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Drugs and Drug Classes Involved in Overdose Deaths Among Females, United States: 1999–2017

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Abstract

Background: Drug overdose deaths among U.S. women have risen steadily from 1999 to 2017, especially among certain ages. Various studies report involvement of drugs and drug classes in overdose deaths. Less is known, however, regarding the combinations that are most often indicated on death certificates, particularly among females. Analyzing mutually, exclusive drug/drug class combinations listed on death certificates of females are the objective of this study.

Materials and Methods: Mortality data for U.S. female residents were obtained from the 1999 to 2017 National Vital Statistics System (n = 260,782). Analyses included deaths with an underlying cause of death based on International Classification of Diseases, 10th Revision (ICD-10) codes for drug overdoses. The drug/drug class involved included individual 4-digit ICD-10 codes in the range T36.0–T50.9, including poisoning deaths due to all drugs, excluding alcohol. Years from 1999 to 2017 were grouped in six β-year categories with the most recent year (2017) left separate for analysis. All drug overdose deaths were analyzed in mutually exclusive categories.

Results: From 1999 to 2017, the top-listed drug/drug class overall and by year grouping was solely “other and unspecified drugs, medicaments and biological substances”; however, that listing dropped from 25.8% from the 1999 to 2001 period to 14.1% in 2017. Overall, the next most frequent single drug/drug class mentions were “natural and semisynthetic opioids” (20,951; 8.0%) and “cocaine” (10,882; 4.2%). Two of the top five drug/drug class

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Authors’ Contributions

A.E.C. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. She was responsible for the concept and design, acquisition of data, analysis and interpretation of the data, and drafting of the final article. J.G.S. was responsible for the concept and design and analysis and interpretation of the data. K.A.M. was responsible for the concept and design, acquisition of data, and analysis and interpretation of the data. A.E.C., J.G.S., and K.A.M. have read and approved the final article.

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combinations included benzodiazepines (“natural and semisynthetic opioids”/“benzodiazepines” and “methadone”/“benzodiazepines”).

Conclusions: Analyzing trends in drugs and drug classes involved in female drug overdose deaths is a critical foundation for developing gender-responsive public health interventions. Reducing high-risk drug use by improving prescribing practices, preventing drug use initiation, and addressing use of multiple drugs can help prevent overdose deaths.

Keywords

drug poisoning; National Vital Statistics System; drug overdose; polydrug; polysubstance

Introduction

Drug overdose death rates among U.S. females have risen steadily from 1999 to 2017 (from 3.9 per 100,000 to 14.4 per 100,000, respectively).[1] Certain age groups of women have been disproportionately affected. From 1999 to 2017, drug overdose death rates increased by ~200% among women aged 35–39 and 45–49 years, 350% among those aged 30–34 and 50–54 years, and nearly 500% among those aged 55–64 years.[2] Research has shown that drug overdose deaths differ by location, race, occupation, and other factors.[3,4] Females may experience different drug overdose-related behaviors and outcomes than males; therefore, females are an important study group to analyze separately in detail. Prescribing practices,[5] treatment-seeking and prescription filling behaviors,[5,6] biological differences,[7] and illicit drug use differences[8] contribute to differences in drug overdose-related behaviors and outcomes between females and males.

Prescription opioids, lethal combinations of prescription and illicit drugs, heroin, and illicitly manufactured fentanyl have impacted the trajectory of drug overdose deaths.[9,10] Studies have investigated drug overdose death rates involving very specific combinations of drugs/drug classes.[11,12] However, many of these studies use methods that categorize a drug overdose death based on “any involvement.” For example, if a drug overdose death involved both “cocaine” and “psychostimulants with abuse potential,” the death would be counted as a drug overdose death due to “cocaine” and would be simultaneously counted as a drug overdose death due to “psychostimulants with abuse potential,” although these data are from a single death. In addition, literal text analyses of death certificates have been performed where text fields of death certificates are scanned for possible inclusion of specific drug names; however, these analyses have not analyzed drug overdose deaths in mutually exclusive categories.[9,13] Using a mutually exclusive capture, if a single death certificate listed the “heroin” and “cocaine” drug codes (T40.1 and T40.5, respectively), this death would be categorized in its own category (“heroin” & “cocaine” drug overdose death). While there is much research on specific drugs involved in drug overdose deaths, less is known regarding which combinations are most often indicated on death certificates, particularly among women.[2] The objective of this study is to fill a critical gap in the literature by investigating drug classes and drug class combinations involved in drug overdose deaths listed on death certificates of females in a mutually exclusive capture.

