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HEALTH AND HUMAN SERVICES**
Substance Abuse and Mental Health
Services Administration
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Background Information

for

Methadone Mortality – A Reassessment

Sponsored by the
Center for Substance Abuse Treatment
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Administration

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Disclaimer

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Dear Colleague:

This document provides background information for the July 20th meeting, “Methadone Mortality – A Reassessment,” to be sponsored by the Center for Substance Abuse Treatment (SAMHSA) of the Substance Abuse and Mental Health Services Administration (SAMHSA). The meeting will bring together epidemiologists, clinicians and educators, regulatory and enforcement officials, patient advocates, and policymakers for an in-depth reassessment of the current knowledge base on methadone-associated deaths and a review of progress in addressing the situation.

As you know, methadone has a long, successful history as a potent analgesic and a highly effective medication for reducing the morbidity and mortality associated with opioid addiction. However, diversion, abuse, and deaths associated with many opioid medications – including methadone – have become a become a significant public health concern.

As the Federal agency tasked with oversight of the nation’s opioid treatment programs, SAMHSA is concerned about these developments. Accordingly, in May 2003, SAMHSA convened a National Assessment of Methadone-Associated Mortality. Participants were tasked with reviewing the available data on methadone-associated deaths; determining whether and to what extent the reported increase in such deaths might be related to the clinical practices of SAMHSA-monitored OTPs; and formulating recommendations to address the problem.

At our July 20th meeting, we propose to reassess the situation, review the progress made to date, and solicit participants’ input as to needed modifications or additions to the strategies currently being pursued. This document provides background information for the reassessment by compiling the latest statistical information on methadone-associated deaths from multiple agencies and organizations, as well as information from the published literature and from participating organizations.

We expect this to be a valuable session, and trust that this background information will enhance the group’s deliberations. Thank you for agreeing to participate.

Sincerely,

H. Westley Clark, M.D., J.D., M.P.H., CAS, FASAM

Director
Center for Substance Abuse Treatment

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BACKGROUND AND OVERVIEW OF THE PROBLEM

Methadone is a medication valued for its effectiveness in reducing the mortality associated with opioid addiction, as well as the various medical and behavioral morbidities associated with addictive disorders. It also is an inexpensive and increasingly popular analgesic medication suitable for the treatment of even the most severe acute or chronic pain in well-selected patients.

Methadone has a number of unique pharmacologic properties, such as its slow onset and long duration of action, its relatively low need for dose escalation because of tolerance, its antagonism of the glutamate receptor N-methyl-D-aspartate (NMDA), its inhibition of serotonin/norepinephrine reuptake, and its very modest cost – all of which make it an appropriate choice for opioid therapy of pain and addiction (Savage, meeting presentation, 2003 [see www.samhsa.gov]; Lobert, 2003; Bruera, 2002; Payte, et al., 1994; Joseph and Woods, 1994; Kreek, 1992; Ettinger, et al., 1979).

Oral methadone, whether used for addiction treatment or pain relief, is available as a solid tablet, a rapidly dissolving wafer (diskette), and a premixed liquid, all of which are essentially bioequivalent (Mallinckrodt, 1995, 2000; Roxane, 1995, 1998, 2000). Each of the formulations is 80 to 95 percent bioavailable (compared with only 30 percent for oral morphine) and readily absorbed (Eap, et al., 2000; Inturrisi, 1972b).

Fatal overdoses of methadone have been reported over the years (Baden, 1970; Gardner, 1970; Clark, et al., 1995; Drummer, et al., 1992). As with most other opioids, the primary toxic effect of excessive methadone is respiratory depression and hypoxia, sometimes accompanied by pulmonary edema and/or aspiration pneumonia (White and Irvine, 1999; Harding-Pink, 1993). Among patients in addiction treatment, the largest proportion of methadone-associated deaths have occurred during the drug's induction phase, usually when (1) treatment personnel overestimate a patient's degree of tolerance to opioids, or (2) a patient uses opioids or other central nervous system (CNS) depressant drugs in addition to the prescribed methadone (Karch and Stephens, 2000; Caplehorn, 1998; Harding-Pink, 1991; Davoli, et al., 1993). In fact, when deaths occur during later stages of treatment, other drugs usually are detected at postmortem examination (Appel, et al., 2000).

In particular, researchers have called attention to the “poison cocktail” resulting from the intake of multiple psychotropic drugs (Borron, et al., 2001; Haberman, et al., 1995), such as alcohol, benzodiazepines, and other opioids. When used alone, many of these substances are relatively moderate respiratory depressants; however, when combined with methadone, their additive or synergistic effects can be lethal (Kramer, 2003; Payte and Zweben, 1998).

The term “methadone-associated mortality” broadly encompasses fatalities in which methadone has been detected during postmortem analysis or is otherwise implicated in a death. Defining methadone's role in such deaths is an unsettled area, complicated by inconsistencies in methods of determining and reporting causes of death, the presence of other central nervous system (CNS) drugs, and the absence of information about the decedent's mortem physical or mental condition and level of opioid tolerance. Moreover, the source, formulation, and quantity of methadone implicated in an individual's death often are difficult to determine.

SAMHSA ACTIVITIES TO ADDRESS METHADONE-ASSOCIATED DEATHS

SAMHSA's role in monitoring adverse events related to methadone is embedded in both its statutory authority and the agency's commitment to promoting the public health. (In 2001, the Secretary of Health and Human Services delegated to SAMHSA the responsibility for regulation and oversight of the Nation's opioid treatment programs [OTPs].)

SAMHSA's current actions to address methadone-associated deaths began in 2002, spurred by reports of drug diversion, abuse, and deaths involving many opioid medications, including methadone. SAMHSA already was collaborating with the Centers for Disease Control and Prevention (CDC), the Drug Enforcement Administration (DEA), the National Institute on Drug Abuse (NIDA), and the Food and Drug Administration (FDA), as well as with agencies in some of the States most directly affected by rising methadone mortality rates. Their reports, coupled with an increase in requests for consultation and assistance from State authorities and practitioners in the field, created added urgency for SAMHSA to evaluate and address the causes of the increase.

To assist it in developing a comprehensive plan and priorities, SAMHSA convened a multidisciplinary group of more than 70 experts – including representatives from various Federal and State agencies, researchers, epidemiologists, pathologists, toxicologists, medical examiners, coroners, pain management specialists, addiction medicine experts, and others – to conduct a National Assessment of Methadone-Associated Mortality in May 2003. Participants were tasked with:

- Reviewing the available data on methadone-associated deaths;
- Determining whether and to what extent such deaths might be related to the clinical practices of SAMHSA-monitored OTPs; and
- Formulating recommendations to address the problem.

Following a careful review of the available data on methadone formulation, distribution, and patterns of prescribing and dispensing, as well as the relevant data on drug toxicology and drug-associated morbidity and mortality, participants arrived at a number of important conclusions regarding the reports of methadone-associated mortality and formulated recommendations for reducing that mortality.

A report reflecting the participants' conclusions and recommendations was released by SAMHSA in February 2004 at a National Conference on Pain & Addiction. The conclusions and recommendations in that report (DHHS publication no. 04-3904) are summarized here.

This document also updates the findings of the 2003 National Assessment using current Federal and State data and the published literature as sources, and summarizes activities in response to the 2003 recommendations and subsequent developments.

FINDINGS OF THE 2003 NATIONAL ASSESSMENT

Following an exhaustive review of the data, participants in the 2003 National Assessment of Methadone-Associated Mortality reached consensus on the following findings:

1. The reported increase in methadone-associated deaths is supported by medical examiner and other data.
2. The increased number of methadone deaths parallels the trend for all opioid analgesics.
3. A majority of methadone deaths are associated with use of the drug for the treatment of pain rather than addiction.
4. Most deaths associated with methadone can be described by one of three scenarios:
 - a. Accumulation of methadone to toxic levels at the start of treatment for pain or addiction (i.e., the induction phase).
 - b. Misuse of diverted methadone at high doses and/or by individuals who had little or no tolerance to the drug.
 - c. Synergistic effects of methadone used in combination with other CNS depressants, such as alcohol, benzodiazepines, or other opioids.
5. The clinical practices of OTPs and their regulation by the Federal government are not responsible for the increase in methadone-associated mortality.

Current information related to each of these findings is presented below as background for deliberations in the 2007 reassessment of methadone-associated mortality.

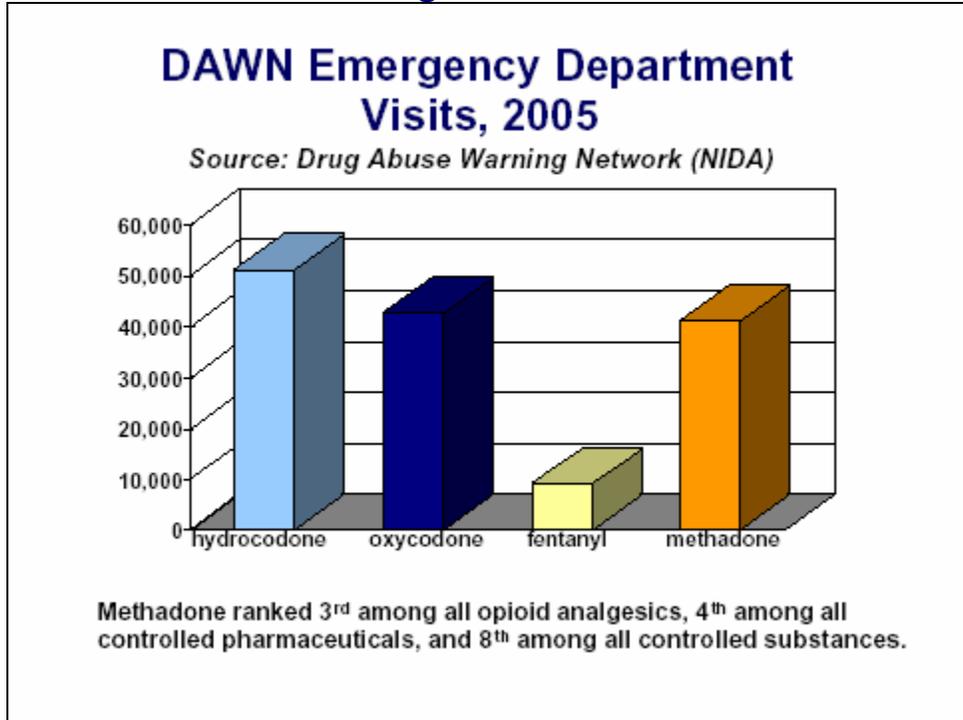
Finding 1: The Data Indicate an Upward Trend in Methadone Deaths

Finding of the 2003 National Assessment: The reported increase in methadone-associated deaths is supported by medical examiner and other data. For example, data from MedWatch – the FDA’s Safety Information and Adverse Event Reporting Program – indicate that 1,114 cases of methadone-associated deaths in adults (an average of 35 per year) were reported between 1970 and 2002. But more methadone-associated deaths were reported in 2001 alone than during the entire period from 1990 through 1999. The number doubled again in 2002 (Ouelette-Hellstrom, et al., meeting presentation, 2003).

In States that have collected, analyzed, and reported relevant data, the number of methadone-associated deaths appears to be increasing, although the absolute number of cases remains a relatively modest portion of the overall number of drug-related deaths (SAMHSA, 2002).

