

Increasing deaths from opioid analgesics in the United States[†]

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SUMMARY

Purpose Since 1990, numerous jurisdictions in the United States (US) have reported increases in drug poisoning mortality. During the same time period, the use of opioid analgesics has increased markedly as part of more aggressive pain management. This study documented a dramatic increase in poisoning mortality rates and compared it to sales of opioid analgesics nationwide.

Methods Trend analysis of drug poisoning deaths using underlying cause of death and multiple cause of death mortality data from the Centers for Disease Control and Prevention and opioid analgesic sales data from the US Drug Enforcement Administration.

Results Unintentional drug poisoning mortality rates increased on average 5.3% per year from 1979 to 1990 and 18.1% per year from 1990 to 2002. The rapid increase during the 1990s reflects the rising number of deaths attributed to narcotics and unspecified drugs. Between 1999 and 2002, the number of opioid analgesic poisonings on death certificates increased 91.2%, while heroin and cocaine poisonings increased 12.4% and 22.8%, respectively. By 2002, opioid analgesic poisoning was listed in 5528 deaths—more than either heroin or cocaine. The increase in deaths generally matched the increase in sales for each type of opioid. The increase in deaths involving methadone tracked the increase in methadone used as an analgesic rather than methadone used in narcotics treatment programs.

Conclusions A national epidemic of drug poisoning deaths began in the 1990s. Prescriptions for opioid analgesics also increased in this time frame and may have inadvertently contributed to the increases in drug poisoning deaths. Copyright © 2006 John Wiley & Sons, Ltd.

KEY WORDS — poisoning; mortality; opioid; analgesic; narcotic; methadone; oxycodone; fentanyl

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INTRODUCTION

The Centers for Disease Control and Prevention (CDC) reports that fatal poisonings increased 25% in the US from 1985 to 1995.¹ A number of states later reported larger increases in fatal poisonings that extended through the latter half of the 1990s.^{2–7} One report, for example, notes that poisoning mortality

rates increased an average of 145% from 1990 to 2001 in 11 states.²

All reports note that the trend is due to an increase in drug poisonings rather than in poisonings from toxic chemicals or alcohol. King County, Washington, reports a 143% increase in opiate deaths from 1990 to 1999.⁶ Maine reports a 373% increase in 'drug deaths' from 1997 to 2002,⁵ while North Carolina reports an 111% increase in unintentional drug-related deaths from 1997 to 2001.³ In each case, the 'drug' category includes both legal and illegal drugs. Polydrug use and drug use with alcohol are common features of all the reports.

During roughly the same time, US health professionals changed the way they managed chronic pain. At the close of the 1980s, pain specialists began to argue that the risk of addiction should not prevent the use of prescription opioid analgesics to manage chronic, nonmalignant pain.^{8–11} Over time, clinical consensus shifted to acknowledge that opioid analgesics had a legitimate and important role in managing chronic pain.^{12–15} This change in thinking probably contributed to the dramatic increase in prescriptions written for opioid analgesics from 1990 to 2002.^{16–18}

Opioid analgesics include semisynthetic derivatives from opium (e.g., oxycodone and hydrocodone) and synthetic agonists with similar action (e.g., fentanyl).¹⁹ The latter category includes methadone, used both as an analgesic and in treatment of heroin addiction. Controlled-release formulations of opioid analgesics have been developed (e.g., OxyContin[®] (Purdue Pharma), based on oxycodone, and MS CONTIN[®] (Purdue Frederick), based on morphine.)

Trends in national drug poisoning mortality in recent years have not been considered in light of the increased use of prescription opioid analgesics. This study's aim was to determine the extent to which opioid analgesics contribute to changes in poisoning mortality in the US; to compare the role of these products to that of street drugs such as heroin and cocaine; and to compare the contributions of different types of opioid analgesics to drug poisoning mortality in recent years.

METHODS

State laws require that deaths from nonnatural causes, including deaths from poisoning (i.e., the damaging effects of ingestion, inhalation, or other exposure to solids, liquids, or gases), be referred to coroners and medical examiners for determination of the cause of death. Coroners and medical examiners identify all the substances that contributed to poisoning deaths and,

where possible, single out the agent or type of agent that was the underlying cause of death. They do not attribute a death to a drug based solely on finding the drug in a postmortem toxicology screen.²⁰ Both the underlying cause and the specific types of poisoning recorded on the death certificate by coroners and medical examiners are coded by the National Center for Health Statistics (NCHS), using the Ninth Revision of the International Classification of Diseases (ICD-9)²¹ for 1979–1998 and the Tenth Revision (ICD-10)²² for 1999–2002.

For this study, we defined deaths due to drug poisoning as those that NCHS coded to poisoning from 'drugs, medicaments, or biological substances.' This definition included deaths due to all types of both licit and illicit drugs. It did not include poisoning from alcohol or tobacco. Deaths involving poisoning by drugs but coded to mental and behavioral disorders or adverse effects were not included in this analysis.