Materials and Methods

Mortality data for U.S. female residents were obtained from the 1999 to 2017 National Vital Statistics System.[14] Analyses are based on information from death certificates filed in the 50 states and the District of Columbia. Deaths of nonresidents (*e.g.*, nonresident aliens; nationals living abroad; and residents of Puerto Rico, Guam, the U.S. Virgin Islands, and other U.S. territories) were excluded. Mortality data are provided to the Centers for Disease Control and Prevention's National Center for Health Statistics (NCHS) through the Vital Statistics Cooperative Program and coded according to the International Classification of Diseases, 10th Revision (ICD-10) by NCHS.[2,8,9] Analyses were restricted to deaths with an underlying cause of death based on the following ICD-10 codes for drug overdoses: X40–X44 (unintentional), X60–X64 (suicide), X85 (homicide), and Y10–Y14 (undetermined intent).[14,15] The drug/drug class involved was based on individual 4-digit ICD-10 codes in the range T36.0–T50.9, which include poisoning deaths due to all drugs, excluding alcohol.[16,17] All drug overdose deaths, whether the ICD code indicated a single drug/drug class or multiple, were analyzed in mutually exclusive categories (9,668 unique combinations were ranked by number of deaths). When the code "other and unspecified drugs, medicaments, and biological substances" (T50.9) was listed with another drug code, the T50.9 code was ignored. Years were grouped in six 3-year categories to illustrate general trends over time, with the most recent year (2017) left separate to aid in understanding the most recent data available. This study involved secondary analysis of existing data and did not involve human subjects; therefore, no Institutional Review Board (IRB) approval was required. SAS® software version 9.4 was used for analyses.

Results

The total number of drug overdose deaths among females from 1999 to 2017 was 260,782 (Table 1). The total number of drug overdose deaths increased each year during the study period (from 5,591 deaths in 1999 to 23,685 in 2017). Age adjusted rates increased from 1999 (3.9 per 100,000) to 2011/12 (10.2) and from 2011/12 to 2017 (14.4).

In 1999, the percentage of drug overdose deaths among females involving one listed drug/drug class was 74.2% and the percentage involving multiple drug/drug classes was 25.8% (Table 1). In 2017, this changed to a nearly even split with 48.3% of the deaths involving one listed drug/drug class and 51.7% listing multiple drugs/drug classes. The number of deaths with one listed drug increased from 1999 (4,150) to 2014 (11,120). The number of deaths with multiple listed drugs/drug classes increased every year from 1999 to 2017.

Overall, 24.3% of the death certificates listed solely "other and unspecified drugs, medicaments, and biological substances" (T50.9; Table 2); however, the sole listing of that code declined over time. The next most frequent single drug/drug class mentions were "natural and semisynthetic opioids" (20,951; 8.0%), "cocaine" (10,882; 4.2%), and "other synthetic narcotics" (10,308; 4.0%). For 1999–2001, "cocaine" was the top single specified drug, which shifted to the "natural and semisynthetic opioids" drug class during the next five 3-year groupings. Overall, the top two most frequently listed multiple drug/drug class combinations were "natural and semisynthetic opioids"/"benzodiazepines" (6,372; 2.5%)

and “heroin”/“cocaine” (2,561; 1.0%) (Table 3). In 2017, “other synthetic narcotics,” which are largely reflective of illegally manufactured fentanyl and other fentanyl analogs, were mentioned in four of the top five combinations.

Discussion

This analysis provides a description of the most frequently listed single and multiple drug/drug class categories involved in drug overdose deaths among females. The methods used in this study are novel since analyses of drugs/drug classes involved in drug overdose deaths often involve isolating specific drugs or combinations of drugs, and this study created mutually exclusive categories across all female drug overdose deaths. The study fills a research gap by determining trends in the most common drug class/drug class combinations listed on death certificates of females. Further, the study indicates a complex and evolving landscape related to drug overdoses as over half of the female death certificates in 2017 listed multiple drug/drug class involvement. The presence of benzodiazepines in the top five multiple drug/drug class overdoses and the absence of benzodiazepines in the top five single drug/drug class overdoses aligns with findings from other research.[12,18–24]

