Methadone-related deaths

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INTRODUCTION

The increasing involvement of methadone in accidental overdose deaths is the subject of several recent reports. The federal government reported more methadone-related deaths in 2001 alone—61—than occurred in the entire 1990s. By 2002, that number had doubled to 123.[1] Individual states are seeing a similar spike, causing state and local medical examiners to publish data seeking to alert the public to the potential danger.[2-8] While the actual numbers may look small, the increases are startling.

To examine this issue, a literature search was conducted for studies related to methadone deaths in the 1990s and 2000s. Available for review was a report from the US Substance Abuse and Mental Health Services Administration (SAMHSA), an additional report covering 11 states, and another six separate state studies containing analyses of state medical examiner data. An email message also was sent to the medical examiner offices of all 50 states and the District of Columbia to request access to any further published studies. Only six replies were received, none of which yielded any further published studies for inclusion.

Of immediate interest to clinicians is whether the increase in methadone-related deaths is tied to the drug's recent emergence as an analgesic to manage chronic, nonmalignant pain. The SAMHSA report draws such a parallel, even concluding that the increase in methadone deaths cannot be traced to doses provided to narcotic addicts by clinics specializing in methadone maintenance treatment (MMT).[9]

While the state reports do not contain data adequate to determine whether the bulk of decedents were abusing methadone, combining it with other substances, or taking methadone as directed for pain, it appears clinicians and patients may underestimate the risk of respiratory depression associated with methadone. Some of this risk arises from methadone's pharmacologic properties, which include a long, variable half-life.

The purpose of this paper is fourfold: 1) to alert clinicians to the rising number of reports of methadone-related deaths, 2) to discuss the relative contribution of methadone prescribed for pain to the incidence of accidental overdose, 3) to consider the possibility that opioid tolerance does not provide as much protection against respiratory depression as often assumed, and 4) to suggest safe methadone prescribing guidelines for use in clinical pain practice. A particular urgency drives this latter need, as methadone's use as an agent for treating chronic pain continues to widen.

RISE IN METHADONE–RELATED DEATHS

SAMHSA data

A 2002 SAMHSA report showed methadone as ranking in the top 10 drugs involved in deaths in 19 US cities. This puts methadone ahead of hydrocodone and oxycodone (in the top 10 for 15 cities each) but behind benzodiazepines (26 cities).[10] This is striking, considering the much higher availability of hydrocodone and oxycodone compared to methadone. The US Drug Enforcement Agency (DEA), using the Automation of Reports and Consolidated Orders System (ARCOS), reports that the amount of methadone manufactured and distributed commercially in the United States grew from 194 g per 100,000 population to 954 g between 1997 and 2002. To compare, oxycodone distribution for the same years grew from 1,668 g to 8,056 g, and hydrocodone increased from 3,249 g to 6,777 g.[8]

In 2004, SAMHSA reported that the increase in methadone-related deaths did not appear to stem from the liquid issued by methadone treatment centers, but instead from an increase in solid tablets or diskettes used to treat pain.[9] Hospital emergency-department visits involving methadone rose 176 percent from 1995 to 2002 and 50 percent from 2000 to 2002, according to SAMHSA's Drug Abuse Warning Network (DAWN).[9] The report names three scenarios as common for methadone deaths: The first is through illicitly obtained methadone used to achieve euphoria. The second is methadone (either illicit or licit) used in combination with other prescription medications, alcohol, opioids, or benzodiazepines. The last scenario is "an accumulation of

methadone to harmful serum levels in the first few days of treatment for addiction or pain, before tolerance is developed."[11] It is this latter possibility that especially concerns pain clinicians and calls for a re-examination of methadone prescribing guidelines.

State data

Several states have noted a rise in methadone-related deaths and have issued reports quantifying its involvement in drug-related deaths overall. In a study of 11 states from 1990 to 2001, death rates from poisonings that were unintentional or of undetermined cause increased by an average of 145 percent.[2] Of the 11 states studied, eight states identified the top poisoning substances for 1999 and 2000. Methadone was among the six most common poisoning substances, involved in 5 percent of unintentional/undetermined poisoning deaths. It should be noted, however, that nonspecific categories such as "other opioids" were common.

