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What does 'polysubstance' really mean? Comparing drug-involved deaths in CDC records vs. detailed medical examiner data from Los Angeles

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Abstract

Introduction: Complex polysubstance use is increasing in the United States. However, most epidemiological literature relies on traditional data sources, especially CDC WONDER, which is limited to employing two ICD-10 codes concurrently. We leverage complete medical examiner records from Los Angeles County to examine the limitations of CDC WONDER data for detecting polysubstance drug deaths.

Methods: Drug-involved deaths occurring in Los Angeles County were described using the CDC WONDER system and Los Angeles County Medical Examiner data. Annual single-drug involvement rates were compared between the two data sources. The average number of drugs, and the proportion of polysubstance deaths involving 3 or more substances was summarized by year. UpSet plot visualization was employed for complex set analysis.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics approval

The authors declare that they have obtained ethics approval from an appropriately constituted ethics committee/institutional review board where the research entailed animal or human participation.

Study protocols were approved by the UCLA Institutional Review Board (IRB-22–1273).

CRediT authorship contribution statement

Joseph R. Friedman: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ruby Romero:** Writing – review & editing, Software, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Arthur Funnell:** Writing – review & editing, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **David Goodman-Meza:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Chelsea L. Shover:** Writing – review & editing, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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Results: Overall concordance in single-substance death counts between CDC WONDER and medical examiner records was high among $n = 6$ substances assessed. The average number of drugs reported per death had a skewed distribution and increased from 1.72 in 2012 to 2.29 in 2023. The percentage of polysubstance deaths with 3+ drugs increased from 51% in 2012 to 74% in 2023. The number of unique polysubstance combinations with 3+ substances increased from 11 in 2012 to 57 in 2023.

Discussion: Although concordance is high for single-substance involvement rates, CDC WONDER fails to capture the majority of polysubstance deaths adequately, as about three-quarters of these deaths are incompletely described using its 2-drug limit. This limitation has worsened as deaths increasingly involve more drugs on average. We illustrate a huge variety of polysubstance combinations that can be seen in medical examiner deaths. As the overdose crisis grows increasingly polysubstance in nature, improving the epidemiological tracking of deaths involving multiple drugs, and drugs not captured by ICD-10 codes currently, is of paramount importance.

Keywords

Health surveillance; Overdose crisis; Polysubstance; Concordance statistics

Introduction

The ongoing overdose crisis in the United States (US) is increasingly characterized by polysubstance involvement, shifting beyond single-drug fatalities to complex combinations that present novel public health challenges (Ciccarone, 2021; J. Friedman & Shover, 2023; Park et al., 2022; Shover et al., 2024). For instance, the fraction of US overdose deaths involving both fentanyl and stimulants surged from 0.6 % in 2010 to 32.3 % in 2021 (J. Friedman & Shover, 2023). This general shift towards polysubstance deaths (in particular fentanyl plus other substances, especially stimulants) is referred to as the “Fourth Wave” of the US overdose crisis (Ciccarone, 2021).

The Fourth Wave of the overdose crisis increasingly features complex polysubstance combinations of various drugs like fentanyl and methamphetamine with more novel substances such as xylazine, medetomidine, nitazenes, novel synthetic benzodiazepines, synthetic cannabinoids, and others (J. Friedman et al., 2022; Giraudon et al., 2024; Laing et al., 2021; Palamar & Krotulski, 2024; Kariisa, 2023). Both intentional and unintentional polysubstance use has risen in the US. Intentional use often involves the simultaneous use of several substances together, which are sold separately, especially methamphetamine together with fentanyl (Ivsins et al., 2022). Unintentional polysubstance use often occurs when drug products expected to only contain one substance contain a polydrug mixture. For instance, e.g. a common scenario would entail a sample expected to contain fentanyl, that is actually composed of fentanyl, xylazine, lidocaine, and BTMPS (Shover, Koncsol et al., 2025). A relatively rarer phenomenon—albeit higher risk for overdose—can be found in expected stimulant samples that are augmented with fentanyl or other high potency synthetic opioids (Wagner et al., 2023).