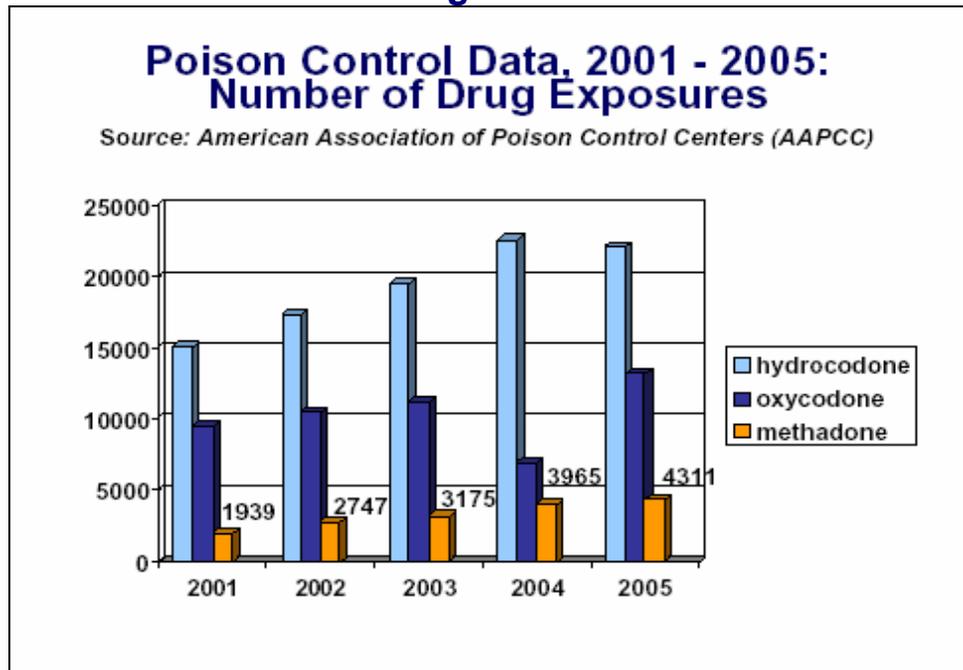
Current Information: Data on drug-related emergency department visits, collected through the Drug Abuse Warning Network (DAWN), show that, in 2005, methadone ranked third among all opioid analgesics, fourth among all controlled prescription medications, and eighth among all controlled substances in emergency department visits (Figure 1).

Figure 1.



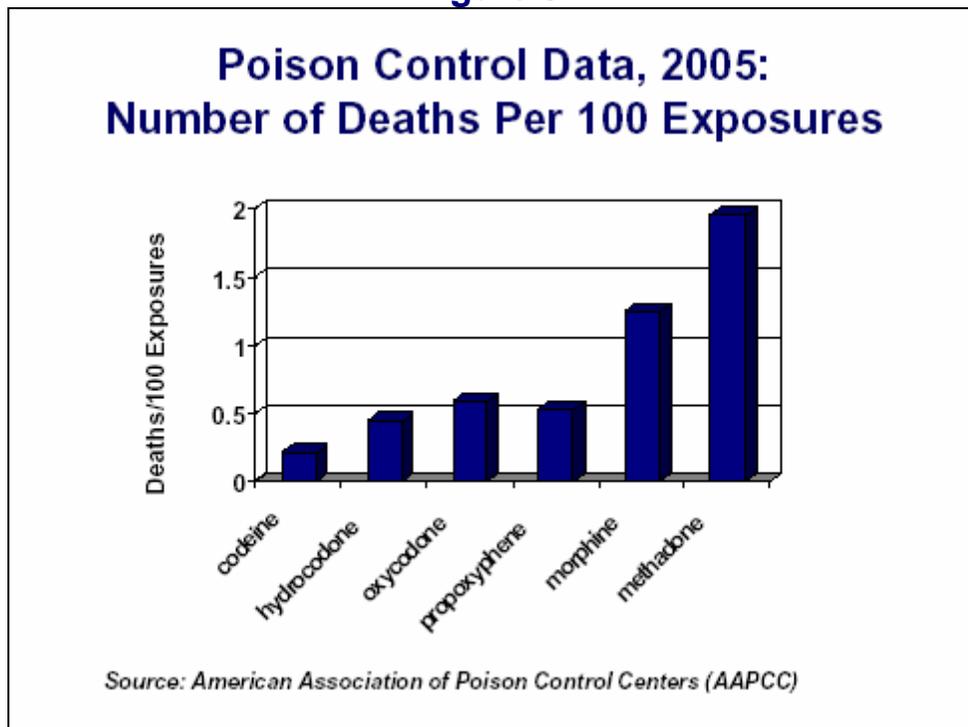
Poison control center data show a steady increase in the number of drug exposures involving methadone between 2001 and 2005, albeit at a rate considerably lower than those for hydrocodone and oxycodone (Figure 2).

Figure 2.



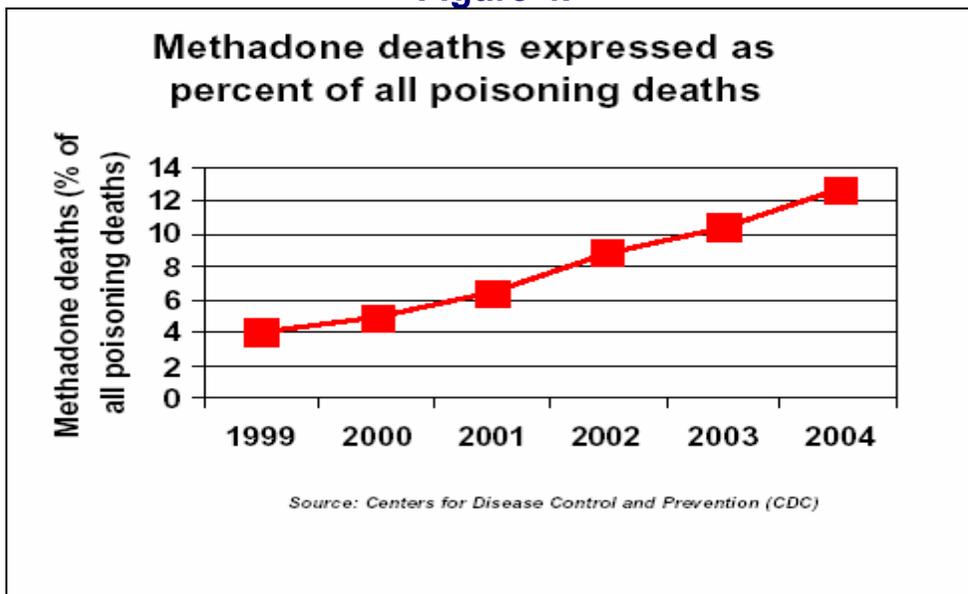
However, data from the poison control centers also show that methadone ranks first in the rate of deaths per 100 exposures, as shown in Figure 3.

Figure 3.



Data from the Centers for Disease Control and Prevention (CDC) show that the number of poisoning deaths related to methadone increased by 390 percent between 1999 and 2004 (from 786 deaths in 1999 to 3,849 deaths in 2004; see Figure 4). The number of methadone poisoning deaths among young people (ages 15-24) increased eleven-fold in that time period (Figure 4).

Figure 4.



States with the largest number of deaths related to methadone in 2004 are shown in Table 1. Those with the greatest rate of increase in methadone-related deaths are shown in Table 2.

Table 1.

States With the Largest Number of Methadone Deaths, 2004		
<i>Source: Centers for Disease Control and Prevention (CDC)</i>		
Ranking	State	Deaths
1	Florida	400
2	North Carolina	245
3	Washington	228
4	Texas	138
5	Ohio	122
6	Kentucky	121
7	Oklahoma	120
8	Virginia	104
9	Tennessee	99
10	West Virginia	99

Table 2.

States With the Largest Rate of Increase in Methadone Deaths, 1999 to 2004			
<i>Source: Centers for Disease Control and Prevention (CDC)</i>			
	1999 Deaths	2004 Deaths	Death Ratios 2004 Deaths/1999 Deaths
Total US	623	3,202	5.1
West Virginia	4	99	24.8
Ohio	7	122	17.4
Louisiana	4	64	16
Kentucky	8	121	15.1
New Hampshire	2	29	14.5
Florida	29	400	13.8
Oregon	5	68	13.6
Pennsylvania	7	88	12.6
Tennessee	8	99	12.4
Wisconsin	6	63	10.5
Maine	5	52	10

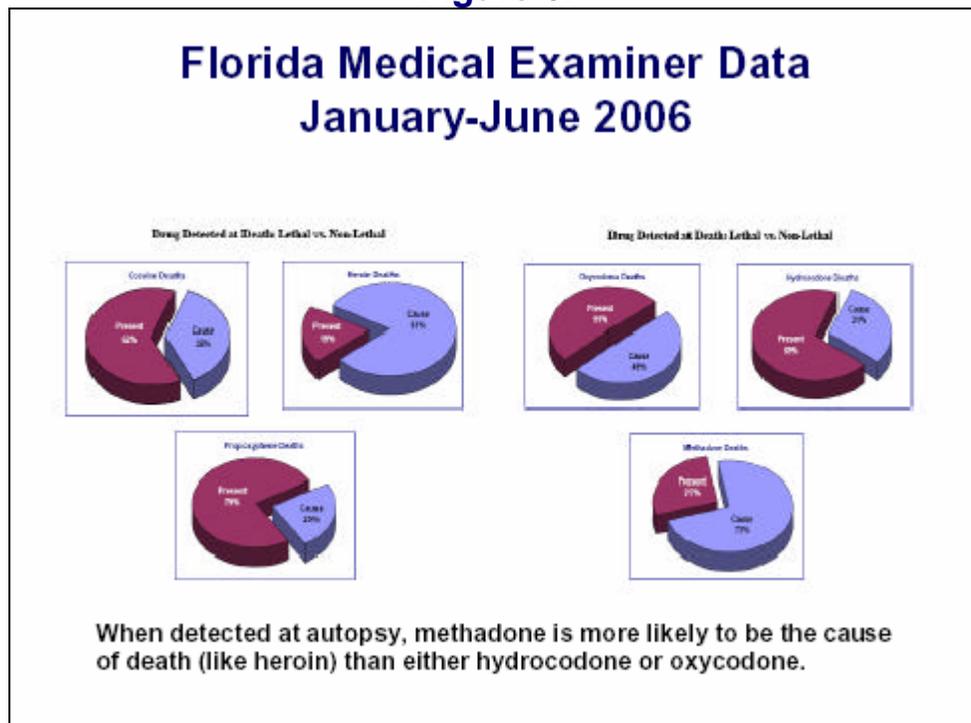
In the Florida Medical Examiner system, which uses a sophisticated protocol to classify and report drug-related deaths, methadone was cited more often than any other licit or illicit drug as a cause of death in the first six months of 2006 (Figure 5).

Figure 5.

Florida Medical Examiner Reports January – June 2006		
<i>Source: Florida Department of Law Enforcement 2006 Interim Drug Report by Medical Examiners</i>		
Drug Found in Body	Total Occurrences	Cause of Death
Heroin	36	29
Fentanyl	85	51
Hydrocodone	346	106
Hydromorphone	63	13
Meperidine	25	3
Methadone	428	312
Morphine	289	106
Oxycodone	377	185
Propoxyphene	155	38
Tramadol	59	18

Florida Medical Examiner data also show that, at autopsy, methadone was more likely to be classified as the direct cause of death (rather than a contributing factor or not a factor) than either hydrocodone or oxycodone (Figure 6).

Figure 6.

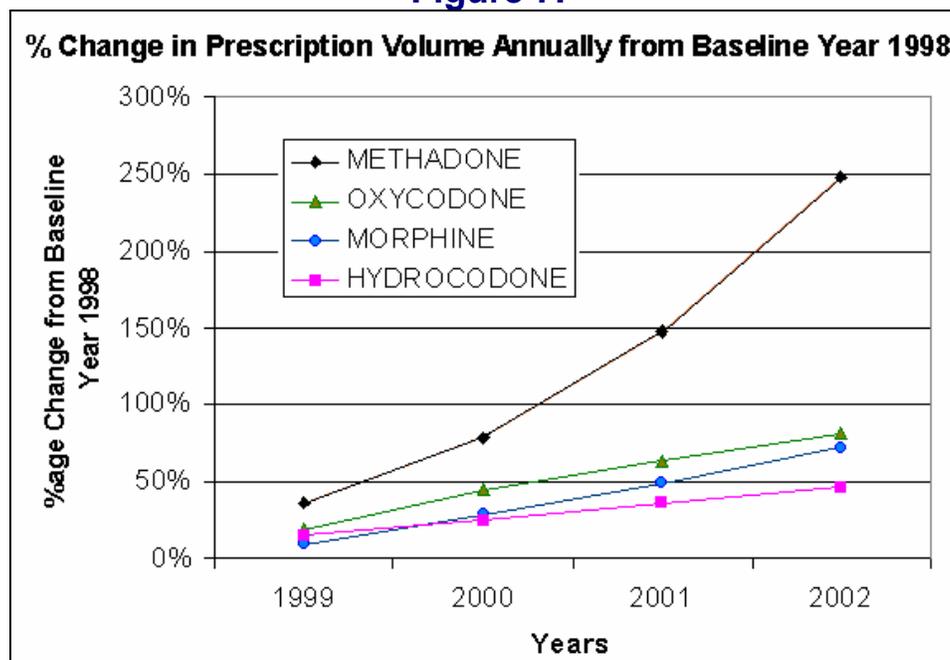


SOURCE: Florida Department of Law Enforcement, 2006 Interim Drug Report by Medical Examiners, Tallahassee, FL.

