By Jonathan J. Lipman, PhD

THE METHADONE POISONING "Epidemic"

Increasing use of Methadone as a pain killer may be fueling a disturbing increase in deaths related to this potent drug.

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Death and morbidity associated with methadone treatment has increased dramatically in recent years, largely in the population prescribed this drug for pain control rather than addiction maintenance. Inadvertent overdose is becoming increasingly common, likely in part because the drug's acute pain-relieving effect lasts only 4 to 6 hours, yet it has a very long and variable plasma half-life of 24 to 36 (in some studies 15 to 55) hours, is stored in body tissues, and toxic accumulation occurs with too-frequent consumption. Adverse effects are most common in patients treated with methadone in combination with other drugs. Both cardiac and respiratory systems are vulnerable targets for the drug's toxic actions, and other co-administered drugs can interactively increase the risk of death through a variety of mechanisms including direct central nervous system depression of respiration, idiosyncratic respiratory vulnerabilities, and lethal cardiac arrhythmias. Idiosyncratic factors also play a part in methadone's cardiac toxicity, and risk factors are well characterized, though perhaps not sufficiently widely known and understood by key stakeholders. The recent change in FDA labeling requirements for the drug—and the November 2006 posting of a government warning regarding its use in pain treatment—has not yet reduced morbidity and mortality associated with methadone as reported in the MedWatch database for the first quarter of 2007.

"Methadone at high doses, or in naive users or idiosyncratically at much lower doses, depresses respiration and may interfere with cardiac function, either or both of which can lead to death."

Joshua Perper, chief medical examiner for Broward County, displays a bottle of methadone collected in a possible drug overdose death. KRT PHOTO BY ANASTASIA WALSH/SOUTH FLORIDA SUN-SENTINEL

Forensic Relevance

Methadone is a synthetic morphine-type (opioid) drug developed in Germany in 1937 and introduced to the United States in 1947 by the Eli Lilly company under the trade name Dolophine®. It is now classified and restricted as a Schedule II drug. Methadone has two principal legitimate clinical uses: [1] substitution treatment of opiate drug dependency, and [2] analgesia for chronic pain. In addition, methadone is also subject to diversion and illicit consumption as a drug of abuse.

Methadone-related cases come under forensic review for a number of reasons, now more than in the past. Methadone toxicity may be sub-lethal (affecting behavior and mental condition) or lethal. Both forms of toxicity are forensically relevant. Accordingly, reasons underlying forensic interest in methadone are similar to reasons underlying forensic interest in any potentially toxic drug that has both therapeutic and abuse potential. More specifically:

[1] Methadone may adversely affect the behavior and/or culpable mental states of criminal defendants or victims or witnesses to crime.

[2] Methadone may affect the mental and/or physical condition of civil litigants and may play a role as an element of disability determination, liability, and/or damages. Liability could be an issue in a motor vehicle accident caused by a methadone-impaired driver or in a medical malpractice case involving negligent prescription. Damages could be an issue in a case where negligent prescription results in death by overdose, or where tortiously-caused injuries result in a need for methadone maintenance treatment for chronic pain.

[3] Illicit use, possession, and/or distribution of methadone itself constitutes a crime. Moreover, when distribution leads to harm to third parties, there may be additional criminal consequences (e.g., homicide charges against a drug supplier when a recipient dies from overdose).

[4] As a toxic substance, methadone may be an instrument for homicide or suicide, or its therapeutic or recreational use may result in accidental death. Sorting among these possibilities is of obvious forensic relevance.

Adverse Outcomes: Sub-lethal Toxicity

Methadone is commonly associated with automobile driving accidents, yet studies on the effect of methadone on psychomotor impairment and neuropsychological function are complicated by the fact that the methadone-using population suffers from multiple co-morbidities, and impairments may be due in part to other factors including chronic pain, psychiatric problems, sequelae of chronic alcohol abuse, and invariably, too, traffic accidents involve other drugs in addition to methadone.

Methadone maintenance patients, addicts taking stable supervised doses to the effects of which they are tolerant (see below), tend to have automobile driving accidents at a rate not greatly dissimilar to the general population (reviewed by Stout & Farell, 2002).

Correlating driving performance deficits with neuropsychological performance deficits proves more complicated: Some studies find no difference between methadone maintenance patients and control groups (Maddux, Williams, & Ziegler, 1977) while others find between 50% to 80% of chronic methadone maintenance patients to be neuropsychologically impaired (Darke, Sims, McDonald, & Wickes, 2000; Dittert, Naber, & Soyka, 1999) with deficits in information processing, memory, attention, and problem solving ability. Yet other studies have concluded that the performance of patients stabilized on methadone for 3 months and tested in driving simulators is similar to community-equivalent control patients (Lenne, Dietze, Rumbold, Redman, & Triggs, 2003). It would seem on balance that the neurobehavioral deficits of the majority of chronic, stable, methadone-treated patients are usually not of a degree to cause accidents, or such patients avoid circumstances in which their impairments may contribute to driving accidents.

