

Editor's Note: Dr Lynn R. Webster, President of the Utah Academy of Pain Medicine and Medical Director of Lifetree Clinical Research® & Pain Clinic in Salt Lake City, began a national educational campaign this summer to inform doctors, chronic pain sufferers, and communities across the country about the increasingly serious issue of unintentional overdose deaths with prescription medications, including methadone. He also recently formed a 501 C 3 organization with a mission to educate physicians, patients, and communities on health issues, with an emphasis on pain-related education and research to offer solutions.

Safety First: Prescribing Methadone for Pain

Lynn R. Webster, MD

Medical Director, Lifetree Clinical Research and Pain Clinic
Salt Lake City, Utah

Dr Webster has indicated that he is a consultant for Cephalon Inc., Pharmaceutical Technologies International Inc., Elan Corporation, and King Pharmaceuticals Inc.; and receives research support from Advanced Bionics Corporation, TorreyPines Therapeutics, Xenoport Inc., Takeda Pharmaceutical, Jazz Pharmaceuticals, Zars Pharma, Forest Laboratories, Merck, Purdue Pharma, Durect Corporation, Mallinckrodt Inc., GlaxoSmithKline, Neurogesx Inc., Predix Pharmaceuticals Inc., and Elite Pharmaceuticals Inc.

Methadone is a powerful, effective medication for pain; but it can also be fatal if prescribed or consumed incorrectly. On November 27, 2006, the FDA issued a public health advisory for methadone, entitled *Methadone Use for Pain Control May Result in Death and Life-Threatening Changes in Breathing and Heart Beat*.¹ This is strong language, but it should not be a surprise to healthcare professionals because any strong pain medication can cause death if used improperly. The FDA advisory contains updated prescribing data and a **black-box warning** that taking more methadone than prescribed “can lead to an overdose and possible death.” This seems appropriate considering the alarming increase in patients who have been harmed by methadone. The intent is to help practitioners keep patients safe. Methadone is a good and useful medication with some special properties that must be respected when prescribing or consuming it for pain.

The involvement of methadone in overdose deaths is increasing, according to both the US Substance Abuse and Mental Health Services Administration (SAMHSA) and medical-examiner data from several states reporting a rise in methadone-related deaths, including Florida (up 51% from 2003-2004), Maryland (up 950% from 1997-2001), North Carolina (up 729% from 1997-2001), and Utah (up 1,358% when comparing the intervals of 1991-1998 with 1999-2003)²⁻⁶. Although it is clear that at least some methadone taken for pain contributed to these fatalities, the exact reasons for the deaths are still unclear.

Clinicians who prescribe methadone for pain and their patients may be underestimating the risk of respiratory depression associated with methadone. The unique pharmacologic properties of methadone may be contributing to the problem. The analgesic half-life is much shorter than the interval during which methadone can cause respiratory depression in the methadone-naïve patient. According to the FDA, pain relief from a dose of methadone lasts approximately 4 to 8 hours, but methadone stays in the body up to 59 hours. Other reports suggest that the methadone half-life can be as long as 100 hours. As a result, methadone may accumulate to a toxic level after the first few days of treatment, and toxicity can occur before the body has had time to develop a tolerance.

More research is needed to establish the cause of death reported, but at least some of the contributing factors and dangers can be discerned.

Overuse in search of pain relief. Patients experiencing uncontrolled pain will take more medication than prescribed, trying to escape the pain. They may reason, in essence, if one tablet is good and two are better, then three must be great. A patient may have done this in the past with a different opioid medication, not realizing that methadone's long, variable half-life makes any deviation from the treatment plan extremely dangerous.

Mixing with alcohol or other drugs: Patients may introduce another danger when mixing methadone with other substances, particularly alcohol or benzodiazepines. Physicians may not realize the additive and potentially synergistic effect on suppressing respiration when methadone is combined with benzodiazepines and great caution is advised during combination therapy.

Too high a dose: Errors also occur when clinicians are initiating methadone therapy, making the conversion from other medications to methadone, or escalating the methadone dose while feeling falsely confident that a patient's opioid tolerance or pain status ensures safety. Although polypharmacy is responsible for most overdose deaths, it is frighteningly clear that at least a few decedents took methadone exactly as their doctors directed and died anyway.

Sleep: Recent preliminary reports suggest methadone may contribute to an increased prevalence in sleep apnea.⁷ Benzodiazepines with methadone appear to be additive in their association with sleep apnea. Caution is advised when either or both drugs are used to facilitate sleep.

Misplaced faith in conversion tables: 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. Therefore, it is potentially dangerous to use the equianalgesic dosing guidelines published in available conversion tables when determining the starting dose of methadone. These tables—which are designed for a single use, not for chronic administration—may also imply no upper limit exists for the starting methadone dose. This is belied by evidence that patients are at risk for overdose during the conversion period.

Cardiac Arrhythmias: Methadone has been shown to produce *Torsades de Pointes* or QTc interval prolongation.⁸ This association appears to be dose related. Therefore, patients on a dose close to or above 100 mg per day should have an EKG to monitor the potential effect of methadone on the QTc interval. Other drugs known to prolong the QTc interval could produce an additive effect and thus the potential for this type of drug interaction must be considered when prescribing methadone.

The FDA warning makes reference to life-threatening risks such as respiratory depression and cardiac arrhythmias in patients receiving methadone. The reasons for some of these risks could encompass several factors such as methadone interactions with concomitant medications, sleep apnea, and the time of the last daily dose in relation to the onset of sleep.

