

Drugs Most Frequently Involved in Drug Overdose Deaths: United States, 2011–2016

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Abstract

Objective—This report identifies the specific drugs involved most frequently in drug overdose deaths in the United States from 2011 through 2016.

Methods—Record-level data from the 2011–2016 National Vital Statistics System–Mortality files were linked to electronic files containing literal text information from death certificates. Drug overdose deaths were identified using the *International Classification of Diseases, Tenth Revision* underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Drug mentions were identified by searching the literal text in three fields of the death certificate: the causes of death from Part I, significant conditions contributing to death from Part II, and a description of how the injury occurred. Contextual information was used to determine drug involvement in the death. Descriptive statistics were calculated for drug overdose deaths involving the 10 most frequently mentioned drugs. Deaths involving more than one drug (e.g., a death involving both heroin and cocaine) were counted in all relevant drug categories (e.g., the same death was included in counts of heroin deaths and in counts of cocaine deaths).

Results—Among drug overdose deaths that mentioned at least one specific drug, the 10 most frequently mentioned drugs during 2011–2016 included fentanyl, heroin, hydrocodone, methadone, morphine, oxycodone, alprazolam, diazepam, cocaine, and methamphetamine. Oxycodone ranked first in 2011, heroin during 2012–2015, and fentanyl in 2016. During the study period, cocaine consistently ranked second or third. From 2011 through 2016, the age-adjusted rate of drug overdose deaths involving heroin more than tripled, as did the rate of drug overdose deaths involving methamphetamine. The rate of drug overdose deaths involving fentanyl and fentanyl analogs doubled each year from 2013 through 2016, from 0.6 per 100,000 in 2013 to 1.3 in 2014, 2.6 in 2015, and 5.9 in 2016. The rate of

overdose deaths involving methadone decreased from 1.4 per 100,000 in 2011 to 1.1 in 2016. The 10 most frequently mentioned drugs often were found in combination with each other. The drugs most frequently mentioned varied by the intent of the drug overdose death. In 2016, the drugs most frequently mentioned in unintentional drug overdose deaths were fentanyl, heroin, and cocaine, while the drugs most frequently mentioned in suicides by drug overdose were oxycodone, diphenhydramine, hydrocodone, and alprazolam.

Conclusions—This report identifies patterns in the specific drugs most frequently involved in drug overdose deaths from 2011 through 2016 and highlights the importance of complete and accurate reporting in the literal text on death certificates.

Keywords: opioid • fentanyl • heroin • cocaine • National Vital Statistics System

Introduction

From 1999 through 2016, the age-adjusted rate of drug overdose deaths in the United States more than tripled from 6.1 per 100,000 to 19.8 per 100,000 (1). Multiple studies have used National Vital Statistics System–Mortality (NVSS–M) data, coded using the *International Classification of Diseases, Tenth Revision* (ICD–10), to examine patterns of drug involvement in overdose deaths (1–5). ICD–10 is the classification system used in the United States to categorize the underlying and multiple causes of death (6). One limitation of this classification system is that, with a few exceptions, ICD–10 codes reflect broad categories of drugs rather than unique specific drugs. For example, oxycodone and hydrocodone are both classified in the same category of natural and semisynthetic opioid analgesics (ICD–10 code T40.2). The broad drug categorizations used in ICD–10 make it difficult to use ICD–10-coded data to monitor trends in deaths involving specific drugs (e.g., deaths involving oxycodone specifically).

To address this limitation, the National Center for Health Statistics (NCHS) and the U.S. Food and Drug Administration (FDA) collaboratively developed methods to search the literal text from death certificates to identify mentions of specific drugs and other substances, and to search contextual terms to identify involvement of the drug(s) or substance(s) in the death (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), and describes the cause of death and other factors or circumstances that contributed to the death. The methods developed by NCHS and FDA search three literal text fields from the U.S. standard death certificate: the causes of death from Part I, significant conditions contributing to death from Part II, and a description of how the injury occurred (7,10).

A previous study presented the findings from use of literal text analysis to identify the specific drugs most frequently involved in drug overdose deaths from 2010 through 2014 (11). This report uses the same methodology and an enhanced search term list to provide results for drug overdose deaths from 2011 through 2016.

Methods

Data source and study population

NVSS–M data from 2011 through 2016 were used in this descriptive analysis. NVSS–M data contain cause-of-death, demographic, and geographic information extracted from death certificates (12). The study population was limited to decedents who were U.S. residents with an ICD–10 underlying cause-of-death of drug overdose: X40–X44 (unintentional), X60–X64 (suicide or intentional self-harm), X85 (assault), and Y10–Y14 (undetermined intent). During the study period, the manner of death was unintentional for 80%–86% of drug overdose deaths, suicide for 8%–13%, homicide for 0.2%, and undetermined intent for 6%–7% (1,13). The underlying cause-of-death codes reflect deaths resulting from acute intoxication from drugs (i.e., drug overdose). Deaths from chronic exposure to drugs (e.g., liver toxicity) or adverse effects experienced from therapeutic or prophylactic dosages of drug were not included. Use of this code set (X40–X44, X60–X64, X85, and Y10–Y14) is consistent with other NCHS publications on drug overdose deaths and facilitates comparison with other analyses using the ICD–10-coded data (1).

NVSS–M files were linked to electronic files containing literal text data, also extracted from death certificates (7). Mentions of drugs or other substances (described below) were identified using the literal text data from three fields of the death certificate: the causes of death from Part I, significant conditions contributing to death from Part II, and a description of how the injury occurred.

Identifying drug mentions and involvement of the drug in the death

The method for searching literal text information to characterize the drugs involved in deaths has been described elsewhere (7). Briefly, the method involves searching the literal text for mentions of drugs and other substances, as well as terms that provide context about the involvement of the drug in the death (i.e., whether the drug contributed to 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 a drug, even though “DRUG” is mentioned in the phrase. The drug or substance mentioned in a literal text field is assumed to be involved in the death unless the contextual information indicates otherwise. Software programs, referred to as the Drug Mention with Involvement (DMI) programs, have been developed using SAS version 9.4 to automate the process (7).

DMI programs identify mentions of drugs and other substances using various search terms. Search terms include generic drug names, brand names, common usage or street names, abbreviations, metabolites, misspellings, and other variations. The list of search terms used in this report is broader than that used in a previous report (7), and was developed to maintain as much substance specificity as possible. The new search term list was applied to the literal text for all years of the study (2011–2016). Because a new search term list was used in this analysis, the results for 2011–2014 may differ slightly from those reported previously (from 0 to 36 additional deaths depending on the drug and the year) (11).