Finding 2: The Increased Number of Methadone Deaths Parallels the Trend for All Opioid Analgesics

Finding of the 2003 National Assessment: The increase in methadone-associated deaths parallels the upward trend in use, abuse, overdoses and deaths associated with all opioid analgesics. According to SAMHSA’s 2001 National Household Survey on Drug Abuse, the number of new non-medical users of prescription drugs increased steadily since the mid-1980s (Figure 7). The greatest part of this increase involved non-medical use of opioid analgesics, which increased from 400,000 persons in the mid-1980s to about two million in 2000 (Crane, meeting presentation, 2003; SAMHSA, 2001).

Figure 7.



SOURCE: Data from IMS Health, National Prescription Audit Plus, courtesy of Laura A. Governale, PharmD., 2003.

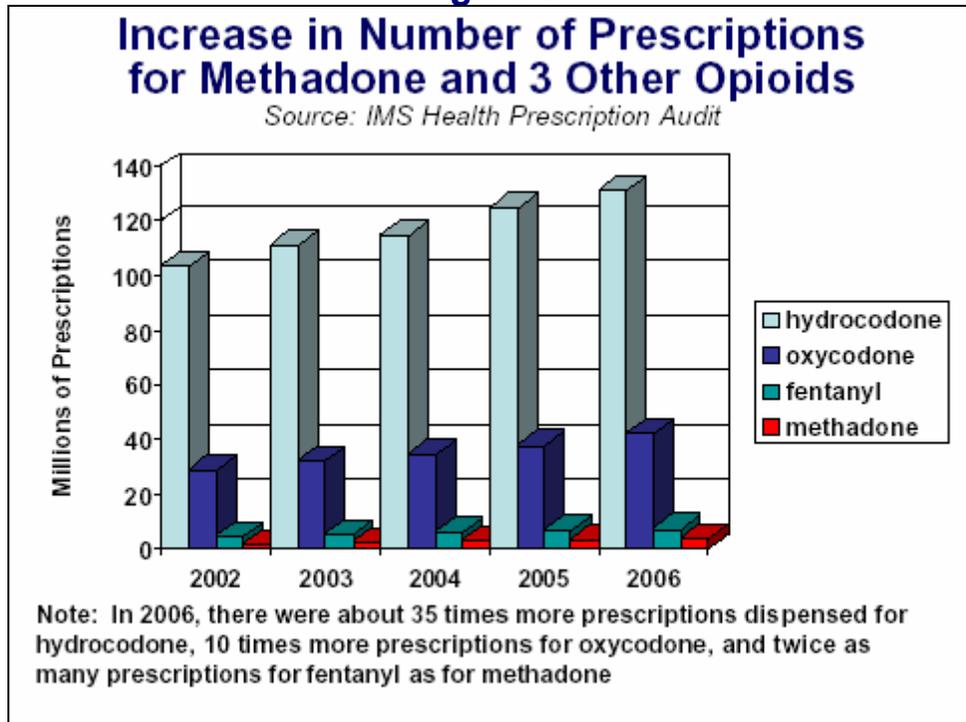
Data from SAMHSA’s Drug Abuse Warning Network (DAWN) indicated that, in 2002, heroin/morphine, cocaine, and alcohol in combination with other drugs – such as opioid analgesics or marijuana – were the substances most often mentioned in national data on drug-related deaths reported through DAWN (SAMHSA, 2003).

From 1994 to 2001, DAWN recorded an increasing number of opioid analgesic mentions in drug-related emergency department visits, with the largest increases reported for oxycodone (352 percent), methadone (230 percent), and hydrocodone (131 percent). In 2001, “opioid dependence” (presumed to involve addiction rather than solely physical dependence) was the most frequently mentioned motive for abuse of opioid analgesics, followed by “suicide attempts,” “psychotropic effects,” and “unknown” or “other” motives (SAMHSA, 2003). Reports from U.S. poison control centers also show that the overall number of opioid-related deaths has been on the rise, with many cases involving oxycodone and hydrocodone (Budnitz, meeting presentation, 2003; Litovitz, et al., 2002; Fingerhut and Cox, 1998; Cone, et al., 2003; Florida Department of Law Enforcement, 2002; Eastwood, 1998).

Similarly, data from the Drug Enforcement Administration (DEA) National Forensic Laboratory System (NFLS) indicate that seizures by law enforcement agencies of illicitly obtained opioid analgesics such as hydrocodone and oxycodone have outpaced seizures of methadone; nevertheless, methadone seizures have been increasing as well (Howard, meeting presentation, 2003).

Current Information: Data from the IMS Health Prescription Audit show an overall increase in the number of prescriptions dispensed for all opioid analgesics in the period 1998 - 2006 (Figure 8).

Figure 8.



Data from the Centers for Disease Control and Prevention (CDC) show that the number of poisoning deaths associated with the use of any drug increased by 54 percent in roughly the same period (Figure 9).

Whereas in 1999, opioid analgesics were listed as the cause of poisoning deaths in 28.1 percent of all cases, by 2002, opioid analgesics were listed in 36.5 percent of poisoning deaths – more than either cocaine or heroin. The category showing the greatest rate of increase was “opioid analgesic without heroin or cocaine,” which rose 129.2 percent. (In contrast, deaths listing heroin without either cocaine or opioid analgesics increased only 23.7 percent, and deaths listing cocaine without heroin or opioid analgesics increased only 16.0 percent. Deaths listing other specified drugs [i.e., specific drugs other than opioid analgesics, heroin, or cocaine] increased 7.4 percent (Paulozzi, Budnitz et al., 2006) (Figure 10).

Figure 9.

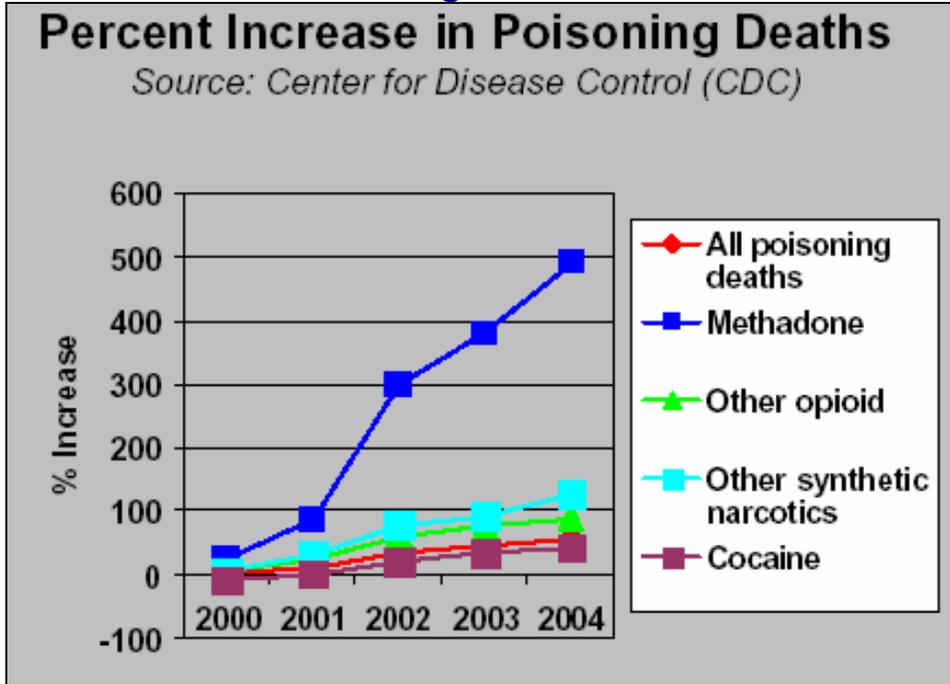
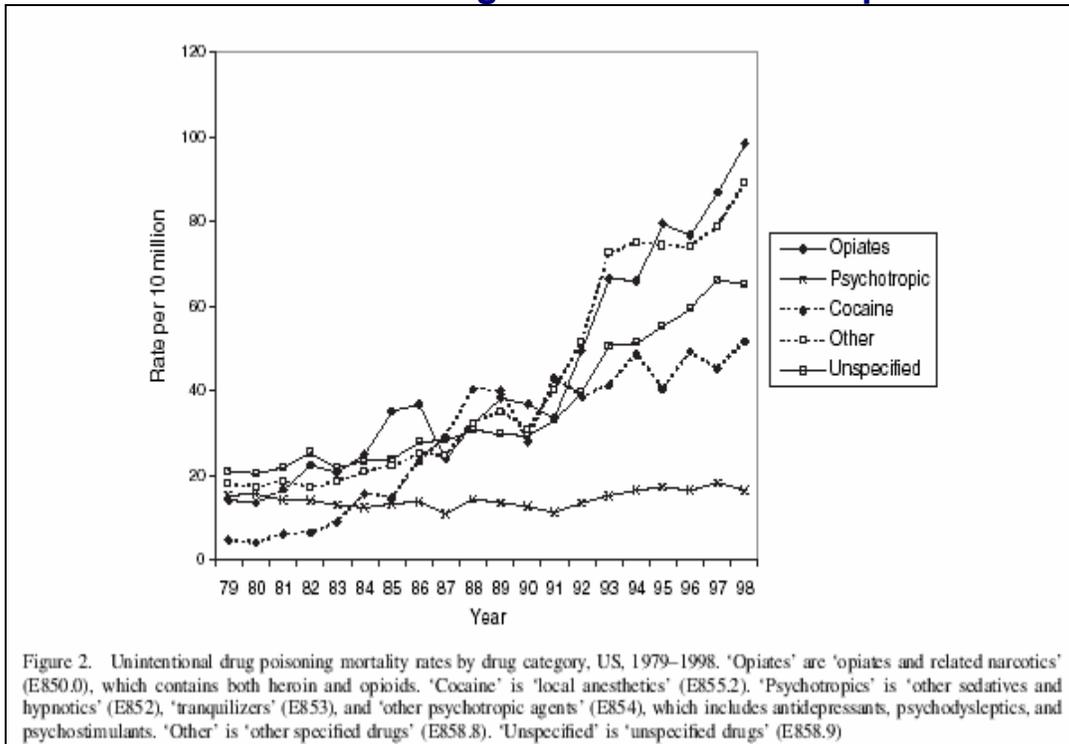


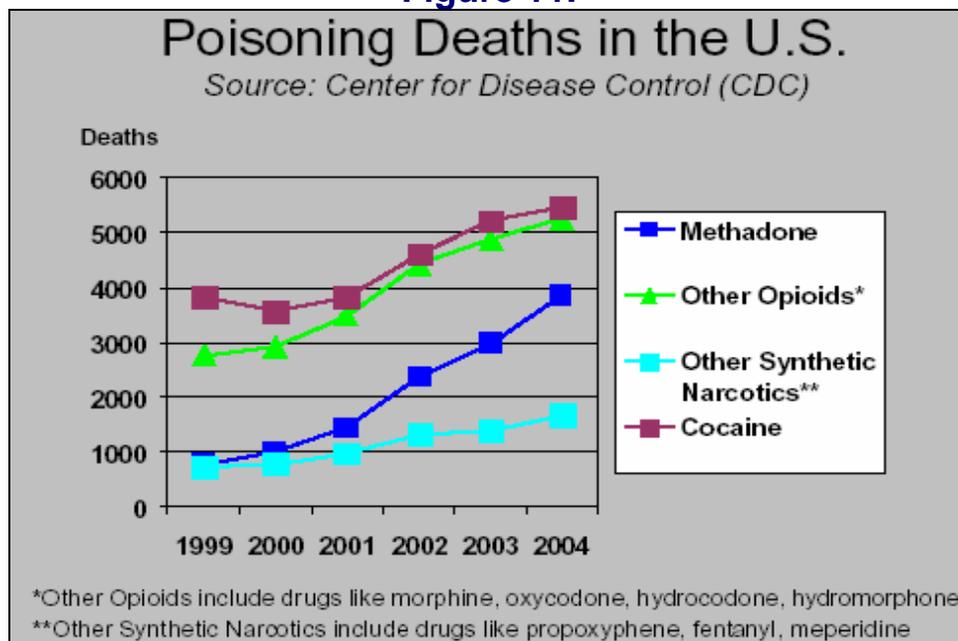
Figure 10.
Increase in Poisoning Deaths Related to Opioids



SOURCE: Paulozzi LJ, Budnitz DS, Yongli X. Increasing deaths from opioid analgesics in the United States. *Pharmacoepidemiology and Drug Safety*. 2006; 15:618–627.