In non-addicted subjects given methadone, however, measurable and dose-related impairments typical of opiate drug effects are seen in choice reaction time and continuous performance test measures (Rothenberg, Schottenfeld, Meyer, Krauss, & Gross, 1977); in attention, perception, and learning tasks (Gritz et al., 1975); and in tests for visual vigilance (Rothenberg, Schottenfeld, Gross, & Selkoe, 1980), although these impairments are less severe than are seen with diazepam or alcohol (Chesher, Lemon, Gomel, & Murphy, 1995).

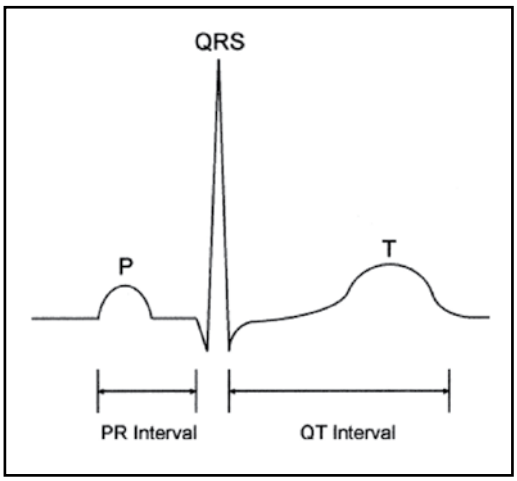
Problems of neurobehavioral impairment due to methadone, thus, typically occur in the early stages of treatment or when a dose-adjustment has been made, as blood levels are rising and before stable plateau-like kinetics have been reached and before the user has subjectively adjusted to, and learned to compensate for, the effects of the drug.

Adverse Outcomes: Lethal Toxicity

Methadone at high doses, or in naïve users or idiosyncratically at much lower doses, depresses respiration and may interfere with cardiac function, either or both of which can lead to death. An additional complication is that of co-morbid illness, which in the methadone maintenance population includes a disproportionately large proportion of HIV/AIDS patients and viral hepatitis patients who acquired their addiction from IV opiate abuse and their illness from needle-sharing. In this tragic population, the secondary treatment of drug-abuse-related illnesses greatly increases the risk of drug interaction with methadone.

Cardiac system. Cardiac problems associated with methadone toxicity and the heart's underlying vulnerability to these can be described in terms of the electrocardiogram (ECG): The *QT interval* of the ECG, measured from the beginning of the QRS complex to the end of the T wave (see **Fig. 1**), represents the duration of activation and recovery of the heart in a single beat as measured by the electrocardiogram. QT intervals corrected for heart rate (QTc) longer than 0.44 seconds are generally considered abnormal, though a normal QTc can be slightly prolonged in some otherwise normal females (up to 0.46 sec). *Torsade de Pointes* (TdP, or *"torsades"*) is defined as a polymorphous ventricular tachycardia in which the morphology, the shape, of the electrocardiogram's QRS complexes varies from beat to beat. The ventricular rate in TdP can range from 150 beats per minute (bpm) to 250 bpm. TdP usually starts with a prolonged QT interval.

At high doses, methadone, even in otherwise normal subjects, is associated with an increased risk for QT prolongation and TdP, especially at very high doses. The risk of QT prolongation appears to be dose-related. Laboratory studies, both *in vivo* and *in vitro*, have demonstrated that prolongation of the QT interval operates through methadone's inhibition of cardiac potassium channels (Islander & Vinge, 2000). Most cases involve patients being treated for pain with large, multiple, daily doses of methadone, although cases have been reported in patients undergoing maintenance treatment of opioid addiction (Krantz, Kutinsky, Robertson, & Mehler, 2003; Walker, Klein, & Kasza,



▲ **Figure. 1** The QT interval of the electrocardiogram (adapted with permission from Crouch et al 2003)

2003). For this reason methadone must be used with extreme caution in vulnerable populations or when co-administered with other drugs known to prolong the QT interval—a list that is extensive and includes antipsychotics, tricyclic antidepressants, beta agonists, and certain antibiotics (see **Table 1**).

