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Methadone Toxicity Fatalities: A Review of Medical Examiner Cases in a Large Metropolitan Area*

ABSTRACT: Over the past several years, Medical Examiners in Kentucky and around the nation have observed a dramatic rise in drug intoxication deaths involving the prescription medication methadone. This documented rise in methadone-related deaths requires a better understanding of methadone's pathophysiology and the ways it contributes to significantly increase morbidity and mortality. This study reviews 176 fatalities ascribed to methadone toxicity by the Office of the Chief Medical Examiner in Kentucky between 2000 and 2004. Postmortem toxicological analysis recorded a more than 10-fold increase in methadone toxicity fatalities, rising from 6 cases in 2000 to 68 cases in 2003. Of the 176 methadone-related fatalities, methadone was the only drug detected in postmortem blood and urine toxicological analyses in 11 (6.25%) cases. The mean methadone blood concentration of all 176 cases was 0.535 mg/L (0.02–4.0). The following psychoactive medications were detected: antidepressants (39.8%), benzodiazepines (32.4%), and other opioids in addition to methadone (27.8%). Cannabinoids were detected in 44 (28.4%) cases and cocaine or metabolite in 34 (21.9%) cases. Of the 95 cases with a known history of methadone use, 46 (48.4%) involved prescription by private physician. The interpretation of blood methadone concentrations alone or combined with other psychoactive drugs requires consideration of the subject's potential chronic use of and tolerance to the drug. A thorough investigation into the practices of procurement and use/abuse of methadone is essential to arrive at the proper designation of the cause of death.

KEYWORDS: forensic science, forensic pathology, forensic toxicology, methadone, opiates, opioids, pain, death

Methadone was initially synthesized as a morphine substitute in Germany during World War II (1) and approved by the U.S. Food & Drug Administration (FDA) in 1947 for use as an analgesic (2). By 1950, physicians prescribed it for the treatment of withdrawal symptoms associated with heroin and other opioids (2). Developed in 1964, methadone maintenance treatment (MMT) has been shown to reduce criminal behavior and mortality associated with heroin use and to decrease disease transmission related to intravenous drug use, notably hepatitis and human immunodeficiency virus (HIV) (3,4). Methadone-associated deaths skyrocketed in the early 2000s: a greater number of these deaths were reported to MedWatch (FDA's Safety Information and Adverse Event Reporting Program) in 2001 alone than in the previous decade; the number doubled once again in 2002 (2). Certain U.S. states have reported a significant increase in methadone-related deaths, specifically Florida (up 51% between 2003 and 2004), Maryland (up 950% between 1997 and 2001), and North Carolina (up 729% between 1997 and 2001) (5).

In May 2003, the Substance Abuse and Mental Health Services Administration Center for Substance Abuse Treatment assembled a multidisciplinary group of 70 experts, including Medical Examiners, toxicologists, epidemiologists, pain management specialists, and addiction medicine experts for "A National Assessment of Methadone-Associated Mortality." They concluded that a dramatic increase in methadone deaths is likely due to a rise in consumption attributable to either: (i) the rise in prescription of oral methadone to outpatients for chronic pain management, or (ii) the greater availability of "street" methadone, which may account for overall increases in illicit drug diversion tactics and usage (6).

The majority of methadone-associated deaths include the presence of at least one other drug, in most cases either another opioid or central nervous system (CNS) depressants such as benzodiazepines (2,6–13). The additive effects of methadone with ethanol, benzodiazepines, or other opioids may be lethal. Interpretation of the postmortem blood methadone concentration poses a difficult challenge to investigators because it is often found in the blood in combination with other drugs (8,9,13,14). In addition, individual tolerance to methadone is a significant factor that influences the analysis of the neurophysiological effect at a given methadone concentration. *Tolerance* is the phenomenon in which an organism is less susceptible to the effect of a drug as a consequence of its prior administration. *Acute tolerance* may develop very rapidly following either a single dose or a few doses taken over a short period of time. *Chronic tolerance* develops from drug administration over a longer period of time and produces reduced drug effects. *Cross-tolerance* may occur when one drug confers tolerance to another. Assessment of tolerance necessitates thorough documentation of the victim's historical use of methadone (15–17).

In light of the drastic increase in methadone-related deaths nationally over the past decade, we present a 5-year (2000–2004) review of fatalities attributed to methadone toxicity in a large metropolitan region of Kentucky. Because various classes of other drugs and other opioids are frequently detected in combination with

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methadone, it is necessary to evaluate potential additive effects. An equally critical facet of this intellectual interpretative process is the collection of historically accurate information about prior use or abuse of methadone. Such data are indispensable in factoring the role of tolerance.

