STATE ISSUE BRIEF
ON METHADONE OVERDOSE DEATHS

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Introduction

Used as a medication since the 1960's to treat heroin addicts and increasingly becoming a treatment for those addicted to other prescription drugs and for pain relief, methadone has come under increased scrutiny with the rise in methadone-associated fatalities over recent years, particularly in certain regions of the country. Although research presented in this Issue Brief supports the fact that this increase correlates with the increased availability of methadone due to increases in the prescribing of methadone for pain, and not with any practices of opioid treatment programs (OTPs), that distinction has not always been understood by the public, and OTPs have been considered guilty by association. For example, although the overdose victim most frequently described in a Charleston Gazette investigative series entitled "The Killer Cure" was someone who had been prescribed methadone in the form of tablets for pain and not an addict receiving methadone from an OTP (Finn & Tuckwiller, 2006), the series' headline seems to have inspired local legislators in West Virginia to seek to restrict new for-profit methadone clinics (Alcoholism Drug Abuse Weekly, 2007). This Issue Brief describes national and State efforts to explore the extent of the problem, the benefits of methadone for addiction treatment and pain management, the risks associated with methadone use, and efforts at a national and State level to better understand the problem and to reduce methadone overdose deaths.

A multidisciplinary group was convened to do a National Assessment of Methadone-Associated Mortality by the Substance Abuse and Mental Health Services Administration's Center for Substance Abuse Treatment (SAMHSA/CSAT) in May 2003, subsequently referred to as the National Assessment (CSAT, 2004*a*, CSAT, 2004*b*). The group's purpose was to address the recent increase in fatalities in which methadone was detected and to determine whether the 2001 revision of Federal guidelines, which allowed OTPs to provide patients who are advanced in treatment to take home doses of methadone on an increased number of days, had contributed to the increase in methadone overdose deaths. After reviewing data on opioid sales, patterns of prescribing and dispensing and data on drug-associated mortality, National Assessment participants concluded that the available data suggested that methadone tablets and/or diskettes that had become available through channels other than OTPs were most likely the central factor in the recent increases in methadone-associated mortality.

In addition to reviewing the current literature, NASADAD developed and distributed a brief inquiry to the State Methadone Authorities (SMAs), responsible for monitoring and regulating opioid treatment programs in their States, in order to collect more recent data at the State level and to explore how States are addressing the issue of methadone overdose deaths.

Benefits of Methadone for Addiction Treatment and Pain Management

For individuals who are addicted to opioids and are unable to stop taking them, methadone is a life-saving medication. Studies have found that only 54-73% of opioid addicts are able to complete medically supervised withdrawal; then at least 75% or more relapse; studies have also found that relative risk of death is 3-4 times greater for persons

dropping out of methadone maintenance treatment than for those patients who continue in treatment (Trachtenberg, Cone, & Leavitt, 2003).

Oral methadone is available as a solid tablet, a rapidly dissolving wafer (diskette) and as a premixed liquid, all of which are essentially bioequivalent (CSAT, 2004*a*). In OTPs, it is generally administered as a liquid, mixed with flavored drinks to make injection unattractive (CSAT, 2005). Because it is administered orally, it eliminates the risks of intravenous drug use, thus reducing the risks of HIV/AIDS infection, hepatitis B and C, tuberculosis, and sexually transmitted diseases. Methadone is also relatively inexpensive; as a Medicaid-approved drug, it can cost as little as $5 a day, including the costs for dispensing and ancillary services. In addition to the strict supervision patients receive in terms of the administration of methadone, OTPs also provide counseling, support and drug testing.

Methadone has unique pharmacologic properties that make it appropriate for addiction treatment (CSAT, 2004*a*): its slow onset allows patients to be monitored as the drug takes effect (which is particularly important in the induction period); and its long duration of action (generally 24 to 36 hours, although it may range from 4 to 91 hours) enables an individual to take only a single daily dose, in contrast with heroin, for which addicts will develop cravings in four to six hours. Because patients do not develop tolerance, there is a low need for dose escalation. Methadone is an opioid agonist that binds to the body's opioid receptors and prevents withdrawal symptoms when a person stops using any other opioid. It also reduces the euphoric effects of other opioids if the patient continues to use. It reduces cravings without producing euphoria or sedation if administered properly (Alberta Alcohol and Drug Abuse Commission, 2006).

Methadone has been researched more than any other drug treatment medication. A multi-disciplinary panel convened in 1997 by the National Institutes of Health (NIH) concluded, after reviewing a large body of research, that methadone maintenance treatment represented the gold standard for reducing illicit opiate drug use, reducing crime, reducing the spread of viral diseases and enhancing social productivity (National Institute of Health, 1998). The California Drug and Alcohol Treatment Assessment (CALDATA) found that for every dollar spent on methadone maintenance treatment, there is a savings to the community of between $4-13 (California Department of Drug and Alcohol Programs, 2004).

The properties that make methadone appropriate for addiction treatment -- long action, low need for dose escalation, and low cost -- apply equally to methadone as a pain medication, and it has been reported that insurance companies have been encouraging physicians to prescribe methadone because of its low cost. The long half-life allows the administration of methadone for pain once a day, (although typically it is administered in smaller doses every three to four hours). Methadone also allows for the use of short-or long-acting break-through medications, i.e. alternative analgesics that are used in addition to methadone when pain becomes acute. However, if break-through narcotics are used, they need to be timed carefully (Powers, 2006). Methadone can also be effective for patients who for some reason cannot take other pain medications, e.g., they are allergic to

morphine, or for whom methadone is the only effective drug because of its unique properties. It has been hypothesized that as law enforcement officials and doctors have grown increasingly concerned with addiction and diversion related to oxycodone, doctors have turned to methadone as both a less expensive medication and one which, because of its slow onset of action and because it is less likely to produce euphoria, would be less prone to diversion and abuse.

