

Maximizing Safety with Methadone & Other Opioids



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A Campaign for Life

Opioids provide life-saving analgesia for the millions of Americans who suffer with chronic pain, yet overdose deaths are rising at an alarming rate, with methadone implicated to a disproportionate degree [Paulozzi et al. 2006; Webster 2005; Warner et al. 2009]. Methadone deaths increased almost seven-fold from 790 in 1999 to 5,420 in 2006, rising faster than deaths from heroin or other opioids, such as oxycodone, hydrocodone, and fentanyl [Warner et al. 2009].

At least some of the deaths appear to be associated with methadone prescribed for pain. The increase in deaths involving methadone (213%) is comparable to the increase in its use for pain management (175%) but not to the increase for opioid-addiction treatment programs (43%) [Paulozzi et al. 2006]. The US Substance Abuse and Mental Health Services Administration (SAMHSA) agrees that the increase in overdose deaths does not correspond to the methadone used in addiction treatment; however, the agency stops short of tracing the increase exclusively to pain treatment [CSAT 2007]. Law-enforcement seizures of methadone increased 262 percent from 2001 to 2007, indicating that diversion for illegal use could drive many deaths [GAO 2009]. Insufficient knowledge among healthcare providers and patients on the safe prescribing and consuming of methadone for pain is another contributing factor to methadone mortality, according to the Government Accountability Office, which analyzed methadone deaths in 2009 [GAO 2009].

Finding solutions is critical. On November 27, 2006, the FDA issued a public health advisory warning of dangers associated with methadone and endorsing more conservative prescribing guidelines [FDA 2006]. Yet many professionals in the medical community who administer methadone for pain remain largely unaware of the need for extraordinary safety measures.

The nonprofit organization LifeSource <<http://www.yourlifeforce.org>> was created to help address these concerns. The first educational initiative from LifeSource – which was started in 2006 – is the *Zero Unintentional Deaths* campaign. This features seminars and media appearances to alert healthcare providers, chronic pain sufferers, and communities to the seriousness of the risk of overdose deaths.

In addition to education that widely disseminates known safety measures for initiating and titrating methadone for pain, a second component of the *Zero Unintentional Deaths* campaign is research. This examines the root causes underlying



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the recent increases in deaths related to prescription opioids, particularly methadone. These two initiatives, education and research, go hand in hand.

Gaps in Clinical Knowledge

The increase in mortality associated with methadone may have many causes. A recent report, authored by an expert panel of physician specialists, epidemiologists, and public-health officials, examined data pertaining to prescription-drug-related deaths. Clear risks included the following [Webster et al. 2011]:

- Methadone was disproportionately involved in a third of opioid-related deaths nationwide during the 2000s, although representing less than 5% of total opioid prescriptions.
- Patients failed to adhere to medical directions, sometimes overusing the medication in an effort to escape pain.
- Patients and nonmedical users mixed methadone with benzodiazepines, street drugs, alcohol, or other central nervous-system depressants.
- Clinicians initiated methadone at too high a dose, escalated doses too rapidly, placed misguided faith in published conversion tables when switching from another opioid to methadone, and were unaware of contributory risks such as sleep apnea and concomitant benzodiazepines.
- Insurance companies and other payers sometimes mandate methadone as first-line therapy for pain due to its low cost.

It appears that clinicians who prescribe methadone for pain and the patients themselves may be underestimating the risk of respiratory depression associated with methadone. Certain research has found that tolerance to respiratory depression is incomplete and outpaced by tolerance to other opioid effects such as euphoria, even in long-term opioid users. Australian researchers White and Irvine [1999], who examined the pharmacologic basis of respiratory depression following opioid administration, found that tolerance to the respiratory-depressant effects of methadone was incomplete as related to the hypoxia-sensitive chemoreceptor mechanism; this contrasted with the carbon dioxide-sensitive chemoreceptor mechanism, which research suggests was complete.

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The pharmacologic properties of methadone have enormous safety implications. Methadone is eliminated from the body at a slower rate than many other medications; its long, variable half-life averages 20 to 35 hours with a range of 5 to 130 hours [Leavitt 2006]. However, analgesia often lasts only about 4 hours. This disparity makes methadone particularly prone to dangerous toxic buildup with potential for respiratory depression.

Genetic contributions may influence vulnerability to overdose. For example, a CYP2B6 gene variant has been linked to the slow metabolism of methadone resulting in high concentrations and, possibly, to methadone-related mortality [Bunten 2011]. A significant correlation was also observed in methadone-related deaths between post-mortem benzodiazepine concentrations and an OPRM1 A118G allele [Bunten 2011].