Similar data have been published by the CDC, showing that between 1998 and 2006, the number of poisoning deaths related to opioids (such as hydrocodone and oxycodone) increased by 90 percent, while the number of poisoning deaths related to methadone increased by 390 percent (Figure 11).

Figure 11.



Finding 3: A Majority of Deaths Associated with Methadone Are Related to Its Use to Treat Pain Rather than Addiction

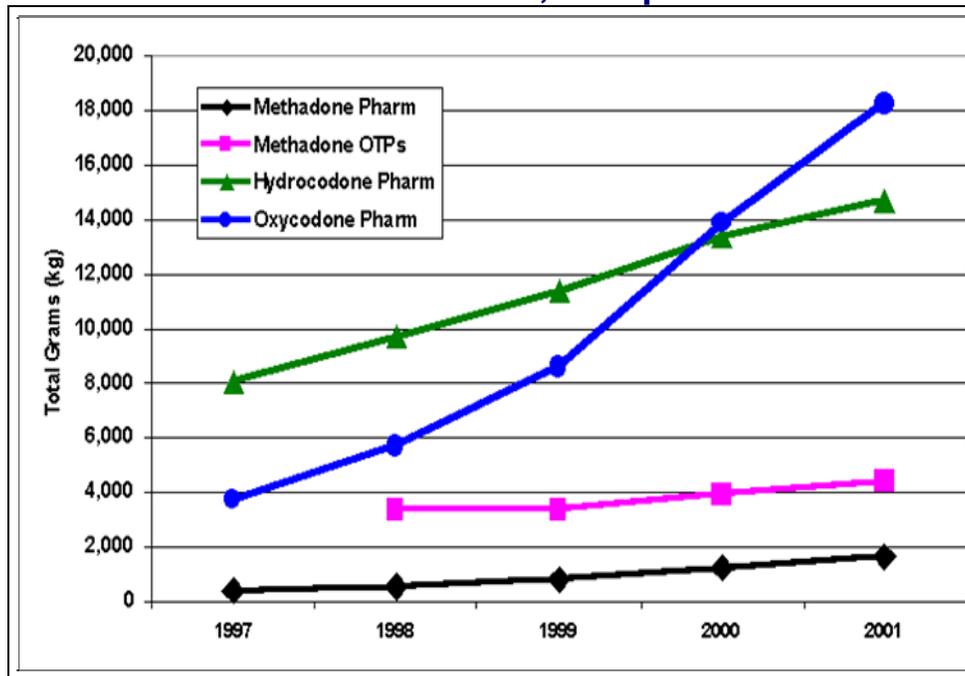
Finding of the 2003 National Assessment: The increase in methadone-related deaths is primarily associated with increased use of the drug for the treatment of pain rather than in the treatment of addiction. The greatest incremental growth in methadone distribution in recent years is associated with use of the drug as an analgesic and its distribution through pharmacies. In fact, distribution of solid methadone formulations (tablets and diskettes), primarily through pharmacies, has surpassed distribution of the liquid formulations that are the mainstay of dispensing in OTPs. From 1998 through 2002, the volume of methadone distributed through pharmacies increased five-fold, whereas the volume distributed through OTPs increased only 1.5-fold. In 2002 alone, pharmacies accounted for 88 percent of all purchases of methadone tablets (DEA, 2003).

Data from the DEA's ARCOS system indicate that the growth in methadone distribution overall has lagged far behind the increases seen for other opioid analgesics, such as oxycodone and hydrocodone products (DEA, 2003).

The DEA data are supported by independent information from IMS Health, which tracks drug prescriptions and sales through selected channels of distribution (Governale, meeting presentation, 2003). From 1998 to 2002, the number of retail prescriptions filled each year for oxycodone, hydrocodone, morphine, and methadone all increased. While fewer prescriptions were written for methadone than for the other three opioids, the number of prescriptions for

methadone increased three-fold between 1998 and 2003 (from 0.5 to 1.8 million prescriptions)—a rate of increase larger than that for the other three drugs. The number of units of methadone in solid form distributed through retail channels averaged a 38 percent annual increase. By comparison, distribution of methadone through OTPs remained relatively flat during the period measured (Howard, meeting presentation, 2003; Figure 12).

Figure 12.
Distribution of Methadone Through OTPs and Pharmacies, Compared

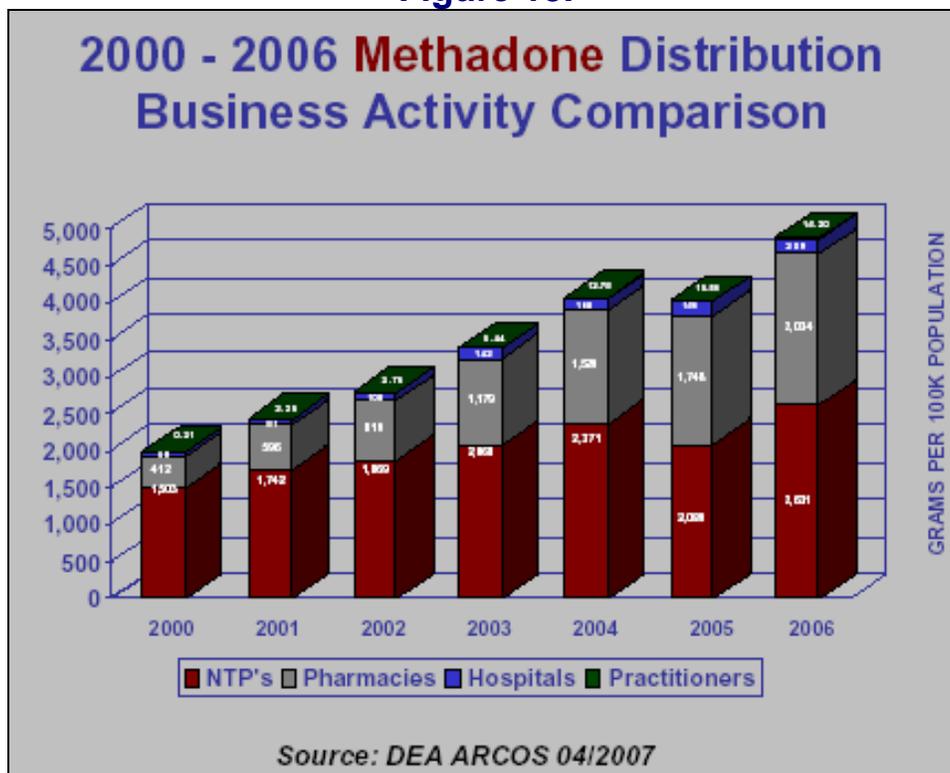


SOURCE: Data derived from DEA ARCOS-2; methadone pharmacy 2000 data are an interpolated estimate, 2003.

Taken together, the data confirm a correlation between increased methadone distribution through pharmacy channels and the rise in methadone-associated mortality. This supports the hypothesis that the growing use of oral methadone, prescribed and dispensed for the outpatient management of chronic pain, explains the dramatic increases in methadone consumption and the growing availability of the drug for diversion to abuse.

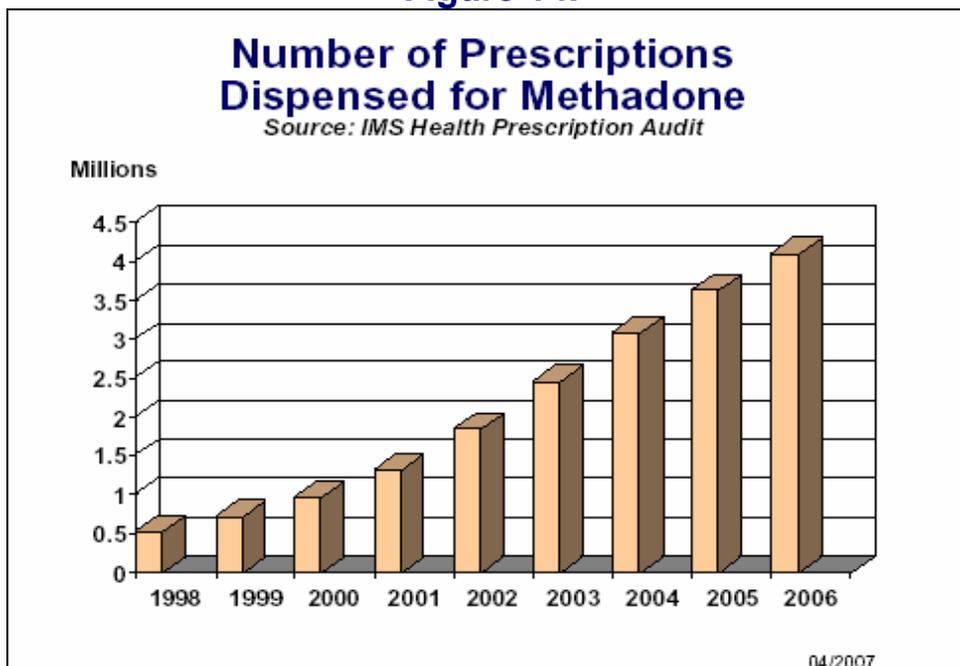
Current Information: Since 2000, retail pharmacies (which dispense methadone tablets and diskettes prescribed for pain management) have accounted for a growing share of overall methadone distribution, as compared to opioid treatment programs (Figure 13).

Figure 13.



Overall, the number of prescriptions dispensed for methadone increased by nearly 700 percent between 1998 and 2006, making more of the drug available (Figure 14).

Figure 14.



Finding 4: Three Scenarios Account for Most Methadone Deaths

Finding of the 2003 National Assessment: A majority of deaths associated with methadone can be described by one of three scenarios, which are:

1. Accumulation of methadone to toxic levels at the start of treatment for pain or addiction (i.e., the induction phase). Among patients in addiction treatment, the largest proportion of methadone-associated deaths have occurred during the drug's induction phase, usually when (1) treatment personnel overestimate a patient's degree of tolerance to opioids, or (2) a patient uses opioids or other central nervous system (CNS) depressant drugs in addition to the prescribed methadone (Karch and Stephens, 2000; Caplehorn, 1998; Harding-Pink, 1991; Davoli, et al., 1993). In fact, when deaths occur during later stages of treatment, other drugs usually are detected at postmortem examination (Appel, et al., 2000).

2. Misuse of diverted methadone at high doses and/or by individuals who had little or no tolerance to the drug. As with most other opioids, the primary toxic effect of excessive methadone is respiratory depression and hypoxia, sometimes accompanied by pulmonary edema and/or aspiration pneumonia (White and Irvine, 1999; Harding-Pink, 1993).

3. Synergistic effects of methadone used in combination with other CNS depressants, such as alcohol, benzodiazepines, or other opioids. Methadone seldom is reported as the sole cause of death. In those relatively rare cases, the drug often was ingested accidentally. The majority of methadone-associated deaths involved at least one other drug, often another opioid or central nervous system depressant such as alcohol or a benzodiazepine (Borron, et al., 2001; Haberman, et al., 1995). In particular, researchers have called attention to the "poison cocktail" resulting from the intake of multiple psychotropic drugs (Borron, et al., 2001; Haberman, et al., 1995) such as alcohol, benzodiazepines, and other opioids. When used alone, many of these substances are relatively moderate respiratory depressants; however, when combined with methadone, their additive or synergistic effects can be lethal (Kramer, 2003; Payte and Zweben, 1998).

