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DATA INSIGHT

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Charting the fourth wave: Geographic, temporal, race/ethnicity and demographic trends in polysubstance fentanyl overdose deaths in the United States, 2010–2021

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Abstract

Aims: To characterize polysubstance death in the United States during the transition to the fourth wave of the drug overdose crisis. To characterize co-involved substances in fatal overdose involving synthetic opioids (mainly illicitly manufactured fentanyl analogues) by year, state, and intersectional sociodemographic groups.

Design: Population-based study of national death records.

Setting: United States.

Participants/cases: All people who died from drug overdose in the United States between 2010 and 2021.

Measurements: Percentage of all fatal overdose involving fentanyls, stimulants, and other drugs. Most commonly co-involved substances in fentanyl overdose by state and year. Percentage of fatal fentanyl overdose co-involving stimulants by state and year. Percentage of fatal fentanyl overdose co-involving stimulants by intersectional region, race/ethnicity, age, and sex.

Findings: The percent of US overdose deaths involving both fentanyl and stimulants increased from 0.6% (n = 235) in 2010 to 32.3% (34 429) in 2021, with the sharpest rise starting in 2015. In 2010, fentanyl was most commonly found alongside prescription opioids, benzodiazepines, and alcohol. In the Northeast this shifted to heroin-fentanyl co-involvement in the mid-2010s, and nearly universally to cocaine-fentanyl co-involvement by 2021. Universally in the West, and in the majority of states in the South and Midwest, methamphetamine-fentanyl co-involvement predominated by 2021. The proportion of stimulant involvement in fentanyl-involved overdose deaths rose in virtually every state 2015–2021. Intersectional group analysis reveals particularly high rates for older Black and African American individuals living in the West.

Conclusions: By 2021 stimulants were the most common drug class found in fentanyl-involved overdoses in every state in the US. The rise of deaths involving cocaine and methamphetamine must be understood in the context of a drug market dominated by illicit fentanyls, which have made polysubstance use more sought-after and commonplace. The widespread concurrent use of fentanyl and stimulants, as well as other polysubstance formulations, presents novel health risks and public health challenges.

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KEYWORDS
fentanyl, fourth wave overdose crisis, overdose surveillance, polysubstance use, stimulants, substance use disorders

INTRODUCTION

The United States (US) overdose crisis has escalated in an exponential fashion for over four decades, yet with a shifting profile of drugs implicated in each successive 'wave' of the crisis [1]. The first wave of the overdose crisis is typically argued to have begun in the late 1990s or early 2000s with the rise of deaths involving prescription opioids, the second wave beginning in 2010 driven by a shift to heroin, and the third wave beginning in 2013 driven by illicit fentanyl analogues [2, 3]. Recently, scholars have argued that the 'fourth wave' of the US overdose crisis has begun, in recognition of rapidly rising polysubstance overdose deaths involving illicitly manufactured fentanyls, with stimulants playing a key role [4–7]. Recent studies have highlighted an increasing rate of polysubstance overdose deaths involving fentanyls and stimulants, disproportionately affecting racial/ethnic minority communities [7]. A wide range of polysubstance formulations have been noted in drug checking and overdose mortality data, with myriad substances implicated across numerous drug classes [8–10]. However, more evidence is needed about exact geographic, temporal, race/ethnicity and demographic trends, as well as which emerging polysubstance formulations are most commonly involved in fatalities.

Here, we leverage the latest complete, finalized national data, with records through 2021, to provide a detailed characterization of emerging trends in polysubstance deaths. We focus on fatal polysubstance overdose involving fentanyl and its analogues, as this has become the most common class of drugs involved in fatal overdose in the United States and is understood to be the single most important driver of the current crisis. We provide novel metrics to describe the signature of polysubstance overdose deaths in the United States, focused on the proportion of fentanyl-involved overdose deaths co-involving a stimulant, as well as the other most commonly co-involved drugs.

METHODS

We obtained finalized death records from the Centers for Disease Control (CDC) and Prevention's Wide-Ranging Online Database for Epidemiologic Research (WONDER) from 2010 through 2021. This is a population-level database representing all deaths occurring in the United States, and therefore, is not subject to sampling uncertainty. We selected all deaths with underlying cause of overdose, using International Classification of Diseases, 10th Edition (ICD-10) codes X40-44, X60-64 or Y10-14. From these, we selected overdose deaths with multiple cause of death code T40.4 (synthetic opioids excluding methadone, a category that is primarily fentanyl and fentanyl analogues). We examined co-involved substances including methamphetamine (T43.6, psychostimulants with abuse potential) [11], cocaine (T40.5), any stimulant (T43.6 or T40.5), benzodiazepines (T42.4), alcohol (T51), prescription opioids (T40.2-3, other opioids) and methadone (T40.3).

