Increase in Unintentional Medication Overdose Deaths
Oklahoma, 1994–2006

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Background: During 1999–2006, rates of unintentional drug-related deaths increased 120% in the U.S.

Purpose: This report describes demographics and trends of unintentional medication overdose deaths among Oklahoma residents to target prevention strategies.

Methods: Oklahoma medical examiner data regarding fatal unintentional poisonings involving at least one prescription or over-the-counter medication during 1994–2006 and opioid retail sales data during 1997–2006 were analyzed during 2008–2009 to determine demographic-specific rates of overdose deaths and changes in 3-year mean death rates.

Results: A total of 2112 fatal unintentional medication overdoses were identified (4.7 deaths/100,000 population) involving a median of two substances/decedent. The highest fatality rates occurred among men (5.9/100,000) and people aged 35–54 years (11/100,000). Crude overdose death rates increased sevenfold during the investigation period, peaking at 11/100,000 in 2006. Death rates increased more for women (ninefold) than men (sixfold); rates among residents of rural counties increased more (eightfold) than urban county rates (sixfold). Leading drug types involved in fatalities were opioids and anxiolytics. The individual drugs contributing most frequently included methadone (31%); hydrocodone (19%); alprazolam (15%); and oxycodone (15%). During 1997–2006, Oklahoma prescription opioid sales increased fourfold. Methadone was associated with the highest number of deaths per equianalgesic dose sold (23.3), whereas hydrocodone and oxycodone had the highest increases in deaths per equianalgesic dose sold (threefold increase each).

Conclusions: Unintentional medication-related deaths are increasing in Oklahoma and often involve multiple substances. Substances most frequently contributing to deaths were prescription opioid analgesics. Prevention strategies should target people aged 35–54 years and emphasize the dangers of coingesting substances and misusing prescription pain medications.

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Introduction

Poisonings are second to only motor-vehicle collisions as a cause of unintentional injury deaths in the U.S. each year.[1,2] Approximately 90% of these poisoning deaths are related to drug overdoses that include either prescription medications or illicit drugs.[1] Drug overdose deaths have more than doubled from approximately 11,000 deaths in 1999 to 26,000 in 2006, rising from 4.0/100,000 population to 8.8/100,000 in 2006.[3] During 1999–2002, deaths attributable to such illegal drugs as heroin and cocaine increased 12% and 23%, respectively, whereas overdose deaths resulting from prescription opioid analgesics increased 91%.[4] At least half of drug overdoses are caused by prescription and over-the-counter drugs, with legal medications replacing illicit drugs as the most common cause of fatal drug overdoses in the U.S.[4]

Of all prescription drugs sold in the U.S., the single most prescribed medication in 2005 was hydrocodone, an opioid analgesic.[5] Approximately 100 million prescriptions were written for hydrocodone, outnumbering prescriptions for the second most popular medication, atorvastatin (a cholesterol-lowering agent), with 63 million prescriptions, and the most commonly prescribed antibi-

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otic, amoxicillin, with 52 million prescriptions.[5] The majority of prescription opioid use is legitimate; however, nonmedical use of controlled medications is increasing. Nonmedical use of prescription drugs increased 81% during 1992–2003.[5] According to surveys by the U.S. Substance Abuse and Mental Health Services Administration,[5] an estimated 49 million people, or one in five people aged ≥12 years, in the U.S. have used prescription drugs nonmedically at some point in their lifetime, making prescription drugs the fourth most abused category of substance after marijuana, alcohol, and tobacco.

Considering the substantial increase in poisoning deaths nationally, an investigation was initiated to evaluate medication-related overdose deaths in Oklahoma. Previous state-level studies have not described deaths relative to availability of substances commonly involved in overdose fatalities. U.S. Drug Enforcement Agency retail sales data for Oklahoma were used to determine deaths per opioid sales and trends for opioids overall and for specific substances. Also, whereas studies that rely exclusively on death certificate data are limited in comparability before and after the 1999 adoption of coding changes in the ICD-10, the present report utilizes state medical examiner data that do not involve ICD-10 coding and have been consistently recorded, allowing analyses over time. Goals of analysis were to determine magnitude and temporal trends of fatalities related to unintentional medication overdoses, describe types of medications involved (including common coingestants), identify populations at risk, and inform healthcare providers and prevention planners.

