

Substance Abuse Treatment

ADVISORY

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EMERGING ISSUES IN THE USE OF METHADONE

This *Advisory* presents information on the increase in deaths related to methadone, particularly in combination with other drugs or substances, but stresses that methadone is effective and safe in the treatment of opioid addiction and chronic pain *when it is used appropriately*. In light of the rise in fatalities associated with the use of methadone, it is important to explore the extent of the problem and the risks associated with methadone use and to identify potential dangers and take action to prevent harm to patients who use methadone for addiction treatment and in managing chronic pain.¹ The Substance Abuse and Mental Health Services Administration (SAMHSA) convened a national assessment conference in 2003 to examine factors behind the increase in methadone-related deaths. A reassessment meeting was convened in July 2007.² The meeting reports, background papers, and other information are available at <http://www.dpt.samhsa.gov/medications/methadone.aspx>.

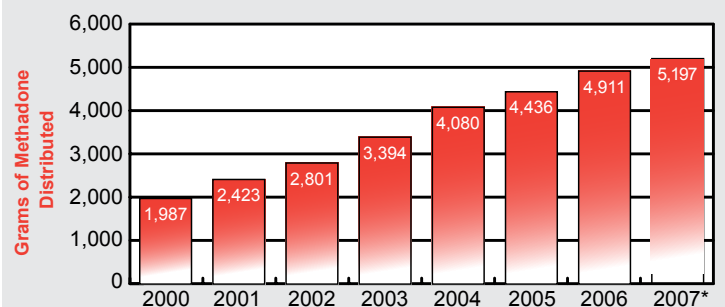
dispense it as a premixed, colored liquid. The Food and Drug Administration (FDA) approved the dispersible tablet for the treatment of addiction but not for pain management. The 5 and 10 mg strength methadone tablets are the only formulations approved by FDA for use in pain management. However, other formulations, including dispersible tablets, have been prescribed for pain control.

Methadone is becoming increasingly available. The amount of methadone distributed or delivered by the manufacturers rose dramatically from 2000 to early 2007, with increases ranging from 9 to 22 percent annually (Figure 1).³ The distribution of all formulations of methadone (liquid, tablet, or dispersible tablet) increased. However, tablets distributed with a prescription through pharmacies had the largest increase. The number of methadone prescriptions dispensed increased by nearly 700 percent between 1998 and 2006. The strongest

Use of Methadone Increasing

Methadone, a synthetic, long-acting opioid, has been used for more than 40 years in the treatment of opioid addiction. During the past 10 years, its use for treating chronic pain has increased. Methadone has been available as an approved narcotic painkiller for more than 50 years. It is available as a liquid, tablet, or dispersible tablet (diskette). Opioid treatment programs (OTPs) generally

Figure 1. Methadone Distribution, per 100k Population, 2000–2007



Source: Feussner using Drug Enforcement Administration data (see note 3).

*Projected



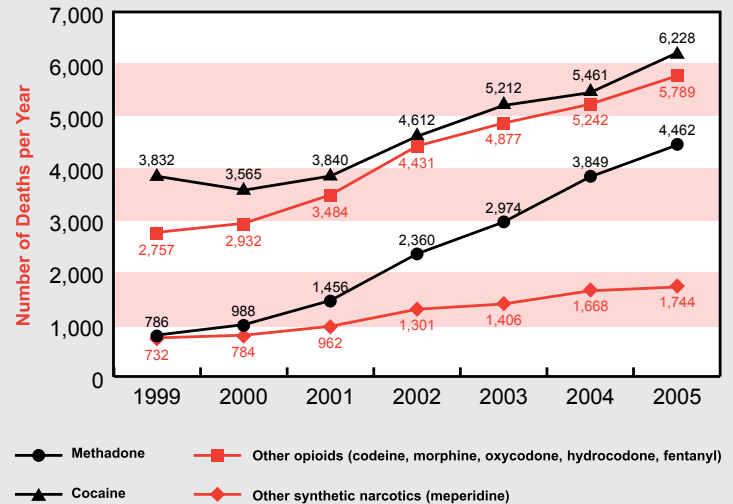
formulation, the 40 mg strength dispersible tablet, had the largest increase of all methadone formulations.⁴