Six states (Florida, Maryland, Maine, New Mexico, North Carolina, and Utah) have all issued recent reports that analyzed state medical examiner data regarding recent drug deaths, including methadone's contribution.[3-8] These reports are similar in structure, although differing in some details. Of particular interest are the data detailing the change in drug-related overdose deaths overall, the change in methadone-related deaths, and methadone's percentage of all drug-related deaths (Table 1).

Decedent characteristics

The extent of analysis regarding decedent characteristics varied greatly from state to state. New Mexico investigators performed extensive, bivariate analyses in which methadone-related deaths were significantly associated with the following covariates: being white (non-Hispanic), death caused by prescription drugs, absence of heroin as a cause of death, absence of alcohol as a cause of death, and the year 1998.[6]

Middle age appears to be a vulnerable period for drug overdose, particularly involving prescription drugs. In the study of 11 states, death rates from unintentional/undetermined poisonings were greatest for persons aged 45 to 54 years (average increase, 359 percent) and 35 to 44 years (average increase, 195 percent).[2] Other states showed similar risk for middle-age patients.

Multiple drug interactions

Some of the states reported the extent to which methadone was found in toxicology reports to be the sole cause of death or one of several contributing factors combined with other prescription drugs, alcohol, or illicit drugs. It should be noted, however, that a single-drug death does not mean no other drugs were present, but that one drug was judged to cause the death. For the year 2002, Florida reported 89 methadone-only deaths and 467 deaths attributed to methadone in combination.[3] New Mexico reported 143 methadone-related deaths from 1998 to 2002, 32 (22.4 percent) of which were single-drug mentions.[6] New Mexico deaths in which methadone was found in combination included 34 (23.8 percent) with prescription drugs and 72 (50.3 percent) with illicit drugs. North Carolina reported a 729 percent increase in single-drug deaths involving methadone, from seven in 1997 to 58 in 2001. Of 316 polydrug deaths in North Carolina, methadone was involved in 51 (16 percent).[7]

The data are intriguing but fail to clarify how often the methadone implicated in drug deaths was instrumental in causing the fatality or was just one factor in a polydrug interaction. At least two states—Maine and Maryland—reported an increase in the trend of overdose deaths attributed to single-drug mentions.[4,5] However, DAWN data point to frequent polydrug involvement: In 43 major US metropolitan areas, nine out of 10 deaths involving narcotic analgesics, including methadone, were multiple-drug deaths.[10]

When a polydrug interaction is documented, benzodiazepines and alcohol are frequently listed as co-causes of death. The exact mechanisms of the interaction of benzodiazepines with methadone, whether additive or synergistic, have been studied[12,13] 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.[13]

Non–United States studies

The 1990s also saw an increase in studies from non-US countries documenting a rise in methadone overdose deaths.[14-16] Most studies from Australia, the United Kingdom, and elsewhere in Europe focused on heroin addicts maintained on methadone. An exception is an Australian study that links a jump in methadone deaths in 1994 to its increased availability as a chronic-pain treatment.[17]

SOURCES OF MISUSED METHADONE

Where most overdose victims obtain the methadone that contributes to their deaths is still unclear. The evidence, although incomplete and sometimes contradictory, indicates a fairly high level of prescription involvement. For example, in Utah, 40 percent of decedents held a valid prescription at the time of death. In New Mexico, of 143 methadone-related decedents from 1998 to 2002, 68 (47.5 percent) had a prescription; 31 had been issued methadone for MMT, 27 for managing pain, and 10 for an unknown reason.[6] Nevada claimed an even higher degree of prescription involvement. In an email message

Table 1. State data: Overall change in drug-related deaths,[a] methadone-related deaths, and methadone's percentage of total drug-related deaths

	Years studied	Change in total drug-related deaths	Change in methadone-related deaths	Methadone percent of total drug-related deaths
Florida	2003 – 2004	N/A	Up 56 percent[b]	7.8 (2004)
Maine	1997 – 2002	up > 400 percent	Up 450 percent[b]	18
Maryland	1997 – 2001	Up 16 percent	Up 950 percent	4 (2001)
New Mexico	1998 – 2002	N/A	Down 35 percent	12.8
North Carolina[c]	1997 – 2001	Up 110 percent	Up 729 percent	19
Utah	1991 – 2003	Up ~ 500 percent[d]	Up 1,358 percent[e]	7.8 (1991 – 1998) 32.7 (1999 – 2003)[e]

