Millennium Health Signals Report®

Volume 8

B. Levi Bolin, PhD
Associate Director, Clinical Affairs
levi.bolin@millenniumhealth.com

Urine Drug Testing (UDT) Rationale

UDT provides objective information to support improved clinical decision making.

UDT helps clinicians to:

- Monitor and support decisions about medication therapy, particularly controlled substances
- Identify recent use of prescription medications, non-prescribed medications, and illicit substances
- Detect medications that may result in drug-drug interactions
- Advocate for and communicate with patients about individual treatment plans
- Identify possible illicit drug use, medication misuse, or diversion

Types of Testing

Presumptive Immunoassay Screen	Definitive Mass Spectrometry
In-office Point-of-Care (POC), or Laboratory Qualitative	Laboratory Quantitative (GC-MS or LC-MS/MS)
Minutes (POC) or days (Lab)	Hours to days
Drug classes and some select meds/substances	Specific medications, substances, and metabolites
Guidance for preliminary treatment decisions	Definitive quantitative results
Higher cutoff levels and cross-reactivity common; more false positives and false negatives	Lower cutoff levels. False positive and false negative results are rare

The clinician must choose testing method based on the needs dictated by the patient's history, presentation, community factors and treatment plan goals. The clinician's rationale for test and the analytes ordered must be documented in the patient's medical record.

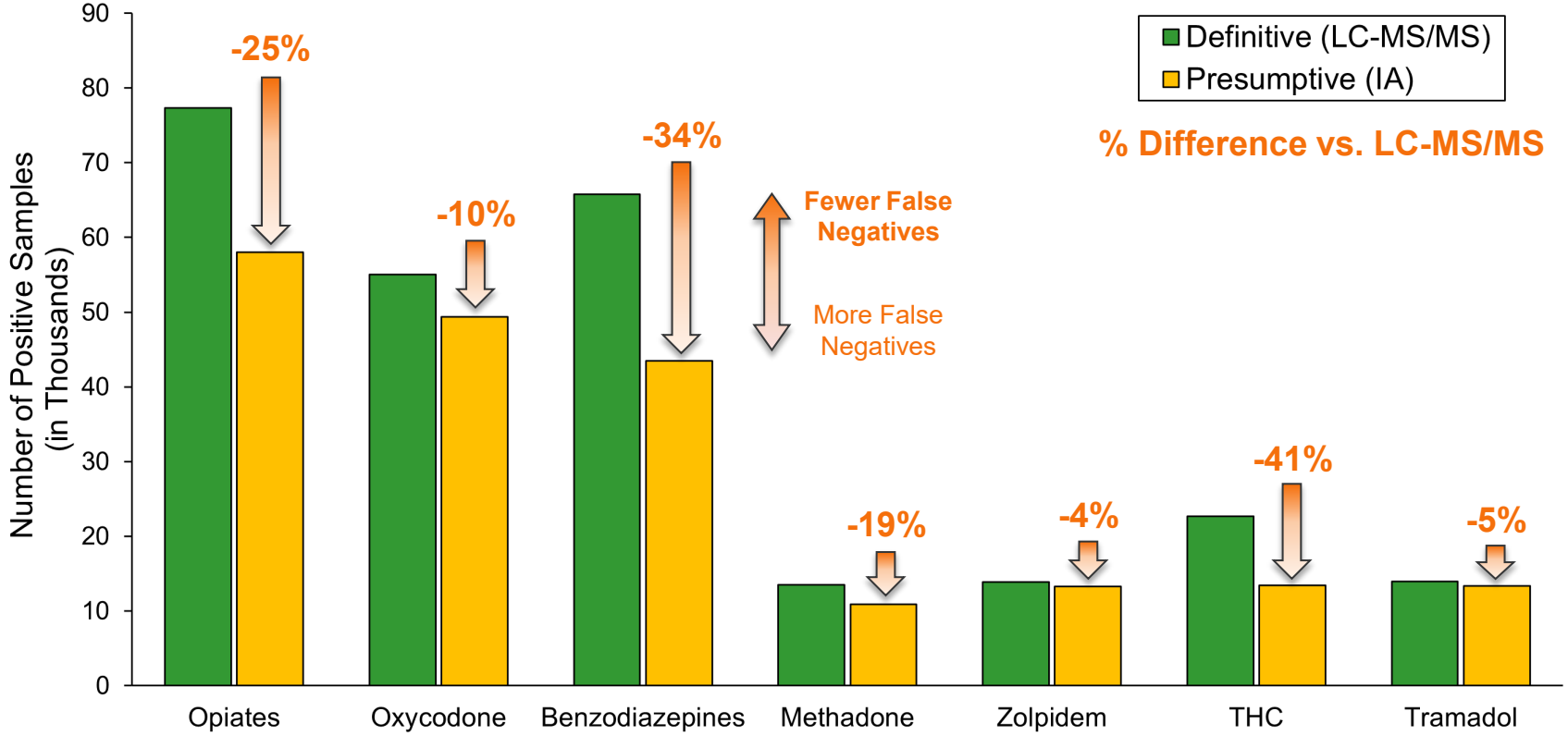
False Negative vs. False Positive

Most Common with Presumptive/Immunoassay-based Tests

False Negative: *The test fails to detect the presence of the drug or metabolites*[1]	**False Positive**: *The test incorrectly detects the presence of the drug when none is present*[1]
Primary Reasons Include: • Higher cutoffs compared to mass spec. • IAs unable to effectively identify some substances (e.g., lorazepam)	Primary Reason: • Cross-reactivity
Potential Adverse Impact on Patient: • Undetected illicit use • Accused of drug diversion • Not receive ongoing meds • Drug interactions	Potential Adverse Impact on Patient: • Discharged from practice • Not having access to care • Legal decisions – lose family, return to jail

1. Center for Substance Abuse Treatment. (2012).Clinical drug testing in primary care. Technical Assistance Publication (TAP) Series, 32. DHHS Publication No. (SMA) 12-4668. Rockville, MD: Substance Abuse and Mental Health Services Administration. Available: http://www.kap.samhsa.gov/products/manuals/pdfs/TAP32.pdf

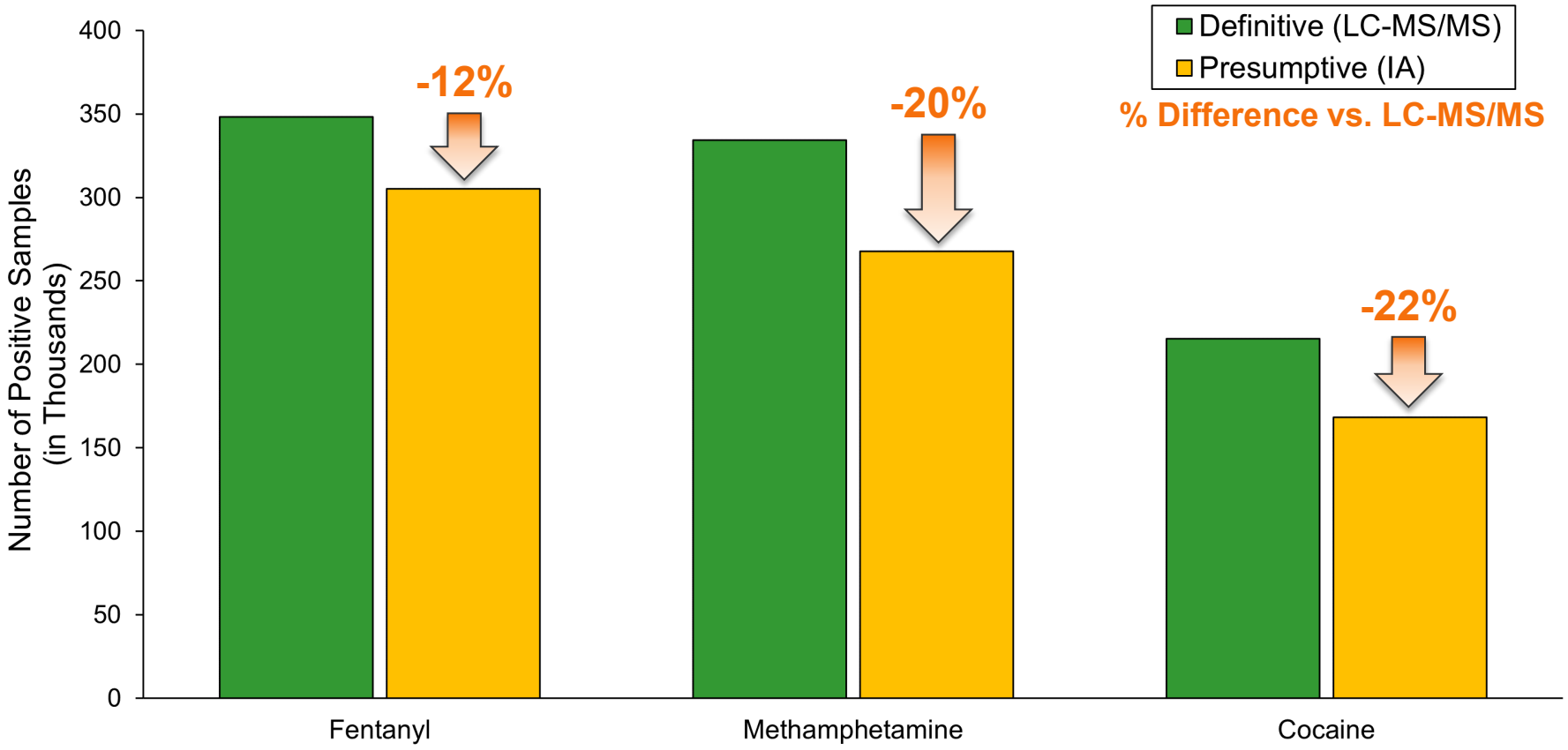
Comparison of Two Common UDT Methods



- 218,927 specimens; 23 analytes
- Laboratory IA screen with reflex of positives to quantitation (only IA positives are sent for more definitive testing)
- Direct definitive testing/quantitative approach

Kirsh K et al. An Analysis of Laboratory Immunoassay Screen with Reflex of Positives to Quantification Versus Definitive Laboratory Quantitation Methodologies for Medication Monitoring. Poster presented at International Conference on Opioids, June 2014, Boston, MA.

Comparison of Two Common UDT Methods



- Specimens (N = 4,808,331) collected between 1/1/19 – 4/19/22
- LC-MS/MS Threshold (ng/ml): Fentanyl (1), Norfentanyl (8), Cocaine (50), Methamphetamine (100)
- IA Threshold (ng/ml): Fentanyl (2), Cocaine (150), Methamphetamine (500)
- Note: Fentanyl positive specimens include those positive for fentanyl and/or norfentanyl

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Test Strip	Drug or Drug Class	Drugs Targeted by an Immunoassay	Substances Known to Cause a False Positive Test Result
AMP	Amphetamine	Amphetamine (i.e., Adderall® & Vyvanse®) *Note: Amphetamine is a metabolic product of Benzphetamine, Desoxyn® & Selegiline.*	Amantadine, Aripiprazole, Atomoxetine, Benzphetamine, Brompheniramine, Bupropion, Chlorpromazine, Desipramine, Dimethylamylamine (DMAA), Ephedrine, Fluorescein, Fluoroquinolones (Ofloxacin, Moxifloxacin, Levofloxacin), Labetalol, Metformin, Metronidazole, Mexiletine, Phentermine, Phenylethylamine, Promethazine, Propranolol, Pseudoephedrine, Ranitidine, Thioridazine, Tolmetin, Tranylcyptomine, Trazodone (m-CPP), Trimethobenzamide, Trimipramine Positives for Amp also caused by over-the-counter (OTC) products containing Levmetamfetamine (l-isomer Methamphetamine)[b] & prescription Selegiline
BAR	Barbiturates	Amobarbital, Butalbital, Phenobarbital, Secobarbital, & other Barbiturates	NSAIDs (Ibuprofen, Naproxen)
BUP	Buprenorphine	Buprenorphine (i.e., Brixadi®, Suboxone®, Sublocade®, Subutex®, Zuzolv®)	Amisulpride, Chloroquine, Codeine, Dihydrocodeine, Hydroxychloroquine (Plaquenil), Levofloxacin, Loperamide, Methadone, Morphine, Sulpride, Tramadol, Trimethoprim
BZO	Benzodiazepines	Benzodiazepines (Alprazolam, Diazepam, Temazepam and other Benzodiazepaines to varying degrees)	Efavirenz, NSAIDs (Ibuprofen, Naproxen, Tolmetin), Oxaprozin, Sertraline
COC	Cocaine	Cocaine	Unknown/Infrequent; Positives for Cocaine also caused by coca leaf tea
FYL/FTY	Fentanyl	Fentanyl, Norfentanyl	Diphenhydramine, Fluoxetine, Haloperidol, Labetalol, Loperamide, MDMA, Methamphetamine, Paliperodone, Pentazocine, Risperidone, TCAs (Amitriptyline), Trazadone
MTD	Methadone	Methadone	Chlorpromazine, Clomipramine, Creatinine, Diphenhydramine, Doxylamine succinate/Pyridoxine HCL, Propafenone, Quetiapine, Tapentadol, Thioridazine, Tramadol, Verapamil
MET	Methamphetamine	Methamphetamine *Note: Methamphetamine is a metabolic product of Benzphetamine, Desoxyn®, & Selegiline.*	Brompheniramine, Bupropion, Chlorpromazine, Ephedrine, Esmolol, Labetalol, Phentermine, Promethazine, Pseudoephedrine, Trazodone Positives for MAMP also caused by OTC products containing Levmetamfetamine (l-isomer Methamphetamine)[b] & prescription Selegiline.
MDMA	Methylenedioxy-methamphetamine	Methylenedioxymethamphetamine	Bath salts (Butylone, Pentylone), Ephedrine, Phentermine, Phenylpropanolamine, Pseudoephedrine, Trazodone
OPI / MOP	Opiates	6-MAM (Heroin metabolite), Codeine, Hydrocodone, Hydromorphone, Morphine	Dextromethorphan, Diphenhydramine, Doxylamine Succinate/Pyridoxine HCL, Fluoroquinolone (Levofloxacin, Ofloxacin, Gatifloxacin), Naloxone, Oxycodone (high conc.), Quinine, Pentazocine, Rifampin, Verapamil Positives for Opiates also caused by poppy seeds (contain Morphine & Codeine)
OXY	Oxycodone	Oxycodone, Oxymorphone	Codeine, Morphine, Hydrocodone, Hydromorphone
PCP	Phencyclidine	Phencyclidine	Desvenlafaxine, Dextromethorphan, Diphenhydramine, Doxylamine, Succinate/Pyridoxine HCL, Imipramine, Ketamine/ Esketamine, Lamotrigine, Meperidine, NSAIDs (Ibuprofen, Naproxen, Tolmetin), Fluoroquinolones (Ofloxacin, Gatifloxacin), Thioridazine, Tramadol, Venlafaxine
THC	THC (Marijuana)	Marijuana, Dronabinol (i.e., Marinol®, Syndros®)	Baby wash products, Efavirenz, Hemp oil/Hemp food products, NSAIDs (Ibuprofen, Naproxen), PPI's (Prilosec, Protonix), Raltegravir, Tolmetin
TCA	Tricyclic Antidepressants	Amitriptyline, Nortriptyline, Imipramine, Desipramine, Doxepin, & other Tricyclics to varying degrees	Carbamazepine[c], Cyclobenzaprine[c], Cyproheptadine[c], Diphenhydramine[c], Hydroxyzine[c], Quetiapine
TML	Tramadol	Tramadol	Fexofenadine, Venlafaxine