We searched the mortality data tapes available from NCHS to generate trends in deaths due to drug poisoning by manner (unintentional, suicide, or undetermined intent) and major class of drug for the years 1979–2002. The generation of mortality trends by major class of drug was limited to unintentional poisoning because ICD-9 lacked the detail necessary to track major classes of drugs for suicides or deaths of undetermined intent. Because ICD-10 replaced ICD-9 in 1999, we calculated the unintentional poisoning mortality rates by major class of drug for 1979–1998 and 1999–2002 separately. In ICD-9, the majority of unintentional poisoning deaths fell into five categories: (1) 'opiates and related narcotics,' including heroin and opioids; (2) cocaine; (3) psychotropic drugs, including sedatives, hypnotics, tranquilizers, and other psychotropic agents such as antidepressants and amphetamines; (4) 'other specified drugs,' a category used primarily for multiple drug involvement (e.g., opiates and cocaine taken together); and (5) 'unspecified drugs,' used primarily when death was attributed to 'drug overdose' without further specification.¹ In ICD-10, the majority of unintentional drug poisoning deaths fell into three categories: (1) 'narcotics and psychodysleptics (hallucinogens),' a combination of categories 1 and 2 of ICD-9; (2) 'other and unspecified' drugs, a combination of categories 4 and 5; and (3) sedatives/psychotropic drugs.

Analysis of specific poisonings among the contributing causes of death was restricted to the years 1999–2002 because ICD-9 poisoning codes do not distinguish between heroin and opioid analgesics. For the analysis of specific poisonings from 1999 to 2002,

we used the multiple cause of death (MCO) Mortality Data from NCHS,²³ limiting the analysis to deaths with an underlying cause of 'narcotics and psychodysleptics' (X42) or 'other and unspecified drugs' (X44). We first identified deaths for which opioid analgesics, heroin or cocaine were included among the codes for causes of death. We categorized the remaining deaths by whether 'other specified' drugs, 'unspecified' drugs, or no drugs were listed.

We further tabulated the opioid analgesic poisonings for 1999 and 2002 according to the opioid classification scheme used by the ICD. The opioid types were: semi-synthetic drugs derived from opium other than heroin (the 'other opioid' category) and drugs synthesized from other parent compounds: methadone and 'other synthetic narcotics.'

We used national resident bridged-race population estimates from NCHS to calculate both underlying cause and multiple cause rates. Rates were age-adjusted to the year 2000 US population by the direct method.

The US Drug Enforcement Administration's (DEA) Diversion Control Program tracks the distribution of all opioid analgesics through commercial channels. The Diversion Control Program requires manufacturers and distributors to report to its Automated Reports and Consolidated Orders System (ARCOS)²⁴ the number of grams of each monitored substance distributed through pharmacies, practitioners, hospitals, teaching institutions, and narcotics treatment

programs. Opioid analgesics imported illegally from abroad are difficult to quantify and are therefore not included.

We selected data on the number of kilograms distributed per 100 000 people for the eight most heavily prescribed opioid analgesics for the years 1999 and 2002 (codeine, oxycodone, hydrocodone, morphine, hydromorphone, methadone, fentanyl, and meperidine). Because opioids vary in potency, sales of individual opioids were standardized by conversion to milligrams (mg) of oral morphine with equivalent analgesic potency before being combined.²⁵ We compared changes in sales volumes for different types of opioids from 1999 to 2002 to changes in the frequency of diagnoses of those types in the mortality data. We divided the number of poisonings from different types of opioids by total sales of each type in oral morphine equivalents to compare the risk across types.

RESULTS

Between 1979 and 1990, the combined mortality rates for unintentional, suicidal, and undetermined drug poisoning increased 13.8% (Figure 1). The mortality rate for unintentional drug poisoning increased 57.9%, an increase of 5.3% per year. From 1990 to 2002, the combined mortality rates for unintentional, suicidal, and undetermined drug poisoning increased 140.8%.

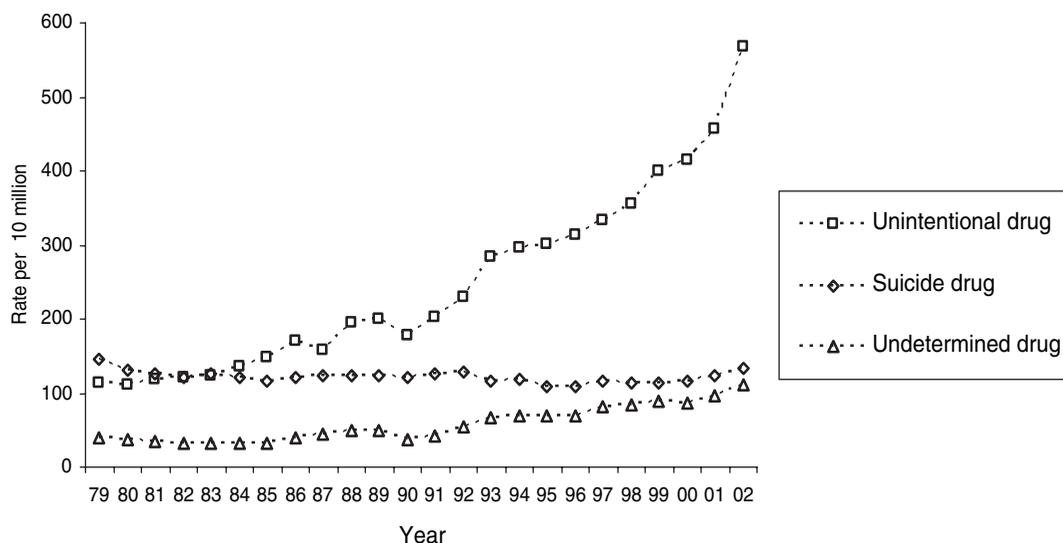


Figure 1. Drug poisoning mortality rates by manner of death, US, 1979–2002. Drug poisoning deaths are coded by ICD-9 E codes from 1979 to 1998 and by ICD-10 X and Y codes from 1999 to 2002. Codes used were: E850–858 and X40–44 for unintentional, E950.0–950.5 and X60–64 for suicide, and E980.0–980.5 and Y10–14 for undetermined poisoning

This was due to a 217.6% increase in unintentional drug poisoning mortality (18.1% per year), a 10.8% increase in suicidal drug poisoning, and a 193.4% increase in undetermined drug poisoning mortality.