Methods

Case Selection and Definitions

Oklahoma has a centralized statewide medical examiner system through provision of state statutes with a mandate to evaluate all unexpected or suspicious deaths. State medical examiner records collected during 1994–2006 were reviewed and analyzed during 2008–2009 for unintentional drug poisoning deaths. A case was defined as a death in an Oklahoma resident in which the medical examiner weighed all available evidence and deemed manner of death as unintentional and cause of death as drug or poison, and in which at least one prescription or over-the-counter medication contributed.

Thus, excluded were overdose deaths involving only illicit drugs, alcohol, inhalants, or poisons in which medications were not mentioned. Substances contributing to the cause of death were determined primarily by the medical examiner's assessment of results from autopsy and toxicologic testing, but also considered additional evidence gathered by scene investigations and the decedent's medical record. Decedent's county of residence was considered urban if the county population exceeded 500 people/square mile of land area (according to the 2000 U.S. census), with the remainder termed rural counties.[6]

Data Sources

Data regarding demographics, date of overdose, substances contributing to death, and assessment of alcohol involvement were collected from the state medical examiner case record. Controlled drug retail sales data were obtained from the U.S. Drug Enforcement Agency's Office of Diversion Control website.[7] Retail sales data for methadone do not include methadone distributed through federal methadone treatment programs. Population rates were calculated by using bridged race demographic estimates from the National Center for Health Statistics.[8]

Analysis

Substances (whether alcohol, illicit drugs, or licit medications) were categorized by substance type. Equianalgesic equivalents were calculated for prescription opioids by using morphine as a reference, as described previously.[4,9] Fatalities related to common opioids were adjusted for retail sales volume by dividing number of deaths associated with a particular opioid by retail sales of that opioid, expressed in equianalgesic units. All temporal trends reported compare 3-year means during the first 3 years of the investigation period (1994–1996) or first 3 years of available retail sales data (1997–1999), with 3-year means during the last 3 years (2004–2006), unless otherwise specified. SAS, version 9.1, was used to determine frequencies, stratify by demographic variables, and test for trends. Wilcoxon rank sums test was used to test for differences in median death rates, and Cochran–Armitage test was used to evaluate temporal trends.

Results

During 1994–2006, a total of 2112 cases were identified as unintentional medication-related overdose deaths (4.7/100,000 population, SE=0.10; Table 1). Crude overdose fatality rates increased sevenfold (Figure 1), with a peak of 11/100,000 in 2006. The majority of deaths involved men (61%), with a 60% higher rate than for women (5.9/100,000 vs 3.6/100,000, SE=0.16 and 0.13, respectively; Table 1). Deaths among men outnumbered those among women each year, but 3-year mean death rates increased sixfold among men, whereas female death rates increased approximately ninefold. Median age of decedents was 42 years, with a range of <1–88 years; women (median age 44 years) were older than men (median age 40 years; $p<0.001$). The highest fatality rates occurred in age groups 35–44 years and 45–54 years, with 11 cases/100,000 population each (SE=0.42 and 0.43, respectively), approximately 2.3 times the overall rate (Table 1). The lowest rates occurred among children aged <15 years (0.2/100,000, SE=0.04) and adults aged ≥65 years (0.6/100,000, SE=0.10).

Fatality rates increased most among those aged 15–24 years and 55–64 years; however, during 2004–2006, mean overdose death rates for people aged 35–54 years were more than double the rates of any other age group. Overall, whites (92%) were over-represented, with a two-

Table 1. Unintentional medication overdose deaths per 100,000 population by demographic characteristics—Oklahoma, 1994–2006

Characteristic	Overall, 1994–2006	1994–1996	2004–2006	Fold increase (1994–1996/ 2004–2006)
Gender				
Male	5.89	1.85	11.74	6.35
Female	3.60	0.81	7.64	9.46
Age (years)				
0–14	0.16	0.18	0.14	0.75
15–24	3.04	0.62	7.61	12.28
25–34	5.73	2.13	11.65	5.47
35–44	11.40	2.90	22.56	7.78
45–54	10.70	2.75	21.78	7.91
55–64	3.49	0.59	7.13	12.13
≥65	0.59	0.52	1.07	2.04
Race/ethnicity				
White	5.68	1.51	12.02	7.95
American-Indian	2.16	0.60	3.98	6.61
Black	1.75	0.66	3.11	4.73
Hispanic	0.65	0.26	1.28	4.94
Asian	0.29	0.85	0	0
Residence type				
Urban county	6.16	1.88	12.01	6.39
Rural county	3.92	1.01	8.30	8.22
Total	4.72	1.32	9.66	7.34

to three-fold higher rate of death (5.7/100,000, SE=0.13) than that for American Indians (2.2/100,000, SE=0.24) and blacks (1.8/100,000, SE=0.22) and nine- to 20-fold higher than Hispanics (0.7/100,000, SE=0.17) and Asians (0.3/100,000, SE=0.21), respectively.

