error was discovered when a visitor reported that the patient was drowsier than usual.

**SAFE PRACTICE RECOMMENDATIONS:** To prevent life-threatening errors with methadone, health care professionals should consider the following risk-reduction actions:

### Prescribing

- Staff members should not prescribe methadone unless they are familiar with the drug's toxicities and unique pharmacological properties.
- The staff should assess the patient's

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risk of abusing the drug and his or her ability to comply with directions for administration. Alternative pain medications should be considered if the risk of abuse is likely.

- Personnel who prescribe methadone for pain should consider each patient to be opioid-naive for the purpose of introducing this drug, no matter how much opioid medication the patient has taken previously. To start, a conservative conversion-ceiling dose of no more than 20 mg/day and 10 mg/day for elderly or infirm patients can be considered.
- Doses should not be adjusted more often than weekly. A steady state of methadone plasma levels should be allowed to develop, and patients should be evaluated and asked whether they have experienced any AEs before the dose is titrated upward.
- Oral liquid doses of methadone should be prescribed in milligrams, never in milliliters alone, because several concentrations of the drug are available (i.e., 5 mg).
- The exact times of administration should be specified. Even daily doses, if taken in the evening one day and in the morning the next day, can lead to an overdose.
- The concomitant use of methadone should be avoided with other narcotics, benzodiazepines, and sedatives, because these agents significantly increase the risk of AEs. If patients must take these medications with methadone, the starting dose and the speed of titration for methadone may need to be adjusted downward.
- It might be prudent to restrict ordering privileges for methadone to prescribers with expertise in managing chronic pain and narcotic addiction.
- Patients should be closely monitored, especially when they begin taking methadone and during dose adjustments.

### Dispensing

- If possible, only one concentration of oral liquid methadone should be stocked in the pharmacy. If more than one concentration is required to manage patients appropriately, prominent warning labels should be applied to distinguish the products.
- Orders for methadone should be accepted only when the dose is prescribed in milligrams.
- To prevent compounding errors, the staff should use only commercially available methadone solutions. If compounding is necessary, the drug should be prepared according to a standard, written formula. The preparation should be documented in a manufacturing log.
- The pharmacist should verify the patient's age, check the patient's medication profile for other sedating drugs, and independently double-check all methadone orders and doses before they are dispensed.
- All unit-doses should be labeled with the exact dose (including strength and total volume for liquid medications), the date, and the time of administration.

### Administration

- Methadone should not be administered until a pharmacist has reviewed the order.
- This drug should not be kept in automated dispensing cabinets or in unit stock unless a patient is receiving the medication. When the patient is discharged, the medication should be sent back to the pharmacy immediately.
- Before administering the first dose of methadone to a patient who has been receiving the drug as an outpatient, the staff should verify when the last dose was taken by asking the patient or by calling the community pharmacy where the patient was receiving the medication. If a dose has not been taken for three consecutive days, the prescriber should be contacted for a dose adjustment to prevent an overdose.
- The staff must adhere to standard medication administration times. If a dose is missed, the staff member should check with the physician before administering the drug later than the scheduled time.
- All staff members should be familiar with the signs of a methadone overdose, such as respiratory depression, lethargy, dizziness, or confusion.

### Counseling Patients

- Pain relief does not last for as long as methadone stays in the body; therefore, patients should not take more methadone than prescribed because levels can accumulate and cause death.
- Methadone can cause life-threatening changes in breathing and heart rate. Patients should seek medical attention if they experience lightheadedness; slow or shallow breathing; confusion or tiredness; or an inability to think, talk, or walk normally.
- Methadone must be taken exactly as prescribed. The physician should be consulted if the patient does not experience the desired effect from the drug after three to five days of use.
- Patients should not start or stop taking other medications or dietary supplements without talking to their physician.
- Patients should not drink alcoholic beverages when taking methadone.

## REFERENCES


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4. FDA. Public health advisory: Methadone use for pain control may result in death and life-threatening changes in breathing and heart beat. November 27, 2006. Available at: www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm124346.htm. Accessed July 5, 2011.


*The reports described in this column were received through the ISMP Medication Errors Reporting Program (MERP). Errors, close calls, or hazardous conditions may be reported on the ISMP Web site (www.ismp.org) or communicated directly to ISMP by calling 1-800-FAIL-SAFE or via e-mail at ismpinfo@ismp.org.* ■