Polysubstance formulations are increasingly described using community-based drug checking technologies leveraging mass spectrometry, Fourier-transform infrared

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spectrometry, and other techniques (Bailey et al., 2023). However, most epidemiological literature describing the US overdose crisis has still primarily relied on traditional data sources – especially official death data from the National Vital Statistics System (NVSS) which can be access via the CDC's Wide-ranging Online Data for Epidemiologic Research (WONDER) system (CDC, WONDER, n.d.; J. Friedman & Shover, 2023). The CDC WONDER system is broadly used by researchers and policymakers to generate summary statistics on-demand, and it has many advantages, including being publicly available and producing continuously updated overdose statistics on an approximately 7 month lag [due to inherent lags in toxicology testing (M. R. Spencer, 2016)].

Disadvantages of CDC WONDER include that it can only pull drug-involved deaths using established ICD-10 codes (e.g. T40.5 which codes for "Cocaine"). Many common substances, including fentanyl and methamphetamine, have no bespoke code, but are tracked using umbrella codes that have come to represent them in a *de-facto* fashion (T40.4 "Other synthetic narcotics" and T43.6 "Psychostimulants with abuse potential", respectively, for these two substances). For instance, although T40.4 mostly codes for fentanyl-involved deaths, a small number of deaths from nitazenes and U-compounds are also likely represented by this ICD-10 code, and it is also not possible to distinguish between standard fentanyl and other fentanyl analogs, such as fluorofentanyl or carfentanil (Shover et al., 2021; Shover, Koncsol et al., 2025). Although fentanyl analogs are currently the most important synthetic opioids in Los Angeles, should nitazenes or another similar agent begin to represent a large share of overdose deaths in the county, there would not be another ICD-10 code available to represent them, and the signal of their emergence would remain mixed with that of fentanyl analogs. Given that CDC WONDER does not facilitate any access to the free text fields on death certificates, there is no ability to systematically leverage information about substances that do not have an established ICD-10 code, or differentiate between drugs represented by the same umbrella code.

Another critical limitation of using CDC WONDER for tracking polysubstance deaths is that the platform allows for assessing deaths using a maximum of two ICD-10 codes. A researcher can therefore generate counts of deaths involving two specific substances (e.g. involving xylazine and fentanyl) but not specifically describe groups of deaths involving 3+ substances (e.g. xylazine, fentanyl, and cocaine), or deaths involving 2 substances but specifically excluding a third substance (e.g. xylazine and cocaine, but not fentanyl) (Friedman, 2025).

CDC WONDER, in effect, aggregates data from the over 2000 medical examiner and coroner's jurisdictions across the US. An alternative strategy to leveraging CDC WONDER to track overdose deaths, is directly obtaining data from these medical examiners and coroners, and aggregating them leveraging fully detailed text fields describing all drugs discovered using toxicological analysis (Shover et al., 2024). We have used this approach across several jurisdictions to provide more in-depth analyses (J. Friedman et al., 2022; Shover et al., 2024). Similarly, the State Unintentional Drug Overdose Reporting System (SUDORS) system aggregates detailed death records from the majority of US states (Tanz et al., 2022) and uses free text fields to assess additional parameters not available in CDC WONDER. However, the underlying data from SUDORS are not made available to

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independent researchers or the public, nor is there a public query system similar to CDC WONDER, which limits the usefulness of the dataset.

Overdose mortality data are initially produced by medical examiners' or coroners' offices, which investigate all 'unnatural' deaths, including those that are drug-related, as well as homicides, suicides, accidents, and deaths occurring under unusual or suspicious circumstances (Shover et al., 2024). Other deaths outside of these circumstances are not investigated by these offices and instead are certified by hospital or outpatient physicians. Medical examiners are physicians appointed to the role, typically with subspecialist training in forensic pathology. Coroners may or may not be physicians, can be elected or appointed, and typically work in more rural jurisdictions. A wide range of practices can be observed between jurisdictions. Medical examiner and coroner death investigations of suspected overdose deaths typically include toxicological testing of blood, urine, or other samples, autopsy, examination of medical records, scene investigation, and interviews with individuals who knew the decreased. The substances included in toxicological testing can vary between jurisdictions, and within jurisdictions over time. For instance, the LA County Medical Examiner did not routinely test for fentanyl in overdose toxicology before 2016 (Data Report: Drug Overdoses in Los Angeles County, 2025). Testing for xylazine has also been somewhat limited. Some jurisdictions perform this testing in-house, whereas others send all samples, or a subset of samples, to large private laboratory services. Death certificates produced by each jurisdiction can include up to four causes (A-D) as well as contributing causes. The term "overdose" is not usually used, however "toxicity," and "intoxication" are widely interpreted to be similar. Death certificates are sent to the CDC for national-level processing and aggregation, at which point specific ICD-10 mortality codes are assigned by medical coders. Substances identified on toxicology testing are only listed on the death certificate if the investigator believes they likely contributed to causing the death, and were not found incidentally, given the circumstances and all available information (Shover et al., 2024).