Materials and Methods

This is a retrospective review (2000–2004) of methadone-related fatalities. Each subject underwent postmortem examination and toxicological analyses at the Office of the Chief Medical Examiner in Louisville, Kentucky. Pursuant to Kentucky Revised Statutes, Chapter 72, a combined Coroner-Medical Examiner system exists in Kentucky and, therefore, a referral to a Medical Examiner for a medicolegal postmortem examination is at the discretion of the Coroner in the county of death. In this study, the Coroner of each jurisdiction supplied pertinent drug history, particularly methadone acquisition and use. The Coroner also documented medical history including treatment for chronic pain. In each autopsy, the age, race, sex, and body mass index (BMI) of the victims were recorded.

Chart review substantiated all blood and urine toxicological findings. In view of the broad overlap in blood methadone concentrations in cases attributed to toxicity in contrast to those of potentially tolerant individuals on maintenance, interpretation of the postmortem blood methadone concentration was individualized for each subject. Evaluation of tolerance included consideration of the history of past exposure, including amount, frequency, and duration of consumption.

The Kentucky Medical Examiner's Forensic Toxicology Laboratory is responsible for the qualitative and quantitative analysis of drugs and poisons within biologic samples procured from decedents undergoing autopsy. Medical Examiners and Coroners interpret the analytical results with other data to determine the cause and manner of death. The laboratory supports all 120 counties in Kentucky. Specimens are submitted to the laboratory in specially designed postmortem collection kits. These kits contain sealed containers for routine submission of blood, urine, and vitreous fluid. Additional specimens may be submitted as necessary, as tailored to case specifics. Powdered sodium fluoride (≥1% concentration) is added to the blood and vitreous containers. Specimens are refrigerated at 8°C until analysis. Long-term storage (≥1 year) is at −20°C.

Blood is analyzed for ethanol and other volatiles using dual-column headspace gas chromatography on a ThermoQuest Trace GC (ThermoQuest, San Jose, CA) equipped with a Gerstel autosampler (Gerstel Inc., Caton Research Center, Baltimore, MD). The screen includes ethanol, methanol, acetone, isopropanol, chloroform, and toluene. The two capillary columns are a Restek®BAC-1 and a Restek®BAC-2 (30 m × 0.32 mm internal diameter) (Restek Corporation, Bellefonte, PA). The operating temperature is 50°C. Confirmation of ethanol is by the Abbott Axsym (Abbott Laboratories, Abbott Park, IL) employing radiative energy attenuation technology.

Blood samples are analyzed on the Abbott Axsym for salicylates, acetaminophen, tricyclic antidepressants, and barbiturates. The complete drug screen involves a liquid–liquid extraction with analysis on Gas Chromatography/Mass Spectroscopy (GCMS). Fifty of the most commonly encountered drugs are calibrated for quantitation and other drugs are quantified as necessary. The measure of accuracy and precision for the extraction process of methadone and other drugs and subsequent analysis by GCMS, based on monitoring QA/QC controls, is as follows: standard deviation = ±0.032 and coefficient of variation = 10.1%.

Urine samples are initially analyzed with the Abbott Axsym utilizing fluorescent polarization immunoassay technology. Six major classes of drugs tested include opiates/opioids, cocaine metabolite, phencyclidine, cannabinoids, benzodiazepines, and amphetamines. Positive results for opiates/opioids, cocaine, or amphetamines are confirmed by GCMS after liquid–liquid extraction.

Results

Demographics

Over the 5-year period (2000–2004), a total of 176 deaths were ascribed to methadone toxicity upon postmortem examination including toxicological analyses. The results revealed a more than 10-fold increase (up 1033%) in methadone-related fatalities, varying from six cases in 2000 to 68 cases in 2003. Sixty percent of the victims were males; all victims were Caucasian. Individuals ranged between 17 and 60 years (mean age 38 years). The time of year was evenly distributed among the months: percentages ranged from 4.5% to 11.9% (Fig. 1). The lowest percentage was recorded in May and June, while the greatest number of individuals died in

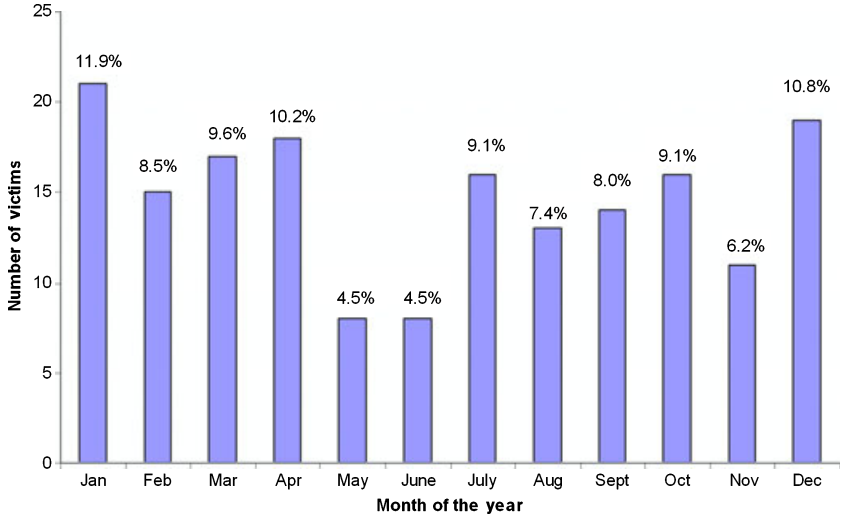

FIG. 1—*Methadone toxicity fatalities at the Office of the Chief Medical Examiner in Kentucky, 2000–2004, by month of death.*

