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Leveraging pooled medical examiner records to surveil complex and emerging patterns of polysubstance use in the United States

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Abstract

Background: The United States (US) is an extreme global outlier for drug-related death rates. However, data describing drug-related deaths are generally available only on an 8–13-month lag. Furthermore, granular details about substance-involvement are often not available, which particularly stymies efforts to track fatal polysubstance and novel psychoactive substance use. Detailed medical examiner records provide a powerful source of information for drug-related death surveillance, but have been underutilized.

Methods: We pooled medical examiner data from five US states and 14 counties that together comprise 18% of the US population to examine demographic, geographic, and drug-specific trends in polysubstance drug-related deaths. We employed mixed effects logistic regression to identify

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CRediT authorship contribution statement

Chelsea L. Shover: Conceptualization, Formal analysis, Methodology, Writing – original draft. **Joseph R. Friedman:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **Ruby Romero:** Data curation, Project administration, Writing – review & editing. **Sergio Jimenez:** Data curation, Writing – review & editing. **Jacqueline Beltran:** Data curation, Writing – review & editing. **Candelaria Garcia:** Data curation, Writing – review & editing. **David Goodman-Meza:** Writing – review & editing, Formal analysis, Visualization.

Declaration of competing interest

The authors have no conflicts of interest to declare.

Ethics

This research was determined by the UCLA Institutional Review Board to be exempt from Institutional Review Board oversight as it involved only data from deceased persons and was therefore not human subjects research.

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demographic factors associated with polysubstance rather than single substance drug-related deaths. We assessed the correlations between drug classes and described geographic variation in the prevalence of specific drugs and the presence of novel and emerging psychoactive substances.

Results: Our sample included 73,077 drug-related deaths from 2012 through early 2022. Nearly two-thirds of drug-related deaths were polysubstance-involved, with the number and percentage growing annually. High percentages of polysubstance drug-related deaths were observed in both urban and rural jurisdictions. After adjusting for year and jurisdiction, female, American Indian and Alaska Native, and White individuals had the most elevated odds of polysubstance drug-related deaths. Drug-related deaths involving benzodiazepines or opioids, whether pharmaceutical or illicit, and other pharmaceutical drugs were most likely to have polysubstance involvement, while methamphetamine-involved deaths were least likely to involve multiple substances. Strong correlations were observed between prescription opioids and prescription benzodiazepines, fentanyl and xylazine, and designer benzodiazepines and novel synthetic opioids.

Conclusions: Analysis of detailed medical examiner records reveals the breadth and complexity of polysubstance drug-related deaths in the US. Future efforts to use this unique resource can improve population-based surveillance of drug-related deaths to better tailor interventions and solutions to this critical health crisis.

Keywords

Epidemiology; Polysubstance; Opioids; Stimulants; Benzodiazepines

Introduction

The United States (US) has entered the “fourth wave” of the overdose crisis, characterized by polysubstance drug-related deaths involving synthetic opioids (e.g., fentanyl) and stimulants (e.g., methamphetamine) (Ciccarone, 2021; Han et al., 2021). Polysubstance use poses unique risks for drug-related death and other health harms (e.g., infective endocarditis, cardiovascular disease) beyond those associated with the use of a single drug (Dai et al., 2022; Glick et al., 2021; Goodwin et al., 2022; Palis et al., 2022). Moreover, there is evidence that individuals engaged in polysubstance use are inadequately treated in the US healthcare system, which largely focuses on single substance use disorders. For example, a study of people with co-occurring opioid and methamphetamine use disorders found that while over 80% were treated for opioid use disorder, less than a quarter were treated for their methamphetamine use disorder (Yen Li et al., 2021).

Despite increased recognition of the importance of polysubstance use to the evolving overdose crisis, data characterizing polysubstance drug-related deaths are hampered by structural data system limitations. National statistics are based on International Classification of Diseases, tenth edition (ICD-10) codes which, at times, lump together dissimilar drugs. For instance, code T40.4 captures both fentanyl, a highly potent synthetic opioid implicated in over 70% of drug-related deaths in the most recently available data, and buprenorphine, a partial opioid agonist used in the treatment of opioid use disorder (National Center for Health Statistics, 2022). Here we employ detailed medical examiner records, which we argue can facilitate surveillance of emerging patterns that are obscured or

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delayed in national statistics (Centers for Disease Control and Prevention, 2022; Friedman et al., 2022a; Shiue et al., 2021; Shover et al., 2020; Shover et al., 2021; Trinidad et al., 2016). In this analysis, we leverage a novel dataset of detailed medical examiner records to characterize demographic, geographic, and specific drug aspects of polysubstance drug-related deaths.