Each search term was mapped to a “principal variant,” the overarching label assigned to a drug, a drug class, or exposure not otherwise specified. For example, terms such as “COCAIEN”, “COCAINE CRACK”, “COCAINE HYDROCHLORIDE”, and “COCAINETOXICITY” were all mapped to the principal variant “COCAINE”. In general, the principal variant was the generic drug name. Some search terms—mostly for combination drug products—were mapped to two or more principal variants. Use of principal variants makes it possible to generate aggregate counts for all search terms that refer to the same drug or substance. Principal variants also were categorized according to whether they referred to specific drugs or substances (e.g., methadone), classes of drugs or substances (e.g., opioids), or nonspecific references to exposures to drugs (e.g., words such as “DRUG”, “MULTIDRUG”, or “POLYPHARMACY”). The DMI Search Terms and principal variants table is provided in an accompanying CSV file (https://ftp.cdc.gov/pub/Health_Statistics/NCHS/Program_Code/dae/).

A frequency distribution of the principal variants identified the top 20 drugs for each year from 2011 through 2016. A referent drug category was created for each of the top 20 drugs. The term “referent drug” in the tables and figures in this report generally refers to a single principal variant for the drug of interest. However, due to the greater detail in the updated principal variant list, some of the referent drug categories are comprised of two or more principal variants, generally reflecting

a drug and its metabolites. For example, the principal variant HYDROCODONE and the principal variant NORHYDROCODONE (a metabolite of hydrocodone) were grouped together to create the referent drug category of HYDROCODONE. The referent group FENTANYL included fentanyl as well as fentanyl metabolites, precursors, and analogs. The grouping of principal variants into referent groups was based on expertise from FDA and NCHS. The referent groups table, which contains a list of search terms and the principal variants included in each referent drug category, is provided in the CSV file (https://ftp.cdc.gov/pub/Health_Statistics/NCHS/Program_Code/oaef/).

Analysis

Results are reported as numbers, percentages, or rates for the deaths involving the referent drug. Deaths involving more than one referent drug (e.g., a death involving both heroin and cocaine) are counted in all relevant drug categories (e.g., the same death is included in counts of heroin deaths and in counts of cocaine deaths); therefore counts are not mutually exclusive. Age-adjusted death rates are calculated using the direct method and the 2000 standard U.S. population (12). Trends in age-adjusted death rates are evaluated using the National Cancer Institute's Joinpoint Regression Program (version 4.6.0.0) (14). Joinpoint software fitted weighted least-squares regression models to the rates on the log transform scale. Allowing one observed time point at each end and two for the middle line segments, the Grid Search Algorithm searched for a maximum of two joinpoints at an overall alpha level of 0.05 (15). Any mention of an annual percent change in this report indicates a statistically significant trend. Comparisons of rates between years were tested for statistical significance using methods described elsewhere (12).

Analyses of mentions of other drugs reported in addition to the referent drug (concomitant drugs) were also conducted. Only deaths with mention of at least two specific drugs (the referent drug and at least one concomitant drug) are included in this analysis. Alcohol, nicotine, and nondrug substances are not included in the analysis.

The numbers and rates of drug-specific overdose deaths shown in the tables and figures should be considered the minimum number or rate for that referent drug category because there could be additional deaths in which the drug was involved, but the drug was not reported in the literal text on the death certificate.

Assessing improvement in reporting on death certificates

The ICD-10 multiple-cause codes T36–T50.8 provide information on the types of drugs or drug classes involved in the death. The percentage of deaths with an underlying-cause code of X40–X44, X60–X64, X85, and Y10–Y14 that have a multiple-cause code of T36–T50.8 is a measure of the specificity of reporting of drugs or drug classes in drug overdose deaths. This measure was used to assess possible changes in reporting through the years of the study. The percentage of drug overdose

deaths with codes T36–T50.8 increased each year (75% in 2011, 76% in 2012, 78% in 2013, 81% in 2014, 83% in 2015, and 85% in 2016).

This improvement in reporting of specific drugs and drug classes during the study period could potentially influence the observed trends in drug overdose deaths for specific drugs (Figures 1–3). To assess the possible influence of improved reporting, an adjustment analysis was conducted. In this analysis, an adjustment factor was applied to each number and age-adjusted rate for drug overdose deaths involving specific drugs. The adjustment factor assumed that the specificity of drug reporting remained constant from 2011 through 2016 at the 2016 rate (i.e., 85.4% of drug overdose deaths with an ICD-10 multiple-cause code of T36–T50.8). A description of the methodology and the results from the adjustment analysis are provided in the [Technical Notes](#).

Results

The number of drug overdose deaths per year increased 54%, from 41,340 deaths in 2011 to 63,632 deaths in 2016 (Table A). From the literal text analysis, the percentage of drug overdose deaths mentioning at least one specific drug or substance increased from 73% of the deaths in 2011 to 85% of the deaths in 2016. The percentage of drug overdose deaths that mentioned only a drug class but not a specific drug or substance declined from 5.1% of deaths in 2011 to 2.5% in 2016. Review of the literal text for these deaths indicated that the deaths that mentioned only a drug class frequently involved either an opioid or an opiate (ranging from 54% in 2015 to 60% in 2016). The percentage of deaths that did not mention a specific drug or substance or a drug class declined from 22% of drug overdose deaths in 2011 to 13% in 2016.

Most frequently mentioned drugs

Table B shows the relative ranking of the top 15 drugs involved in drug overdose deaths for each year from 2011 through 2016 among deaths that mentioned at least one specific drug. The number of deaths for each drug should be interpreted in light of the improvements in reporting as described in Table A, and should be considered the minimum number for that drug because there could be additional deaths in which the drug was involved, but the drug was not reported in the literal text.

The top 15 drugs were identified based on the number of drug overdose deaths per referent drug category. While the ranking changed from year to year, the top 10 drugs involved in overdose deaths remained consistent throughout the 6-year period. The top 10 drugs belonged to three drug classes:

- Opioids: fentanyl, heroin, hydrocodone, methadone, morphine, and oxycodone
- Benzodiazepines: alprazolam and diazepam
- Stimulants: cocaine and methamphetamine

The drugs that ranked 11–15 varied from year to year and included such drugs as diphenhydramine, citalopram, acetaminophen, carisoprodol, tramadol, oxymorphone, amitriptyline, clonazepam, gabapentin, and amphetamine.