Risks Associated with Methadone Use

Although methadone has been shown to have a favorable safety profile when used as indicated (Zweben & Payte, 1990) and few serious adverse reactions and no cumulative organ damage have been associated with daily administration of appropriate doses over more than 20 years in some patients (Appel, Joseph & Richman, 2000; Blackmund, Meyer, Von Zielonka & Eichenlaub, 2001; Bell & Zador, 2000), there are also risks associated with its use. Methadone is a very potent drug which, if it accumulates in the body, can cause respiratory depression and hypoxia, sometimes accompanied by pulmonary edema and/or aspiration pneumonia (White & Irvine, 1999; Harding-Pink, 1993). In the words of the Food and Drug Administration (FDA) in its recent public health advisory on methadone used for pain control " methadone can cause slow or shallow breathing and dangerous changes in heart beat that may not be felt by the patient" (Food and Drug Administration Public Health Advisory, 2006). Because of the slow onset of symptoms, the overdose victim might be able to engage in conversation when awake, then slowly appear drowsy (not an unusual sign to family members who are accustomed to seeing a heroin addict in such condition and, in the case of pain patients, perhaps a welcome sign that the medication is working) and then fall asleep, never to wake up. The warning signs of respiratory depression, such as loud snoring, may appear too late for family members to notice.

For patients in addiction treatment, historically the largest proportion of methadone-associated deaths have occurred during the first few weeks of treatment, when treatment personnel overestimate a patient's degree of tolerance to opioids or, at any time in treatment, when a patient uses opioids or other central nervous system depressant drugs (Karch & Stephens, 2000; Caplehorn, 1998; Harding-Pink, 1991). When inducing methadone, it is difficult to predict how methadone will be absorbed, because methadone can accumulate rapidly and unpredictably in the blood serum, due to individual differences in metabolism and other characteristics of the patient (Srivastava & Kahan, 2006). Methadone's elimination half-life averages 24 to 36 at steady state but ranges from 4-91 hours (CSAT, 2004*b*), and its rate of clearance from the body has been reported to vary by a factor of almost 100 (Hall, Lynskey & Degenhardt, 1999).

Very importantly, tolerance to the respiratory effect does not necessarily develop at the same rate as tolerance to the euphoric and analgesic effect (White & Irvine, 1999). Also, methadone takes much longer to metabolize in patients who are opioid-naïve than for those who have achieved a steady-state level (Wolff, Sanderson, Hay & Ralstrick, 1991). (The term "opioid-naïve" also includes incarcerated heroin addicts or detoxified methadone patients who have abstained from opiates and mistakenly believe they can

resume their opiate use at their former level and are thus more likely to overdose.) A dose that is therapeutically appropriate for a stabilized patient, and which for some patients must be high in order to be effective, can be lethal for a naïve patient. For safety reasons, U.S. Federal regulations establish a maximum first dose of no more than 30 mg; however, Federal product labeling and treatment guidelines emphasize that dosing must be individualized carefully during the induction process. Initial dosing and adjustments to dosing during treatment phases must consider if there are other complicating factors, such as dependence level, low body weight, other medications, medical diseases, and genetic factors. If withdrawal symptoms persist at 2-4 hours, an additional 5-10 mg. is allowed, but the total first-day dose cannot exceed 40 mg. unless the program physician specifically documents the need for more (Addiction Treatment Forum, 2006). In administering the proper dose, the OTP must maintain a fine balance between giving the patient enough methadone to minimize withdrawal symptoms (thereby engaging the patient in treatment and discouraging the use of opiates and other drugs) and preventing overdose from too high a level of methadone. The National Assessment noted that OTP client deaths during induction in the US are now infrequent due to Federal regulations as well as to improvements in client care that resulted from SAMHSA requirements that OTPs must be accredited (CSAT, 2004*a*).

The other major risk factor for methadone overdose deaths is poly-substance abuse. CNS depressants like benzodiazepines and alcohol that might not be lethal on their own react synergistically with methadone to cause respiratory depression. A New South Wales study found evidence of poly-substance use in 92% of drug-related deaths that occurred during the first week of methadone maintenance treatment (Zador & Sunjic, 2000) and another study found that benzodiazepines were a co-intoxicant in the majority of methadone-related deaths in an Alabama county (Mikolaenko, Robinson & Davis, 2002).

Although OTPs in the United States are aware of these risks and have adopted policies and practices to address them, it is not at all clear that the doctors prescribing pain tablets are similarly aware. It was not until November 2006 that the FDA instituted its warning about the risks of methadone for pain control (See Resource List) and recommended that initial doses not exceed 30 mg. per day. Until that time, the package insert said that the usual adult dose is 2.5 mg to 10 mg every three or four hours as necessary, or up to 80 mg. a day, a potentially lethal dose if taken as directed and much more than is recommended for OTP patients at induction. Experts state that while 10 mg. might seem like a perfectly reasonable starting dose to a doctor unfamiliar with methadone, and used to writing prescriptions for 5 to 10 mg. of morphine, no more than 2.5 mg of methadone should be prescribed initially (Finn and Tuckwiller, 2006).