The Trouble With Conversion Tables

Another problem is over-reliance on published conversion tables for methadone. The doses recommended by conversion tables fail to account for the accumulated toxicity and polydrug interactions that can occur with around-the-clock methadone. Most conversion tables use a ratio to estimate the equianalgesic dose of one opioid to another. It is often assumed that the

tolerance achieved by a patient on a current regimen of opioids allows the clinician to begin methadone at a rate equal to the exact morphine equivalent.

However, cross tolerance is incomplete even for individuals currently prescribed high doses of other opioids. These tables – which are designed for a single use, not for chronic administration – may imply no upper limit exists for the starting methadone dose. One table suggests a conversion rate of 5% to 10% of the oral morphine dose, which may be far too high. For example, if an opioid-tolerant individual were taking up to 500 mg of morphine-equivalent opioids per day, the starting methadone dose could be as high as 50 mg a day. Consider also that prior to the 2006 FDA advisory, package insert guidelines had allowed for a starting daily methadone dose as high as 80 mg. Initial doses like these could prove dangerously high due to methadone's wide variability of half-life and the accumulation that occurs with multiple doses.

The Need for Research

To stop the deaths, we must understand clearly what is causing them. The reasons are likely multi-faceted and poorly articulated to date. No systematic analysis so far has determined what percentage of decedents were A) taking methadone correctly as prescribed for pain, B) taking more methadone than prescribed while chasing greater pain relief or seeking to relieve a comorbid mental disorder, C) mixing methadone with other prescription drugs, street drugs, or alcohol, or D) taking methadone recreationally to seek a high.

Causes for methadone-associated fatalities are likely multifaceted and are poorly articulated to date.

Current death certificates fail to provide for adequate collection of decedent factors that are needed to accurately analyze methadone-related deaths. In addition, improvements are needed in toxicology categories used to code and classify which specific opioids are responsible for deaths as reported in vital statistics databases. Enhancements in these areas would help in the collection of better evaluative data, including the extent to which methadone caused, contributed to, or was present but not contributory in investigated deaths [Webster & Dasgupta 2011].

The data gap invites misinformation. The mass media frequently portray methadone as a deadly street drug, calling it “highly addictive” [Leinwand 2007]. Often, it goes unreported that many people whose pain would otherwise go uncontrolled use methadone and other opioids safely and effectively. And thousands treated in methadone maintenance treatment programs have literally been saved as a result of methadone.

The motivation to hold someone accountable frequently arises even in the absence of all the facts. This dynamic was clearly observed in the media and regulatory frenzy that surrounded OxyContin abuse in the early 2000s. The possibility that a similar fate awaits methadone dramatically underscores the urgent need for quality data.

Research Goals and Concerns

When we begin to ask the right questions, we will start to get useful answers. Based on the literature, patient characteristics that should be examined in methadone-related deaths include: history, duration, and intensity of pain condition, presence of concurrent opioids or other medications, gender, age, race/ethnicity, geographic area (particularly whether urban or rural), body mass index, duration of methadone usage and daily average dose during the last 2 weeks of life, histories of substance abuse and mental illness, and presence of co-occurring disorders such as sleep apnea or cardiac problems [Webster & Dasgupta 2011]. For instance, in Utah, more prescription-drug deaths occurred among people who

Asking the right questions will help produce useful answers for explaining opioid-related deaths.

were overweight than among those who were not [UDOH 2005]. Sleep apnea is of particular interest, and early research found a dose-response relationship of sleep apnea to methadone and benzodiazepines in patients with chronic pain [Webster et al. 2007]. In addition, middle age appears to be a vulnerable period for overdose involving prescription drugs.

The analysis must be carefully performed. It is difficult to determine a cause of death from postmortem methadone blood levels alone. A wide range of postmortem concentrations of methadone is given as fatal, and bias may exist toward assigning an opioid as the cause of death whenever it is present in a toxicology report. Difficulty exists in pinpointing a blood level of methadone that would be toxic in most individuals [Karch & Stephens 2000; Mikolaenko et al. 2002; Pirnay et al. 2004; Wolf et al. 2004]. The undertaking is even more complicated when pain is involved, since levels of methadone typically reported as a cause of death may actually be at therapeutic levels in some patients with chronic pain on long-term methadone therapy.

When a polydrug interaction is documented, benzodiazepines and alcohol are frequent co-causes of death. The exact mechanisms of the interaction of benzodiazepines with methadone, whether additive or synergistic, have been studied [Mikolaenko et al. 2002; Pirnay et al. 2004] but need to be better understood. In addition to their sedative effects, some benzodiazepines can alter the rate at which methadone is metabolized in the system. This drug interaction can make interpretation of postmortem results difficult [Pirnay et al. 2004].