Some uncertainty exists regarding the degree to which CDC WONDER and medical examiner data perfectly represent one another – given potential differences in underlying data definitions. For instance, although counts of drug-involvement in deaths can be compared head-to-head between medical examiner data and CDC WONDER data, death certificates do not contain the ICD-10 codes required to define a death as primarily an "overdose" in nature, and instead list a wider array of terms such as "intoxication" or "toxicity". It is therefore difficult to perform an exact comparison of "overdose deaths" between the two sources.

In this analysis we leverage complete medical examiner records from the medical examiner's office of Los Angeles County – the nation's largest county, and likely one of the largest medical examiner jurisdictions. We compare CDC WONDER data for Los Angeles County to this more direct data source, to see which fraction of deaths are incompletely described using traditional approaches. We hypothesized that concordance would be high for single-death comparisons, nevertheless confirming this provides useful reassurance of the validity of comparing the two data sources. We hypothesized that a high fraction of

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polysubstance deaths would have >2 drugs present, and would therefore be incompletely characterized by CDC WONDER.

Methods

Counts of drug-involved deaths occurring in Los Angeles County were described using the CDC WONDER system (CDC WONDER, n.d.) from 2018 to 2023 (the latest year with finalized data from CDC WONDER). To mimic the nature of the medical examiner data, underlying causes of death were not restricted. Drug-involved deaths were pulled using multiple cause of death codes for fentanyl (T40.4), methamphetamine (T43.6), cocaine (T40.5), heroin (T40.1), prescription opioids (T40.2 and T40.3), and benzodiazepines (T42.4). Deaths were pulled by year and single substance involvement.

Medical examiner data from Los Angeles County were requested and assembled using previously described processes for 2012 through 2023 (Shover et al., 2024). Specific substance involvement was determined searching across the various cause of death and other free text fields available from each death certificate, using natural language processing methods (Fine-tuned BioClinicalBERT models) to classify deaths into different substance-involvement types [published separately (Funnell et al., 2025) and see code in Github repository: https://github.com/ROSLA-UCLA/ROSLA-HEAL-Data]. Deaths were categorized as involving fentanyl, methamphetamine, cocaine, heroin, prescription opioids, benzodiazepines, alcohol, xylazine, and ‘others’. The ‘others’ category captured a large number of other substances that appeared much less commonly. Polysubstance deaths were defined as those involving 2 or more substances. The average number of drugs present per death was calculated per year using the 9 aforementioned categories, by defining the number of drugs present for each death, and calculating the annual average of this quantity. Similarly, the proportion of polysubstance deaths (those involving at least 2 substances) containing at least 3 drugs was calculated per year. Given the use of the ‘others’ category, these summary statistics likely represent a slight underestimate, or a trimmed mean, but there were relatively few deaths involving the ‘others’ category and only one other drug, therefore this limitation was unlikely to greatly impact statistics regarding the percent of polysubstance deaths with greater than 2 substances. All polysubstance combinations in medical examiner data containing >2 substances were visualized using UpSet plot visualization (Lex et al., 2014).

Concordance between CDC WONDER and medical examiner data was assessed for 6 substances by aligning annual death counts involving each substance using scatter plots with lines of equality and lines of best fit calculated using ordinary least squares regression.

Data were visualized using R version 4.4.1 and the ggplot2 package. Study protocols were approved by the UCLA Institutional Review Board (IRB-22–1273).

Results

The distribution of number of substances involved in drug involved deaths was visualized by year (Fig. 1, Part A). The average number of drugs present per drug-involved death, and the percent of polysubstance deaths that would not be fully characterizable using the CDC

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WONDER system given a 2-drug limit, were summarized by year (Fig. 1, Part B and C). The distribution of drugs involved per death was skewed for all years of available data. Over time, the fraction of deaths involving only one substance shrank, while the fraction containing 3 or more substances increased (Fig. 1, Part A). The average number of drugs present per drug-involved death increased from 1.72 in 2012 to a peak of 2.28 in 2023 (Fig. 1, Part B). The percentage of polysubstance deaths that would not be fully characterizable using the CDC WONDER system given a 2-drug limit, increased from 51 % in 2012 to a peak of 74 % in 2023.

