

Millennium Health Signals Report™

Volume 6



The “Fourth Wave”

The Rise of Stimulants and the Evolution of Polysubstance Use in America’s Fentanyl Crisis

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Millennium Health is an accredited specialty laboratory with over 15 years of experience in drug testing. We provide objective information about patients' recent use of prescription medications and/or illicit drugs which helps clinicians monitor and treat millions of Americans living with chronic pain, substance use disorders, mental health disorders or other health conditions. Our ability to monitor drug use trends allows us to alert clinicians, health agencies and others to real-time drug use changes to help inform more targeted drug overdose prevention and response strategies to save lives.

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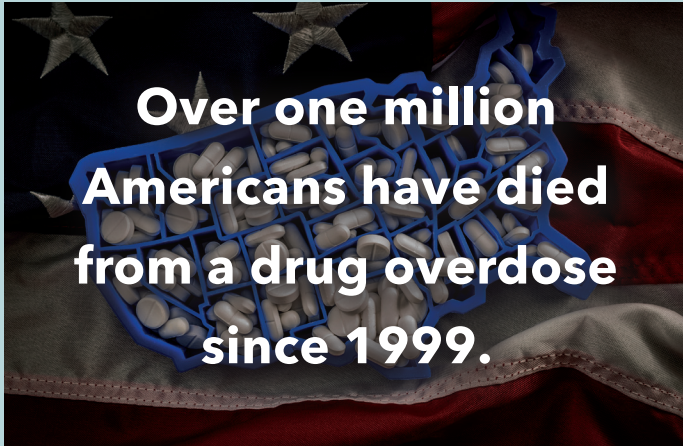
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While we at Millennium Health work with many groups to look at numbers and statistics to help understand and address this epidemic, we also never forget that each one of these overdose numbers was a person. It was someone with a family, a community, and a life that touched others. The reality is that the official overdose statistics, that seem so overwhelming on their face, vastly understate the impact that this epidemic is having on our society.

We also keep in mind that the word “overdose” is an overly broad term and unfortunately may not always reflect the unique and individualized set of circumstances that led to each tragic demise. For example, the person who loses their battle with addiction and the person who was poisoned by a single, fentanyl-laced counterfeit pill are both said to have “overdosed.” However, the underlying causes and the steps needed to address these scenarios are very different, which makes finding solutions that much more difficult.

While the challenges of the overdose epidemic are both large and complex, there is progress to be made. Two pieces of information that are critical and relevant to better understanding all

overdose situations is knowing what drugs caused them and how the illegal drug supply is changing. Quite simply, it is tough to organize a battle if we don’t know exactly what we are fighting against. However, this is anything but straightforward as we know from our own data that the illegal drug supply has tremendous variability across the country and is changing constantly.

Our goal with each edition of our Signals Report is to provide an update on these trends, and we believe that timely information such as this can help at multiple levels. Individual providers are well served by knowing the drugs that are prevalent in their local communities. Local advocacy and public health groups can better educate and prepare their local communities based on the trends. At the national level, regulators and policy makers can gain insights into what impact their efforts are having and what resources they will need to be in a position to respond effectively.

We take tremendous pride in being a partner and a resource to so many amazing individuals and groups across the country who are using our data and clinical resources in support of their efforts to address this crisis. ***This includes clinicians, researchers, academic institutions, federal agencies, state offices, advocacy groups, reporters, teachers, and so many others who are carrying the flag in our battle against the overdose epidemic. We would like to thank each of you for the work that you are doing and invite any others to reach out to us if you believe that we can be of assistance.***

We hope you find this edition of the Millennium Health Signals Report to be interesting and valuable, and we look forward to many more in the future.



Scott Walton
Chief Executive Officer,
Millennium Health

America's overdose epidemic is complex and has been broadly described as consisting of three "waves" of overdose deaths involving prescription opioids (Wave 1), heroin (Wave 2), and fentanyl (Wave 3).^{1,2} From 2013 to 2021, the number of fentanyl-involved overdose deaths[†] increased 84-fold, totaling nearly 261,000 lives lost.³ However, non-opioid drugs are also frequently involved in fatal opioid overdoses and our understanding of how polysubstance use impacts overdose vulnerability and treatment responses remains relatively limited.^{4,5} More recently, a "fourth wave" of drug overdose deaths involving fentanyl and stimulants (i.e., methamphetamine and/or cocaine) has emerged.⁶ In 2010, stimulants were co-involved in less than 1% of fentanyl overdose deaths nationally. By 2021, stimulant-fentanyl co-involvement had grown, accounting for nearly one third (32.3%) of all fatal fentanyl overdoses.⁷

To better address a growing and ever-changing overdose epidemic, timely sources of data that provide detailed insight into current drug use trends are needed. Urine drug test (UDT) data have shown to significantly correlate with national overdose mortality patterns over time⁸ and may offer particularly relevant information on

shifting drug use trends that correspond with the evolving nature of the overdose crisis. Because UDT data update rapidly (i.e., daily), they can inform responses to address the fentanyl crisis and help save lives. Therefore, these data warrant thoughtful consideration.

This volume of the Millennium Health Signals Report™ has three objectives: (1) illustrate that UDT results tightly correlate with trends in fentanyl-related overdose mortality, (2) explore changes in the co-detection of prescription opioids, heroin, methamphetamine, and cocaine in fentanyl-positive specimens, and (3) provide insight into recent trends in polysubstance use among people who use fentanyl.

Throughout the Report, the findings are anchored around three key takeaways (see below) with the goal of highlighting the utility of UDT data to inform clinical practice and efforts to respond to America's evolving fentanyl crisis. We join with all of those dedicated to stemming the tide of this latest scourge as we work together to address the challenge of polysubstance use and take steps to prevent the next wave that will undoubtedly come crashing in.

Key Takeaways

1

Urine Drug Testing (UDT) Data Tightly Correlate with Trends in Fentanyl-Involved Overdose Mortality and Closely Follow the Evolution of America's Fentanyl Crisis

2

For the First Time, in 2023 both Methamphetamine and Cocaine were Detected in Fentanyl-Positive UDT Specimens More Often than Heroin and Prescription Opioids Nationally and in Nearly Every State

