

Drugs Most Frequently Involved in Drug Overdose Deaths: United States, 2010–2014

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Abstract

Objectives—This report identifies the specific drugs most frequently involved in drug overdose deaths in the United States from 2010 through 2014.

Methods—The 2010–2014 National Vital Statistics System mortality files were linked to electronic files containing literal text information from death certificates. Drug overdose was defined using the *International Classification of Diseases, Tenth Revision* underlying cause-of-death codes X40–X44 (unintentional), X60–X64 (suicide), X85 (homicide), and Y10–Y14 (undetermined intent). Among deaths with an underlying cause of death of drug overdose, the literal text in three fields of the death certificate (i.e., the cause of death from Part I, significant conditions contributing to death from Part II, and a description of how the injury occurred from Box 43) were searched to identify drug mentions. Search term lists were developed using existing drug classification systems as well as from manual review of the literal text. The search term list was then used to identify the specific drugs involved in overdose deaths. Descriptive statistics were reported for drug overdose deaths involving the 10 most frequently mentioned drugs on death certificates. Tables and figures presenting information on the specific drugs involved in deaths are based on deaths with mention of at least one specific drug on the death certificate.

Results—From 2010 through 2014, the number of drug overdose deaths per year increased 23%, from 38,329 in 2010 to 47,055 in 2014. During this time period, the percentage of drug overdose deaths involving at least one specific drug increased, from 67% in 2010 to 78% in 2014. Among drug overdose deaths with at least one drug specified on the death certificate, the 10 drugs most frequently involved in overdose deaths included the following opioids: heroin, oxycodone, methadone, morphine, hydrocodone, and fentanyl; the following benzodiazepines: alprazolam and diazepam; and the following stimulants: cocaine and methamphetamine. During this 5-year period, the age-adjusted

rate of drug overdose deaths involving heroin more than tripled, and the rate of drug overdose deaths involving methamphetamine more than doubled. The rate of drug overdose deaths involving fentanyl more than doubled in a single year (from 2013 to 2014). In 2014, of the 36,667 drug overdose deaths involving at least one specific drug, 52% of these deaths specified one drug, 38% specified two or three drugs, and 11% specified four or more drugs.

Conclusions—Analysis of the literal text from death certificates can be used to identify patterns in the specific drugs most frequently involved in drug overdose deaths. From 2010 through 2014, the top 10 drugs involved were the same, but the relative ranking and age-adjusted rates for deaths involving these drugs changed. Literal text analysis also revealed that many drug overdose deaths involved multiple drugs. Findings should be interpreted in light of the improvement in the quality of the data that resulted from better reporting of specific drugs on death certificates from 2010 through 2014. Relative increases in the death rates involving specific drugs and the rankings of these drugs may be affected by improvements in reporting, real increases in the numbers of death, or both.

Keywords: opioid • benzodiazepine • stimulant • death certificate • National Vital Statistics System

Introduction

From 1999 through 2014, the age-adjusted rate for drug overdose deaths more than doubled, from 6.1 per 100,000 population in 1999 to 14.7 in 2014 (1). Multiple studies using National Vital Statistics System mortality data (NVSS–M) have helped inform the nation about this growing public health concern (1–4).

The *International Classification of Diseases, Tenth Revision* (ICD–10), which is the classification system currently used to categorize the underlying and multiple causes of death, is limited

in its ability to classify the specific drugs. In ICD–10, drugs are often grouped into broad categories, making it difficult to identify deaths involving a specific drug. For example, oxycodone and morphine are both classified in the same category of Natural and semisynthetic opioid analgesics (ICD–10 code T40.2) (5).

To better understand the contribution of specific drugs to drug overdose deaths, researchers have turned to the literal text on death certificates (6,7). The literal text is the written information provided by the medical certifier, usually a medical examiner or coroner in the case of drug overdose deaths (8,9), that describes the cause of death as well as other factors or circumstances that contributed to the death. The literal text has been used in other studies to investigate sudden unexplained infant deaths, cancer, and influenza (10–13).

The National Center for Health Statistics (NCHS) and the U.S. Food and Drug Administration (FDA) collaboratively developed a method to analyze the death certificate literal text to identify specific drugs involved in deaths. Details of this method are described elsewhere (14). In this report, the method was applied to provide a more in-depth understanding of the national picture of the drugs involved in drug overdose deaths.

This report highlights the findings for the specific drugs most frequently mentioned as being involved in drug overdose deaths from 2010 through 2014.

Methods

Data source and study population

This descriptive analysis was conducted using data from NVSS–M from 2010 through 2014. NVSS–M contains cause of death, demographic, and geographic information extracted from death certificates (15). The study population was limited to U.S. residents with an underlying cause of death of drug overdose (ICD–10 codes X40–X44, X60–X64, X85, and Y10–Y14). Drug overdose deaths included all intents (i.e., unintentional, suicide, homicide, and undetermined), as there is variation in the intent reported across states (16). This code set limits the deaths to acute intoxication from drugs (i.e., drug overdose) as opposed to chronic exposure leading to death (e.g., liver toxicity) or adverse effects experienced from therapeutic or prophylactic dosages of drugs. Use of this code set is consistent with other NCHS and Centers for Disease Control and Prevention publications on drug overdose deaths and facilitates comparability with other analyses using the ICD–10-coded data (1–4).

NVSS–M files were linked to electronic files containing literal text data that were also extracted from death certificates (15). Drug mentions (described below) were identified using the literal text data from three fields of the death certificate: (1) the cause of death from Part I, (2) significant conditions contributing to death from Part II, and (3) a description of how the injury occurred from Box 43 (17). For some deaths, the literal text was uninformative, because (1) the fields only contained information about the status of the investigation (e.g., mentions of “PENDING” or “UNDER INVESTIGATION”) or (2) the literal text was not available (i.e., no text in the three literal text fields) (14).

Identifying drugs involved

For this report, drugs of interest included pharmaceutical and nonpharmaceutical drugs, including specific drugs, classes of drugs, and nonspecific references to exposures to drugs (e.g., words such as “DRUG,” “MULTIDRUG,” and “POLYPHARMACY”). Substances that were excluded from consideration as a drug included alcohols (e.g., ethanol and isopropyl alcohol), nicotine, food and food additives (e.g., starch), excipients, gases (e.g., helium and carbon monoxide), airborne contaminants (e.g., soot), industrial chemicals (e.g., ethylene glycol), periodic table elements (e.g., lithium and iodine), and substances with no known industrial, pharmaceutical, or abuse application. Mention of alcohol was noted only when the death also included mention of a drug on the death certificate.

The method used to characterize the drugs involved in deaths using the literal text was recently developed and is described in a separate companion report (14). This method searches the literal text fields for mentions of drugs as well as for terms that provide context about drug involvement. Software programs (referred to as the Drug Mentioned with Involvement [DMI] programs) were developed using SAS Version 9.3 to automate the process (18).