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, 2011–2016

Drug overdose deaths	2011		2012		2013		2014		2015		2016	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
All drug overdose deaths	41,340	100.0	41,502	100.0	43,982	100.0	47,055	100.0	52,404	100.0	63,632	100.0
Drug overdose deaths with mention of at least one specific drug or other substance	30,103	72.8	30,923	74.5	33,640	76.5	37,631	80.0	43,141	82.3	54,137	85.1
Drug overdose deaths with mention of a class only (no specific drug or other substance)	2,122	5.1	2,093	5.0	1,918	4.4	1,653	3.5	1,650	3.1	1,566	2.5
Drug overdose deaths without mention of a specific drug, other substance, or class ¹	9,115	22.0	8,486	20.4	8,424	19.2	7,771	16.5	7,613	14.5	7,929	12.5

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

NOTES: Drug overdose deaths are identified using *International Classification of Diseases, Tenth Revision* (ICD-10) underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Percentages may not add to 100 due to rounding. The reporting of at least one specific drug or drug class in the literal text, as identified using ICD-10 multiple cause-of-death codes T36–T50.8, improved from 75% of drug overdose deaths in 2011 to 85% of drug overdose deaths in 2016.

SOURCE: NCHS, National Vital Statistics System, Mortality files linked with death certificate literal text, 2011–2016.

For the top 15 drugs:

- Among drug overdose deaths that mentioned at least one specific drug, oxycodone ranked first in 2011, heroin from 2012 through 2015, and fentanyl in 2016.
- In 2011 and 2012, fentanyl was mentioned in approximately 1,600 drug overdose deaths each year, but mentions increased in 2013 (1,919 deaths), 2014 (4,223 deaths), 2015 (8,251 deaths), and 2016 (18,335 deaths). In 2016, 29% of all drug overdose deaths mentioned involvement of fentanyl.
- The number of drug overdose deaths involving heroin increased threefold, from 4,571 deaths or 11% of all drug overdose deaths in 2011 to 15,961 deaths or 25% of all drug overdose deaths in 2016.
- Throughout the study period, cocaine ranked second or third among the top 15 drugs. From 2014 through 2016, the number of drug overdose deaths involving cocaine nearly doubled from 5,892 to 11,316.
- The number of drug overdose deaths involving methamphetamine increased 3.6-fold, from 1,887 deaths in 2011 to 6,762 deaths in 2016.
- The number of drug overdose deaths involving methadone decreased from 4,545 deaths in 2011 to 3,493 deaths in 2016.

Age-adjusted rates for drug overdose deaths involving the most frequently mentioned drugs, 2011–2016

Trends from 2011 through 2016 in the age-adjusted rates of drug overdose deaths involving the 10 most frequently mentioned drugs are shown in Figures 1–3. Improvements in reporting should be considered when interpreting these trends (see [Technical Notes](#)). As a reference, from 2011 through 2016, the age-adjusted rate of all drug overdose deaths, whether or not

a specific drug was mentioned, increased from 13.2 per 100,000 to 19.8, an average increase of 9% per year.

- From 2011 through 2016, the age-adjusted rate of drug overdose deaths involving heroin more than tripled from 1.5 per 100,000 population to 5.1. The rate increased on average by about 34% per year from 2011 through 2014, and by about 20% per year from 2014 through 2016 ([Figure 1, Table](#)).

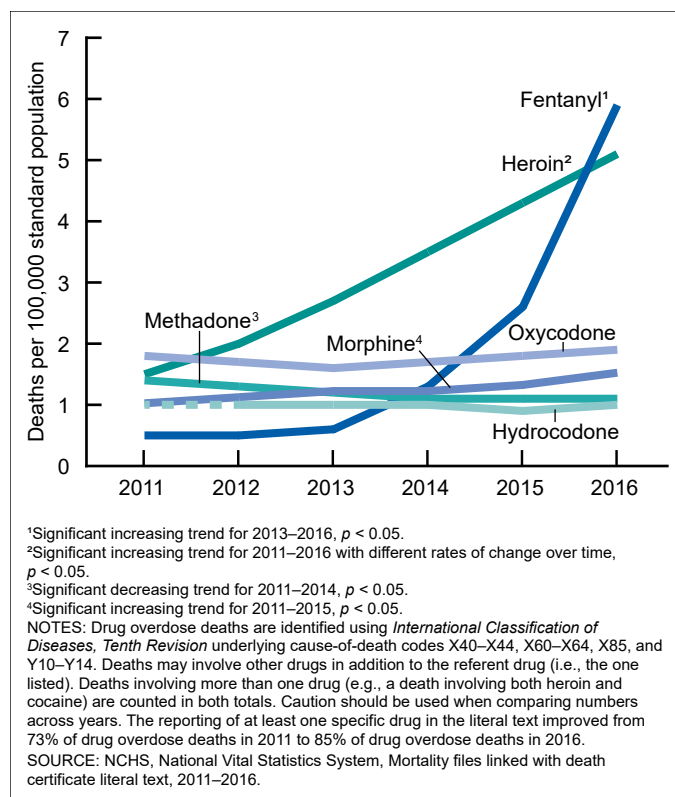


Figure 1. Age-adjusted rates for drug overdose deaths involving selected opioids, 2011–2016

Table B. Top 15 drugs involved in drug overdose deaths: United States, 2011–2016

2011 (n = 41,340)				2012 (n = 41,502)			2013 (n = 43,982)			
Rank ¹	Referent drug	Number of deaths ²	Percent of deaths ³	Referent drug	Number of deaths ²	Percent of deaths ³	Referent drug	Number of deaths ²	Percent of deaths ³	
1	Oxycodone	5,587	13.5	Heroin	6,155	14.8	Heroin	8,418	19.1	
2	Cocaine	5,070	12.3	Oxycodone	5,178	12.5	Cocaine	5,319	12.1	
3	Heroin	4,571	11.1	Cocaine	4,780	11.5	Oxycodone	4,967	11.3	
4	Methadone	4,545	11.0	Methadone	4,087	9.8	Morphine	3,772	8.6	
5	Alprazolam	4,066	9.8	Alprazolam	3,803	9.2	Alprazolam	3,724	8.5	
6	Morphine	3,290	8.0	Morphine	3,513	8.5	Methadone	3,700	8.4	
7	Hydrocodone	3,206	7.8	Hydrocodone	3,037	7.3	Methamphetamine	3,194	7.3	
8	Methamphetamine	1,887	4.6	Methamphetamine	2,267	5.5	Hydrocodone	3,113	7.1	
9	Diazepam	1,698	4.1	Fentanyl	1,615	3.9	Fentanyl	1,919	4.4	
10	Fentanyl	1,662	4.0	Diazepam	1,577	3.8	Diazepam	1,618	3.7	
11	Diphenhydramine	1,226	3.0	Diphenhydramine	1,300	3.1	Diphenhydramine	1,360	3.1	
12	Oxymorphone	1,190	2.9	Citalopram	1,042	2.5	Tramadol	1,009	2.3	
13	Citalopram	1,043	2.5	Tramadol	935	2.3	Clonazepam	946	2.2	
14	Acetaminophen	879	2.1	Oxymorphone	866	2.1	Citalopram	914	2.1	
15	Tramadol	849	2.1	Amitriptyline	835	2.0	Amitriptyline	815	1.9	