Another question is whether cost issues are driving medical decision making. Methadone is less expensive than many other medications for pain. So, it is worth asking whether patients without insurance are frequent consumers of methadone and also whether some insurance companies require that methadone be tried because of its lower cost. If so, payers may be pressuring physicians who are unfamiliar with methadone to prescribe it ahead of other opioids, and patients may be using methadone solely because they can afford nothing else.

Along with that, it also is possible that a subset of patients likely to be noncompliant is gaining greater access to methadone. Or, perhaps when more methadone is prescribed, it simply translates into more methadone available for misuse (and to potentially be diverted). These questions must be asked so we can gain accurate and helpful answers.

The Need for Education

Patients and the public need to know how to protect themselves and their loved ones from overdose if methadone is used. Practitioners should counsel patients and family members as to methadone's potential for respiratory depression and the absolute necessity of never taking a non-prescribed extra dose of methadone or mixing it with unauthorized substances.

Patients should be counseled as follows: [PainSAFE 2011]

- 1) Never take a prescription pain medication unless it is prescribed for you.
- 2) Do not take pain medication with alcohol.
- 3) Do not take more doses than prescribed.
- 4) Mixing pain medications with sedative or anti-anxiety medications can be dangerous. Follow doctor directions carefully.
- 5) Avoid using pain medications to facilitate sleep.
- 6) Lock up prescription pain medications away from children, other family members, and visitors.

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Patients and the public need education on how to avoid methadone overdose. Practitioners should provide appropriate counseling.

Cautions for prescribers:

Methadone's pharmacologic properties necessitate a conservative approach even for the most opioid-tolerant patients. Rotating from a different opioid to methadone can be dangerous and requires extreme caution. Careful monitoring of the individual patient's response is key, as well as some precautions...

- Experts recommend using a far more conservative calculation when converting from another opioid to methadone than the standard opioid conversion ratio [Fine et al. 2009]; however, even the most conservative conversion calculation may not be safe for some patients. Because conversion calculations may bear little relationship to a safe methadone starting dose, it is better not to use a conversion table at all. At present, the safest course is to consider your patient as opioid naïve for purposes of introducing methadone.
- Safe practice supports starting the conversion with a ceiling dose of no more than 15 mg/day (10 mg/day for elderly or infirm patients).
- Adjust other medications *down slowly (20%-30% per week)*, while titrating methadone *up slowly (no more than 10 mg per week)* as a concurrent process. During titration, patients may be provided with short-acting opioids for breakthrough pain to prevent overuse of methadone in case of inadequate pain control. Assess patients weekly during this period and counsel them to call the clinic with any concerns.
- Dose changes should not occur more often than weekly to allow steady state blood levels of methadone to develop and for the peak side effects to become clear. It may take up to 6 weeks to complete the opioid rotation to methadone. Patience is important.
- If patients are taking concomitant benzodiazepines, the starting dose and speed of methadone titration may need to be adjusted downward [Webster 2005].

These initial dosing guidelines may appear overly cautious to pain practitioners and are even more conservative than dosing guidelines published by the FDA [FDA 2006] and by physician-specialist consensus panels [Chou et al. 2009; Fine et al. 2009]. But more aggressive pain control may follow once the mechanisms underlying the increases in overdose deaths are further researched and better understood.

Take-Away Message

Methadone mentions in overdose deaths have increased with its wider availability to treat pain. Because elimination of preventable deaths is of paramount importance, the medical establishment must urgently respond to any clinical misapplications of opioids. The goal is *Zero Unintentional Deaths* — which is also the name of an education campaign designed to spread the message that opioids entail risks, but those risks can be managed.

All opioids must be respected as powerful medications. Careless prescribing and consuming can be lethal.

Methadone for pain incurs unique safety risks if incorrectly prescribed. It has a long elimination half-life, with analgesia that may last 4 to 8 hours and respiratory depression effects that could linger closer to 2 days on average. Its properties heighten the risk for drug-drug interactions, thereby resulting in unexpectedly excessive initial dosing, among other dangers.

A primary goal of the *Zero Unintentional Deaths* Campaign is to keep methadone available to patients who need it. Methadone is an effective opioid for pain, it has excellent bioavailability, is a good match with most short-acting opioids used to treat breakthrough pain, and is very affordable. Its continued value as an analgesic depends on educating all practitioners who prescribe methadone to treat pain on its unique properties.

Not only methadone but all opioids must be respected as powerful medications. Careless prescribing and consuming of opioids can be lethal. Patients need to know that methadone and other opioids should not be treated like aspirin or ibuprofen, to be increased at will. Finally, because many people are still undertreated for pain, these problems must be swiftly addressed.

Opioid therapy entails risks, but those risks can be effectively and safely managed.

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