Methadone-Related Deaths Rising

Obtaining an accurate picture of methadone deaths is very difficult, in part because medical examiners across the country do not use the same methods to determine or the same terminology to record cause of death. For example, distinctions are not made among “methadone as the cause of death,” “death related to methadone use,” and “death associated with methadone use.” Therefore, it is difficult to obtain enough data to confirm whether methadone deaths are linked more to OTPs or to pain treatment situations. What is known, considering the inconsistent information, is that the increase in deaths from methadone is part of an overall increase in poisoning deaths, most of which are unintentional drug overdoses. However, methadone-related deaths are increasing at a faster rate than other poisoning deaths. According to data from the National Center for Health Statistics, from 1999 to 2005 methadone-related poisoning deaths increased by 468 percent, while total poisoning deaths increased by only 66 percent.⁵ In addition, methadone-related poisoning deaths had the greatest percentage increase of deaths compared with other opioids.⁵ However, even with this increase in percentages, the actual number of deaths mentioning methadone poisoning continues to be smaller than the number of deaths from other opioids or cocaine (Figure 2).

The Researched Abuse, Diversion and Addiction-Related Surveillance® System (known as RADARS® System) obtains data on prescription drug abuse from many sources, including poison control centers, key informant centers, law enforcement, and OTPs. Poison control center data from 2003 to 2006 showed that patients filling prescriptions for methadone had the highest fatal poisoning rate for all people filling prescriptions. During the same period, according to RADARS System data, the source and formulation of the methadone could not be determined in 70 percent of all methadone-associated deaths. However, the tablet form

Figure 2. Number of Poisoning Deaths Mentioning Specific Narcotics and Cocaine, United States, 1999–2005



Source: Fingerhut for the Centers for Disease Control and Prevention (see note 5).

of methadone was implicated in 25 percent of reported cases, suggesting that methadone may have been prescribed and was not dispensed from OTPs.⁶

Approximately 35 percent of methadone deaths were characterized as resulting from an abuse episode. Unlike most other opioid-related deaths, two-thirds of the methadone deaths involved use of multiple drugs, especially antidepressants, alcohol, and cocaine.⁶

Methadone Is Safe When Used Properly

Methadone is safe *when used appropriately*. It can be life saving for individuals dependent on opioids. Any practitioner prescribing or dispensing methadone needs to appreciate that methadone is powerful, with the potential for serious adverse effects. The rising number of methadone-related deaths necessitates a review of both methadone’s adverse effects and the safe treatment practices in OTPs to ensure that methadone is used *safely and appropriately in those settings*.

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Clinical Issues: Risk Factors for Adverse Events Related to Methadone Used in the Treatment of Opioid Dependence

- **Simultaneous patient abuse of substances such as benzodiazepines, other opioids, cocaine, or alcohol.** The majority of people admitted for methadone maintenance treatment of heroin and other opioid abuse also use other substances, including alcohol, cocaine, marijuana, and tranquilizers.⁷ Some patients continue using heroin, other drugs, and alcohol after admission to treatment.⁸ Polysubstance abuse, at levels that are not necessarily lethal if each substance were used alone, may have a synergistic effect with the prescribed methadone. This mixing of drugs can cause more severe respiratory depression (slow or shallow breathing), central nervous system (CNS) depression and excessive sleepiness, and abnormal heart rhythms (see cardiac screening below). These conditions can lead to overdose (poisoning). Other potential interactions can slow or stop bowel movements.⁹
- **Interactions between prescribed medications.** Methadone adversely interacts with numerous prescribed medications, potentially causing the same serious effects discussed above. The Resource List (page 6) provides links to Web sites listing methadone drug interactions.

Update on Limited Distribution of 40 mg Dispersible Tablet

As of January 1, 2008, manufacturers of the 40 mg strength methadone hydrochloride tablets (dispersible) have voluntarily agreed to distribute only to facilities authorized for detoxification and maintenance treatment of opioid addiction and to hospitals. The manufacturers' wholesale distributors will no longer supply this formulation to any facility not meeting the above criteria.¹⁰

- **Methadone accumulation in the body that can result in harmful or toxic levels.** Methadone is a long-acting medication with a long half-life. This half-life varies greatly from person to person and ranges between 8 and 59 hours in different studies.¹¹ Methadone can remain in the liver and other tissues such as fat cells from which it is slowly released back into the bloodstream. This slow release from these tissues may prolong the duration of methadone's action despite low levels in a person's plasma. If the occurrence of this slow release from tissues while a person is taking additional methadone doses causes toxic levels, methadone can cause respiratory depression, low levels of oxygen in the blood, or CNS depression—conditions leading to overdose. Because these symptoms of overdose may develop slowly, warning signs may appear only after the patient has left the clinic, too late for medical intervention.
- **Methadone's peak respiratory depressant effects.** The peak respiratory depressant effects of methadone typically occur later and persist longer than its other peak effects, particularly during the initial dosing period. This phenomenon occurs because methadone's elimination half-life is longer than the duration (4 to 8 hours) of its action. If a patient takes more doses of methadone faster than his or her body can metabolize it, serious toxicity or poisoning can result. If a patient's methadone dose is increased too quickly (see next bullet), or the patient does not ingest take-home doses as directed, respiration can be affected.
- **Poor clinical practice during the start of methadone treatment (induction dosing phase).** Among patients in addiction treatment, the largest proportion of methadone-associated deaths has occurred during the methadone induction phase, usually when (1) treatment personnel overestimate a patient's degree of tolerance for opioids or (2) a patient uses opioids or other CNS depressant drugs in addition to the prescribed methadone.¹²
- **Cardiac screening.** Methadone puts some patients at an elevated risk to develop torsades de pointes (a serious abnormal heart rhythm). The Center for Substance Abuse Treatment convened the National Assessment