Four of the five major drug categories accounted for essentially all of the increase in unintentional drug poisoning mortality from 1990 to 1998: opiates, cocaine, 'other specified,' and 'unspecified' (Figure 2). Rates in these four categories doubled or tripled from 1990 to 1998, whereas the rate for psychotropic drugs increased 29.4%. Rates for all other drug categories (not shown) declined 12.6%. By 1998, deaths from these four major drug categories accounted for 85.3% of all unintentional drug-poisoning deaths.

From 1999 to 2002, most of the continued increase in the unintentional drug-poisoning category was accounted for by the ICD-10 categories of 'narcotics and psychodysleptics' or 'other and unspecified drugs' (Figure 3). Combined, codes for these two categories accounted for 10 295 (92.3%) of all unintentional drug poisoning deaths in 1999 and 15 125 (92.2%) of all unintentional drug poisoning deaths in 2002.

MCOD data from 1999 to 2002 indicate that the number of deaths listing opioid analgesics increased 91.2%, while the number listing cocaine or heroin increased 22.8% and 12.4%, respectively (Table 1).

The most rapidly increasing category was 'opioid analgesic without heroin or cocaine,' which rose 129.2%. Deaths listing heroin without either cocaine or opioid analgesics increased only 23.7%, and deaths listing cocaine without heroin or opioid analgesics increased only 16.0%. Deaths listing other specified drugs (i.e., specific drugs other than opioid analgesics, heroin, or cocaine) increased only 7.4%.

In 1999, opioid analgesic poisoning was listed among the cause of death codes in 2891 (28.1%) deaths, fewer than cocaine and more than heroin. Opioid analgesics were listed without cocaine or heroin in 1942 (18.9%) deaths. But by 2002, opioid analgesics were listed in 5528 (36.5%) deaths, more than either cocaine or heroin. Opioids were listed without cocaine or heroin in 4451 (29.4%) deaths that year, more than the combined number of deaths listing either cocaine alone (2569) or heroin alone (1061). This increase—in 'opioids without heroin or cocaine'—accounted for half of the overall increase in the drug poisoning deaths in 1999–2002.

The highest age-specific rates (not shown) were in the 40- to 49-year age group for both decedents with 'opioid analgesic without cocaine or heroin' poisoning and decedents with heroin or cocaine poisoning without opioid analgesic poisoning. Males made up

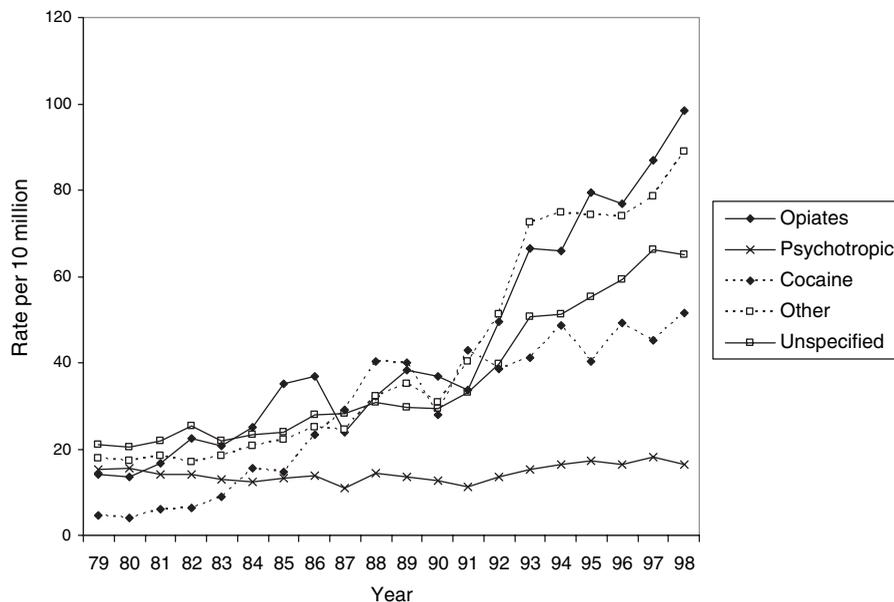


Figure 2. Unintentional drug poisoning mortality rates by drug category, US, 1979–1998. 'Opiates' are 'opiates and related narcotics' (E850.0), which contains both heroin and opioids. 'Cocaine' is 'local anesthetics' (E855.2). 'Psychotropics' is 'other sedatives and hypnotics' (E852), 'tranquilizers' (E853), and 'other psychotropic agents' (E854), which includes antidepressants, psychodysleptics, and psychostimulants. 'Other' is 'other specified drugs' (E858.8). 'Unspecified' is 'unspecified drugs' (E858.9)