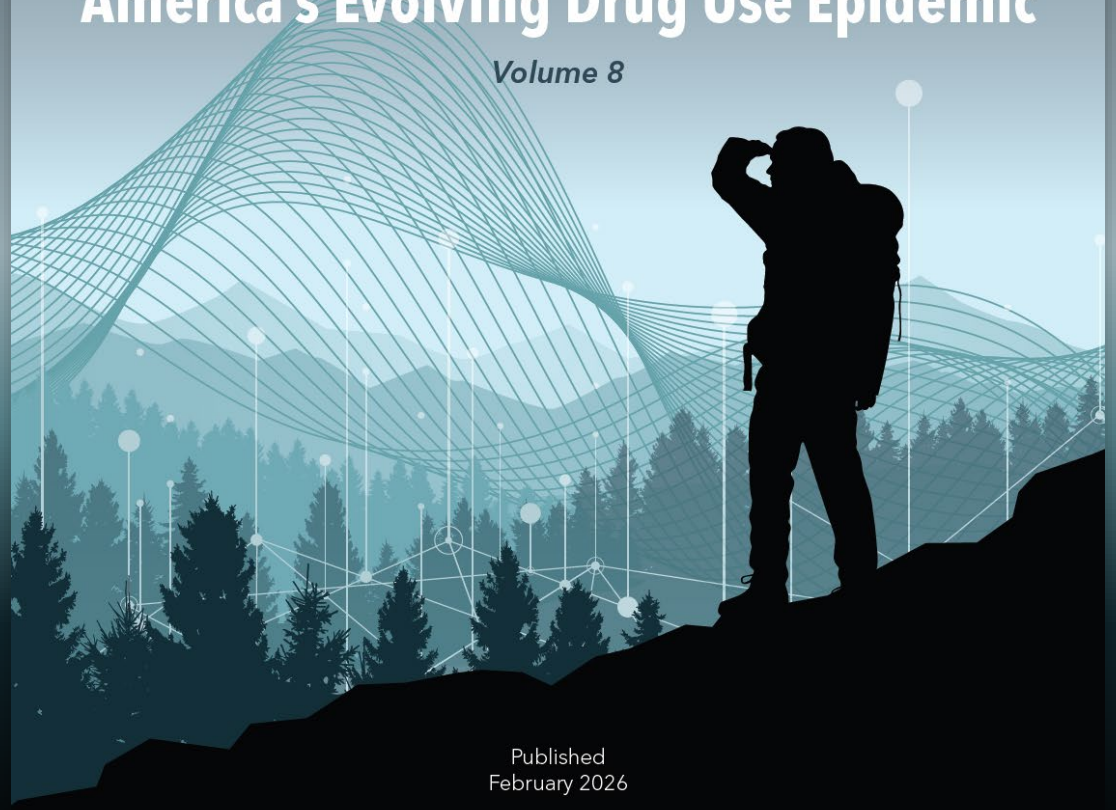
MILLENNIUM HEALTH

Signals Report®

LAY OF THE LAND

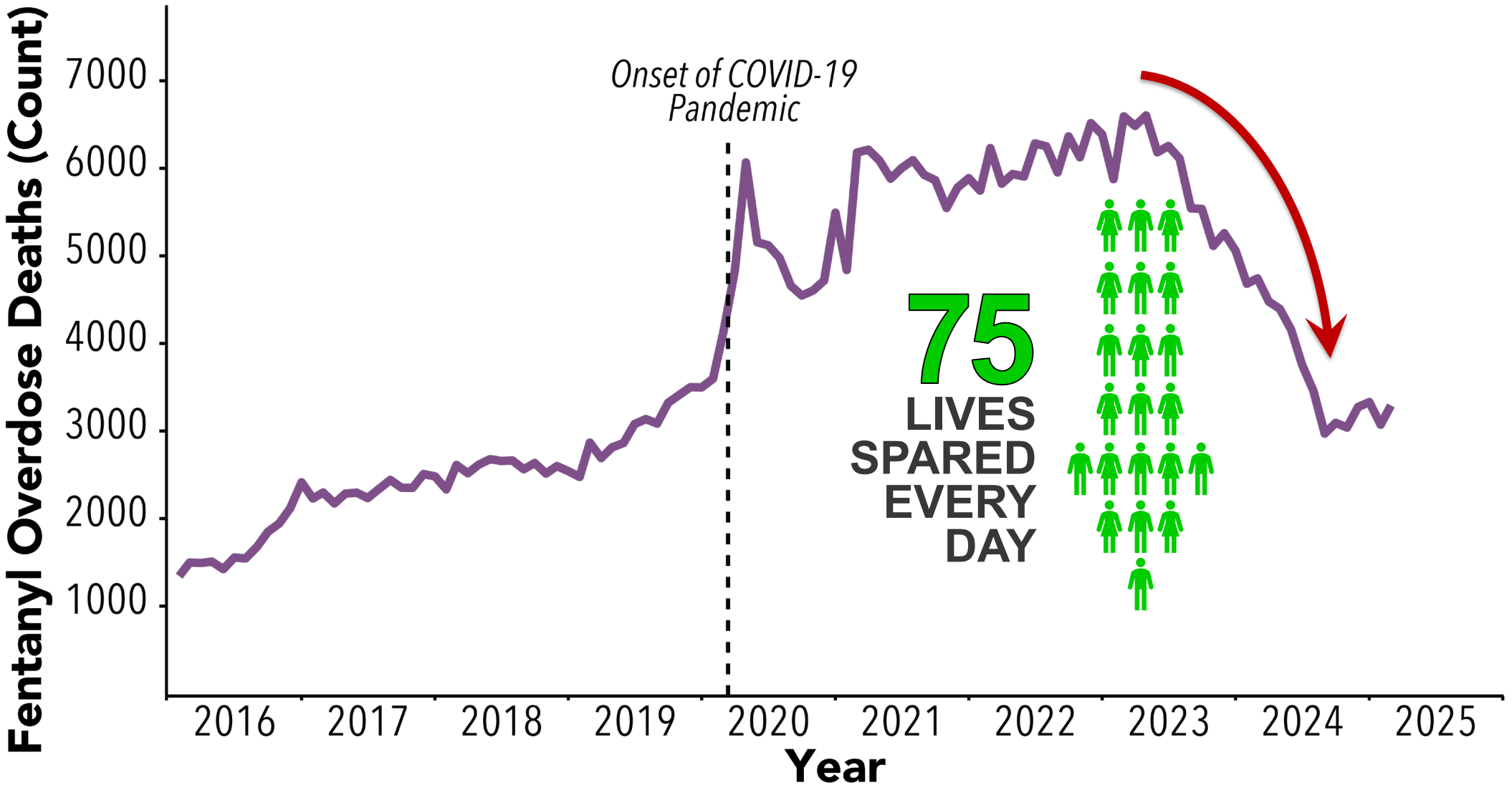
Encouraging Signs and Persistent Challenges Dot the Terrain of America's Evolving Drug Use Epidemic

Volume 8



Published
February 2026

Figure 1: National Fentanyl Overdose Mortality



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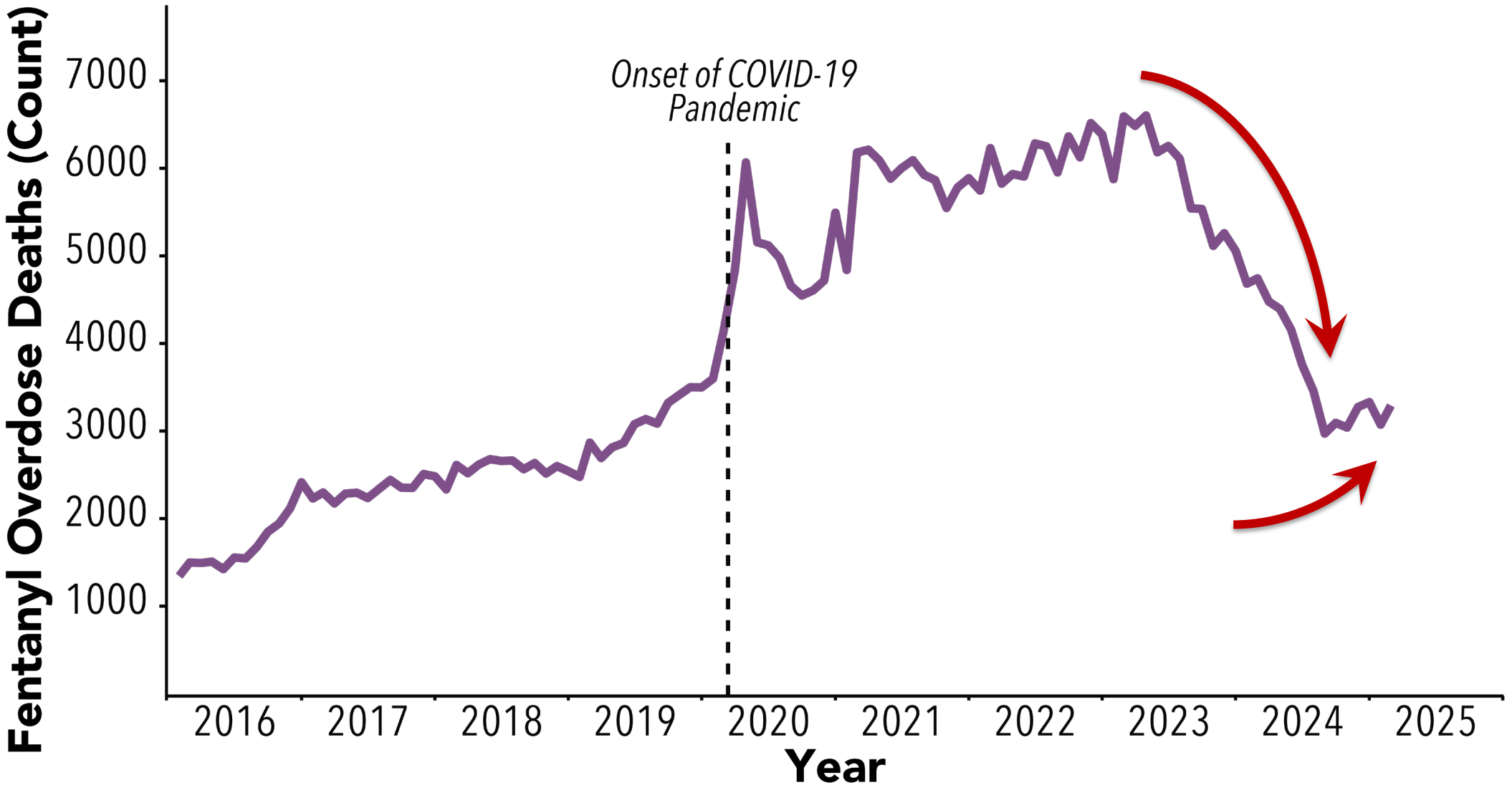

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Figure 2: Regional Fentanyl-Related Overdose Mortality

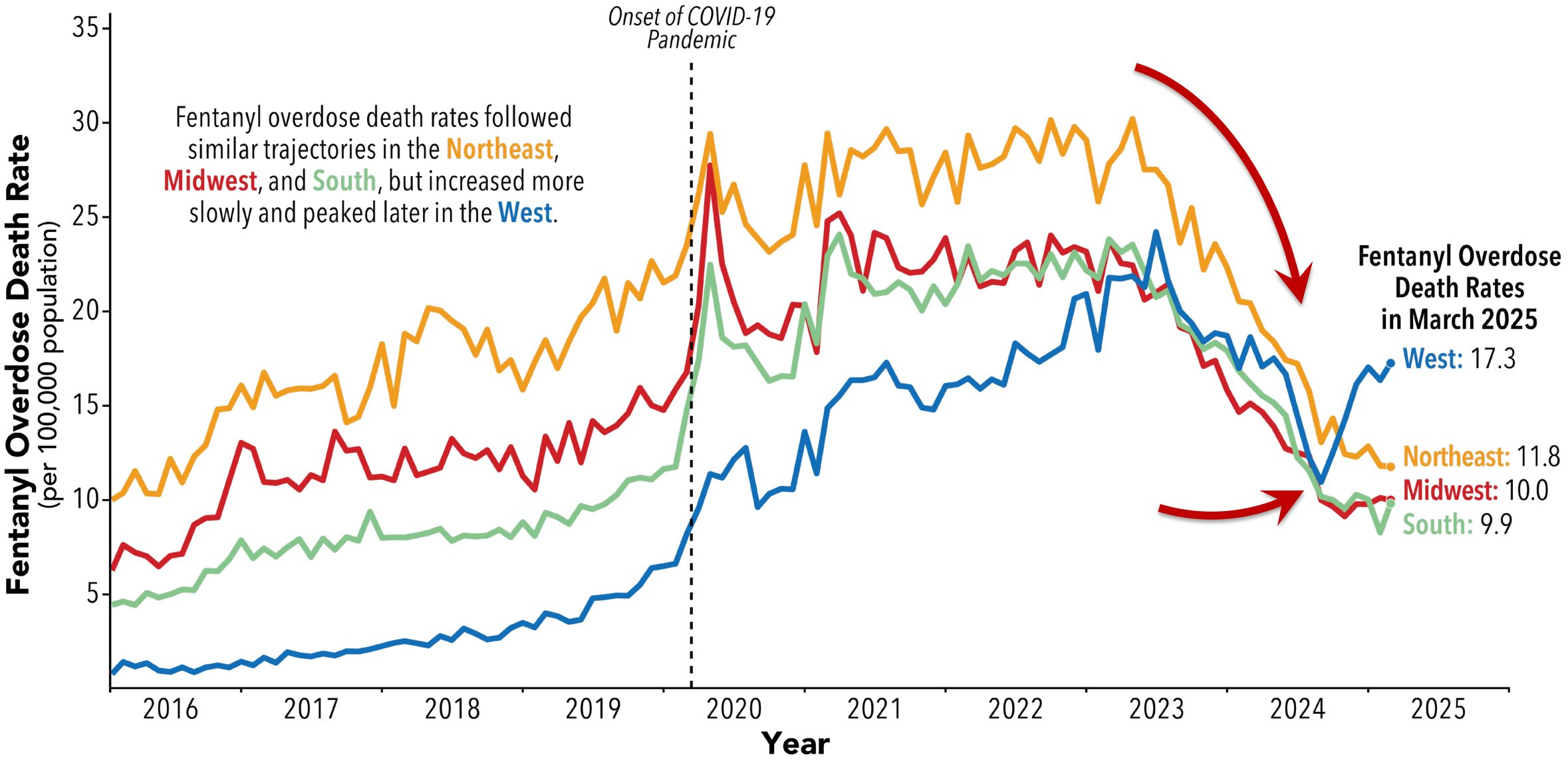

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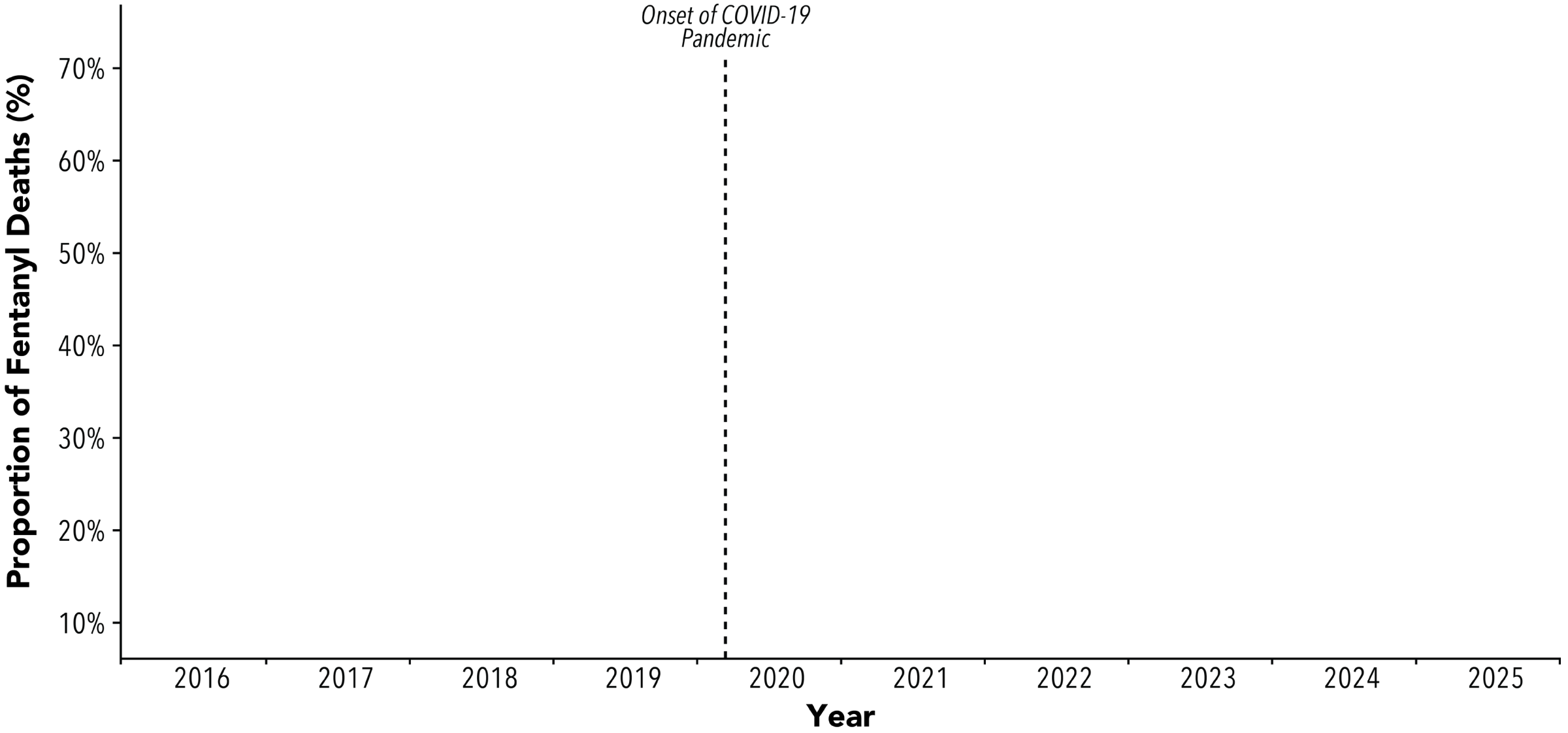
Figure 3: Co-Involvement of Stimulants and Other Opioids in Fentanyl Overdose Deaths