Current Information: Paulozzi and colleagues (2006) report that, from 1979 to 2002, "unintentional" poisonings accounted for the majority of the increase in overall drug-related deaths (as compared with "suicide" or "undetermined") (Figure 15).

Moreover, they found that four of the five major drug categories – opiates, cocaine, "other specified," and "unspecified." – accounted for essentially all of the increase in unintentional drug poisoning mortality from 1990 to 1998 (Figure 10). Deaths from these four major drug categories accounted for 85.3 percent of all unintentional drug-poisoning deaths (Paulozzi et al., 2006).

From 1999 to 2002, most of the continued increase in the unintentional drug poisoning category was accounted for by the ICD-10 codes for "narcotics and psychodysleptics" or "other and unspecified drugs" (Figure 16).

Figure 15.
Reasons for Drug-Related Deaths, 1979-2002

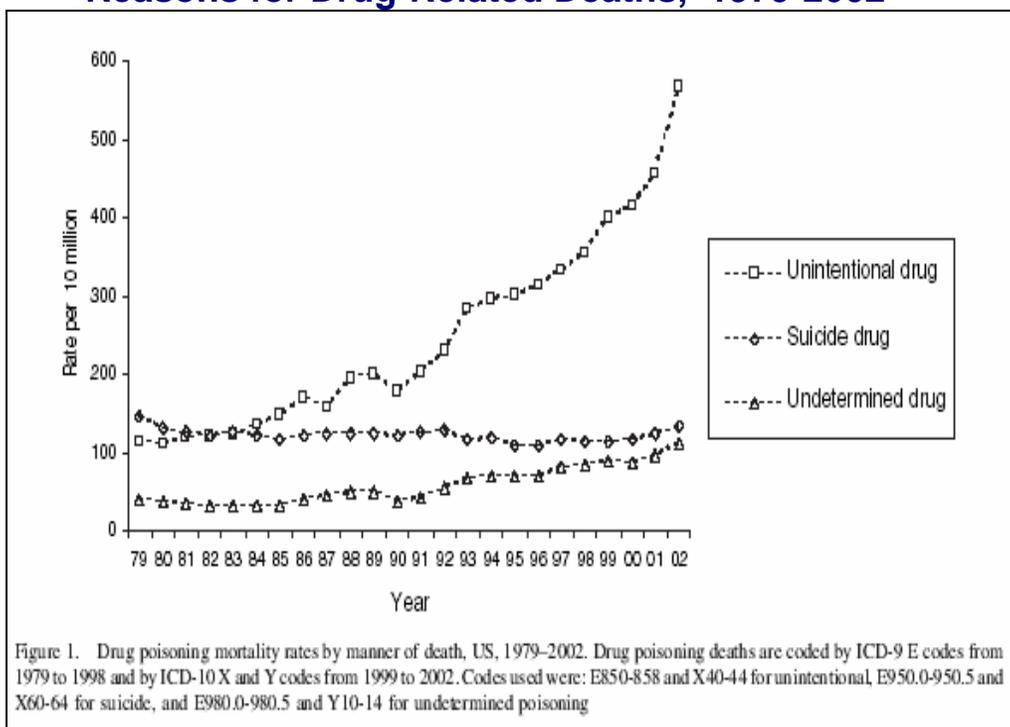
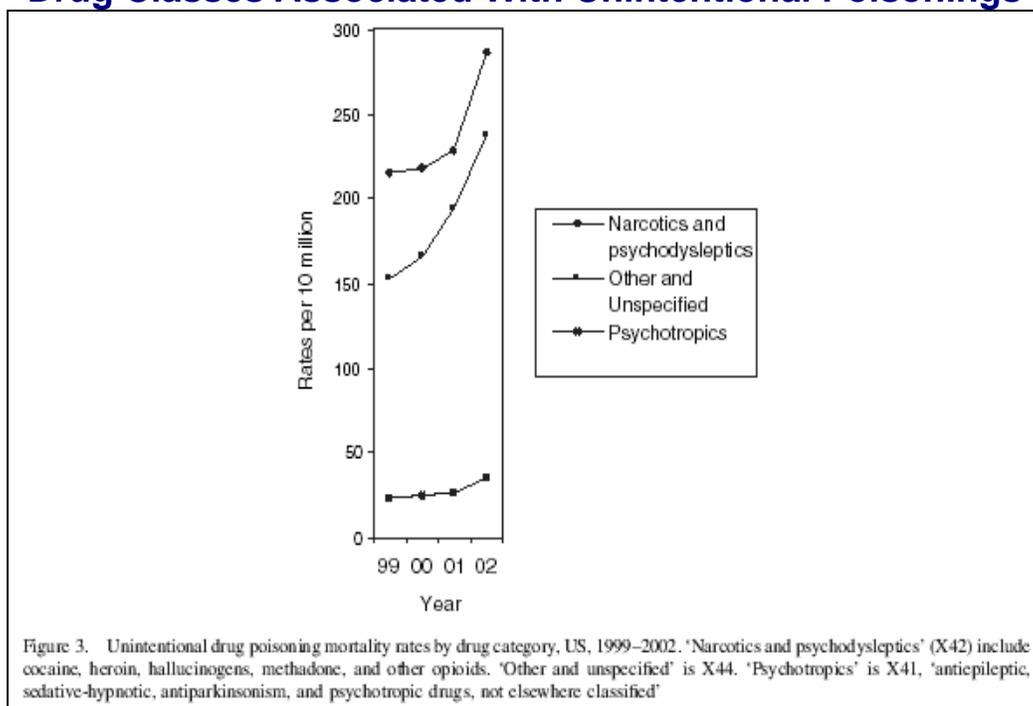


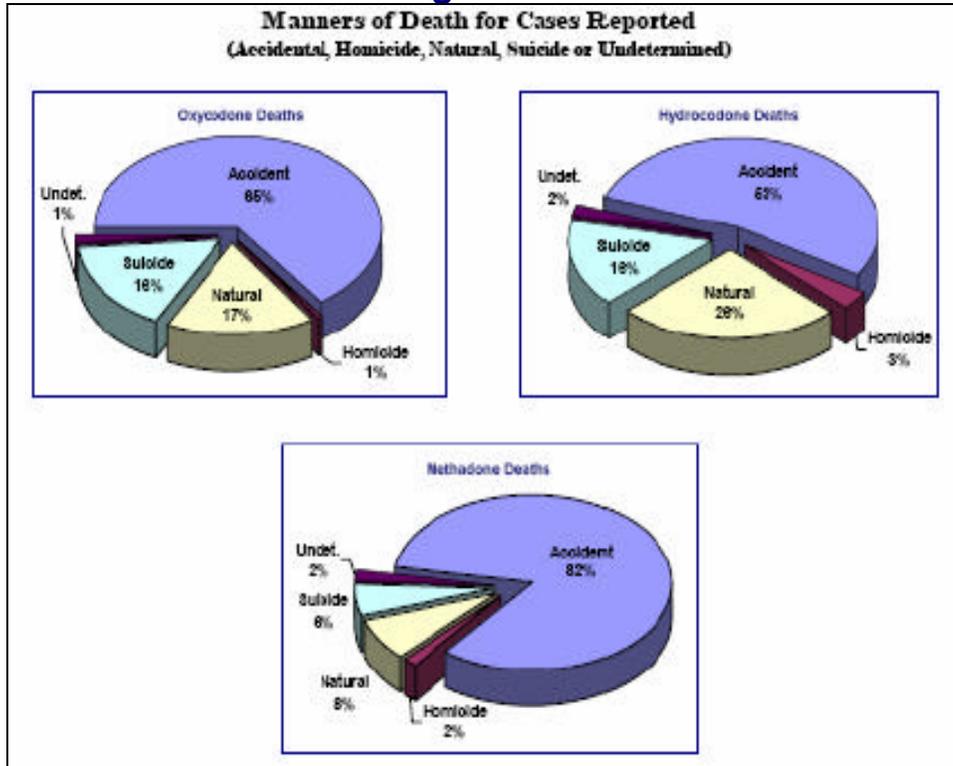
Figure 16.
Drug Classes Associated With Unintentional Poisonings



SOURCE: Paulozzi LJ, Budnitz DS, Yongli X. Increasing deaths from opioid analgesics in the United States. *Pharmacoepidemiology and Drug Safety*. 2006; 15:618–627.

Similarly, Florida Medical Examiner data show that, in the period January – June 2006, methadone-associated deaths were more likely to be classified as “unintentional” than were deaths attributed to either hydrocodone or oxycodone (Figure 17).

Figure 17.



SOURCE: Florida Department of Law Enforcement, 2006 Interim Drug Report by Medical Examiners, Tallahassee, FL.

Finding 5: Actions by OTPs and the Federal Government Are Not the Cause of the Increase in Methadone Deaths

Finding of the 2003 National Assessment: The clinical practices of OTPs and the regulatory practices of SAMHSA and other Federal agencies are not responsible for the increase in methadone-associated mortality.

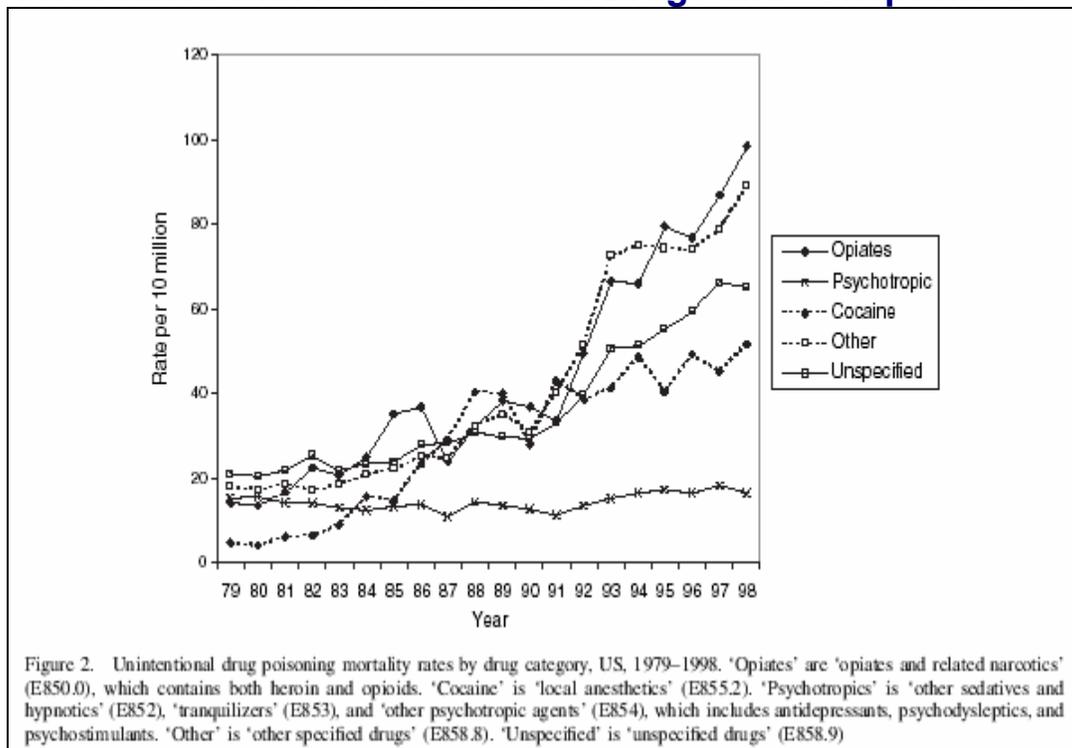
Examination of the data available to the National Assessment participants indicates that OTPs and the 2001 regulatory changes (42 CFR Part 8, which allows patients to take home doses of methadone on an increased number of days) *did not* have a significant effect on rates of methadone-associated mortality. In the cases in which the sources of methadone associated with deaths could be traced, methadone obtained legally from OTPs did not appear to be involved.