of Methadone-Associated Mortality meeting in May 2003, at which preliminary evidence suggesting pro-arrhythmic properties of methadone was presented. This meeting was reconvened on July 20, 2007, and titled Methadone Mortality—A Reassessment. One action that emerged was formation of a multi-disciplinary expert panel on the cardiac effects of methadone, charged with formulating a clinical practice guideline to ensure cardiac safety of patients in opioid treatment. The expert panel includes key stakeholders with backgrounds in addiction medicine, cardiology, electrophysiology, pain management, epidemiology, and development, as well as representatives from FDA and the National Institute on Drug Abuse. The clinical practice guideline is expected to be disseminated within the next 12 months.

- **Poisoning that occurs when methadone is diverted for nonmedical use.** Deaths can occur when people who have no or low opioid tolerance take too large a dose or mix methadone with other respiratory or CNS depressants. Children also have accidentally ingested take-home doses of methadone, with fatal results.^{1,2,5,6}

Improving Patient Safety in Opioid Addiction Treatment

The increase in methadone-related deaths has resulted in changes in recommendations and procedures from the manufacturers of the drug itself (see sidebar on page 3), FDA (see sidebar on page 5), and SAMHSA.

Several measures can improve patient safety. These include updating induction protocols, educating medical and other staff members, monitoring patients' health while in treatment, improving procedures for take-home medications, carefully assessing each patient for the use of other drugs or medications, and reevaluating patient education procedures.

As with other opioids, methadone may impair mental and physical abilities required in operating an automobile or heavy machinery. Patients should be cautioned about this adverse effect.

Evidence-based practice guidelines and standards of care exist for the use of methadone for opioid dependence (see the Resource List on page 6). The standards emphasize providing quality care through individualized treatment planning, person-focused care, medical supervision, and detailed assessment of patients.¹³ In 2007, SAMHSA sent a "Dear Colleague letter"¹⁴ to programs recommending that they reevaluate their induction procedures. The letter stated that, even though Treatment Improvement Protocol (TIP) 43, *Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs*,⁹ and methadone drug labeling state that a typical first dose of methadone for a patient actively abusing opioids is 20 to 30 mg, some patients need a much lower dose. According to 42 Code of Federal Regulations (CFR), Part 8, § 12(h) (3)(ii), "the initial dose of methadone **shall not exceed** 30 milligrams and the total dose for the first day shall not exceed 40 milligrams" (emphasis added). The initial methadone dose should be appropriate for the individual patient, with the maximum initial dose being 30 mg. Clearly, a 30 mg dose should not be the initial dose for all patients.¹⁴ There is no regulatory dose restriction when methadone is prescribed for pain.

"the initial dose of methadone shall not exceed 30 milligrams and the total dose for the first day shall not exceed 40 milligrams."

Patients are in a critical phase during induction, before their bodies achieve a steady state, which is when methadone is eliminated from the blood at the exact rate that more is added.⁹ The potential for adverse events during the 2-week induction process makes it imperative that the OTP physician determine the admitting diagnosis, initiate treatment, and set the beginning dosages.¹⁴ More intensive monitoring during the induction phase is essential to prevent the adverse events discussed above. Withdrawal assessments such as the Subjective Opiate Withdrawal

FDA Activity

- In November 2006, FDA announced a revised package insert for methadone, including a black-box warning. (See <http://www.fda.gov/cder/foi/label/2006/006134s028lbl.pdf>.)
- In November 2006, FDA issued “Information for Healthcare Professionals, Methadone Hydrochloride, FDA ALERT [11/2006]: Death, Narcotic Overdose, and Serious Cardiac Arrhythmias.” (See <http://www.fda.gov/cder/drug/InfoSheets/HCP/methadoneHCP.htm>.)
- In July 2007, FDA issued “Public Health Advisory, Methadone Use for Pain Control May Result in Death and Life-Threatening Changes in Breathing and Heart Beat.” (See <http://www.fda.gov/cder/drug/advisory/methadone.htm>.)
- More FDA information is summarized at <http://www.fda.gov/cder/drug/infopage/methadone/default.htm>.