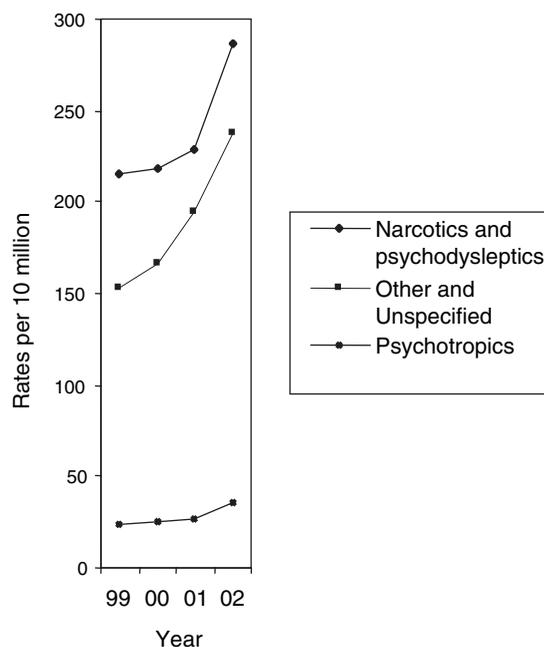


Figure 3. Unintentional drug poisoning mortality rates by drug category, US, 1999–2002. 'Narcotics and psychodysleptics' (X42) include cocaine, heroin, hallucinogens, methadone, and other opioids. 'Other and unspecified' is X44. 'Psychotropics' is X41, 'antiepileptic, sedative-hypnotic, antiparkinsonism, and psychotropic drugs, not elsewhere classified'

Table 1. Deaths from 'narcotics and psychodysleptics' and 'other and unspecified' drugs* by major type of drug poisoning, US, 1999–2002

Drug Type [†]	1999	2000	2001	2002	Percentage change (1999–2002)
Opioid analgesic					
Without heroin or cocaine	1942	2368	3149	4451	+129.2
With heroin, without cocaine	367	260	228	260	–29.2
With cocaine, without heroin	469	418	519	724	+54.4
With heroin and cocaine	113	84	86	93	–17.7
Total [‡]	2891	3130	3982	5528	+91.2
Cocaine					
Without heroin or opioid [‡]	2215	2113	2197	2569	+16.0
Total	3182	3022	3197	3909	+22.8
Heroin					
Without cocaine or opioid [‡]	858	942	928	1061	+23.7
Total	1723	1693	1637	1937	+12.4
Cocaine and heroin without opioid [‡]	385	407	395	523	+35.8
Other specified drugs [‡]	1666	1668	1636	1790	+7.4
Unspecified drugs [‡]	2255	2532	2885	3635	+61.2
No drugs listed [‡]	25	19	11	19	–24.0
Total number	10 295	10 811	12 034	15 125	+46.9

*Deaths from 'narcotics and psychodysleptics' are those coded to ICD-10 code X42. Deaths from 'other and unspecified' drugs are those coded to X44.

[†]'Opioid analgesic' is defined as T40.2 ('other opioids'), T40.3 ('methadone'), or T40.4 ('other synthetic narcotics'). 'Cocaine' is defined as T40.5. 'Heroin' is defined as T40.1. 'Other specified drugs' are all other codes from the T36–T50.8 range. 'Unspecified drugs' are defined as T50.9.

[‡]These rows are included in the column totals.

Table 2. Death certificate poisoning occurrences* and sales in kilograms by type of opioid analgesic, US, 1999 and 2002

Type of opioid analgesic	1999	2002	Percentage change
'Other opioid' type			
Number of occurrences	2520	3967	+57.4
Sales			
Codeine	23 917.1	22 633.7	-5.4
Oxycodone	9 717.6	22 376.9	+130.3
Hydrocodone	12 101.6	18 822.6	+55.5
Morphine	6 804.9	10 264.3	+50.8
Hydromorphone	292.5	473.4	+61.8
Total in morphine equivalents [†]	33 381.7	56 752.3	+70.0
Occurrences/total sales	0.08	0.07	-7.4
Methadone			
Number of occurrences	754	2361	+213.1
Sales			
Through narcotics treatment programs	3671.8	5263.4	+43.3
Through other outlets	965.0	2649.6	+174.6
Total in morphine equivalents [†]	34 775.7	59 347.2	+70.7
Occurrences/Total Sales	0.02	0.04	+83.5
'Other synthetic narcotic' type			
Number of occurrences	481	982	+104.2
Sales			
Fentanyl	107.1	242.0	+125.9
Meperidine	5539.6	5412.4	-2.3
Total in morphine equivalents [†]	8589.5	18 693.3	+117.6
Occurrences/Total Sales	0.06	0.05	-6.2
Total			
Number of occurrences	3755	7310	+94.7
Sales in morphine equivalents [†]	76 747.0	134 792.7	+75.6
Occurrences/total sales	0.05	0.05	+10.8

*Among deaths codes to 'narcotics and psychodysleptics' or 'other and unspecified' drugs.

[†]Calculation of oral morphine equivalents used the following assumptions: (1) All drugs other than fentanyl are taken orally; fentanyl is applied transdermally. (2) These doses are approximately equianalgesic: morphine: 30 mg; codeine: 200 mg; oxycodone and hydrocodone: 30 mg; hydromorphone: 7.5 mg; methadone: 4 mg; fentanyl: 0.4 mg; meperidine: 300 mg.

69.2% of the decedents in the opioid analgesic-alone group and 72.9% of the decedents in the heroin or cocaine-alone group.

There were an average of 1.3 opioid analgesic poisoning codes listed for each opioid-analgesic-related death in both 1999 and 2002. In 2002, 'other opioids' accounted for 54% of poisonings, methadone for 32%, and 'other synthetic narcotics' for 13% (Table 2). The number of poisonings in the 'other opioid' category increased 57% from 1999 to 2002, while sales increased 70%. 'Other synthetic narcotic' poisoning increased 104%, while sales increased 118%. The increase in methadone poisoning (213%) is comparable to the increase in sales of methadone through pharmacies for pain management (175%) but not to the increase in methadone distribution through narcotics treatment programs (43%).