2014 (n = 47,055)				2015 (n = 52,404)			2016 (n = 63,632)			
Rank ¹	Referent drug	Number of deaths ²	Percent of deaths ³	Referent drug	Number of deaths ²	Percent of deaths ³	Referent drug	Number of deaths ²	Percent of deaths ³	
1	Heroin	10,882	23.1	Heroin	13,318	25.4	Fentanyl	18,335	28.8	
2	Cocaine	5,892	12.5	Fentanyl	8,251	15.7	Heroin	15,961	25.1	
3	Oxycodone	5,431	11.5	Cocaine	7,324	14.0	Cocaine	11,316	17.8	
4	Alprazolam	4,237	9.0	Oxycodone	5,792	11.1	Methamphetamine	6,762	10.6	
5	Fentanyl	4,223	9.0	Methamphetamine	5,092	9.7	Alprazolam	6,209	9.8	
6	Morphine	4,024	8.6	Alprazolam	4,801	9.2	Oxycodone	6,199	9.7	
7	Methamphetamine	3,747	8.0	Morphine	4,226	8.1	Morphine	5,014	7.9	
8	Methadone	3,498	7.4	Methadone	3,376	6.4	Methadone	3,493	5.5	
9	Hydrocodone	3,299	7.0	Hydrocodone	3,051	5.8	Hydrocodone	3,199	5.0	
10	Diazepam	1,748	3.7	Diphenhydramine	1,798	3.4	Diazepam	2,022	3.2	
11	Diphenhydramine	1,614	3.4	Diazepam	1,796	3.4	Diphenhydramine	2,008	3.2	
12	Tramadol	1,175	2.5	Clonazepam	1,328	2.5	Clonazepam	1,656	2.6	
13	Clonazepam	1,139	2.4	Gabapentin	1,222	2.3	Gabapentin	1,546	2.4	
14	Citalopram	1,014	2.2	Tramadol	1,177	2.2	Tramadol	1,250	2.0	
15	Oxymorphone	909	1.9	Oxymorphone	1,006	1.9	Amphetamine	1,193	1.9	

¹Ranks were not tested for statistical significance.

²Number of drug overdose deaths involving the referent drug.

³Percentage of drug overdose deaths involving the referent drug.

NOTES: Drug overdose deaths are identified using *International Classification of Diseases, Tenth Revision* (ICD–10) 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 or drug class in the literal text, as identified using ICD–10 multiple cause-of-death codes T36–T50.8, improved from 75% of drug overdose deaths in 2011 to 85% of drug overdose deaths in 2016.

SOURCE: NCHS, National Vital Statistics System, Mortality files linked with death certificate literal text, 2011–2016.

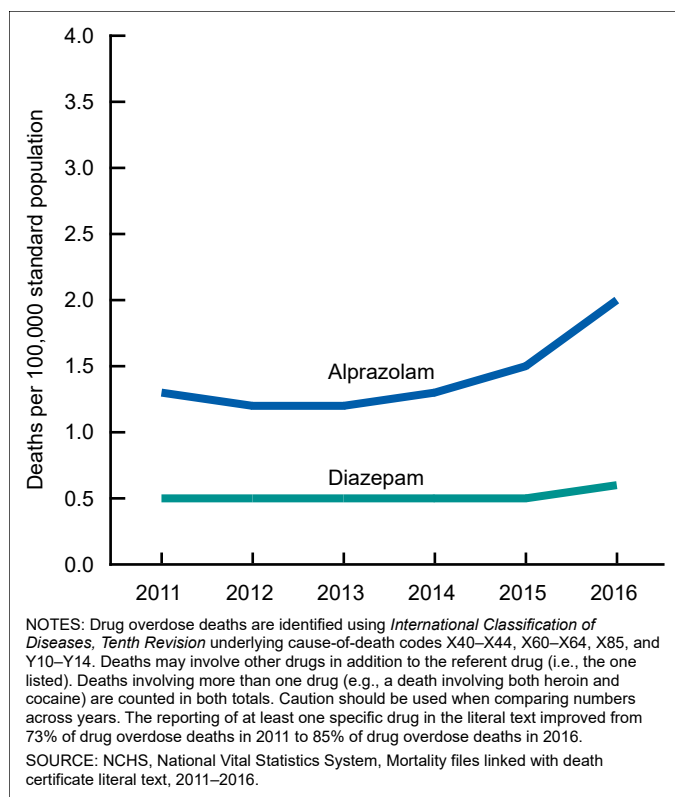


Figure 2. Age-adjusted rates for drug overdose deaths involving selected benzodiazepines, 2011–2016

- From 2011 through 2013, there was no statistical change in the age-adjusted rate of drug overdose deaths involving fentanyl. From 2013 through 2016, the rate increased on average by about 113% per year, from 0.6 per 100,000 population in 2013, to 1.3 in 2014, 2.6 in 2015, and 5.9 in 2016.
- The age-adjusted rate of drug overdose deaths involving morphine increased from 1.0 per 100,000 population in 2011 to 1.5 in 2016. The rate increased on average by about 6% per year from 2011 through 2015. Between 2015 and 2016, the rate changed 18%, however, this trend was not statistically significant.
- The age-adjusted rate of drug overdose deaths involving methadone decreased from 1.4 per 100,000 population in 2011 to 1.1 in 2016. The rate decreased on average by about 10% per year from 2011 through 2014. From 2014 through 2016, there was no significant change in the rate.
- From 2011 through 2016, there was no significant change in the age-adjusted death rate for drug overdose deaths involving hydrocodone.
- The age-adjusted rate of drug overdose deaths involving oxycodone decreased from 1.8 per 100,000 population in 2011 to 1.6 in 2013, then increased to 1.9 in 2016; however, these decreasing and increasing trends were not statistically significant.
- The age-adjusted rate of drug overdose deaths involving alprazolam decreased from 1.3 per 100,000 population in 2011 to 1.2 in 2013, then increased to 2.0 in 2016; however, these decreasing and increasing trends were not statistically significant (Figure 2, Table).