3

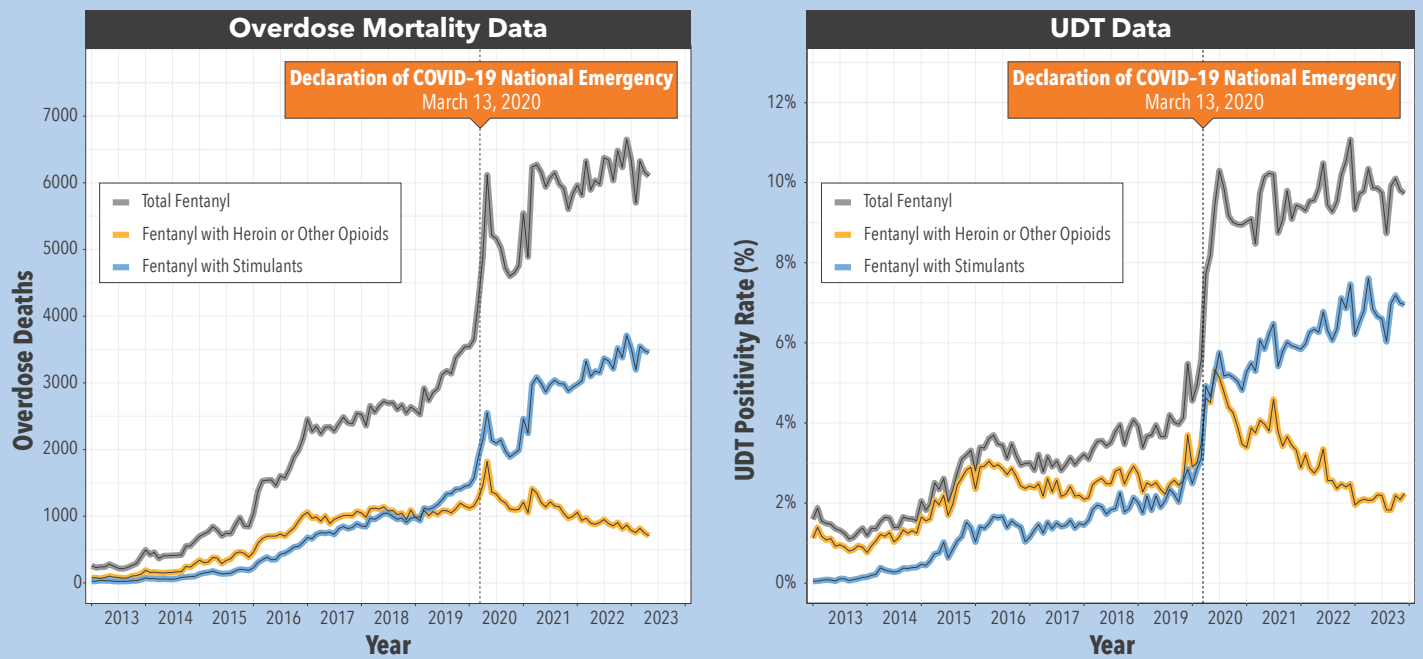
Nearly 93% of Fentanyl-Positive Specimens in 2023 Contained Additional Drugs Including a Wide Range of Potentially Dangerous Drugs

† The Centers for Disease Control and Prevention (CDC) uses the classification "Synthetic Opioids other than Methadone" which includes fentanyl. We use the term "fentanyl" for simplicity because the majority of deaths within this class involve fentanyl.

1: UDT Data Tightly Correlate with Trends in Fentanyl-Involved Overdose Mortality and Closely Follow the Evolution of America's Fentanyl Crisis

- Public health surveillance data that provide timely insight into current drug use trends are needed to better understand and mount data-driven responses to a continually evolving drug overdose epidemic
- Figure 1 shows how national trends in UDT data align with fentanyl-related overdose mortality over time

Figure 1. Comparison of Fentanyl UDT Data and Fentanyl-Related Overdose Mortality



Left Panel: Monthly total synthetic opioid overdose deaths (MCD T40.4, mostly illicitly manufactured fentanyl, referred to as "fentanyl" for simplicity; gray line) and those co-involving stimulants (blue line) including cocaine (MCD T40.5) and psychostimulants with abuse potential (MCD T43.6, mostly methamphetamine) or other naturally derived and semisynthetic opioids (i.e., "Other Opioids"; orange line) including heroin (MCD T40.1) and natural opioid analgesics and semi-synthetic opioids (MCD T40.2) from January 2013 through May 2023. Overdose mortality data for 2022 and 2023 are provisional. Right Panel: Monthly urine drug testing (UDT) positivity rates for fentanyl (total, gray line) and when co-detected with stimulants (i.e., cocaine and methamphetamine, blue line) or heroin and other opioids (i.e., heroin and/or morphine and prescription opioids including hydrocodone, hydromorphone, oxycodone and oxymorphone without a reported prescription; orange line) in patient specimens collected from 2013 through December 15, 2023. Positivity rates were estimated using logistic regression. See Methods for further detail.

Interpretation and Key Findings

- Fentanyl overdose deaths and fentanyl detection in UDT have increased dramatically and very similarly since 2013
- The most common substances found with fentanyl in fatal overdoses (left panel) and UDT (right panel) have gradually shifted over time from heroin and other opioids (—) to stimulants (—), including methamphetamine and cocaine
- **Millennium Health's definitive UDT data are highly correlated with overdose mortality and remain a key data source because of its specificity and timeliness. This is despite the significant impacts of the pandemic and the continually evolving nature of the overdose crisis. UDT data can be used to help plan public health interventions for areas of high drug concentration, predict areas of future concern, and gauge the success of ongoing interventions.**

Discussion

The findings demonstrate that urine drug test results provide near real-time insights into complex and shifting patterns of drug use.

Figure 1 shows that UDT data from fentanyl-positive specimens tightly correlate with trends in fentanyl-related overdose mortality across time and are generally consistent with the progression of the “triple-wave epidemic” and the emergence of a “fourth wave” co-involving fentanyl and stimulants.^{4,5,6,9}