In 2002, total opioid analgesic sales of 134 793 kg in morphine equivalents corresponded to 46.8 kg per 100 000 people or 468 mg per person. Most of the total morphine equivalents prescribed in 2002 came from

prescriptions for drugs in the 'other opioid' and methadone categories. When the number of death certificate poisoning codes was divided by total sales in morphine equivalents in each of the three opioid types in 2002, the smallest ratio was observed for methadone, with 0.04 occurrences of methadone poisoning for every kilogram sold. However, methadone was the only category for which the ratio of poisonings to sales increased from 1999 to 2002.

DISCUSSION

Unintentional drug poisoning mortality in the US rose from 1990 to 2002. Among such poisonings, the largest increase in the 1990s was in the opiate category of drugs, which included both heroin and opioid analgesics. By 1999, when different codes became available for heroin and opioid-analgesic-related

deaths, opioid analgesics already constituted a significant portion of opiate deaths. Opioid analgesics also accounted for much of the increase from 1999 to 2002 and were involved in more deaths than either heroin or cocaine by 2002. Licit drugs have therefore recently replaced illicit drugs as the most common cause of fatal drug poisoning in the US.

Numerous data sources indicate a large and growing problem with opioid analgesics in the US. The Drug Abuse Warning Network (DAWN) maintains a database of deaths reported by medical examiners in 38 metropolitan areas. It indicates that the most common drugs reported in single-drug deaths in 2002 were cocaine, heroin/morphine, and opioid analgesics.²⁶ The DAWN database of emergency department data similarly indicates that, among ED visits related to drug abuse from 1999 to 2002, visits related to heroin increased 14%, visits related to cocaine increased 18%, and visits related to opioid analgesics increased 73%. By 2002, the four leading drugs reported from DAWN EDs were cocaine, marijuana, opioid analgesics, and heroin, in that order.²⁷ Similarly, the admission rate for treatment of prescription opioid abuse in the US increased from 14 per 100 000 in 1992 to 35 per 100 000 in 2002.²⁸ Finally, data from the annual National Survey on Drug Use and Health indicate that the number of self-reported new, nonmedical users of prescription pain relievers began to increase rapidly after 1990. By 2002, an estimated 11 million people reported nonmedical use of prescription pain relievers in the past year, substantially more than the number reporting use of cocaine or heroin. Of these, 1.5 million reported heavy enough usage to meet the criteria for dependence on or abuse of pain relievers.²⁹

The patterns seen here for opioid types are also consistent with the ranking of and trends in specific opioids reported in DAWN ED visits. Among an estimated 76 971 abuse-related ED visits reported to DAWN in 2002, the leading opioid analgesics were the 'other opioids'—hydrocodone, reported in 25 297 visits, and oxycodone, reported in 22 397 visits. Methadone was reported in 11 709 visits. The synthetic opioids fentanyl and meperidine were reported in 1506 and 722 visits, respectively. All but meperidine experienced large increases in numbers of visits from 1999 to 2002.²⁷ Taken together with the results of this study, this suggests that hydrocodone, oxycodone, and methadone likely played a larger role in the increase of unintentional poisoning mortality than other synthetic opioids like fentanyl and meperidine.

The increase in drug poisoning since 1990 coincides with a dramatic increase in the prescription of major types of opioid analgesics, as physicians were encouraged to prescribe stronger analgesics (i.e., opioids) for pain management. Worldwide consumption of morphine, hydrocodone, oxycodone, fentanyl, and methadone, most of which is accounted for by the US, increased at least fourfold from 1990 to 2002.³⁰ ARCOS data for 1990–1996 show upward trends in per capita sales of fentanyl, morphine, and oxycodone and decreasing trends for meperidine.¹⁶ US prescription audits have shown two- to fivefold increases in the number of prescriptions written for hydrocodone, oxycodone, fentanyl, and morphine from 1994 to 2001.³¹ The increase in the number of prescriptions from 1999 to 2002 was reported recently for selected drugs: oxycodone prescriptions rose 50% to approximately 29 million in 2002; fentanyl prescriptions rose 150% to 4.6 million; and morphine prescriptions rose 60% to 3.8 million.³² These increases are comparable to the increases in ARCOS except for oxycodone, for which sales in kilograms rose faster than numbers of prescriptions, suggesting that the number of milligrams of oxycodone per prescription increased over that time span.

Overall, the relative increase in ARCOS opioid sales (76%) from 1999 to 2002 was consistent with the relative increase in opioid poisoning (95%). In addition, the relative increases in sales of 'other opioids' and other synthetic opioids after 1999 were comparable to the relative increase in those categories in the mortality data. The increase in methadone poisoning, however, more closely matched the increase in methadone sales through pharmacies than the increase in methadone distribution through narcotics treatment programs. Recent studies conclude that reports of increases in methadone-associated mortality are likely due to methadone distributed through pharmacies rather than through narcotics treatment programs.^{33,34} The increasing ratio of poisoning to total sales for methadone may be because pharmacy sales became a larger share of total methadone sales from 1999 to 2002.