Methods

Our research team systematically contacted medical examiner and coroner jurisdictions requesting detailed individual-level death records. Five states (Alaska, Connecticut, Minnesota, North Carolina, Wyoming) and 14 US counties voluntarily provided detailed death certificate data in spreadsheet files. Combined, these jurisdictions represent all four US Census regions and account for 18% of the US population (U.S. Census Bureau, 2021). The population density in these jurisdictions ranges from very rural (1.3 persons per square mile in Alaska) to very urban (5,583 persons per square mile in Cook County, IL) (U.S. Census Bureau, 2022). Not all jurisdictions could provide data for the entire 2012–2022 period. As such, jurisdictions contributed data covering varied periods of time between 2012 and early 2022. The number of records and years included are listed in Table 1.

For this analysis, we investigate “drug-related” deaths, as opposed to “overdose” deaths, in order to provide the most comparable assessment of trends between jurisdictions, given the information consistently provided on death certificates. Jurisdiction-level variation in US death certificate data have been well-documented in the literature; however, broad commonalities in their process facilitate comparison across jurisdictions (Warner et al., 2013). Generally, medical examiner or coroner offices are tasked with investigating all potential drug-related or overdose deaths (as well as all homicides, suicides, unattended deaths, and various other categories). These offices do not investigate all deaths that occur in a given jurisdiction, as some deaths are certified by other physicians (e.g. deaths that occur in the course of hospitalization or following a documented course of disease). Medical examiner and coroner death investigations may include post-mortem toxicological testing of blood, urine, or other specimens, autopsy, review of medical records, observation at scene of death, and interviews with family members or friends. The specific substances tested for in post-mortem toxicology varies both between and within jurisdiction, with some jurisdictions conducting all testing in an in-house lab, others using send-out testing to large private, national laboratories for all cases, and still others employing a combination of these approaches (e.g. testing for a standard list of drugs in-house and sending-out for more complex or ambiguous cases).

US death certificates can include up to four causes (A-D) as well as contributing causes. These do not typically include the term “overdose,” though the more commonly-employed terms “toxicity,” and “intoxication” can be understood to have a similar meaning. ICD-10 mortality codes are assigned for all deaths – including those not investigated by a medical examiner or coroner – separately from the death investigation, and are not typically available from a jurisdiction’s medical examiner or coroner’s office. ICD-10 mortality codes distinguish between “underlying” versus “multiple” cause of death, which does not map perfectly onto the A-D plus contributing causes schema. Overdose surveillance data in

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the US using ICD-10 mortality codes typically include the following underlying causes of death: Unintentional drug poisonings (X40-X44); Intentional drug poisonings (X60-X64); Homicide drug poisonings (X85); and undetermined drug poisonings (Y10-Y14).Only a few drugs and drug classes have their own three-digit ICD-10 code (e.g., heroin (T40.1), cocaine (T40.5), benzodiazepines (T42.4)) which can be listed as multiple but not underlying cause of death, whether the underlying cause is drug poisoning or something else. Many drugs and medications are grouped from longer ICD-10 codes into a three-digit category that contains multiple distinct drugs. ICD-10 mortality codes beyond three digits are generally not available. It is important to note that ICD-10 codes are assigned based on death certificate data, so the limitations of toxicological testing and determination of cause inherent in the fragmented death investigation system are carried forward into national surveillance data.

Substances identified through toxicological testing are only listed on the death certificate if the death investigator determines they contributed to causing death. For example, a death certificate for a decedent in a shooting homicide with a toxicological finding of a low level of cocaine would be unlikely to include the term “cocaine.” Conversely, the death certificate for an accidental drowning where the decedent had substantial levels of fentanyl detected upon toxicological testing would likely include the term “fentanyl” in the list of causes or contributing causes. Using the methods employed in the current analysis, only the second example would be classified as a drug-related death.