Certain populations are idiosyncratically more vulnerable than others to suffering from prolonged QT and TdP even in the absence of drugs. Risk factors include female sex, elderly, significant bradycardia, hypokalemia, hypomagnesemia, and underlying cardiac disease such as cardiomyopathy, arrhythmias, and myocardial ischaemia. Because women normally have a longer QT interval than men, and because the interval increases with age, elderly women are at a particularly increased idiosyncratic risk. Cardiotoxic interactions are not the only danger of drug interaction with methadone. Certain drugs such as selegiline and rasagiline, the monoamine oxidase type-B inhibitors (MAOI-Bs), interact dangerously with methadone, and can cause excitation, sweating, rigidity, hypertension, severe respiratory depression, coma, and peripheral vascular collapse, possibly resulting in death. At least 2 weeks should elapse between stopping these MAOI-B drugs and starting methadone (Azilect, 2006; Emsam, 2007).

Respiratory system. Concomitant use of methadone with another central nervous system (CNS) depressant can lead to additive respiratory depression, and the list of CNS depressants is large indeed, including alcohol, sedatives, anxiolytics, muscle relaxants, anti-epileptic drugs, and tranquilizers. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant, because respiratory depression, hypotension, and profound sedation or coma may result. To add to the complexity of risks, some CNS depressants are also included among the drugs which prolong the heart's QT interval.

Pulmonary edema is also a common manifestation of opiate, including methadone, toxicity (Gottlieb & Boylen, 1974). A white or pink watery froth is seen around the nostrils and lips of the usually comatose patient, and respiratory depression, cyanosis, and constricted pupils (an opiate effect) are usually evident. Moist rales, rhonchi, and wheezes may be heard over the chest. Naloxone, the specific opiate antagonist, is always administered (IV bolus followed by continuing IV infusion) to reverse central respiratory depression, but it does not reverse pulmonary edema, which is treated with intubation, mechanical ventilation, intravenous steroids, and diuretics, the latter with caution because opioids reduce blood pressure (Presant, Knight, & Klassen, 1975).

Pneumonia is a common respiratory complication of pulmonary edema resulting from non-fatal methadone poisoning. It may follow a pulmonary infarct or bacterial invasion. Another common complication of methadone—or any opiate—poisoning is regurgitation pneumonitis, with increasing hypoxemia being evident, because opiates are quite emetic in effect. They also suppress the cough reflex (one reason why opiates are prescribed), which may contribute to yet another pulmonary complication of atelectasis.

Is there an epidemic of lethal methadone cases?

Between 1998 and 2003, prescriptions for hydrocodone, oxycodone, and methadone all increased markedly, and methadone use increased from 0.5 to 1.8 million prescriptions. Continuing this trend, unique patient prescriptions for methadone increased 80% from 2005 to 2006, this increase largely accounted for by pharmacy dispensing rather than self-dispensing methadone maintenance programs (Reuter, 2004). With this increase in methadone use has come an increase in methadone-related deaths.

An increase in death associated with methadone was apparently first noted, at least in the lay press, by investigative reporters Scott Finn and Tara Tuckwiler in West Virginia in 2003 (West Virginia Gazette, 2003). Following up on this report, or perhaps independently, the National Center for Health Statistics (NCHS) (Fingerhut, 2007) found that in the United States, methadone was a factor in the deaths of 3,849 people in 2004, an increase of 390% from the 1999 figure of 786, and an increase of almost 900 deaths from the previous year. Deaths due to all poisonings increased only 54% in this 1999–2004 time period. During 2003 methadone-related deaths rose 29%, while all poisonings rose only 6%. Methadone was responsible for more deaths than any single prescription pain-

Table 1: Drugs that prolong the heart's QT interval (see text for abbreviations, list adapted from Clinical Pharmacology, 2007)

Higher risk for QT prolongation:

- Class IA antiarrhythmics: disopyramide, procainamide, quinidine
- Class III antiarrhythmics (amiodatone, bretylium, dofetilide, ibutilide, sotalol),
- astemizole, arsenic trioxide, bepridil, cisapride, chloroquine, clarithromycin droperidol, erythromycin, grepafloxacin, halofantrine, haloperidol, levomethadyl, Pentamidine
- Certain phenothiazines (chlorpromazine, mesoridazine, and thioridazine),
- Pimozide, probucol, sparfloxacin, and terfenadin

Lower but possible risk of QT prolongation and TdP include:

Abarelix, alfuzosin, amoxapine, apomorphine, beta-agonists, certain quinolones (ofloxacin, ciprofloxacin, gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin), clozapine, cyclobenzaprine, dasatinib, dolasetron, flecainide, halogenated anesthetics, lapatinib, local anesthetics, maprotiline, mefloquine, octreotide, olanzapine, ondansetron, paliperidone, palonosetron, some phenothiazines (fluphenazine, perphenazine, prochlorperazine, and trifluoperazine), propafenone, quetiapine, ranolazine, risperidone, sertindole, sunitinib, tacrolimus, telithromycin, tricyclic antidepressants when given in excessive doses or overdosage, troleandomycin (based on interactions with macrolides), vardenafil, vorinostat, or ziprasidone

killer listed in the NCHS report, including oxycodone, fentanyl, morphine, and codeine. Between 73% and 79% of poisoning deaths mentioning methadone were classified as unintentional, with an additional 11% to 13% being of undetermined intent. The number of deaths in 2004 was five times the number in 1999. Among those aged 55 to 64 years, the death rate due to methadone in 2004 was seven times the rate in 1999; for those in each of the 10-year age groups covering the span 25–54 years, the rates in 2004 were 3–5 times the rates in 1999. The largest increase, however, was noted for young persons 15 to 24 years; the rate in 2004 was 11 times that in 1999. In those states with the largest numbers of methadone-related deaths (greater than 50 for at least 3 of the 6 years of the survey) the ratio of 2004:1999 numbers was reported as: West Virginia (25:1), Kentucky (15:1), Florida and Oregon (both 14:1), North Carolina and Texas (7:1), Virginia (6:1), and Washington (5:1). New York showed no overall change (ratio 1:1) during the 6 years of the survey (Fingerhut, 2007). Clearly the regional differences require further study in order to address countermeasures specific to the population 'overdosing,' yet globally the phenomenon, described more fully below, has been attributed to a combination of inadvertent overdose and drug interaction in patients prescribed their drugs by their primary care providers (PCPs) in an attempt to treat a pain condition.

Causes of Adverse Methadone Outcomes

Not surprisingly, causes of adverse outcomes from the use of methadone appear multifactorial and require an understanding of both the pharmacology of methadone and of the particular types of human errors associated with its prescription and use.

Changes in Attitudes Toward Treating Pain

One factor in methadone's injudicious prescription and use is likely common to the forces encouraging analgesic prescription in general. The historical undertreatment of pain is a serious problem that has become a current focus of educational, legislative, and patient advocacy. Undertreatment is a problem in both acute pain and chronic pain populations, and, among the latter population, benign and malignant subgroups each have their own unique needs for pain control strategies. Pain is described as an "epidemic" by the American Academy of Pain Management (AAPM), affecting millions in the United States. Fifty million Americans are partially or totally disabled by pain, and 45% of all Americans seek care for persistent pain at some point in their lives (APS, 1999). If untreated, pain can lead to depression, loss of sleep, depressed immune function, change in eating patterns, decreased mobility, and other long-term deleterious effects in addition to morbidities due to the underlying cause of the pain. With proper and timely pain treatment, these effects may be minimized or eliminated.

New regulations governing hospital practice promulgated by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), which came into force January 1, 2001, require health-care workers to treat pain as 'the fifth vital sign,' and educational initiatives are currently being introduced throughout practitioner training and established practice guidelines to introduce the JCAHO mandates as these pertain to clinical care. This initiative continues the earlier work of the International Association for the Study of Pain (IASP) and the AAPM into raising physician and nurse awareness of the need for humane treatment of pain and promoting the doctrine that pain is both unnecessary and avoidable with appropriate drug treatment (AGS Panel, 1998).

Pharmacology of Methadone

Half-life

Methadone is highly lipophilic with rapid gastrointestinal absorption and onset of action. It has a large initial volume of distribution with slow tissue release. Oral bioavailability is high (80%). Unlike morphine, its metabolites are not active and therefore no dose adjustment is necessary in renal failure patients. The major route of metabolism is hepatic with significant fecal excretion; renal excretion can be enhanced by urine acidification (pH <6.0). The serum methadone level typically reaches a peak in 2 to 4 hours on average (range 1 to 5 hours) after dosing, but its elimination half-life is much longer and the patient's physiologic response may be influenced by many factors.

To clarify the term *half-life*: After the passage of one half-life of time, plasma levels will fall to one-half of their original level. After the second half-life, they will fall one-half again, to one-quarter of their original level. After a third half-life's passage, they will fall by one-half again—to one-eighth of their original level, and so on. We usually assume that 5 to 7 half-lives are required to clear a drug from the body.

In contrast to its comparatively short-acting relative morphine, whose average elimination half-life ranges from 2 to 3 hours (longer in men than women), the half-life of methadone averages **24 to 36 hours** at steady state, but may range from 4 to 91 hours, and its rate of clearance from the body can vary by a factor of almost 100 (Inturrisi & Verebely, 1972; Loimer & Schmid, 1992; Payte & Zweben, 1998). The long half-life of methadone is in part a result of the drug being stored extensively in the liver and to a lesser extent in other body tissues. The amount in the blood stream is kept relatively constant in the regular user by slow release of methadone from these tissue stores. (For review, see Leavitt, 2003).