TABLE 1—*Methadone toxicity fatalities at the Office of the Chief Medical Examiner in Kentucky, 2000–2004.*

Categorization of cases	Number of cases	Concentration of methadone (blood) (mg/L)
Methadone only (blood and urine)	11 (6.25%)	0.2–2.4 (0.725)
Methadone only (blood); Other drugs detected in urine	11 (6.25%)	0.177–1.7 (0.62)
Methadone and benzodiazepines only (blood and urine)	8 (4.5%)	0.2–1.0 (0.548)
Total: methadone and all drugs (blood and urine)	176	0.02–4.0 (0.535)

December and January. 134 (76.1%) victims were pronounced dead at a residential home; the remainder of subjects were pronounced dead at one of the following: hospital, 30 cases (17.0%); hotel, four cases (2.3%); public location, three cases (1.7%); jail, one case (0.57%); and an unspecified location, four cases (2.3%).

Postmortem Toxicological Analyses

Of the 176 methadone-related fatalities, methadone was the only drug detected in postmortem blood and urine toxicological analyses in 11 (6.25%) cases (Table 1). Methadone concentrations in the blood in these cases ranged from 0.2 to 2.4 mg/L (mean 0.725 mg/L). Furthermore, methadone was the only drug in blood in an additional 11 (6.25%) cases in which various drugs were detected in the urine, as follows: benzodiazepines in six cases, cannabinoids in three cases, and benzodiazepines and cannabinoids in two cases. The combination of only methadone and benzodiazepines was detected in the blood and urine in eight (4.5%) cases. Cases in which only methadone was detected in the postmortem blood and urine had the highest mean blood methadone concentration (0.725 mg/L); cases including methadone and all other drugs had the lowest methadone concentration (0.535 mg/L). Blood methadone concentrations in the latter group ranged from 0.02 to 4.0 mg/L.

In an effort to evaluate the possible role of tolerance, we evaluated the postmortem blood methadone concentration for each victim in light of the reported or documented use of methadone. The majority (86.4%) of victims had a negative blood ethanol concentration, 90 (84.1%) men and 62 (89.8%) women (Table 2). The additional psychoactive medications were detected in blood: antidepressants (39.8%), benzodiazepines (32.4%), and opioids in addition to methadone (27.8%). Promethazine and diphenhydramine, were frequently present with methadone, 14.2% and 10.2%, respectively. Roughly twice as many women were positive for antidepressants and promethazine compared to men, (55.1% vs. 29.9%) and (20.3% vs. 10.3%), respectively. A higher percentage of men tested positive for opioids in addition to methadone compared to women (31.8% vs. 21.7%). A similar percentage of men and women had detectable benzodiazepines (33.6% vs. 30.4%) and diphenhydramine (9.3% vs. 11.6%). The blood collection sites were as follows: peripheral, 134 (76.1%); central, 16 (9.1%); and unspecified, 26 (14.8%). The retrieval of blood from a site other than peripheral may have proven necessary due to an inability to access the peripheral site.

TABLE 2—*Postmortem toxicological analyses of methadone toxicity fatalities at the Office of the Chief Medical Examiner in Kentucky, 2000–2004.*

Psychoactive substance	Total (n = 176)	Males (n = 107)	Females (n = 69)
Blood	176 (100%)	107 (100%)	69 (100%)
Ethanol			
Negative	**152 (86.4%)**	**90 (84.1%)**	**62 (89.8%)**
≤0.1%	16 (9.1%)	11 (10.3%)	5 (7.2%)
0.1–0.2%	7 (4.0%)	5 (4.7%)	2 (2.9%)
0.2–0.3%	1 (0.57%)	1 (0.93%)	0 (0%)
Antidepressants	70 (39.8%)	**32 (29.9%)**	**38 (55.1%)**
Benzodiazepines	57 (32.4%)	36 (33.6%)	21 (30.4%)
Opiods in addition to methadone	49 (27.8%)	**34 (31.8%)**	15 (21.7%)
Promethazine	25 (14.2%)	**11 (10.3%)**	**14 (20.3%)**
Diphenhydramine	18 (10.2%)	10 (9.3%)	8 (11.6%)
Urine	155 (88.1%)	103 (96.3%)	52 (75.4%)
Cannabinoids	44 (28.4%)	**34 (33.0%)**	**10 (19.2%)**
Cocaine or metabolite	34 (21.9%)	**20 (19.4%)**	**14 (26.9%)**