Within OTPs, patient deaths during the start-up (induction) phase—the period of highest risk for in-treatment mortality—are rare due to Federal regulations that impose specific requirements on the induction (“loading”) dose, as well as improvements in patient care that resulted from the SAMHSA requirement that OTPs must be accredited.

Further, the growth in the number of OTPs administering methadone and in the number of persons receiving methadone treatment has been modest and does not parallel the rate of increase in methadone-associated deaths. Although the data remain incomplete, National Assessment participants concurred that methadone tablets and/or diskettes that have become available through channels *other than OTPs* (such as retail pharmacies) are most likely the central factor in recent increases in methadone-associated mortality.

Current Information: The upward trend in fatalities involving methadone appeared before SAMHSA changed its regulations governing take-home medications (Kallan, 1998). Between 1979 and 1990, the combined mortality rates for unintentional, suicidal, and undetermined drug poisoning increased 13.8 percent. By comparison, the combined mortality rates for unintentional, suicidal, and undetermined drug poisoning more than doubled between 1990 and 2002, reaching 140.8 percent. This was the result of a 217.6 percent increase in deaths attributed to unintentional drug poisonings (18.1 percent per year), a 10.8 percent increase in deaths attributed to suicide, and a 193.4 percent increase in drug poisonings in which the motivation could not be determined (Figure 18).

Figure 18.
Rates of Increase in Unintentional Poisoning Deaths
Associated with Four Classes of Drugs and “Unspecified”



SOURCE: Paulozzi LJ, Budnitz DS, Yongli X. Increasing deaths from opioid analgesics in the United States. *Pharmacoepidemiology and Drug Safety*. 2006; 15:618–627.

Thus, the upward trend in opioid distribution and associated deaths took hold long before the SAMHSA regulatory changes in 2001.

RECOMMENDATIONS AND RELATED ACTIONS

To address the problems identified in their findings, participants in the 2003 National Assessment of Methadone-Associated Mortality agreed on the following recommendations:

1. A uniform nomenclature, case definitions, and standards for toxicological testing should be established.
2. More useful data are needed.
3. Health care professionals need better training in how to address pain and addiction.
4. Public perceptions of methadone should be addressed.
5. Public policies must respond to multiple needs.

The rationale for each recommendation – as well as actions on the part of SAMHSA and other agencies/organizations in response to the recommendations – are described below. We thank the named organizations and agencies for providing descriptions of their activities.

Recommendation 1: Uniform Nomenclature, Case Definitions and Standards

Recommendation from the 2003 National Assessment: A uniform nomenclature, case definitions, and standards for toxicological testing should be established. Comparison of data from various epidemiologic databases or studies of methadone-associated mortality is made unduly difficult by the fact that such databases do not employ a common nomenclature, case definitions, or standards for toxicological testing.

- 1.1. Professional organizations need to agree on a uniform nomenclature that clearly distinguishes physiologic dependence and drug tolerance (which occur with many commonly used opioid medications) from addiction (which is a chronic, relapsing, neurobiological disorder with behavioral manifestations).
- 1.2. Scientifically concise, universally accepted case definitions could address the critical distinction between deaths caused by methadone and deaths in which methadone is a contributing factor or merely present. Once standard case definitions have been adopted, investigative techniques for medical examiners and coroners can be enhanced and standardized.
- 1.2. Standards should be developed to guide toxicological testing in cases of suspected drug-induced deaths. Participants in the 2003 Assessment suggested that the Food and Drug Administration provide reference standards for such toxicological tests, with input and assistance from interested professional organizations.
- 1.4. Development of a central repository for opioid-related medical examiner/coroner cases – that is, a National Opioid Death Registry – would facilitate the necessary data compilations and analyses. National Assessment participants concluded that Federal

support and involvement would be needed to ensure that comprehensive toxicological analyses are conducted in all local jurisdictions and reported to such a national registry.

Actions That Address the Recommendation: Actions by Federal agencies and private sector organizations that are responsive to the 2003 recommendations include – but are not limited to – the following:

American Pain Society, American Academy of Pain Medicine, and American Society of Addiction Medicine: APS, AAPM and ASAM have jointly developed a model nomenclature, which has been widely disseminated through publication in the Societies’ journals and on websites, etc. (*Appendix A-1*).

Mallinckrodt (now Covidien): Mallinckrodt is considering a proposal to fund research that would further clarify the issues surrounding the characterization of deaths attributed to methadone. This project involves medical examiners, physicians, and epidemiologists reviewing cases of methadone attributed mortality in the state of Utah. Mallinckrodt has discussed the proposal with the lead investigator. While the research has substantial merit and the information is sorely needed, the company has some concerns that support of the research by any pharmaceutical manufacturer who supplies methadone would result in the results of the information being questioned. The proposal remains under consideration.

National Association of Alcohol and Drug Abuse Directors: NASADAD surveyed its member State Methadone Authorities on the subject of methadone-associated deaths (Trick, 2007). Specifically, State officials were asked whether the medical examiner/s in their state distinguished between deaths *caused* by methadone and deaths in which methadone is a contributing factor or is merely present.

In their responses to NASADAD’s inquiry, numerous State staff said that their local medical examiner regularly ruled that any case in which methadone was present was considered a methadone overdose death. Similarly, several State officials noted that case definitions varied from medical examiner to medical examiner.

State agency staff also reported that their medical examiners often attributed deaths to methadone overdose even though toxicology reports showed highly toxic levels of benzodiazepines and diphenhydramine combined with therapeutic or even subtherapeutic levels of methadone. This is consistent with the findings of Karch & Stephens (2000), who noted that many studies were undertaken before medical examiners had developed the relatively recent understanding that drugs redistribute throughout the body after death, making it difficult to determine the true concentration of methadone or any other drug. One study found a 100 percent discrepancy between methadone concentrations in samples collected from different sites of the same body (Milroy, 2000).

Results of the survey have been compiled in a NASADAD Issue Brief, published in March 2007. (*A copy of the Issue Brief has been provided in the handout material.*)

Substance Abuse and Mental Health Services Administration: Based on the advice of its Working Group on Case Definitions, SAMHSA determined that its highest priority activities in this area ought to involve:

- Collecting information on case definitions currently in common use;
- Drafting a model policy statement on uniform case definitions, and
- Promoting adoption of the uniform case definitions by the relevant professional bodies.

Acting on these priorities, SAMHSA tasked the Working Group with researching and drafting a statement setting forth model uniform case definitions (*Appendix A-2*). The completed draft

statement currently is undergoing peer review and validation studies. On completion, the draft statement and supporting data will be submitted to the National Association of Medical Examiners for possible adoption.

SAMHSA also will assist in disseminating the new definitions to medical examiners and coroners nationwide.

Recommendation 2: More Useful Data

Recommendation from the 2003 National Assessment: Greater flexibility is needed in the design and evaluation of datasets and the performance of data analyses. Procedures for accessing new and existing data also should be simplified. Specifically:

- 2.1. Better information is needed on the uses and limitations of data from various existing data sets and data collection systems. It also would be helpful to understand how data from various sources could be integrated to develop more comprehensive analyses. For example, it would be useful to compare data from IMS Health, ARCOS, or State prescription monitoring programs (PMPs) with medical examiner data to assess methadone prescribing trends and patterns in regions that report increased cases of methadone-associated deaths.
- 2.2. Better information is needed to describe how methadone-associated deaths occur. For example, data could help us understand whether the drug's potential for lethality may be the result of a slow onset of action, leading to repeated dosing—and, ultimately, overdose—as an individual attempts to achieve the desired drug effect.
- 2.3. Accurate information is needed to identify the formulations and sources of methadone associated with fatalities (e.g., thefts, robberies or diversion from medical practices, pharmacies, or OTP clinics). For example, current data indicate that most methadone-associated deaths, where dosage form information is available, involve 5 and 10 mg tablets. However, it is not clear whether those tablets are obtained through legal prescriptions, prescription forgeries, other diversion tactics, or pharmacy thefts or robberies.
- 2.4.1. More information is needed about the population being legitimately prescribed methadone for pain—their health history, concomitant use of other medications, and current or past involvement with alcohol or other drugs.

In identifying data needs, National Assessment participants concluded that it would be helpful to know of any specific national and local concerns. They urged that research be interdisciplinary, involving stakeholders from various fields. They also recommended that the Federal government develop a special Working Group to focus on this issue.

Actions That Address the Recommendation: Actions by Federal agencies and private sector organizations that are responsive to the 2003 recommendations include – but are not limited to – the following:

American Association for the Treatment of Opioid Dependence (AATOD) and RADARS: The American Association for the Treatment of Opioid Dependence gathers anecdotal reports from Board members and member programs with regard to the changing patterns of opioid use/abuse being reported by newly admitted patients.

In response to trends identified through these reports, AATOD designed a study involving 75 independent opioid treatment programs (OTPs) in more than 30 states in the country, representing every major region in the United States. AATOD worked with patient advocates in designing the survey instrument and field-tested the survey in December 2004, before launching the survey on January 1, 2005. The study is part of the RADARS Reporting System, which is currently managed through the Denver Health and Hospital Authority under the direction of Richard Dart, M.D., Ph.D.

The study has tracked changing characteristics as patients enter methadone treatment programs throughout the United States. Since January 2005, more than 19,000 patients have completed survey instruments on or near admission to OTPs. The early results have been published in the journal *Drug and Alcohol Dependence* (2007).

Drug Enforcement Administration: The Drug Enforcement Administration has three data collection systems that capture essential information about methadone and other controlled substances:

ARCOS: The Automation of Reports and Consolidated Orders System (ARCOS) accumulates and summarizes reports from manufacturers and distributors regarding their controlled substances transactions. All legal transactions involving controlled drugs, from the point of manufacture or importation through distribution to pharmacies and other retail outlets, are captured in the ARCOS system.

NFLIS: The National Forensics Laboratory Information System (NFLIS) systematically collects results from drug analyses conducted by State and local forensic laboratories, and reflects drug evidence seized by law enforcement agencies. Approximately 300 State and local forensic laboratories in the United States analyze nearly 2 million drug items each year. At one time, the system encompassed 34 State lab systems and 49 local or municipal labs, for a total of 179 individual laboratories.

STRIDE: The System to Retrieve Information from Drug Evidence (STRIDE) is a forensic laboratory database that contains information on drug evidence seized by the DEA.

Food and Drug Administration: The Food and Drug Administration’s MedWatch Adverse Event Reporting System (AERS) allows – but does not require – physicians to report patients’ adverse reactions to prescribed drugs. It is a national system that covers patients in private medical practices, hospital emergency departments and clinics.

Mallinckrodt (now Covidien): Mallinckrodt has made significant investments in obtaining longitudinal patient data, prescription data, and outcomes data on methadone. The company has evaluated a number of vendors who provide data, either in the form of longitudinal patient data, prescription data, adverse event data, or information on other trends in abuse or diversion.

Mallinckrodt subscribed to a national pharmacy benefits management database to obtain data on the use of methadone, including concomitancy, switching, dosing, titration, as well as physician prescribing patterns of methadone.

Mallinckrodt submitted and received data on adverse events from the FDA AERS system through the Freedom of Information Act. That data was received July 5, 2007 and will soon be reviewed and analyzed.

National Association of State Alcohol and Drug Abuse Directors: In response to a brief survey from the National Association of Alcohol and Drug Abuse Directors (Trick, 2007), 22 State Methadone Authorities (AR, CO, ID, IN, KY, LA, ME, MN, MI, MS, NH, NM, NC, OK, PA, RI, SC, TX, VA, WA, WI, WV) provided information on the following topics:

- Increases in methadone-associated deaths
- Articles in local newspapers about such deaths
- Steps taken by OTPs to reduce methadone-associated deaths
- Efforts with medical examiners or hospitals to better define methadone-associated deaths
- Other initiatives (e.g., with primary care physicians or pain specialists, PMPs, and the media) to prevent methadone deaths or to clarify popular misconceptions about methadone.