The DMI programs automate the identification of mentions of drugs within the literal text using various search terms. Search terms included generic drug names or other variants (e.g., brand names, common usage or street names, abbreviations, metabolites, misspellings, and variants not otherwise specified [NOS]). Search terms were categorized by whether they referred to specific drugs (e.g., methadone), classes of drugs (e.g., opioids), or exposures NOS (e.g., pharmaceutical). Each search term was mapped to a principal variant, usually the generic drug name, thus enabling aggregate counts for all search terms that referred to the same drug.

The DMI programs also identified combinations of words adjacent to each search term to provide context, and for the purposes of this study, to identify instances when the drug was not involved in the death. For example, the phrase “METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS INFECTION” does not suggest drug involvement in mortality, but rather a type of bacterial infection. Similarly, the phrase “NOT DRUG RELATED” clearly indicates that the death did not involve drugs, even though “DRUG” is mentioned in the phrase. Unless the contextual information indicated otherwise, drugs mentioned in the literal text were assumed to be involved in the death.

The DMI programs enabled the identification of concomitant drug mentions (i.e., mentions of multiple drugs involved in the death) as well as the identification of concomitant mentions of drugs and alcohol within the literal text.

Analysis

Results were reported as numbers, percentages, or rates for each drug of interest, referred to as the referent drug. Age-adjusted death rates were calculated using the direct method and the 2000 standard U.S. population (15). Trends in death rates and number of deaths were evaluated using the JoinPoint Regression Program (19). Any mention of an average percent change (APC) in this report indicates a statistically significant

trend. Comparisons of rates between years were tested for statistical significance using methods described elsewhere (15). A statement that a given death rate is higher or lower than another rate indicates that the change in rates was statistically significant at an alpha level of 0.05.

Analyses of other drugs involved in death along with the referent drug, referred to as concomitant drugs, were also conducted. Only deaths with at least two specific drugs (i.e., the referent drug and at least one concomitant drug) involved in death were included in these analyses. For deaths with two or more specific drugs involved in death, the average number of drugs other than the referent drug was calculated.

Results

From 2010 through 2014, the number of drug overdose deaths per year increased 23%, from 38,329 in 2010 to 47,055 in 2014 (Table A). During this same time period, the specificity of drug information in the literal text fields of the death certificate improved. There was a steady increase in the percentage of drug overdose deaths involving at least one specific drug, from 67% in 2010 to 78% in 2014. There was a decline in the percentage of deaths involving only a drug class (e.g., "OPIOID") but not a specific drug (from 4% of drug overdose deaths in 2010 to 3% in 2014). A review of the literal text for these deaths indicated that the mentioned class was either an opioid or opiate (ranging from 69% in 2014 to 74% in 2011). There were also steady declines in the percentage of deaths without mention of a specific drug or drug class, from 29% of drug overdose deaths in 2010 to 19% in 2014. These deaths frequently involved multiple drugs (e.g., mentions of "POLYPHARMACY," "MULTIDRUG," and "DRUGS"), ranging from 40% in 2010 to 51% in 2014.

Drug overdose deaths with mention of at least one specific drug

Tables B–E and Figures 1–5 present information on the specific drugs involved in the deaths where at least one specific drug was mentioned on the death certificate (Tables 1–5). The drug overdose death rate involving any particular drug in any particular year should be considered the minimum rate, as there may be additional deaths in which the drug was involved but not specified in the literal text. Moreover, these results should be interpreted in light of the improved reporting of specific drugs in the literal text. For instance, the relative increase in the deaths involving a specific drug over time could reflect either improvements in reporting of that specific drug, an increase in drug overdose deaths involving that drug, or both. In addition, the rankings of the drugs might also be impacted if the reported drugs are distributed in a different way than unreported drugs.

Table B shows the ranking of the top 10 drugs involved in drug overdose deaths for each year from 2010 through 2014. These top 10 drugs belong to three drug classes: opioids (heroin, oxycodone, methadone, morphine, hydrocodone, and fentanyl), benzodiazepines (alprazolam and diazepam), and stimulants (cocaine and methamphetamine). While the ranking changed from year to year, the top 10 drugs involved in drug overdose deaths remained consistent throughout the 5-year period.

- Oxycodone ranked first in 2010 and 2011 among drug overdose deaths. Heroin ranked first from 2012 through 2014.
- The number of drug overdose deaths that involved heroin more than tripled, from 3,020 deaths, or 8% of all drug overdose deaths in 2010, to 10,863 deaths, or 23% of all drug overdose deaths in 2014.
- Each year, cocaine ranked second or third among drugs involved in drug overdose deaths.
- From 2010 through 2012, fentanyl was involved in approximately 1,600 drug overdose deaths each year. Fentanyl involvement increased to 1,905 deaths in 2013 and to 4,200 deaths in 2014.
- The number of drug overdose deaths that involved methadone decreased, from 4,408 in 2010 to 3,495 in 2014.
- The number of drug overdose deaths that involved methamphetamine increased, from 1,388 in 2010 to 3,728 in 2014.

Figures 1–3 and Tables 1–3 show the trends from 2010 through 2014 in the age-adjusted rates of drug overdose deaths involving the top 10 mentioned drugs on death certificates. The improvements in reporting should be considered when interpreting these trends.

- From 2010 through 2014, the age-adjusted rate of all drug overdose deaths—whether or not a specific drug was involved—increased, from 12.3 to 14.7 per 100,000 population with an estimated APC of 4.1%.
- Among deaths with at least one drug specified on the death certificate, there was also an increase in the age-adjusted mortality rate, from 8.2 per 100,000 population in 2010 to 11.5 per 100,000 in 2014 (APC = 7.9%).
- From 2010 through 2014, the age-adjusted rate of drug overdose deaths involving heroin more than tripled, from 1.0 per 100,000 population to 3.5 per 100,000 (APC = 36.3%) (Figure 1, Table 1).
- The age-adjusted rate of drug overdose deaths involving morphine also increased, from 0.9 per 100,000 population in 2010 to 1.2 per 100,000 in 2014 (APC = 7.9%) (Figure 1, Table 1).
- The age-adjusted rate of drug overdose deaths involving methadone decreased, from 1.5 per 100,000 population in 2011 to 1.1 per 100,000 in 2014 (APC = -6.8%) (Figure 1, Table 1).
- From 2013 through 2014, the age-adjusted rate of drug overdose deaths involving fentanyl increased, from 0.6 per 100,000 population to 1.3 per 100,000 in a single year (Figure 1, Table 1).
- From 2010 through 2014, the age-adjusted rate of drug overdose deaths involving cocaine steadily increased, from 1.4 per 100,000 population to 1.8 per 100,000 (APC = 5.8%) (Figure 3, Table 3).
- The age-adjusted rate of drug overdose deaths involving methamphetamine more than doubled, from 0.5 per 100,000 population in 2010 to 1.2 per 100,000 in 2014 (APC = 25.4 %) (Figure 3, Table 3).