TABLE 3—*Methadone acquisition in the methadone toxicity fatalities at the Office of the Chief Medical Examiner in Kentucky, 2000–2004.*

Methadone acquisition	Number of victims
Private physician	46 (48.4%)
Illicit means	19 (20.0%)
Methadone treatment clinic	9 (9.5%)
Unknown means	21 (22.1%)
Total	95 (54.0%)

Urine was present and, therefore, collected in 155 (88.1%) cases. The urine screen confirmed opioids in 101 (65.2%) cases and benzodiazepines in 89 (57.4%) cases (Table 3). Cannabinoids were detected in 44 (28.4%) cases and cocaine or metabolite in 34 (21.9%) cases. A higher percentage of men had cannabinoids in urine compared to women (33.0% vs. 19.2%), while more women than men had cocaine or metabolites (26.9% vs. 19.4%).

History of Methadone Use and Acquisition of Methadone

The Coroners investigating each death documented 95 (54.0%) victims who had used methadone. The means of acquisition of methadone is listed in Table 3. Of the 46 individuals receiving physician-prescribed methadone, 23 (50.0%) had either initiated or filled their prescriptions <10 days prior to death. For example, a 28-year-old man had been involved in separate motor vehicle collisions, one several years earlier and another 4 months prior to death. In the more recent crash he fractured two ribs and experienced right shoulder and spine pain. By history, the subject had tachycardia and pulmonary disease not otherwise specified. A naïve methadone user, he was prescribed methadone 40 mg/day 3 days prior to his death. Postmortem toxicology detected blood methadone at 0.2 mg/L, hydrocodone 0.18 mg/L, venlafaxine 0.73 mg/L, and acetaminophen 16 mg/L; the urine drug screen was positive for opiates. While the majority of cases of physician-prescribed methadone were for treatment of cervical and lumbar pain, several patients were prescribed methadone for other kinds of pain, as follows: two with chest pain and one each with dental pain, pain following a hernia repair, "loin pain," and "sinus problems."

One-third of the victims had been undergoing pain management, as supported by the Coroner's investigation. In a subset of cases, autopsy confirmed the presence of surgical scars, suggesting the basis for pain management: lumbar (24 cases [13.6%]) or other significant scar (43 [24.4%]). The average BMI in kg/m^2 was 26.2, specifically, 26.4 for males and 26.0 for females. In this group eighty-four (47.7%) subjects bore at least one tattoo.

Nine individuals with a history of drug use received treatment at a methadone maintenance program. Of these nine victims, four had also suffered bodily injury resulting in persistent pain. In one case, a 47-year-old woman in a motor vehicle crash 10 years prior to her

death experienced cerebral trauma resulting in a posttraumatic grand mal seizure disorder. Subsequently involved in two other motor vehicle accidents, she sustained arm and spinal fractures. The Coroner documented that the victim habitually complained of extreme pain and abused pain medications. She was also depressed due to an impending divorce. Two months prior to death, physicians at a methadone clinic discontinued all previously prescribed pain medications and prescribed methadone. Postmortem toxicology detected methadone 1.5 mg/L, promethazine 0.2 mg/L, and olanzapine 0.08 mg/L in the blood. Postmortem urine screen was qualitatively positive for methadone, promethazine, and benzodiazepines.

Of the 176 victims of a methadone-related death, Coroner's reports indicated that nineteen decedents had acquired the methadone illicitly. Of these, 10 individuals had purchased "street" methadone, and seven were either given or surreptitiously obtained the drug from a family member or friend. In one case, a 20-year-old male recovering heroin addict with a history of seizures succumbed to the toxic effects of methadone. The decedent's father reported that a pharmacy delivered a methadone prescription to the wrong apartment. The methadone was intended for a cancer patient living in another apartment. Without showing his identification, the addict kept the prescription and subsequently consumed seven methadone tablets. Postmortem toxicological analysis detected the following drugs in blood: methadone 0.17 mg/L, diphenhydramine 0.07 mg/L, dextromethorphan 0.05 mg/L, and oxycodone 0.04 mg/L. Urine drug screen revealed opioids, including oxycodone and methadone, diphenhydramine, and amphetamines, specifically, methylenedioxymethamphetamine. Death was attributed to polypharmacy intoxication. In another case, a 32-year-old man, a prison employee, habitually obtained and consumed the prisoners' medications discarded at the facility. Toxicology detected tramadol 0.1 mg/L, methadone <0.05 mg/L, and oxycodone 0.12 mg/L in the blood. Urine drug screen was positive for opiates and cocaine metabolite.