People residing in urban counties had 1.6 times higher overall rates of overdose deaths than rural county residents. Although overall mean and median fatality rates for urban counties (6.2 and 6.8 deaths/100,000, SE=0.20 and 0.22, respectively) were higher than overall mean and median rates for rural counties (3.9/100,000 and 3.5/100,000, SE=0.12 and 0.10, respectively; $p=0.05$), rate of deaths increased 1.3 times more in rural counties than urban counties during the investigation period (rural county deaths increased eightfold, whereas urban deaths rose sixfold; $p=0.08$). Median age of decedents did not differ by urban or rural residence ($p=0.6$).

Among all decedents, 1934 (91%) had ingested medications alone; 169 (8%) had ingested an illicit substance along with medication; and one person (0.05%) had used inhalants in addition to medication. The majority of cases (56%) had more than one substance contributing to the overdose, with a median of two substances per person (mean=1.8 substances/person); 17% had more than three substances involved. Prescription opioid analgesics were involved in 83% of fatalities, and 21% involved antianxiety agents. Alcohol was considered a contributing factor by the medical examiner in 404 cases (19%) and documented by toxicologic testing among 260 (12%) fatalities (Table 2). Men were 1.6 times more likely to have alcohol involved than women (95% CI=1.3, 2.2), but alcohol risk did not vary between whites and nonwhites.

Of the 3743 identifications of substances contributing to deaths, opioids constituted 53% and antianxiety agents 12%. In particular, prescription opioid analgesics accounted for four of the five most frequent drugs identified, and these four combined to make up 43% of all substances involved in deaths. The only nonprescription substances among the 15 most frequently contributing substances were alcohol, cocaine, and acetaminophen. Among all unintentional overdose deaths, the five individual substances most frequently contributing to deaths were methadone (31% of fatalities); hydrocodone (19%); alprazolam (15%); oxycodone (15%); and morphine (12%; Table 2). Deaths related to opioids, antianxiety agents, and muscle relaxants each increased 11-fold, whereas deaths involving alcohol or central nervous system stimulants (e.g., cocaine, methamphetamine) increased fivefold and sixfold, respectively.

Deaths among men were marginally more likely to involve prescription opioids than were deaths among women (risk ratio [RR]=1.1, 95% CI=1.02, 1.1),

but an increasing proportion of prescription opioid-related deaths during the evaluation period involved women, compared with men ($p=0.01$). Cointoxication of medications with illicit substances was approximately two times more likely among nonwhites than whites (RR=1.9, 95% CI=1.3, 3.0), but it did not vary significantly by gender.