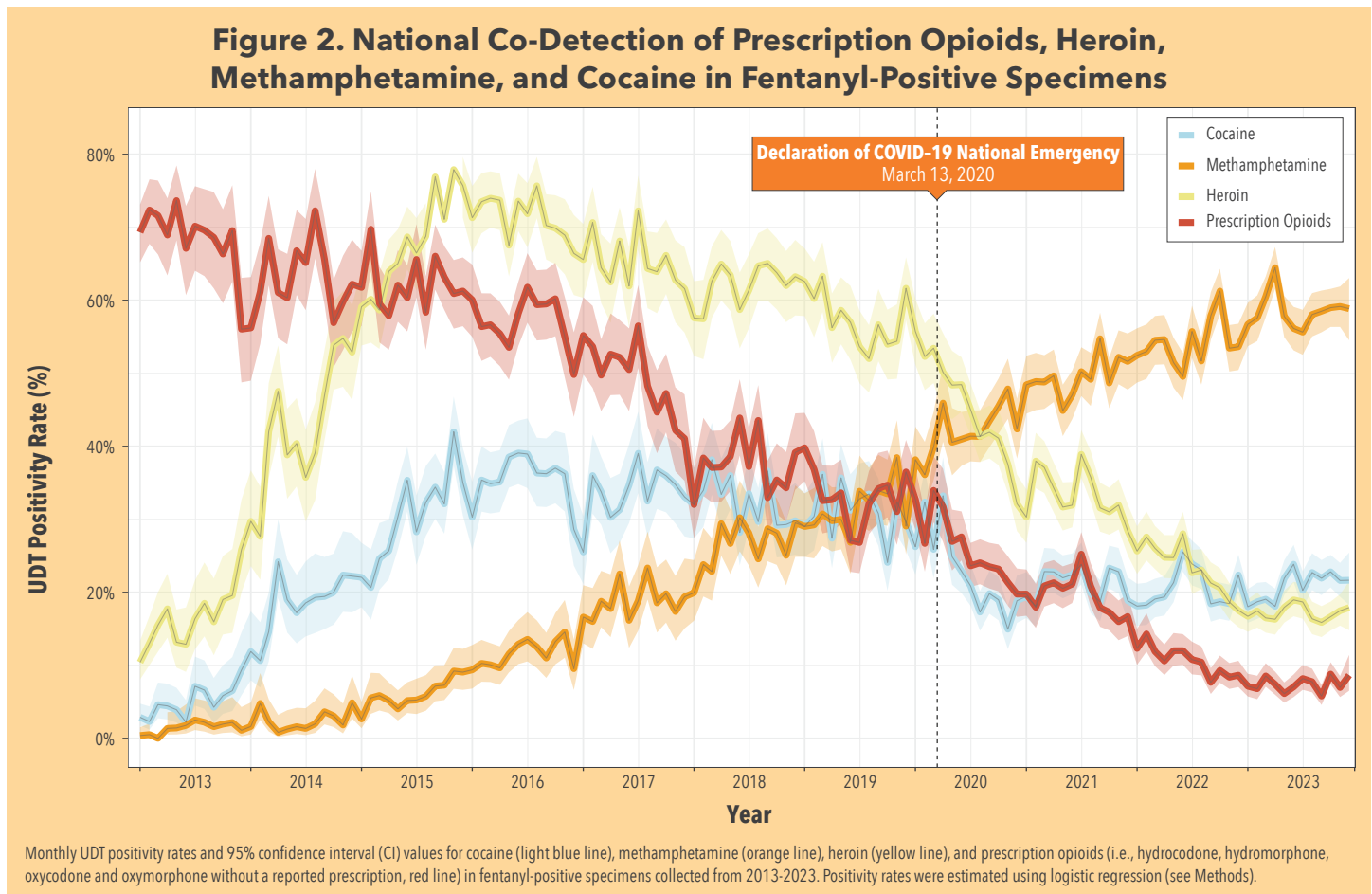
The fact that national trends in UDT data are consistent with those of overdose mortality suggests they may measure complementary aspects of the evolving fentanyl crisis.

From a public health surveillance and community response perspective, the timeliness of UDT data is a significant strength compared to other sources of data that may lag in time. This collectively suggests that UDT data warrant consideration as a rapidly updating source of information to support efforts to better understand and mount data-driven responses to a continually evolving public health crisis.



2A: For the First Time, in 2023 both Methamphetamine and Cocaine were Detected in Fentanyl-Positive UDT Specimens More Often than Heroin and Prescription Opioids

- Figure 2 shows shifting trends in the co-detection of prescription opioids, heroin, methamphetamine, and cocaine nationally to provide insight into how each has changed over time



Interpretation and Key Findings

- Methamphetamine was the most common drug found in fentanyl-positive specimens in 2023; it was detected in 60% of fentanyl-positive specimens in 2023 and has consistently increased each year, up 875% since 2015
- Cocaine is now the second most-detected drug in fentanyl-positive specimens; up 318% between 2013 and 2023
- Heroin detection in fentanyl-positive specimens has dropped by 75% since peaking in 2016, returning to near 2013 levels
- Prescription opioid positivity in specimens positive for fentanyl reached a historic low in 2023, down 89% since 2013
- For all analytes, changes from 2022 to 2023 were smaller but consistent with trends in prior years
- The lack of FDA-approved medications for stimulant use disorders limits the clinical tools that are available and increases the complexity and intensiveness of treatment regimens for those with co-occurring opioid and stimulant use disorders, as well as those with primary stimulant use disorders.***

Note: Values reported in the Interpretation and Key Findings are based on yearly averages.

Discussion

Our analysis of trends in the detection of fentanyl with other opioids (i.e., heroin and prescription opioids) or stimulants (i.e., methamphetamine and cocaine) revealed stimulants are now detected more frequently than prescription opioids and heroin in fentanyl-positive specimens.

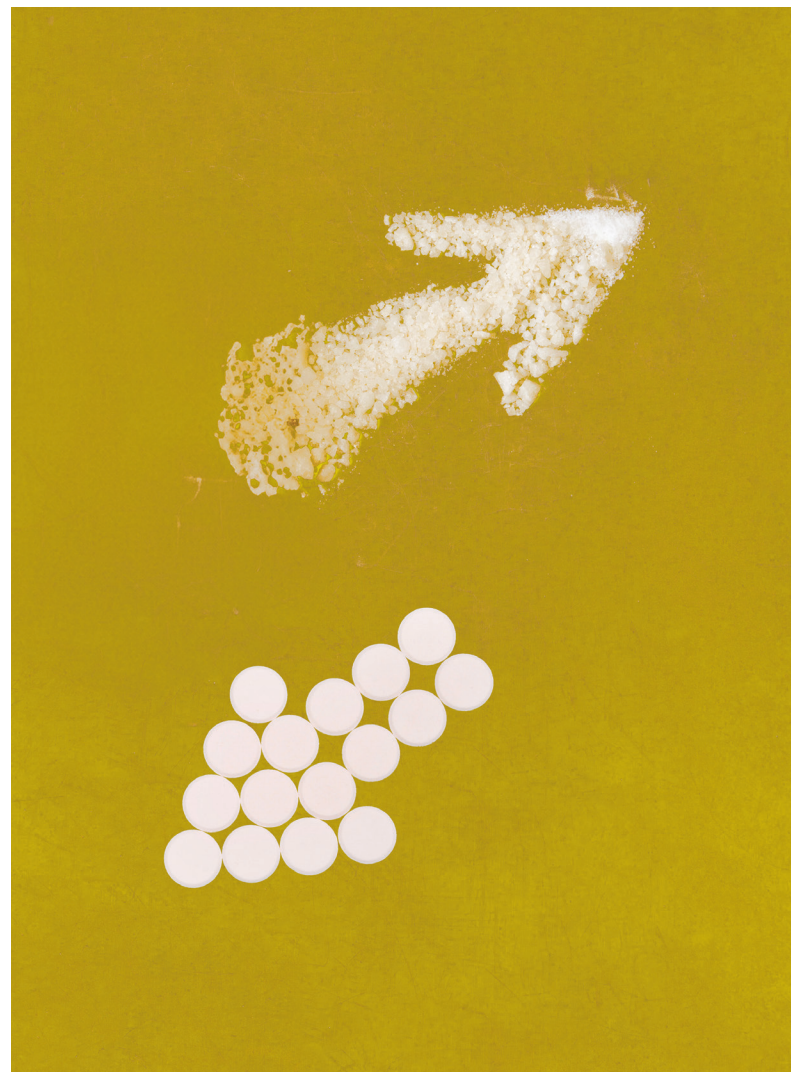
Although most concentrated in the West, Midwest, and portions of the South in 2023 (see Table 1), striking increases in methamphetamine use among people who use fentanyl have been observed across the country since 2015.