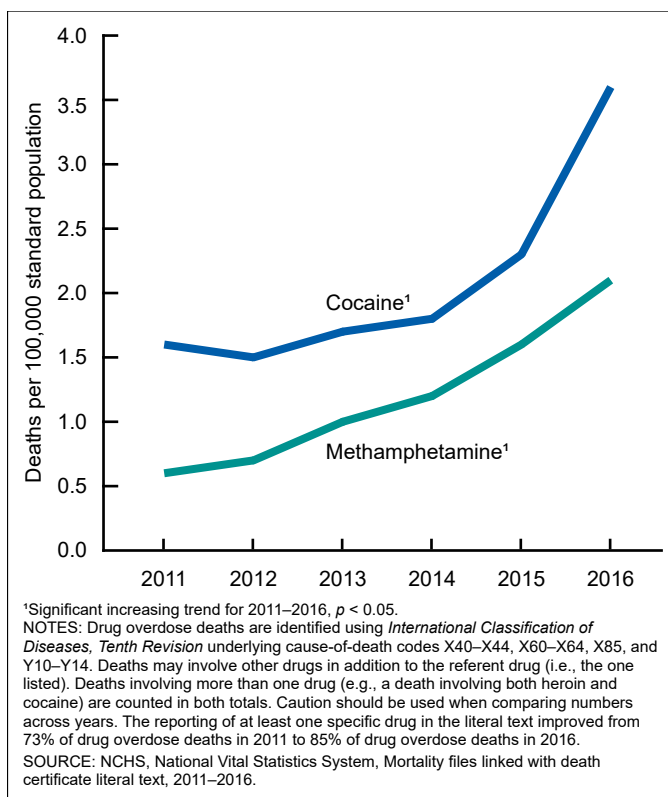


Figure 3. Age-adjusted rates for drug overdose deaths involving selected stimulants, 2011–2016

- From 2011 through 2016, there was no significant change in the age-adjusted rate for drug overdose deaths involving diazepam.
- The age-adjusted rate of drug overdose deaths involving cocaine increased from 1.6 per 100,000 population in 2011 to 3.6 in 2016. The rate increased on average by about 18% per year (Figure 3, Table).
- The age-adjusted rate of drug overdose deaths involving methamphetamine more than tripled from 0.6 per 100,000 population in 2011 to 2.1 in 2016. The rate increased on average by about 29% per year.
- In the adjustment analysis, the findings for the trends in rates based on observed and adjusted numbers were, in general, the same for fentanyl, oxycodone, diazepam, cocaine, and methamphetamine (see Technical Notes). For heroin, the inflection point in 2014 was no longer found, resulting in a percent change in the rate of about 24% per year from 2011 through 2016. For morphine, the inflection point in 2015 was no longer found, resulting in a percent change in the rate of about 5% per year from 2011 through 2016. For methadone, rates decreased by about 12% per year from 2011 through 2014, and by about 3% from 2014 through 2016. For hydrocodone, there was a significant decline in the age-adjusted rates of about 4% per year from 2011 through 2016. For alprazolam, the inflection point in 2013 was no longer found, and as with the observed values, the increasing trend from 2011 through 2016 was not statistically significant.

Drug overdose deaths in 2016 involving multiple drugs

Table C shows the percentage of drug overdose deaths with concomitant involvement of other drugs for the top 10 drugs involved in drug overdose deaths in 2016. The percentage of deaths with concomitant involvement of other drugs varied by drug. For example, almost all drug overdose deaths involving alprazolam or diazepam (96%) mentioned involvement of other drugs. In contrast, 50% of the drug overdose deaths involving methamphetamine, and 69% of the drug overdose deaths involving fentanyl mentioned involvement of one or more other specific drugs.

Table D shows the most frequent concomitant drug mentions for each of the top 10 drugs involved in drug overdose deaths in 2016.

- Two in five overdose deaths involving cocaine also mentioned fentanyl.
- Nearly one-third of drug overdose deaths involving fentanyl also mentioned heroin (32%).
- Alprazolam was mentioned in 26% of the overdose deaths involving hydrocodone, 22% of the deaths involving methadone, and 25% of the deaths involving oxycodone.
- More than one-third of the overdose deaths involving cocaine also mentioned heroin (34%).
- More than 20% of the overdose deaths involving methamphetamine also mentioned heroin.

Most frequently mentioned drugs involved in drug overdose deaths in 2016, by intent of death

Table E shows the top 10 drugs involved in drug overdose deaths in 2016 by intent of death, for deaths in which at least

one specific drug was identified. Results are shown for unintentional drug overdose deaths (ICD-10 underlying-cause codes X40–X44), suicides by drug overdose (ICD-10 underlying-cause codes X60–X64), and drug overdose deaths for which the intent could not be determined (undetermined intent; [ICD-10 underlying-cause codes Y10–Y14]). The results for 110 deaths with an intent of homicide (ICD-10 underlying-cause code X85) are not shown due to small numbers.

In 2016, unintentional drug overdose deaths most frequently mentioned fentanyl, heroin, and cocaine, while suicides by drug overdose most frequently mentioned oxycodone, diphenhydramine, hydrocodone, and alprazolam. Methadone ranked in the top 10 for unintentional and undetermined intent deaths, but not among suicides by drug overdose. Quetiapine, tramadol, bupropion, and zolpidem ranked in the top 10 for suicides by drug overdose, but not for unintentional drug overdose deaths and overdose deaths of undetermined intent.

Discussion

Findings for specific drugs

From 2011 through 2016, the number of drug overdose deaths increased by 54%, from 41,340 deaths in 2011 to 63,632 deaths in 2016. 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.

Among drug overdose deaths that mentioned at least one specific drug, oxycodone ranked first in 2011, heroin ranked first from 2012 through 2015, and fentanyl ranked first in 2016. Cocaine ranked second or third throughout the study period.