Suicidal Manner of Death in Methadone Fatalities

Six methadone fatalities were classified as suicide by multiple substance intoxication all involving methadone. The following drugs were detected in the postmortem bodily fluids: antidepressants (five cases, 83.3%), benzodiazepines (four cases, 66.7%), and other opioids in addition to methadone (three cases, 50%). A 48-year-old Caucasian woman with a history of intravenous drug abuse although no history of methadone use called a friend and told him "it was over." A 49-year-old Caucasian man with a history of HIV and cachexia had not previously consumed methadone. A 44-year-old Caucasian with a history of lumbar surgical intervention had been prescribed methadone by her physician. She advised her sister by telephone that she intended to commit suicide; a suicide note was discovered at the scene. An obese (BMI = 31) 48-year-old woman had a history of chronic osteomyelitis with chronic ulcerations and psychiatric treatment for depression. She had been discharged from the hospital 1 month prior to death after treatment for a *Staphylococcus aureus* wound of the plantar surface with bone erosions of the right foot. She had been consuming physician-prescribed methadone. A 23-year-old Caucasian man had expressed suicidal ideation stemming from the overwhelming responsibility of caring for his younger brother with muscular dystrophy. The victim informed his brother that he had consumed 40 tablets of their mother's methadone prescription. The Coroner reported that the decedent "likes to take hydrocodone or oxycodone" although had been a novice methadone user. The final suicide case was a 45-year-old Caucasian female with a history of several lumbar surgeries and implantation of an internal morphine pump and spinal stimulator. She had sustained a work-related injury 2 months prior to her death and had been prescribed methadone by her physician.

Discussion

The conclusion that a methadone intoxication is fatal is not determined solely by considering the blood concentration of the opioid. Three components are integral in the investigation of a methadone toxicity fatality, namely, (i) the interaction of methadone with other drugs detected in the postmortem bodily fluids; (ii) the decedent's history of methadone use; and (iii) genetic predisposition for CYP 3A4 metabolism. These three crucially interconnected features require conservative interpretation of methadone blood concentrations capable of causing death. Three circumstances are frequently encountered in methadone-associated fatalities: (i) toxic concentrations of methadone during the induction period (prior to methadone steady-state concentrations or tolerance) in situations of MMT or legitimate methadone distribution for pain management; (ii) use of diverted methadone by individuals; and (iii) additive effects of a CNS-depressant such as benzodiazepines, ethanol, or other opioid in conjunction with methadone (6).

Several studies in the literature have discussed the role of polydrug interactions involving methadone (7–11). Barret et al. (7) reviewed 91 cases in which methadone was detected in Harris County, Texas between 1987 and 1992. Mikolaenko et al. (8) surveyed 101 methadone-detected cases in Jefferson County, Alabama from 1982 to 2000. Wolf et al. (9) analyzed cases involving the presence of methadone in Palm Beach County, Florida, between 1998 and 2002. Perret et al. (10) investigated 106 lethal drug intoxications, 36 involving methadone, in Geneva, Switzerland, from 1994 to 1998. Pirnay et al. (11) reviewed 35 methadone-associated deaths in Paris, France between 1997 and 2002. The present study and the report by Perret et al. (10) specifically address methadone-related fatalities. These two investigations are in contrast to the other four referenced retrospective studies, which consisted of reviews of cases in which methadone was detected in the postmortem fluids of all causes and manners of death in their respective jurisdictions.

Table 4 summarizes the prevalence of polydrug fatalities involving methadone. The present study and the five previous studies report few cases in which methadone was the only drug detected in the postmortem fluids. Two studies, respectively by Barrett et al. (7) and by Mikolaenko et al. (8), report similar percentages of cases involving methadone in combination with at least one other drug, 84.6% and 85.1%, respectively. Ninety-eight (78.4%) cases in the investigation by Wolf et al. (9) were deemed "methadone toxicity" or "combined drug toxicity." Of these 98 cases, methadone

TABLE 4—*Polydrug prevalence in postmortem bodily fluids in methadone-related fatalities.*

Studies	Years of study	Number of victims
Present study, KY (n = 176)	2000–2004	165 (93.8%)
Barrett et al. (7), TX (n = 91)	1987–1992	77 (84.6%)
Mikolaenko et al. (8), AL (n = 101)	1982–2000	86 (85.1%)
Wolf et al. (9), FL (n = 98)*	1998–2002	94 (95.9%)
Perret et al. (10), Geneva, Switzerland (n = 36)	1994–1998	35 (97.2%)
Pirnay et al. (11), Paris, France (n = 35)	1997–2002	34 (97.1%)

*Includes only cases of "methadone toxicity" and "combined drug toxicity."

was the sole drug detected in only four cases. Perret et al. (10) documented 36 methadone-associated deaths; all but one had either medications besides methadone or illicit drugs present in blood or urine. The present study demonstrated that methadone was the sole drug detected in blood and urine in only 11 (6.25%) cases. In an additional 11 (6.25%) cases, methadone was the sole substance detected in blood; other drugs (benzodiazepines and/or cannabinoids) were also present in urine.