Despite nearly doubling from 2015 to 2017, rates of cocaine use among those who use fentanyl have held relatively steady at the national level since then. Cocaine use among people who use fentanyl has been more common in the eastern half of the U.S. over time and grew more entrenched in this area in 2023, especially along the eastern seaboard (see Table 1). These geographical patterns of stimulant detection in fentanyl-positive UDT specimens are also largely consistent with the results of a recent study that showed where each one was most frequently co-involved in fentanyl overdose deaths through 2021.⁷

The results of our analyses also reveal shifting patterns of opioid use among those who use fentanyl. More specifically, they showed progressive declines in prescription opioid use from 2015 to 2023 and captured the crest and fall of heroin use in this group. Interestingly, the detection of heroin and prescription opioids fell by almost half from 2019 to 2021. Although the

waves of heroin and prescription opioid use in this group had been steadily receding since 2016, these dramatic reductions coincided with the harrowing surge in fentanyl use that followed the onset of the COVID-19 pandemic in 2020.

These diverging trends in fentanyl and heroin or prescription opioid use signal that a tidal shift in the “opioid epidemic” occurred during this period as fentanyl cemented its position of dominance and became the primary illicit opioid for many.



2B: Co-Detection of Fentanyl and Stimulants, Especially Methamphetamine, Increased in ALL Regions from 2015 to 2023; Prescription Opioids and Heroin Decreased in Nearly Every Region Over This Same Period

- National trends in UDT data show that people who use fentanyl are increasingly also using cocaine and methamphetamine, but these trends vary by region
- Table 1 shows changes in the co-detection of prescription opioids, heroin, cocaine, and methamphetamine by U.S. Census division to illustrate regional variability over time

Table 1. Positivity Rates for Prescription Opioids, Heroin, Methamphetamine, and Cocaine Co-Detection Over Time

Prescription Opioids in Fentanyl-Positive Specimens by U.S. Census Division									
	Pacific	Mountain	West North Central	West South Central	East North Central	East South Central	Mid Atlantic	South Atlantic	New England
2015	54.8%	72.7%	56.3%	58.0%	61.8%	57.4%	64.7%	65.9%	51.1%
2017	53.8%	68.5%	57.7%	72.1%	39.9%	48.4%	63.0%	55.6%	33.5%
2019	54.1%	38.4%	40.3%	68.0%	25.1%	28.7%	40.4%	38.4%	18.7%
2021	34.4%	18.9%	19.8%	27.0%	11.8%	12.8%	21.9%	25.4%	7.2%
2023	7.0%	5.5%	5.8%	15.3%	7.0%	10.9%	10.2%	10.8%	3.7%

Heroin in Fentanyl-Positive Specimens by U.S. Census Division									
	Pacific	Mountain	West North Central	West South Central	East North Central	East South Central	Mid Atlantic	South Atlantic	New England
2015	37.8%	20.8%	58.8%	17.0%	81.6%	40.3%	65.3%	72.7%	66.9%
2017	49.2%	29.7%	69.8%	38.5%	69.3%	68.2%	66.0%	74.9%	47.1%
2019	56.5%	33.7%	76.4%	67.0%	57.9%	62.1%	67.4%	62.3%	41.5%
2021	52.0%	25.1%	38.5%	54.6%	27.0%	35.0%	36.4%	37.6%	21.5%
2023	14.6%	9.5%	16.9%	36.5%	22.4%	19.7%	31.9%	25.9%	14.6%

Methamphetamine in Fentanyl-Positive Specimens by U.S. Census Division									
	Pacific	Mountain	West North Central	West South Central	East North Central	East South Central	Mid Atlantic	South Atlantic	New England
2015	10.6%	4.9%	21.8%	7.1%	6.6%	11.4%	3.7%	4.0%	3.8%
2017	28.9%	14.4%	47.8%	16.3%	18.5%	37.1%	8.4%	7.4%	10.5%
2019	52.7%	36.3%	49.2%	33.0%	28.8%	46.5%	15.2%	14.8%	20.5%
2021	66.0%	62.0%	50.0%	36.9%	37.1%	50.4%	24.5%	26.0%	39.4%
2023	70.6%	77.1%	54.3%	41.6%	38.6%	47.8%	18.1%	26.7%	34.1%

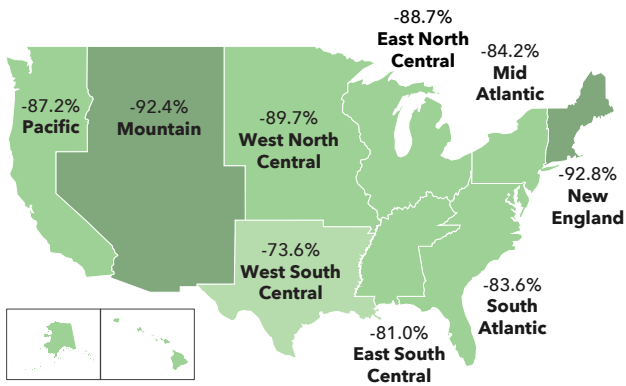
Cocaine in Fentanyl-Positive Specimens by U.S. Census Division									
	Pacific	Mountain	West North Central	West South Central	East North Central	East South Central	Mid Atlantic	South Atlantic	New England
2015	11.5%	1.1%	5.9%	3.6%	37.7%	14.2%	28.4%	38.4%	26.5%
2017	16.5%	10.8%	15.9%	15.4%	38.8%	22.4%	29.4%	45.9%	36.2%
2019	13.1%	12.2%	25.2%	29.0%	38.3%	18.0%	34.3%	43.1%	43.9%
2021	9.4%	10.4%	13.1%	30.4%	35.1%	20.8%	39.7%	36.2%	40.9%
2023	12.7%	9.7%	17.9%	25.4%	38.2%	24.4%	31.3%	43.5%	54.9%



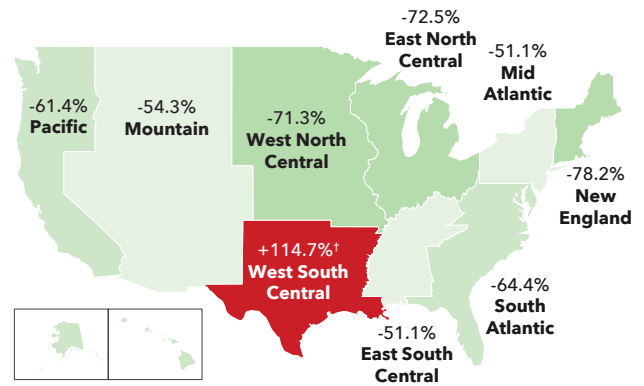
UDT positivity rate values for prescription opioids (hydrocodone, hydromorphone, oxycodone and oxymorphone; without a reported prescription), heroin (and/or morphine), methamphetamine, and cocaine in fentanyl-positive specimens collected in 2015, 2017, 2019, 2021, and 2023 by U.S. Census Division. Positivity rates were estimated using logistic regression (see Methods).