An analysis of trends among the most frequently mentioned drugs showed that, for several drugs, the age-adjusted rate of

Table C. Number and percentage of deaths with concomitant drug involvement for drug overdose deaths involving the top 10 drugs: United States, 2016

Referent drug	Number of drug overdose deaths involving the referent drug	Number of drug overdose deaths involving the referent drug and one or more concomitant drugs	Percentage of drug overdose deaths involving the referent drug and one or more concomitant drugs
Opioids			
Fentanyl	18,335	12,694	69.2
Heroin	15,961	11,248	70.5
Hydrocodone	3,199	2,743	85.7
Methadone	3,493	2,551	73.0
Morphine	5,014	4,175	83.3
Oxycodone	6,199	5,027	81.1
Benzodiazepines			
Alprazolam	6,209	5,970	96.2
Diazepam	2,022	1,951	96.5
Stimulants			
Cocaine	11,316	8,363	73.9
Methamphetamine	6,762	3,370	49.8

NOTES: Drug overdose deaths are identified using *International Classification of Diseases, Tenth Revision* underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Only deaths with at least one specific drug identified are included in the analysis.

SOURCE: NCHS, National Vital Statistics System, Mortality files linked with death certificate literal text, 2016.

Table D. Most frequent concomitant drugs for drug overdose deaths involving the top 10 drugs: United States, 2016

Referent drug	Number of drug overdose deaths involving the referent drug	Most frequent concomitant drug		Second most frequent concomitant drug		Third most frequent concomitant drug	
		Concomitant drug	Number and percentage ¹ of deaths involving both drugs	Concomitant drug	Number and percentage ¹ of deaths involving both drugs	Concomitant drug	Number and percentage ¹ of deaths involving both drugs
Opioids							
Fentanyl	18,335	Heroin	5,915 (32.3)	Cocaine	4,598 (25.1)	Alprazolam	1,760 (9.6)
Heroin	15,961	Fentanyl	5,915 (37.1)	Cocaine	3,804 (23.8)	Alprazolam	1,668 (10.5)
Hydrocodone	3,199	Alprazolam	822 (25.7)	Oxycodone	551 (17.2)	Fentanyl	478 (14.9)
Methadone	3,493	Alprazolam	751 (21.5)	Fentanyl	528 (15.1)	Heroin	483 (13.8)
Morphine	5,014	Fentanyl	1,612 (32.1)	Cocaine	846 (16.9)	Heroin	687 (13.7)
Oxycodone	6,199	Alprazolam	1,571 (25.3)	Fentanyl	1,150 (18.6)	Morphine	668 (10.8)
Benzodiazepines							
Alprazolam	6,209	Fentanyl	1,760 (28.3)	Heroin	1,668 (26.9)	Oxycodone	1,571 (25.3)
Diazepam	2,022	Oxycodone	576 (28.5)	Fentanyl	502 (24.8)	Heroin	404 (20.0)
Stimulants							
Cocaine	11,316	Fentanyl	4,598 (40.6)	Heroin	3,804 (33.6)	Alprazolam	1,031 (9.1)
Methamphetamine	6,762	Heroin	1,477 (21.8)	Fentanyl	753 (11.1)	Cocaine	562 (8.3)

¹Percentage of drug overdose deaths involving the referent drug that also involved the concomitant drug. Deaths may involve more than one concomitant drug in addition to the referent drug.

NOTES: Drug overdose deaths are identified using *International Classification of Diseases, Tenth Revision* underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Only deaths with at least one specific drug identified are included in the analysis.

SOURCE: NCHS, National Vital Statistics System, Mortality files linked with death certificate literal text, 2016.

Table E. Top 10 drugs involved in drug overdose deaths, by intent of death: United States, 2016

Rank ¹	Unintentional (n = 54,793)			Suicide (n = 5,086)			Undetermined (n = 3,643)		
	Referent drug	Number of deaths ²	Percent of deaths ³	Referent drug	Number of deaths ²	Percent of deaths ³	Referent drug	Number of deaths ²	Percent of deaths ³
1	Fentanyl	16,981	31.0	Oxycodone	648	12.7	Fentanyl	1,185	32.5
2	Heroin	15,075	27.5	Diphenhydramine	576	11.3	Heroin	766	21.0
3	Cocaine	10,618	19.4	Hydrocodone	472	9.3	Morphine	619	17.0
4	Methamphetamine	6,448	11.8	Alprazolam	468	9.2	Cocaine	579	15.9
5	Alprazolam	5,510	10.1	Acetaminophen	343	6.7	Oxycodone	322	8.8
6	Oxycodone	5,225	9.5	Quetiapine	297	5.8	Methadone	264	7.2
7	Morphine	4,122	7.5	Morphine	268	5.3	Alprazolam	225	6.2
8	Methadone	3,110	5.7	Tramadol	266	5.2	Methamphetamine	195	5.4
9	Hydrocodone	2,556	4.7	Bupropion	264	5.2	Hydrocodone	169	4.6
10	Diazepam	1,723	3.1	Zolpidem	251	4.9	Diphenhydramine	152	4.2

¹Ranks were not tested for statistical significance.

²Number of drug overdose deaths involving the referent drug.

³Percentage of drug overdose deaths involving the referent drug.

NOTES: Drug overdose deaths are identified using *International Classification of Diseases, Tenth Revision* underlying cause-of-death codes X40–X44 (unintentional), X60–X64 (suicide), and Y10–Y14 (undetermined). Only deaths with at least one specific drug identified are included in the analysis. The results for 110 deaths with an intent of homicide (X85) are not shown due to small numbers. 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.

SOURCE: NCHS National Vital Statistics System, Mortality files linked with death certificate literal text, 2016.

drug overdose deaths increased considerably within a relatively short period. From 2011 through 2016, the rate of drug overdose deaths involving heroin more than tripled, as did the rate of drug overdose deaths involving methamphetamine. The rate of drug overdose deaths involving fentanyl and fentanyl analogs doubled each year from 2013 through 2016, from 0.6 per 100,000 in 2013 to 1.3 in 2014, 2.6 in 2015, and 5.9 in 2016. Among the drugs discussed in this report, only methadone showed a decreasing drug overdose death rate, from 1.4 per 100,000 in 2011 to 1.1 in 2016.

Results from the literal text analysis highlight the concomitant occurrence of more than one drug in many drug overdose deaths. For the top 10 drugs involved in drug overdose deaths in 2016, the proportion of deaths involving both the referent drug and at least one other concomitant drug ranged from 50% for methamphetamine to 96% for alprazolam or diazepam. Approximately 70% of drug overdose deaths involving fentanyl or heroin—the top two drugs involved in drug overdose deaths in 2016—involved at least one other specific drug.