We measured the annual percentage of overdose deaths that involved (1) fentanyl; (2) stimulants; (3) fentanyl and stimulants; and (4) neither fentanyl nor stimulants. We, then, measured the most commonly co-involved substance at the state level over the study period. For intersectional analysis, to have a large enough sample to simultaneously stratify by census region, race/ethnicity, sex and age group (given that the CDC WONDER platform suppresses counts below n = 10 deaths), we combined all fentanyl deaths from 2016 to 2020.

RESULTS

The four waves of the United States overdose are depicted in Figure 1. The onset of the first, second, third and fourth waves are defined respectively, by the initial rises in prescription opioids (in the early 2000s), heroin (in 2010), fentanyl without stimulants (in 2013) and fentanyl with stimulants (in 2015). Removing fentanyl-co-involved deaths, we observe that prescription opioid- and heroin-driven waves reached inflection points and begin to decline in 2010 and 2015, respectively.

The polysubstance characteristics of fentanyl-involved overdose mortality shifted dramatically throughout the 2010 to 2021 period. As overdose deaths rose in the United States from 38 329 in 2010 to 106 699 in 2021, the percent involving both fentanyl and stimulants concurrently rose from 0.6% (n = 235) to 32.3% (n = 34 429) (Figure 2). The proportion of deaths involving fentanyl without stimulants also rose from 7.2% in 2010 to a peak of 35.7% in 2020, before declining slightly to 33.9% in 2021. The proportion with stimulants and no fentanyl remained relatively more stable, from 14.8% in 2010 to 17.9% in 2021. The proportion containing neither fentanyl nor stimulants fell from 77.3% in 2010 to 16.0% in 2021.

In 2010, fentanyl was most often co-involved with prescription opioids (19 states), alcohol (18 states) and benzodiazepines (eight states), with that general pattern seen across all four major census regions (Figure 3). This pattern shifted earliest in the Northeast, as heroin became the most common co-involved substance in 2014 in five states (of nine total in the region). Cocaine became the most commonly co-involved substance among states in the Northeast in 2019 with seven states. By 2021, all states in the Northeast had a stimulant as the most common co-involved substance, with seven having cocaine and two having methamphetamine. Among states in the West region, a mixture of prescription opioids, benzodiazepines and alcohol were the most common co-involved substances until 2020, when methamphetamine was the most common in 10 states (of 12 in the region), which grew to all 13 states by 2021. The Midwest and the South saw a more mixed profile, with brief periods of heroin/fentanyl predominance in numerous states between 2016 and 2018. By 2021, methamphetamine and cocaine were the only leading co-involved substances represented in these regions, with 19 and 10, respectively, of a total 28 states and the District of Columbia.

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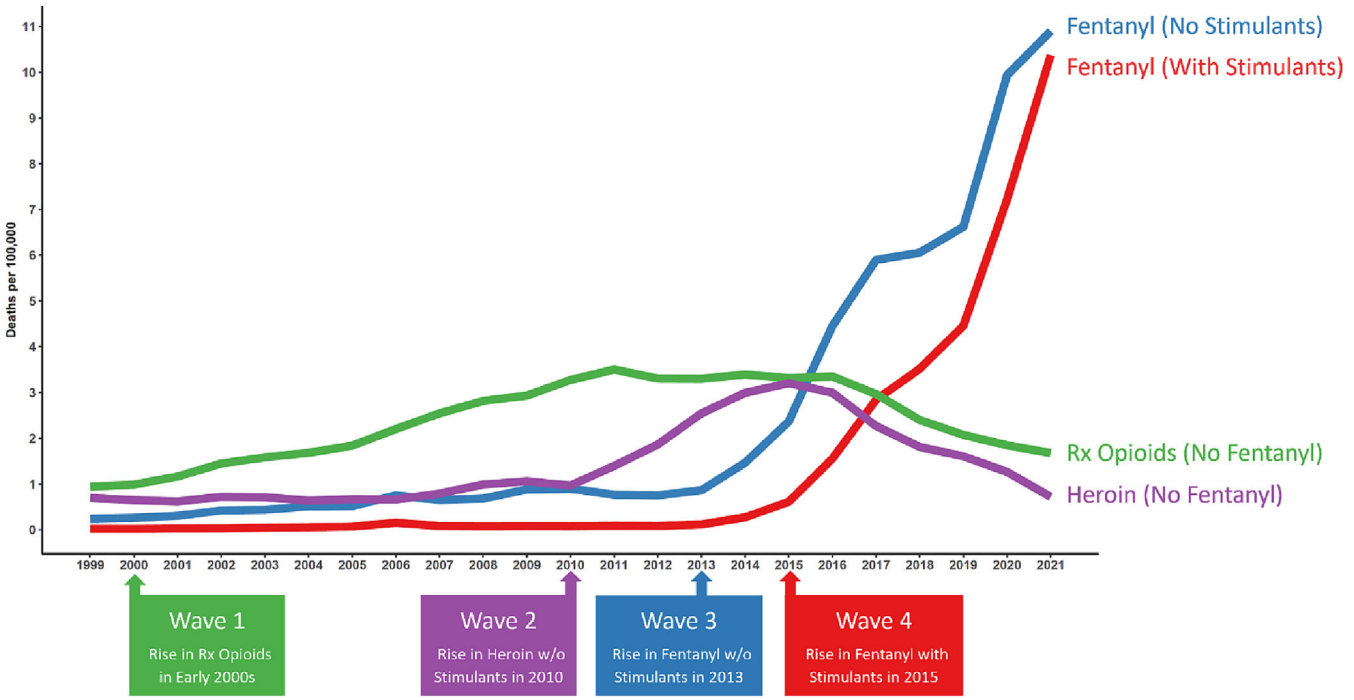