The other critical issue is that, while the respiratory depressive effect of methadone generally lasts up to 24 hours but can last up to 91 hours in some people, the FDA Alert on methadone (2006) notes that the analgesic effect may last only 4-8 hours, so without being explicitly warned to take only the amount prescribed, the pain patient may be inclined to take more pills. With regard to the dangers of using other drugs, the FDA Alert and the FDA Public Health Advisory (2006) do refer to the dangers of mixing

methadone with other medicines or supplements, but prior to those warnings physicians might not have been aware of those dangers.

Increase in Methadone Overdose Deaths

One of the key recommendations of the National Assessment was the need for a uniform case definition for methadone-associated mortality and uniform reporting methods, which distinguish between deaths caused by methadone and deaths in which methadone is a contributing factor or is merely present, and when other drugs or illnesses may have played a larger role. In their response to NASADAD's inquiry, numerous States mentioned that their local medical examiner regularly ruled that any case in which methadone was present was considered a methadone overdose death. Similarly, several States noted that case definitions varied from medical examiner to medical examiner. States also reported that medical examiners would often rule that a case was due to methadone overdose even though it showed highly toxic levels of benzodiazepines and diphenydramine and only therapeutic levels or even sub-therapeutic levels of methadone. In their review of methadone death studies, Karch & Stephens (2000) 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% discrepancy between methadone concentrations in samples collected from different sites of the same body (Milroy, 2000).

Another issue is that medical examiners often do not distinguish whether the methadone is in tablet or liquid form. When sold as an analgesic, methadone is dispensed in tablet or diskette form; OTPs provide their methadone primarily in daily doses of liquid methadone, with patients allowed to take home methadone in tablet form only after they have been stabilized and have earned that privilege through compliance with program rules and objectives. However, OTPs have been becoming much more restrictive in allowing tablet take-homes in light of the recent increase in overdose deaths. The National Assessment concluded that when information on formulation is available, most methadone-associated deaths involve 5 and 10 mg. tablets (CSAT, 2004*a*).

Despite these caveats, it is clear that the increase in methadone's role in overdose deaths has been real and substantial. In 1999, methadone was coded separately from other opiates on death certificates -- making it possible to examine deaths in which methadone was mentioned as distinct from other opiate analgesics (e.g., oxycodone and hydrocodone) and from heroin. The Centers for Disease Prevention and Control (CDC) reported that, in the years 1999-2004, the number of all poisoning deaths in the US increased 54 percent to 30,908, while the number of poisoning deaths mentioning methadone increased 390 percent to 3,849 (Fingerhut, 2006). Poisoning deaths mentioning methadone increased from 4 percent of all poisoning deaths in 1999 to 13 percent of all poisoning deaths in 2004, with the increase in methadone-related poisoning deaths in those years being greater than for all other narcotics. Rather than comparing States to each other, the CDC reported the following examples of the ratio of deaths

within each State in 2004 as compared to those in 1999, in States with large numbers of methadone-related deaths (defined as greater than 50 for at least 3 of the 6 years): West Virginia (25:1), Kentucky (15:1), Florida and Oregon (14:1), North Carolina and Texas (7:1), Virginia (6:1) and Washington (5:1).

Paulozzi, Budnitz, and Xi (2006) hypothesized that these large increases in deaths involving methadone (and other opioid analgesics) were related to the increases in the 1990s of prescriptions for opioid analgesics, as physicians developed the consensus that opioid analgesics were a legitimate and important public health response to under-treated chronic pain. The Drug Enforcement Administration's (DEA) Automation of Reports and Consolidated Orders System (ARCOS) is able to track sales of methadone by formulations and final destination (pharmacy, hospital, OTP). In their trend analysis of mortality data from the CDC and data on opioid analgesic sales from ARCOS data, the authors found that in the years between 1999 and 2002, the number of opioid analgesic poisonings listed on death certificates increased 91.2%, surpassing heroin and cocaine poisonings, which increased 12.4% and 22.8%, respectively. Among opioid analgesic poisonings, 54% were from semi-synthetic opioids (oxycodone and hydrocodone); 32% were from methadone; and 13% were from other synthetic opioids, e.g. fentanyl. The authors reported that the increases in deaths generally matched the increase in sales for each type of opioid, and that the increase in deaths tracked the increase in methadone used as an analgesic rather than methadone used in narcotics treatment programs.

Although it is clear that increased sales have made these opiate analgesics in tablet form more available, data on the sources of the opiate analgesics involved in fatalities is unclear. The National Assessment called for increased research on the sources of methadone implicated in overdose deaths (CSAT, 2004*a*). The source of methadone may come from legitimate pain prescriptions or from the black market. Diversion of methadone may be from family members using other family members' prescriptions or from theft from pharmacies. One study suggests that thefts from pharmacies is a significant problem; in a review of DEA data from 22 Eastern States between 2000 and 2003, 12,894 theft/loss incidents were reported from various sources but the majority (89.3%) from pharmacies; most of those dosage units diverted were oxycodone (4,434,731), next was 1,026,184 for morphine, and then 454,503 for methadone (Joranson & Gilson, 2005).

State-Level Review

A number of States provided NASADAD with information on methadone overdose deaths in their State. Texas' inquiry response noted that the number of death certificates with a mention of methadone showed a steady increase (but very few included information of the form of methadone involved, whether pill, diskette or liquid) from 62 in 2000, to 90 in 2001, to 134 in 2002, to 122 in 2003, to 164 in 2004, to 203 in 2005, while the number of overdose deaths reported of clients in OTPs remained constant throughout those years, within a range of 14–23. In a study of deaths in Harris County, TX from 1987 through 1992 where methadone was detected by postmortem drug testing (Barrett, Luk, Parrish & Jones, 1996), for all years studied the use of multiple drugs was

the leading cause of death among people in whom methadone was detected and they did not find evidence that the cause of the deaths could be attributed solely to methadone toxicity.