Evidence also suggests that at least some of these deaths are related to intentional abuse of drugs—not to therapeutic dosing errors among those suffering chronic pain. First, the age and sex distributions of the decedents in this study, primarily middle-aged and male, do not match those of people who typically experience chronic pain, who are more likely to be female and older.³⁵ Instead, the demographics of these decedents match those of individuals dying from abuse of drugs such as heroin and cocaine.³⁶ Second, a

significant percentage (19.5%) of the deaths associated with opioid analgesics in this study also list illicit drugs of abuse such as heroin and cocaine. Third, medical examiners in states reporting epidemics of opioid poisoning have found that most victims of unintentional drug poisoning have a history of substance abuse and do not have a prescription for the opioid.^{3,5}

Drug users may not appreciate that prescription opioids cause dose-related respiratory depression,^{19,37–41} especially when taken in combination with alcohol or other drugs that depress respiration. The potential for overdose has increased since 1990 with the increased use of the long-acting drug methadone and controlled-release formulations of oxycodone and fentanyl. Users may accumulate toxic levels by mistakenly dosing themselves repeatedly when the desired euphoric or analgesic effect is slow in coming. In addition, abusers have learned to crush controlled-release pills and grind up patches and then inject or ingest them, thus releasing the entire dose over a short time.^{39,42,43}

In summary, this and other studies provide ecological evidence that the increased prescribing of opioid analgesics is related to the increase in US drug poisoning mortality since 1990. Alternative explanations for the poisoning increase, however, deserve consideration. One possibility is that social factors have led to a dramatic increase in drug abuse and that drug abusers would have died from heroin or cocaine overdoses if opioid analgesics had not been available. This possibility cannot be excluded, although there is no evidence in these data that current users of illicit drugs switched to opioid analgesics; poisoning deaths from both types of drugs increased. Abusers of opioid analgesics may have obtained drugs through the internet from foreign sources;⁴⁴ however, the DEA has reported that this is a relatively recent phenomenon⁴⁵ that cannot account for the mortality increase prior to 2000. It has also been suggested⁴⁶ that alcohol and drugs used in concert with opioid analgesics share the responsibility for the increased mortality. However, our study showed that many opioid analgesic deaths occurred without involvement of heroin or cocaine, and it is not clear what other types of drugs could be driving the upward trend. The only other major category of licit drugs associated with drug overdoses in DAWN data is the psychotropic agent category,²⁷ and deaths attributed to such drugs showed only a slight increase since 1990 in our study. Similarly, deaths attributed to alcohol poisoning increased only 8% from 1999 to 2002.⁴⁷

Reporting artifacts are unlikely explanations for these findings. Unintentional poisoning deaths, for example, might have increased if medical examiners began to code more suicides and deaths of undetermined intent as unintentional. This does not appear to be the case, because there were too few deaths in these other categories to have accounted for the increase in unintentional deaths. Medical examiners may have tested more aggressively for oxycodone and methadone in the wake of related publicity,^{48–50} but this could not have accounted for the doubling of synthetic opioid poisoning, about which there has been relatively little publicity for over a decade. This study cannot exclude the possibility that medical examiners and coroners have begun to report poisoning at lower blood levels than previously so that opioid analgesics that were once incidental findings in deaths due to illicit drugs are now listed as contributing causes of death. However, there was no increase in heroin deaths also listing opioid analgesics or in heroin and cocaine deaths also listing opioid analgesics. In addition, the number of opioid analgesics per death did not increase from 1999 to 2002. Finally, there was no change in how poisoning deaths were coded between 1999 and 2002. There was a small change in how deaths were assigned to unintentional poisoning with the introduction of ICD-10 in 1999. As a result, deaths were 3.6% more likely to be coded as unintentional poisoning in ICD-10 than in ICD-9.⁵¹ Accounting for this difference would have an almost imperceptible effect on the trends shown here.

This study depends on the accuracy of vital statistics information. Previous studies have found that, while vital records undercount poisoning deaths when compared with medical examiner data,^{4,52} they have few false positives⁴ and show the same trends as medical examiner data.⁵² Even if some death certificates incorrectly identified deaths as due to opioids, the frequency of such errors would have increased dramatically to have accounted for the rate increase.

This study probably underestimates rather than overestimates the problem of fatal drug poisonings related to opioid analgesics. First, this study did not examine the classes of drugs involved in suicides or deaths of undetermined intent because ICD-9 lacked detail in the coding of such deaths. A cursory examination of the MCODE file for 1999–2002, however, indicated that opioid analgesic poisoning was often identified in both types of death. Second, the study does not include deaths coded to mental and behavioral problems; such deaths are not classified as

KEY POINTS

- Unintentional poisoning mortality in the US from drugs (both licit and illicit) more than tripled from 1990 to 2002 with 43% of the increase occurring between 1999 and 2002.
- Between 1999 and 2002, opioid analgesic poisoning surpassed cocaine and heroin poisoning as the most frequent type of drug poisoning found on death certificates.
- Among opioid analgesic poisonings, 54% were from semi-synthetic opioids, for example, oxycodone and hydrocodone; 32% were from methadone; and 13% were from other synthetic opioids, for example, fentanyl.
- The rate of increase in sales generally matched the rate of increase in death certificate occurrences for each type of opioid analgesic.
- Increasing medical use of opioid analgesics may have inadvertently contributed to an ongoing poisoning epidemic in the US.

poisonings, even though the cause of death in many cases is a drug overdose.^{1,4} Third, the study does not include poisoning deaths attributed to nonopioids even though opioid analgesics were involved in some cases. Fourth, the study misses any deaths involving opioid analgesics that were coded as 'unspecified narcotic' poisoning.