The 10 most frequently mentioned drugs were often found in combination with each other. Drug combinations often involved drugs of different drug classes. For example, the opioid fentanyl and the stimulant cocaine were mentioned concomitantly in nearly 4,600 deaths. The opioid oxycodone and the benzodiazepine alprazolam were mentioned concomitantly in more than 1,500 deaths. In some instances, the most frequently mentioned concomitant drug was in the same drug class as the referent drug. For example, the opioids fentanyl and heroin were both mentioned in approximately 5,900 deaths. While the literal text can be used to identify the mention of the two drugs (fentanyl and heroin), the details to distinguish whether the heroin and fentanyl were taken as one (i.e., heroin laced with fentanyl) or as two separate drugs are often not available.

The drugs most frequently mentioned in the literal text varied by the intent of the drug overdose death. In 2016, unintentional drug overdose deaths most frequently mentioned fentanyl, heroin, and cocaine, while suicides by drug overdose more frequently mentioned oxycodone, diphenhydramine, hydrocodone, and alprazolam.

Data considerations and study limitations

This report used analysis of the literal text on death certificates to identify the drugs involved in overdose deaths (7). Software programs search the literal text for mentions of drugs and for terms that provide context about the involvement of the drug in the death. As shown in [Table C](#), drug overdose deaths frequently involve multiple drugs. For deaths in which multiple drugs are involved, whether the death was caused by just one of the drugs present or was caused by a combination of some or all of the drugs present cannot be determined from the literal text analysis. This limitation in identifying the specific contribution of any given drug to the death should be considered when reviewing the findings in this report.

Reporting of deaths with at least one specific drug in the death certificate literal text improved from 73% of drug overdose deaths in 2011 to 85% in 2016. While improved reporting enhances the quality of the data, it also creates complexity in interpreting the trends and rankings observed. The findings in this report should be considered in light of the improvements in reporting. For example, some of the observed increase from 2011 through 2016 in drug overdose deaths involving the top 10 drugs is likely attributable to improvements in reporting. However, it is unlikely that the large increases seen for some drugs such as fentanyl, heroin, cocaine, and methamphetamine (i.e., drugs with an annual percent increase in mortality rates of 18% or greater) are due solely to improvements in reporting. True increases in the number of deaths involving these drugs are likely to have occurred. Similarly, decreases in rates such as those seen for drug overdose deaths involving methadone are likely to be, at least in part, due to a true decrease. It is also possible that the improvements in reporting could obscure real decreases. For example, using observed values, there was no statistically significant change in the age-adjusted rate of drug overdose deaths involving hydrocodone from 2011 through 2016. However, after adjustment for improved reporting (see [Technical Notes](#)), the age-adjusted rate of drug overdose deaths

involving hydrocodone showed a significant decline of about 4% per year from 2011 through 2016.

Methods based on literal text analysis are dependent on the quality and completeness of the literal text, which may vary from jurisdiction to jurisdiction due to variation in death investigation and reporting practices or other differences in the medicolegal death investigation systems across the United States (16,17). Issues that contribute to variation in literal text information on drug overdose deaths have been discussed in detail elsewhere (11,18), and briefly, include certain factors.

Variation in death investigation practice and reporting—This includes whether or not toxicological laboratory testing is performed to determine the type(s) of drugs present. The substances tested for and the circumstances under which the tests are performed may vary by jurisdiction, decedent, and over time.

Interpretation of toxicology results—Interpretation of findings depends on which tests are ordered, the characteristics of the causative agent(s), the characteristics of the metabolites, and other evidence gathered during the investigation and examination.

Attribution to a specific drug—Some drugs have the same metabolites or are metabolites of other drugs, potentially resulting in misattribution of the specific drugs involved in the death. For example, mentions of morphine may actually refer to involvement of heroin because morphine is a metabolite of heroin (9). This could potentially result in underestimation of the number of deaths involving heroin and overestimation of the number of deaths involving morphine.

Determination of which 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, while others may list multiple drugs because they believe the drugs to be of equal lethality or that the interaction of all drugs mentioned is important. Some certifiers may not want to impose an order when listing the drugs that were present. Others have noted that space limitations in the software programs they use to complete electronic death registration limit their ability to include all drugs that contributed to the death.

These and other factors may contribute to the variation in the completeness and accuracy of the information on the death certificate about the specific drugs involved in the death. The literal text analysis is dependent on the quality of the information available. Therefore, the results presented in this report should be considered the minimum number or rate for that specific drug because there could be additional deaths in which the drug was involved, but the drug was not reported in the literal text.

Finally, it is possible that drugs rarely seen in drug overdose deaths were not included in the search term list used in this study, despite the multiple avenues taken to develop the list of search terms (7). This also could result in underestimation of the number of deaths involving a specific drug.

Conclusions

Literal text analysis can be used to extract key information from death certificates to improve national monitoring of drug overdose deaths. This report identifies the specific drugs most frequently mentioned in drug overdose deaths from 2011 through 2016, and shows that the most frequent drugs mentioned varied over time and by intent of death (i.e., unintentional drug overdose, suicide by drug overdose, and overdose death of undetermined intent). Results from the literal text analysis also confirm that many drug overdose deaths involve multiple drugs.

With slight modification, the methods used in this report can be used to identify deaths involving newly approved prescription drugs and new substances of abuse. Periodic updating of search terms and text search capabilities is essential for the ongoing surveillance and monitoring of emerging trends in drug overdose deaths using literal text analysis. In addition, this report highlights the critical importance of reporting the specific drugs involved in drug overdose deaths in the literal text on death certificates.

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Detailed Table

Age-adjusted rates for drug overdose deaths involving selected opioids, benzodiazepines, and stimulants: United States, 2011–2016 11

Table. Age-adjusted rates for drug overdose deaths involving selected opioids, benzodiazepines, and stimulants: United States, 2011–2016

Referent drug	2011	2012	2013	2014	2015	2016
Opioids						
Fentanyl	0.5	0.5	0.6	1.3	2.6	5.9
Heroin	1.5	2.0	2.7	3.5	4.3	5.1
Hydrocodone	1.0	1.0	1.0	1.0	0.9	1.0
Methadone	1.4	1.3	1.2	1.1	1.1	1.1
Morphine	1.0	1.1	1.2	1.2	1.3	1.5
Oxycodone	1.8	1.7	1.6	1.7	1.8	1.9
Benzodiazepines						
Alprazolam	1.3	1.2	1.2	1.3	1.5	2.0
Diazepam	0.5	0.5	0.5	0.5	0.5	0.6
Stimulants						
Cocaine	1.6	1.5	1.7	1.8	2.3	3.6
Methamphetamine	0.6	0.7	1.0	1.2	1.6	2.1

NOTES: Drug overdose deaths are identified using *International Classification of Diseases, Tenth Revision* (ICD-10) 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 or drug class in the literal text, as identified using ICD-10 multiple cause-of-death codes T36–T50.8, improved from 75% of drug overdose deaths in 2011 to 85% of drug overdose deaths in 2016.