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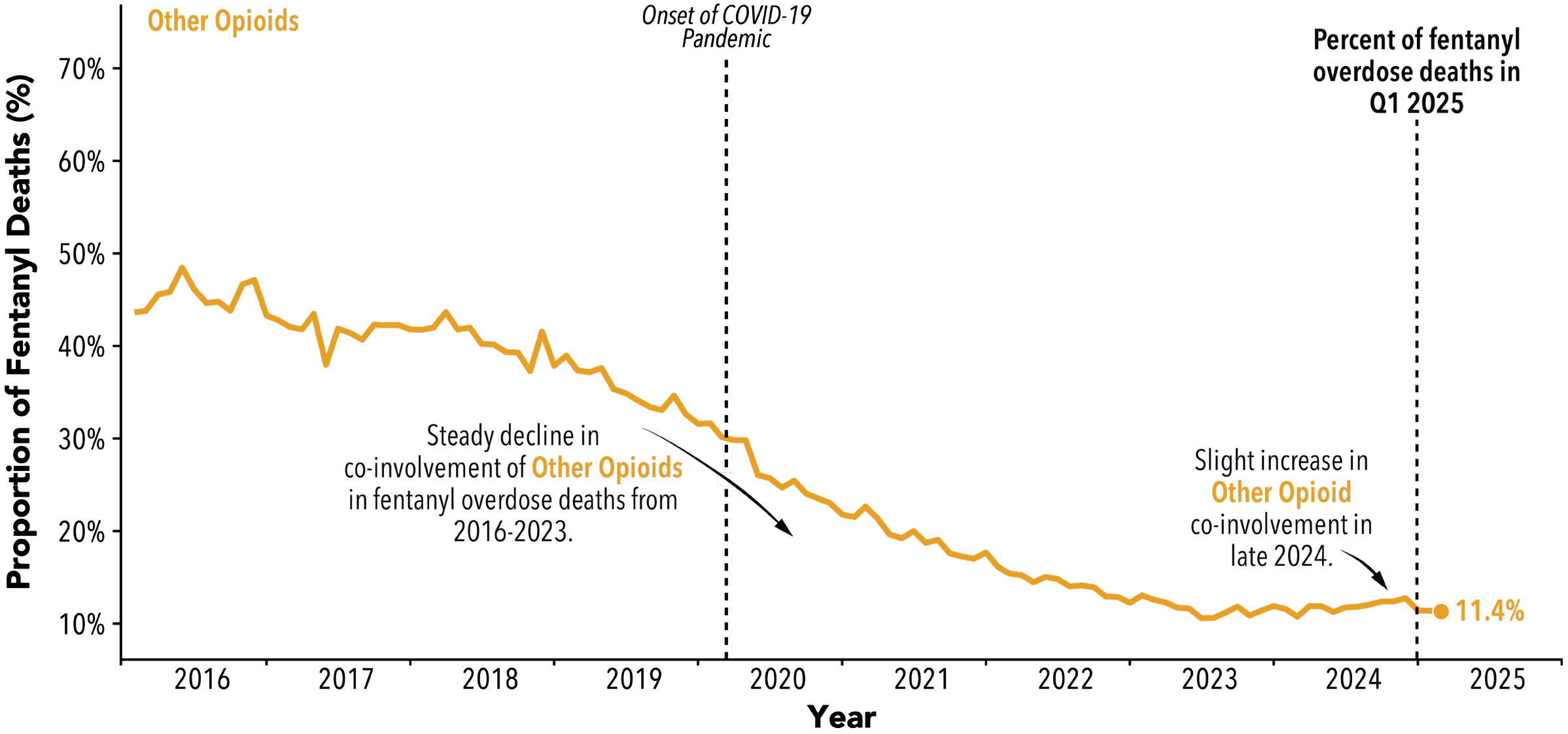

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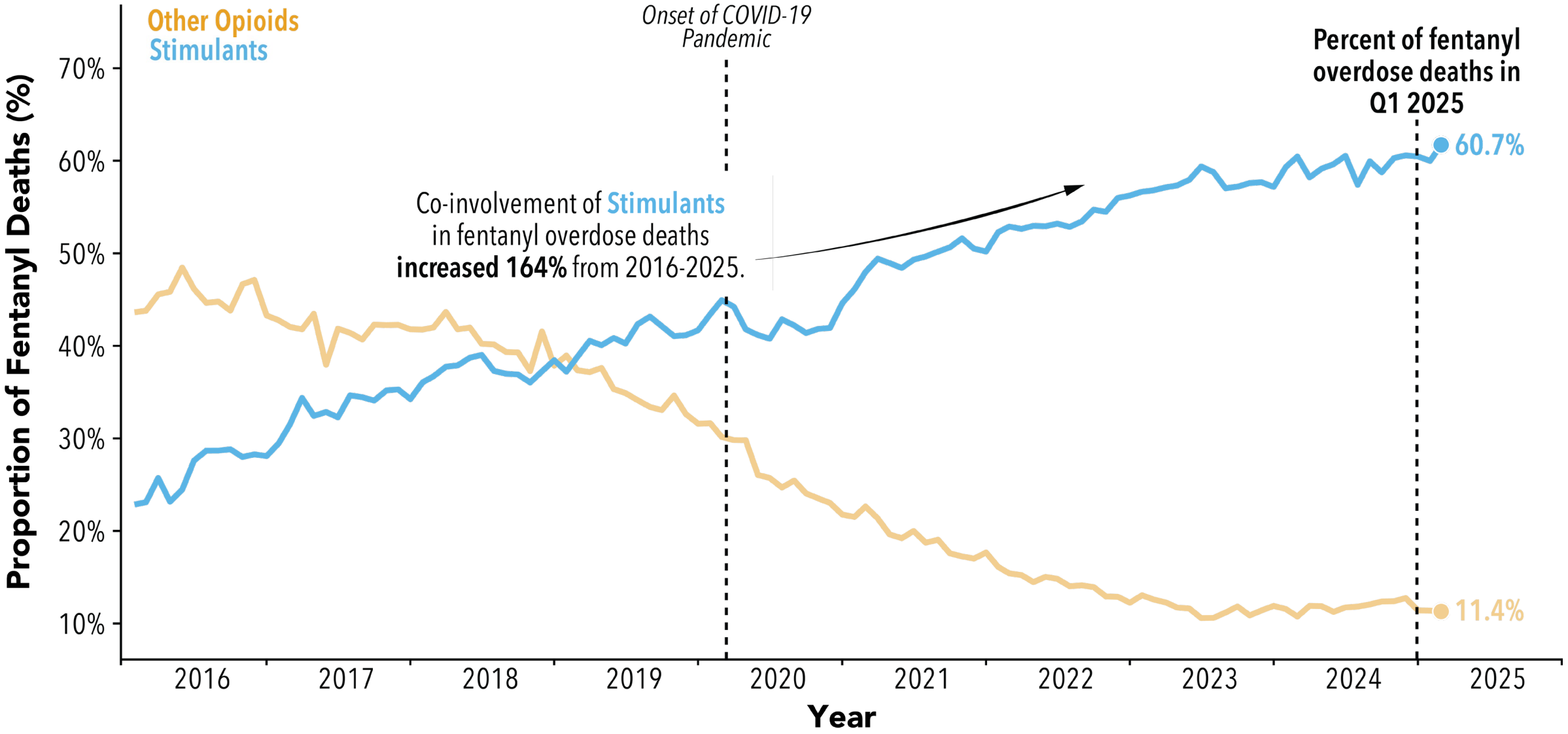

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General Methodology

- Retrospective, cross-sectional analysis of de-identified, aggregated urine drug testing results derived from testing with liquid chromatography-tandem mass spectrometry (LC-MS/MS)
- More than **1.69M urine specimens** (>530K unique patients) collected from patients ≥18 years of age in multiple healthcare specialties between January 1, 2016 and November 30, 2025
- All specimens associated with a SUD diagnosis code (ICD-10: F11, F13, F14, F15, F16, F18, F19)
- All results consistent with illicit/non-prescribed use (i.e., no reported prescription for any drug studied)
- No more than one specimen per patient within a 30-day period

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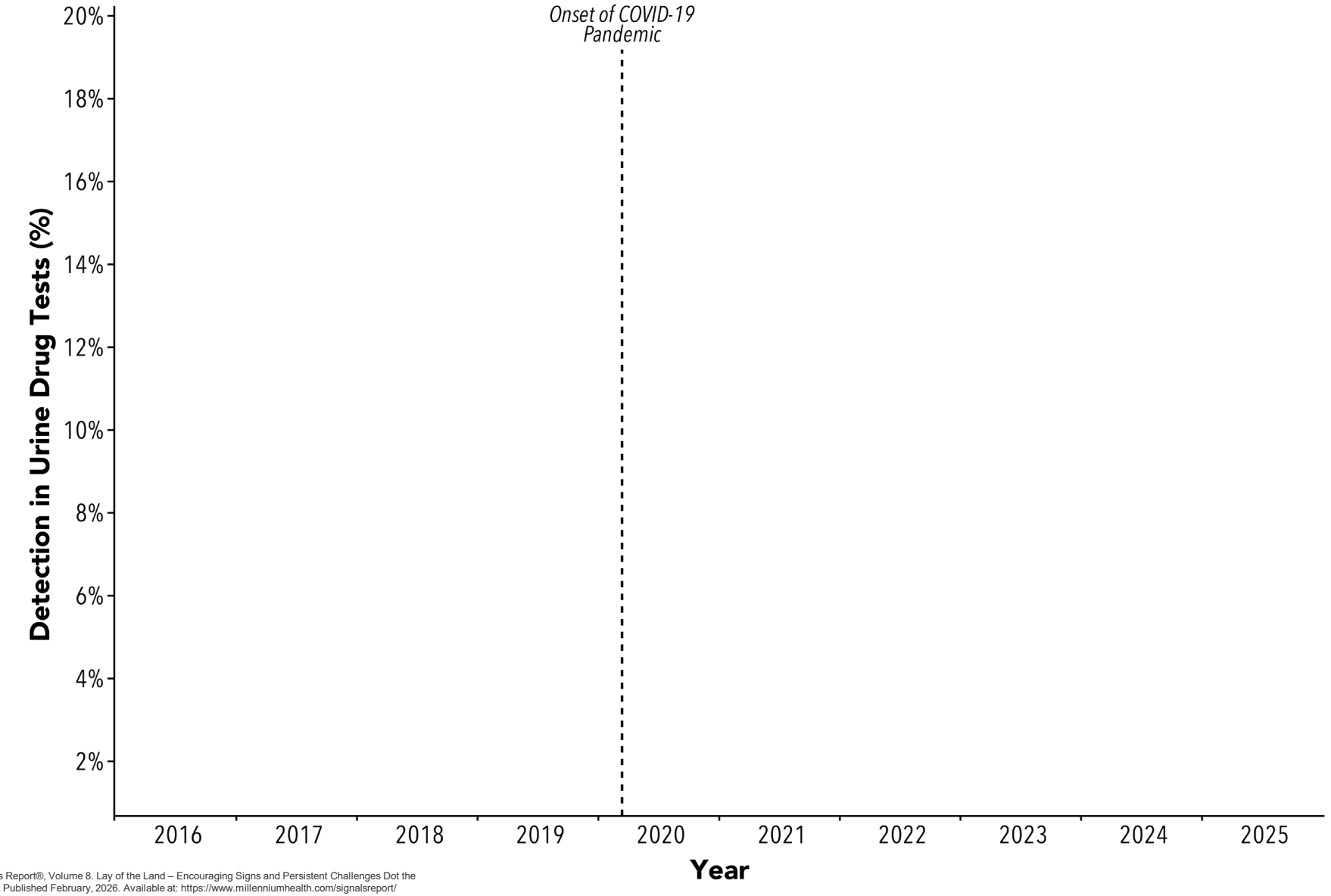
Figure 4: National Fentanyl Detection and Associated Polysubstance Use



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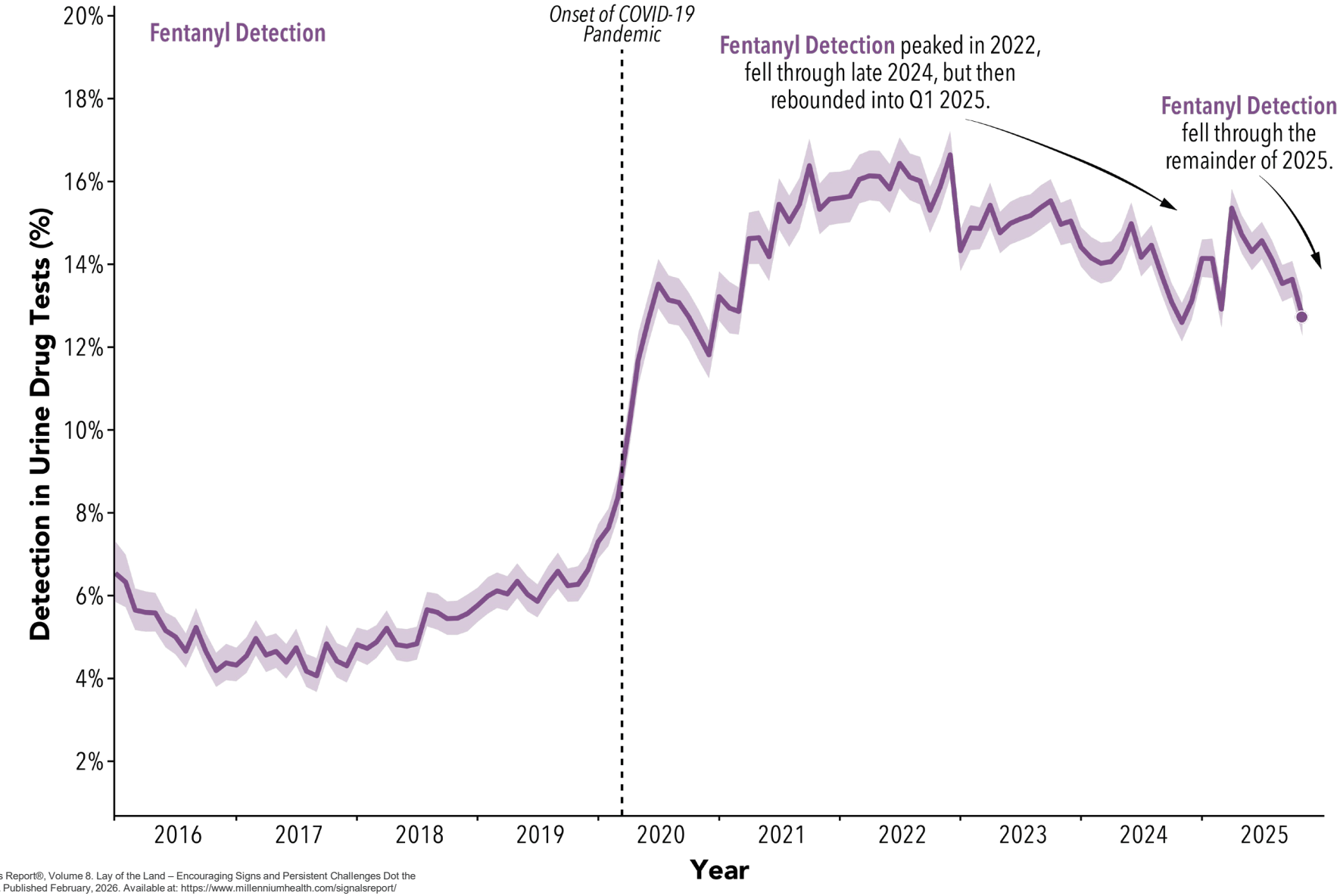