Figure 3. Percent Change in Prescription Opioid, Heroin, Methamphetamine, and Cocaine Detection in Fentanyl-Positive Specimens from 2015 to 2023

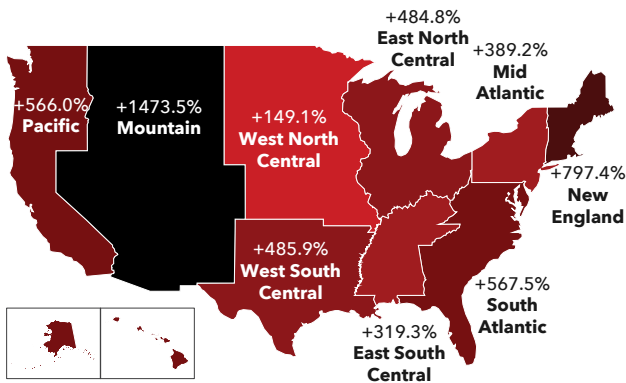
Prescription Opioids in Fentanyl-Positive Specimens



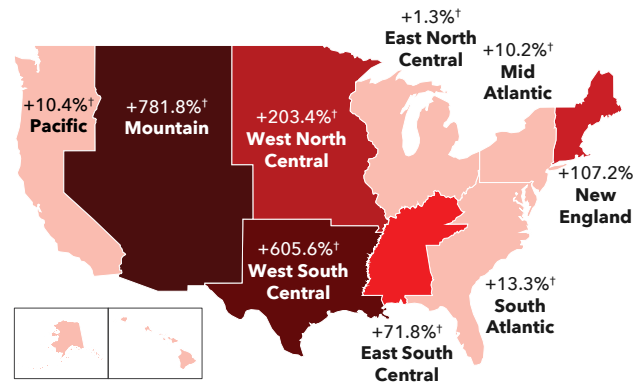
Heroin in Fentanyl-Positive Specimens



Methamphetamine in Fentanyl-Positive Specimens



Cocaine in Fentanyl-Positive Specimens



Percent Change in UDT positivity rates from 2015 to 2023 (green = decrease, red = increase) for prescription opioids (hydrocodone, hydromorphone, oxycodone and oxymorphone; without a reported prescription), heroin (and/or morphine), methamphetamine, and cocaine in fentanyl-positive specimens by U.S. Census Division. Percent change was calculated as: % Change = (2023 positivity rate - 2015 positivity rate)/2015 positivity rate × 100. **Data from 2023 were compared with 2015 data to illustrate how use of these drugs has changed during the "fourth wave" of the overdose epidemic among people who use fentanyl.** † = not a statistically significant change

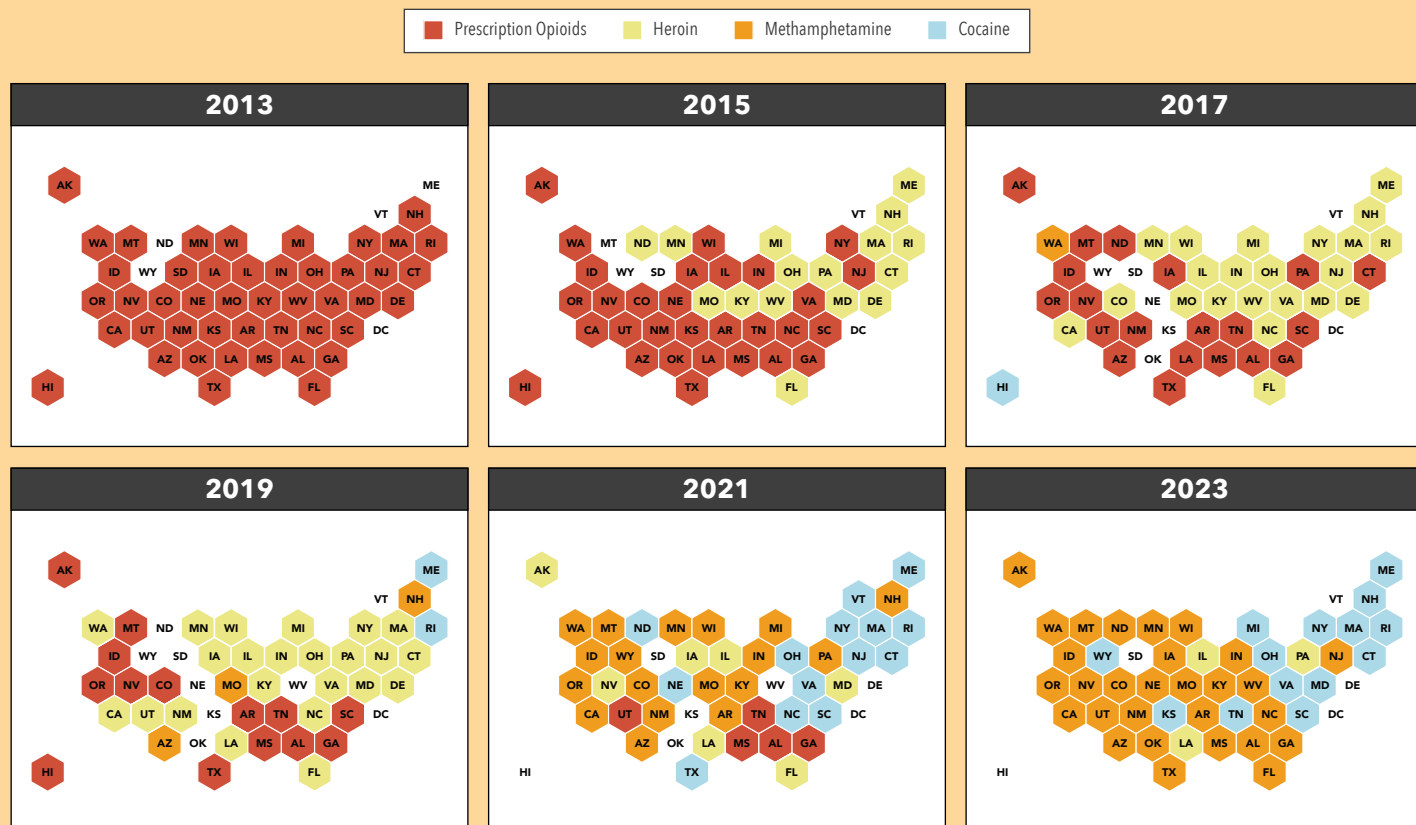
Interpretation and Key Findings

- Prescription opioid and heroin detection in fentanyl-positive specimens decreased in all regions of the U.S. from 2015 to 2023 with the exception of heroin in the West South Central region
- Methamphetamine and cocaine detection in fentanyl-positive specimens increased in all U.S. Census Divisions since 2015
- *The rise in cocaine and methamphetamine nationally does not seem to be driven by one or even a few regions of the country. Stimulants are a serious national challenge emphasizing the need for continued progress on the national plan to address methamphetamine supply, use, and consequences.*¹⁰

2C: In 2023, Cocaine and Methamphetamine were Detected in Fentanyl-Positive Specimens More Often than Heroin & Prescription Opioids in Nearly Every State

- Drug use trends may differ within regions and state-level data may help to inform public health policy and clinical decision-making
- Figure 4 shows which drug was most often found with fentanyl in UDT over time

Figure 4. Most Co-Detected Drug in Fentanyl-Positive Specimens Over Time by State



The most frequently detected drug or drug class by state based on UDT positivity rates for prescription opioids (hydrocodone, hydromorphone, oxycodone and oxymorphone; without a reported prescription), heroin (and/or morphine), methamphetamine, and cocaine in fentanyl-positive specimens collected in 2013, 2015, 2017, 2019, 2021, and 2023. Positivity rates were calculated and the drug or drug class with the highest positivity rate in a given state for each year was selected for display. Unfilled hexagons represent states without fentanyl-positive specimens that had ordered UDT results for all four drugs or drug classes of interest.