The increase in drug overdose deaths seen between 2013 and 2017 and increases in “synthetic opioids” for drug overdose deaths coincides with rising drug overdose deaths involving illicitly manufactured fentanyl.[25] U.S. law enforcement-obtained drug products testing positive for fentanyl increased by 426%, and synthetic opioid-involved drug overdose deaths increased by 79% between 2013 and 2014.[26] Heroin, cocaine, and methamphetamine are also likely to have contributed to this increase, since these drugs, along with illicitly manufactured fentanyl, were involved in 85% of all drug overdose deaths (either alone or in combination). Rates of drug overdose deaths involving cocaine decreased from 2006 to 2012; however, rates began to climb again after this period.[27] The presence of multiple drugs involved in drug overdose deaths and the involvement of both prescription and illicitly manufactured drugs, makes a public health approach to drug overdose prevention complex.[28]

There are a few known limitations to this study. Alcohol was not examined in this analysis, but may have been present in a portion of drug overdose deaths. This analysis acknowledges the limitations of death certificates to fully understand the changing landscape of drug overdose fatalities.[9,12] Listing of a drug may be due to substances tested for, or the circumstances under which tests are performed, access and use of standardized drug testing technology, or state drug testing requirements, and these all may have changed during the study period.[29] The finding in this study indicating decreasing percentages of “other and unspecified” listings on death certificates of female decedents may be due to improvements in drug capture. A drug class listed on a death certificate could include multiple drugs (*e.g.*, tramadol and fentanyl both fall under the same drug class).[1] In addition, details on death certificates may vary state by state and may provide more or less context regarding the circumstances and drugs involved in drug overdose deaths.[30] Further, even though guidance indicates that medical certifiers should list drugs on death certificates which are only present in substantial enough concentrations to cause or contribute to a drug overdose death, it

cannot be determined exactly how much each drug class contributed to a drug overdose death where multiple drug classes are involved.[29]

Conclusions

Analyzing trends in drugs and drug classes involved in drug overdose deaths among females is a critical foundation for developing gender-responsive public health interventions. These findings can inform interventions that address the lethality of drugs being used (alone or in combination) or that address the initiation of drug misuse (*e.g.*, inappropriate prescribing; illicit drug use). A comprehensive approach which includes the full spectrum of prevention and treatment services is likely necessary to reduce drug overdose deaths. For example, health care providers who treat women for pain, depression, or anxiety can discuss treatment options that consider the unique biopsychosocial needs of women.[7] Access to gender-responsive treatment services can help reduce harmful outcomes of substance use disorders. Electronic health records and prescription drug monitoring programs may be used to monitor potentially risky drug combinations and provide opportunities for clinical intervention. Reducing high-risk drug use by improving prescribing practices, preventing initiation of drug use, and addressing use of multiple drugs can help prevent overdose deaths. Naloxone distribution—especially for bystanders who may be able to reverse an opioid overdose—and enhanced linkage to care can also assist in reducing overdoses involving prescription and/or illicitly manufactured drugs.[27] Overdose deaths continue to be unacceptably high, and efforts are needed to reduce the number of deaths in this evolving epidemic.

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Table 1.

Number of Drug Overdose Deaths Among Females: Single versus Multiple Drug/Drug Class Mentions

Year	Deaths with one listed drug class[a] (Row % of total drug overdose deaths)	Deaths with multiple listed drug classes (Row % of total drug overdose deaths)	Total drug overdose deaths (Age-adjusted rate per 100,000)
1999	4,150 (74.2)	1,441 (25.8)	5,591 (3.9)
2000	4,272 (73.0)	1,580 (27.0)	5,852 (4.1)
2001	4,887 (72.6)	1,849 (27.4)	6,736 (4.6)
2002	6,051 (71.3)	2,439 (28.7)	8,490 (5.8)
2003	6,724 (71.6)	2,662 (28.4)	9,386 (6.4)
2004	7,245 (70.3)	3,059 (29.7)	10,304 (6.9)
2005	7,705 (69.5)	3,384 (30.5)	11,089 (7.3)
2006	8,524 (68.0)	4,008 (32.0)	12,532 (8.2)
2007	9,267 (67.6)	4,445 (32.4)	13,712 (8.8)
2008	9,436 (67.5)	4,546 (32.5)	13,982 (8.9)
2009	9,655 (67.0)	4,756 (33.0)	14,411 (9.1)
2010	10,214 (66.7)	5,109 (33.3)	15,323 (9.6)
2011	10,709 (65.5)	5,643 (34.5)	16,352 (10.2)
2012	10,680 (65.2)	5,710 (34.8)	16,390 (10.2)
2013	11,027 (64.2)	6,156 (35.8)	17,183 (10.6)
2014	11,120 (61.0)	7,123 (39.0)	18,243 (11.1)
2015	11,110 (57.1)	8,337 (42.9)	19,447 (11.8)
2016	11,692 (53.0)	10,382 (47.0)	22,074 (13.4)
2017	11,440 (48.3)	12,245 (51.7)	23,685 (14.4)
Overall	165,908 (63.6)	94,874 (36.4)	260,782 (8.9)