For this analysis, we assessed deaths that listed one or more of the following substances as a cause or contributing factor in the death certificate: fentanyl and fentanyl analogs, heroin, prescription opioids, novel synthetic opioids (e.g. nitazenes, brorphine, U-47700), methamphetamine (with or without other amphetamines), amphetamine (without methamphetamine), cocaine, 3,4-methylenedioxymethamphetamine (MDMA), benzodiazepines (prescription and designer), thienodiazepines, Z-drugs such as Zolpidem, phencyclidine, xylazine, other illicit drugs (ketamine, gamma hydroxybutyrate, synthetic cannabinoids, cannabinoids), antidepressants, gabapentinoids, other pharmaceutical drugs, over the counter medications, or inhalants (e.g. nitrous oxide, butane gas). Supplemental Table 1 contains a full list of over the counter and other prescription drugs included. We used a machine learning algorithm described elsewhere for initial classification (Goodman-Meza et al., 2022), followed by keyword-matching for less common substances. We excluded drug-related deaths where alcohol was the only substance listed, as these were often attributed to conditions arising from chronic alcohol use (e.g., cirrhosis, ketoacidosis) rather than acute intoxication. We further classified drugs by likely source: illicit (including “street drugs” and designer drugs not approved by the US Food and Drug Administration), pharmaceuticals (including prescription and over the counter drugs), and other (e.g., alcohol, inhalants). As the sample included locations with heterogeneous cannabis laws, we included both natural and synthetic cannabinoids in the illicit category, noting that there were no examples of natural cannabinoids other than tetrahydrocannabinol listed on death certificates. Various synthetic cannabinoids were listed as such or by specific compound name. Recognizing that overlap is possible in the illicit and pharmaceutical categories (e.g., fentanyl can be prescribed but in the US street drug supply it is overwhelmingly from illicitly manufactured sources), we use these categories as a proxy for both regulatory status and likely source of acquisition rather than a judgment of their medicinal value.

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We classified a death as a polysubstance drug-related death if substances from two or more categories of drugs were listed on the death certificate. It is not possible to determine based on death certificate data (or ICD-10 mortality codes) whether co-occurrence of substances represents simultaneous use of multiple substances in one product (e.g., a speedball containing heroin and cocaine), simultaneous use of multiple products (e.g., taking multiple pills), or use of multiple substances in succession (e.g., taking a pill in the afternoon and smoking fentanyl in the evening). Therefore, our methods – like all large analyses of mortality data without detailed observation of scene or interviews with witnesses – capture polysubstance use in an approximate fashion.

Statistical methods

We employed chi-square tests to compare differences in polysubstance involvement by demographic, geographic, and specific substances. For each specific drug or drug class of interest, we calculated the inter-drug correlations across the entire dataset. To identify demographic correlates of polysubstance drug-related deaths, we fit a mixed effects logistic regression model with polysubstance involvement as the outcome, sex, age, and race/ethnicity as independent variables, and year and jurisdiction as random effects to control for any potential compositional bias. In the adjusted model, we selected as reference groups for categorical variables the group with the lowest percentage of polysubstance involvement (e.g., for race/ethnicity, we used Asian as the reference group to facilitate easier comparison between odds ratios over 1). Finally, we calculated the three most commonly involved drugs in drug-related deaths in each jurisdiction with full-year data for 2021, and determined the set of drugs that were not reported in each jurisdiction that year.

Ethics

This research was determined by the UCLA Institutional Review Board to be exempt from Institutional Review Board oversight as it involved only data from deceased persons and was therefore not human subjects research.

Results

We assess a final sample size of 73,077 drug-related deaths, with records spanning from 2012 through early 2022 (Table 1). The majority (63%, n=46,090) involved two or more substances, with 29% (n=21,455) involving three or more substances. Most (84%) drug-related deaths involved illicit drugs, about a third (35%) involved pharmaceuticals, and 20% simultaneously involved drugs likely to be illicit and drugs likely to be pharmaceutical in origin. Of drug-related deaths involving pharmaceuticals, 85% were polysubstance-involved, compared to 63% of deaths involving illicit drugs.

In bivariate comparisons, polysubstance involvement was most common among women ($p<0.001$), people aged 25–49 years ($p<0.001$), and the following racial and ethnic groups: American Indian or Alaska Native, Black or African American, more than one race, and White ($p<0.001$). There was considerable heterogeneity in polysubstance involvement by jurisdiction, with Alaska; Connecticut; North Carolina; Cook County, IL; Milwaukee County, WI; Montgomery County, PA all having more than 70% polysubstance involvement.

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Polysubstance involvement was least common in Sacramento County, CA, where two-thirds of drug-related deaths involved only one substance.