Interpretation and Key Findings

- In 2013, prescription opioids were detected most frequently in fentanyl-positive specimens in all states
- Heroin detection in fentanyl-positive specimens topped the list in the majority of states in 2017 and 2019
- Between 2019 and 2021, a dramatic shift occurred; cocaine and methamphetamine were most commonly detected in fentanyl-positive specimens in more states than heroin and prescription opioids combined
- In 2023, methamphetamine (29 states) was the most detected drug in fentanyl-positive specimens, followed by cocaine (14 states); prescription opioids were no longer most common in any state
- ***National, regional, and state-level UDT data all suggest that people who use fentanyl are now, intentionally or unintentionally, much more likely to also use methamphetamine and cocaine.***

3A: In 2023, Most People who Used Fentanyl with the Other Primary Drivers of Overdose Death Used Fentanyl and Methamphetamine Only, Followed by Fentanyl and Cocaine Only or All Three Combined

- Complex and evolving drug combinations impact overdose vulnerability and alter clinical presentation and/or treatment responses^{4,5}
- Figure 5 shows how specific, multi-drug combinations have changed over time

Figure 5. National UDT Positivity Rates for Specific Drug Use Combinations Over Time

Drug Combination	2015	2019	2023
	0.76%	7.5%	53%
	1.5%	9%	9.8%
	0.1%	1.9%	8.5%
	1.1%	10%	7.7%
	15%	14%	3.7%
	0.62%	4.3%	3.5%
	9.2%	10%	3.4%
	17%	6.6%	2.7%
	2%	11%	2%
	0.63%	0.8%	1.6%
	28%	10%	1.1%
	1.7%	4.1%	0.79%
	21%	8.3%	0.71%
	0.99%	1%	0.61%
	0.05%	0.22%	0.39%

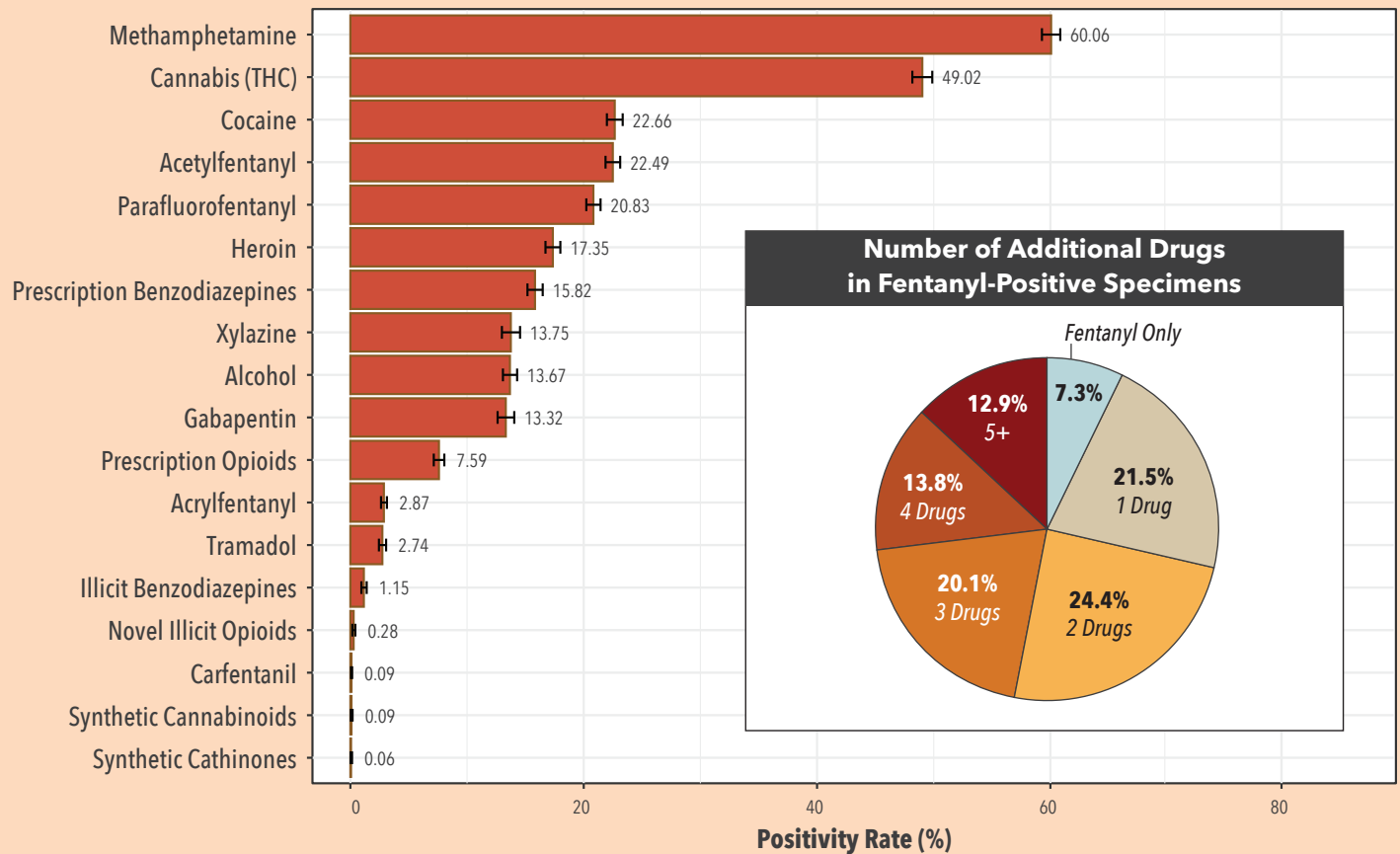
= Fentanyl
 = Prescription Opioids
 = Heroin
 = Methamphetamine
 = Cocaine
 0 10 20 30 40 50

The percentage of fentanyl-positive specimens that were positive for each specific, mutually-exclusive combination of drugs in the United States in 2015, 2019, and 2023. UDT Positivity Rates were estimated in fentanyl-positive specimens collected in 2015, 2019, and between January 1st and December 15th, 2023, using logistic regression. All specimens evaluated had ordered and valid test results for all of the four drugs or drug classes. See Methods for full description of drug classes.