FIGURE 1 Four waves of overdose mortality. A simplified schema of the four waves of the United States overdose mortality crisis. Waves 1 and 2 are represented by deaths involving commonly prescribed opioids and heroin, respectively, but excluding fentanyl co-involved deaths. Fentanyl-co-involved deaths are excluded for illustrative purposes here because the precipitous rise of fentanyl-involved deaths starting in 2013 has had the effect of raising deaths rates for a whole host of other substances used together with fentanyls, despite fentanyls representing the key driving factor in wave 3 and 4. Here, we can observe that prescription opioid- and heroin-driven waves reach inflection points and begin to decline in 2010 and 2015 respectively, after removing the inflating effects from fentanyl co-involvement. Wave 3 and wave 4 are separated by showing fentanyl deaths not involving, and involving, stimulants respectively as distinct trends, revealing the short ~2-year lag between the two waves. Data were obtained from Centers for Disease Control and Prevention's Wide-Ranging Online Database for Epidemiologic Research.

In 2021, methamphetamine co-involvement was highest in states in the West (Alaska, California, Hawaii, New Mexico, Oregon and Washington), as well as West Virginia and Kentucky (Figure 4). Cocaine co-involvement was highest in Rhode Island, Vermont, Massachusetts and high across a swath of states in the Northeast and Southeast. Benzodiazepine co-involvement in 2021 was highest in Texas Utah, Arkansas and Massachusetts.

Virtually all states observed an increase in the proportion of fentanyl deaths involving stimulants between 2015 and 2021 (Figure 5). By 2021, the states with the highest proportions included Alaska (66.0%), West Virginia (59.8%), Rhode Island (58.6%), Hawaii (58.5%) and California (58.1%) (Figure 5). The states with the lowest proportions in 2021 included New Hampshire (22.3%), Nebraska (30.0%) and Wyoming (30.6%).

Figure 6 shows the proportion of fentanyl deaths containing stimulants for groups defined by the intersection of census region, race/ethnicity, gender and 10-year age groups, between 2016 and 2020. Table 1 also highlights trends separate by census division, age, gender, census division, race and ethnicity in 2021. Both overall, and in specific intersectional groups, the highest prevalence of stimulant involvement in fentanyl overdose deaths was observed in individuals ages 25 through 54, with generally lower rates among the youngest and oldest individuals. The intersectional groups with the highest proportions included 65 to 74-year-old non-Hispanic Black or African American women living in the West (73.3%), as well as 55 to 65-year-old Black or African American men living in the West (68.7%).

Although men represented a much larger share of all fentanyl overdose deaths, with 51 031 among men versus 19 571 among women in 2021, they had largely comparable rates of stimulant co-involvement (48.3% among men and 50.1% among women). Among census divisions, the proportion of fentanyl deaths involving a stimulant ranged from 41.6% in the West North Central division, to 56.4% in the Pacific.

DISCUSSION

The rise of illicitly manufactured fentanyls has ushered in an overdose crisis in the United States of unprecedented magnitude [4, 12–14]. This has created conditions that have promoted a number of other shifts in the illicit drug supply, leading to rising polysubstance overdose deaths—the so-called 'fourth wave' of the crisis, especially involving stimulants and fentanyl co-use starting in 2015 [4, 8]. Mixtures of fentanyl analogues and drugs of various drug classes, such as