Until more research is available to clarify the risk factors, clinicians should start methadone therapy with a low dose and titrate slowly to an analgesic effect. As with all opioids, the starting dose of methadone depends on the patient's age, degree of opioid tolerance, severity of pain, concomitant medications, and general health. Yet methadone's pharmacologic properties call for a conservative approach for even the most opioid-tolerant patients. Careful monitoring of the individual patient's response is key.

The FDA advisory refutes dosing recommendations that were too lenient in the past and may have led practitioners to prescribe pain medication at higher-than-safe dosages. For now, safe practice supports starting the conversion with a ceiling dose of no more than 30 mg/day (10 mg/day for elderly or infirm patients). Dose changes should not occur more often than weekly, to allow a steady state of methadone to develop and for the peak side effects to become evident. If patients are taking concomitant benzodiazepines, the starting dose and speed of titration may need to be adjusted downward.

For patients who are being converted from another opioid to methadone, clinicians should slowly titrate the other opioid downward as they slowly titrate methadone upward. This practice will minimize the risk of

unintentional overdose by the patient who is trying to control their pain but finds methadone only works for 4 to 6 hours.

Patient counseling must include an emphasis on following all medical instructions to the letter: no escalation of doses and no mixing of methadone with other prescriptions, alcohol, or illicit substances. Patients should be warned that any deviation in this regard can be fatal.

These guidelines represent a more conservative recommendation than is seen elsewhere. Certainly, some patients are able to tolerate a much more rapid conversion or titration. Nevertheless, given the reports of deaths associated with methadone, these starting guidelines should help clinicians ensure patient safety and give methadone pain therapy a greater chance of success.

The FDA advisory emphasizes the importance of knowing the signs of methadone overdose and getting medical attention immediately if any of the following occur:

- Trouble breathing or shallow breathing
- Extreme tiredness or sleepiness
- Blurred vision
- Inability to think, talk or walk normally
- Feeling faint, dizzy or confused

Banning methadone for pain is not the answer. Methadone has proved to be an effective treatment for several chronic pain conditions. It has excellent bioavailability, is a good match with most short-acting opioids used to treat breakthrough pain, is very affordable and possesses long-acting pharmacologic properties that make it especially attractive for treating pain patients at risk for abusing prescription opioids. Its continued value as an analgesic depends on clarifying methadone's unique properties to all practitioners who use methadone to treat pain. Because many thousands of people are still undertreated for pain, these problems must be swiftly addressed and a national education program launched now.

DTP – Please set this as a box within the article.

Many more studies are needed to determine the root causes of deaths involving methadone. Until more data are available, patients should be advised of a few vital, yet simple, steps to avoid a tragedy associated with the misuse of methadone and other pain medications:

- 1. Never take a prescription painkiller unless it is prescribed to you.** Everyone responds differently to pain medications. What is safe for one person may not be safe for another.
- 2. Do not take pain medicine with alcohol.** Never mix the two; it is a dangerous combination that can be deadly. Alcohol increases the toxicity of pain medication.
- 3. Do not take more doses than prescribed.** Even after the effects of pain medicine seem to have worn off, it is still depressing the respiratory system. Some medications like methadone may relieve pain for a few hours but will have a prolonged respiratory depressant effect. The body must develop a tolerance to the respiratory depressant effects before the dose can be increased.
- 4. Use of other sedative or antianxiety medications can be dangerous.** Combining pain medicines with other sedative drugs, such as valium, can increase the toxicity of the pain medication. Only take other medications if directed by the prescribing doctor.
- 5. Avoid using narcotic medications to facilitate sleep.** Narcotic medications can suppress respiration during sleep. Speak to your physician about safe methods to manage pain during sleep.
- 6. Lock up prescription painkillers.** If consumed by children or other family members, or stolen and sold on the street, prescription pain medicine can kill.

References:

1. Methadone Use for Pain Control May Result in Death and Life-Threatening Changes in Breathing and Heart Beat. Available at: <http://www.fda.gov/medwatch/safety/2006/safety06.htm#Methadone>. Accessed December 14, 2006.
2. Centers for Disease Control and Prevention (CDC). Unintentional and undetermined poisoning deaths – 11 states, 1990-2001. *MMWR Morb Mortal Wkly Rep.* 2004;53:233-238.
3. Center for Substance Abuse Treatment, Methadone-Associated Mortality: Report of a National Assessment, May 8-9, 2003. CSAT Publication No. 28-03. Rockville, MD: Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration, 2004. Available at: <http://dpt.samhsa.gov/reports/index.htm>.
4. Findings and recommendations of the task force to prevent deaths from unintentional drug overdoses in North Carolina, 2003. N.C. Department of Health and Human Services, Division of Public Health, Injury and Violence Prevention Branch, Raleigh, N.C. Submitted April 2004.
5. Utah Department of Health (UDOH) and Centers for Disease Control and Prevention (CDC). Increase in poisoning deaths caused by non-illicit drugs – Utah, 1991-2003. *MMWR Morb Mortal Wkly Rep.* 2005; 54:33-36.
6. Webster LR. Methadone-related deaths. *Journal of Opioid Management.* 2005;1:211-217.
7. Webster LR, Grant BJB, Choi Y. Sleep apnea associated with methadone and benzodiazepine therapy [Abstract]. Presented at the American Academy of Pain Medicine 22nd Annual Meeting, February 22-25, 2006, San Diego, CA. Poster 165.
8. Kornick CA, Kilborn MJ, Santiago-Palma J, et al. QTc interval prolongation associated with intravenous methadone. *Pain.* 2003;105:499-506.