In two studies in Maine, the effort was made to collect data on two kinds of deaths: methadone-induced deaths (deaths in which methadone was mentioned by the medical examiner on the death certificate as an immediate or underlying cause, either alone or in combination with other drugs), and methadone-related deaths (deaths in which methadone is mentioned as a significant condition contributing to death) as distinct from the larger group of deaths in which methadone was detected, which might include such instances as when methadone was at therapeutic levels and some other mechanism caused the death. This distinction was not generally made in other States' data, where any case in which methadone was detected was considered a methadone overdose death.

The first study of drug-related mortality patterns in Maine from 1997-2002 (Sorg & Greenwald, 2002) found that methadone and heroin were the individual drugs most frequently identified in toxicology tests, each present in about a quarter of the cases. When looking at drugs mentioned on the death certificate as the cause of death or significant contributing factor, methadone was identified in 18% of cases. In an additional 5% of cases, the death certificate specified "poly-drug" as the cause and methadone was found in toxicology. Other (non-methadone) opioid analgesics causing death were oxycodone (7%), propoxyphene (4%), fentanyl (5%), and hydrocodone (3%). Detailed examination of the 2001 case files revealed that fewer than half the deaths involving methadone had a documented prescription. Complicating the issue of determining cause of death, many overdose victims were described as having other physical conditions, such as cardiovascular disease, lung disease, obesity or chronic pain, that were likely to have exacerbated their respiratory difficulties or lethal drug interactions.

A more recent examination of overdose deaths in Maine (Sorg, Greenwald & Marden, to be published in 2007, See Resource List), showed that methadone-induced and methadone-related deaths increased most dramatically between 2001 and 2002, from 15 in 2001 to 57 in 2002, then declined to 47 in 2003, and increased to 65 in 2004. These deaths appear to have stabilized at 67 in 2005, and preliminary estimates of 2006 data suggest totals similar to 2005. For the period 2003-2005, 35% of all drug-induced and drug-related deaths were methadone-induced or methadone-related. During 2005, in those deaths for which methadone form was known, more than half were associated with the tablet form.

In their report *Methadone Use and Abuse in Kentucky*, the Kentucky Office of Drug Control Policy concluded that 50% of overdose deaths involved methadone, frequently in combination with other drugs (e.g., using benzodiazepine to increase the euphoric effect of methadone) or with other contributory factors, such as drowning, alcoholism, diabetes, and hypertension. An analysis of medical examiner reports of Kentucky poisoning deaths for the year 2005 revealed that, in the majority of cases, multiple drugs had been

involved. Out of 163 poisoning deaths, in 75 cases methadone was mentioned, with 17 mentioning methadone alone.

In response to an epidemic of increased overdose deaths (with overdoses involving methadone spiking to 175 Statewide in 2002), North Carolina worked with CDC investigators to conduct an intensive examination of 1,096 medical examiner reports from 1997 to 2001, and also convened a 25-member task force to examine the data and make recommendations on how the State should respond (N.C. Department of Health and Human Services, 2004). Medical examiner records contain more information than death certificates on decedent demographics and underlying cause of death, and because of a centralized system in North Carolina, investigators were confident that they were able to collect good quality data.

When looking at multiple drugs implicated in overdose deaths (about a third of the cases), alcohol was most frequently implicated as the primary cause of death (31% of cases) with 16% for methadone. However, when examining unintentional deaths from a single licit opioid (which increased 300% in this five-year period, accounting for 88% of the overall increase in drug-overdose deaths) there was a 7-fold increase in unintentional deaths from methadone. The investigators surveyed the OTPs in the fall of 2002, and found that, of the 198 persons listed as having died from unintentional overdoses of methadone for the period 1997-2001, only 4% of the decedents were current or former patients of OTPs at the time of their death. Because of policies in North Carolina that are more restrictive than Federal guidelines regarding methadone take-home policies, it was felt that OTPs were not a significant source for diversion of methadone implicated in the overdose deaths.

Virginia also provided a Roanoke Times article (Hammack, 2006) describing the regional nature of their prescription drug problem and some detailed information on 2003 prescription drug overdose deaths which, although not addressing methadone overdose deaths per se, provides insight into the types of people who are overdosing and how prevention efforts might be targeted. Southwest Virginia has seen a disproportionately high number of fatal drug overdoses in the past couple of years. In 2003, fatal drug overdoses reached a record high of 223. While the State-wide rate was 6.7 per 100,000, Lee County recorded 11 drug deaths or a rate of 46 per 100,000 residents, with four other counties in the region having a rate of more than 30 deaths per 100,000. With occupations such as coal mining, logging and farming that produce a high rate of injury and disability, pain medications have been increasingly prescribed. This increase in the availability of pain medications could possibly contribute to diversion of methadone.