[a] A drug was either the direct cause of death or a significant underlying factor; [b] Methadone increase as a cause of death; [c] Unintentional overdose deaths only; [d] Increase from 1991 to 2003; [e] Compared the intervals of 1991–1998 to 1999–2003.

dated May 10, 2005, the Washoe County Coroner said Nevada had experienced approximately a fourfold increase in methadone-related deaths in the past two years, with the majority of victims holding valid prescriptions for methadone. North Carolina found that 73 of 92 decedents for whom information could be documented had held a valid prescription written for them by a physician.[7] In contrast to these reports, Oklahoma showed that close to two-thirds of methadone-related overdose victims in 2001 and 2002 held no valid prescription, leading state medical officials to blame black-market purchases for many of the deaths.[1] Exactly how popular methadone is as a drug of abuse is unknown; however, methadone's unique pharmacologic properties make it relatively ineffective in producing the type of high sought by addicts. Methadone's use by narcotic addicts to medicate withdrawal symptoms is well known and can increase the risk of overdose.

One wonders whether greater distribution at the end of the 1990s contributed to the spike seen in some states in methadone-related overdose deaths. As mentioned previously, SAMHSA's report points to the drug's increased availability by means of prescriptions for chronic pain. Some states reported a rise in deaths paralleling the rise in quantities of methadone shipped to the state. Utah, for example, from 1997 to 2002, saw a sixfold increase in methadone distribution not explained by the needs of addiction treatment programs.[8] The higher quantities of trafficked methadone did indeed coincide with a higher incidence of fatality. In a conversation with the author in March 2005, Utah's state medical examiner traced most of the prescription methadone involved in accidental deaths to the offices of general practitioners across the state rather than pain specialists, highlighting the need for the wider publicizing of sound, safe prescribing guidelines to nonspecialists.

However, availability cannot explain everything, and the factors contributing to methadone overdose appear complex. In North Carolina, the 2001 average of retailed methadone per DEA registrant was 47 g (36 percent above national average). However, counties with above-average retailed methadone did not have a concurrently high overdose rate, perhaps indicating under-treated pain in low-retail areas. Just how much fraud is involved in the obtainment of methadone will likely remain unclear in the absence of a statewide prescription monitoring program, North Carolina investigators concluded.[7]

METHADONE AS PAIN TREATMENT

Methadone has proved to be an effective treatment for several chronic pain conditions, and many clinicians consider its long-acting pharmacologic properties especially valuable in treating patients at high risk for abusing prescription opioids. This characteristic, along with its being relatively inexpensive and a good match with most short-acting opioids used to treat breakthrough pain, make methadone an attractive choice for treating chronic pain. There is increasing pressure from third-party payers to prescribe methadone as a first-choice opioid analgesic due to its relative low cost.

Methadone's profile as a long-acting agent brings with it certain cautions, however. The drug's long and variable half-life contributes to a clinical picture in which physiologic response can vary greatly from one person to the next. Its half-life can range from four to 91 hours, and clearance from a person's system can vary by a factor of almost 100.[7] At the International Conference on Pain and Chemical Dependency in February 2004, Richard Payne, MD, then-president of the American Pain Society, warned that these properties of methadone bring the potential for multiple drug interactions and named rising safety concerns about its use as one of the barriers to effective pain medicine.

TOLERANCE AND RESPIRATORY DEPRESSION

The protection offered by opioid tolerance against the risk of opioid-induced respiratory depression has been an accepted fact of chronic opioid therapy for pain. This treatment principle is presented in a consensus statement from the American Academy of Pain Medicine and the American Pain Society:

> It is now accepted by practitioners of the specialty of pain medicine that respiratory depression induced by opioids tends to be a short-lived phenomenon, generally occurs only in the opioid-naive patient, and is antagonized by pain. Therefore, withholding the appropriate use of opioids from a patient who is experiencing pain on the basis of respiratory concerns is unwarranted.[18]

This view has been bolstered by several researchers, including Fohr, who performed an exhaustive literature review to demonstrate that the belief opioids hasten death via respiratory depression is "more myth than fact."[19]

However, other research—some of it methadone specific—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, who examined the pharmacologic basis of respiratory depression after 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 the research suggested was complete.[20]