The long half-life of methadone makes it almost ideal for use as a substitute for illicit opioids with shorter half-lives such as heroin or morphine, because the methadone-maintained patient is freed from the turbulent subjective "highs" and "lows" of shorter-acting drugs, freed from the necessity of re-dosing every few hours to avoid withdrawal, and is able to hold a job and attend to the needs of daily living without focusing on and obsessing about the always impending need for the next 'fix.' Dosing can be once-daily, un-yoking the addict from the drug consumption cycle. Further, by gradually and very carefully increasing the methadone dose over time, the addict can be rendered so severely opiate tolerant that the illicit opiate doses typically available to the user will have little or no euphoric effect. Thus, high doses—doses that would be lethal to an opiate-naïve person—are the norm in the methadone-maintained population. About 20% of the estimated 810,000 heroin addicts in the United States receive methadone maintenance (American Methadone Treatment Association, 1999).

As a corollary of its relatively long half-life, when taken regularly, every 8 to 12 hours, methadone concentrations in the body, measured in blood, build up slowly until a steady state plateau is reached—the process can take a week or, in some individuals, longer, to achieve (Leavitt, 2003; Eap, Buelin, & Baumann, 2002; Payte & Khuri, 1993).

During the initial methadone-induction period, prior to steady state being reached, an essential consideration is that about half of each day's dose remains in the body and is added to the next day's consumption, producing rising serum methadone levels *even without any increase in dose* (Payte, 2002, as cited in Leavitt, 2003). After each increase in methadone dosage, it will take 4 to 5 days,

or more, to achieve steady state at the new total dose (Payte, Zweben, & Martin, 2003). **Therefore, adding dose increases before a full steady state has been reached at a current dose must be considered cautiously, because failing to wait until steady state has been reached before increasing to the next dose level can easily result in overdose.**

Drug Interactions

As previously discussed, methadone may interact with other CNS depressants to produce lethal respiratory depression—people die because they simply stop breathing as a result of the depression of the brain's respiratory centers. In addition, the combination of methadone with other drugs may interfere with the enzymes responsible for methadone's metabolism, thereby increasing methadone's serum concentration and leading to overdose. Because methadone is commonly taken in combination with other drugs, including over-the-counter preparations, specialist neuropharmacological consultation regarding potential drug interactions is often required.

More specifically, methadone is metabolized by processes in the liver that employ Cytochrome P450 (known as CYP), particularly the 3A4, 2C, and 2D6 subtypes of this polymorphous enzyme system. N-demethylation results in the formation of the inactive metabolite, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP). Some drugs (e.g., amiodarone, clarithromycin, erythromycin, or diltazem) may increase plasma methadone concentrations by inhibiting cytochrome P450 3A4. All selective serotonin reuptake inhibitor (SSRI) antidepressants may inhibit CYP 3A4, 2C, and/or 2D6 to varying degrees (Hansten, 2007).

These SSRI antidepressants (e.g., sertraline [Zoloft®], fluvoxamine [Luvox®], and fluoxetine [Prozac®], among others) may increase methadone plasma levels upon co-administration with methadone, and the combination can result in increased opiate effects and/or toxicity. Thus, methadone-treated patients co-administered SSRIs should be carefully monitored, and dosage adjustment should be undertaken if warranted (Dolophine®, 2006). Fluoxetine may inhibit the metabolism of methadone via CYP 3A4 and is a relatively potent inhibitor of CYP2D6 (Prozac, 2003). Interestingly, in patients treated with methadone, it has been shown that plasma levels of the R-enantiomer (the active analgesic species of the methadone molecule) is increased by the addition of fluoxetine, and both the R- and S-enantiomer are increased in patients receiving fluvoxamine, an inhibitor of CYP2C19 and CYP3A4. In some patients receiving methadone for opiate dependence, the addition of fluvoxamine has produced a substantial increase in methadone serum concentrations and has been associated with symptoms of methadone toxicity ("Fluvoxamine," 2005).

Tolerance

There is no "toxic level" of methadone. Rather, people die of so-called "overdose" as a result of the effect of a blood level that exceeds their individual tolerance to the drug's toxic effects on respiration and heart function. The majority of people who die as a result of taking methadone have post-mortem blood concentrations that would produce no adverse effects in a patient chronically maintained on the drug. Overdose, then, is an idiosyncratic phenomenon depending on individual susceptibility, co-morbid illness, drug use history, and—often—the interactive effects of other drugs taken.