Table A. Number and percentage of drug overdose deaths with mention of a specific drug, with mention of only a drug class, and with no mention of a drug class or specific drug: United States, 2010–2014

	2010		2011		2012		2013		2014		2010–2014	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
All drug overdose deaths	38,329	100.0	41,340	100.0	41,502	100.0	43,982	100.0	47,055	100.0	212,208	100.0
Drug overdose deaths with mention of at least one specific drug	25,651	66.9	29,049	70.3	29,875	72.0	32,502	73.9	36,667	77.9	153,744	72.4
Drug overdose deaths with mention of only a drug class	1,612	4.2	1,902	4.6	1,900	4.6	1,703	3.9	1,448	3.1	8,565	4.0
Drug overdose deaths without mention of a drug class or specific drug ¹	11,066	28.9	10,389	25.1	9,727	23.4	9,777	22.2	8,940	19.0	49,899	23.5

¹Category includes drug overdose deaths with mentions of drug exposures not otherwise specified (e.g., mention of “POLYPHARMACY” or “DRUG”), uninformative text, and drug overdose deaths with no drug mentions identified (e.g., text stating “OVERDOSE” with no mention of a drug).

NOTES: Drug overdose deaths are identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Numbers may not add to 100 due to rounding.

SOURCE: NCHS, National Vital Statistics System, Mortality files linked with death certificate literal text.

Table B. Top 10 drugs involved in drug overdose deaths: United States, 2010–2014

Rank ¹	2010			2011			2012			2013			2014		
	Referent drug	Number of deaths	Percent	Referent drug	Number of deaths	Percent	Referent drug	Number of deaths	Percent	Referent drug	Number of deaths	Percent	Referent drug	Number of deaths	Percent
	<i>(n = 38,329)</i>			<i>(n = 41,340)</i>			<i>(n = 41,502)</i>			<i>(n = 43,982)</i>			<i>(n = 47,055)</i>		
1	Oxycodone	5,256	13.7	Oxycodone	5,574	13.5	Heroin	6,151	14.8	Heroin	8,412	19.1	Heroin	10,863	23.1
2	Methadone	4,408	11.5	Cocaine	5,035	12.2	Oxycodone	5,169	12.5	Cocaine	5,289	12.0	Cocaine	5,856	12.4
3	Cocaine	4,312	11.2	Heroin	4,563	11.0	Cocaine	4,759	11.5	Oxycodone	4,954	11.3	Oxycodone	5,417	11.5
4	Alprazolam	3,677	9.6	Methadone	4,540	11.0	Methadone	4,081	9.8	Morphine	3,771	8.6	Alprazolam	4,217	9.0
5	Heroin	3,020	7.9	Alprazolam	4,043	9.8	Alprazolam	3,785	9.1	Alprazolam	3,696	8.4	Fentanyl	4,200	8.9
6	Morphine	2,941	7.7	Morphine	3,290	8.0	Morphine	3,508	8.5	Methadone	3,693	8.4	Morphine	4,022	8.5
7	Hydrocodone	2,844	7.4	Hydrocodone	3,196	7.7	Hydrocodone	3,023	7.3	Methamphetamine	3,185	7.2	Methamphetamine	3,728	7.9
8	Fentanyl	1,645	4.3	Methamphetamine	1,884	4.6	Methamphetamine	2,262	5.5	Hydrocodone	3,105	7.1	Methadone	3,495	7.4
9	Diazepam	1,448	3.8	Diazepam	1,695	4.1	Fentanyl	1,605	3.9	Fentanyl	1,905	4.3	Hydrocodone	3,274	7.0
10	Methamphetamine	1,388	3.6	Fentanyl	1,656	4.0	Diazepam	1,567	3.8	Diazepam	1,601	3.6	Diazepam	1,729	3.7

¹Ranks were not tested for statistical significance.

NOTES: Drug overdose deaths are identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Deaths may involve other drugs in addition to the referent drug (i.e., the one listed). Deaths involving more than one drug (e.g., a death involving both heroin and cocaine) are counted in both totals. Caution should be used when comparing numbers across years. The reporting of at least one specific drug in the literal text improved, from 67% of drug overdose deaths in 2010 to 78% of drug overdose deaths in 2014.

SOURCE: NCHS, National Vital Statistics System, Mortality files linked with death certificate literal text.

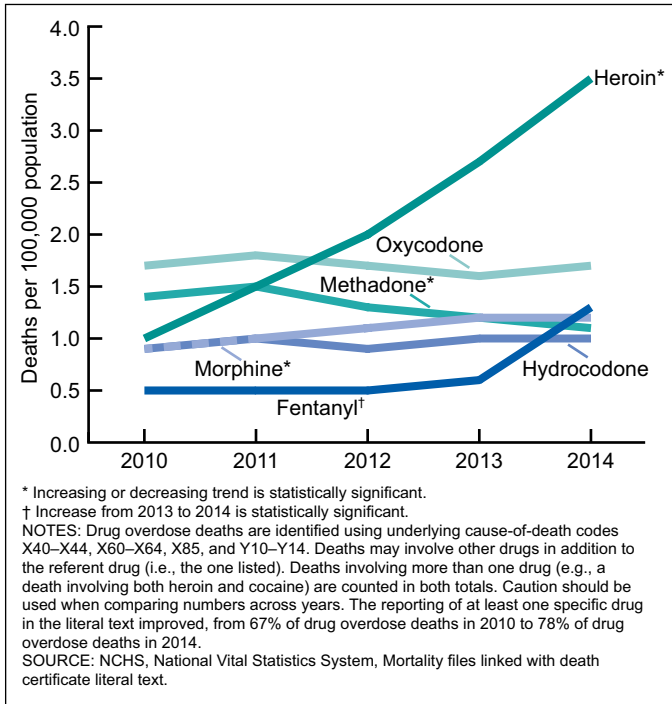


Figure 1. Age-adjusted rates for drug overdose deaths involving selected opioids: United States, 2010–2014

Drug overdose deaths involving multiple drugs

Figure 4 shows the number of drug overdose deaths in 2014 by the number of specific drugs involved in the death (Table 4). Of the 36,667 drug overdose deaths with at least one mention of a specific drug, 52% mentioned only one specific drug (18,931 deaths), 26% mentioned two (9,351 deaths), 12% mentioned three (4,521 deaths), 6% mentioned four (2,041 deaths), and 5% mentioned five or more (1,823 deaths). Among drug overdose deaths with at least one mention of a specific drug, the average number of specific drugs mentioned was 1.9.

Table C shows the percentage of drug overdose deaths with concomitant drugs for drug overdose deaths involving the top 10 drugs in 2014. The percentage of deaths involving concomitant drugs varied by referent drug. For example, the majority of the drug overdose deaths involving methamphetamine did not involve other drugs. In contrast, among deaths involving alprazolam and diazepam, more than 95% involved other drugs. The average number of concomitant drugs involved (excluding the referent drug) also varied among the top 10 drugs involved in drug overdose deaths. For example, drug overdose deaths involving diazepam or alprazolam had on average more than two additional drugs involved in death. Drug overdose deaths involving fentanyl, heroin, cocaine, or methamphetamine had on average fewer than two additional drugs involved in death.