In the multivariate model, each additional year of age was associated with slightly lower odds of polysubstance involvement, about one percent lower odds for each year of age (Table 2, and see a detailed age pattern in Table 1). Female decedents had significantly higher odds of polysubstance involvement (aOR = 1.21, 95% CI, 1.17, 1.25). Asian decedents had the lowest odds of polysubstance involvement. Comparatively, American Indian and Alaska Native individuals (aOR 1.86, 95% CI 1.54, 2.23) and White individuals (aOR 1.68, 95% CI 1.47, 1.91) had the highest odds of polysubstance involvement.

Of the drug classes examined, drug-related deaths related to methamphetamine or inhalants were least likely to be polysubstance-involved. In contrast, over 90% of drug-related deaths related to benzodiazepines, thienodiazepines, and z-drugs—regardless of whether they were pharmaceuticals or designer drugs—were polysubstance-involved, as did over 90% of deaths involving novel synthetic opioids, and all non-opioid prescription drugs (antidepressants, gabapentinoids, or other prescription drugs). Fig. 1 displays correlations between drug classes. The most substantial overlap occurred between prescription opioids with prescription benzodiazepines, and designer benzodiazepines with novel synthetic opioids. There was also appreciable overlap between all classes of prescription drugs, and between fentanyl and xylazine. All but one of 918 xylazine-involved deaths were polysubstance-involved. Though drug-related deaths involving both pharmaceuticals and illicit drugs were relatively common, accounting for one third of all polysubstance drug-related deaths, the correlations were lowest between illicit stimulants (i.e., methamphetamine and cocaine) and prescription drugs of all classes.

In 2021, there were geographic patterns in the specific drug combinations involved in drug-related deaths. Of the five states and eight counties with data corresponding to the full year 2021, fentanyl was part of the most common polysubstance combination in all but one jurisdiction (Table 3). In all jurisdictions in the Western Census Region, the most common combination included fentanyl and methamphetamine, though Alaska's most common combination also included heroin. Most jurisdictions in the other three Census Regions had fentanyl and cocaine as the most common polysubstance combination, with the exception of Minnesota (fentanyl and methamphetamine), Summit County, OH (fentanyl and methamphetamine), and Travis County, TX (methamphetamine and cocaine).

Discussion

Drawing on a novel dataset comprised of medical examiner records representing all four US Census Regions and a wide range of rural and urban environments, we identified key trends in polysubstance drug-related deaths. We find that the proportion of drug-related deaths that were polysubstance-involved was high and increasing each year. Women, American Indian and Alaska Native, and White individuals faced the highest burden of polysubstance drug-related deaths during the study period. Polysubstance involvement was more common among younger people, with the highest percentages among individuals aged 25–49. There was substantial geographic variation in both polysubstance involvement and in specific

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drugs implicated. Polysubstance involvement was more common in both the most rural (Alaska) and most urban (Cook County, IL) jurisdictions included in the sample, as well as several eastern and midwestern jurisdictions with population densities in between these extremes, suggesting that demographic factors may be more important than population density. . Generally, novel psychoactive substances (e.g., xylazine, novel synthetic opioids, designer benzodiazepines) were more present in eastern and midwestern jurisdictions, which may reflect well-documented geographic patterns of temporal drug trends (Friedman et al., 2022b; Shover et al., 2020; Warner et al., 2013).

Our data suggest an accelerating rate of polysubstance use of opioids and stimulants—warranting particular concern given that concurrent use of both drug classes has been associated with heightened drug-related death compared to the use of either drug classes alone (Palis et al., 2022). Though men substantially outnumber women in drug-related death rates, and may report greater rates of polysubstance use (Goodwin et al., 2022), we found that a greater proportion of drug-related deaths among women were polysubstance-involved. This may be partially explained by previous epidemiological work showing that drug-related deaths among women were more likely to involve pharmaceuticals (Skurtveit et al., 2022; Wightman et al., 2021), which we find to be more closely associated with polysubstance drug-related deaths compared to illicit drugs.