Tolerance is defined as a reduced response to one or more effects of a drug after repeated administrations (Leavitt, 2003; Kosten & George, 2002; O'Brien, 1996). Essentially, opioid receptors on nerve cells become less sensitive to opioid stimulation, and more drug is needed to achieve the same effects. However, tolerance develops much more rapidly to some opioid effects than others. For example, tolerance develops quickly to the euphoric effects of opioids, while tolerance to gastrointestinal effects (e.g., constipation), sedation, or respiratory depression is slower to develop. This can be potentially fatal if users ingest increasingly greater amounts for purposes of obtaining the euphoric effect (Harden, 2002; White & Irvine, 1999) or in pursuit of analgesia. Tolerance development is specific to the drug class, such that tolerance to the respiratory depressant effects of opiates does not affect tolerance to the respiratory effect of other non-opioid central nervous system (CNS) depressant drugs. In the case of methadone, tolerance development is incomplete (Kosten & George, 2002), so that respiratory depressant effects of other opiates, or acutely excessive methadone, may not be completely attenuated even in persons at stabilized methadone-maintenance doses.

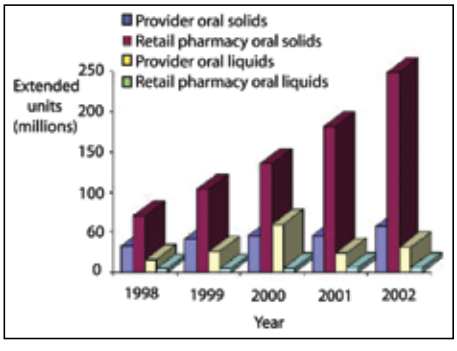
Tolerance to opiates is lost quite rapidly, so that upon resuming the opiate regimen after a period of abstinence the user is required to begin re-initiated treatment at a lower dose than previously. Failure to recognize this may have lethal consequences, particularly with methadone in light of the discrepancy between pharmacodynamic and pharmacokinetic time courses. Thus, not unexpectedly, Strang et al. (2003) found that patients who "successfully" completed inpatient detoxification and abstinence were more likely than other patients to have died of opiate overdose within a year of detoxification.

Human Errors

Methadone is sold as both liquid and solid (tablet, diskette, and soluble tablet) formulations, the liquid being used principally in methadone maintenance programs. Although use of all formulations of methadone has shown steady, incremental growth over the past several years, the distribution of tablets (most often used in pain management) and diskettes has surpassed that of liquid formulations. For example, the rate of increase from 1999 to 2002 was far greater for sale of tablets (331 percent) than for either diskettes (147 percent) or liquids (175 percent). In 2002, about 55 percent of all methadone distributed nationwide was in the form of tablets or diskettes (Howard, meeting presentation, 2003, as cited in CSAT, 2004). See **Figure 2**.

With respect to fatal overdose, studies have confirmed that the source of the methadone in the overdose cases of recent years is not the methadone maintenance clinics but general practitioners prescribing the drug ostensibly for pain control. In a Utah study, 48 of the 114 deceased were themselves prescribed the drug, the rest either obtaining it from a family member or an undetermined source. About 20 percent of West Virginians who died from methadone overdose had no other drug in their systems. According to the National

▼ **Figure 2.** Number of units of methadone distributed 1998-2002 through retail and other channels, by dosage form (Data from IMS Health, Retail and Provider Perspective, courtesy of Laura A. Governale, PharmD (adapted from CSAT, 2004)



▲ The casket containing the body of Anna Nicole Smith is ushered into Mount Horeb Baptist Church by pallbearers for her funeral in Nassau, Bahamas, on March 2, 2007. She and her son, 6 months earlier, both had their deaths linked to methadone use. (Carl Juste/Miami Herald/MCT)

Center for Health Statistics, between 1999 and 2004, the unintentional death increase in West Virginia increased (per 100,000 of the population) by 24.8%, in Kentucky by 15.1%, in North Carolina by 7.2%, and by 5.1% in the United States as a whole (Reuter, 2007).

Problems with Methadone Analgesia

Why should a disproportionate number of fatal overdoses come from the population receiving methadone for pain control as compared to addicts receiving it for treatment of opiate addiction? Certainly the drug is cheap, and certainly it is a good and powerful pain killer. Analysis of this question benefits, in the first instance, from understanding that human errors contributing to methadone overdose appear significantly related to failure (perhaps especially by prescribers) to respect important differences between addiction and pain treatment contexts.