Also mentioned in the Roanoke Times article is a preliminary analysis of 223 deaths in 2003 by Dr. Martha Wunsch, which showed two groups of users: the first group is described as a party crowd, about two thirds of them white males between the ages of 18 and 25 who take multiple prescription painkillers, often mixing them with cocaine and tranquilizers. They do not have prescriptions for the drugs they abuse, and apparently get them on the black market. The second group of overdose victims is more likely to be women older than 40 who suffer from chronic pain that is often coupled with psychiatric

disorders, who are prescribed so many medications that they lose track of how much they took and when. The article also provided data collected by Dr. William Massello, an assistant chief medical examiner for the State, who noted that the region's death toll from fatal drug overdoses appears to have stabilized in the 200 to 220 range over the past three years. Of the 216 overdoses in 2005, 70 involved methadone, 51 were caused by hydrocodone, and 36 involved oxycodone. Dr. Massello noted that virtually all of the methadone deaths handled by his office had been caused by pills or wafers, and thus thought not to be dispensed by OTPs.

Virginia also provided an analysis of accidental prescription drug overdose deaths in Southwest Virginia in 2003, prepared by Timothy H. Powell of the Office of the Chief Medical Examiner. Of those 168 deaths, 39.9% had a history of mental illness; 67.3% of drug abuse; 39.9% chronic illness; 53 % of pain; 6.5% of treatment for drug abuse; and 7.1% of a previous overdose. Methadone was listed as present in 44.6% of those deaths, followed by 16.1% for hydrocodone, 10.7% oxycodone, 8.3% fentanyl, and 3.6% for propoxyphene. In 26.8% of those deaths, the prescription for the drug involved was their own.

Efforts to Reduce Methadone Overdose Deaths

At the national level, government agencies have responded to increased concern about methadone overdose deaths with a number of initiatives. SAMHSA convened the 2003 National Assessment conference and the FDA issued an Alert, a Public Health Advisory, and a revised methadone package insert with a black box warning and recommended a lower starting dose. In addition, SAMHSA is developing several continuing medical education programs on methadone for pain physicians, doctors prescribing controlled substances, emergency medicine and trauma surgeons, and internal and family medicine physicians.

Another important Federal initiative is that, in 2002, Congress appropriated funding to the U.S. Department of Justice to support the development of prescription drug monitoring programs (PDMPs) among the States. These automated information collection systems help prevent and detect the diversion and abuse of pharmaceutical controlled substances, by keeping track of prescription sales at the retail level, identifying patients who are doctor shopping or are purchasing more of a drug than one patient could be reasonably expected to use, and referring those patients to drug treatment**.** The National Alliance for Model State Drug Laws (NAMSDL) counts 24 States as having operational programs and laws establishing such programs (AL, CA, HI, ID, IL, IN, KY, ME, MA, MI, MS, NV, NM, NY, OH, OK, PA, RI, TX, UT, VA, WA, WV, and WY); 9 States that have enacted legislation but do not yet have operational programs, and 8 States that have legislation pending (NAMSDL, 2007). As States increasingly develop the ability to analyze data from PDMPs in conjunction with analyses of data from medical examiners, it might be possible to get a much better idea of the sources of the drugs implicated in overdose deaths. For instance, if national data reveals that a large proportion of drugs implicated in overdose deaths are taken from friends and family, then

efforts to prevent overdose might be targeted at encouraging patients to dispose of expired or unneeded medication.

In response to a brief NASADAD Inquiry, twenty-two 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 in the following areas:

- increases in methadone overdose deaths
- articles in local newspapers about such deaths
- practices in OTPs to respond to the issue of methadone overdose deaths
- work with medical examiners or hospitals to better define methadone overdose deaths
- work with others (e.g., primary care or pain physicians, PDMPs, the media) to prevent overdose deaths or to clarify popular misconceptions.

Ten States (about 50% of those who responded to the inquiry) noted significant increases in methadone overdose deaths in their States: AR, ME, KY, NC, NH, OK, TX, VA, WA, and WV. Some States provided descriptive details and other States provided data. In Oklahoma, three groups were described as being involved: pain management patients taking methadone in ways other than prescribed, youth and young adults abusing methadone, and patients in one OTP clinic where there was an apparent spike in deaths at initiation. Six States reported overall increases in methadone overdose deaths through 2005: AR, CO, ME, TX, WA, and WV (with a slight drop in 2003 for ME, TX and WV). For example, Washington provided data on methadone-detected deaths from 2000 to 2005 in 4 counties (60% 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 or when it was found with other drugs, both for the year 2005: Kentucky noted that of 75 deaths in which methadone was detected, in 17 deaths methadone was the sole agent; 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% increase from 2005 of 81 deaths to 126 deaths in 2006, and West Virginia noted a 28% decrease from 122 in 2005 to 88 in 2006.

Seven States reported that there had been articles on methadone overdose deaths (AR, KY, NH, NC, VA, WA, and WV). In West Virginia, the Charleston Gazette's six-month investigation and extensive series on methadone overdose deaths (Finn and Tuckwiller, 2006) is credited with bringing attention to the need for a FDA warning and improved training for pain physicians. There was also renewed criticism from local legislators of clinics in the State, necessitating the need for clinics to justify their presence in the community on the most basic level. North Carolina reported that articles regarding adults were in the press several years ago and the Raleigh Observer had carried a series of articles within the last year on adolescent methadone overdose deaths. Virginia reported a number of articles on frequent prescription drug overdose deaths in Southwestern

Virginia. Washington referenced a number of articles that described the State's methadone overdose problem (as well as overdoses caused by other drugs) that also contained explicit warnings about not taking too many methadone pain tablets.