Further support for this finding comes from a study of the chemical control of breathing, performed before and after the administration of the daily dose of methadone in 14 former heroin addicts. The former addicts were enrolled in an MMT program and were taking 60 to 100 mg per day. Subjects in one group had taken methadone for less than two months, while members of a second group had taken the drug from eight to 43 months. The study found that during the first two months of MMT, patients showed continual alveolar hypoventilation owing to depression of central (CO_2) and peripheral (hypoxia) chemoreception. Then, after five months, alveolar hypoventilation was eliminated as the CO_2-sensitive chemoreflex acquired full tolerance to methadone at the maintenance dose level. Also, they found that tolerance of the hypoxia-sensitive chemoreflex developed more slowly and is never complete.[21]

Further cautions arise not from errors in application, but from the potential that certain patient characteristics, as yet minimally studied and poorly understood, amount to risk factors for accidental overdose death. Utah data, for instance, show a predominance of overdose deaths in overweight individuals, perhaps implicating sleep apnea.[8]

While undue fear of inducing respiratory depression should not be allowed to interfere with appropriate delivery of effective pain relief via opioid therapy, attention should be paid to the research that warns against considering opioid tolerance an absolute protection against respiratory depression.

STUDY CAVEATS

The literature review methods used for this report could not be considered exhaustive, and additional data may exist covering methadone-related deaths. Only published works were included, and no data were analyzed that reported on limited geographic areas within states. The limitations in the data-gathering and analysis methods of initial death investigators raise several serious issues not to be minimized. First, the assignment of a cause of death is a tricky business, particularly when multiple substances are present in the body and their relative contributions are unclear. Second, bias may exist toward assigning an opioid as the cause of death whenever it is present in a toxicology report. Third, difficulty exists in pinpointing a blood level of methadone that would be toxic in most individuals.[12,13,22,23] The lowest postmortem concentrations of methadone given as fatal in several studies ranged from 0.06 to 0.32 mg per L.[13] The lethal level is subject to a number of variables such as the decedent's history of opioid use, the presence of chronic pain, and the action of polydrug combinations. Levels of methadone reported as the cause of death may actually be therapeutic in some chronic pain patients on long-term methadone therapy for pain.

Yet, if methods used by state medical examiners to investigate overdose deaths are imperfect, it is reasonable to surmise that they are, at least, fairly consistent from year to year. The rise in overdose deaths related to methadone—and, indeed, to other categories of prescription drugs—during the preceding decade and beyond has been well documented and would appear to be independent of the data-gathering methods used.

This information suggests the need to review safe

guidelines for methadone prescribing. The process of designing safe, effective dosing guidelines is complicated by the difficulty in pinpointing any reliable, lethal dose of methadone. It is difficult to determine whether the methadone blood levels found after death reflect the medication taken as prescribed or in excess of the prescribed quantity. The time of day methadone is taken may also have an effect. Because methadone's distinct contribution to overdose death is difficult to isolate, it is better for clinicians to err on the side of caution.

PRESCRIBING GUIDELINES: LOOKING FOR SAFETY

The sources and means by which misused methadone becomes available will doubtless become clearer as evidence accumulates. In the meantime, it is obvious that the misuse of methadone by patients who held valid prescriptions is responsible for at least a segment of the deaths observed. Therefore, it is imperative that the medical establishment responds to any clinical misapplications that are occurring. Arresting preventable deaths is of paramount importance. This also throws the discussion open to a certain amount of theorizing until more evidence is available.

When accidental death does occur as a result of methadone that was legally prescribed, two sources of error are suspect. One is error introduced by clinicians while initiating methadone therapy for pain, making the conversion from other medications to methadone, or escalating the methadone dose while feeling falsely secure in the belief that a patient's opioid tolerance or pain status ensures safety. The second source of error can be introduced by patients in their consumption of methadone in ways not directed by the physician or in combination with other substances. Patient error may stem from escalating doses of methadone tablets against medical orders while seeking greater pain relief. Patients seeking optimal pain relief sometimes think, 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.

Methadone conversion tables

Clinicians, perhaps over-reliant on published conversion tables, may not be taking into account the long and widely variable half-life of methadone as they convert from what is believed to be equianalgesic doses of other opioids. During this process, clinicians may overestimate the protection afforded by a patient's previous opioid tolerance and underestimate the risk of overdose.