Figure 5 shows the percent distribution of the number of concomitant drugs for overdose deaths involving the top 10 drugs in 2014 (Table 5). For example, for drug overdose deaths involving methamphetamine, 55% had no concomitant mentions, 25% mentioned one other drug, 18% mentioned two to four other drugs, and 1% mentioned five or more drugs. In contrast, for drug overdose deaths involving diazepam, 3% had

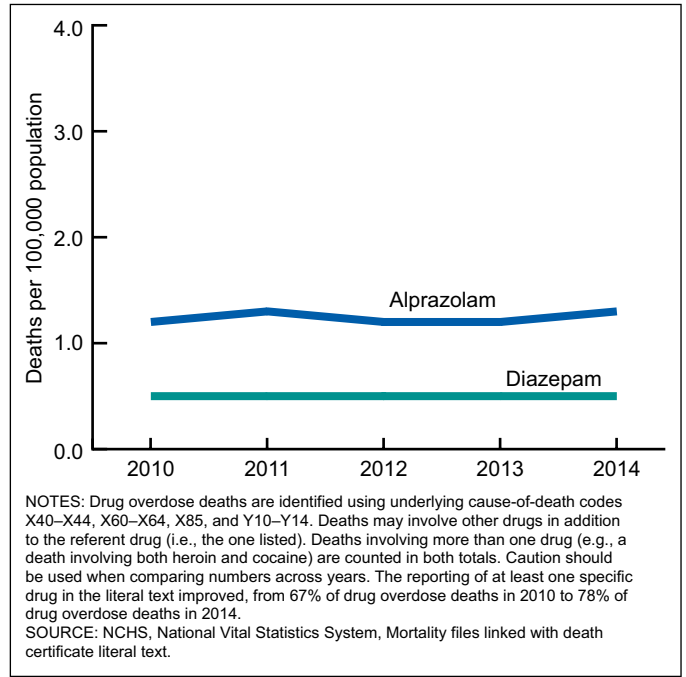


Figure 2. Age-adjusted rates for drug overdose deaths involving selected benzodiazepines: United States, 2010–2014

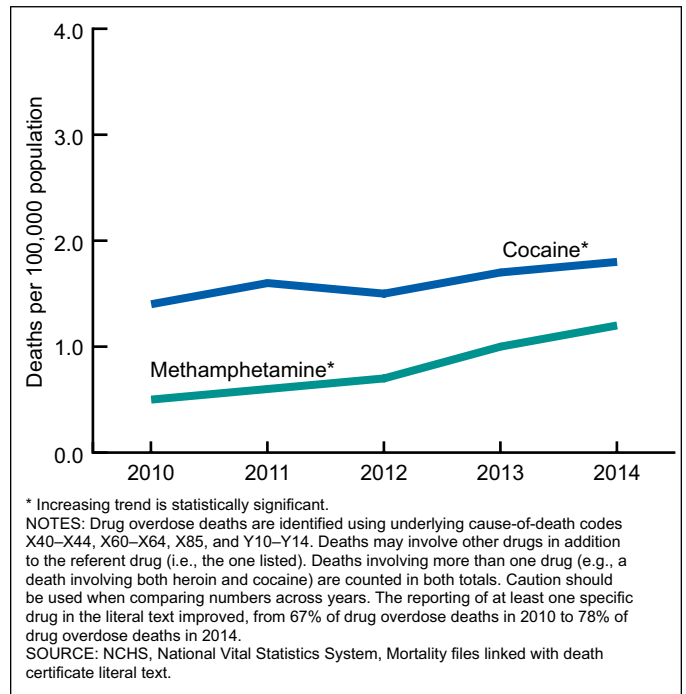


Figure 3. Age-adjusted rates for drug overdose deaths involving selected stimulants: United States, 2010–2014

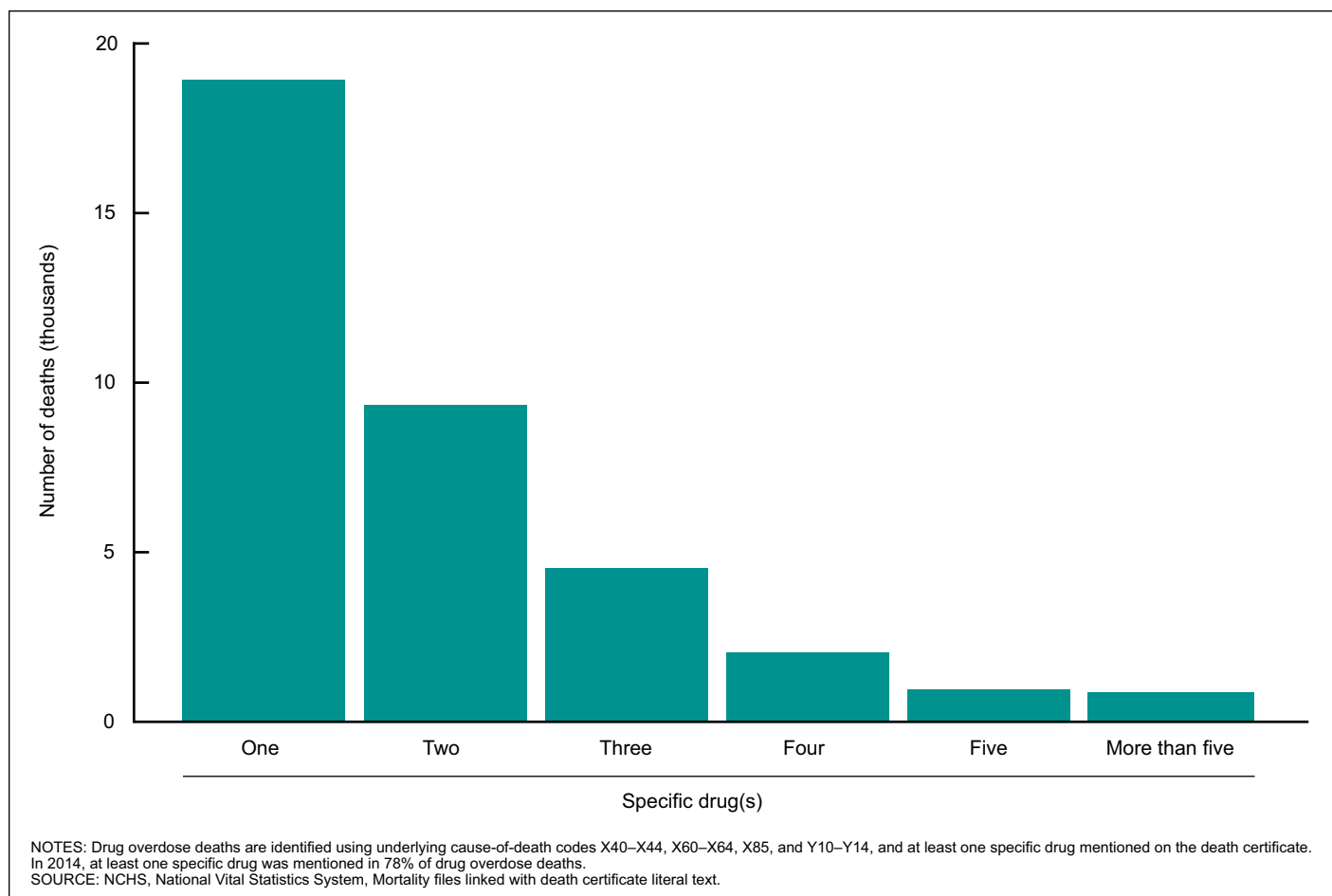


Figure 4. Number of drug overdose deaths, by the number of specific drugs involved: United States, 2014

no concomitant mentions, 22% mentioned one other drug, 62% mentioned two to four other drugs, and 13% mentioned five or more other drugs.