In the United States, methadone can legally be prescribed as an analgesic—as a pain reliever—by any prescriber, but, since 1973, to prescribe it as a treatment or maintenance drug solely for opiate addiction (outside of its time-limited use in a hospital where the admission is for other purposes) requires special training, special personnel, special permissions, and special facilities using special record-keeping requirements dedicated to the purpose (Rosenbaum, 1995). The opening of such facilities requires community approval, which can be hard to obtain, and the strategy of requiring such facilities has ensured that addicts are made to congregate at these treatment centers, often having to relocate miles from their homes and families for this purpose.

The lethality of methadone in the population prescribed this drug for pain control has been laid at least in part on a failure of non-specialist practitioners, and the patients they advise, to properly understand the difference between opiate-dependent pain patients and the methadone maintenance population of addicts, who are for the most part not in pain and not otherwise dosing to achieve pain relief and who may comfortably and slowly, stepwise and cautiously, ramp up their methadone dose under close supervision, to ultimately take very large doses of the drug per day.

Furthermore, just because methadone is used in maintenance of opiate addicts, it is not a "treatment" for dependence or tolerance in opiate-using pain patients. The pain patient is driven by need for pain control, and breakthrough pain drives analgesic consumption, yet despite its long elimination half-life, the acute analgesic effect of methadone lasts **only 4 to 6 hours**. As a result, patients taking the drug on a twice-daily (every 12 hours) schedule with the intention of pain relief may feel the subjective need to take another dose after this short 4 to 6 hour interval, leading to increased accumulation and toxicity and death. Guidelines for the use of methadone in pain control emphasize the need to carefully tailor dose and regimen to the individual (see Gouldin, Kennedy, Ralph, & Small, 2000; Tennant, 2007).

In sum, methadone's long half-life, the very reason why it is ideal for addict maintenance, can render it dangerous in pain-management contexts. The long plasma half-life is not matched with the relatively shorter analgesic time course of the drug. When the analgesic effect wears off, patients naturally want more relief, and the recurrence of symptoms encourages patients to take methadone at a frequency that results in escalating accumulation in the body. Patients may be further misled into such a tragic course of conduct if they assume that methadone can be safely taken at the briefer intervals typically employed with other, shorter-acting, analgesic drugs (which may even be concomitantly prescribed for "breakthrough" pain). As is painfully obvious, death can result from nothing more than misguided attempts to treat pain.

Product Labeling

Blame for methadone deaths has been laid also at the product labeling. Until November 2006, the package insert for methadone included reference to a potentially fatal (for opiate-naïve patients) "usual adult dose" for pain patients—up to 80 milligrams a day. In addition to revising the package insert, providing a black box warning and reducing the recommended maximum dose to 30mg per day, the FDA in November 2006 issued a Public Health Advisory entitled "Methadone Use for Pain Control May Result in Death" (FDA, 2006).

Most recently the journals of the medical and professional pain management societies have been publishing articles and editorials on the subject of methadone lethality in pain management (see Tennant, 2007 and Kuehn, 2007). Yet pain management specialists are likely not the primary offenders, because, like the methadone maintenance clinics, their staffing level and familiarity with the hazards of methadone pharmacokinetics and pharmacodynamics typically provides for a cautious and well-managed approach of the opiate-treated patient.

It is not yet clear what effect the November 2006 cautionary, educational, regulatory, and labeling changes will have on prescribing practices. Death due to methadone typically strikes while serum levels rise early in the intended course of treatment, however, comparing statistics on methadone-related morbidity between the first quarters of 2006 and 2007 would seem likely to capture this statistic.

The U.S. Food and Drug Administration (FDA) maintains a database of Adverse Event Reports (AERs) which consolidates reports from practitioners and the pharmaceutical industry. The program is called MedWatch. Reports can be filed by mail or on the Web and are analyzed quarterly. Data for the first quarter (Q1, 1 January to 30 March) of 2007 are currently available at time of writing (MedWatch, 2007). Certain outcomes reported in the database lie outside of the scope of interest of this present review (the teratogenic outcome of congenital anomaly, for instance). A small number of reports do not describe the AER outcome, yet the data is

	2004				2005				2006				2007
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1
Total AER cases in quarter	65,975	60,222	75,451	70,752	76,180	80,614	81,314	88,518	89,527	79,597	71,724	83,229	88,832
Total Methadone cases	152	268	261	423	226	254	294	520	179	328	240	367	331
Dead	35	111	70	210	57	50	82	318	39	87	69	182	79
Required Hospital	65	82	74	94	85	109	110	96	53	109	82	105	89
Required intervention	2	0	3	5	3	1	4	1	2	3	3	0	9
Long term consequences	2	2	5	6	4	2	1	2	5	31	6	3	16
Disability	3	8	9	12	16	17	7	19	11	13	4	6	3
Congenital anomaly	0	0	1	1	0	1	0	1	5	2	0	51	0
Other outcome	18	49	41	59	46	47	63	55	46	58	56	19	108
No outcome reported	27	16	65	36	15	27	27	28	18	25	20	182	27
Methadone cases/1000 AER	2.30	4.45	3.46	5.98	2.97	3.15	3.62	5.87	2.00	4.12	3.35	4.41	3.73
% of methadone cases dead	23.03	41.42	26.82	49.65	25.22	19.69	27.89	61.15	21.79	26.52	28.75	49.59	23.87