The full set of polysubstance deaths containing clusters of 3 or more substances (which therefore could not be completely captured by CDC WONDER data) were visualized for 2012, 2018, and 2023. The total number of unique polysubstance combinations with >2 substances increased from $n = 11$ in 2012 to $n = 57$ in 2023. The most prevalent cluster in 2012 was the combination of methamphetamine, heroin, and prescription opioids. The most common cluster in 2023 was methamphetamine, cocaine, and fentanyl. In 2012 there were no combinations involving 5 or 6 drugs, and only $n = 1$ combination involving 4 drugs. By 2023, $n = 18$ combinations involved 4 drugs, $n = 3$ combinations involved 5 drugs, and $n = 2$ combinations involved 6 drugs.

Concordance in single-substance death counts were also assessed between CDC WONDER and medical examiner records, for 6 substances of interest, and overall was high. Fentanyl and heroin deaths had near perfect concordance. Methamphetamine death numbers were initially higher in CDC WONDER data in 2018 compared to medical examiner data for the same year, but concordance improved by 2023, with 1599 and 1578 deaths reported respectively. Deaths reported for prescription opioids, and benzodiazepines were higher among CDC WONDER compared to medical examiner data across all years examined.

Discussion

This study leveraged complete medical examiner data from Los Angeles County (the US's most populous county) and compared it to CDC WONDER data to see which fraction of deaths are incompletely described using traditional approaches. We find that CDC WONDER fails to capture the majority of polysubstance deaths adequately. A very large fraction of polysubstance deaths (about three-quarters) were incompletely described using the 2-drug limit employed by CDC WONDER. This severity of this limitation increased over time, as the complexity of polysubstance overdose deaths increased. We illustrate a huge variety of polysubstance deaths that can be seen in medical examiner deaths. Much of this variation is lost in the aggregation process used in CDC WONDER output.

Despite this poor ability to track polysubstance deaths, we did find that concordance was generally high for trends describing single-substance drug deaths, such as fentanyl, heroin, or methamphetamine. For broader categories of drugs (benzodiazepines and prescription opioids), we found CDC WONDER slights overpredicted the medical examiner approach, which likely reflects differences between coding practices and the lists of substances we included in these categories.

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Some solutions to the limitations of CDC WONDER have already been proposed. For instance, the State Unintentional Drug Overdose Reporting System (SUDORS) system aggregates more detailed death records from the majority of states (Tanz et al., 2022), in a similar fashion to independent research groups that have aggregated medical examiner records (Shover et al., 2024). Although SUDORS has a public data visualization providing limited summary statistics, the underlying data are not available to researchers or the public, limiting the usefulness of the information. More detailed free-text information is also collected by the National Vistal Statistics System (which also feeds mortality data in CDC WONDER), which has been used for specific analyses conducted by government researchers (M. Spencer et al., 2023). Therefore, there is no clear logistical reason why CDC WONDER or another platform could not provide a) aggregate statistics using more than two multiple cause of death codes, allowing for more complex polysubstance death assessments and b) access to information contained in free text fields allowing for the quantification of substances not captured in existing ICD-10 codes. The first practice would be relatively straightforward to implement, but may require additional storage or processing power from government servers. The second practice would likely require the implementation of a standardized keyword search approach for public-facing queries, to limit differences that could be introduced from researchers using distinct language processing models. Investing in these practices would likely greatly improve the productivity of research in this area. However, it would require government expenditure in transparency, and updates to existing systems.

It is also worth noting that the underlying data from NVSS (those used in CDC WONDER) are also available in public use and restricted use Multiple Cause of Death files, which provide individual-level death records that list more than two ICD-10 codes. However, these files have several limitations that complicate their use for rapid public health monitoring or overdose prevention. Both public and restricted-use files are available on a considerably longer time delay. Whereas CDC WONDER provides provisional data on an approximately 7-month lag, these files reflected finalized data available 1–2 years after a death has occurred. Further, the public-use version of these files only provide data at the national level, with no state or other geographic identifiers, which drastically reduces the actionability of findings. Restricted-use files may include geographic identifiers, but require additional delays related to application and federal and institutional approval processes, and must be analyzed on dedicated, highly secure computer systems. These files may provide valuable access for researchers with the time, institutional ability, and computational capacity to analyze them, however they have less reach and impact than the public-facing CDC WONDER system.