Our findings on racial and ethnic disparities in polysubstance drug-related deaths should be considered in light of evidence of growing racial disparities in drug-related deaths in recent years (Friedman and Hansen, 2022c; Han et al., 2022; Humphreys et al., 2022), as well as previous epidemiological findings that American Indian and Alaska Natives have had elevated rates of polysubstance drug-related deaths involving opioids (Qeadan et al., 2022). In the early 2000s opioid-related death rates grew the fastest among American Indian and Alaska Native and White individuals (Humphreys et al., 2022), which were the racial groups with the highest burden of polysubstance drug-related deaths in the current analysis. However, substantial work has shown that opioid-related deaths among Black and African Americans has surpassed that of White individuals in more recent years, and drug-related mortality among Hispanic and Latin Americans has grown more quickly than other groups (Friedman and Hansen, 2022c; Romero et al., 2023). It is therefore important to note that the share of drug-related deaths in these racial and ethnic groups attributable to polysubstance is also substantially elevated. Future work developing and expanding strategies to provide culturally competent overdose prevention and other harm reduction services targeted to people who use multiple substances is critical to reduce these disparities (Anastario et al., 2022; Febres-Cordero et al., 2023).

Limitations

Although the jurisdictions represented cover a large proportion of the US population, they may not provide findings that are fully generalizable to other parts of the US. Because data were provided voluntarily, this should be considered to be a convenience sample, and it is possible that jurisdictions that did not provide these data differ systematically from those that did. Previous work has shown how jurisdictions differ in how they certify drug-related deaths and identify specific drugs (Warner et al., 2013), including which substances are

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part of standard toxicological screening, autopsy rate, how deaths are classified, as well as differences between medical examiner versus coroner systems (Denham et al., 2022). The keyword matching techniques used to identify specific substances likely missed less-common drugs and medications. There may be limited instance of drug name misspellings, which would lead to misclassification and underestimation of the importance of each drug class. Our analysis was not able to identify when a death involved more than one drug from the same drug class; thus, the true amount of polysubstance involvement may be even higher when considering deaths that involve, for example, two prescription opioids or multiple fentanyl analogues. As with any research relying on medical examiner data, identification of specific substances is only possible so far as medical examiner offices test for these substances. Budget constraints, technology, and varying awareness of emerging drug trends may result in under-testing for less common or newer drugs (Ropero-Miller et al., 2020). Using contributory cause of death, as we did, may mitigate some of these concerns (Boslett et al., 2020). Jurisdictions may have differential rates of prescribing medications, which could influence which substances are implicated in drug-related deaths.

Public health implications

Our analysis identifies important facets of polysubstance drug-related deaths that would be impossible to determine using standard national datasets. The substantial overlap between illicit and pharmaceutical substances highlights the need for service providers to consider that an individual presenting for one kind of treatment or harm reduction service may be knowingly or unknowingly using substances in multiple drug classes. Community-based drug checking interventions can shed light on this and provide a better understanding of the illicit drug supply (Maghsoudi et al., 2022), as well as informing the degree to which polysubstance drug-related deaths arise from intentional polysubstance use versus unintentional use, contamination, or misrepresented products. Drug seizure data can also provide key information, but these sources are often made public only after considerable delay, if at all. Broad spectrum naloxone training and provision is necessary to reverse opioid related overdoses (Febres-Cordero et al., 2023), but it may not be a sufficient intervention in the setting of increasing deaths due to polysubstance use (Messinger et al., 2023). Interventions in the management of stimulant and benzodiazepine overdoses are increasingly necessary. In the absence of direct antagonists to stimulants to reverse overdoses, safe environments (e.g., overdose prevention sites) and safe supply of substances for people with stimulant use disorder are potential interventions to reduce the number of polysubstance use deaths(Chalfin et al., 2023; Fleming et al., 2020; Harding et al., 2022; Lambdin et al., 2022; Mansoor et al., 2022). Analysis of detailed medical examiner records reveals the breadth and complexity of polysubstance drug-related deaths in the US. Future efforts to use this unique resource can improve population-based surveillance of drug-related deaths to better tailor interventions and solutions to this critical health crisis.