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—designed for a single use, not for chronic administration—may also imply that 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. One table suggests a conversion rate of 5 to 10 percent of the oral morphine dose. This may be far too high. For example, if the opioid-tolerant individual were taking up to 500 mg per day of pharmaceutical narcotics, the starting methadone dose could be as high as 50 mg per day. This might not be problematic for one dose, but could prove too high for the accumulation that occurs with multiple doses when considering methadone's wide variability of half-life. The doses recommended by conversion tables fail to take into account the potential for accumulated toxicity and for polydrug interactions that can occur with around-the-clock methadone.

New guidelines: Start low, titrate slow

Speaking at the California Society of Addiction Medicine Conference in October 2004, Mary Jeanne Kreek, MD, recommended a starting dose of methadone for chronic pain of 10 mg, bid. She suggested this be titrated slowly to an analgesic, still-low dose, delivered twice a day—thrice at the most. If patients have been taking high doses of other opioids, they may be quite opioid tolerant. Still, the starting dose should be low and the titration slow, Kreek recommended.

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. Because such large variability exists in the responses of individuals, it is always necessary to start with a low dose and titrate slowly to an analgesic effect. For this reason, the guidelines that follow do not differ much between opioid-tolerant and opioid-naïve individuals. Careful monitoring of individual patient response is key. Keeping these thoughts in mind, the guidelines recommended for initiating methadone therapy are shown in Table 2.

For now, safe practice supports starting the conversion with a ceiling dose of no more than 20 mg per day, 10 mg per day for elderly or infirm patients. Dose changes should not occur more often than weekly to

Table 2. Suggested guidelines for initiating methadone for pain		
Total daily morphine	**Starting methadone dose**	
	Healthy adults aged < 70 yr	**Adults with chronic illness or aged > 70 yr**
Opioid naïve	5 mg tid	2.5 mg bid
60 mg to 100 mg	5 mg tid	5 mg bid
> 100 mg	5 mg qid	5 mg bid

allow a steady state of methadone to develop and for the peak side effects to become clear. 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 downward the other opioid as they slowly titrate methadone upward. This practice will minimize the risk of withdrawal and of overdose involving methadone or a combination of the two opioids.

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 dangerous, even fatal.

These guidelines represent a more conservative recommendation than 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. Safety must come first. More aggressive pain control may follow once the mechanisms behind the increase in methadone-related deaths are further researched and better understood.

CONCLUSION

Methadone has unique properties that may make it subject to overdose, especially during its initial use. It is important to clarify these properties to all practitioners who use methadone to treat pain. These problems must be swiftly dealt with. Many thousands of people are still under-treated for pain. The quickest way for practitioners, many of whom already fear treating pain with opioids, to lose confidence in opioid therapy is for pain specialists to fail to acknowledge problems with opioid toxicity when they arise.

Many questions must still be answered in future research: What is the primary source—or sources—of misused methadone? Is it possible to reach a medical consensus on the doses, combinations, or other factors that turn methadone lethal? Which patient characteristics are also risk factors for accidental overdose when prescribed methadone for pain? Does the time of day at which methadone is consumed influence the potential for a fatal dose? Is there opioid-specific tolerance to respiratory depression? How much cross-tolerance between opioids can be developed? What factors will influence the degree of cross-tolerance? Is tolerance to respiratory depression reduced with concomitant medications commonly used in treating chronic pain? If so, how much and which concomitant medications pose the greatest risk?

Until these questions are answered, physicians must adopt a cautious, conservative approach to the use of methadone and closely monitor patient response. Continued trust in the principles of pain management depends on the widespread availability of dosing guidelines that do no harm. In the case of methadone prescribing for pain, a certain urgency exists in this respect.