3B: Nearly 93% of Fentanyl-Positive Specimens in 2023 Contained Additional Substances Including a Wide Range of Potentially Dangerous Drugs

- No assessment of polysubstance use is complete without investigating a wide range of substances
- Figure 6 shows the prevalence of fentanyl-associated polysubstance use involving a diverse array of substances in 2023 as well as the percentages of specimens that were positive for fentanyl only and up to five or more additional drugs

Figure 6. National UDT Positivity Rates for Fentanyl-Associated Polysubstance Use in 2023



The percentage of fentanyl-positive specimens in the United States in 2023 that were positive for various illicit and non-prescribed drugs and drug classes (bar graph) and the percentage of fentanyl-positive specimens that contained zero (i.e., fentanyl only) to five or more additional drugs (inset pie chart). UDT Positivity Rates were estimated in fentanyl-positive specimens collected between January 1st and December 15th, 2023 using logistic regression. Note that xylazine testing began in April 2023. See Methods for detailed drug class descriptions.

Interpretation and Key Findings

- 93% of fentanyl-positive specimens contained an additional drug
 - 21.5% were positive for one additional drug, 58.3% were positive for 2-4 additional drugs, and 12.9% were positive for 5 or more additional drugs
- 60% of fentanyl-positive specimens contained methamphetamine and more than 22% were positive for cocaine
- Almost half (49%) were also positive for cannabis (THC) and nearly 14% were positive for alcohol
- Xylazine was detected in nearly 14% of fentanyl-positive specimens in 2023
- ***Fentanyl-associated polysubstance use involving an array of potentially dangerous drugs, and now especially stimulants, renders the reality of caring for people who use drugs as challenging as any time in history.***

Discussion

Although we are unquestionably experiencing a public health crisis that is anchored around fentanyl, this volume of the Signals Report highlights that polysubstance use has been a consistent, yet evolving, theme beneath the waves.

Virtually every data point throughout the Report constitutes fentanyl-associated polysubstance use, as they all represent the detection of other substances (e.g., methamphetamine) in fentanyl-positive specimens.

These complex, underlying patterns of polysubstance use also reveal how the echoes of previous waves of the epidemic—involving prescription opioids and heroin—have reverberated through the more recent ones. For example, Figure 5 shows that fentanyl was often found in combination with prescription opioids and/or heroin in 2015, but the combination of all three was most common. Cocaine was also frequently found in specimens that contained this trio of opioids (i.e., fentanyl, prescription opioids, and heroin) in 2015, suggesting that “speedball” use was also common among a subset of individuals who used heroin and a broader range of opioids, including fentanyl. Interestingly, combinations of fentanyl and stimulants in the absence of heroin were detected in UDT relatively infrequently (< 2%) in 2015. Congruent with the broader shifts away from prescription opioid and heroin use toward stimulants in this population, fentanyl was most commonly found alongside methamphetamine or cocaine individually (53% and 9.8%, respectively), or all together (8.5%) in 2023.

Lastly, our analysis of polysubstance use among people who use fentanyl in 2023 offers more

detailed insights into the other drugs that they use and their relative prevalence (see Figure 6).

The results show that these individuals are using a diverse array of drugs at appreciable rates, some which may not be intentional because they are often found in complex drug mixtures sold as heroin and/or fentanyl.

Indeed, almost 93% of fentanyl-positive specimens in 2023 were positive for additional drugs and nearly 47% were positive for three or more. When combined, these drugs may increase overdose vulnerability, modify responses to overdose reversal agents (i.e., naloxone), and enhance clinical complexity to further complicate treatment efforts.^{4,5,11} Some of these drugs—like carfentanil and xylazine—have understandably garnered significant media attention given their potential implications for fatal overdose outbreaks and other unsettling effects (e.g., xylazine-associated skin lesions), but our findings clearly show that stimulant use is by comparison far more common in this group.

From a clinical perspective, there are fewer evidence-based tools available to effectively treat stimulant use disorders compared to opioid use disorders.

Because there are currently no FDA-approved medications for stimulant use disorders, behavioral interventions remain the standard of care.^{12,13}

Although behavioral therapies like cognitive behavioral therapy (CBT) and motivational

interviewing (MI) have clinical benefit, other techniques have demonstrated greater efficacy to improve clinical outcomes.

More than three decades of research has shown that contingency management (CM) is among the most effective behavioral interventions for stimulant use disorders and is one of the four evidence-based practices recommended by the Substance Abuse and Mental Health Services Administration (SAMHSA).¹²

Rooted in basic learning theory, CM involves delivering tangible rewards (i.e., positive reinforcers) when the occurrence of a desired behavior or outcome can be objectively verified. For example, a patient with a stimulant use disorder who is participating in a CM program to promote abstinence may receive rewards (e.g., prizes) when they provide a drug-free urine specimen. Under this arrangement, drug abstinence as verified by UDT is reinforced, increasing the likelihood that the patient continues to remain abstinent in the future.

However, despite its well-documented efficacy and growing interest in CM among clinicians, practical and systemic challenges (e.g., complex implementation and limited reimbursement) that hamper its widespread dissemination and use in clinical practice still need to be addressed.

Although it is difficult to anticipate what may lie beyond the horizon, timely sources of data—such as UDT—may help to identify emerging threats and shifting patterns of substance use to reveal

underappreciated layers of complexity in an everchanging drug use landscape.

As highlighted in this volume of the Signals Report, the overwhelming majority of people who use fentanyl engage in intentional and unintentional polysubstance use—now mostly involving the use of stimulants—which creates unique treatment challenges that are further compounded by temporal and geographical variations in polysubstance use trends.¹¹

It is therefore essential that clinicians maintain awareness of how patterns of polysubstance use are changing over time in their area. In partnership with clinicians, researchers, public health officials, policy makers, government agencies, and law enforcement officials, we remain committed to providing timely information about ongoing trends in drug use, including polysubstance use, to help inform data-driven efforts to stem the tide of America's fentanyl crisis and improve the lives of individuals who use drugs. ■

UDT Data - Sample Population

This cross-sectional analysis includes the evaluation of de-identified and aggregated definitive urine drug testing (UDT) results derived from testing with liquid chromatography-tandem mass spectrometry (LC-MS/MS) on unique patient specimens from across the U.S. and multiple health care specialties. The LC-MS/MS testing method is a laboratory-developed test with performance characteristics determined by Millennium Health, San Diego, California, which is certified by the Clinical Laboratory Improvement Amendments (CLIA) and accredited by the College of American Pathologists (CAP) for high-complexity testing.