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Millennium In-Depth Co-Positivity Tracker

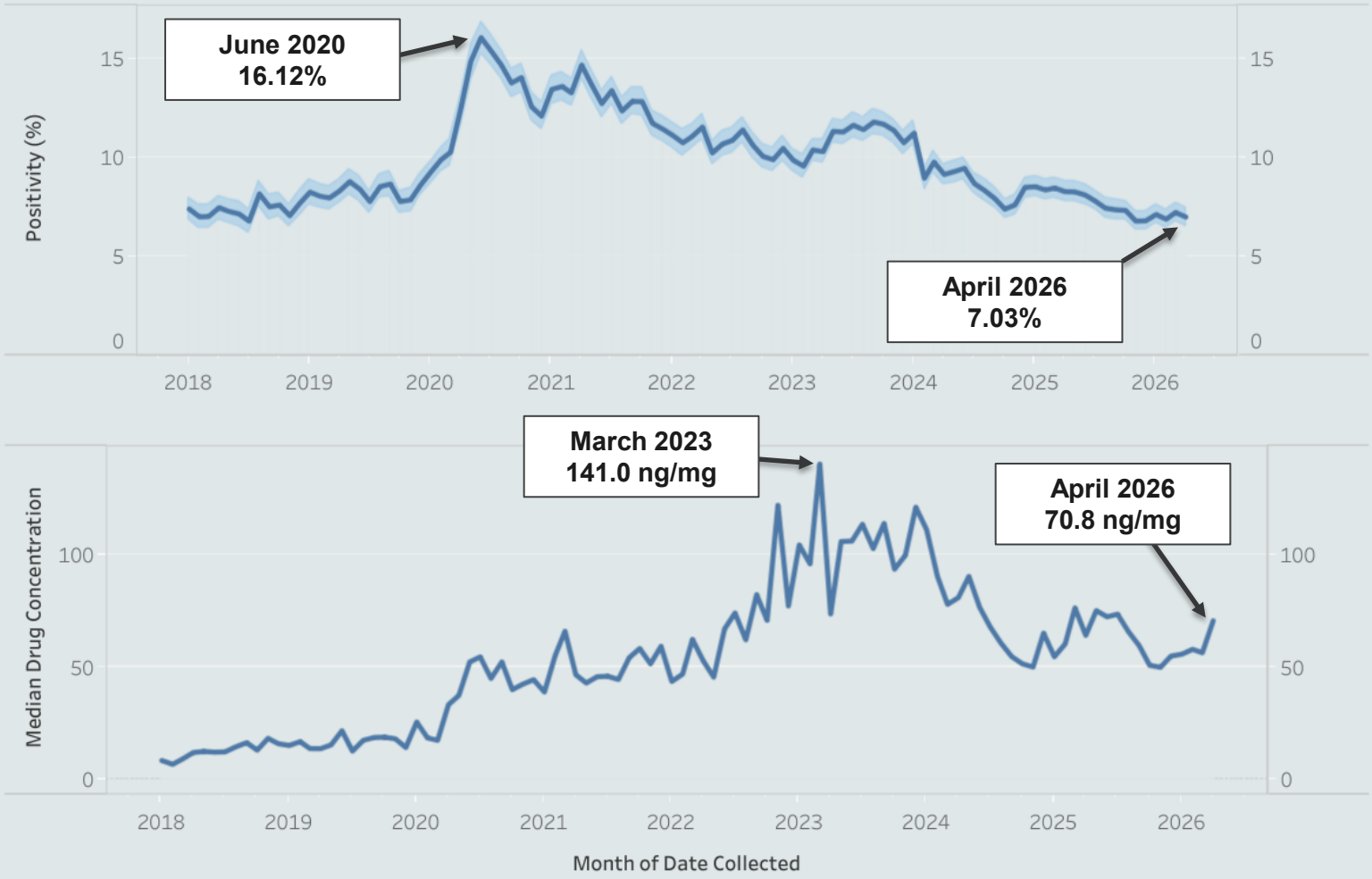
In this application, you can explore drug positivity and mean concentrations (for positive tests) filtered by positivity. For example, if Fentanyl is selected in the first filter, results will be shown within all positive fentanyl tests. Results can be filtered by state/region by selecting state(s) on the map to the right. All results from Millennium 30-day UDT dataset.

Filter by Positive UDT for: <No Filter>

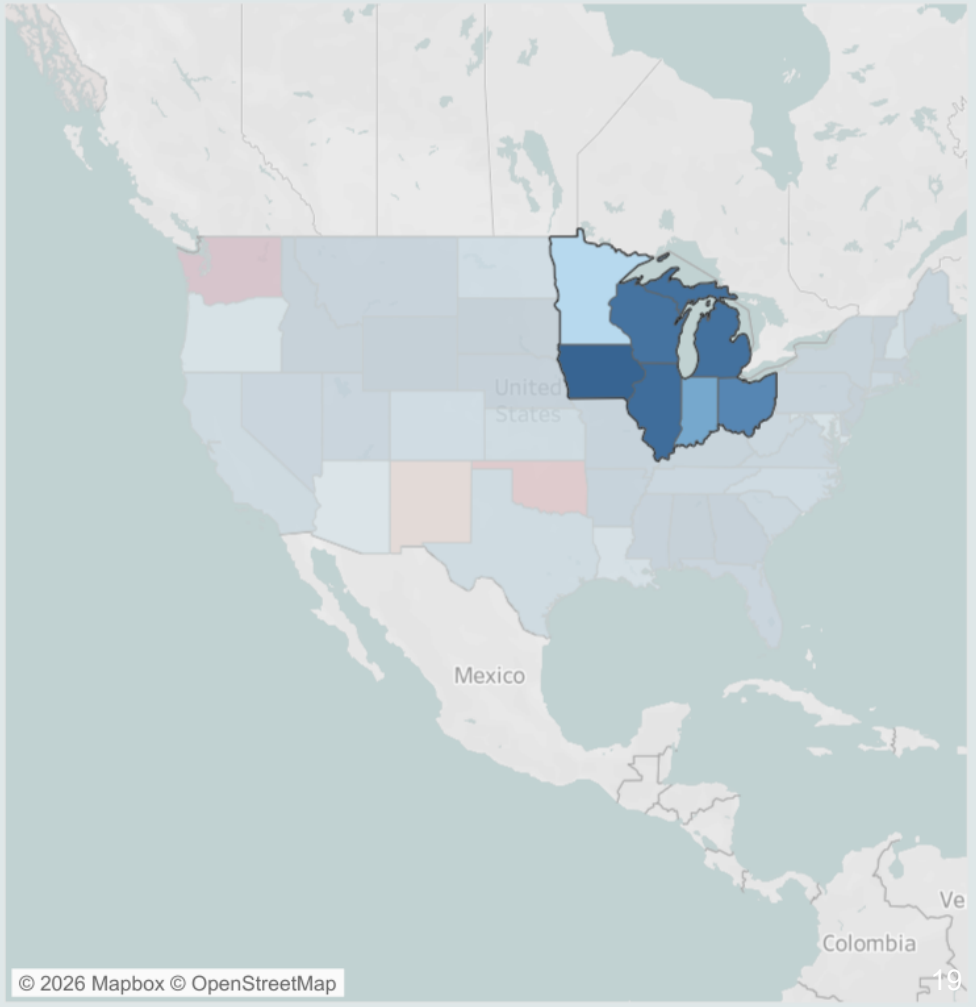
Drug to Analyze: Fentanyl

ADDITIONAL FILTERS Sex: All Has SUD Dx: YES Age Group: All Client Specialty Group: All

Positivity and Concentration



State Selector



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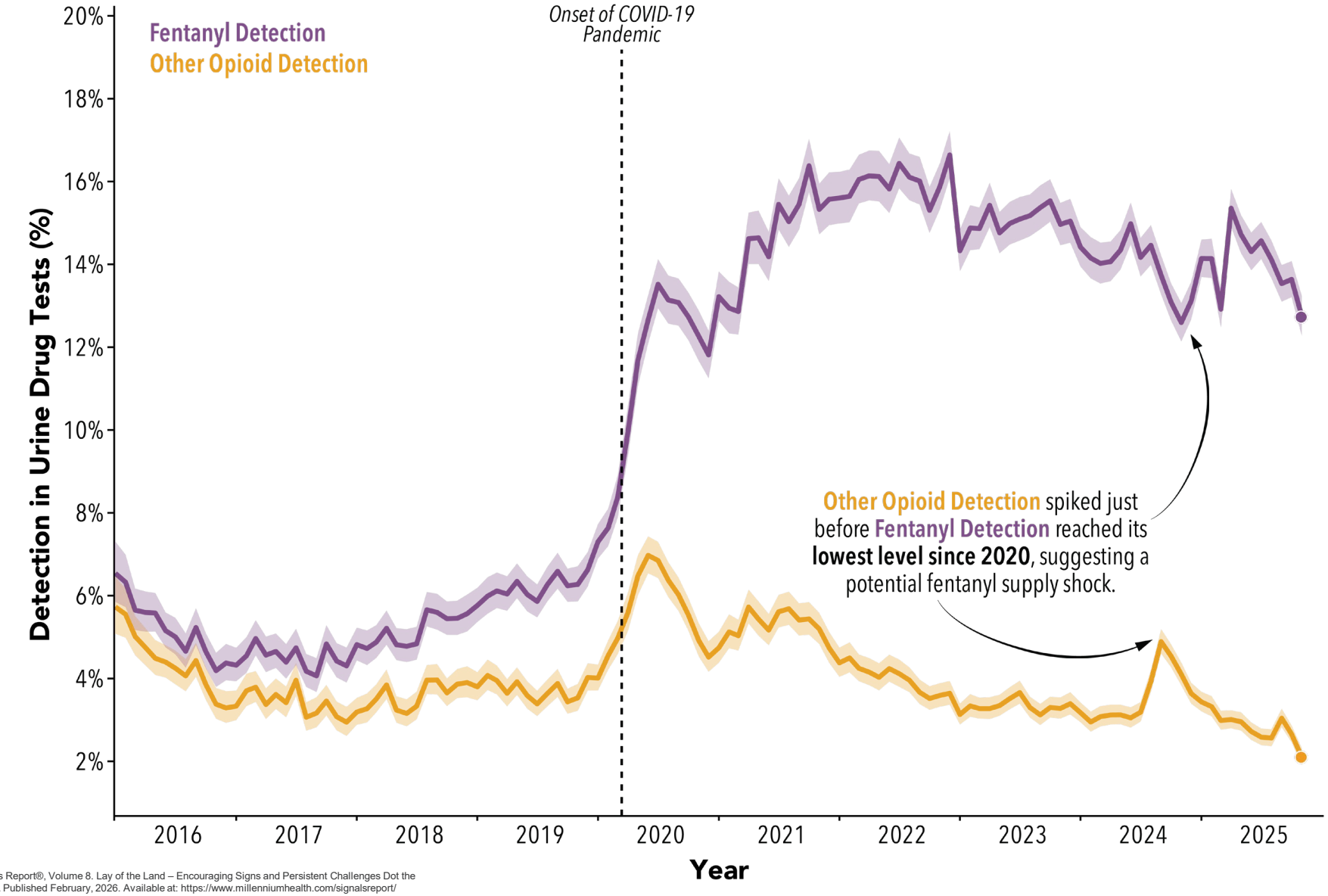

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Fentanyl Supply Shock & Overdose Deaths

ANALYSIS

Check for updates

POLICY ARTICLE

DRUG POLICY

Did the illicit fentanyl trade experience a supply shock?

A synthesis of government and social media data suggests a disruption, possibly tied to events in China

Kasey Vangelov[1], Keith Humphreys[2], Jonathan P. Caulkins[3], Harold Pollack[4], Bryce Pardo[5], Peter Reuter[1,6]

Fatal overdoses from synthetic opioids, most notably fentanyl, steadily increased more than 25-fold in the United States over 15 years, peaking at 76,000 in 2023 (*1*). This trend began to sharply reverse in mid-2023, dropping the annual rate of fentanyl overdose deaths (ODDs) by over a third by the end of 2024 (*1*). Explaining this unexpected drop is of major scientific and policy interest. Whether a supply shock could account for a substantial part of the decline is challenging to determine because drug trafficking organizations operate in secret. Synthesizing data from the US and Canadian governments and from discussions on the social media platform Reddit, we suggest there was a major disruption in the illicit fentanyl trade, possibly tied to Chinese government actions, that translated into sharp reductions in overdose mortality beginning in mid- or late-2023 and continued into 2024 across both the US and Canada.

Supply shocks sometimes produce large and rapid changes in the severity of drug problems. The early proliferation and overprescribing of prescription opioid pain medications beginning in the late 1990s and traffickers' introduction of fentanyl into the North American illicit drug supply around 2014 are two prominent examples of supply changes that sharply increased drug-related morbidity and mortality (*2*). In the opposite direction, the pronounced drought in Australia's heroin supply in early 2001 (the causes of which are still debated) was followed by a 60% decline in opioid overdose mortality (*3*). The Chinese government's scheduling of the potent synthetic opioid carfentanil in 2017, legally designating the drug as potentially dangerous and tightening regulatory controls on it accordingly, immediately preceded a sharp drop in both seizures of and deaths from this fentanyl analog in the Midwest US region where it was prevalent (*4*). Controls on precursor chemicals used in the manufacture of drugs can sometimes shock markets; increased controls on pseudoephedrine, required to make methamphetamine, reduced availability and harm from that drug for at least some months (*5*).

CONVENTIONAL INDICATORS OF DRUG SUPPLY AND ITS RELATIONSHIP TO PUBLIC HEALTH

We begin with two standard indicators of drug supply: drug purity and counts of seizures of drugs by law enforcement. Drug dealers often adapt to supply shortages by lowering purity more than raising prices. This is akin to the "shrinkflation" seen in many consumer products in recent years. Documented historical examples include European and clined by more than half from their May 2023 peak. The average purity of fentanyl pills also fell, albeit slightly less (by one-third, to roughly 1.5%) and slightly later than the decline in powder purity and deaths.

The correspondence is broader than just those downturns. Across the entire monthly series from January 2019 to October 2024, the rate of synthetic opioid ODDs was correlated with the purity of fentanyl in the form of both pills [correlation coefficient r = 0.62; 95% confidence interval (CI): 0.44 to 0.74] and powder (r = 0.37; 95% CI: 0.15 to 0.56) (see the first figure).

The number of drug seizures tends to positively correlate with supply. Semiannual counts of fentanyl seizures reported publicly by the US National Forensic Laboratory Information System (NFLIS) peaked in the first half of 2023, fell by 15% in the second half of 2023, and were 37% below peak by the second half of 2024 [see supplementary materials (SM)]. In theory, seizures could have fallen despite stable supply if enforcement ebbed. However, given the sustained public and political attention to the fentanyl crisis throughout this period, reduced supply seems the more plausible explanation for declining seizure numbers.

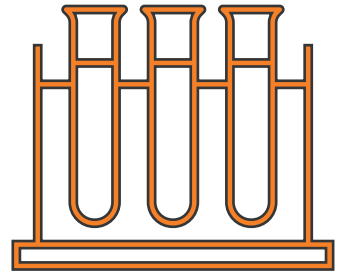
AN UNCONVENTIONAL INDICATOR OF ILLICIT DRUG SUPPLY SHOCKS

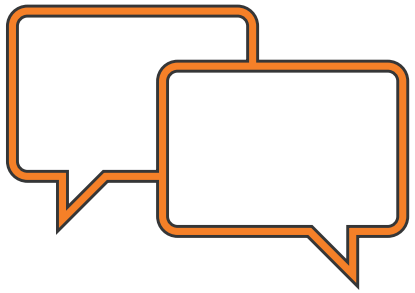
Another avenue for attempting to determine whether a supply disruption took place is to gather data from customers. Given the challenges of recruiting persons purchasing illegal drugs to participate in research and the more general difficulties of tracking drug problems in real time, some researchers are finding productive uses for social media postings as drug problem indicators (*9*).