Supplementary Material

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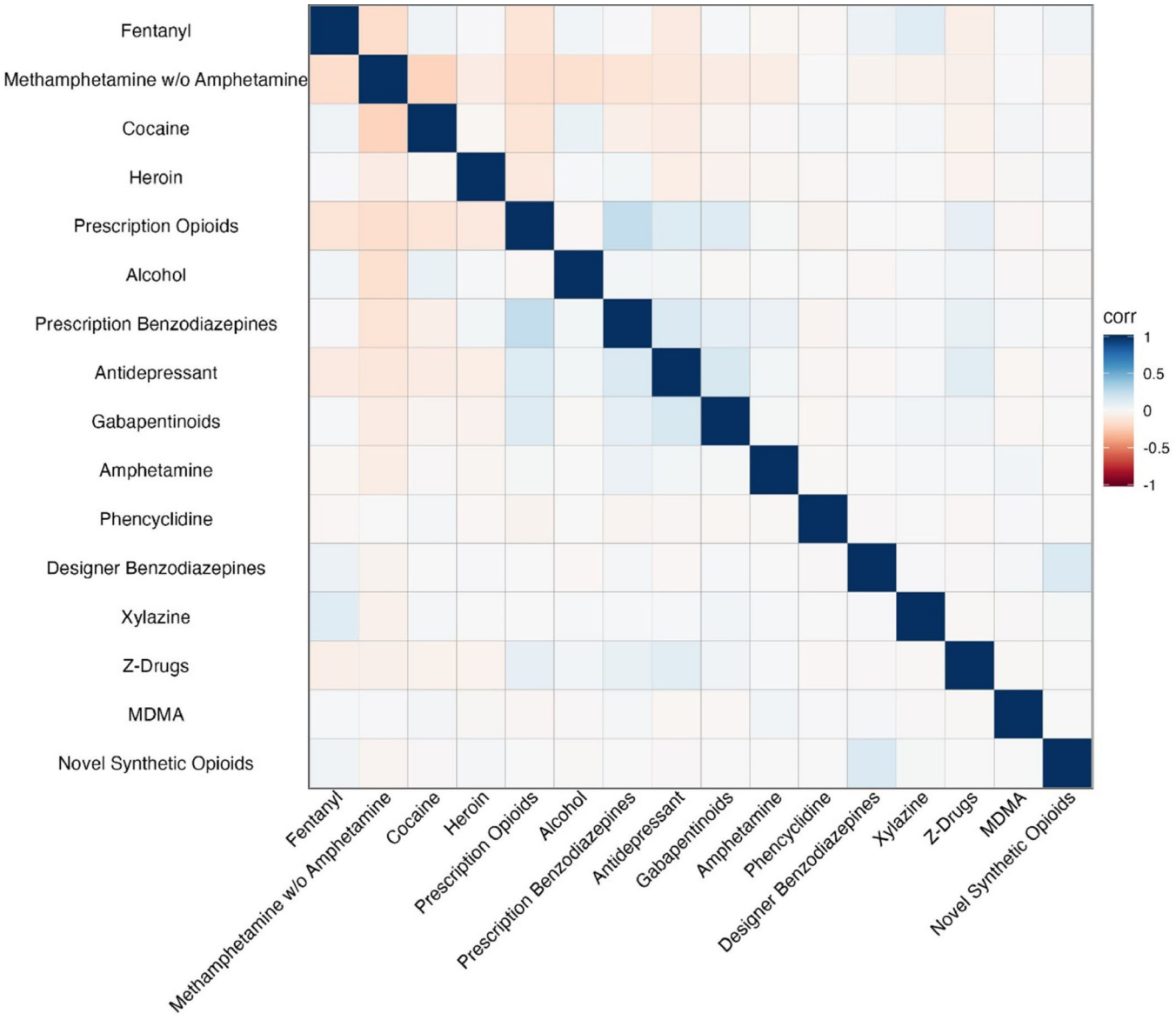


Fig. 1.

Correlations between specific substances involved in drug-related deaths, select US jurisdictions, 2012–2021.

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Table 1

Characteristics of single- and polysubstance drug-related deaths in select U.S. jurisdictions.