Drug overdose deaths were identified using ICD-10 underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. National Vital Statistics System—Mortality. Captures drug codes T36.0–T50.9, including “other and unspecified drugs, medicaments, and biological substances” (T50.9). Overdose deaths where T50.9 is listed with only one other drug class, is categorized as a single drug class overdose death.

[a]Includes drug poisoning overdose deaths with no drug class code identified (<0.1% of all drug poisoning deaths).

ICD-10, International Classification of Diseases, 10th Revision.

Table 2.

Drug/Drug Class Involved in Drug Overdose Deaths Among Females by Single Drug Mention

Rank	1999–2001	2002–2004	2005–2007	2008–2010	2011–2013	2014–2016	2017	Overall
	Drug name No. of deaths (%)[a]	Drug name No. of deaths (%)[a]	Drug name No. of deaths (%)[a]	Drug name No. of deaths (%)[a]	Drug name No. of deaths (%)[a]	Drug name No. of deaths (%)[a]	Drug name No. of deaths (%)[a]	Drug name No. of deaths (%)[a]
1	Other[b]	Other[b]	Other[b]	Other[b]	Other[b]	Other[b]	Other[b]	Other[b]
	4,676 (25.8)	7,391 (26.3)	9,806 (26.3)	12,566 (28.8)	13,723 (27.5)	11,903 (19.9)	3,328 (14.1)	63,393 (24.3)
2	Cocaine	Natural and semisynthetic opioids	Natural and semisynthetic opioids	Natural and semisynthetic opioids	Natural and semisynthetic opioids	Natural and semisynthetic opioids	Other synthetic narcotics	Natural and semisynthetic opioids
	1,233 (6.8)	2,042 (7.3)	2,968 (8.0)	4,063 (9.3)	4,796 (9.6)	4,692 (7.9)	2,033 (8.6)	20,951 (8.0)
3	Natural and semisynthetic opioids	Cocaine	Cocaine	Methadone	Heroin	Heroin	Natural and semisynthetic opioids	Cocaine
	1,119 (6.2)	1,816 (6.5)	2,422 (6.5)	2,090 (4.8)	1,829 (3.7)	3,041 (5.1)	1,271 (5.4)	10,882 (4.2)
4	Other and unspecified narcotics	Methadone	Methadone	Cocaine	Methadone	Other synthetic narcotics	Psychostimulants with abuse potential	Other synthetic narcotics
	874 (4.8)	1,427 (5.1)	2,272 (6.1)	1,510 (3.5)	1,659 (3.3)	2,911 (4.9)	1,123 (4.7)	10,308 (4.0)
5	Antidepressants[c]	Other and unspecified narcotics	Other synthetic narcotics	Other synthetic narcotics	Cocaine	Psychostimulants with abuse potential	Cocaine	Methadone
	825 (4.6)	1,096 (3.9)	1,188 (3.2)	1,491 (3.4)	1,417 (2.8)	2,212 (3.7)	817 (3.5)	9,472 (3.6)

Only the top five drugs/drug class combinations are listed for each year grouping. Therefore, frequencies will not add to all drug overdoses and percentages do not add up to 100%. Drug overdose deaths were identified using ICD-10 underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Drug/drug class codes: heroin (T40.1); natural and semisynthetic opioids (e.g., oxycodone and hydrocodone) (T40.2); methadone (T40.3); other synthetic narcotics excluding methadone (e.g., fentanyl and tramadol) (T40.4); cocaine (T40.5); other and unspecified narcotics (T40.6); benzodiazepines (T42.4); tricyclic and tetracyclic antidepressants (T43.0); other and unspecified antidepressants (T43.2); psychostimulants with abuse potential (T43.6); other and unspecified drugs, medicaments and biological substances (T50.9). National Vital Statistics System—Mortality.

[a]Percentage of all drug overdose deaths in the year group.

[b]Other and unspecified drugs, medicaments, and biological substances (T50.9).