In view of the high prevalence of methadone-associated fatalities in combination with other drugs, the death investigator should undertake a thorough analysis of the polydrug interactions that interplay in these cases. Methadone is a synthetic opioid with excellent oral bioavailability of up to 80%, low cost, ability to control pain unresponsive to other opioids, and long half-life averaging 24–36 h and ranging from 4 to 91 h (2,18–21). The whole blood (plasma or serum) methadone concentration and the half life are dependent upon a host of factors, including the presence of other medications and conditions affecting the consumer's health, diet, and age (2). The onset of analgesia typically begins within 30–60 min after oral administration, and effective pain relief may persist for 4–6 h (22). The peak methadone plasma concentration usually occurs 2.5–4 h after intake (18).

Methadone is primarily metabolized in the liver by cytochrome CYP3A4 and to a lesser extent by CYP2D6 and CYP1A2. Metabolism may be affected by particular drugs that induce or inhibit these liver enzymes (18,23,24). Inducers of CYP 3A4 (rifampin, phenytoin, phenobarbital) increase methadone clearance and decrease the elimination half-life and plasma concentration, which may prompt the methadone abstinence (withdrawal) syndrome (18,21,23,25). Inhibitors of CYP 3A4 (ketoconazole, fluconazole, erythromycin) may decelerate methadone's metabolism, thereby increasing the plasma concentration and duration of its effects. Methadone induces the production of the hepatic enzymes, thus, accelerating its metabolism in chronic methadone users (21,26). Contrarily, methadone naïve individuals lack the primed enzyme scheme, delaying methadone's clearance and increasing the risk of an overdose. Eap et al. (18) stress that the significant interindividual variability in methadone pharmacodynamics necessitates an individualized treatment plan in the prescribing of methadone. Furthermore, a specialized clinical regimen, which is based on an understanding of methadone metabolism, is recommended during medication discontinuation: methadone withdrawal may result when inhibitors of CYP enzymes are discontinued, and methadone toxicity may ensue when administration of a CYP-inducing drug ceases (21).

Two previous studies, Mikolaenko et al. (8) and Perret et al. (10) reported that benzodiazepines were the most common co-intoxicant with methadone, accounting for 59.4% of cases in the former study and in 50% of cases in the latter. Besides methadone, the benzodiazepine, diazepam, was the most frequently encountered drug in Mikolaenko et al.'s (8) retrospective review, Barrett et al.'s (7) investigation (41.8% of cases), Pirnay et al.'s (11) review (28.6% of cases), and in the present study (20.4% of cases).

The risk of methadone toxicity is highest during the induction phase (27–30). The most commonly reported adverse effects are respiratory depression, nausea, vomiting, dizziness, pruritus, stupor, hypotension, and urinary retention (1,18). Significant risk factors associated with adverse reactions include a high starting dosage, concurrent consumption of ethanol and benzodiazepines, morbid obesity, sleep apnea, severe asthma, and right heart failure (18,19,21). The combined pathopharmacological effects of methadone with ethanol and benzodiazepines increase the likelihood of an overdose. Ethanol and benzodiazepines are weak respiratory depressants. In conjunction with a powerful respiratory depressant such as an opioid, they increase the opioid's effect (21,23). In addition, benzodiazepines may exacerbate upper airway obstruction, a hypothesized contributing factor to methadone's potency (27).

In the present study, 46 of the 176 victims succumbing to methadone toxicity received a prescription from a private physician. Of these, 22 (47.8%) filled the prescription <10 days prior to their death. A mix of other psychoactive medications was detected with methadone, as follows: antidepressants (54.5%), opiates in addition to methadone (40.9%), and benzodiazepines (18.2%). The high number of deaths during the induction phase of methadone treatment, which consisted of multiple drugs combined with methadone, stands out and strongly suggests an additive effect by these drugs during a vulnerable period of methadone consumption.

Analysis of postmortem methadone blood concentrations requires caution due to the overlap between potentially fatal doses of methadone and clinically effective doses (1,14). For example, a 30 mg daily dose of methadone may result in a fatality without effectively achieving analgesia in a given patient (28). Studies have demonstrated a higher postmortem blood methadone concentration in those in MMT compared to nontolerant individuals. Worm et al. (15) demonstrated a higher mean blood methadone concentration in patients undergoing MMT compared to subjects who were not (0.47 mg/L vs. 0.27 mg/L). Similarly, Heinemann et al. (16) concluded that individuals with a history of MMT had higher blood methadone concentrations than untreated persons (mean concentrations 0.62 μg/mL vs. 0.43 μg/mL).