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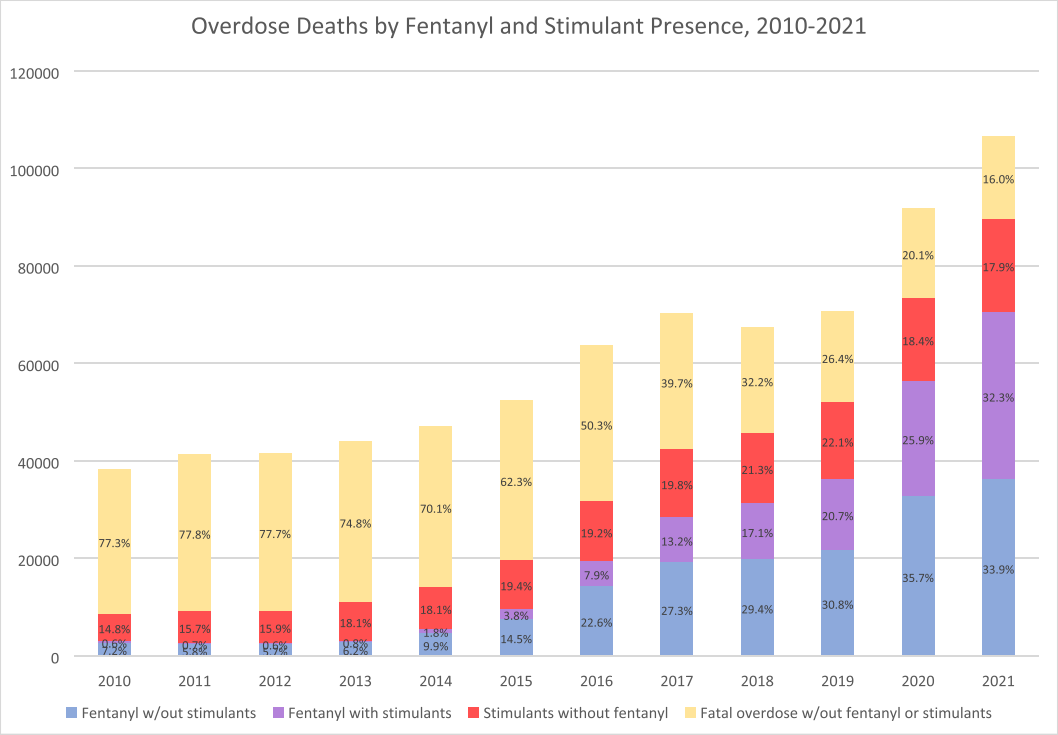


FIGURE 2 Overdose deaths by fentanyl and stimulant presence, 2010–2021. The total number of drug overdose deaths occurring in the United States (US) is shown by year (as the height of each bar), and fentanyl and stimulant involvement with color and percent of the total shown in text. Data were obtained from Centers for Disease Control and Prevention's Wide-Ranging Online Database for Epidemiologic Research. Of note, small increases in absolute number of deaths might be expected based on population change alone, as the US population grew 7.5% between 2010 and 2021.

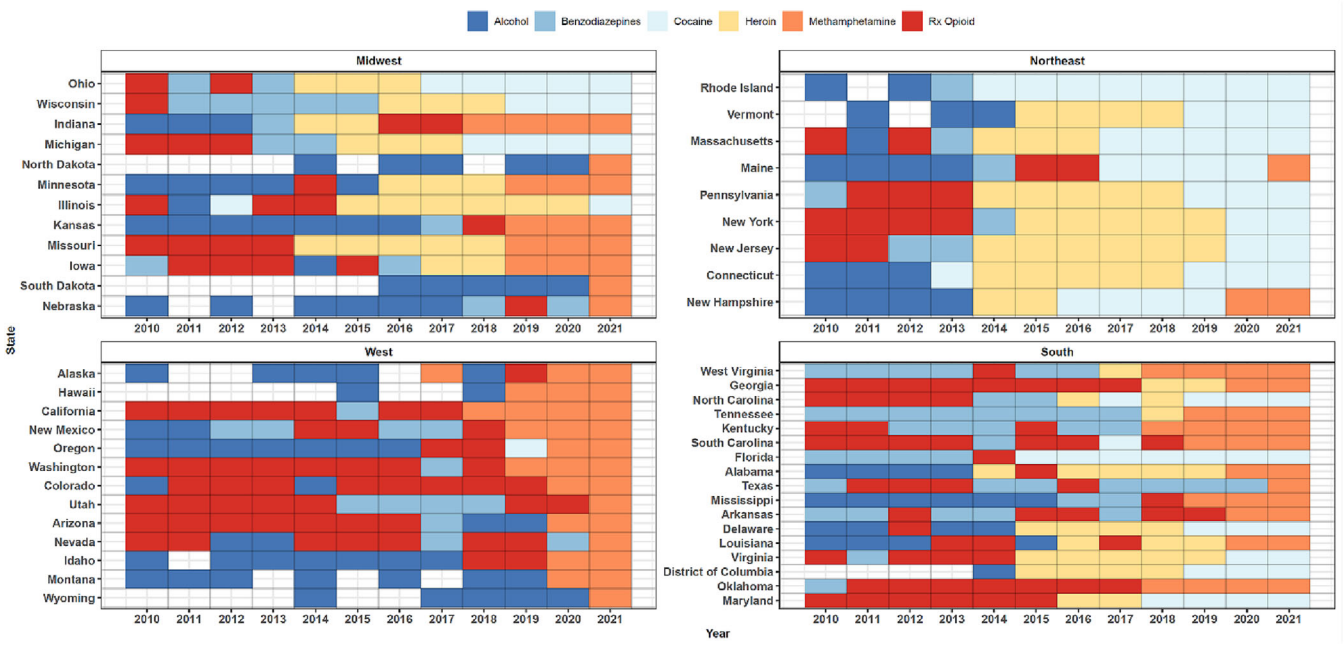


FIGURE 3 Most common drug co-involved in overdose mortality with fentanyls, by state and year, 2010–2021. The most common drugs co-involved with fentanyls in drug overdose deaths are shown by state and year, grouped separately by four United States census regions. Data were obtained from Centers for Disease Control and Prevention's Wide-Ranging Online Database for Epidemiologic Research (CDC WONDER). Instances were fewer than 10 deaths involved stimulants and fentanyls are suppressed by CDC WONDER, and therefore, not shown.