CONCLUSIONS

Although the information in this study about poisoning mortality trends was not available at the time, the Food and Drug Administration (FDA) issued a new prescription drug safety plan targeted at opioids in March, 2004.⁵³ The FDA's plan concentrated on ensuring that opioid analgesics were clearly labeled to communicate the conditions for safe and effective use. The plan also emphasized the importance of better education of health care providers. However, given the severity of the problem revealed in mortality statistics, the sizeable increases in opioid sales in both 2003 and 2004,²⁴ and anecdotal evidence from 2005 that the problem of nonmedical use of opioids is worsening,⁵⁴ additional corrective actions may be necessary. The overall goal should be to identify ways to reduce deaths from opioid analgesics without diminishing the quality of care for patients with a legitimate need for pain management.

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REFERENCES

1. Fingerhut LA, Cox CS. Poisoning mortality, 1985–1995. *Pub Health Rep* 1998; **113**: 218–233.
2. Centers for Disease Control and Prevention. Unintentional and undetermined poisoning deaths—11 states, 1990–2001. *MMWR* 2004; **53**: 233–238.
3. Sanford C. Deaths from unintentional drug overdoses in North Carolina, 1997–2001: A DHHS investigation into unintentional poisoning-related deaths. Available at: <http://www.dhhs.state.nc.us> [Accessed 6 July, 2004].
4. Landen MG, Castle S, Nolte KB, et al. Methodological issues in the surveillance of poisoning, illicit drug overdose, and heroin overdose deaths in New Mexico. *Am J Epidemiol.* 2003; **157**: 273–278.
5. Sorg MH, Greenwald M. Maine drug-related mortality patterns: 1997–2002. Available at: <http://www.state.me.us/ag/pr/drugreport.pdf> [Accessed 13 August, 2004].
6. Centers for Disease Control and Prevention. Unintentional opiate overdose deaths—King County, Washington, 1990–1999. *MMWR* 2000; **49**: 636–640.
7. Centers for Disease Control and Prevention. Increase in poisoning deaths caused by non-illicit drugs—Utah, 1991–2003. *MMWR* 2005; **54**: 33–36.
8. Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: Report of 38 cases. *Pain* 1986; **25**: 171–186.
9. Friedman DP. Perspectives on the medical use of drugs of abuse. *J Pain Symp Manage* 1990; **5**: S2–S5.
10. Melzack R. The tragedy of needless pain. *Sci Amer* 1990; **262**: 27–33.
11. Hill CS. Influence of regulatory agencies on the treatment of pain and standards of medical practice for the use of narcotics. *Pain Digest.* 1991; **1**: 7–12.
12. Lamberg L. New guidelines for managing chronic pain in older persons. *JAMA* 1998; **280**: 311–312.
13. American Academy of Pain Medicine and American Pain Society. The use of opioids for the treatment of chronic pain: a consensus statement from the American Academy of Pain Medicine and the American Pain Society. *Clin J Pain* 1997; **13**: 6–8.
14. American Society of Anesthesiologists. Practice guidelines for chronic pain management: a report of the American Society of Anesthesiologists Task Force on Pain Management, Chronic Pain Section. *Anesthesiol* 1997; **86**: 995–1004.
15. Institute of Medicine. Approaching death: Improving care at the end of life—a report of the Institute of Medicine. *Health Serv Res* 1998; **33**: 1–3.
16. Joranson DE, Ryan KM, Gilson AM, Dahl JL. Trends in medical use and abuse of opioid analgesics. *JAMA* 2000; **283**: 1710–1714.
17. Novak S, Nemeth WC, Lawson KA. Trends in medical use and abuse of sustained-release opioid analgesics: a revisit. *Pain Med* 2004; **5**: 59–65.
18. Gilson AM, Ryan KM, Joranson DE, Dahl JL. A reassessment of trends in the medical use and abuse of opioid analgesics and implications for diversion control: 1997–2002. *J Pain Symp Manage* 2004; **28**: 176–188.