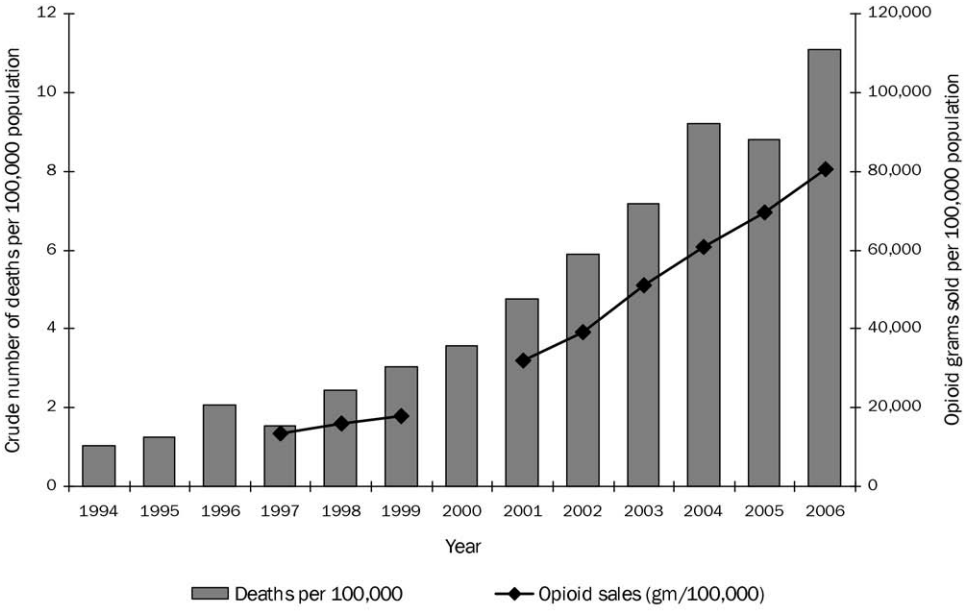

Figure 1. Unintentional medication-related overdose death rates and total sales of prescription opioids by year, Oklahoma, 1994–2006

Annual numbers of deaths related to individual opioid medication overdoses are displayed in Figure 2. Deaths related to all opioids except meperidine increased during the analysis period. Among the three opioids associated with ≥50 fatalities in 2006, deaths associated with oxycodone increased 12-fold, methadone eightfold, and hydrocodone sevenfold. Combined sales of controlled opioid drugs increased fourfold during the same period (Figure 1). After adjusting for annual volume of retail sales for each medication, we determined the number of deaths per equianalgesic dose for selected opioids (Figure 3). Methadone was associated with the highest number of deaths per equianalgesic dose each year (23.3 overall), and morphine was most often second (14.6 deaths/equianalgesic dose sold overall), but neither increased during the analysis period. Overall, oxycodone and hydrocodone were associated with 12.2 and 10.8 deaths/equianalgesic dose sold, respectively, and both increased approximately threefold during the investigation period.

Discussion

The present evaluation demonstrates that an epidemic of unintentional medication overdose deaths poses an emerging public health problem in Oklahoma. Fatality rates increased sevenfold from the beginning 3 years of the analysis period to the last 3 years. Overdose risk in Oklahoma varied by demographic group, with the highest rates among people aged 35–54 years, men, and whites, but the increase in deaths among women was 50% greater than the increase among men. Men, whites, and people aged 35–54 years have previously been identified as groups most at risk,[4,10–12] and women have been observed to have higher increases in poisoning death rates than men.[1,10,12–14]

Similar to prior analyses of national data,[1,2] the present analysis determined that age-specific poisoning mortality rates increased most in the group aged 15–24 years, but it also identified an equally high increase in overdose rates among people aged 55–64 years. Whereas certain previous analyses[10] have concluded that rural areas have the highest death rates, similar to the experience reported for Utah,[13] the current investigation suggested that urban areas have higher overall fatality rates (compared with rural counties), yet rural counties experienced a greater increase in death rates during the analysis period.

The majority of fatalities involved prescription opioid analgesics, and opioid-related deaths increased at a faster pace than overall deaths. Increases in deaths from opioid overdoses have been reported[10,11,13–15] in other states as well. Methadone was involved in the highest number of deaths, followed by hydrocodone, alprazolam, and oxycodone. Methadone might be particularly dangerous because effects can be prolonged substantially by repeated dosing. Deaths per sales of methadone might have been overestimated, however, because Drug Enforcement Agency retail sales data do not include drugs dispensed by federal opiate treatment programs, thus underestimating the total grams of methadone distributed. Nevertheless, recent reports[4,15] indicate that methadone clinics do not contribute the majority of methadone involved in over-

Table 2. Individual substances involved in unintentional medication overdose deaths: Oklahoma, 1994–2006, *n* (%)

Substance	Overall[a]	1994–1996[b]	2004–2006[c]
Methadone	653 (30.9)	21 (16.0)	377 (36.6)
Hydrocodone	407 (19.3)	9 (6.9)	220 (21.4)
Alprazolam	320 (15.2)	8 (6.1)	219 (21.3)
Oxycodone	311 (14.7)	1 (0.8)	174 (16.9)
Morphine	263 (12.5)	31 (23.7)	101 (9.8)
Alcohol	260 (12.3)	25 (19.1)	115 (11.2)
Propoxyphene	140 (6.6)	14 (10.7)	46 (4.5)
Fentanyl	124 (5.9)	2 (1.5)	78 (7.6)
Carisoprodol	97 (4.6)	8 (6.1)	40 (3.9)
Diazepam	94 (4.5)	8 (6.1)	37 (3.6)
Amitriptyline	87 (4.1)	8 (6.1)	33 (3.2)
Cocaine	85 (4.0)	10 (7.6)	45 (4.4)
Acetaminophen	76 (3.6)	8 (6.1)	33 (3.2)
Cyclobenzaprine	74 (3.5)	0	43 (4.2)
Methamphetamine	72 (3.4)	4 (3.1)	43 (4.2)
Olanzapine	37 (1.8)	0	16 (1.6)
Codeine	34 (1.6)	2 (1.5)	15 (1.5)
Other substance[d]	609 (28.8)	58 (44.3)	229 (22.3)