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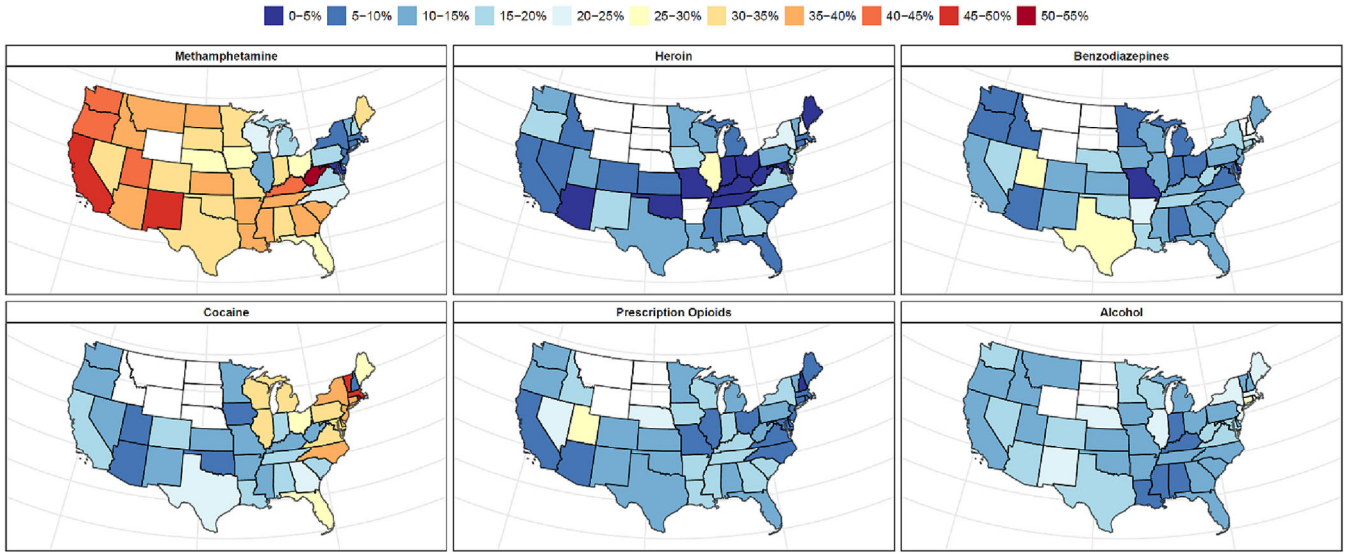


FIGURE 4 Percent of fentanyl overdose deaths containing other drug classes by state, 2021. The percent of fentanyl-involved overdose deaths co-involving other drugs in 2021 is shown for six drug classes by state. Data were obtained from Centers for Disease Control and Prevention's Wide-Ranging Online Database for Epidemiologic Research (CDC WONDER). Instances were fewer than 10 deaths involved a given substance and fentanyls are suppressed by CDC WONDER, and therefore, not shown.