SOURCE: NCHS, National Vital Statistics System, Mortality files linked with death certificate literal text, 2011–2016.

Technical Notes

Assessment of trends in drug-specific rates using an adjustment factor to account for improvements in reporting of specific drugs

The percentage of drug overdose deaths with an *International Classification of Diseases, Tenth Revision* multiple cause-of-death code T36–T50.8 indicates the reporting of specific drugs and drug classes in mortality data. During the study period 2011–2016, the percentage of drug overdose deaths with a multiple cause-of-death code T36–T50.8 increased from 74.9% of deaths in 2011 to 85.4% in 2016.

The improvement in reporting of specific drugs and drug classes during the study period could potentially influence the observed trends in drug overdose deaths for specific drugs (Figures 1–3). To assess the possible influence of improved reporting, an adjustment analysis was conducted. In this analysis, an adjustment factor was applied to each number and age-adjusted rate for drug overdose deaths involving the top 10 drugs involved in drug overdose deaths during 2011–2016. The adjustment factor was based on two assumptions: (1) the percentage of deaths with one or more drugs or drug classes specified in each year from 2011 through 2016 was the same and equal to the percentage in 2016 (85.4%), and (2) in each year, the distribution of deaths by specific drug was the same for deaths that identified one or more specific drugs, as for deaths that did not identify a specific drug. The adjustment factor was used to estimate the rate if the percentage of deaths with one or more drugs or drug classes specified had been uniform from 2011 through 2016.

The [Technical Notes Table](#) shows the crude rate, age-adjusted rate, and age-adjusted rate after application of the factor to adjust for improved reporting. The findings for the 2011–2016 trends in rates based on observed and adjusted numbers were, in general, the same (i.e., a statistically significant increase, decrease, or no change in the rate) for fentanyl, oxycodone, diazepam, cocaine, and methamphetamine. For heroin, the inflection point in 2014 was no longer found, resulting in a percent change in the rate of about 24% per year from 2011 through 2016. For morphine, the inflection point in 2015 was no longer found, resulting in a percent change in the rate of about 5% per year from 2011 through 2016. For methadone, rates decreased by about 12% per year from 2011 through 2014, and by about 3% from 2014 through 2016. For hydrocodone, there was a significant decline in the age-adjusted rates of about 4% per year from 2011 through 2016. For alprazolam, the inflection point in 2013 was no longer found, and as with the observed values, the increasing trend from 2011 through 2016 was not statistically significant.

Table. Crude rates, age-adjusted rates, and adjusted age-adjusted rates for drug overdose deaths involving selected drugs, 2011–2016

Drug	Crude rate						Age-adjusted rate						Trend 1		Trend 2		Adjusted age-adjusted rate						Trend 1		Trend 2	
	2011	2012	2013	2014	2015	2016	2011	2012	2013	2014	2015	2016	Years	Annual percent change	Years	Annual percent change	2011	2012	2013	2014	2015	2016	Years	Annual percent change	Years	Annual percent change
Opioids																										
Fentanyl	0.53	0.51	0.61	1.32	2.57	5.67	0.53	0.52	0.61	1.34	2.64	5.89	2011–2013	8.4	2013–2016	¹ 113.3	0.60	0.59	0.67	1.42	2.71	5.89	2011–2013	6.1	2013–2016	¹ 107.0
Heroin	1.47	1.96	2.66	3.41	4.14	4.94	1.47	1.99	2.70	3.50	4.27	5.10	2011–2014	¹ 33.7	2014–2016	¹ 20.0	1.67	2.23	2.96	3.71	4.39	5.10	2011–2016	¹ 23.7
Hydrocodone	1.03	0.97	0.98	1.03	0.95	0.99	1.01	0.96	0.96	1.02	0.92	0.95	2011–2016	-1.0	1.15	1.08	1.06	1.08	0.94	0.95	2011–2016	¹ -3.7
Methadone	1.46	1.30	1.17	1.10	1.05	1.08	1.44	1.29	1.17	1.07	1.05	1.08	2011–2014	¹ -9.6	2014–2016	0.4	1.64	1.46	1.29	1.14	1.08	1.08	2011–2014	¹ -11.8	2014–2016	¹ -2.7
Morphine	1.06	1.12	1.19	1.26	1.31	1.55	1.03	1.10	1.16	1.24	1.29	1.53	2011–2015	¹ 5.7	2015–2016	17.6	1.18	1.23	1.28	1.31	1.33	1.53	2011–2016	¹ 4.6
Oxycodone	1.79	1.65	1.57	1.70	1.80	1.92	1.79	1.66	1.55	1.69	1.78	1.91	2011–2013	-6.5	2013–2016	7.0	2.04	1.87	1.70	1.79	1.83	1.91	2011–2013	-8.4	2013–2016	3.7
Benzodiazepines																										
Alprazolam	1.30	1.21	1.18	1.33	1.49	1.92	1.32	1.23	1.20	1.33	1.52	1.96	2011–2013	-6.7	2013–2016	18.2	1.51	1.38	1.31	1.41	1.56	1.96	2011–2016	5.8
Diazepam	0.54	0.50	0.51	0.55	0.56	0.63	0.54	0.49	0.50	0.55	0.55	0.63	2011–2016	3.5	0.61	0.55	0.55	0.58	0.56	0.63	2011–2016	0.7
Stimulants																										
Cocaine	1.63	1.52	1.68	1.85	2.28	3.50	1.62	1.52	1.67	1.85	2.29	3.55	2011–2016	¹ 18.4	1.85	1.71	1.83	1.96	2.36	3.55	2011–2016	¹ 15.2
Methamphetamine	0.61	0.72	1.01	1.18	1.58	2.09	0.62	0.73	1.02	1.18	1.60	2.12	2011–2016	¹ 28.6	0.71	0.82	1.12	1.25	1.64	2.12	2011–2016	¹ 25.1

... Category not applicable.

¹Significant change in rate, $p < 0.05$.

NOTES: Drug overdose deaths are identified using *International Classification of Diseases, Tenth Revision* 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 rates. Trends in death rates were evaluated using the Joinpoint Regression Program set to identify a maximum of two joinpoints.

SOURCE: NCHS, National Vital Statistics System, Mortality files linked with death certificate literal text, 2011–2016.

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