	Total[a]		One substance[b]		Polysubstance[b]		chi2
Sex							p<0.001[c]
Male	51,822	71%	19,582	38%	32,340	62%	
Female	20,567	28%	7,108	35%	13,459	65%	
Unknown	688	1%	297	43%	391	57%	
Race/Ethnicity							p<0.001[d]
American Indian or Alaska Native	1,026	1%	370	36%	656	64%	
Asian	1,007	1%	538	53%	469	47%	
Black or African American	15,043	21%	5,775	38%	9,268	62%	
Hispanic or Latin American	6,486	9%	3,097	48%	3,389	52%	
Native Hawaiian or Other Pacific Islander	79	0.1%	54	68%	25	32%	
White	45,756	63%	15,880	35%	29,876	65%	
Other	345	0%	122	35%	223	65%	
More than one race	1,517	2%	480	32%	1,037	68%	
Unknown	1,818	2%	671	37%	1,147	63%	
Age group							p<0.001[e]
0–13 years	280	0.4%	236	84%	44	16%	
14–18 years	414	1%	261	63%	153	37%	
19–24 years	5,559	8%	2,230	40%	3,329	60%	
25–29 years	7,640	10%	2,490	33%	5,150	67%	
30–39 years	16,632	23%	5,189	31%	11,443	69%	
40–49 years	15,216	21%	5,283	35%	9,933	65%	
50–59 years	17,157	23%	6,675	39%	10,482	61%	
60–69 years	8,422	12%	3,750	45%	4,672	55%	
70 years and older	1,425	2%	742	52%	683	48%	
Unknown	332	0%	131	39%	201	61%	
Source of drugs							
Illicit drugs	61,463	84%	22,585	37%	38,878	63%	p<0.001
Pharmaceuticals	25,475	35%	3,843	15%	21,632	85%	p<0.001

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	Total[a]		One substance[b]		Polysubstance[b]		chi2
Illicit drugs and pharmaceuticals	14,779	20%	–	–	–	–	
Other	14,409	20%	–	–	–	–	
Specific substances							
Opioids	52,109	71%	11,881	23%	40,228	77%	p<0.001
Fentanyl and fentanyl analogs	33,162	45%	6,668	20%	26,494	80%	p<0.001
Heroin	16,907	23%	2,769	16%	14,138	84%	p<0.001
Prescription opioids	14,598	20%	2,421	17%	12,177	83%	p<0.001
Nitazenes, brorphine, U-47700	339	0.5%	23	7%	316	93%	p<0.001
Opioids, unspecified	814	1%	0	0%	814	100%	–
Stimulants	37,881	52%	12,988	34%	24,893	66%	p<0.001
Methamphetamine (w/ or w/out amphetamine)	19,464	27%	8,386	43%	11,078	57%	p<0.001
Amphetamine (w/out methamphetamine)	1,156	2%	186	16%	970	84%	p<0.001
Cocaine	19,374	27%	4,367	23%	15,007	77%	p<0.001
MDMA	459	1%	49	11%	410	89%	p<0.001
Benzodiazepines, thienodiazepines, and z-drugs	12,483	17%	216	2%	12,267	98%	p<0.001
Prescription benzodiazepines	10,382	14%	132	1%	10,250	99%	p<0.001
Designer benzodiazepines/thienodiazepines	972	1%	28	3%	944	97%	p<0.001
Z-drugs	772	1%	0	0%	772	100%	p<0.001
Benzodiazepines, unspecified	1,326	2%	61	5%	1,265	95%	p<0.001
Phencyclidine	1,051	1%	210	20%	841	80%	p<0.001
Xylazine	918	1%	1	0.1%	917	100%	p<0.001
Other illicit drugs	913	1%	107	12%	806	88%	p<0.001
Alcohol	14,050	19%	–	–	–	–	
Antidepressants	4,569	6%	403	9%	4,166	91%	
Gabapentinoids	2,869	4%	36	1%	2,833	99%	
Other prescription medications	4,020	6%	228	6%	3,792	94%	
Over the counter medications	3,502	5%	623	18%	2,879	82%	
Inhalants	411	1%	312	76%	99	24%	
Jurisdiction States							p<0.001
Alaska	730	1%	195	27%	535	73%	
Connecticut	7,709	11%	1,239	16%	6,470	84%	

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	Total[a]		One substance[b]		Polysubstance[b]		chi2
Minnesota	5,530	8%	2,322	42%	3,208	58%	
North Carolina	7,413	10%	2,075	28%	5,338	72%	
Wyoming	923	1%	418	45%	505	55%	
Counties							
Cobb, GA	901	1%	283	31%	618	69%	
Cook, IL	11,068	15%	2,616	24%	8,452	76%	
Harris, TX	3,472	5%	1,216	35%	2,256	65%	
Jefferson, AL	554	1%	203	37%	351	63%	
Los Angeles, CA	13,596	19%	7,012	52%	6,584	48%	
Maricopa, AZ	4,601	6%	1,948	42%	2,653	58%	
Milwaukee, WI	2,497	3%	710	28%	1,787	72%	
Montgomery, PA	1,058	1%	275	26%	783	74%	
Pinal, AZ	415	1%	231	56%	184	44%	
Sacramento, CA	1,721	2%	1,137	66%	584	34%	
San Diego, CA	6,068	8%	2,583	43%	3,485	57%	
Summit, OH	1,337	2%	674	50%	663	50%	
Tarrant, TX	2,851	4%	1,602	56%	1,249	44%	
Travis, TX	632	1%	248	39%	384	61%	
Total	73,077	100%	26,987	37%	46,090	63%	

[a]. Column percentages.