In particular, Reddit participants frankly discuss drug availability and quality. We therefore analyzed Reddit posts containing the word "fentanyl" (including misspellings and slang terms such as "fetty") across six subreddits: r/fentanyl, r/heroin, r/opiates, r/meth, r/cocaine, and r/mdma. Within these posts, we tracked mentions of the word "drought" (and similar terms, such as "shortage") monthly from January 2021 through January 2025. We then manually verified that drought references pertained to fentanyl availability rather than other contexts.

These Reddit data show a first notable peak in mention of drought in July 2023, followed by a much more pronounced spike beginning in late 2023 and continuing until it was cut short by moderator intervention (see the second figure). In January 2024, the r/fentanyl subreddit

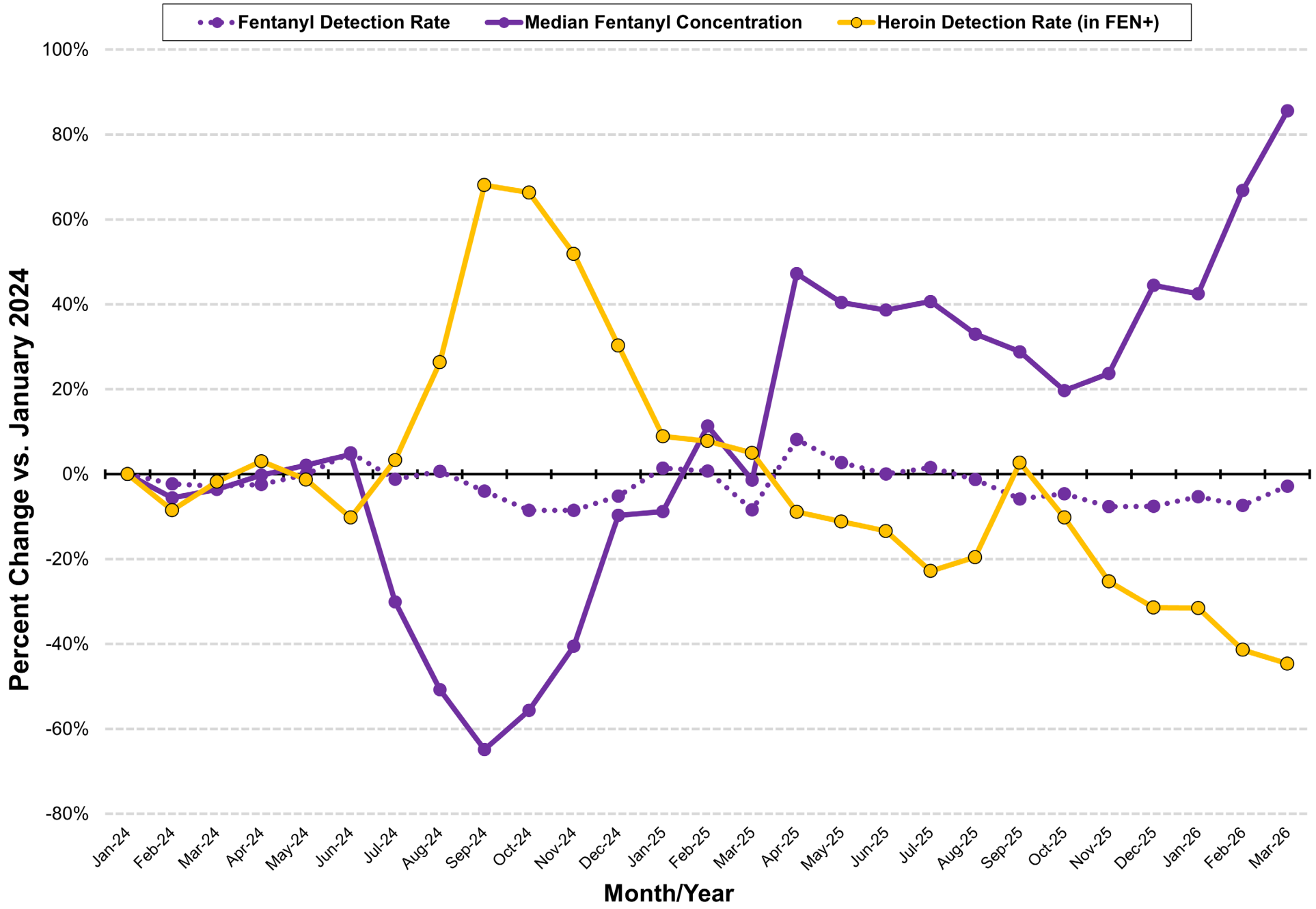
Overdose death rates and the **purity of fentanyl powder** analyzed by the DEA **fell by ~50%** from May 2023 – December 2024



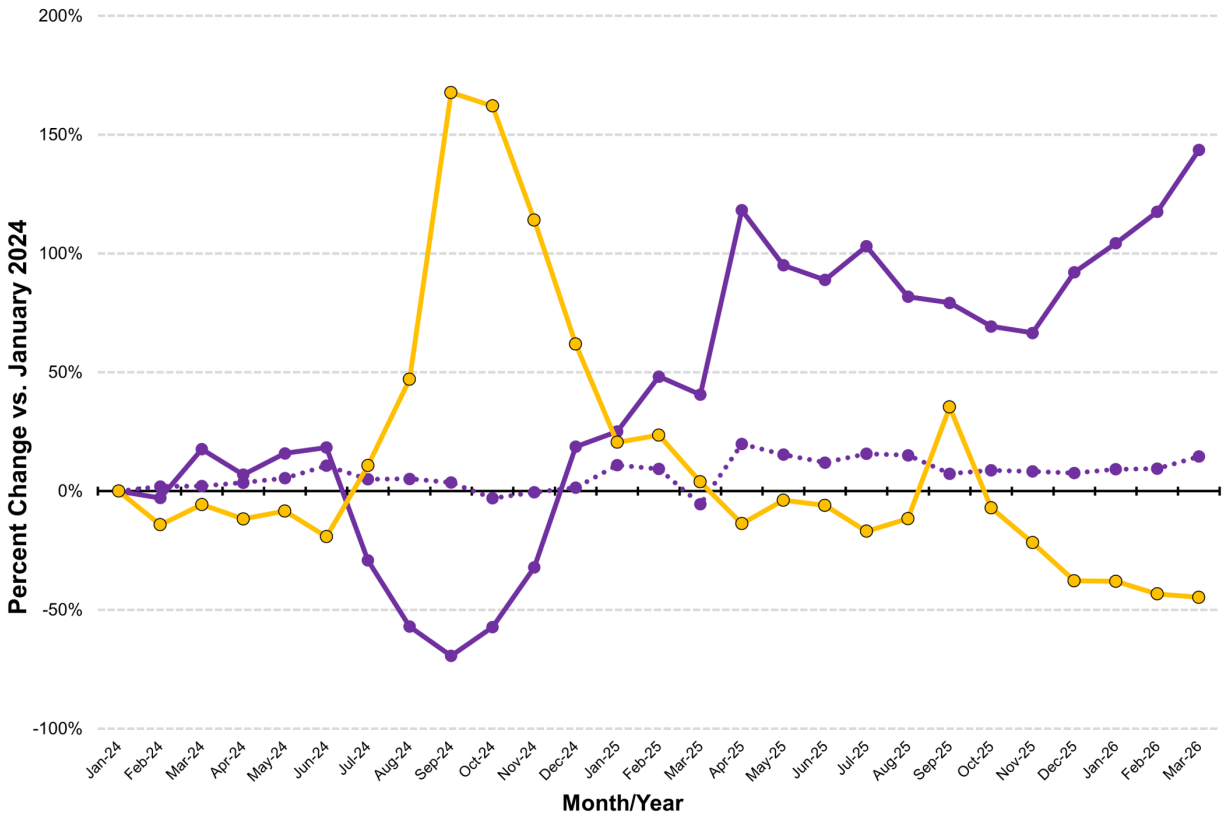


Discussions of "**fentanyl drought**" on Reddit spiked in December 2023 and August-October 2024

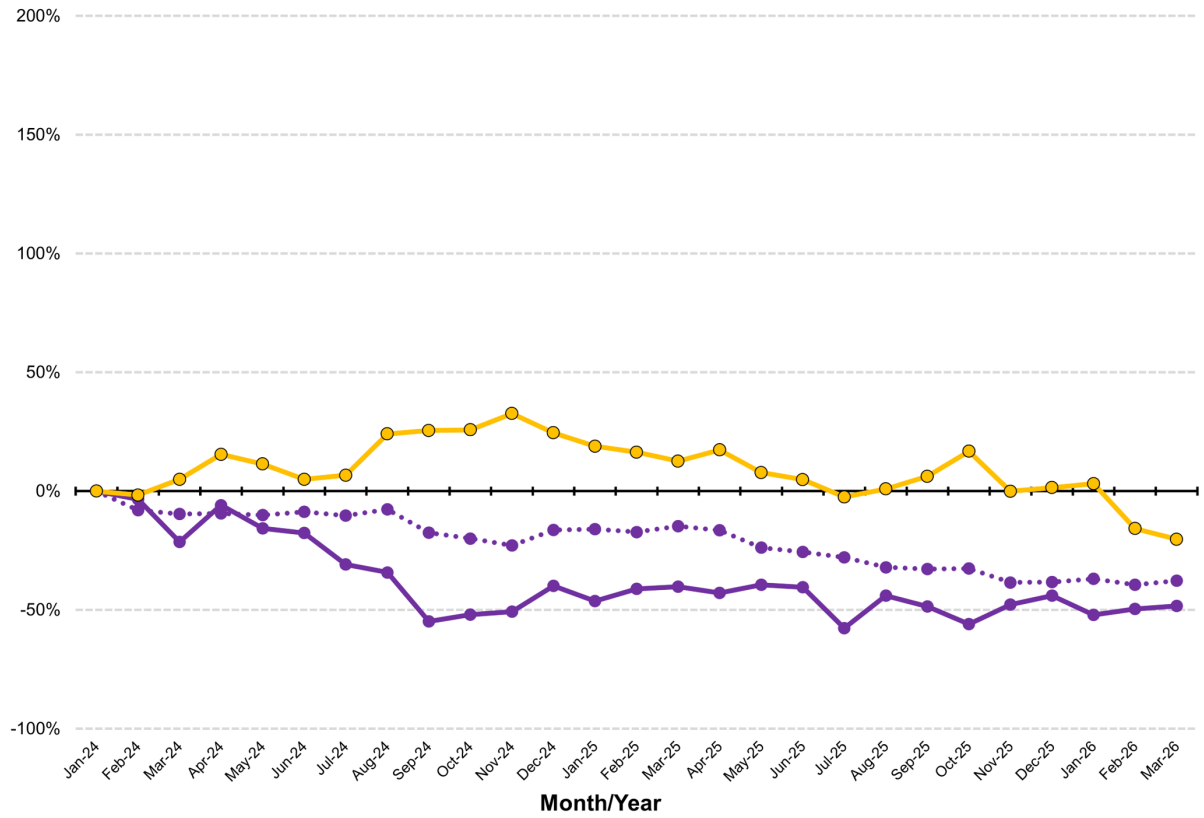
1. Vangelov K, Humphreys K, Caulkins JP, Pollack H, Pardo B, Reuter P. Did the illicit fentanyl trade experience a supply shock?. Science. 2026;391(6781):134-136. doi:10.1126/science.aea6130



WESTERN REGION



ALL OTHER REGIONS



Fentanyl Detection Rate | Median Fentanyl Concentration | Heroin Detection Rate (in FEN+)

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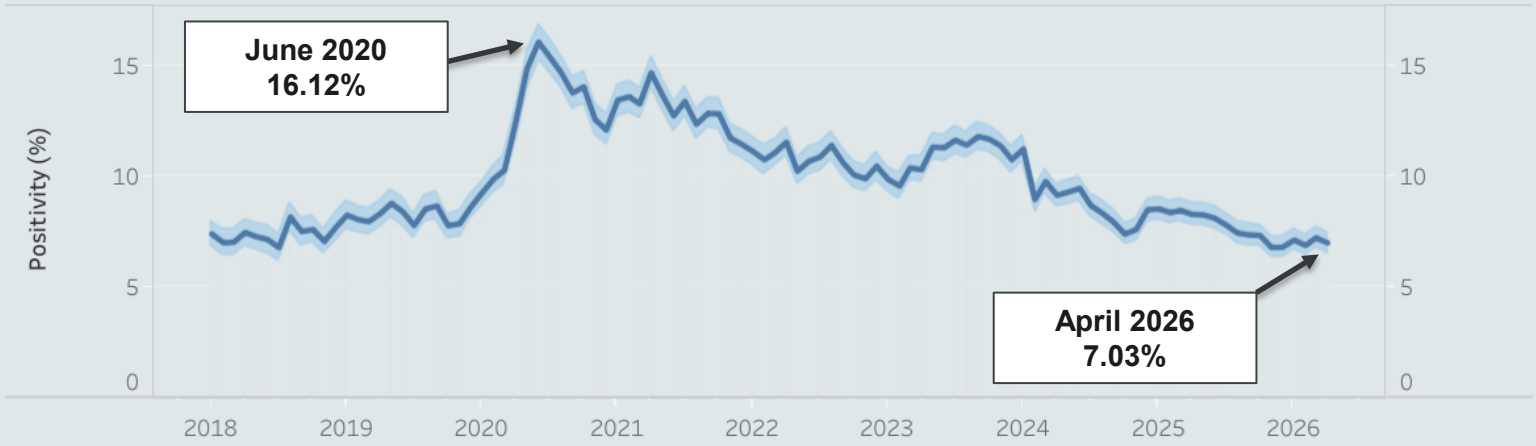
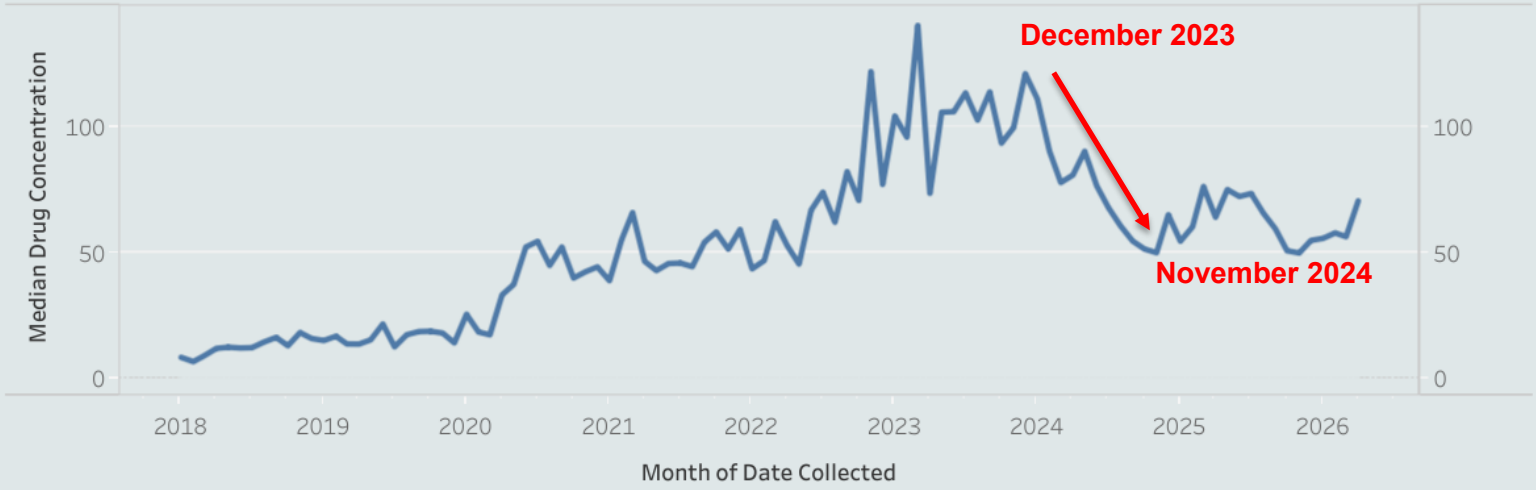
Drug to Analyze:	Fentanyl