Scale (SOWS)¹⁵ and the Clinical Opiate Withdrawal Scale (COWS)¹⁵ are valuable tools during this treatment phase.

All dosing adjustments must consider the patient’s characteristics and status. These can include the patient’s dependence level, body mass, other medications, medical conditions, and genetic factors. The OTP must maintain a balance to provide the patient with enough methadone to minimize withdrawal symptoms but not enough to cause an adverse event. If the patient develops symptoms of withdrawal, he or she could relapse to gain relief.

To prevent respiratory depression, methadone should be administered cautiously to patients with medical conditions affecting their breathing, including asthma, chronic obstructive pulmonary disease, heart disease, severe obesity, sleep apnea syndrome, kyphoscoliosis, or CNS depression.¹⁶

Screen Patients for Other Substance and Medication Use

Screening measures can include oral assessments, careful observation of patients, and additional random drug tests. Some programs use “point of collection” screens or tests to determine whether patients have taken substances that could interact with methadone. Within limits, these drug tests can show whether a patient is taking the methadone or diverting it. The tests also can reveal whether the patient is taking other illicit substances. With this information,

treatment providers can prevent potentially dangerous interactions with other medications or illicit substances.

Increase Caution Regarding Take-Home Medications

OTP staff members must balance the desire to keep patients and the community safe against their desire to help patients normalize their lives by providing doses of methadone to take home for unsupervised use. A program that is closed on holidays and Sundays may give a patient take-home doses, but the program medical director must determine that the patient is responsible enough to handle opioid medications for unsupervised use. The medical director must evaluate the patient and should document the evaluation in the patient’s chart.

The medical director must make take-home decisions according to the eight criteria specified in the Federal regulations (42 CFR, Part 8, § 12(i)) and the patient’s length of time in treatment. Careful assessments determine whether patients meet the eight criteria.⁹ Patients who meet the regulatory requirements for unsupervised or take-home use of medication should be counseled by program staff on the risks of using other drugs or medications.¹³ Patients should be encouraged to sign release forms so that OTP physicians can contact other healthcare providers to identify all the patients’ prescriptions. All decisions should be documented in patients’ charts.¹⁷

In some States, OTP physicians access State Prescription Drug Monitoring programs to determine whether patients are receiving prescriptions for medications that could interact with methadone.

Some jurisdictions require that OTPs operate 7 days a week to avoid the need for take-home doses. This requirement is consistent with the consensus panel recommendations in TIP 43.⁹ According to SAMHSA guidance,¹⁷ if the medical director determines a patient is ineligible for take-home doses, an OTP that closes for Sundays and/or holidays should arrange for the patient to take methadone under supervision.

Programs may conduct random call-backs, asking patients to return to the facility before their scheduled appointments and bring with them the remainder of their take-home medication. Staff members can then determine whether the correct amount of methadone remains or whether it has been diverted.⁹ Some States require that patients carry take-home doses in locked boxes or use other secure methods of transporting and storing the medication.

Educate OTP Staff

To ensure good practice, medical and program staff members should receive ongoing education that updates their awareness about the following:

- Current knowledge, such as lower recommended induction dosages;
- Current information on what is known about methadone's pharmacology, adverse effects, abuse potential, and withdrawal symptoms;
- The risks of misuse of methadone;
- Procedures for obtaining a thorough medical and psychosocial history of the patient; and
- Protocols for appropriate dosing and patient monitoring.

Educate Patients

Patients may be less likely to use or handle methadone in a risky manner when they know the possible dangers.

Resource List

Center for Substance Abuse Treatment. (2005). *Medication-assisted treatment for opioid addiction in opioid treatment programs* (Treatment Improvement Protocol Series 43, HHS Publication No. SMA 05-4048). Rockville, MD: Substance Abuse and Mental Health Services Administration. Retrieved April 13, 2009, from <http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat5.chapter.82676>

Leavitt, S. B. (Ed.) (2006). *Pain treatment topics: Methadone-drug* interactions (*Medications, illicit drugs, & other substances)*. Glenview, IL: Mallinckrodt Pharmaceuticals. Retrieved April 13, 2009, from http://pain-topics.org/pdf/Methadone-Drug_Intx_2006.pdf