States described practices used by OTPs in their States to respond to the issue of methadone overdose deaths. State Methadone Authorities have always required policies of OTPs limiting opportunities for diversion (diversion plans are part of the accreditation process) but with the recent methadone overdose deaths, policies have become even more restrictive. When beginning methadone maintenance treatment, patients must come into the clinic for their daily dose, with the exception of Sundays and holidays when clinics are closed. In the past, after following clear rules for program compliance, meeting program goals, showing clean urine drug screens, etc. and having been in the program a minimum of 90 days, patients have been allowed to take home tablets. The Rhode Island SMA described the normal procedures: "OTP programs are required to provide patients with information on the safe use and storage of take-home medications. All patients are required to carry take-homes in locked boxes or other secure methods for transport. Programs routinely and randomly perform call-backs for patient receiving take-home privileges. Most programs require coordination with other prescribing physicians in order for the patients to qualify for take-home privileges. Review of medication interactions occurs with the patient and their physicians."

However, in light of the rise in overdose deaths, eight States (AR, KY, ME, MI, NM, WA, WV, and WI) noted that they provide liquid take-homes only, except for in selected cases in WI and ME where patients were about to travel on airplanes and could not carry on liquids. KY, ME, NH and RI have instructed their OTPs to be open on Sundays, thus for the first days of treatment (the number varies from State to State) no take-home doses are allowed. West Virginia will be keeping their clinics open on Sundays effective September 2007. AR, CO, KY, MI, NC, OK, RI, and WI have take-home guidelines that are more restrictive than the Federal guidelines.

Drug tests have long been a routine part of OTP practices, ensuring compliance with program rules and limiting opportunities for deadly drug interactions. (See Resource List for guidelines regarding drug interactions with methadone.) Two States commented on their benzodiazepine policy. Colorado noted that some programs have developed policies that don't allow patients to go above a certain methadone dose if the patient is taking benzodiazepines and they don't have an approved prescription. Arkansas noted that they are in the process of developing new policies regarding benzodiazepines, and that one program had already developed a new policy. Programs will generally attempt to wean patients off benzodiazepines, but distinctions are made between licit and illicit use. With illicit benzodiazepine use, patients are required to undergo inpatient detoxification and a higher level of care, with discharge from the program if they refuse or are unable to discontinue use. With licit benzodiazepine use, patients with a prescription are frequently required to sign a release so that the OTP can ensure coordination of care with the patient's physician.

In studies of overdose victims in the general population, Maine and Virginia noted the frequent occurrence in fatality cases of illnesses, including mental illness or a variety of illnesses requiring medications that might interact with methadone; thus coordination of care with other physicians is an important part of overdose prevention policies. A Texas study that examined deaths of OTP patients (Maxwell, Pullum & Tannert, 2005) found there were two cohorts: younger OTP patients were more likely to die from trauma and overdose, thus recommending that counseling on issues of poly-pharmacy and the need for lifestyle changes be targeted at that cohort, whereas older patients were more likely to die of chronic diseases such as heart or liver disease, cancer or respiratory diseases and, thus the OTP's role in facilitating access to medical care was an important one. A Rhode Island OTP has developed a coordination of care document that must be completed by a non-OTP physician in order for any long-term medication to be accepted as valid.

Another practice noted by States was the provision of Narcan which, if injected, can reverse the effect of an opiate overdose. Baca and Grant (2005) reviewed a number of studies describing the circumstances surrounding heroin overdose deaths and why the provision of Narcan would be an effective intervention, and many of these circumstances apply to methadone overdose deaths as well. In many fatal heroin overdoses there is ample opportunity for intervention and the majority of deaths occur in the company of others and at home. Witnesses only call an ambulance in 10% of cases, fearing police involvement, ambulance costs and negative experiences with hospital staff. Though the effects of a methadone overdose will take longer to appear than those of a heroin overdose, there are clear warning signs that persons can be educated to recognize. The Portland (ME) Overdose Prevention Project describes the following signs: not breathing, turning blue, not responding, and snoring deeply, and the project's poster provides a drawing of the recovery position, lying face down with head turned to the side, and brain at the same level of or lower than heart (See Resource List).

New Mexico noted that the State's Harm Reduction Program (Infectious Disease Bureau, NMDOH) began a Narcan Training Program for heroin users and their families**.** New Mexico has enacted legislation that holds harmless the use of Narcan by non-health care workers (and other States, such as Illinois, are exploring enacting similar legislation). As of March 2006, 1356 participants had been trained to administer Narcan and use rescue breathing on an overdose victim. The Harm Reduction Program is also working with State Police and the Albuquerque Police Department to increase the number of officers trained in Narcan administration in the event of first response to an opiate overdose. New Mexico supports policy development for the availability of non-prescription Narcan to all prescription opioid users (and training of family and friends), not only heroin users. Rhode Island also noted that there is currently a pilot program for the distribution of Narcan through one of the local hospitals. Wisconsin distributes Narcan through its street outreach program operated by the AIDs program.

Three States noted their training of OTP staff to be more attentive to the risks involved in methadone use: Rhode Island noted that it had just recently provided a mandatory training for all OTPs on risk assessment. Virginia asked OTPs to review current policies and procedures to insure proper orientation of patients to dangers of methadone induction

and use with other drugs. Additionally, Virginia provided statewide training to OTP nurses on the dangers of methadone and will provide statewide training to OTP counselors. OTP doctors are e-mailed articles related to methadone-related deaths.