[a]A total of 3743 substances were identified on toxicologic testing among 2112 decedents. Because each decedent might have had >1 substance involved in their death, frequencies for individual substances total >100%.
[b]During 1994–1996, a total of 217 substances were identified among 131 decedents.
[c]During 2004–2006, a total of 1864 substances were identified among 1029 decedents.
[d]*Other substance* includes 80 substances in the overall analysis, none of which make up >1% of total substances detected on toxicologic testing; other substances with >20 positive tests in the overall analysis include diphenhydramine, doxepin, citalopram, tramadol, venlafaxine, meperidine, butalbital, promethazine, hydromorphone, and mirtazapine.

doses. Systematic underreporting of methadone sales is a consistent factor and thus unlikely to influence apparent trends. Nationally, increased opioid-related deaths paralleled increased sales trends.[4]

Methadone and morphine deaths paralleled increased sales in Oklahoma, but increases in oxycodone- and hydrocodone-related deaths outpaced increased sales of these drugs. Factors contributing to emergence of hydrocodone and oxycodone among leading opioids in- deaths per sales are unknown. One reason might be that hydrocodone is more readily available for diversion because it is classified in a less-restricted category of controlled substance than methadone or morphine and might have gained in popularity among abusers because of easier access. In contrast, however, oxycodone is in the higher-restricted category. Increase in oxycodone deaths per retail sales might be accounted for in part by the 1996 introduction of a controlled-release formulation of oxycodone[16] that might be more prone to unintentional overdose by its relatively slower onset and longer duration of action. Slower onset after ingestion might prompt the user to take additional opioids before full effect of the oxycodone is realized, potentially resulting in an overdose, and tampering with tablets (e.g., chewing, crushing, or dissolving them) might result in a larger amount of drug released in a shorter period, predisposing to overdose.

The majority of deaths in the analysis presented here were attributed to concurrent ingestion of multiple substances. Other studies have also reported deaths from polysubstance overdoses to be common (national mean of 1.3 opioid analgesics/decedent[4] and mean of 2.0 prescription drugs/case in West Virginia[15]). Multidrug events have also been observed with increasing frequency in drug-related emergency department visits recorded by Drug Abuse Warning Network surveillance,[16] a system that monitors drug-related visits to hospital emergency departments. In certain instances, levels of any one medication involved in polysubstance overdoses might not have been lethal; however, taking medication in combination with other prescription drugs, over-the-counter medications, illicit drugs, or alcohol contributed additive side effects that were fatal. For example, opioid analgesics, antianxiety agents, skeletal muscle relaxants, and alcohol can each cause sedation and respiratory depression; taken in combination, even at correct doses, additive respiratory depression can result in apnea and death. The general public

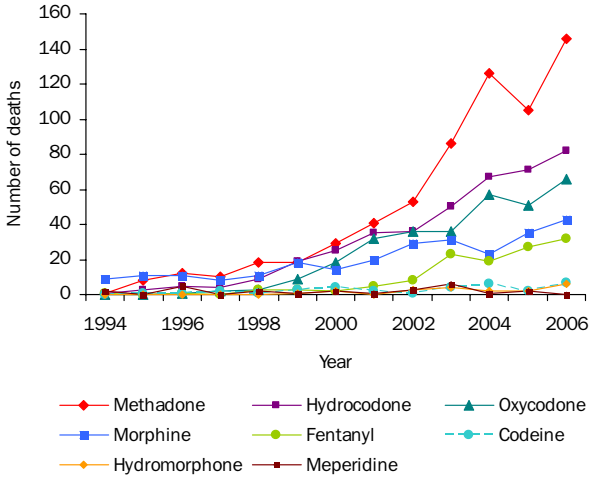

Figure 2. Unintentional medication overdose deaths by opioid substance and year, Oklahoma, 1994–2006

might not be aware of the risk of consuming multiple prescription medications concurrently or of the danger of combining substances.