▲ **Table 2.** Adverse Event Report (AER) counts and outcomes extracted from quarterly FDA MedWatch reports between Q1 2004 and Q1 2007

of interest to the present review, because it provides a census of methadone-related incident reports and records the mortality within this cohort. To perform the analysis, the raw ascii drug text files for the four quarters of 2004, 2005, 2006, and the first quarter of 2007 were searched for the keyword "methadone" and the case numbers (unique patient ID numbers) of the identified methadone-associated cases were imported into an excel worksheet. The raw ascii text files were then searched again for all other drugs (in addition to methadone) associated with the previously-identified case numbers and this information added to the Excel worksheet. The separate corresponding "outcome files" (also ascii text files) were then searched for outcomes associated with the previously identified case numbers, and these outcomes imported into the worksheet in affiliation with the drug lists for each case number. The assembled worksheet could then be searched and summarized using standard Excel methods. **Table 2** provides the statistics related to AERs citing methadone as one of the drugs involved in the adverse event.

For the year 2004 (the last year of the NCHS survey of death certificates [Fingerhut, 2007] currently available), it is clear that the MedWatch AER data represent only a small fraction of methadone morbidity cases. NCHS counted 3,849 deaths involving methadone in 2004, yet the MedWatch database for 2004 captures only 426 (Q1 through Q4 combined, Table 2). Although 3 years of data is insufficient to develop a meaningful regression analysis, also apparent in the data of **Table 2** is a quarterly variation in both methadone reports and methadone lethality, which seems to indicate that, at least in the years surveyed, the fourth quarter methadone-related morbidity censuses are larger, and first quarter censuses are smaller than the census in other quarters. Mortality appears to follow a similar end-of-year preponderance, insofar as the Q4 death rate (% of methadone AER cases dead) is disproportionately greater than that in other quarters. In terms of early indications of a significant post-November 2006 drop in methadone-related morbidity or mortality, however, these data provide no such indication when first quarter 2007 data are compared with those of other years' first quarters surveyed.

It is not clear why the fourth quarter should contain both more methadone-related cases and a disproportionately greater methadone-related death rate. The FDA MedWatch staff advises (personal communication) that all data are entered in real-time, as reported to them, with no "bureaucratic" or 'book-keeping' delays in entry. One possibility is that corporate reporters (pharmaceutical companies) may possibly delay provision of information until their annual reports are due at the end of the year, but the current survey did not seek to answer this question by matching reporters to reports. Future studies are planned.

Reporting in the FDA MedWatch system is voluntary for practitioners—though compulsory for industry—so that these data are neither complete nor all-inclusive either as to patient numbers or other drugs taken, yet of the cohort who died taking methadone in the first quarter of 2007, the majority were also taking other psychiatric and pain-related non-opiate drugs. In 20 cases (25%) they were taking other opiates, while in 38 cases (48%) they were also taking benzodiazepines. Of the group hospitalized, only 21/89 (23.5%) were taking another opiate and 22/89 (or 24.7%) were co-administering a benzodiazepine (z-drugs, such as Ambien, Sonata, or Lunesta, were not counted as benzodiazepines in this total).

The MedWatch data provide only an incomplete snapshot, and we need to await follow-up survey reports from the CDC, but initial indications are that the FDA's warning has not yet reduced Adverse Event Reports for methadone.

Conclusions

The current health-care environment, with its recently-adopted renewed emphasis on universal pain management, is undoubtedly at least partly responsible for the increased number of prescriptions of methadone to the pain patient population. Increased morbidity and mortality associated with methadone in the pain patient population is disproportionately larger than that associated with other analgesics and initial indications in the FDA's MedWatch database do not—yet—confirm the early success of public health measures taken to counter this increase. Careful attention to the avoidance of dangerous interactive drug combinations would be helpful in reducing morbidity and mortality, as would careful medical screening to identify individuals idiosyncratically at risk of adverse effects. As to the reason why patients take more than is safe or prescribed, however: practitioner and patient education regarding methadone's shorter analgesic time-course relative to its longer pharmacokinetic half-life, responsible for its propensity to accumulate

in the body when over-used, would seem the only solution.

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