Ten States (CO, KY, NH, NM, RI, TX, VA, WA, WI, and WV) described their involvement in working with medical examiners or hospitals to better define methadone overdose deaths. Colorado makes an effort to educate medical examiners, although most have their own policies in place. Kentucky noted that in their discussions with medical examiners studying overdose deaths, OTPs have been able to make the case that the absence of any of the unique orange liquid provided by OTPs in those investigated cases, combined with the OTPs' careful tracking of all administered doses, supports the fact that OTPs are not a source for the methadone involved in overdose deaths. North Carolina noted that they are beginning discussions with their Chief Medical Examiner on a standard case definition, with particular attention to the need to consider the extremely high tolerance for methadone that patients in treatment may have. West Virginia noted that they are involved in monthly meetings with the Domestic Violence Fatality Review Committee, a multidisciplinary group that involves medical examiners.

Several States are in the process of finalizing studies which will yield important information. As part of a collaborative effort between the Office of Chief Medical Examiner and the University of Maine's Margaret Chase Smith Policy Center, the report, "Maine Drug-Induced and Drug-Related Deaths, 1997-2006" is about to be published. New Mexico noted that an earlier study of medical examiner data for all unintentional drug overdose deaths in New Mexico between 1998 and 2002 was being updated with 2003-2005 data. A number of studies in Washington show promise. The University of Washington, Alcohol and Drug Abuse Institute is working with local public health offices to analyze data in the Seattle/King County area to attempt to identify opiate tolerance, interruption in tolerance, source of opiates, and motivation(s) for using. As described in a conversation with Dr. Caleb Benta-Green (3/2/07), the hope is that the study will identify important types of information that are not currently being considered by medical examiners (but that would not be difficult to collect, e.g., a finding of heroin in the body) so that those items would be flagged and become a routine part of the process. Data on this study will be presented at the June 2007 National Institute of Drug Abuse's Community Epidemiology Workgroup meeting. The State toxicology lab is also comparing drug concentrations in the blood of three different populations--deceased, DUI cases, and people in drug treatment—which are known to overlap widely, resulting in a better understanding of what levels of drugs are normal for drug treatment patients. The Washington State Department of Health is also currently conducting a research project which will conclude with a report entitled, "Poisoning and Drug Overdose in Washington State."

States are working with a variety of other public agencies, physicians, and media to assist in the gathering of data, to promote preventive measures and to better inform public debate. North Carolina's Task Force to Prevent Deaths from Unintentional Drug Overdoses has published a report with 24 recommendations (See Resources List). Some of the recommendations include the following: that a leadership group be formed to be

made up of officials from the Department of Health and Human Resources and the Department of Justice that meets four times a year, increased surveillance and monitoring of eight different types of data, the establishment of a prescription drug monitoring program, educational interventions for the general public (e.g., 911) and for professionals, and improved clinical interventions.

Kentucky's Office of Drug Control Policy is working through insurance companies, the Board of Medical Licensure, the Pharmacists Association and managed care companies to educate about the dangers of using methadone in combination with other drugs, and encourage use of the Kentucky All Schedule Prescription Electronic Reporting system as standard practice. Since many Kentucky residents seek to enroll in OTPs across State lines due to Kentucky's strict requirements, Kentucky officials will be contacting officials in neighboring States to discuss possible diversion issues.

With regard to PDMPs in other States, Virginia has expanded in June of 2006 from a pilot program in Southwest Virginia to a State-wide program that covers all scheduled prescription drugs. Colorado has just started their PDMP, and, in response to one of the recommendations of their Task Force, North Carolina has recently enacted legislation that allows for a PDMP. New Mexico plans in mid-2007 to use medical examiner data to link methadone decedents with the first year of prescription drug monitoring data in New Mexico. Indiana's PDMP is in its infancy. Arkansas has already begun working with the State Board of Pharmacy to develop and implement a policy requiring that warning labels be placed on methadone pills that are filled by retail pharmacies.

Because of recent overdose deaths involving fentanyl-tainted heroin, a number of States have become very active in terms of outreach, prevention efforts, and distribution of Narcan, and Michigan noted the creation of a Task Force to deal with the issue. Illinois has been at the forefront of this issue and the Division of Alcohol and Substance Abuse has developed a number of new collaborative relationships with police departments, professional associations, medical examiners, and community organizations because of fentanyl-related overdoses.

New Hampshire's SMA has appeared on radio programs with the director of an OTP clinic to discuss methadone overdose deaths. Indiana has facilitated workshops with the Indiana Counselors Association on Alcohol and Drug Abuse and the Indiana Association of Court Alcohol and Drug Program Directors.

Three States (FL, WV, and WA) have been involved in initiatives that target physicians. In Florida in 2002, the Department of Health and the Department of Children and Families' Substance Abuse Program developed a letter for pain physicians and placed it on web sites of all professional associations representing prescribing practitioners. The letter recommended that physicians take a number of steps to investigate the patient's drug history and use of opiates and other substances, consult with OTPs, develop referral arrangements, request the patient to sign a release allowing OTPs to confirm if a patient is enrolled in a program, educate patients about contraindications regarding methadone, and request the patient to sign an agreement for medication management.

The West Virginia Division of Alcohol and Drug Abuse is working with the Association of Alcohol and Drug Abuse Counselors to provide six trainings for physicians and other interested health professionals regarding prescription drug abuse and appropriate treatment.

Washington State's Division of Alcohol and Substance Abuse is collaborating with other divisions within the Health and Recovery Services Administration to work with physicians, hospitals, and medical associations to encourage health care providers to conduct screening for alcohol and drug use, abuse, and dependence and, as part of that effort, a toolkit is provided. Particularly relevant for States interested in collaborating with pain physicians on the subject of methadone, the toolkit includes an interagency guideline on opioid dosing for chronic non-cancer pain and a chronic pain contract and a disclosure form (See Resource List).