Both postmortem redistribution and site dependence of methadone play important roles in the toxicological evaluation of methadone-associated fatalities (14,28,31). In Milroy and Forrest's (14) study of 111 methadone deaths examined at the University of Sheffield, 26 cases underwent multiple site sampling. These authors determined a 100% discrepancy between methadone concentrations in samples taken respectively from the arm and the leg in certain cases. Levine et al. (31) evaluated the methadone concentrations in heart blood and blood of alternate sites in 15 methadone-positive cases of various causes of death at the Office of the Chief Medical Examiner in Maryland. Their study demonstrated no consistent trend of one site yielding a higher or lower concentration than another site.

An individual's reaction to a specific methadone blood concentration is significantly dependent on his/her physiologic tolerance to this drug. Table 5 lists a series of questions that the

TABLE 5—*Factors considered in the interpretation of postmortem drug concentrations.*

1. What is the history of the death? Was this a sudden death or one with a period of unconsciousness? Is there a clear anatomical cause of death?
2. What is the drug use pattern? A known drug user vs. a naïve user? What is the prescription history, when were they filled, how were they prescribed, and how many are missing? (Remember, people may sell their medications or share with others)
3. Was there an occasion that would have prevented drug use, e.g., jail? This could result in a loss of tolerance
4. What drugs are involved? What are the combinations and are they additive or antagonistic?
5. What are the measured metabolites?
6. Where was the specimen taken? Was there more than one sample? Were the specimens specific for the analytes of interest (tissues, vitreous, urine, CSF, hair)?
7. What was the postmortem interval? Was there any emergency treatment given? Did a transfusion occur?
8. Don't interpret urine concentrations
9. Don't assume toxicity from gastric concentrations
10. Consider each drug individually; the pharmacokinetics and pharmacology will be different. Only then begin looking at interactions

Coroner/Medical Examiner/Toxicologist may consider during the interpretation of postmortem drug concentrations. In the current study, the significance of the postmortem blood concentration was interpreted for each subject based on the historical use of methadone. The present study is in accord with the studies of both Wolf et al. (9) and Milroy and Forest (14) in that the methadone blood concentration is higher in methadone toxicity cases. Our findings are directly contrary to those of Mikolaenko et al. (8) with relation to the methadone-benzodiazepine interaction. The mean methadone blood concentration in the present study, where only methadone was detected in the blood and urine, was 0.725 mg/L (0.2–2.4). The mean methadone blood concentration was slightly lower at 0.62 mg/L (0.177–1.7) in those cases where methadone alone was in blood and other drugs were present in urine. The lowest mean methadone blood concentration was observed in the cases where only methadone and benzodiazepines were detected in blood and urine, specifically, 0.548 mg/L (0.2–1.0). The mean methadone blood concentration of all 176 cases was 0.535 mg/L (0.02–4.0). The additive effect of methadone with other classes of drugs such as benzodiazepines, ethanol, and antidepressants, causes death at a methadone blood concentration lower than in cases where methadone is the only drug present. Not only do ethanol and benzodiazepines provide an additive effect with methadone, the polypharmacy may lead to a fatal consequence with a lower methadone blood concentration. In this respect, it is of utmost importance for the treating clinician to be cognizant of all drugs consumed by a patient and to adjust the methadone dose accordingly.

In addition to the determination of the methadone blood concentration, we evaluated each of the drugs detected in the postmortem blood toxicology. Table 6 lists the most commonly detected antidepressants, benzodiazepines, and opioids in addition to methadone and their ranges of concentration. Diazepam was the most common drug besides methadone present in postmortem blood, specifically, in 36 cases. The drug–drug interactions between methadone and these psychoactive substances account for the high number of methadone-associated polypharmacy fatalities in this study.

The drastic increase in deaths due to methadone warrants more intense scrutiny by law enforcement into the acquisition of the drug and by the medical community about prescribing practices. Ballesteros et al. (32) conducted a review of Medical Examiners' cases in which methadone was the primary cause of death between 1997 and 2001 in North Carolina. They noted a five-fold increase in deaths due to methadone, varying from 12 cases in 1997 to 80 in 2001. Of the 97 cases documenting the source of methadone, 73 (75%) had been prescribed by a physician, while 24 (25%) had illicitly acquired the drug. In addition, all North Carolina opiate treatment programs reviewed the list of decedents and determined that only 8 (4%) had been clients. The findings in the present study closely mirror those in North Carolina. We observed a 10-fold increase in methadone fatalities, rising from six cases in 2000 to 68 in 2004. Of the 95 cases with a known history of methadone use, 46 (48.4%) involved prescription by private physician, 19 (20.0%) obtained the drug illegally, nine (9.5%) received it through a methadone treatment clinic, and 21 (22.1%) acquired methadone by unknown means.

