National and Regional Trends in Fentanyl-Associated Polysubstance Use: A Cross-Sectional Analysis of Urine Drug Testing in the United States, 2016–2025

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BACKGROUND:

- The rise of fentanyl as a driver of overdose and death in the United States (US) has coincided with an evolving landscape of polysubstance use, where stimulants and other illicit drugs are increasingly used concomitantly. Understanding these patterns is critical to inform public health interventions and treatment strategies in response to the evolving opioid crisis.

RESEARCH QUESTION:

- Among patients in the US who use fentanyl, what are the national and regional patterns in concomitant use of other illicit drugs, and how have these trends changed over time?

METHODS:

UDT Data and Sample Population

- Retrospective, cross-sectional analysis of de-identified and aggregated definitive urine drug testing (UDT) results derived from testing with liquid chromatography-tandem mass spectrometry (LC-MS/MS) on patient urine 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.
- More than 1.69 million UDT specimens representing over 530,000 unique patients were included in the analysis.
- Urine specimens were collected from patients ≥18 years of age between January 1, 2016, and November 30, 2025. Specimens were excluded from analysis if they were collected within 30 days of the previous specimen for any given patient.
- Urine specimens were selected based on the presence of a substance use disorder (SUD) diagnosis code provided by the ordering clinician (ICD-10 codes: F11, F13-16, F18-F19).
- We studied UDT results consistent with illicit and/or non-prescribed use of the following drugs (specific analytes tested in parentheses): cocaine (benzoylecgonine), methamphetamine (methamphetamine), fentanyl (fentanyl, norfentanyl), heroin (6-monoacetylmorphine, morphine), and prescription opioids (hydrocodone, norhydrocodone, hydromorphone, oxycodone, noroxycodone, oxymorphone).

Overdose Mortality Data

- National drug overdose deaths were identified in the National Vital Statistics System (NVSS) multiple cause-of-death mortality files using ICD-10 underlying cause-of-death codes X40–44 (unintentional), X60–64 (suicide), X85 (homicide), or Y10–14 (undetermined intent). Overdose death data were downloaded from CDC Wonder (www.wonder.cdc.gov) on February 12, 2026. **Note:** Data for 2024 and 2025 are provisional.
- Overdose Death Rates were calculated as: (number of deaths/regional yearly population) × 100,000 × 12 (rounded to the nearest tenth). This rate calculation reflects the monthly estimate of the number of deaths per 100,000 people per year.

Statistical Methods

- UDT detection rates were modeled using logistic regression. Different model specifications were used depending on the analysis requirements. Adjusted positivity rates (Least Square Mean marginal rates) and 95% confidence interval (CI) values were estimated.

DISCUSSION:

- Overdose deaths fell dramatically at the national level from mid-2023 through late 2024, but there are regional differences to consider.[1]
- Urine drug testing data revealed decreases in the detection of fentanyl that corresponded with a spike in the detection of other opioids (i.e., heroin) in real time, suggesting increased volatility in the illicit opioid supply. These findings are consistent with and complement recent research that suggested there may have been a shock to the illicit fentanyl supply in 2023-2024, which may help to explain the dramatic declines in overdose deaths in recent years.[2]
- Illicit stimulant use continued to rise through 2025 in the population using fentanyl, suggesting that it is playing an increasingly important role in America's overdose crisis and drug use epidemic.[3]
- Urine drug testing data may be used to help inform clinical practice, develop and refine harm reduction and overdose prevention strategies, improve our understanding of current overdose mortality trends, and guide data-driven efforts to respond to a continually evolving drug use and overdose epidemic.[3]

References:

1. Post LA, Ciccarone D, Unick GJ, et al. Decline in US Drug Overdose Deaths by Region, Substance, and Demographics. *JAMA Netw Open*. 2025;8(6):e2514997. doi:10.1001/jamanetworkopen.2025.14997
2. Vangelov K, Humphreys K, Caulkins JP, Pollack H, Pardo B, Reuter P. Did the illicit fentanyl trade experience a supply shock?. *Science*. 2026;391(6781):134-136. doi:10.1126/science.aea6130
3. Millennium Health, LLC. Millennium Health Signals Report®, Volume 8. Lay of the Land – Encouraging Signs and Persistent Challenges Dot the Terrain of America's Evolving Drug Use Epidemic. Published February, 2026. Available at: https://www.millenniumhealth.com/signalsreport/

Figure 1. Monthly Fentanyl-Related Overdose Rates for the Four U.S. Census Regions

Monthly total synthetic opioid overdose death rate (MCD T40.4, mostly illicitly manufactured fentanyl, referred to as "fentanyl" for simplicity U.S. Census regions from January 2016 through July 2025.

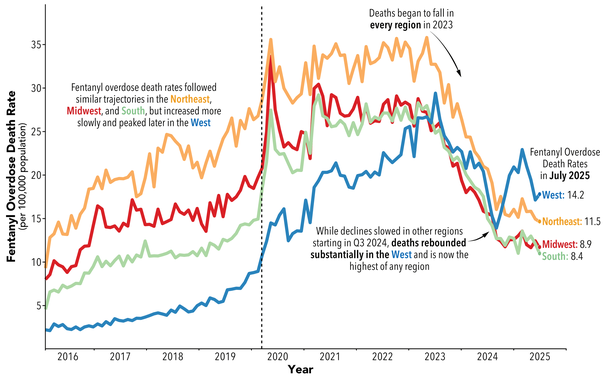


Figure 2. Monthly UDT Detection Rates for Fentanyl, Fentanyl with a Stimulant and Fentanyl with an Opioid

Monthly UDT Detection rates (95% CI) for fentanyl, fentanyl with a stimulant (cocaine or methamphetamine) and fentanyl with an opioid (heroin or prescription opioids).

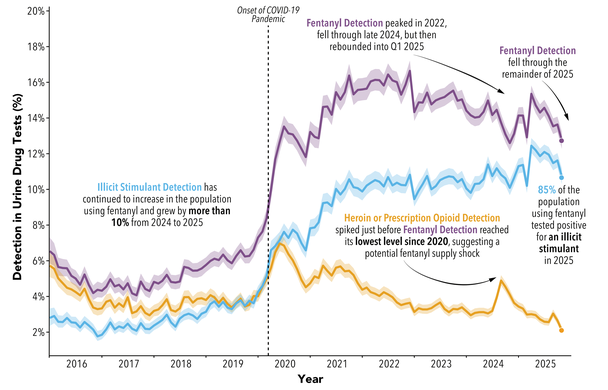
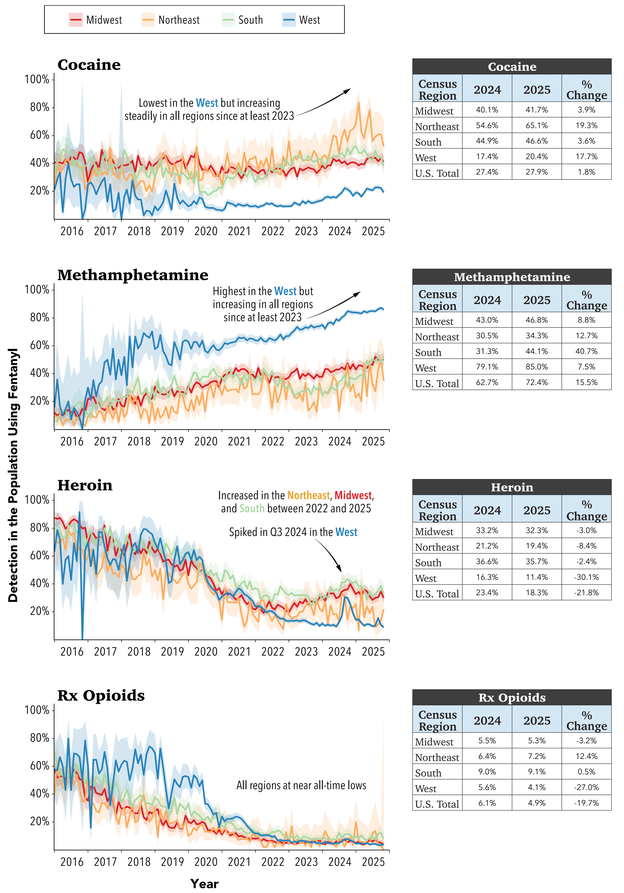