[b]. Row percentages.

[c]. Excludes unknown.

[d]. Combines NHOPI and Other due to small sample sizes, excludes unknown.

[e]. Combines 0–13 and 14–18 due to small sample sizes, excludes unknown.

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Table 2

Mixed effects logistic regression of demographic correlates of polysubstance involvement in drug-related deaths with jurisdiction as random effects (n=70,917).

	Crude OR	95% CI	Adjusted OR	95% CI
Sex				
Female	1.18	(1.14, 1.23)	1.21	(1.17, 1.25)
Male (ref)	–	–	–	–
Age (per year)	0.99	(0.99, 0.99)	0.99	(0.99, 0.99)
Race/ethnicity*				
American Indian or Alaska Native	1.88	(1.56, 2.26)	1.86	(1.54, 2.23)
Asian (ref)	–	–	–	–
Black or African American	1.20	(1.05, 1.37)	1.27	(1.11, 1.46)
Hispanic or Latin American	1.50	(1.31, 1.72)	1.48	(1.29, 1.70)
More than one race	1.35	(1.13, 1.61)	1.31	(1.10, 1.56)
Other	1.50	(1.18, 1.90)	1.50	(1.18, 1.91)
White	1.59	(1.39, 1.81)	1.68	(1.47, 1.91)
Year	1.1	(1.09, 1.11)	1.1	(1.1, 1.1)

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Table 3

Most common polysubstance combinations involved in drug-related deaths, 2021.

Jurisdiction	Population per square mile, 2020 US Census	n	Most Common	Second Most Common	Third Most Common
States					
Alaska	1.3	228	Methamphetamine, Fentanyl, Heroin (N=23)	Methamphetamine, Fentanyl (N=20)	Rx Opioids, Methamphetamine, Fentanyl (N=18)
Connecticut	744.7	1,519	Fentanyl, Cocaine (N=149)	Fentanyl, Alcohol (N=92)	Fentanyl, Cocaine, Alcohol (N=91)
North Carolina	71.7	1,383	Fentanyl, Cocaine (N=347)	Methamphetamine, Fentanyl (N=219)	Fentanyl, Cocaine, Alcohol (N=132)
Minnesota	214.7	2,589	Methamphetamine, Fentanyl (N=154)	Fentanyl, Alcohol (N=53)	Fentanyl, Cocaine (N=49)
Wyoming	5.9	188	Methamphetamine, Fentanyl (N=12)	Fentanyl, Heroin (N=10)	Methamphetamine, Alcohol (N=10)
Counties					
Cobb, GA	2,254.8	168	Fentanyl, Cocaine (N=13)	Methamphetamine, Fentanyl (N=11)	Fentanyl, Alcohol (N=8)
Cook, IL	5,583.0	2,126	Fentanyl, Cocaine (N=230)	Fentanyl, Heroin (N=146)	Fentanyl, Alcohol (N=110)
Los Angeles, CA	2,466.9	2,766	Methamphetamine, Fentanyl (N=511)	Fentanyl, Cocaine (N=123)	Fentanyl, Alcohol (N=81)
Pinal, AZ	79.3	145	Methamphetamine, Fentanyl (N=20)	Rx Opioids, Fentanyl (N=5)	Fentanyl, Cocaine (N=5)
Sacramento, CA	1,642.1	397	Methamphetamine, Fentanyl (N=29)	Fentanyl, Alcohol (N=11)	Rx Opioids, Methamphetamine (N=10)
Summit, OH	1,309.2	218	Methamphetamine, Fentanyl (N=50)	Fentanyl, Cocaine (N=20)	Fentanyl, Alcohol (N=13)
Tarrant, TX	2,439.2	493	Fentanyl, Cocaine (N=30)	Methamphetamine, Fentanyl (N=19)	Fentanyl, Alcohol (N=14)
Travis, TX	1,297.9	214	Methamphetamine, Cocaine (N=7)	Fentanyl, Rx Benzos (N=6)	Cocaine, Alcohol (N=6)