TABLE 6—*Leading psychoactive substances besides methadone detected in postmortem blood toxicological analyses of methadone toxicity fatalities at the Office of the Chief Medical Examiner in Kentucky, 2000–2004.*

Psychoactive substances in blood	Range of concentration (mg/L)
Antidepressants (n = 70)	
Sertraline (n = 16)	<0.05–1.9
Amitriptyline (n = 15)	0.05–3.7
Fluoxetine (n = 13)	0.07–5.0
Citalopram (n = 13)	0.05–2.0
Benzodiazepines (n = 57)	
Diazepam (n = 36)	<0.05–0.68
Nordiazepam (n = 33)	<0.05–0.45
Alprazolam (n = 15)	<0.005–6.0
Opiods in addition to methadone (n = 49)	
Oxycodone (n = 19)	<0.05–1.2
Hydrocodone (n = 16)	<0.05–2.5
Propoxyphene (n = 12)	<0.05–0.415

Accidental methadone fatalities in children have been reported in the literature since the initiation of methadone maintenance clinics designed for adults (14,33). Smialek et al. (33) reported four cases of pediatric methadone deaths between the ages of 5 weeks and 3 years at the Wayne County Medical Examiner's Office in Detroit, MI. The postmortem blood methadone concentrations ranged between 0.006 and 0.11 mg/dL (=0.06 and 1.1 mg/L). One infant succumbed after nursing. His mother, a former heroin addict, was maintained on methadone during and after her pregnancy. Milroy and Forrest (14) encountered five cases of methadone deaths in children aged 2 to 13 years. The postmortem blood concentrations ranged between 200 and 489 μg/L (=0.200 and 0.489 mg/L). We encountered a single pediatric case involving a 17-month-old boy who died from methadone toxicity in 2002. This case did not fulfill the criteria of the other methadone-related deaths in our study and, therefore, was not included in the tabulations. The infant's mother was a "methadone patient" who, drinking liquid methadone at home, noticed that her infant was holding an empty cup. She subsequently rocked her son to sleep without seeking immediate medical attention. The mother later discovered him unresponsive and cyanotic. The infant was transported to the local emergency department, arriving in cardiopulmonary arrest. His weight was 26 pounds, and he was 33.5 inches tall. Postmortem toxicology recorded blood concentrations of methadone at 0.65 mg/L and diphenhydramine at 1.2 mg/L. Postmortem urine screen was negative. The infant's mother subsequently pleaded guilty to lesser charges of reckless homicide. In light of the increases in both methadone prescriptions for outpatient pain control and illicit methadone use, special attention should be addressed to the safety precautions associated with methadone in the household setting.

Conclusions

The significant increase in methadone-related fatalities in Kentucky and nationally at the turn of the 21st century is a newly emergent public health issue. Several explanations for this increase may include: (i) a difference in Medical Examiners' practices in interpreting the same data and determining the cause of death in these cases; (ii) a lack of uniformity among Medical Examiners in assigning a cause of death; (iii) increased methadone consumption by means of methadone maintenance therapy, more prescriptions for chronic pain, and more illicit abuse due to easier availability; (iv) increased use of methadone in combination with other drugs whose additive effects cause death; and (v) the individuals succumbing to a methadone-related death may be poor metabolizers and, thus, more susceptible to the toxic effects of methadone.

Preventative strategies should encourage promotion of more astute awareness among physicians and the public of the pathophysiology of methadone and, in particular, the deleterious interaction with other psychoactive drugs. The vast majority of cases in

this study involved polypharmacy, specifically, methadone combined with antidepressants, benzodiazepines, or opioids in addition to methadone. Ethanol was detected in a minority of cases. Given the confounding issue of individual tolerance to methadone, interpretation of postmortem blood concentrations was individualized in each case. A key component of the analysis consisted of detailed consideration of historical use of methadone. Half of the individuals obtaining physician-prescribed methadone either initiated or refilled the prescriptions <10 days prior to death. The high number of deaths, which not only occurred during the induction phase of methadone use but also involved various combinations of psychoactive drugs (polypharmacy) with methadone, strongly suggests an additive effect between methadone and these drugs during a vulnerable period of consumption.

Research provides evidence for the important role of pharmacogenetics in an individual's metabolism of methadone and other opioids (25). Several scientific ways to determine whether the individual is tolerant or susceptible to methadone at lower concentrations may include: (i) analysis of liver methadone concentrations; (ii) measurement of blood 2-ethyldine-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), a major methadone metabolite, as higher concentrations may indicate prior methadone usage and tolerance; and (iii) the pharmacogenomics factor in that methadone toxicity may be due to allelic variance (as methadone is metabolized by cytochrome CYP 1A2, 3A4, and 2D6) leading to poor or intermediate metabolism and a greater likelihood of a fatality. Further forensic study should focus on the interplay of drug metabolism with potential genetic links in individuals who die from opioid drug intoxication.

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