Table D shows the most frequent concomitant drugs for each of the top 10 drugs involved in drug overdose deaths in 2014.

- One in five drug overdose deaths involving heroin also involved cocaine.
- Alprazolam was involved in 26% of the drug overdose deaths involving hydrocodone, 23% of the deaths involving oxycodone, and 18% of the deaths involving methadone.
- More than one-third (37%) of the drug overdose deaths involving cocaine also involved heroin.
- Nearly 20% of the overdose deaths involving methamphetamine also involved heroin.

Alcohol involvement in drug overdose deaths

In 2014, alcohols, including ethanol and isopropyl alcohol, were involved in 15% of all drug overdose deaths and 17% of the drug overdose deaths that mentioned involvement of at least one specific drug. Table E shows the frequency of alcohol involvement among drug overdose deaths involving specific drugs.

- Alcohol involvement was mentioned in 12%–22% of the drug overdose deaths involving fentanyl, heroin, hydrocodone, morphine, oxycodone, alprazolam, diazepam, or cocaine.

- Alcohol involvement was mentioned in less than 10% of the drug overdose deaths involving methadone and methamphetamine.

Discussion

Study findings

The number of drug overdose deaths in the United States has increased substantially over the past two decades (1,20). From 2010 through 2014, the number of drug overdose deaths increased by 23%, from 38,329 in 2010 to 47,055 in 2014. The most frequently mentioned drugs involved in these deaths were the opioids: heroin, oxycodone, methadone, morphine, hydrocodone, and fentanyl; the benzodiazepines: alprazolam and diazepam; and the stimulants: cocaine and methamphetamine.

Reporting of specific drugs

The reporting of specific drugs on death certificates improved during the study period. In 2010, 67% of drug overdose deaths included mentions of specific drugs compared with 78% in 2014. Drug overdose deaths that did not mention a specific drug fall into two groups—those in which only a drug class was mentioned (3%–4% of all drug overdose deaths),

Table C. Percentage of deaths with concomitant drug involvement and average number of concomitant drugs for drug overdose deaths involving the top 10 drugs: United States, 2014

Referent drug	Number of drug overdose deaths involving referent drug	Percentage of drug overdose deaths involving referent drug and concomitant drugs	Average number of concomitant drugs involved ¹
Opioids			
Fentanyl	4,200	63.9	1.9
Heroin	10,863	51.6	1.6
Hydrocodone	3,274	80.4	2.4
Methadone	3,495	63.5	2.0
Morphine	4,022	72.2	2.1
Oxycodone	5,417	76.2	2.3
Benzodiazepines			
Alprazolam	4,217	95.5	2.3
Diazepam	1,729	96.7	2.8
Stimulants			
Cocaine	5,856	66.1	1.7
Methamphetamine	3,728	45.0	1.8

¹Deaths involving referent drug and at least one concomitant drug were included in the analysis. Results show average number of other drugs involved (i.e., average does not include referent drug).

NOTE: Drug overdose deaths are identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14.

SOURCE: NCHS, National Vital Statistics System, Mortality files linked with death certificate literal text.

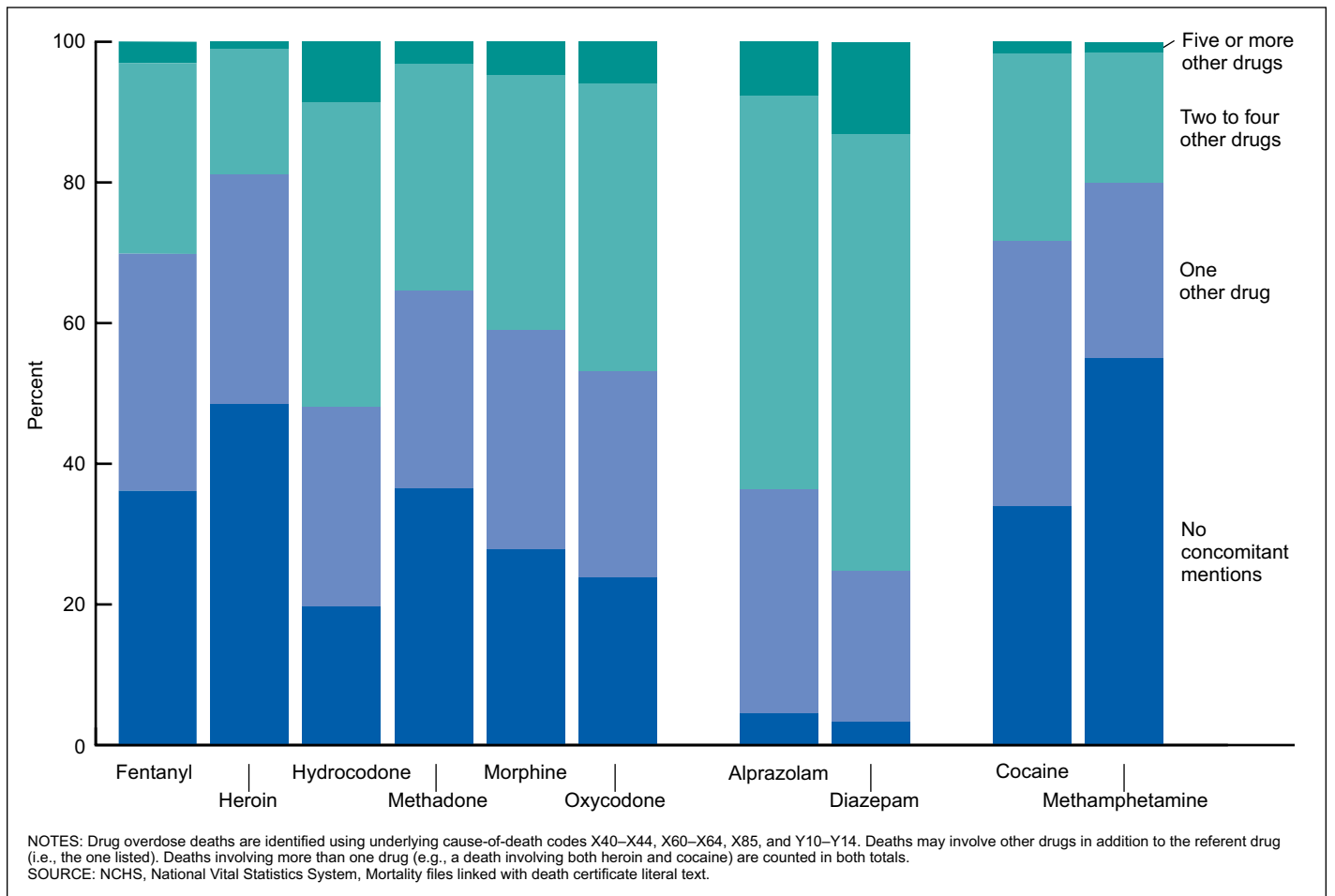


Figure 5. Percent distribution of deaths involving concomitant drugs for the top 10 drugs involved in drug overdose deaths: United States, 2014