ADDITIONAL FILTERS Sex: All Has SUD Dx: YES Age Group: All Client Specialty Group: All

Positivity and Concentration





State Selector

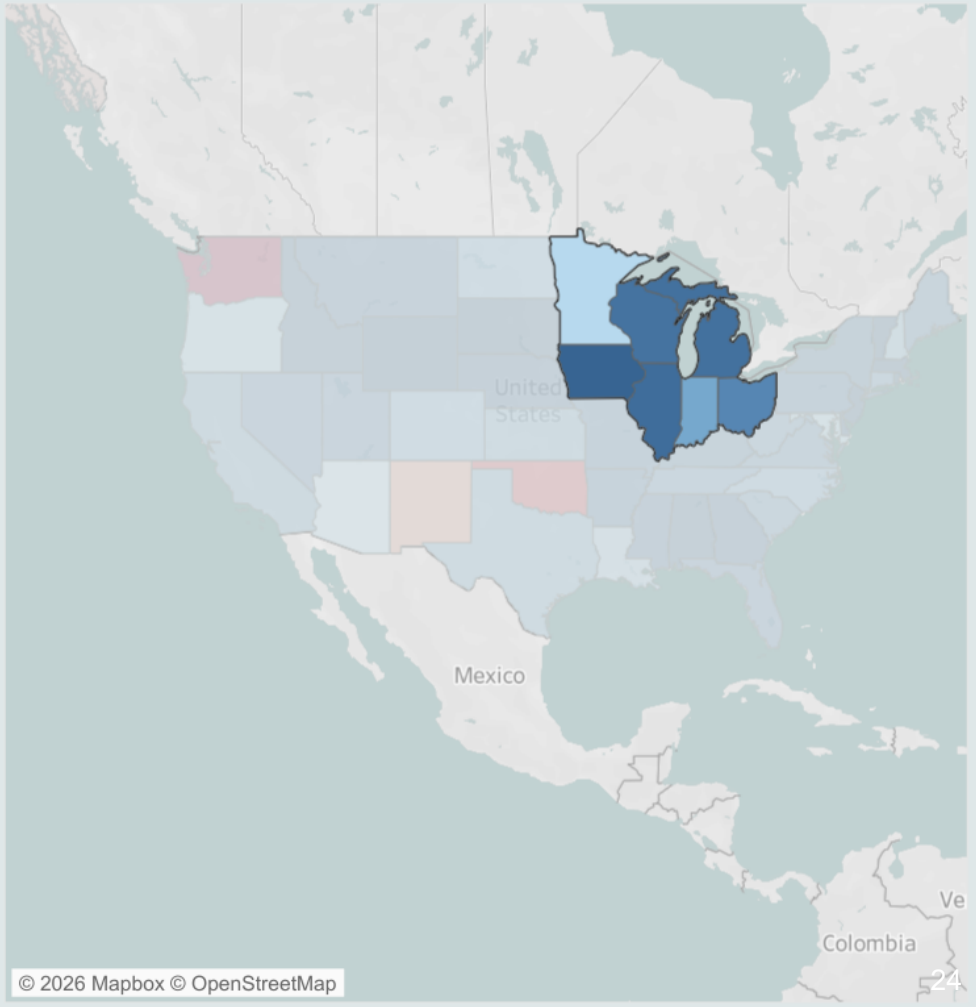
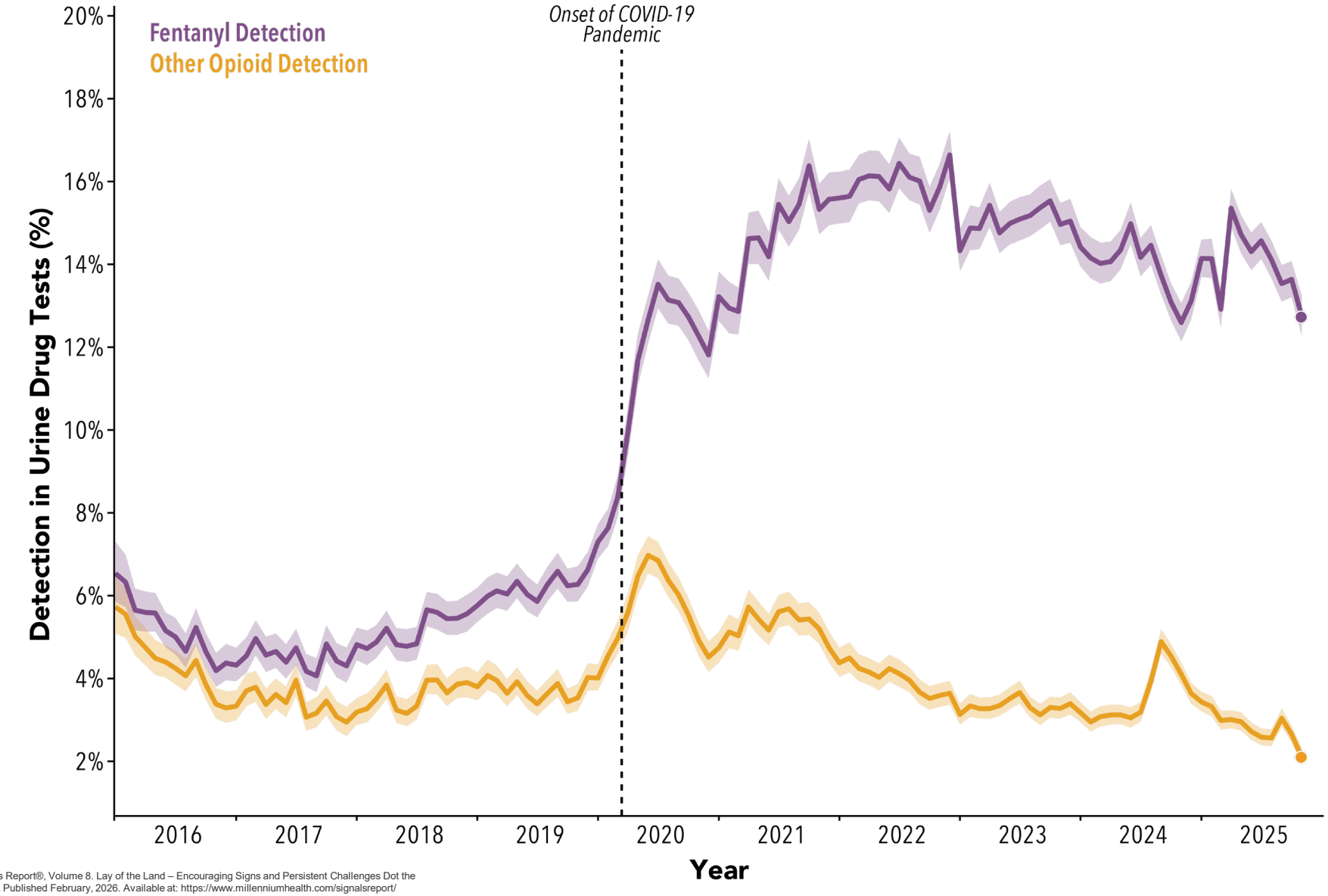


Figure 4: National Fentanyl Detection and Associated Polysubstance Use



1. 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/

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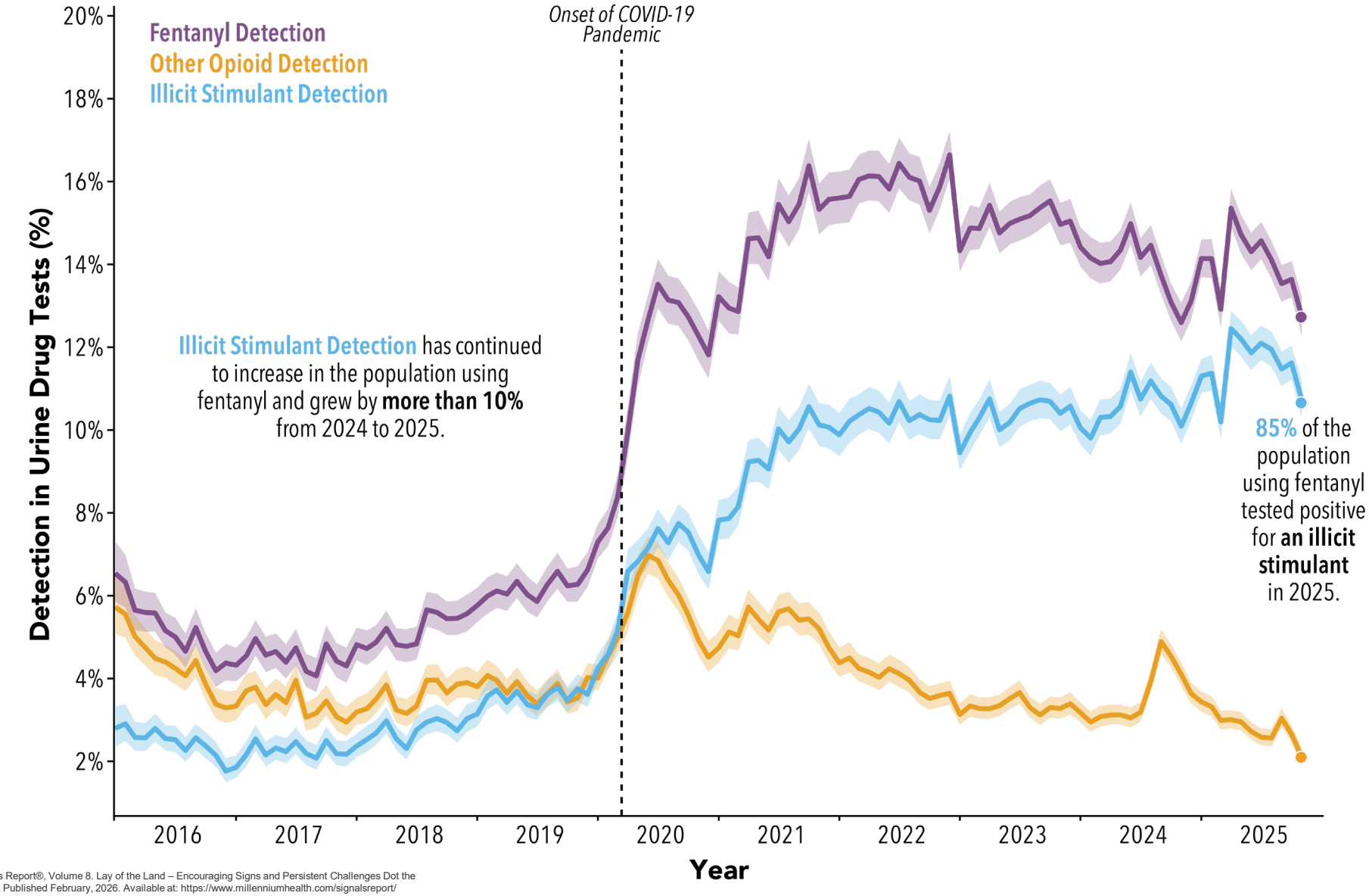

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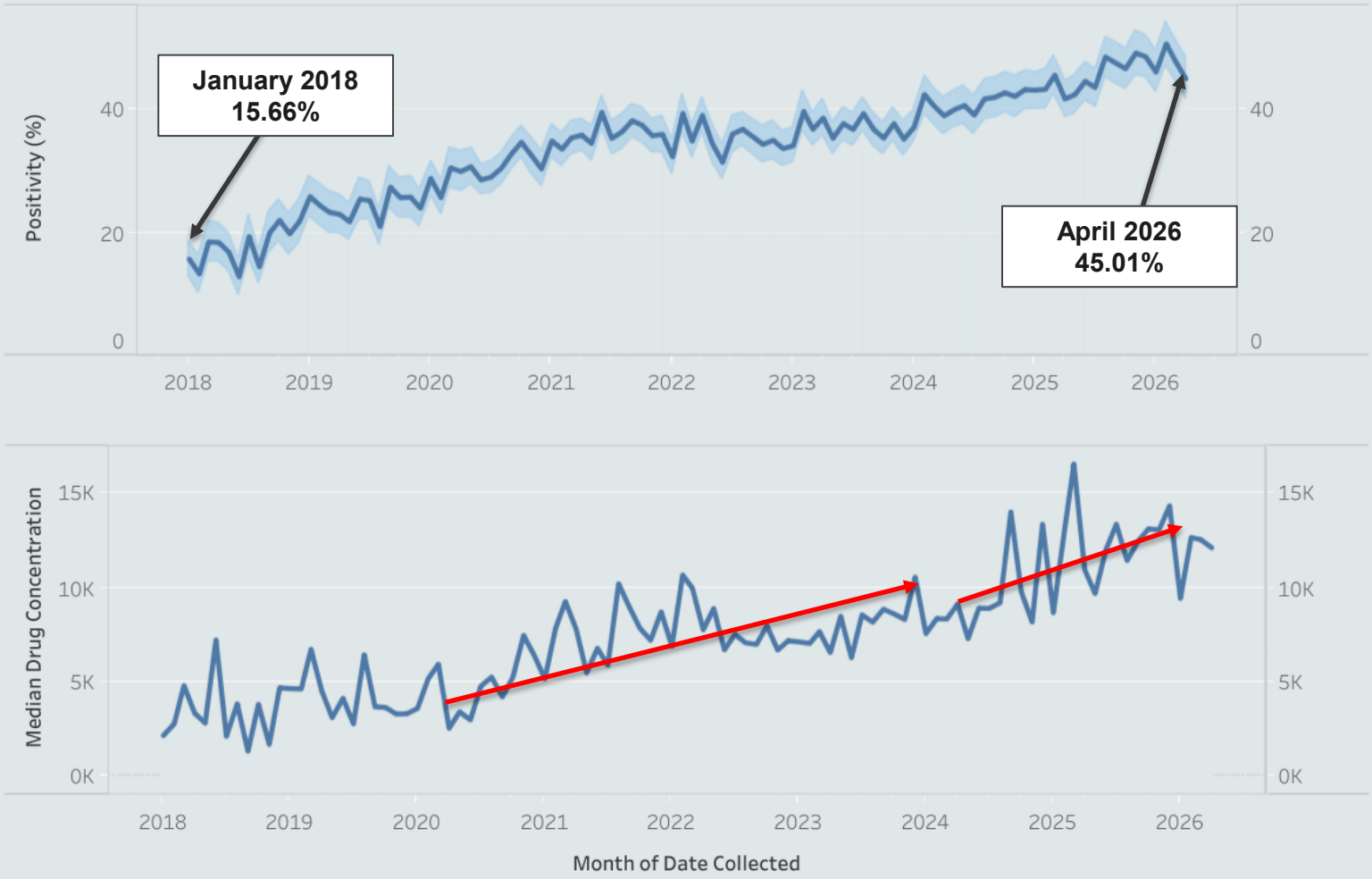
Millennium In-Depth Co-Positivity Tracker

In this application, you can explore drug positivity and mean concentrations (for positive tests) filtered by positivity. For example, if Fentanyl is selected in the first filter, results will be shown within all positive fentanyl tests. Results can be filtered by state/region by selecting state(s) on the map to the right. All results from Millennium 30-day UDT dataset.