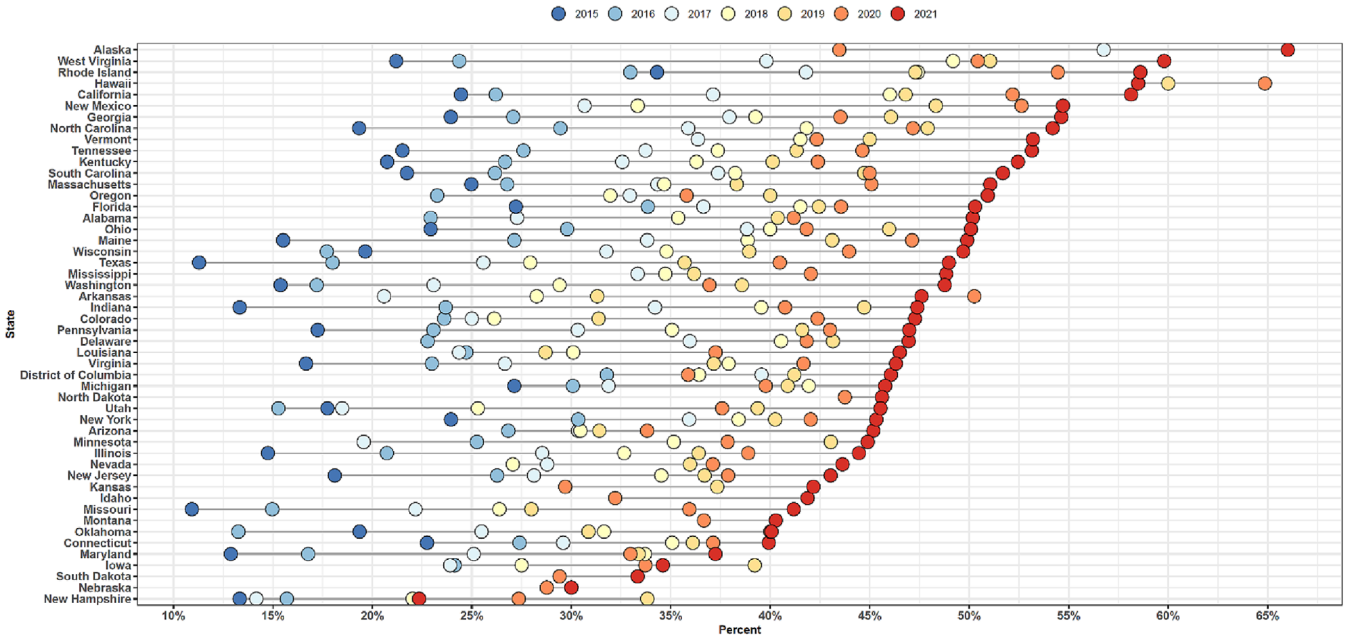


FIGURE 5 Percent of fentanyl overdose deaths involving stimulants by state and year, 2015–2021. The percent of fentanyl-involved overdose deaths co-involving stimulants is shown by state and year between 2015 and 2021. Data were obtained from Centers for Disease Control and Prevention's Wide-Ranging Online Database for Epidemiologic Research (CDC WONDER). Instances were fewer than 10 deaths involved stimulants and fentanyls are suppressed by CDC WONDER, and therefore, not shown.

stimulants, benzodiazepines, tranquilizers and other opioids have been noted in distinct geographies [4, 8, 9, 15]. Here, we provide a comprehensive characterization of the rising fentanyl-based polysubstance overdose crisis, detailing shifts in specific drug combinations over time, and which geographic, racial/ethnic and demographic groups are the most affected.

In 2010, fentanyl was most commonly found alongside prescription medication (opioids and benzodiazepines) and alcohol (i.e. largely products produced in legal markets). Over the past decade this has shifted first to heroin-fentanyl combinations in specific states, and then universally to illicit stimulants. The fraction of all overdose deaths involving both fentanyl and stimulants grew rapidly between

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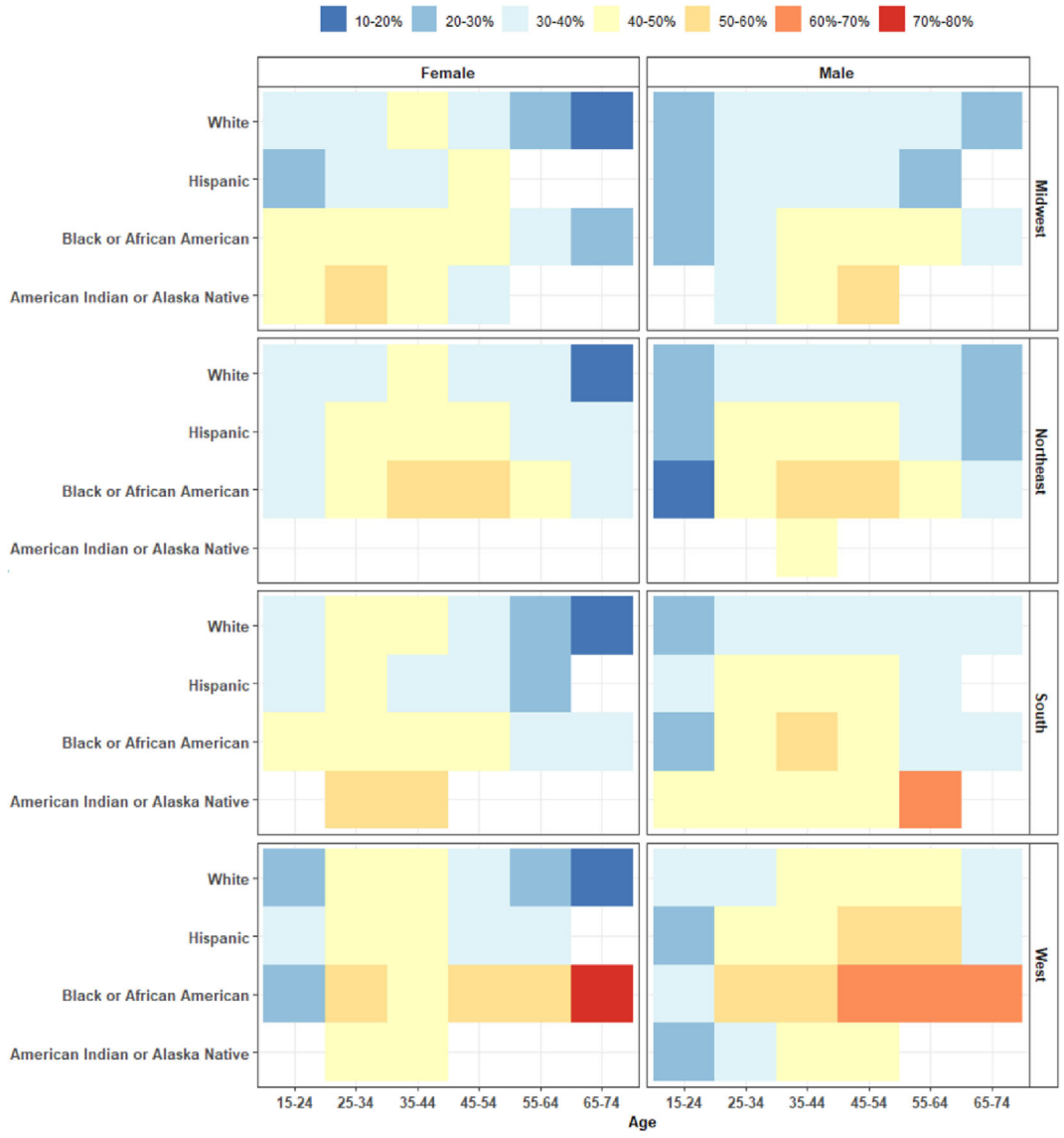