Figure 3. Regional, Monthly UDT Detection Rates for Cocaine, Methamphetamine, Heroin and Prescription Opioids in the Population Using Fentanyl

Monthly UDT Detection rates (95% CI) for a stimulant (cocaine or methamphetamine) or opioid (heroin or prescription opioid) in the population testing positive for fentanyl by U.S. Census Region.



Cocaine

Census Region	2024	2025	% Change
Midwest	40.1%	41.7%	3.9%
Northeast	54.6%	65.1%	19.3%
South	44.9%	46.6%	3.6%
West	17.4%	20.4%	17.7%
U.S. Total	27.4%	27.9%	1.8%

Methamphetamine

Census Region	2024	2025	% Change
Midwest	43.0%	46.8%	8.8%
Northeast	30.5%	34.3%	12.7%
South	31.3%	44.1%	40.7%
West	79.1%	85.0%	7.5%
U.S. Total	62.7%	72.4%	15.5%

Heroin

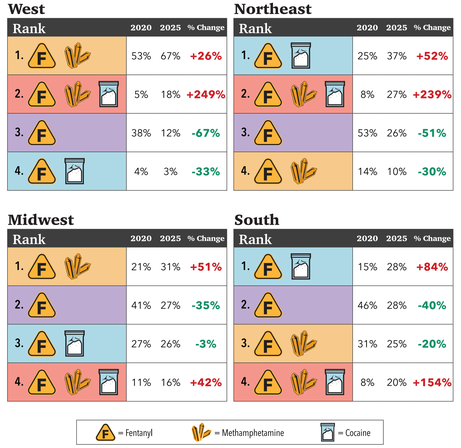
Census Region	2024	2025	% Change
Midwest	33.2%	32.3%	-3.0%
Northeast	21.2%	19.4%	-8.4%
South	36.6%	35.7%	-2.4%
West	16.3%	11.4%	-30.1%
U.S. Total	23.4%	18.3%	-21.8%

Rx Opioids

Census Region	2024	2025	% Change
Midwest	5.5%	5.3%	-3.2%
Northeast	6.4%	7.2%	12.4%
South	9.0%	9.1%	0.5%
West	5.6%	4.1%	-27.0%
U.S. Total	6.1%	4.9%	-19.7%

Figure 4. Stimulant Use Combinations in the Population Using Fentanyl

Rank-ordered detection rates for methamphetamine, cocaine, methamphetamine and cocaine, and neither stimulant in the population using fentanyl in 2020 and 2025 and Percent Change from 2020 to 2025 by U.S. Census region.



- As methamphetamine (western regions) and cocaine (eastern regions) co-use continued to climb between 2020-2025, the **use of fentanyl without an illicit stimulant** fell everywhere.
- Over this same period, the **detection of fentanyl with both cocaine and methamphetamine more than doubled throughout much of the country**, suggesting that people who use fentanyl are increasingly gravitating toward using any available stimulant.

Figure 5. Most Co-Detected Drug in the Population Using Fentanyl

Hexbin maps showing the most frequently detected drug or drug class based on state-level, relative detection rates for methamphetamine, cocaine, heroin (and/or morphine), and prescription opioids (hydrocodone, hydromorphone, oxycodone and oxymorphone; without a reported prescription) in specimens testing positive for fentanyl collected in 2024 to 2025.