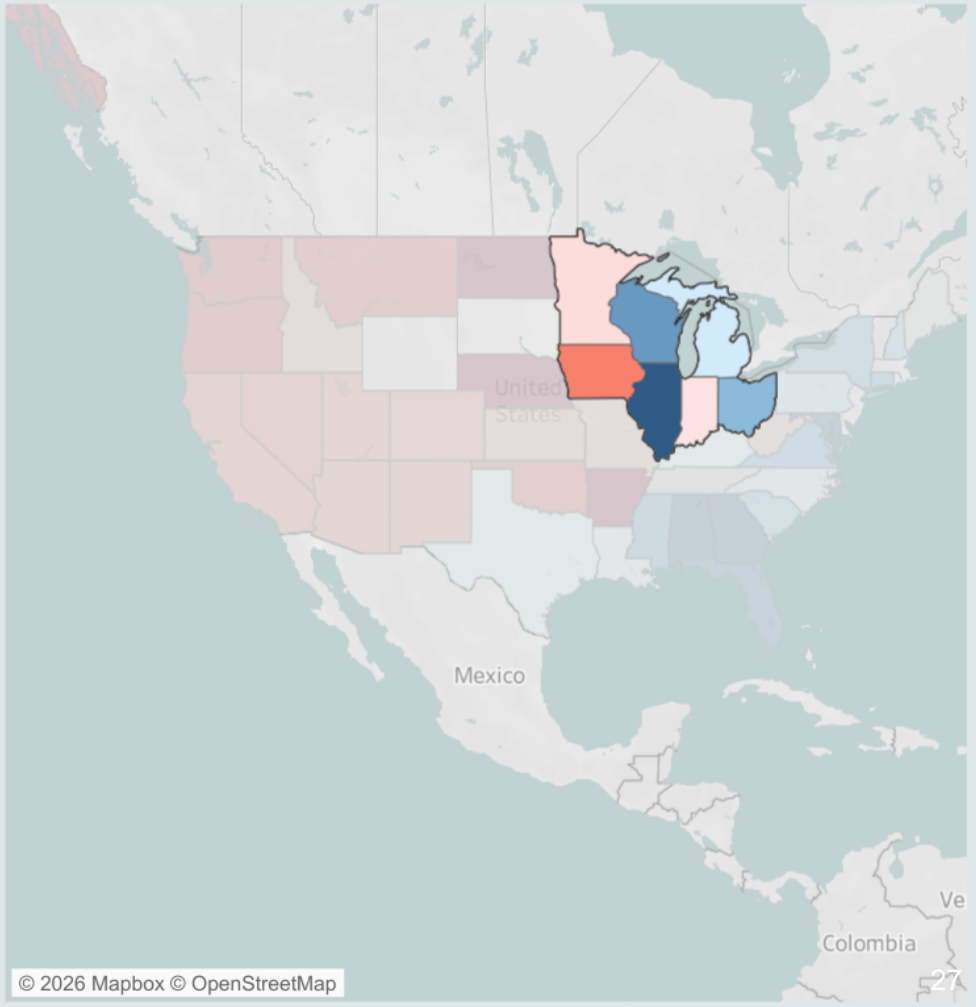
Filter by Positive UDT for:	Fentanyl
Drug to Analyze:	Methamphetamine

ADDITIONAL FILTERS Sex: All Has SUD Dx: YES Age Group: All Client Specialty Group: All

Positivity and Concentration



State Selector



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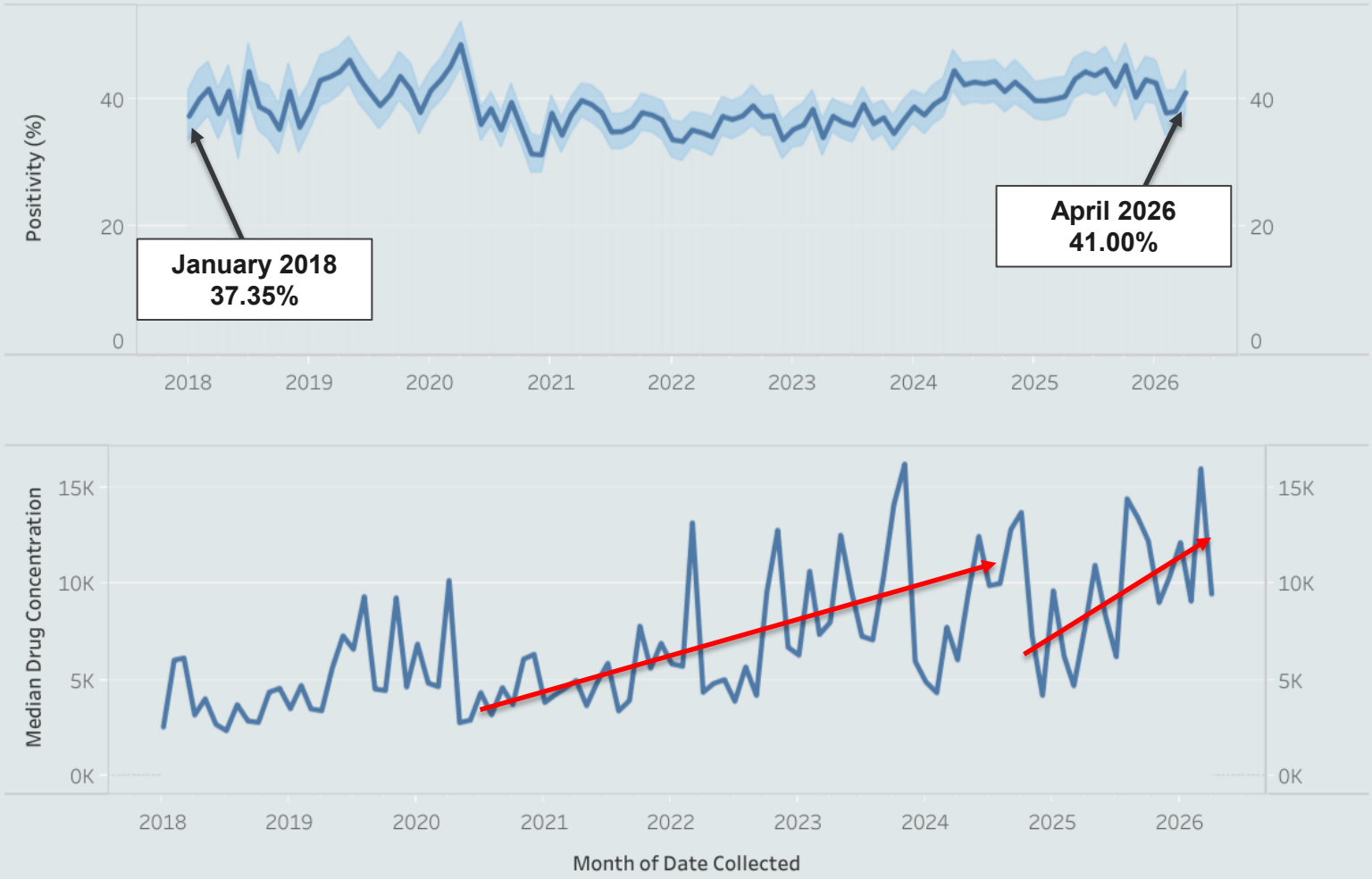
Filter by Positive UDT for: Fentanyl

Drug to Analyze: Cocaine

ADDITIONAL FILTERS Sex: All Has SUD Dx: YES Age Group: All Client Specialty Group: All

Positivity and Concentration



State Selector

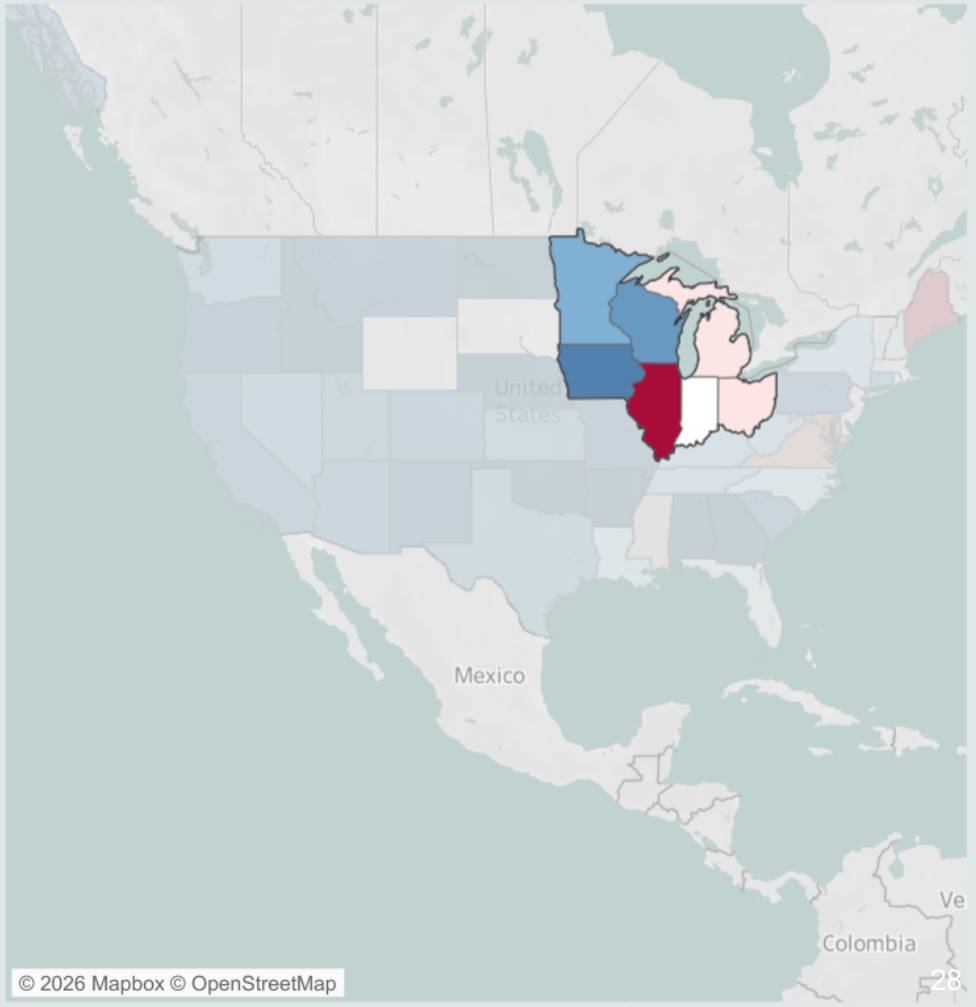
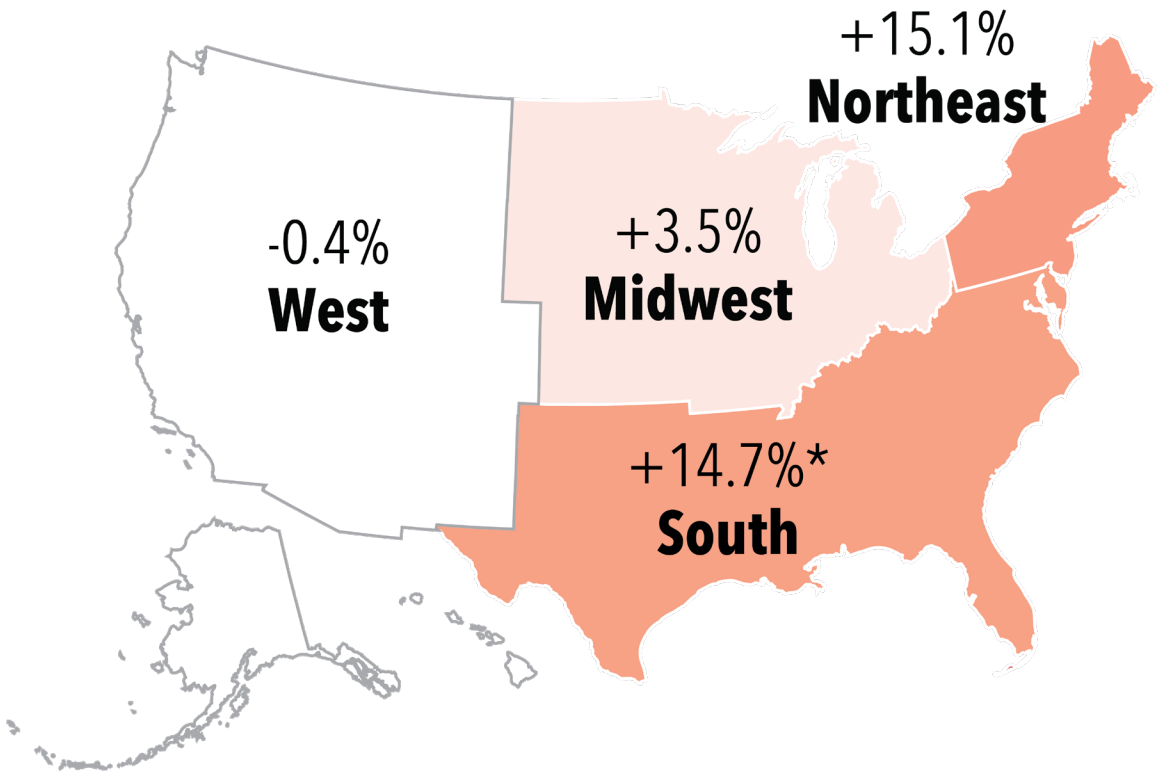


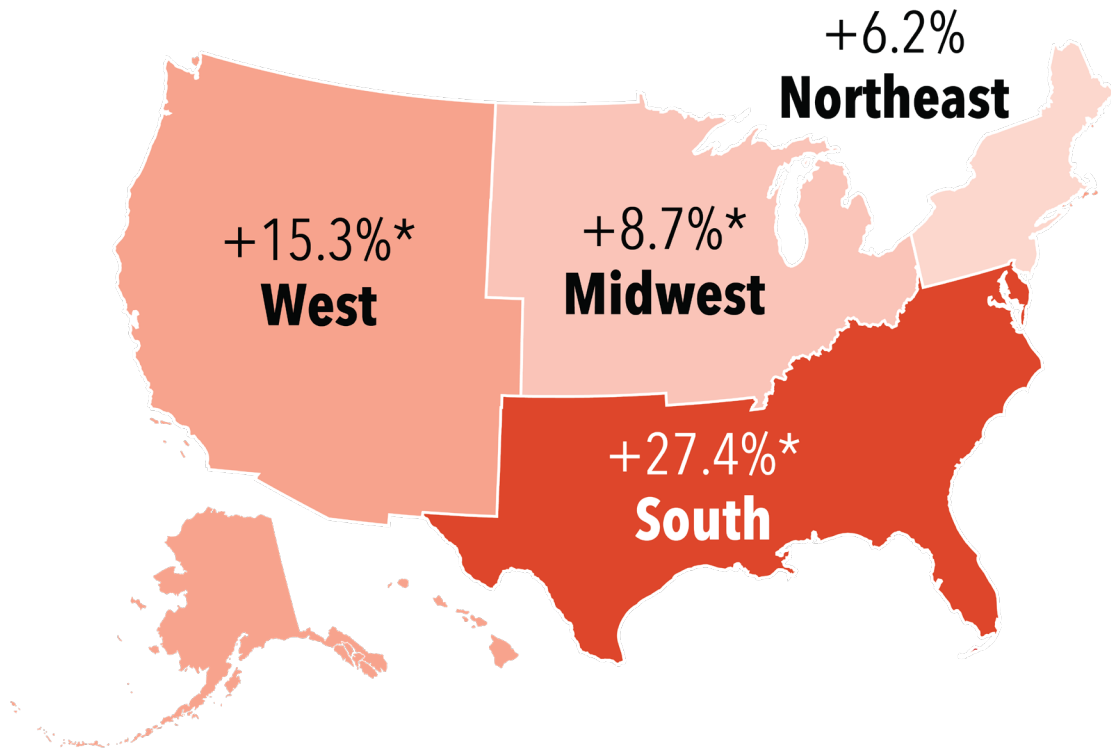
Figure 9: Percent Change in Detection Rates for Illicit Stimulants in the Absence of Fentanyl, 2024-2025

Methamphetamine Detection in the Absence of Fentanyl



+4.5%* - U.S. Total

Cocaine Detection in the Absence of Fentanyl



+13.5%* - U.S. Total

1. 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/

Are We Equipped to Traverse the Challenging Terrain Ahead?