Table D. Most frequent concomitant drugs for drug overdose deaths involving the top 10 drugs: United States, 2014

Referent drug	Number of deaths involving referent drug	Most frequent concomitant drug			Second most frequent concomitant drug				
		Concomitant drug	Deaths involving both drugs		Concomitant drug	Deaths involving both drugs			
			Number	Percentage ¹		Number	Percentage ¹		
Opioids									
Fentanyl	4,200	Heroin	954	22.7	Cocaine	614	14.6		
Heroin	10,863	Cocaine	2,181	20.0	Fentanyl	954	8.7		
Hydrocodone	3,274	Alprazolam	836	25.5	Oxycodone	520	15.8		
Methadone	3,495	Alprazolam	634	18.1	Oxycodone	352	10.0		
Morphine	4,022	Oxycodone	572	14.2	Heroin	518	12.8		
Oxycodone	5,417	Alprazolam	1,252	23.1	Morphine	572	10.5		
Benzodiazepines									
Alprazolam	4,217	Oxycodone	1,252	29.6	Heroin	839	19.8		
Diazepam	1,729	Oxycodone	566	32.7	Hydrocodone	324	18.7		
Stimulants									
Cocaine	5,856	Heroin	2,181	37.2	Fentanyl	614	10.4		
Methamphetamine	3,728	Heroin	734	19.6	Morphine	300	8.0		
Referent drug	Third most frequent concomitant drug			Fourth most frequent concomitant drug			Fifth most frequent concomitant drug		
	Concomitant drug	Deaths involving both drugs		Concomitant drug	Deaths involving both drugs		Concomitant drug	Deaths involving both drugs	
		Number	Percentage ¹		Number	Percentage ¹		Number	Percentage ¹
Opioids									
Fentanyl	Oxycodone	423	10.0	Alprazolam	402	9.5	Morphine	358	8.5
Heroin	Alprazolam	839	7.7	Methamphetamine	734	6.7	Morphine	518	4.7
Hydrocodone	Diazepam	324	9.8	Morphine	309	9.4	Heroin	257	7.8
Methadone	Cocaine	337	9.6	Heroin	314	8.9	Diazepam	232	6.6
Morphine	Alprazolam	487	12.1	Cocaine	470	11.6	Fentanyl	358	8.9
Oxycodone	Diazepam	566	10.4	Hydrocodone	520	9.5	Heroin	427	7.8
Benzodiazepines									
Alprazolam	Hydrocodone	836	19.8	Methadone	634	15.0	Morphine	487	11.5
Diazepam	Alprazolam	314	18.1	Heroin	302	17.4	Morphine	283	16.3
Stimulants									
Cocaine	Morphine	470	8.0	Alprazolam	440	7.5	Oxycodone	418	7.1
Methamphetamine	Cocaine	241	6.4	Amphetamine	181	4.8	Alprazolam	151	4.0

¹Percentage of deaths involving concomitant drug among deaths involving referent drugs. Deaths may involve more than one concomitant drug in addition to referent drug. Deaths involving more than one drug (e.g., a death involving both heroin and cocaine) are included in both totals (i.e., as a referent drug and concomitant drug).

NOTE: Deaths are identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14.

SOURCE: NCHS, National Vital Statistics System, Mortality files linked with death certificate literal text.

Table E. Percentage of deaths with concomitant alcohol involvement for drug overdose deaths involving the top 10 drugs: United States, 2014

Referent drug	Number of drug overdose deaths involving referent drug	Drug overdose deaths with concomitant alcohol involvement	
		Number	Percentage
Opioids			
Fentanyl	4,200	513	12.2
Heroin	10,863	2,252	20.7
Hydrocodone	3,274	562	17.2
Methadone	3,495	342	9.8
Morphine	4,022	522	13.0
Oxycodone	5,417	905	16.7
Benzodiazepines			
Alprazolam	4,217	652	15.5
Diazepam	1,729	374	21.6
Stimulants			
Cocaine	5,856	1,210	20.7
Methamphetamine	3,728	257	6.9

NOTES: Drug overdose deaths are identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Deaths may involve other drugs in addition to the referent drug (i.e., the one listed). Alcohol involvement included mentions of ethanol, isopropyl alcohol, and a nonspecific reference to alcohol.

SOURCE: NCHS, National Vital Statistics System, Mortality files linked with death certificate literal text.

and those with no mention of involvement of a specific drug or drug class (19%–30% of all drug overdose deaths). Of the deaths with only a drug class mentioned, more than two-thirds involved either opioids or opiates. Of the deaths with no mention of involvement of a specific drug or drug class, nearly 50% had some indication that the deaths involved multiple drugs (e.g., mentions of “POLYPHARMACY,” or “MULTIDRUG”) (14).

The reporting of specific drugs on the death certificate has been previously examined using ICD–10 coded data (16,21). In an analysis using 2008–2010 mortality data, drug specificity ranged across different states. For example, in one state, about one-third of drug overdose deaths had the drugs specified on the death certificate, whereas in several other states, more than 95% of the deaths had the drugs specified. In the past 5 years, there have been many activities to engage stakeholders to improve reporting (22).

The findings in this report should be interpreted in light of the improvements in the quality of the data during the study period. For example, some of the observed increases in the rates of drug overdose deaths involving the top 10 drugs is likely attributable to improvements in reporting.

Findings for specific drugs

The analyses of trends showed that, for some drugs, the age-adjusted rate of drug overdose deaths increased considerably within a relatively short time frame. For example, during the 5-year period, the rate of drug overdose deaths involving heroin more than tripled, and the rate of drug overdose deaths involving methamphetamine more than doubled. The rate of drug overdose

deaths involving fentanyl more than doubled in a single year (from 2013 to 2014). Among the drugs discussed in this report, only methadone showed a decreasing drug overdose death rate, from 1.5 per 100,000 population in 2011 to 1.1 in 2014. In light of the improvements in the reporting of specific drugs involved in drug overdose deaths, decreases in the rates of drug overdose deaths involving methadone are likely to be at least in part due to real decreases.