FIGURE 6 Percent of fentanyl overdose deaths involving stimulants by intersectional region, race/ethnicity, age, gender, 2016–2020. The percent of fentanyl-involved overdose deaths co-involving stimulants is shown for intersectional groups defined by census region, race/ethnicity, age and gender. Data were obtained from Centers for Disease Control and Prevention's Wide-Ranging Online Database for Epidemiologic Research (CDC WONDER). Data are pooled for the years 2016–2020, representing the latest 5 years available in a single data pull from CDC WONDER (finalized records from 2021 are available separately). Instances were fewer than 10 deaths involved stimulants and fentanyls are suppressed by CDC WONDER, and therefore, not shown.

2010 and 2021 and is on track to represent the single largest component of the overdose crisis in the near future. However, this has occurred in a distinct fashion based on geography and time. The northeastern states nearly universally saw a distinct period of heroin-fentanyl co-involvement, which was also found in some parts of the Midwest and South, but was completely absent from the western states (which transitioned rapidly from black tar heroin to fentanyl with methamphetamine co-involvement). By 2021, cocaine predominated in the Northeast and methamphetamine had become the most common drug found alongside fentanyls in the rest of the country.

There are now two basic archetypes of states in the United States with respect to overdose death rates: (a) states where fentanyl and cocaine co-use predominates; and (b) states where fentanyl and methamphetamine co-use predominates, with surprising little overlap between these two groups. These dynamics warrant considerable additional study, but we suspect they reflect the combination of very low-cost, high-purity methamphetamine outcompeting cocaine and other stimulants at the national level, in addition to an enduring, well-entrenched illicit cocaine market in the Northeast and other pockets of the country [16].

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TABLE 1 Percent of fentanyl overdose deaths containing stimulants by key socio-demographic characteristics, 2021.

	Fentanyl	Fentanyl and stimulants	% Fentanyl deaths with stimulants
Sex			
Male	51 031	24 630	48.3
Female	19 571	9799	50.1
Race/ethnicity			
Non-Hispanic			
American Indian or Alaska Native	805	422	52.4
Asian	464	213	45.9
Black or African American	13 592	7187	52.9
Native Hawaiian or Pacific Islander	57	27	47.4
More than one race/ethnicity	816	388	47.5
White	45 592	21 749	47.7
Hispanic			
American Indian or Alaska Native	86	46	53.5
Asian	26	Suppressed	–
Black or African American	316	150	47.5
Native Hawaiian or Pacific Islander	19	11	57.9
More than one race/ethnicity	149	71	47.7
White	8255	3914	47.4
Age group, years			
<15	193	18	9.3
15–24	5936	1945	32.8
25–34	18 585	8691	46.8
35–44	19 000	10 071	53.0
45–54	13 467	7322	54.4
55–64	10 792	5400	50.0
65–74	2452	941	38.4
>74	168	37	22.0
Census division			
New England	4855	2260	46.5
Middle Atlantic	10 807	4904	45.4
East North Central	12 485	5943	47.6
West North Central	3069	1276	41.6
South Atlantic	17 673	8795	49.8
East South Central	5832	3042	52.2
West South Central	3682	1740	47.3
Mountain	4178	1947	46.6
Pacific	8020	4522	56.4

Note: The percent of fentanyl-involved overdose deaths co-involving stimulants is shown for 2021 separately by census division, race and ethnicity, age and gender. Data were obtained from CDC WONDER. Instances were fewer than 10 deaths involved stimulants and fentanyls are suppressed by CDC WONDER, and therefore, not shown.