Of the respondents, 10 (AR, ME, KY, NC, NH, OK, TX, VA, WA, and WV) reported significant increases in methadone-associated deaths in their States. Oklahoma reported that three groups were involved in such deaths: (1) pain patients taking methadone in ways other than prescribed; (2) youth and young adults who abused methadone; and (3) patients in one OTP where there was an apparent spike in deaths during the induction phase.

Six States (AR, CO, ME, TX, WA, and WV) reported overall increases in methadone overdose deaths through 2005. For example, Washington provided data on methadone-detected deaths from 2000 to 2005 in four counties (60 percent of the population).

For accidental deaths in which methadone was detected, the figures show a steady increase: 53 in 2000, 59 in 2001, 91 in 2002, 100 in 2003, 143 in 2004, and 185 in 2005. Two States made the distinction between deaths in which methadone was the sole agent and deaths in which methadone was combined with other drugs, both for the year 2005: Kentucky noted that of 75 deaths in which methadone was detected, methadone was the sole agent in 17 deaths; New Hampshire noted that in the 49 overdose deaths in which methadone was detected, 20 deaths

were methadone alone. Both those States noted that none of the methadone involved in those cases came from OTPs.

New Mexico reported a general increase in deaths until 2004 (27 in 2001, 26 in 2002, 34 in 2003, 44 in 2004) and a decrease to 34 in 2005. Two States were able to provide 2006 data; Arkansas noted a 55 percent increase from 2005 of 81 deaths to 126 deaths in 2006, and West Virginia noted a 28 percent decrease from 122 in 2005 to 88 in 2006. (*A copy of the Issue Brief has been provided in the handout material.*)

National Institute on Drug Abuse: In order to examine methadone-associated mortality and available data sources in Community Epidemiology Network (CEWG) areas, the National Institute on Drug Abuse (NIDA) convened a panel session on Methadone-Associated Mortality during the June 2003 CEWG meeting. The panel consisted of CEWG representatives from Texas and Seattle, as well as representatives from CSAT and SAMHSA's DAWN.

CEWG members continue to report on methadone activity in their metropolitan areas at their semi-annual meetings.

RADARS: Operated by the Rocky Mountain Poison Control & Drug Center, the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) system was established in 2002 as part of a post-marketing surveillance plan. It is designed to obtain quantitative and qualitative information on the relative rates of abuse, addiction, and diversion of commonly prescribed prescription analgesics (initially, morphine, buprenorphine, fentanyl, hydrocodone, hydromorphone, and oxycodone). This dataset is not available to the public.

Substance Abuse and Mental Health Services Administration: At present, SAMHSA is monitoring data on methadone-associated deaths through three types of data collection activities:

Office of Applied Studies: SAMHSA's Office of Applied Studies systematically collects and reports data on a variety of health indicators, such as drug-related visits to hospital emergency departments (DAWN), drug use in the population as a whole (NSDUH) and admissions to opioid treatment programs (TEDS).

DAWN: The Drug Abuse Warning Network (DAWN) collects data on drug-related deaths from medical examiner/coroner systems in approximately 50 metropolitan areas and from 8 States with centralized medical examiner systems (Maine, Massachusetts, Maryland, New Hampshire, New Mexico, Oklahoma, Utah, and Vermont). The participating jurisdictions are not sampled, therefore DAWN does not have the capability to produce any national estimates of mortality. However, the availability of State-level data means that deaths in rural as well as urban areas can be analyzed, and State-level rates can be calculated.

The Network collects data on all deaths where drugs played a role, either directly (such as an overdose) or indirectly (such as a fatal car crash where drugs were involved). Detailed drug information is captured. The mortality data can be analyzed based on the manner of death, drug(s) involved, decedent demographic characteristics, and other characteristics.

The DAWN emergency department (ED) component yield information about the morbidity associated with drug use, misuse, and abuse. DAWN collects data on drug-related ED visits

from a nationally-representative sample of general, non-Federal hospitals. Any ED visit related to recent drug use is captured by DAWN, regardless of the motive for taking the drug. DAWN collects data on all types of drugs—illicit, prescription and over-the-counter medications, dietary supplements, and inhalants. Data are collected on alcohol when it is combined with another drug; ED visits where alcohol is the only substance involved are included if the patient was under age 21. National estimates and estimates for a selection of metropolitan area are produced annually.

NSDUH: The National Survey on Drug Use and Health collects data on nonmedical use of methadone in the respondent's lifetime, as part of the module on nonmedical use of prescription pain relievers. In 2005, NSDUH data showed an estimated 1.6 million lifetime nonmedical users of methadone among the estimated 32.7 million lifetime nonmedical users of any prescription pain reliever. Although lifetime use is not a strong indicator for surveillance, as it tends to reflect use in the past, special analyses of the NSDUH data can make it more useful. For example, by selecting recent first-time nonmedical users of prescription pain relievers based on NSDUH questions on initiation, and then looking at methadone use among this group, we can construct an indicator of recent use among this restricted group. Based on the NSDUH data aggregated for 2002 through 2004, for example, 2.2 percent of past-year initiators of nonmedical use of pain relievers had used methadone nonmedically during that time period.

TEDS and N-SSATS: The Treatment Episode Data Set collects data on admissions to addiction treatment programs, primarily at publicly funded treatment facilities. One of the variables collected is planned use of opioid replacement therapy in treatment. However, TEDS captures only a subset of admissions where opioid replacement therapy is planned. It does not cover many OTPs that are privately funded. The National Survey of Substance Abuse Treatment Services (N-SSATS), a survey of all known substance abuse treatment facilities, regardless of funding source, collects data on whether facilities offer methadone and buprenorphine treatment services. For those that do, the number of clients that receive methadone or buprenorphine from the facility on a point-prevalence date are obtained.

Independent Epidemiologic Studies: SAMHSA has commissioned independent studies of methadone-associated morbidity and mortality. Such studies employ data from public sources such as State Medicaid drug utilization review programs and private sources such as IMS Health, which tracks prescriptions dispensed through data on sales volumes, pricing and market share – by product, company, region and distribution channel.

Monitoring Published Reports: An information specialist tracks and reports published studies of methadone-related morbidity and mortality ([Appendix B-1](#))

Data monitored through all three methods continue to show an increase in methadone-associated deaths, and that the increase is related primarily to use of the drug to treat pain rather than addiction.

Veterans Administration: The Department of Veterans Affairs (VA) Pharmacy Benefits Management Strategic Healthcare Group (PBMSHG) is in the process of evaluating methadone-related deaths and other adverse events, relative to those of other opioids, through several methods:

- Analysis of all-cause mortality and respiratory depression among patients prescribed methadone versus other opioids, using the pharmacy prescription claims and diagnosis (ICD-9)-based databases.
- Adverse Drug Experience Reporting System (ADERS), a new VA-wide computerized method for voluntary reporting of adverse drug reactions.
- The VA National Center for Patient Safety database of voluntary reports of adverse events and near misses considered for Root Cause Analyses.
- The VA MedWatch database of voluntarily reported adverse drug reactions relayed to the FDA's MedWatch program.

Recommendation 3: Training of Health Care Professionals

Recommendation from the 2003 National Assessment: Health care professionals need better training in how to manage pain and addiction, both of which are medical disorders for which health professionals have an ethical obligation to provide the best available treatment. All FDA-approved opioid medications, including methadone, are powerful and useful drugs in such treatment. On the other hand, inappropriate prescribing, misuse, and abuse of prescription opioids (including methadone) are serious public health problems attended by substantial morbidity and mortality.

- 3.1. The diagnosis and treatment of both pain and addiction, as well as the appropriate use of various therapies for their treatment, should be part of the core educational curricula for all health care professionals.
- 3.2. Physicians need to understand methadone's pharmacology and "best practices" for its use, as well as specific indications and cautions to consider when deciding whether to use this medication in the treatment of pain or addiction. (While this recommendation is relevant to the educational needs of the medical community as a whole, it has particular resonance for staff of opioid treatment programs and physicians who provide pain treatment.)
- 3.3. It would be helpful to know what information individuals are receiving from their physicians when methadone is prescribed, and whether patients and prescribers fully understand the potential dangers of methadone misuse and abuse.
- 3.4. Better information is needed about the nature of education and prevention messages currently being communicated to and by the public, patients, practitioners, and the media. Given inaccurate or incomplete information, patients may be deterred from seeking treatment using methadone or other opioid drugs for legitimate medical problems, including both pain and addiction.

The medical community and government agencies share a dual responsibility for ensuring that methadone and related medications continue to be available for therapeutic use, as well as for preventing their misuse or abuse.

Actions That Address the Recommendation: Actions by Federal agencies and private sector organizations that are responsive to the 2003 recommendations include – but are not limited to – the following:

American Association for the Treatment of Opioid Dependence: AATOD continues to produce an all-day training event, “Opioid Maintenance Pharmacotherapy: A Course for Clinicians,” as part of its annual conference (http://www.aatod.org/pdfs/2007_Conference_Registration.pdf). On average, more than 125 physicians and other medical professionals attend this training event at each annual conference. AATOD has collaborated with NIDA in producing the event and hopes to expand the training opportunity through other funding sources in the coming years.

AATOD’s policy statement on training of OTP medical directors, adopted March 19, 2004, is posted at http://www.aatod.org/policy_medical.html. The statement makes the following specific recommendation to the field: “The AATOD Board of Directors recommends that every OTP in the United States evaluate the current qualifications of its medical practitioners to be certain that all are properly trained and subscribing to current therapeutic practices with regard to the use of methadone and buprenorphine. It is critically important to have well-trained medical practitioners employed and retained within the OTP setting in order to best respond to the changing needs of the patient population. It is also recommended that all OTP medical practitioners take specialized training courses concerning the use of methadone, buprenorphine, and other approved medications for the treatment of opioid dependence.”

The AATOD Board of Directors also has approved training for medical practitioners in Opioid Treatment Programs (OTPs). These training courses seek to fulfill the recommendation contained in AATOD’s policy statement, to the extent that available funding will allow.

AATOD has produced risk management training events during its national conferences, building on the association’s work with the Legal Action Center, representatives of the professional liability insurance industry, and experienced treatment practitioners. A third risk management training will be conducted during the 2007 AATOD conference. The Legal Action Center has been a strong collaborator in recruiting expert faculty for this training, as has SAMHSA/CSAT and its various contractors.

American Medical Association: The AMA hosts an online pain education course on its website (www.ama-assn.org), accompanied by a statement of AMA policy on the use of controlled drugs to control pain, and links to additional educational resources (*Appendix C-1*).

Federation of State Medical Boards (FSMB): Some 20 states have adopted the “Model Guidelines for the Use of Controlled Substances for the Treatment of Pain,” initially promulgated by FSMB in 1998 and updated in 2004 (*Appendix C-2*). In many states, regulatory, law enforcement and health agencies have endorsed the principles outlined in the FSMB guidelines, as have the DEA, the American Pain Society, and the National Association of State Controlled Substance Authorities (Joranson, Carrow et al., 2002).

Food and Drug Administration: The Food and Drug Administration held a conference call with a health care provider groups in November 2006 to draw their attention to the new label warnings for methadone.

Mallinckrodt (now Covidien): Following the 2003 National Assessment of Methadone-Associated Mortality, and even before the final report was issued to the public in February 2004, Mallinckrodt strengthened its programs to help better educate health care professionals, as well as patients and the public. These efforts were directed through the independently produced project, *Addiction Treatment Forum* and its associated website at *ATForum.com*. This effort has been solely sponsored by Mallinckrodt since its founding in 1992. A primary focus of Addiction Treatment Forum has been the safe and effective prescribing and use of methadone for opioid addiction.

Addiction Treatment Forum makes available to healthcare professionals and interested others its quarterly evidence-based newsletter at no cost. This is mailed in printed form to more than 12,000 requesters and is available to the public at *ATForum.com* – all at no cost to recipients. Additionally, bimonthly news/research updates are posted at the website.