Beyond these limitations to the formatting of already existing data, overdose surveillance is also limited by undertesting of drugs on autopsy, especially for novel synthetic substances. It is likely that the data reported here are an underestimate of the true degree of polysubstance complexity in Los Angeles overdose decedents, given that some novel substances are not routinely tested for. The panel of drugs tested for in a given jurisdiction can also shift over time, for instance, the Los Angeles Medical Examiner’s office was not routinely testing for fentanyl in toxicological testing of overdose deaths prior to 2016. This is a limitation for the tracking of novel substances, which can appear to rise in prevalence due to true increased

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prevalence, or simply due to improved testing rates. This is also a limitation for the current analysis, as some degree of increasing polysubstance use may relate to increased testing rates (in particular the initiation of testing for fentanyl in Los Angeles in 2016).

Novel substances are increasingly proliferating in the Fourth Wave of the overdose crisis. The ability to accurately detect them will rely on expanded, comprehensive toxicological testing. The over 2000 medical examiner jurisdictions currently employ a wide range of toxicological practices, and many do not routinely test for novel substances of increasing importance (e.g. nitazenes, medetomidine, novel synthetic benzodiazepines). One potential solution is for all jurisdictions, perhaps especially smaller jurisdictions, to send samples to large national laboratories using standardized methods to test for a wide range of novel substances by default in any suspected overdose death. Although many jurisdictions already contract with private laboratory services for this testing, federal coordination and oversight would provide improved uptake and standardization.

A further issue is the inability to track novel substances that do not have a dedicated ICD-10 code in CDC WONDER or NVSS Cause of Death files. As recommended above, a move towards making free text information on death certificates would greatly improve this limitation.

As the overdose crisis grows increasingly polysubstance in nature, improving the epidemiological tracking of deaths involving multiple drugs, and drugs not captured by ICD-10 codes, is of paramount importance. Here we highlight the gaps in existing traditional epidemiological sources which may serve as a motivating example for future improvements. As an increasing fraction of overdose deaths in the US involve polysubstance combinations and novel substances that do not have an ICD-10 code, the public health importance of improved tracking mechanisms grows. Better surveillance of these novel substances would allow federal, state, and local actors to track the emergence of public health challenges related to substance use, and guide prevention efforts. A coordinated response to the overdose crisis will be considerably stymied if the nature of deaths cannot be fully characterized due to information system limitations.

Beyond death records, other systems drawing on emergency medical services and drug checking data from harm reduction programs, can provide more timely signals of shifting drug trends to guide rapid public health responses (J. Friedman et al., 2020; J. R. Friedman, 2024; Palamar & Krotulski, 2024; Shover, Godvin et al., 2025). As other regions also increasingly experience polysubstance deaths—and the rise of synthetic substances like nitazenes and novel synthetic benzodiazepines (European Monitoring Centre for Drugs & Drug Addiction., 2021; Giraudon et al., 2024)—similar efforts to robustly and routinely track polysubstance combinations will be valuable for global public health monitoring (Figs. 2 and 3).

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References

Bailey K, Abramovitz D, Artamonova I, Davidson P, Stamos-Buesig T, Vera CF, Patterson TL, Arredondo J, Kattan J, Bergmann L, Thihalolipavan S, Strathdee SA, & Borquez A (2023). Drug checking in the fentanyl era: Utilization and interest among people who inject drugs in San Diego, California. The International Journal on Drug Policy, 118, Article 104086. 10.1016/j.drugpo.2023.104086

CDC WONDER. (n.d.). https://wonder.cdc.gov/.

Ciccarone D (2021). The rise of illicit fentanyls, stimulants and the fourth wave of the opioid overdose crisis. Current Opinion in Psychiatry, 34(4), 344–350. 10.1097/YCO.0000000000000717 [PubMed: 33965972]

Data Report: Drug Overdoses in Los Angeles County. (2025). Los angeles county department of public health. http://publichealth.lacounty.gov/sapc/MDU/SpecialReport/Report-on-Drug-Overdoses-in-Los-Angeles-County.pdf.

European Monitoring Centre for Drugs and Drug Addiction. (2021). New benzodiazepines in Europe: A review. Publications Office. https://data.europa.eu/doi/10.2810/725973.