19. Schumacher MA, Basbaum AI, Way WL: Opioid analgesics and antagonists. In *Basic and Clinical Pharmacology*, Katzung BE (ed.). Lange Medical Books: New York, NY, 2004: 497–516.
20. Stephens B, Jentzen J, Karch S, Wetli C, Mash D. National Association of Medical Examiners Position Paper on the certification of cocaine-related deaths. *Am J Foren Med Pathol* 2004; **25**: 11–13.
21. World Health Organization (WHO). *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death, 9th Revision*. World Health Organization: Geneva, Switzerland, 1977.
22. World Health Organization (WHO). *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*. WHO: Geneva, Switzerland, 1992.
23. Centers for Disease Control and Prevention. *Public Use Data File Documentation: Multiple Cause of Death for ICD-10 2002 Data*. National Center for Health Statistics: Hyattsville, MD, 2004.
24. US Department of Justice (USDOJ), Drug Enforcement Administration. ARCOS: Automation of Reports and Consolidated Orders System. Available at: <http://www.deadiversion.usdoj.gov/arcos/index.html> [Accessed 27 March, 2005].
25. Gammaitoni AR, Fine P, Alvarez N, McPherson M, Bergmark S. Clinical application of opioid equianalgesic data. *Clin J Pain*. 2003; **19**: 286–297.
26. US Department of Health and Human Services (USDHHS), Substance Abuse and Mental Health Services Administration, Office of Applied Studies, and Drug Abuse Warning Network. Mortality data from the Drug Abuse Warning Network, 2002. Available at: http://DAWNinfo.samhsa.gov/old_dawn/pubs_94_02/mepubs/default.asp [Accessed 16 December, 2004].
27. US Department of Health and Human Services (USDHHS), Substance Abuse and Mental Health Services Administration, Office of Applied Studies, and Drug Abuse Warning Network. The DAWN Report—trends in drug-related emergency department visits, 1994–2002 at a glance. Available at: http://dawninfo.samhsa.gov/old_dawn/pubs_94_02/shortreports/files/DAWN_EDvisits_glance.pdf [Accessed 17 December, 2004].
28. US Department of Health and Human Services (USDHHS) Substance Abuse and Mental Health Services Administration Office of Applied Studies Drug and Alcohol Services Information System. The DASIS Report—treatment admissions in urban and rural areas involving abuse of narcotic painkillers: 2002 update. Available at: www.oas.samhsa.gov/2k4/ruralPainTX/ruralPainTX.pdf [Accessed 17 December, 2004].
29. US Department of Health and Human Services (USDHHS) Substance Abuse and Mental Health Services Administration Office of Applied Studies. Results from the 2002 National Survey on Drug Use and Health: national findings. Available at: www.oas.samhsa.gov/nhsda/2k2nsduh/Results/2k2Results.htm [Accessed 17 December, 2004].
30. International Narcotics Control Board. *Narcotic drugs, estimated world requirements for 2005—statistics for 2003*. United Nations: New York, NY, 2004. Report No. E/F/S.05.XI.7.
31. Zaczyn J, Bigelow G, Compton P, Foley K, Iguchi M, Sannerud C. College on Problems of Drug Dependence taskforce on prescription opioid non-medical use and abuse: position statement. *Drug Alc Depend* 2003; **69**: 215–232.
32. Compton WM, Volkow ND. Major increases in opioid analgesic abuse in the United States: concerns and strategies. *Drug Alc Depend* 2006; **81**: 103–107.
33. Ballesteros MF, Budnitz DS, Sanford CP, Gilchrist J, Agyekum GA, Butts J. Increase in deaths due to methadone in North Carolina. *JAMA*. 2003; **290**: 40.
34. Center for Substance Abuse Treatment. *Methadone-associated mortality: Report of a national assessment*. Rockville, MD: substance abuse and mental health services administration; 2003. Report No. 04-3904.
35. Elliott AM, Smith KI, Penny KI, Smith WC, Chambers WA. The epidemiology of chronic pain in the community. *Lancet*. 1999; **354**: 1248–1252.
36. Kallan JE. Drug abuse-related mortality in the United States: patterns and correlates. *Am J Drug Alc Abuse* 1998; **24**: 103–117.
37. Yeadon M, Kitchen I. Opioids and respiration. *Prog Neurobiol* 1989; **33**: 1–16.
38. Wolff K. Characterization of methadone overdose: clinical considerations and the scientific evidence. *Ther Drug Monit* 2002; **24**: 457–470.
39. Kuhlman JJ, McCaulley R, Valouch TJ, Behonick GS. Fentanyl use, misuse, and abuse: A summary of 23 postmortem cases. *J Anal Toxicol* 2003; **27**: 499–504.
40. Saarialho-Kere U, Mattila MJ, Seppala T. Psychomotor, respiratory, and neuroendocrinological effects of a mu-opioid receptor agonist (oxycodone) in healthy volunteers. *Pharm Toxicol* 1989; **65**: 252–257.
41. Oikkala KT, Hamenen K, Seppala T, Maunukela EL. Pharmacokinetics and ventilatory effects of intravenous oxycodone in postoperative children. *Br J Clin Pharmacol* 1994; **38**: 71–76.
42. Sajjan A, Corneil T, Grzybowski S. The street value of prescription drugs. *Can Med Assoc J* 1998; **159**: 139–142.
43. US Department of Justice (USDOJ), Drug Enforcement Administration. Drug intelligence brief—OxyContin: pharmaceutical diversion. Available at: <http://www.usdoj.gov/dea/pubs/intel/02017/02017.html> [Accessed 17 December, 2004].
44. Forman RF. Availability of opioids on the internet. *JAMA* 2003; **290**: 889.
45. Harris G. Two agencies to fight online narcotics sales. *New York Times* October 18, 2003: 1.
46. Cone EJ, Fant RV, Rohay JM, et al. Oxycodone involvement in drug abuse deaths. A DAWN-based classification scheme applied to an oxycodone postmortem database containing over 1,000 cases. *J Anal Toxicol* 2003; **27**: 57–67.
47. Centers for Disease Control and Prevention. Web-based Injury Statistics Query and Reporting System (WISQARS) [Online]. (2003) National Center for Injury Prevention and Control, Centers for Disease Control and Prevention (producer). Available at: www.cdc.gov/ncipc/wisqars [Accessed 22 March, 2005].
48. Roche T. The potent perils of a new drug. *Time Magazine* January 8, 2001: 47.
49. Clines F, Meier B. Cancer painkillers pose new abuse threat. *The New York Times*. February 9, 2001: A1.
50. White J. Virginia police fear rise of new drug. *The Washington Post*. February 10, 2001: B2.
51. Anderson R, Minino A, Fingerhut L, Warner M, Heinen M. Deaths: injuries, 2001. *National vital statistics reports* 2004; **52**: 1–88.
52. Pollock DA, Holmgren P, Lui K, Kirk ML. Discrepancies in the reported frequency of cocaine-related deaths, United States, 1983 through 1988. *JAMA* 1991; **266**: 2233–2237.
53. Food and Drug Administration (FDA). Drugs@FDA. Available at: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/> [Accessed 29 April, 2004].
54. Bowman R. Prescription for crime. *Time Magazine* March 28, 2005: 50–51.