Specimens were collected between January 1, 2013, and December 15, 2023. Included specimens were from patients aged 18 years or older. Specimens were collected from health care practices from all 50 states. A single specimen per patient was selected based on the earliest collection date. **More than 4.1 million specimens were used for the analysis.**

We examined analyte results consistent with either illicit or non-prescribed substance use only. The following drugs and drug categories were studied (specific analytes tested in parentheses): cocaine (benzoylecgonine), methamphetamine (methamphetamine), fentanyl (fentanyl, norfentanyl), fentanyl analogs (4-ANPP (4-ANPP), acetylfentanyl (acetylfentanyl, acetylnorfentanyl), carfentanil (carfentanil), acrylfentanyl (acrylfentanyl) and parafluorofentanyl (parafluorofentanyl)), heroin (6-monoacetylmorphine, morphine), cannabis (delta-9-tetrahydrocannabinol carboxylic acid [cTHC]), xylazine (xylazine, 4-OH xylazine), synthetic cannabinoids (AB-FUBINACA-M3, 5F-ADB-M7, MDMB-FUBINACA-M1, JWH018-METABOLITE, JWH073-METABOLITE, RCS4-

METABOLITE, XLR11/UR144), synthetic cathinones (eutylone, methylone), alcohol (EtG, EtS), gabapentin (gabapentin), tramadol (tramadol, O-desmethyl-tramadol, N-desmethyl-tramadol), prescription benzodiazepines (alpha-hydroxyalprazolam, 7-aminoclonazepam, lorazepam, nordiazepam, oxazepam and temazepam), illicit benzodiazepines (8-aminoclonazolam, etizolam, alpha-hydroxyetizolam, flualprazolam, flubromazolam), novel illicit opioids (2-methyl-AP-237, bupropion, metonitazene) and prescription opioids (hydrocodone, norhydrocodone, hydromorphone, oxycodone, noroxycodone, oxycodone). If any parent drug or metabolite within a drug category was ordered and detected in a specimen, the result for that drug or drug category was considered positive.

Note that morphine is both a metabolite of heroin and an individual drug which may lead to an overestimation of heroin positivity. Specimens with reported prescriptions for any of the drugs and drug categories above were excluded from analysis. Testing for fentanyl analogues is only performed if the specimen is positive for fentanyl. Fentanyl analogue testing began in July 2019, except for parafluorofentanyl, which began in August 2022. Xylazine testing began in April 2023 and novel illicit opioids and illicit benzodiazepines testing began in August 2022.

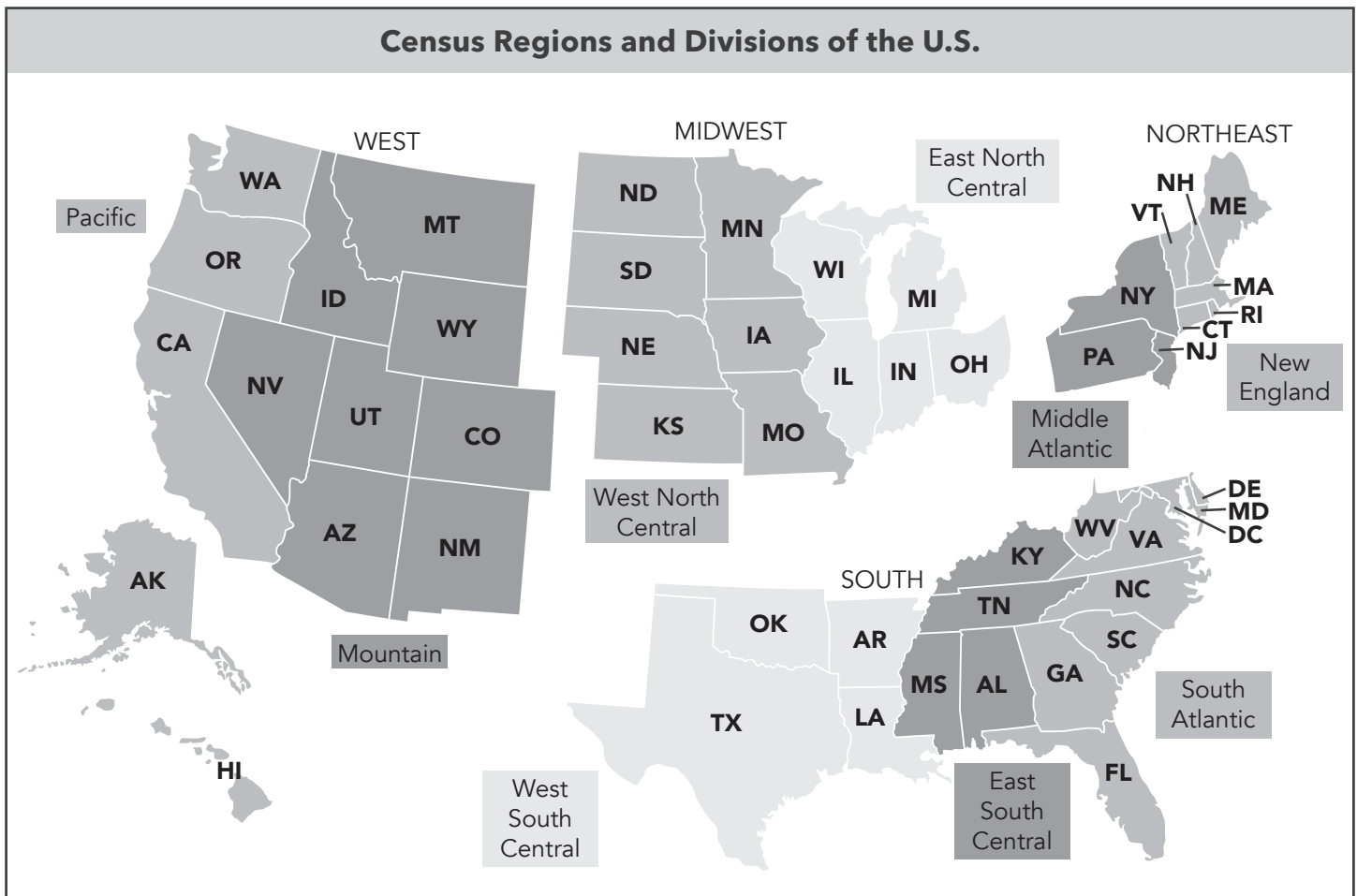
Overdose Mortality Data

Drug overdose deaths were identified in the National Vital Statistics System multiple cause-of-death mortality files by using International Classification of Diseases, Tenth Revision (ICD-10) underlying cause-of-death codes X40-44 (unintentional), X60-64 (suicide), X85 (homicide), or Y10-14 (undetermined intent). Drug involvement in deaths was defined using

the following ICD-10 multiple cause-of-death (MCD) codes: synthetic opioids (T40.4, mostly fentanyl), stimulant deaths (psychostimulants with abuse potential (T43.6) and/or cocaine (T40.5)), and opioid deaths (prescription opioids (T40.2), heroin (T40.1)). Monthly raw death counts during the January, 2013-May, 2023 period were analyzed; provisional overdose deaths between January, 2022 and May, 2023 were downloaded on December 7, 2023.¹⁴

Statistical Methods

UDT positivity rates were modeled using logistic regression. Different model specifications were used depending on the analysis requirements (see figure and table legends for included variables). Adjusted positivity rates (Least Square Mean marginal rates) and adjusted odds ratios (aOR) were estimated. 95% CI values for aOR and positivity rates (predicted probability) were estimated, and P values were Tukey corrected for multiple comparisons, where appropriate.



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