Friedman J, Beletsky L, & Schriger DL (2020). Overdose-related cardiac arrests observed by emergency medical services during the US COVID-19 epidemic. JAMA Psychiatry. 10.1001/jamapsychiatry.2020.4218

Friedman J, Montero F, Bourgois P, Wahbi R, Dye D, Goodman-Meza D, & Shover C (2022). Xylazine spreads across the US: A growing component of the increasingly synthetic and polysubstance overdose crisis. Drug and Alcohol Dependence, 233, Article 109380. 10.1016/j.drugalcdep.2022.109380

Friedman JR (2024). Tracking drug overdose in Latin America: The epidemiological potential of prehospital and emergency department data. American Journal of Public Health, 114(11), 1153–1155. 10.2105/AJPH.2024.307862 [PubMed: 39357006]

Friedman JR (2025). Assessing an ICD-10 code approach for estimating xylazine-involved overdose deaths in the United States. Drug and Alcohol Dependence., Article 112781. 10.1016/j.drugalcdep.2025.112781

Friedman J, & Shover CL (2023). Charting the fourth wave: Geographic, temporal, race/ethnicity and demographic trends in polysubstance fentanyl overdose deaths in the United States, 2010–2021. Addiction, 118(12), 2477–2485. 10.1111/add.16318 [PubMed: 37705148]

Funnell AJ, Petousis P, Harel-Canada F, Romero R, Bui AAT, Koncsol A, Chaturvedi H, Shover C, & Goodman-Meza D (2025). Improving drug identification in overdose death surveillance using large language models. https://arxiv.org/abs/2507.12679.

Giraudon I, Abel-Ollo K, Vanaga-Arāja D, Heudtlass P, & Griffiths P (2024). Nitazenes represent a growing threat to public health in Europe. The Lancet Public Health. 10.1016/S2468-2667(24)00024-0. 0(0).

Ivsins A, Fleming T, Barker A, Mansoor M, Thakarar K, Sue K, & McNeil R (2022). The practice and embodiment of “goofballs”: A qualitative study exploring the co-injection of methamphetamines and opioids. International Journal of Drug Policy, 107, Article 103791. 10.1016/j.drugpo.2022.103791

Kariisa M (2023). Illicitly manufactured fentanyl–Involved overdose deaths with detected xylazine—United States, January 2019–June 2022. MMWR. Morbidity and Mortality Weekly Report, 72. 10.15585/mmwr.mm7226a4

Laing MK, Ti L, Marmel A, Tobias S, Shapiro AM, Laing R, Lysyshyn M, & Socías ME (2021). An outbreak of novel psychoactive substance benzodiazepines in the unregulated drug supply: Preliminary results from a community drug checking program using point-of-care and confirmatory methods. International Journal of Drug Policy., Article 103169. 10.1016/j.drugpo.2021.103169

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Lex A, Gehlenborg N, Strobelt H, Vuillemot R, & Pfister H (2014). UpSet: Visualization of intersecting sets. IEEE Transactions on Visualization and Computer Graphics, 20(12), 1983–1992. 10.1109/TVCG.2014.2346248 [PubMed: 26356912]

Palamar JJ, & Krotulski AJ (2024). Medetomidine infiltrates the US illicit opioid market. JAMA, 332(17), 1425. 10.1001/jama.2024.15992 [PubMed: 39230918]

Park JN, Schneider KE, Fowler D, Sherman SG, Mojtabai R, & Nestadt PS (2022). Polysubstance overdose deaths in the fentanyl era: A latent class analysis. Journal of Addiction Medicine, 16(1), 49. 10.1097/ADM.0000000000000823 [PubMed: 33675604]

Shover CL, Falasinnu TO, Freedman RB, & Humphreys K (2021). Emerging characteristics of isotonitazene-involved overdose deaths: A case-control study. Journal of Addiction Medicine, 15(5), 429–431. 10.1097/ADM.0000000000000775 [PubMed: 33234804]

Shover CL, Friedman JR, Romero R, Jimenez S, Beltran J, Garcia C, & Goodman-Meza D (2024). Leveraging pooled medical examiner records to surveil complex and emerging patterns of polysubstance use in the United States. International Journal of Drug Policy., Article 104397. 10.1016/j.drugpo.2024.104397