Methadone (Dolophine) prescribing information. Retrieved April 13, 2009, from http://www.fda.gov/cder/drug/infopage/methadone/dolophine_PI.pdf

National Drug Intelligence Center, U.S. Department of Justice. (2007). *Methadone diversion, abuse, and misuse: Deaths increasing at alarming rate* (Document ID: 2007-Q0317-001). Washington, DC: Author. Retrieved April 13, 2009, from <http://www.usdoj.gov/ndic/pubs25/25930/index.htm>

Education methods should engage patients. Brochures, pamphlets, and other educational resources need to be presented using language and formats that each patient can understand. Early in treatment, in particular, the patient may need information presented in ways that are concrete, simple, repetitive, and easy to understand. Because the greatest number of OTP methadone-associated deaths occur during the induction stage, it is especially important to communicate effectively with patients during this phase. However, patient education needs to continue during all phases of treatment. Patients need the following:

- **Information about the safe use and storage of take-home methadone.** OTP staff members need to warn patients about the danger of accidental overdose by

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people living with the patients or who have access to the methadone. Methadone must be kept out of the reach of children who may inadvertently drink the colored liquid and overdose. Small children, because of their lower weight, could easily be poisoned if they consumed a methadone dose calibrated for an adult's weight.

- **Counseling to take methadone exactly as prescribed.** Patients given take-home doses should be advised that taking more methadone than prescribed can cause breathing to slow or stop and can cause death.
- **Counseling about interactions with other prescription and over-the-counter medications.** Patients need to talk to their healthcare provider about taking or stopping other medications. These other medicines may interfere with the effectiveness of methadone. They may also interact with methadone, potentially leading to a toxic buildup of methadone in the body that can trigger dangerous and potentially fatal changes in breathing or heart beat.
- **Information about the signs of methadone overdose.** These signs include trouble breathing or shallow breathing; extreme tiredness or sleepiness; blurred vision; inability to think, talk, or walk normally; and feeling faint, dizzy, or confused. Patients, especially patients new to methadone, need to be told that these symptoms can occur even when patients have not purposefully abused the medication or taken “extra” doses. If these symptoms or signs develop, patients should get medical attention immediately.

Educate Family Members and Significant Others

Many OTP patients have family members and significant others who are involved in their treatment and recovery. As part of the family education component of treatment and recovery, family members and significant others need to be educated about the topics listed above. Safe storage of take-home doses is particularly important if children are present in the residence. To help prevent diversion of methadone, patients and family members need to make sure that the medication is securely stored at home, preferably

in a locked safe box, to prevent unauthorized access. Any misuse or unauthorized use of a patient's methadone needs to be reported to the appropriate staff at the OTP, and steps should be taken to provide immediate medical attention, as necessary, in the event of accidental poisoning.

Notes

- ¹Center for Substance Abuse Treatment. (2007). *Background information for Methadone Mortality—A Reassessment*. Rockville, MD: Substance Abuse and Mental Health Services Administration. Retrieved April 13, 2009, from http://www.dpt.samhsa.gov/pdf/MethadoneBackgroundPaper_72007_2_.pdf
- ²Center for Substance Abuse Treatment. (2007, July). *Summary report of the meeting: Methadone Mortality—A Reassessment*. Rockville, MD: Substance Abuse and Mental Health Services Administration. Retrieved April 13, 2009, from http://www.dpt.samhsa.gov/pdf/Methadone_Report_10%2018%2007_Brief%20w%20attach.pdf
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- ⁹Center for Substance Abuse Treatment. (2005). *Medication-assisted treatment for opioid addiction in opioid treatment programs* (Treatment Improvement Protocol Series 43, HHS Publication No. SMA 05-4048). Rockville, MD: Substance Abuse and Mental Health Services Administration.
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- ¹³Center for Substance Abuse Treatment. (2007). *Guidelines for the accreditation of opioid treatment programs*. Rockville, MD: Substance Abuse and Mental Health Services Administration. Retrieved April 13, 2009, from <http://www.dpt.samhsa.gov/regulations/accreditation.aspx>
- ¹⁴Clark, H. W. (2007). Importance of determining initial methadone dose. *Dear Colleague letter*. Retrieved April 13, 2009, from <http://www.dpt.samhsa.gov/pdf/dearColleague/09-04-07%20DearColleagueLetter%20on%20Dosing.pdf>
- ¹⁵Center for Substance Abuse Treatment. (2004). *Clinical guidelines for the use of buprenorphine in the treatment of opioid addiction* (Treatment Improvement Protocol Series 40, HHS Publication No. SMA 04-3939). Rockville, MD: Substance Abuse and Mental Health Services Administration.
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