Because the Office of Substance Abuse (OSA) in Maine has oversight of the Prescription Monitoring Program, they use their program as a way to communicate with medical professionals about addiction and diversion. In addition, the OSA participates in overdose prevention committees in two communities, Portland and Kennebec Valley. The Portland group consists of treatment providers, emergency room physicians, law enforcement, EMT's and others. The Portland group has designed and distributed a poster and cards with overdose information. The OSA designed and purchased phone cards to be provided to patients at the clinics and other locations statewide. The Kennebec Valley Overdose Prevention Task Force was modeled on the Portland group, and will produce a DVD focused on treatment, recovery and overdose prevention (See Resources List).

Described above are initiatives developed by individual States to address local concerns about the rise in methadone overdose deaths, but it also important to note that, through conference calls and frequent communication between SMAs and Federal officials, States are able to learn from each other and to benefit from a national perspective. For example, when West Virginia develops physician training curricula, other States can use those as a model; when one SMA requests a coordination of care document, Rhode Island provides one. When Federal officials become concerned with an issue such as methadone overdose deaths, conference calls can be used as a forum for reinforcing policies that are already in place and/or discussing the issue with the SMAs.

Summary

Although the research described above does not suggest that OTP patients have been a significant source for methadone implicated in overdose deaths, OTPs have responded to the issue of methadone overdose deaths within their programs. Diversion control plans have long been standard practice in OTPs, but in light of the recent rise in methadone overdose deaths, programs have taken steps to limit opportunities for diversion by following even stricter guidelines than before, allowing only liquid take-homes and opening their programs on Sundays.

OTP patients are vulnerable to overdose when they are being initiated into methadone use, due to the great variability in individual tolerance to methadone. Although relatively rare, overdose deaths do occur in OTPs at initiation, and it is important that when such deaths occur, that every effort be made to understand the event and to determine whether any new practices could be recommended to prevent such deaths. States have different requirements regarding the reporting of overdoses and deaths; one possible area for a future Federal/State cooperative initiative could be to develop a standardized system whereby an adverse event would be reported immediately to Federal authorities so that an effort could be made to collect more information on the circumstances surrounding the event in a timely manner.

Another area of vulnerability to methadone overdose is when OTP patients use other licit or illicit drugs, either unintentionally or intentionally for euphoric effect, and the medications interact with methadone to cause an overdose. As described above, OTPs have long instituted a number of practices to guard against potentially fatal drug interactions, such as performing careful assessments when admitting patients, counseling patients as to the risks of using other drugs, performing random drug tests, and requesting that patients sign release forms so that OTP physicians are allowed to contact other physicians to make sure that medications are being appropriately prescribed and that medical care can be coordinated. With the rise in methadone overdose deaths, these practices have received increased attention and should continue to be a focus of staff training, balanced by the understanding that the many patients with complex co-occurring disorders should not be denied access to the treatment they need.

In addition to responding to methadone deaths within their programs, States have proactively sought to communicate with and inform other public agencies, medical professionals, research institutions, prescription drug monitoring programs, public media, and community organizations. With the recent application of methadone in the general population to deal with pain, dramatic increases in methadone overdose deaths have occurred. Many research questions remain to be answered with regard to these deaths and better data on the sources of the methadone implicated in the death is needed. Questions remain as to the extent to which methadone has been an incidental rather than a causal factor in overdose deaths. Although determining cause of death will continue to be a complex issue, it is hoped that Federal and State efforts to develop a standard case definition will yield valuable information. With the linking of data from prescription drug monitoring programs to that of medical examiners, investigators may be able to yield better information on the sources of prescription drugs implicated in overdose deaths. As the FDA warnings and initiatives to better educate medical professionals take hold, it is hoped that methadone will be prescribed for pain by physicians who are extremely knowledgeable about the benefits and risks of methadone use, and will fully educate their patients as to the risks involved.

Resource List

FDA Public Health Advisory: (2006). Methadone Use for Pain Control May Result in Death.
http://www.fda.gov/cder/drug/advisory/methadone.htm

Methadone (Dolophine) Prescribing Information
http://www.fda.gov/cder/drug/infopage/methadone/dolophine_PI.pdf

Findings and Recommendations of the Task Force to Prevent Deaths from Unintentional Drug Overdoses in North Carolina, 2003.
http://www.communityhealth.dhhs.state.nc.us/Injury/FRTFPD_UDONC2003-Complete.pdf

Methadone-Drug Interactions. Prepared by the Addiction Treatment Forum. Can be accessed at:
http://www.atforum.com/SiteRoot/pages/addiction_resources/Drug_Interactions.pdf

Maine Report about to be published: Sorg, M.H., Greenwald, M. & Marden, K.A. (2007). Maine Drug-Induced and Drug-Related Deaths, 1997-2006. Margaret Chase Smith Policy Center, University of Maine, Orono, ME.

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Washington State Toolkit for Health Professionals:
http://fortress.wa.gov/dshs/maa/pharmacy/Toolkit.htm.

Washington State Agency Medical Directors' Group *Interagency Guideline on Opioid Dosing for Chronic Non-Cancer Pain*
http://www.agencymeddirectors.wa.gov/Files/OpioidGdline.pdf

Chronic Pain Contract
http://fortress.wa.gov/dshs/maa/pharmacy/ChronicPainAgreement.doc

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