The results from the literal text analysis highlight the involvement of multiple drugs in many drug overdose deaths. In 2014, of the 36,667 drug overdose deaths that mentioned at least one specific drug involved in death, almost one-half (48%) mentioned the involvement of more than one specific drug on the death certificate. A small percentage of deaths (5%) involved five or more specific drugs. For the top 10 drugs involved in drug overdose deaths in 2014, the proportion of deaths that involved at least one other drug ranged from 45% to 97%. The average number of other drugs involved varied by drug. For example, more than 95% of drug overdose deaths involving diazepam or alprazolam also involved other drugs, with an average of two other drugs being mentioned as involved in the death. In contrast, 52% and 45% of drug overdose deaths involving heroin or methamphetamine, respectively, involved other drugs, with an average of fewer than two additional drugs mentioned.

The combinations of drugs in drug overdose deaths are important to consider when interpreting the study findings. Importantly, the most frequently mentioned drugs involved in drug overdose deaths were often mentioned with each other. For example, heroin and cocaine were involved concomitantly in more than 2,000 deaths. Another pair, oxycodone and alprazolam, were involved concomitantly in more than 1,000 deaths. Studies using the NVSS ICD–10-coded data have shown that benzodiazepines were involved in more than 30% of drug overdose deaths involving opioid analgesics (3). Recently, FDA started requiring its strongest warning to the drug labeling of prescription opioid pain and prescription opioid cough medicines and benzodiazepines after a review found that the growing combined use of opioid medicines with benzodiazepines or other drugs that depress the central nervous system have resulted in serious side effects, including slowed or difficult breathing and deaths (23).

The most frequently mentioned concomitant drug often belonged in another drug class than the referent drug. However, in some instances, the most frequently mentioned drug was in the same class as the referent drug, and was assigned the same ICD–10 code. For example, hydrocodone and oxycodone are classified to the same ICD–10 code—Natural and semi-synthetic opioid analgesic (T40.2)—and there were more than 500 deaths in 2014 involving both hydrocodone and oxycodone.

In 2014, 6,976 (15%) drug overdose deaths also involved alcohols. Alcohol involvement in drug overdose deaths may have been underestimated. Other analyses on the reporting of alcohol involvement on death certificates have shown that alcohol was frequently underreported (24,25).

Using the literal text

Currently, data from NVSS are used to quantify the size and scope of fatal drug overdoses in the United States and to track national trends (1). NVSS mortality data are an important source of information on drug overdose deaths as it has been collected using a consistent method over a long period of time. In addition, the NVSS mortality data have other strengths, such as coverage of all deaths to residents in the United States, including those occurring in rural areas or outside of a health care setting. Although analysis of the NVSS mortality data have provided valuable information on drug overdose deaths, the current classification system, ICD–10, is limited in its ability to describe the specific drugs involved. For example, of the top 10 drugs involved in drug overdose deaths, only heroin (T40.1), methadone (T40.3), and cocaine (T40.5) have separate ICD–10 codes.

This report demonstrates the utility of supplementing the ICD–10-coded data in NVSS with information on the specific drugs involved in deaths using information from the death certificate literal text. All of the data in the NVSS mortality files are based solely on information captured on the death certificate. The cause-of-death information is coded according to ICD–10 (5). Historically, the ICD–10 codes are used to classify the drugs and chemicals involved in the deaths. In this study, the specific drugs involved were extracted from the death certificate literal text using a new method (14).

Using this new method, it is possible to identify the specific drugs involved in drug overdose deaths, which is an enhancement to the traditional method of identifying drugs using broad ICD–10 drug categories. Most importantly, the new method allows for the identification of drugs that are not identified separately in ICD–10. For example, from 2010 through 2014, oxycodone, hydrocodone, and morphine were among the top 10 drugs involved in drug overdose deaths, but all were classified to Natural and semi-synthetic opioid analgesic (T40.2) in ICD–10 (26).

Data from the literal text could potentially be used to detect emerging trends. For instance, the methods could be modified to identify deaths involving newly approved prescription drugs and new substances of abuse. In order to detect emerging trends, periodically updating the text search capabilities is critical.

Data quality and other study limitations

The findings in this report must be interpreted with the potential variation in death investigation and reporting practices in mind. In most instances, drug overdose deaths are investigated and certified by a medical examiner or coroner, as these deaths are generally sudden and unexpected (27), and more than three-quarters occur outside of a health care setting (28). Medical examiners and coroners use forensic autopsy, toxicological tests, death scene information, medical history, as well as other ancillary tests and reports to determine the cause of death as well as the drugs involved (9,29).

While there are recommendations on methods for investigation and certification of drug-related deaths (8,9), variation in death investigation practice and reporting may occur and impact the

measurement of overdose death rates overall as well as rates involving specific drugs. For instance, at autopsy, toxicological tests may or may not be performed to determine the type of drugs present. The substances tested for, and the circumstances under which the tests are performed, may vary by jurisdiction, decedent, and over time.

Toxicology plays an important role in the detection of specific drugs; however, interpretation of toxicology results for drug-related deaths is not straightforward. The interpretation depends on what tests were ordered, characteristics of the causative agents, characteristics of metabolites, and other information gathered during the investigation and examination.

While there are standard panels of assays to test for drugs, not all drugs are covered by these panels, and specific tests must be ordered during the death investigation (9). In addition, as exemplified by the recent increase in deaths involving fentanyl analogs, these panels must be kept up to date with the latest profiles (30). The findings from toxicological tests and death scene investigation are not always able to distinguish subtle differences in the possible causative agents in drug overdose deaths. For example, the synthetic opioid fentanyl is manufactured both for pharmaceutical purposes and also illicitly, and it is not always possible to distinguish postmortem whether the drug was manufactured pharmaceutically or illicitly (31).

Some drugs have the same metabolites or are metabolites of other drugs, potentially resulting in misattribution of the specific drugs involved in death. For example, in this report, mentions of morphine may actually refer to heroin, because morphine is a metabolite of heroin (9). In some cases toxicological markers are present, such as 6-monacetylmorphine (6-MAM), which indicate that the morphine was metabolized from heroin (9). This report found 518 concomitant mentions of heroin and morphine in 2014, suggesting that the medical examiner or coroner might not have been able to determine the specific drug contributing to the overdose. A review of some of these cases revealed that the word “PROBABLE” sometimes appeared before the word “HEROIN.” In this analysis, heroin and morphine were considered as mutually exclusive drugs. This could potentially result in some underestimation of the number of deaths involving heroin and some overestimation of the number of deaths involving morphine.

Medical examiners and coroners also take into account death scene information when investigating drug overdose deaths (9,29). For example, drug paraphernalia may suggest illicit use. Multiple pills found in gastric contents could also indicate suicidal intention. Drugs found at the scene may also give some indication of whether the drugs were taken together (e.g., heroin laced with fentanyl) and provide more information about the source of the drug, which may be difficult to determine based on postmortem toxicological analysis (9).