[c]Tricyclic and tetracyclic antidepressants (T43.0).

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Table 3.

Drug/Drug Class Involved in Drug Overdose Deaths Among Females by Multiple Drug Mentions

Rank	1999–2001	2002–2004	2005–2007	2008–2010	2011–2013	2014–2016	2017	Overall
	Drug name No. of deaths (%)[a]	**Drug name No. of deaths (%)[a]**	**Drug name No. of deaths (%)[a]**	**Drug name No. of deaths (%)[a]**	**Drug name No. of deaths (%)[a]**	**Drug name No. of deaths (%)[a]**	**Drug name No. of deaths (%)[a]**	**Drug name No. of deaths (%)[a]**
1	Cocaine & Other and unspecified narcotics	Cocaine & Other and unspecified narcotics	Natural and semisynthetic opioids & Benzodiazepines	Natural and semisynthetic opioids & Benzodiazepines	Natural and semisynthetic opioids & Benzodiazepines	Natural and semisynthetic opioids & Benzodiazepines	Heroin & Other synthetic narcotics	Natural and semisynthetic opioids & Benzodiazepines
	428 (2.4)	476 (1.7)	632 (1.7)	1,228 (2.8)	1,678 (3.4)	1,843 (3.1)	730 (3.1)	6,372 (2.5)
2	Heroin & Cocaine	Natural and semisynthetic opioids & Benzodiazepines	Methadone & Benzodiazepines	Methadone & Benzodiazepines	Heroin & Cocaine	Heroin & Other synthetic narcotics	Other synthetic narcotics & Cocaine	Heroin & Cocaine
	200 (1.1)	316 (1.1)	391 (1.1)	460 (1.1)	485 (1.0)	953 (1.6)	729 (3.1)	2,561 (1.0)
3	Natural and semisynthetic opioids & Cocaine	Heroine & Cocaine	Cocaine & Other and unspecified narcotics	Natural and semisynthetic opioids & Other and unspecified antidepressants	Methadone & Benzodiazepines	Heroin & Cocaine	Natural and semisynthetic opioids & Benzodiazepines	Natural and semisynthetic opioids & Other synthetic narcotics
	165 (0.9)	268 (1.0)	375 (1.0)	308 (0.7)	436 (0.9)	827 (1.4)	527 (2.2)	2,140 (0.8)
4	Natural and semisynthetic opioids & Benzodiazepines	Natural and semisynthetic opioids & Cocaine	Methadone & Cocaine	Natural and semisynthetic opioids & Methadone	Natural and semisynthetic opioids & Other and unspecified antidepressants	Natural and semisynthetic opioids & Other synthetic narcotics	Natural and semisynthetic opioids & Other synthetic narcotics	Methadone & Benzodiazepines
	148 (0.8)	208 (0.7)	355 (1.0)	304 (0.7)	391 (0.8)	754 (1.3)	422 (1.8)	2,029 (0.8)
5	Natural and semisynthetic opioids & Antidepressants[b]	Methadone & Cocaine	Natural and semisynthetic opioids & Cocaine	Natural and semisynthetic opioids & Other synthetic narcotics	Natural and semisynthetic opioids & Other synthetic narcotics	Other synthetic narcotics & Cocaine	Heroin & Other synthetic narcotics & Cocaine	Cocaine & Other and unspecified narcotics
	113 (0.6)	207 (0.7)	293 (0.8)	303 (0.7)	324 (0.7)	567 (1.0)	368 (1.6)	1,912 (0.7)

Only the top five drugs/drug class combinations are listed for each year grouping. Therefore, frequencies will not add to all drug overdoses and percentages do not add up to 100%. Drug overdose deaths were identified using ICD-10 underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Drug/drug class codes: heroin (T40.1); natural and semisynthetic opioids (*e.g.*, oxycodone and hydrocodone) (T40.2); methadone (T40.3); other synthetic narcotics excluding methadone (*e.g.*, fentanyl and tramadol) (T40.4); cocaine (T40.5); other and unspecified narcotics (T40.6); benzodiazepines (T42.4); tricyclic and tetracyclic antidepressants (T43.0); other and unspecified antidepressants (T43.2); psychostimulants with abuse potential (T43.6); other and unspecified drugs, medicaments and biological substances (T50.9). National Vital Statistics System—Mortality.

[a]Percentage of all drug overdose deaths in the year group.

[b]Tricyclic and tetracyclic antidepressants (T43.0).