In addition, Addiction Treatment Forum has produced a series of evidence-based, peer-reviewed “white paper” clinical guidance reports to help educate practitioners about selected topics of concern regarding the effective and safe prescribing of methadone. As with the quarterly newsletter, these have been distributed in print format and also via download from the website – free of charge. (*A copy of the ATF White Paper on drug interactions is available on the Resource table.*)

In 2004, Mallinckrodt embarked on a program to take training directly into the facilities of OTPs. The Mallinckrodt Methadone Training Program currently consists of a series speaker/slide presentations divided into 8 modules on selected topics of importance. The modules were developed by the editorial staff of Addiction Treatment Forum, who also trained Mallinckrodt representatives in the effective delivery of each program at meetings held at clinic locations. Addiction counselors are granted continuing education credits for their participation in these programs. Continuing education credits for nurses and other staff are under examination.

Finally, following the 2003 National Assessment Workshop, Mallinckrodt began to consider an educational project to address concerns surrounding the safe prescribing and use of all opioid analgesics, including methadone. This culminated in the development in late 2005 of *Pain Treatment Topics* and the launch of the *Pain-Topics.org* website on January 1, 2006. Mallinckrodt is the founding and currently sole sponsor of that project.

Pain Treatment Topics is independently produced, with its own independent medical advisory board, and is Internet-based. Its mission is to serve as a non-commercial resource for health care professionals by providing access to clinical news, information, research, and education for a better understanding of evidence-based pain management practices. The website is open to anyone without cumbersome registration, and all educational materials produced by Pain Treatment Topics (as well as from almost all other sources presented) are available at no charge. An important emphasis at the website is on the safe and effective prescribing and use of opioid analgesics and an understanding of the interface between pain and addiction.

(It should be noted that, to our knowledge, Mallinckrodt is the only manufacturer that has been as dedicated to, and invested so heavily in, educational projects to further the safe prescribing and use of methadone in OTPs. This has been accomplished during more than 15 years via Addiction Treatment Forum. Additionally, our support of the newer Pain Treatment Topics

project represents our commitment to helping promote the safe and effective use of all opioid analgesics, including methadone, within the pain management community.)

National Institute on Drug Abuse: The National Institute on Drug Abuse and the American Medical Association cosponsored a meeting in March 2007 on “Pain, Opioids, and Addiction: An Urgent Problem for Doctors and Patients.” The purpose of the meeting was to inform researchers and practitioners about the science surrounding the intersection of addiction and pain management.

The meeting was certified to provide Continuing Medical Education credits to physicians, and Mary Jean Kreek, M.D. – a member of the original team that developed methadone maintenance treatment for heroin addiction – spoke on that topic and the use of methadone today.

New York – New Jersey AIDS Education and Training Center (AETC): The New York-New Jersey AETC at Columbia University published “Pain Management/Addiction Management Medications and HIV Antiretrovirals – A Guide to Interactions for Clinicians” in Fall 2004. The pocket-sized, spiral bound booklet succinctly reviews current data on potential interactions between antiretroviral medications and a variety of drugs used to treat pain and addiction, including methadone.

The New York-New Jersey AETC is funded by the Health Resources and Services Administration (HRSA) and is part of the National AIDS Education and Training Center Program, a network of 15 federally funded regional centers that conduct targeted multidisciplinary HIV/AIDS education and training programs for health care providers.

Copies of the Guide can be obtained from the New York-New Jersey AETC central office by phoning 212-305-8291. Additional information is available at the NY-NJ AETC website: www.nynjaetc.org.

Substance Abuse and Mental Health Services Administration: SAMHSA programs in place or in development to educate health care professionals about the appropriate use of methadone include:

- A SAMHSA Treatment Improvement Protocol (TIP) on management of addicted patients who have co-occurring psychiatric disorders. The TIP provides clinical guidance on one of the factors most often implicated in methadone-associated deaths.
- In 2006, SAMHSA published a Substance Abuse in Brief Fact Sheet (Vol. 4, Issue 1) on “Pain Management Without Psychological Dependence: A Guide for Healthcare Providers.” The Fact Sheet is designed to help health care professionals effectively manage pain, distinguish between physical and psychological dependence, and reduce their patients’ risk of psychological dependence on opioids during pain management.
- Training workshops on a variety of topics, offered at annual meetings of the American Association for the Treatment of Opioid Dependence (AATOD), the association of opioid treatment professionals.

- Development of a computerized patient intake questionnaire (PODS) that will provide physicians with an immediate print-out of a patient's drug use history and other risk factors for problems with opioid analgesics. SAMHSA helped support development of the questionnaire, which addresses the problem many physicians have in knowing which patients are good candidates for treatment with powerful pain medications, including methadone. Design of the instrument is complete and has been favorably reviewed by an independent panel of experts. The developers now are writing the computer software to support data entry and scoring.
- Participation with the American Academy of Pain Medicine, the American Academy of Family Practitioners, and other medical organizations to develop a CME course on the use of methadone to treat pain (including pain in patients who have a current addiction problem or who are at risk for or in recovery from addiction (*Appendix C-3*)).

Pilot tests of key program elements were conducted in September and December 2006 with very positive results. Using information from the pilot sessions, SAMHSA is collaborating with the New York State Academy of Family Physicians and the Cleveland Clinic to host the initial offerings of the course in September 2007, and is working with Medscape to offer the course on that popular physician education website.

- A symposium on the use of methadone to treat pain at the 7th International Conference on Pain and Chemical Dependency, June 24, 2007, in New York City.

Veterans Administration: The Department of Veterans Affairs (VA) has developed and/or collaborated in the following educational initiatives:

- VA and the Department of Defense (DoD) collaboratively developed a clinical practice guideline on opioid therapy for chronic pain; this tome reiterates the PBMSHG's methadone dosing recommendations in chronic pain.
- VA's National Pain Management Strategy Coordinating Committee (NPMSCC) gave a series of presentations on pain management in April 2007 at the VA/DoD's conference on Evolving Paradigms: Providing Health Care to Transitioning Combat Veterans.
- VA's PBMSHG and NPMSCC are planning to add a new chapter on methadone dosing to an existing Web-based continuing education program on the use of opioids in acute and chronic pain. The new chapter will discuss methadone dosing in greater detail than that currently covered in the program.
- VA's PBMSHG and NPMSCC are also planning to co-lead a breakout session at the 1st Annual VA Clinical Pharmacy Programming Conference (September 2007) to inform clinical coordinators about methods to promote education within their facilities on appropriate use of methadone.
- VA's PBMSHG and NPMSCC also are planning to highlight methadone as part of the VA's High Alert Medications – Opioids initiative.

Recommendation 4: Public Perceptions of Methadone

Recommendation from the 2003 National Assessment: Public perceptions of methadone should be addressed. For example, there is a need for professional organizations and regulatory agencies to present scientific evidence and credible data to counter misinformation about methadone and “methadone clinics” (OTPs) presented in the mass media.

The public needs to know that methadone-associated mortality is being addressed, and that when methadone is prescribed, dispensed, and used appropriately, related mortality is virtually eliminated. To this end, National Assessment participants agreed that professional associations, provider organizations, and advocacy groups need to be engaged in public information activities.

Actions That Address the Recommendation: Actions by Federal agencies and private sector organizations that are responsive to the 2003 recommendations include – but are not limited to – the following:

American Association for the Treatment of Opioid Dependence (AATOD): The American Association for the Treatment of Opioid Dependence has worked consistently to develop positive media messages with regard to methadone maintenance treatment and the success of methadone patients. AATOD’s Public Relations/Media Committee worked with other individuals to develop the first Community Education Kit, “Medication Assisted Treatment for the 21st Century,” which was launched at during AATOD’s 2000 annual conference in San Francisco. This valuable community kit has been updated and reproduced several times since then, and is having a very significant impact on how programs are able to influence community attitudes and public perceptions toward the opioid treatment system.

AATOD also has worked with pharmaceutical companies and media consultants to develop training materials to help treatment professionals and patient advocates deliver clear messages to the media about the opioid treatment system. For example, VistaPharm has funded the Executive Communications Group to present media training events at AATOD annual conferences (a third training event is scheduled for the 2007 annual conference in San Diego). This national training event grew out of regional training activities, which were successful in helping provide the media with accurate information.

In addition, AATOD will convene a specialized media training strategy session in August 2007 to reflect current challenges to the treatment system in the form of reports of methadone-associated mortality.

Food and Drug Administration: The Food and Drug Administration developed Patient Package Inserts for methadone products to provide patients receiving methadone prescriptions with information about the risks of methadone use (*Appendix D-1*).

Mallinckrodt (now Covidien): Following the 2003 National Assessment of Methadone-Associated Mortality, and even before the final report was issued to the public in February 2004, Mallinckrodt strengthened its programs to help better educate health care professionals, as well

as patients and the public. These efforts were directed through the independently produced project, *Addiction Treatment Forum* and its associated website at *ATForum.com*.

Addiction Treatment Forum has produced a series of 21 brochures for patients on various topics of importance and these have been made available in printed format free of charge to Mallinckrodt-customer clinics for distribution to all patients. Currently, these also are available at the for download, reproduction, and distribution by any interested party, all at no cost.

Substance Abuse and Mental Health Services Administration: SAMHSA's Office of Communications has developed an advertising campaign to alert the public about potential misuse of prescription medications, including take-home doses of methadone prescribed for addiction or methadone tablets or diskettes prescribed for pain. This is relevant to reports of children and other household members ingesting toxic doses of methadone stored in family medicine cabinets and other places to which they have access (*Appendix D-2*).

Veteran's Administration: The Veterans Health Administration's Pharmacy Benefits Management Strategic Healthcare Group posted Methadone Dosing Recommendations for Treatment of Chronic Pain on its website ([http://www.pbm.va.gov/monitoring/Methadone%20Dosing%20Final%20\(Rev%20081103\).pdf](http://www.pbm.va.gov/monitoring/Methadone%20Dosing%20Final%20(Rev%20081103).pdf); last revised, 2003). This document states that accruing experience suggests that methadone can be safely used when initial doses are small, conversion ratios are adjusted to the previous opioid dose, and dosage is slowly titrated to patient response.

Recommendation 5: Public Policies

Recommendation from the 2003 National Assessment: Policies regarding the use of opioid medications should address the needs of law enforcement and regulatory agencies, professional education, pain management, and addiction treatment providers. For example, National Assessment participants agreed that broad regulatory actions directed toward all OTPs, such as State-imposed restrictions on prescribing methadone, are unlikely to be effective.

The exception would be actions focusing on particular programs or geographic areas where problems are identified. In the absence of such specific problems, generalized actions against OTPs would have no effect on the overall mortality problem at best and, at worst, could have damaging effects on the availability of a vital treatment modality.

Actions That Address the Recommendation: Actions by Federal agencies and private sector organizations that are responsive to the 2003 recommendations include – but are not limited to – the following:

Drug Enforcement Administration: The Drug Enforcement Administration regulates methadone, which is classified in Schedule II of the Federal Controlled Substance Act. DEA sets the annual production quota for methadone, and reports that the quota increased by about 250% between 1998 and 2006 (the number of prescriptions for methadone increased by nearly 700% in the same period). DEA further reports that this increased use is primarily associated with use of methadone in pain management rather than addiction treatment.

Food and Drug Administration: Following an extensive literature review, the Food and Drug Administration updated the labels for methadone products to provide current information on pharmacology, drug-drug interactions, and dosing recommendations. New warnings (boxed) alert practitioners to the risk of accidental overdose during treatment initiation and during conversion from other opioids, risk of fatal respiratory depression, and risk of cardiac conduction effects including QT prolongation and torsades de pointes (*Appendix E-1*).

State Prescription Monitoring Programs (PMPs): Prescription monitoring programs (PMPs) facilitate the collection, analysis, and reporting of information on the prescribing, dispensing, and use of controlled substances (GAO, 2002). Most such programs employ electronic data transfer systems, under which prescription information is transmitted from the dispensing pharmacy to a state agency, which collates and analyzes the information. Monitoring programs that required the use of special prescription forms (once known as “triplicate prescription programs” or “multiple-copy prescription programs”) have largely been phased out, although the California, New York and Texas PMPs employ special state-issued prescription forms in combination with electronic reporting (Alliance for Model State Drug Laws, 2006), and the Washington State’s medical board requires some physicians to use them for a defined period of time as part of a practice monitoring program.

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