Strengths of the present analysis compared to some other state-level investigations are access to medical examiner data consistently recorded from 1994 to 2006, analysis of demographic trends in unintentional overdose deaths over time, and use of retail sales data as a reflection of changing availability of prescription opioid medications. Studies that rely on death certificate coding alone are limited by the change in coding standards in 1999 such that deaths before and after the change cannot readily be compared; in the present study, however, data derived from the state medical examiner did not depend on ICD coding and were consistently recorded over the investigation period. Medical examiner evaluations are mandated by state statute for unexpected or suspicious deaths and are likely to capture nearly all overdose-related deaths as well as provide toxicologic testing with detailed information regarding substances involved.

The current evaluation is subject to certain limitations. Some deaths might not have been recognized as unexpected or suspicious (particularly among older adults with chronic conditions) and not reported to the medical examiner, thus underestimating the number of drug-related deaths. Deaths coded as undetermined manner of death (approximately 4%–10% of poisoning deaths each year) might actually have been unintentional but may not have been included in this analysis. State medical examiner data limit drug coding to a maximum of four substances per fatality, possibly leading to an underestimate of the number and types of medications contributing to polysubstance overdoses. In addition, medical examiner data often lack information related to the source of drugs; therefore, it was unknown whether medications had been the decedents' own medication obtained from a valid prescription or if medication had been diverted illegally.

Studies from other states[10,13,17] indicate that most decedents do not have prescriptions for medications involved in unintentional overdose deaths. Collaboration and data sharing with the state prescription drug monitoring program (PDMP) potentially can remedy this data gap. State PDMPs are designed to reduce abuse of controlled pharmaceutic substances. Thirty-eight states have such programs,[18,19] and more are considering legislation. By using PDMP data, a West Virginia study[15] determined that 63% of overdose deaths were associated with pharmaceutic diversion; 21% had evidence of doctor shopping (when one patient visits numerous doctors and pharmacies to obtain controlled medications); and substance abuse indicators were present in 95%.

On the basis of these findings, recommendations are that healthcare providers, pharmacists, and injury prevention professionals educate the public about the potential dangers of prescription medication. Educational messages might include the following: Medications should not be taken that were prescribed for others and should not be taken in a manner other than that clearly indicated on the label or packaging. Patients should be encouraged to fully disclose to prescribers all medications being taken and should be warned not to coingest prescription drugs with other prescription or over-the-counter medications having similar side-effect profiles unless previously discussed with their physician. Likewise, patients should be cau-

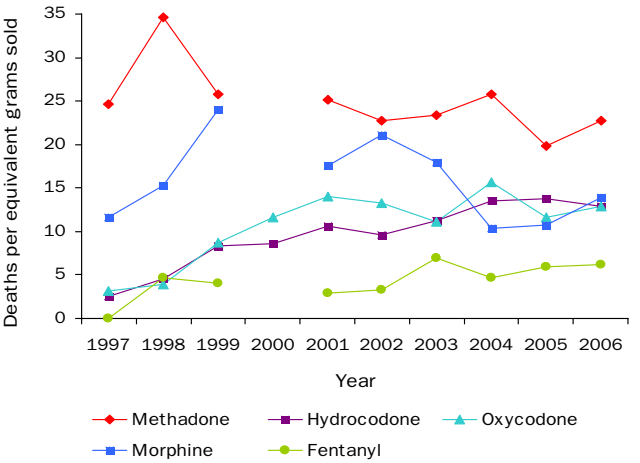

Figure 3. Unintentional medication overdose deaths per equianalgesic dose sold by opioid substance and year, Oklahoma, 1997–2006

tioned of the danger of combining prescription medications with alcohol or illicit drugs.

Additional recommendations are that prescribers and pharmacists use PDMP services where available. Programs often provide patient-specific drug information so that providers can review patterns of prescription drug use by individual patients before prescribing or dispensing additional medications. Also, public health professionals could collaborate with state PDMPs to further describe demographics of overdose victims and clarify the appropriate audience to which preventive messages should be targeted. Lastly, ongoing public health surveillance is recommended for medication-related fatalities. Case-report forms could be developed to facilitate collection by the medical examiner of data regarding drug source and decedent history of substance abuse. Central statewide medical examiner data can be reviewed for trends in unintentional overdoses and to measure the impact of public health interventions.

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