Abbreviation: CDC WONDER, Centers for Disease Control and Prevention's Wide-Ranging Online Database for Epidemiologic Research.

The rise of deaths involving cocaine and methamphetamine must be understood in the context of a shifting illicit opioid drug market increasingly dominated by illicit fentanyls [13]. Recent ethnographic and qualitative research suggests that fentanyls have created conditions that make polysubstance use more sought-after and commonplace [17, 18]. For instance, many individuals report that mixing a small amount of methamphetamine into injected doses of fentanyl subjectively prolongs the onset of withdrawal symptoms, increases euphoria, decreases overdose risk and improves energy levels required to continue to collect funds for the next set of drug

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purchases [17–19]. These perceived advantages may be particularly important given the short duration of fentanyls, requiring individuals to inject far more frequently than heroin, and the heightened overdose risk from each injection [13]. Similar findings have been reported in qualitative studies of xylazine and other drugs commonly added to fentanyls, suggesting possible structural similarities across various emerging polysubstance patterns [8]. Given the increased risk of negative health outcomes such as overdose not fully responsive to naloxone often requiring additional life-saving measures such as airway management, precise surveillance of specific drug formulations and sociodemographic groups affected is essential [8].

Surveillance of the evolving polysubstance overdose crisis presents numerous challenges. Many resources in the current data landscape to track overdose mortality in the United States are not optimized to track the polysubstance formulations now driving the crisis, as they cannot routinely show the prevalence of complex sets of drug co-involvement in overdose deaths [20]. Furthermore, many novel substances increasingly involved in overdose, such as the veterinary tranquilizer xylazine, are not universally tested for in autopsy toxicology investigations [8]. Drug checking technologies used by local public health agencies and client-facing harm reduction clinics, as well as universal routine testing for novel psychoactive substances in autopsy toxicology, represent important avenues to improve surveillance of the growing polysubstance drug crisis facing the United States [21]. Supply-side drug market surveillance leveraging law enforcement seizures has also offered important insights [22, 23], although such records are often not made publicly available in a timely or detailed fashion.

An additional critical consideration is the growing prevalence of counterfeit pills, which resemble psychoactive pharmaceuticals such as oxycodone or alprazolam, but contain illicit fentanyls, often mixed with other illicit substances such as stimulants, benzodiazepines, xylazine and other opioids [21–23]. In recent years, counterfeit pills have grown to represent over a quarter of all illicit fentanyl seizures [22]. Counterfeit pills have the potential to transform overdose risk as they may expand the markets for illicit synthetic drugs to subpopulations, such as adolescents, who may be less likely to consume powder fentanyl products [24-26]. In the ongoing surveillance of the US overdose crisis, tracking deaths involving counterfeit pills versus other formulations represents an important dimension that is currently difficult within the existing data landscape.

Limitations

There are limitations to this study that should be considered. As we highlight here, the landscape of polysubstance overdose has been evolving in a highly rapid manner. Therefore, even the most current results may simply represent snapshots of shifting dynamics that will soon change. Further, fatal overdose is the most readily available metric, as there are highly limited toxicological surveillance data on nonfatal overdose in the United States. However, they do not represent the totality of use practices, rather the fraction of drug use most likely to result in death. The categories of drugs assessed here are also limited by current CDC classification schemes, which limit within-category assessment. For instance, is it not possible to distinguish between prescription benzodiazepines and novel synthetic benzodiazepines, or between fentanyl analogues and nitazines. Finally, particularly for the intersectional group analysis, stratification has led to small sample sizes for some analytical units, although samples sizes for most of the analysis were robust. The analysis was not pre-registered and the results should be considered exploratory.

CONCLUSIONS

We provide a detailed description of the fourth wave of the US overdose crisis—characterized by sharply rising polysubstance overdose deaths involving illicitly manufactured fentanyls. Stimulant-fentanyl co-involvement is rapidly becoming the largest component of the crisis, with a distinct pattern seen by over time and by geography and sociodemographic groups. The regional patterning of cocaine-fentanyl in the Northeast and methamphetamine-fentanyl in the rest of the country is particularly notable. The widespread concurrent use of fentanyl and stimulants, as well as other polysubstance formulations, presents numerous novel health risks and public health challenges. Moving forward, ongoing nuanced surveillance is needed to track this rapidly shifting phenomenon.

AUTHOR CONTRIBUTIONS

Joseph Friedman: Conceptualization (equal); data curation (equal); formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); resources (equal); software (equal); supervision (equal); validation (equal); visualization (equal); writing—original draft (equal); writing—review and editing (equal). **Chelsea Shover:** Conceptualization (equal); data curation (equal); formal analysis (supporting); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); resources (equal); software (equal); supervision (equal); validation (equal); visualization (equal); writing—original draft (supporting); writing—review and editing (equal).

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DECLARATION OF INTERESTS

None.

DATA AVAILABILITY STATEMENT

All data used for this article are publicly available from CDC WONDER: https://wonder.cdc.gov/.

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