During death investigations, medical examiners and coroners may use medical history, such as prescription history obtained from Prescription Drug Monitoring Programs (PDMP) (32). However, in many states, medical examiners and coroners do not have access to PDMP data (33).

Once the medical examiners and coroners have investigated the death, they will complete the death certificate. When

determining the drugs to report on the death certificate, some medical certifiers focus on a single lethal drug rather than listing multiple drugs involved in the death. Alternatively, some may choose to list a variety of drugs. Sometimes they use vague terms such as “POLYPHARMACY” and “MULTIDRUG.”

In other cases, when no drug is specified, the certifier might not know the drugs involved in death. This can occur if the decedent is hospitalized for a period of time before death. Hospitals retain the blood specimen for a limited time. In other cases, there may not be an adequate sample for forensic toxicology, as may be the case if the body is not recovered for an extended period of time after the death occurred.

Conclusions

In summary, this report provides a picture of the most frequent drugs involved in drug overdose deaths in the United States, and highlights the frequency of deaths involving multiple drugs. The report also demonstrates the ability of a new method for abstracting data from the death certificate to enhance national monitoring of drug overdose deaths, and it emphasizes the need to include specific drugs involved in the death on the death certificate.

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Table 1. Crude and age-adjusted rates for drug overdose deaths involving selected opioids: United States, 2010–2014

Opioid	Crude death rate					Age-adjusted death rate				
	2010	2011	2012	2013	2014	2010	2011	2012	2013	2014
Fentanyl	0.5	0.5	0.5	0.6	1.3	0.5	0.5	0.5	0.6	1.3
Heroin	1.0	1.5	2.0	2.7	3.4	1.0	1.5	2.0	2.7	3.5
Hydrocodone	0.9	1.0	1.0	1.0	1.0	0.9	1.0	0.9	1.0	1.0
Methadone	1.4	1.5	1.3	1.2	1.1	1.4	1.5	1.3	1.2	1.1
Morphine	1.0	1.1	1.1	1.2	1.3	0.9	1.0	1.1	1.2	1.2
Oxycodone	1.7	1.8	1.6	1.6	1.7	1.7	1.8	1.7	1.6	1.7

NOTES: Drug-poisoning deaths are identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Deaths may involve other drugs in addition to the opioid listed. Deaths involving more than one drug (e.g., a death involving both heroin and cocaine) are counted in both rates. Caution should be used when comparing numbers across years. The reporting of at least one specific drug in the literal text improved, from 67% of drug overdose deaths in 2010 to 78% of drug overdose deaths in 2014.

SOURCE: NCHS, National Vital Statistics System, Mortality files linked with death certificate literal text.

Table 2. Crude and age-adjusted rates for drug overdose deaths involving selected benzodiazepines: United States, 2010–2014

Benzodiazepine	Crude death rate					Age-adjusted death rate				
	2010	2011	2012	2013	2014	2010	2011	2012	2013	2014
Alprazolam	1.2	1.3	1.2	1.2	1.3	1.2	1.3	1.2	1.2	1.3
Diazepam	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

NOTES: Drug-poisoning deaths are identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Deaths may involve other drugs in addition to the benzodiazepine listed. Deaths involving more than one drug (e.g., a death involving both heroin and cocaine) are counted in both rates. Caution should be used when comparing numbers across years. The reporting of at least one specific drug in the literal text improved, from 67% of drug overdose deaths in 2010 to 78% of drug overdose deaths in 2014.

SOURCE: NCHS, National Vital Statistics System, Mortality files linked with death certificate literal text.

Table 3. Crude and age-adjusted rates for drug overdose deaths involving selected stimulants: United States, 2010–2014

Stimulant	Crude death rate					Age-adjusted death rate				
	2010	2011	2012	2013	2014	2010	2011	2012	2013	2014
Cocaine	1.4	1.6	1.5	1.7	1.8	1.4	1.6	1.5	1.7	1.8
Methamphetamine	0.4	0.6	0.7	1.0	1.2	0.5	0.6	0.7	1.0	1.2

NOTES: Drug-poisoning deaths are identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Deaths may involve other drugs in addition to the stimulant listed. Deaths involving more than one drug (e.g., a death involving both heroin and cocaine) are counted in both rates. Caution should be used when comparing numbers across years. The reporting of at least one specific drug in the literal text improved, from 67% of drug overdose deaths in 2010 to 78% of drug overdose deaths in 2014.

SOURCE: NCHS, National Vital Statistics System, Mortality files linked with death certificate literal text.

Table 4. Number of drug overdose deaths, by the number of literal text mentions of specific drugs involved: United States, 2014

Number of specific drugs involved in death	Number of drug overdose deaths	Percent
At least one.....	36,667	100.0
One.....	18,931	51.6
Two.....	9,351	25.5
Three.....	4,521	12.3
Four.....	2,041	5.6
Five.....	962	2.6
Six or more.....	861	2.3

NOTES: Drug overdose deaths are identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14, and at least one specific drug mentioned on the death certificate. In 2014, at least one specific drug was mentioned in 78% of drug overdose deaths.

SOURCE: NCHS, National Vital Statistics System, Mortality files linked with death certificate literal text.

Table 5. Percent distribution of deaths involving concomitant drugs for top 10 drugs involved in drug overdose deaths: United States, 2014

Referent drug	Total number of drug overdose deaths involving referent drug	Number of drug overdose deaths involving referent drug:				Percentage of drug overdose deaths involving referent drug only	Percentage of drug overdose deaths involving referent drug:		
		No other drug	Plus one other drug	Plus two to four other drugs	Plus five or more other drugs		Plus one other drug	Plus two to four other drugs	Plus five or more other drugs
Opioids									
Fentanyl.....	4,200	1,517	1,416	1,139	128	36.1	33.7	27.1	3.0
Heroin.....	10,863	5,261	3,551	1,934	117	48.4	32.7	17.8	1.1
Hydrocodone.....	3,274	643	932	1,417	282	19.6	28.5	43.3	8.6
Methadone.....	3,495	1,275	984	1,124	112	36.5	28.2	32.2	3.2
Morphine.....	4,022	1,120	1,254	1,454	194	27.8	31.2	36.2	4.8
Oxycodone.....	5,417	1,288	1,592	2,210	327	23.8	29.4	40.8	6.0
Benzodiazepines									
Alprazolam.....	4,217	188	1,348	2,357	324	4.5	32.0	55.9	7.7
Diazepam.....	1,729	57	372	1,072	228	3.3	21.5	62.0	13.2
Stimulants									
Cocaine.....	5,856	1,984	2,214	1,556	102	33.9	37.8	26.6	1.7
Methamphetamine.....	3,728	2,049	929	691	59	55.0	24.9	18.5	1.6

NOTES: Drug overdose deaths are identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Deaths may involve other drugs in addition to the referent drug (i.e., the one listed). Deaths involving more than one drug (e.g., a death involving both heroin and cocaine) are counted in both totals (i.e., as a referent drug and as an "other" drug).

SOURCE: NCHS, National Vital Statistics System, Mortality files linked with death certificate literal text.

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