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REFERENCES

1. Randerson J: Painkiller linked to rise in overdose deaths. March 6, 2004. Available online at: *http://www.newscientist.com.*
2. Centers for Disease Control and Prevention: Unintentional and undetermined poisoning deaths—11 states, 1990-2001. *MMWR Morb Mortal Wkly Rep.* 2004; 53(11): 233-238.
3. Florida Department of Law Enforcement: 2004 report of drugs identified in deceased persons by Florida medical examiners. Available online at: *http://www.fdle.state.fl.us/publications/Examiners/2004MERDrugReport.pdf.* Last accessed August 4, 2005.
4. Sorg MH, Greenwald M: Maine Drug-Related Mortality Patterns: 1997-2002. In cooperation with the Maine Office of the Attorney General and the Maine Office of Substance Abuse. Released Dec. 27, 2002. Available online at: *http://www.state.me.us/ag/pr/drugreport.pdf.* Last accessed April 6, 2005.
5. Lehder DM, Arria A, Artigiani EE, et al.: Alcohol and drug-related overdose deaths in Maryland: 1997-2001. Available online at: *http://www.cesar.umb.edu/cesar/pubs/20021101.pdf.*

Last accessed August 4, 2005.
6. Shah N, Lathrop SL, Landen MG: Unintentional methadone-related overdose death in New Mexico (USA) and implications for surveillance, 1998-2002. *Addiction.* 2005; 100: 176-188.
7. Findings and recommendations of the task force to prevent deaths from unintentional drug overdoses in North Carolina, 2003. North Carolina Department of Health and Human Services, Division of Public Health, Injury and Violence Prevention Branch, Raleigh, NC. Available online at *http://www.communityhealth.dhhs.state.nc.us/Injury/FRTFPD_UDDNC2003-Complete.pdf.* Last accessed August 25, 2005.
8. Increase in poisoning deaths caused by non-illicit drugs—Utah, 1991-2003. Performed by the Utah Department of Health (UDOH) and Centers for Disease Control and Prevention (CDC). *MMWR Morb Mortal Wkly Rep.* 2005; 54(02): 33-36.
9. 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 online at: *http://dpt.samhsa.gov/reports/index.htm.*
10. Substance Abuse and Mental Health Services Administration, Office of Applied Studies: Mortality data from the Drug Abuse Warning Network, 2000. DAWN Series D-19, DHHS Publication No. (SMA) 02-3633. Rockville, MD: 2002.
11. Substance Abuse and Mental Health Services Administration: Methadone deaths not linked to misuse of methadone from treatment centers. News Release, Feb. 6, 2004. Available online at: *http://www.samhsa.gov.*
12. Mikolaenko I, Robinson CA Jr, Davis GG: A review of methadone deaths in Jefferson County, Alabama. *Am J Forensic Med Pathol.* 2002; 23(3): 299-304.
13. Pirnay S, Borron SW, Giudicelli CP, et al.: A critical review of the causes of death among post-mortem toxicological investigations: Analysis of 34 buprenorphine-associated and 35 methadone-associated deaths. *Addiction.* 2004; 99(8): 978-988.
14. Cairns A, Roberts ISD, Benbow EW: Characteristics of fatal methadone overdose in Manchester, 1985-94. *BMJ.* 1996; 313: 264-265.
15. Vormfelde SV, Poser W: Death attributed to methadone. *Pharmacopsychiatry.* 2001; 34: 217-222.
16 Auriacombe M, Franques P, Tignol J: Deaths attributable to methadone vs. buprenorphine in France [Letter]. *JAMA.* 2001; 285(1): 45.
17. Williamson PA, Foreman KJ, White JM, et al.: Methadone-related overdose deaths in South Australia, 1984-1994. How safe is methadone prescribing? *Med J Aust.* 1997; 166(6): 302-305.
18. The use of opioids for the treatment of chronic pain: A consensus statement from American Academy of Pain Medicine and American Pain Society. Approved by the AAPM Board of Directors on June 29, 1996. Approved by the APS Executive Committee on August 20, 1996. Accessed from *http://www.ampainsoc.org/advocacy/opioids.htm* July 19, 2005. Under review.
19. Fohr SA: The double effect of pain medication: Separating myth from reality. *J Palliat Med.* 1998; 1(4): 315-328.
20. White JM, Irvine RJ: Mechanisms of fatal opioid overdose. *Addiction.* 1999; 94(7): 961-972.
21. Santiago TV, Pugliese AC, Edelman NH: Control of breathing during methadone addiction. *Am J Med.* 1977; 62(3): 347-354.
22. Karch SB, Stephens BG: Toxicology and pathology of deaths related to methadone: Retrospective review. *West J Med.* 2000; 172: 11-14.
23. Wolf BC, Lavezzi WA, Sullivan LM, et al.: Methadone-related deaths in Palm Beach County. *J Forensic Sci.* 2004; 49(2): 375-378.