Shover CL, Godvin ME, Appley M, Pyfrom EM, Castrillo FM, Hochstatter K, Nadel T, Garg N, Koncsol A, Friedman JR, Molina CA, Romero R, Harshberger B, Gonzalez JAM, Spoliansky J, Laurel S, Jalayer E, Ruelas J, Gonzales J, … Sisco E (2025). UV stabilizer BTMPS in the illicit fentanyl supply in 9 US locations. JAMA., Article e2427550. 10.1001/jama.2024.27550

Shover CL, Koncsol AJ, Godvin ME, Goodman-Meza D, Pardo B, Poimboeuf M, Molina CA, Romero R, Feng J, & Friedman JR (2025). High variation in purity of consumer-level illicit fentanyl samples in Los Angeles, September 2023–April 2025. International Journal of Drug Policy, 145, Article 104977. 10.1016/j.drugpo.2025.104977

Spencer M, Cisewski J, Warner M, & Garnett M (2023). Drug overdose deaths involving Xylazine, United States, 2018–2021. National Center for Health Statistics (U.S.). 10.15620/cdc:129519

Spencer MR (2016). Timeliness of death certificate data for mortality surveillance and provisional estimates. CDC Vital Statistics Rapid Release, 8.

Tanz LJ, Dinwiddie AT, Snodgrass S, O'Donnell J, & Mattson CL (2022). A qualitative assessment of circumstances surrounding drug overdose deaths during. SUDORS Data Brief.

Wagner KD, Fiuty P, Page K, Tracy EC, Nocera M, Miller CW, Tarhuni LJ, & Dasgupta N (2023). Prevalence of fentanyl in methamphetamine and cocaine samples collected by community-based drug checking services. Drug and Alcohol Dependence, 252, Article 110985. 10.1016/j.drugalcdep.2023.110985

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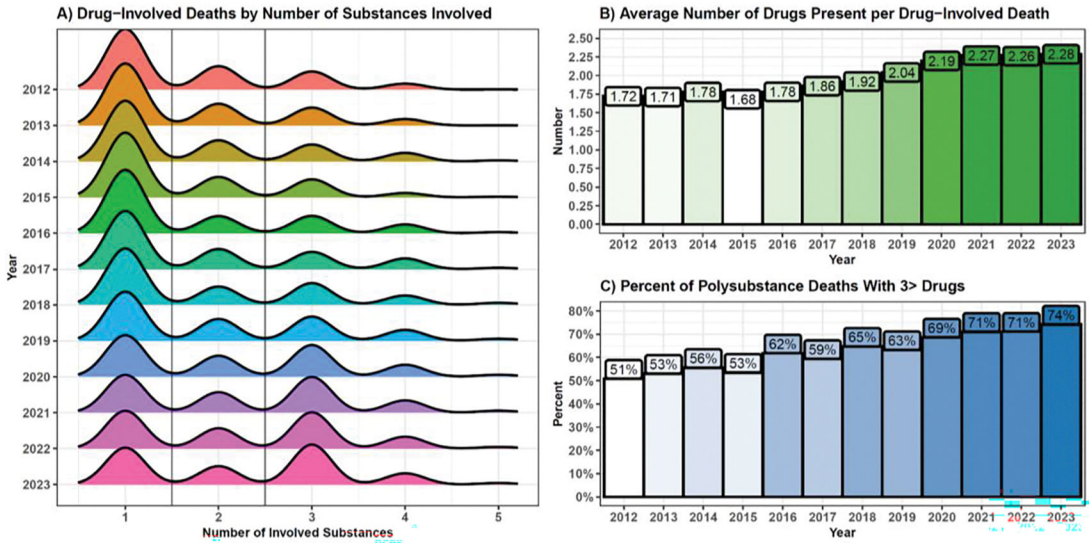


Fig. 1. Number of substances seen in drug-involved deaths in LA medical examiner data.

Part A) Shows the distribution of number of substances involved in drug involved deaths by year. Vertical lines separate 1 death and 2 deaths (the border of polysubstance vs non polysubstance) as well as 2 deaths and 3 deaths (the border between polysubstance deaths fully characterizable, or not fully characterizable, using the current CDC WONDER system). Part B) Average number of drugs present per drug-involved death by year. Intensity of color represents the magnitude of the number. Part C) Percent of polysubstance deaths (meaning 2+ substances) that would not be fully characterizable using the CDC WONDER system given a 2-drug limit) by year. Intensity of color represents the magnitude of the percent.

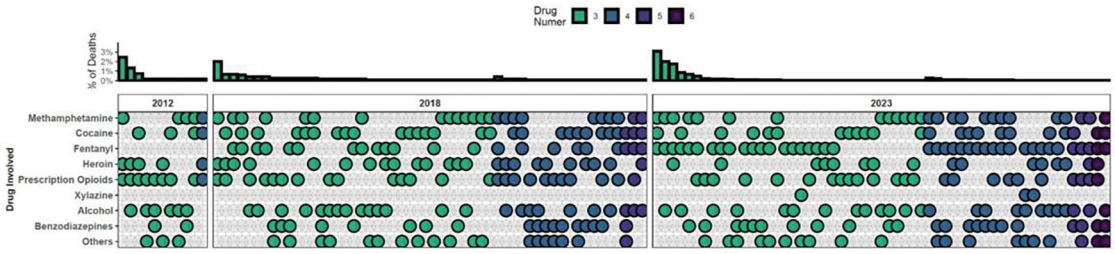


Fig. 2. Substance clusters observed among deaths involving 3+ deaths.

Clusters of deaths involving 3 or more substances (which therefore could not be completely captured by CDC WONDER data) are shown for 2012, 2018, and 2023. One column represents a particular cluster of substances for a given year. On the bottom panel, one row represents the presence or absence (with a present or absent dot) of a given substance. Dot color corresponds to number of drugs involved. On the top panel, the proportion of all drug deaths in a given year represented by a given cluster is shown. Overall, the number of columns per box reflects the total number of unique 3+ drug polysubstance combinations seen in a given year, with larger boxes over time reflecting a greater number of combinations. An increased number of columns over time with darker colors indicate a greater number of polysubstance combinations with 4, 5, or 6 drugs. Overall increased complexity and prevalence of polysubstance use over time can be seen.

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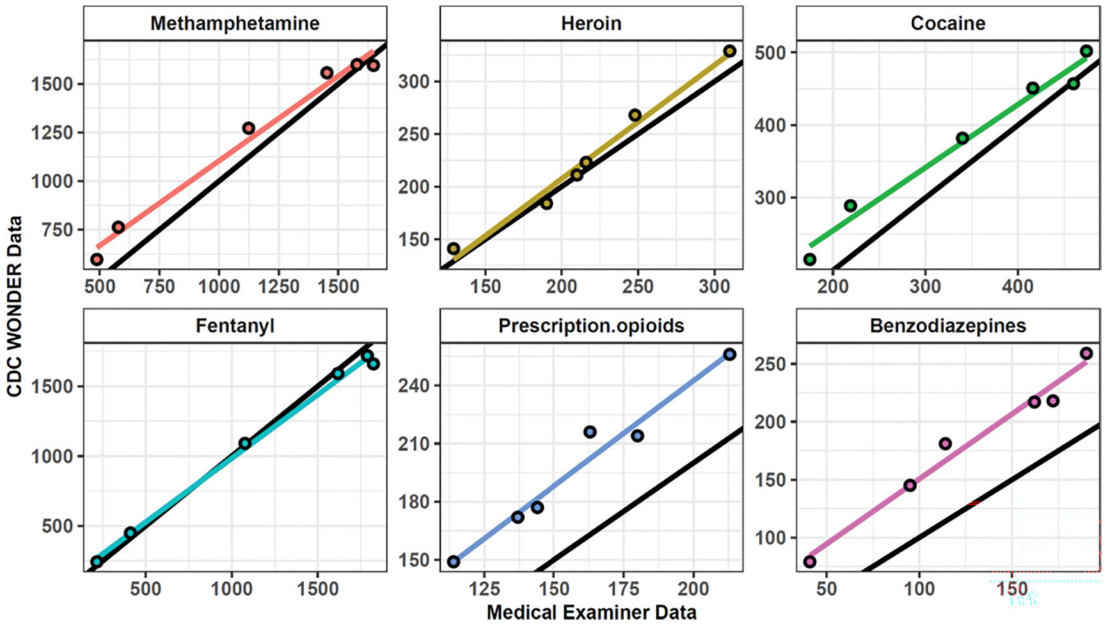


Fig. 3. Drug-involved deaths in CDC wonder vs. LA county medical examiner data, 2018–2023.
For 6 drugs of interest, counts of drug-involved deaths from CDC WONDER for LA County are compared on the y axis, to counts from medical examiner data for the same substance-involved deaths on the x-axis. A line of equality is shown for each substance in black. One point represents one year of data.