Negative Consequences of Stimulant Use

Physical Health

- Exhaustion/sleep deprivation
- Cardiovascular effects (e.g., racing/irregular heartbeat, stroke, heart attack)
- Cardiovascular disease
- Motor disturbances (e.g., facial "tics")
- Difficulty breathing
- Increased risk for seizures
- Increased risk for Parkinson's disease
- Increased infectious disease risk (HIV, hepatitis C)

Mental Health

- Anxiety
- Memory lapses ("blackouts")
- Paranoia
- Delusions
- Hallucinations
- Agitation
- Aggressive behavior
- Psychosis
- Increased risk for other psychiatric conditions (e.g., schizophrenia)

Note: See **References** in 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/

Effective Interventions Desperately Needed…

FDA-Approved Medications

Opioid Use Disorder
Buprenorphine
Methadone
Naltrexone

Opioid Overdose
Naloxone
Nalmefene

Stimulant Use Disorders
TBD

Stimulant Overdose
TBD

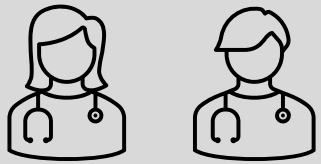
Off-Label Use[1]

Antidepressants

Anticonvulsants

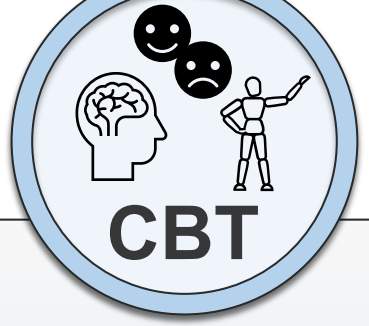
Opioid Antagonists

Rx Stimulants



1. Clinical Guideline Committee (CGC) Members ; ASAM Team ; AAAP Team ; IRETA Team . The ASAM/AAAP Clinical Practice Guideline on the Management of Stimulant Use Disorder. J Addict Med. 2024;18(1S Suppl 1):1-56. doi:10.1097/ADM.0000000000001299

Common Behavioral Interventions…



Cognitive Behavioral Therapy

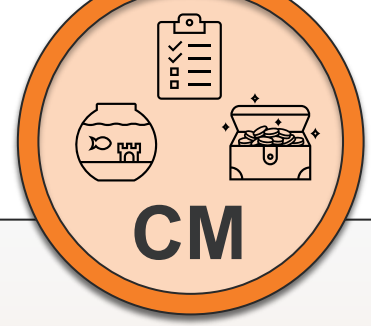
Common Form of Talk Therapy Focused on Changing Patterns of Thinking and Unhelpful Behavior

Motivational Interviewing

Therapeutic Communication Style Focused on the "Language of Change"

Community Reinforcement Approach

Comprehensive Intervention Focused on Shifting Reinforcement Away From Drug Use Toward Healthy Behaviors



Contingency Management

Reinforcement-Based Behavioral Intervention that Provides Incentives for Reaching Treatment Goals

1. InformedHealth.org [Internet]. Cologne, Germany: Institute for Quality and Efficiency in Health Care (IQWiG); 2006-. In brief: Cognitive behavioral therapy (CBT) [Updated 2025 Aug 21]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279297/
2. Miller, W.R. & Rollnick, S. (2013) Motivational Interviewing: Helping people to change (3rd Edition). Guilford Press.
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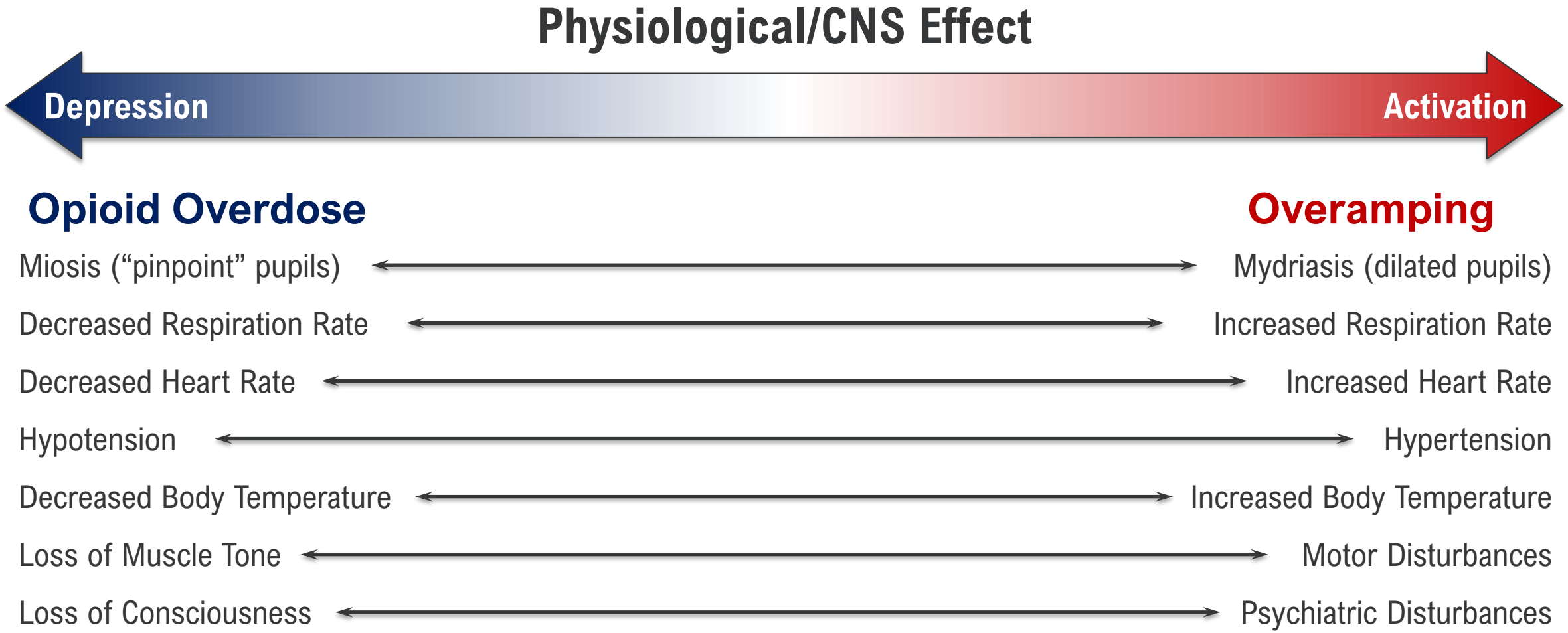
4. Rawson RA, Erath TG, Chalk M, et al. Contingency Management for Stimulant Use Disorder: Progress, Challenges, and Recommendations. J Ambul Care Manage. 2023;46(2):152-159. doi:10.1097/JAC.0000000000000450

Overdose vs. Overamping…



1. California Department of Public Health. Signs of a drug-related overdose. Updated September 29, 2025. Available at https://www.cdph.ca.gov/Programs/CCDPHP/sapb/Pages/Signs-of-overdose.aspx
2. Treatment for Stimulant Use Disorders: Updated 2021 [Internet]. Rockville (MD): Substance Abuse and Mental Health Services Administration (US); 1999. (Treatment Improvement Protocol (TIP) Series, No. 33.) Chapter 3—Medical Aspects of Stimulant Use Disorders. Available from: https://www.ncbi.nlm.nih.gov/books/NBK576550/

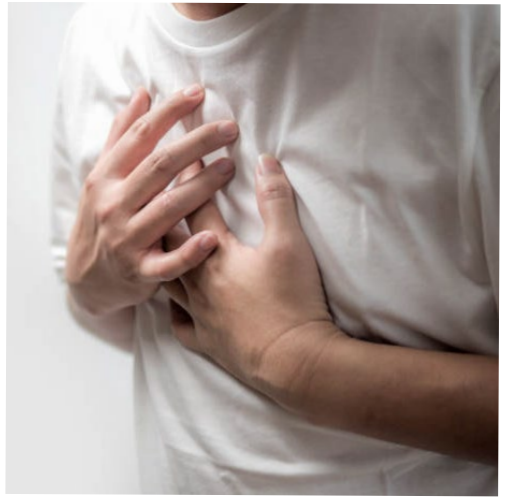
Overdose vs. Overamping…

Opioid Overdose Symptoms

- Constricted “pinpoint” pupils
- Slow, irregular, weak or stopped breathing
- Snoring, gurgling, choking sounds
- Slow, irregular, and/or weak heartbeat
- Low blood pressure
- Discolored (blue, purple) lips, fingernails, toenails
- Pale, cold clammy skin
- Change in mental status
- Loss of consciousness (unresponsive to voice or touch)
- Loss of muscle tone (limp body)

1. California Department of Public Health. Signs of a drug-related overdose. Updated September 29, 2025. Available at https://www.cdph.ca.gov/Programs/CCDPHP/sapb/Pages/Signs-of-overdose.aspx

Overdose vs. Overamping…

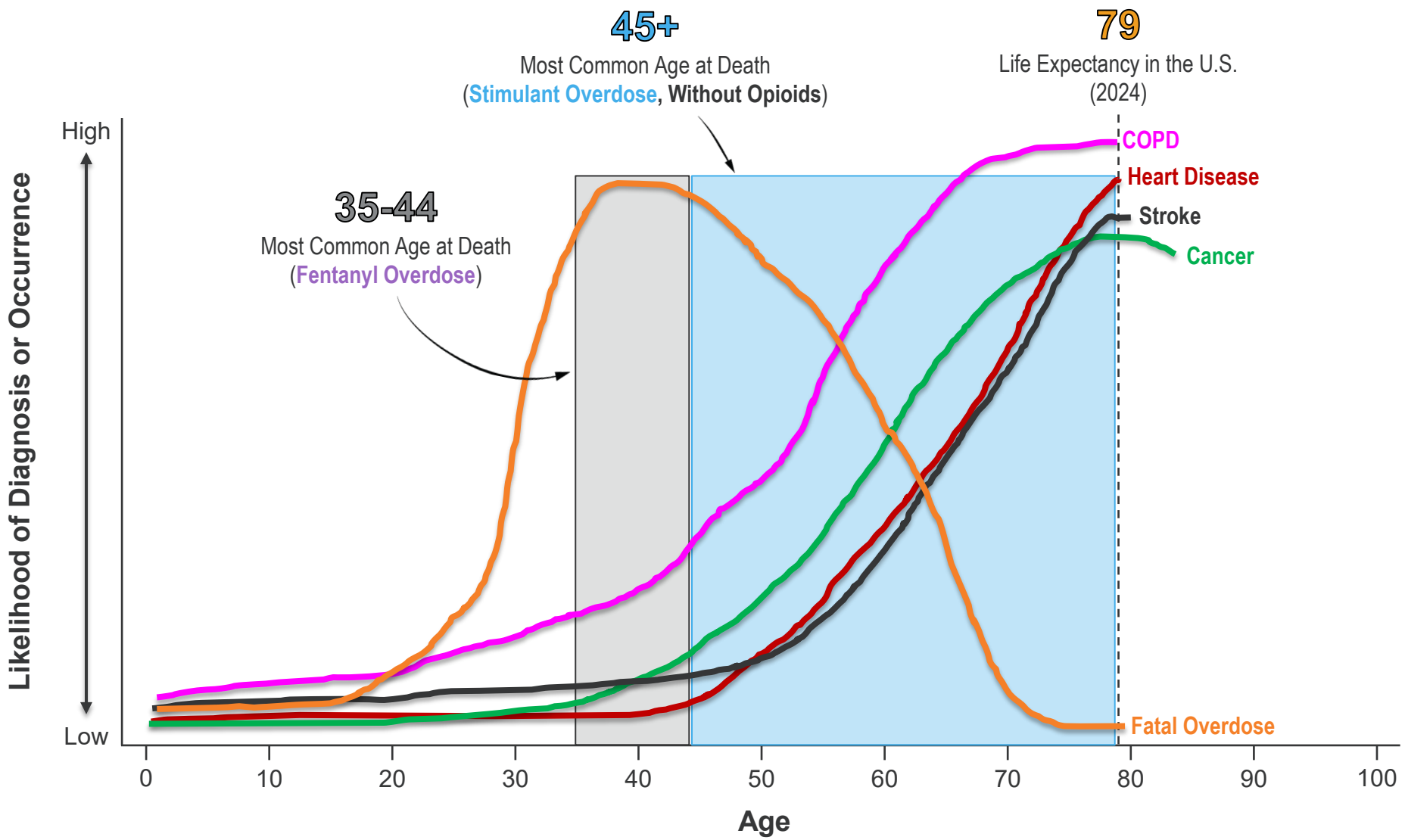


Overamping Symptoms

- Dizziness, headache
- Vomiting, cramps, excessive sweating
- Dilated pupils
- Elevated body temperature
- High blood pressure
- Elevated and/or irregular heartbeat
- Chest pain, heart palpitations
- Uncontrolled movements (e.g., tremor, tics, flailing)
- Rapid, irregular breathing
- Change in mental status, confusion
- Anxiety, panic, paranoia, delusions, hallucinations, acute psychosis
- Agitation, aggressive behavior
- Convulsions, seizure
- Heart attack, stroke

1. California Department of Public Health. Signs of a drug-related overdose. Updated September 29, 2025. Available at https://www.cdph.ca.gov/Programs/CCDPHP/sapb/Pages/Signs-of-overdose.aspx
2. Treatment for Stimulant Use Disorders: Updated 2021 [Internet]. Rockville (MD): Substance Abuse and Mental Health Services Administration (US); 1999. (Treatment Improvement Protocol (TIP) Series, No. 33.) Chapter 3—Medical Aspects of Stimulant Use Disorders. Available from: https://www.ncbi.nlm.nih.gov/books/NBK576550/

Thinking Longer-Term…



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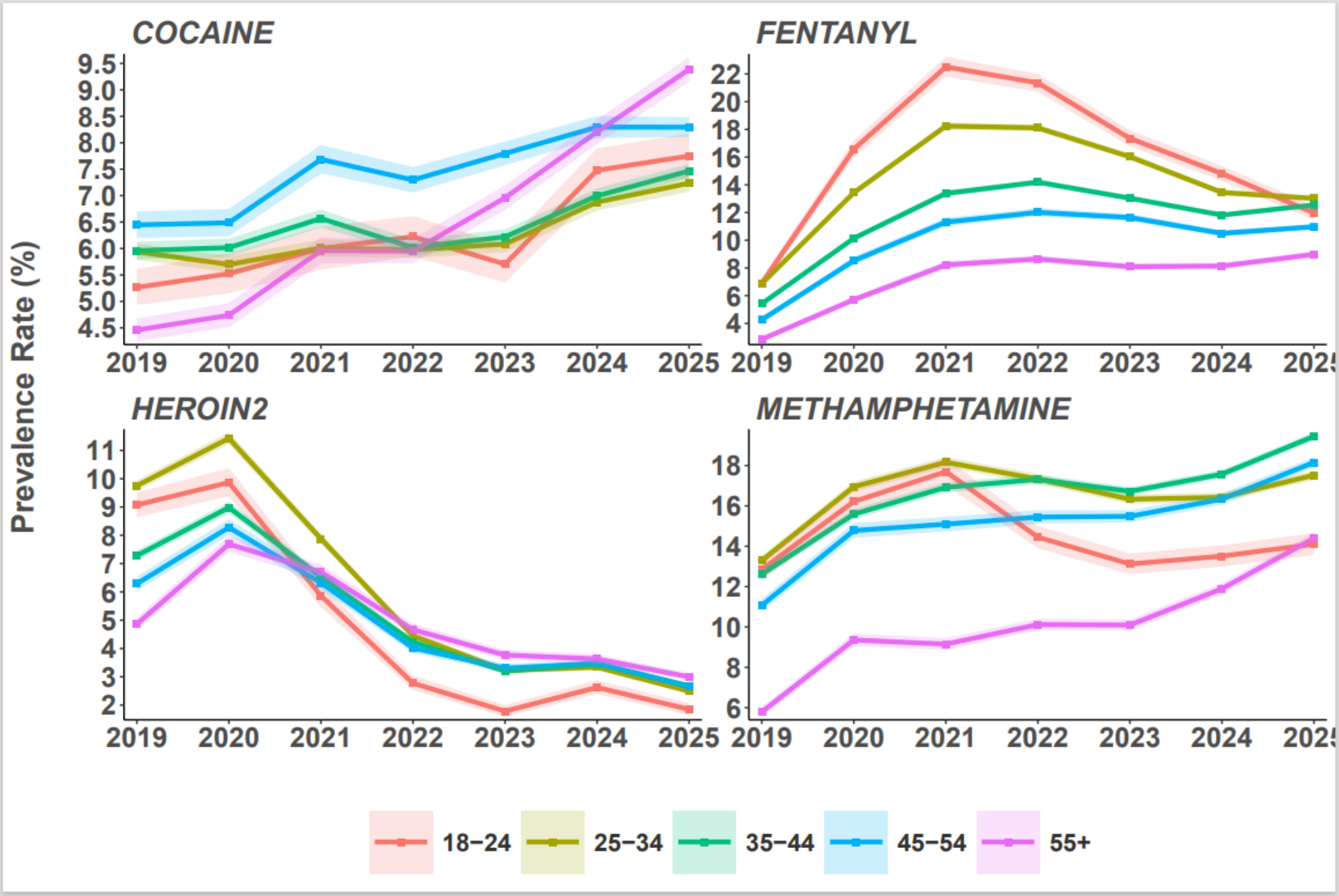
7. National Cancer Institute. Age and Cancer Risk. Updated May 2, 2025. Accessed February 5, 2026. Available at: https://www.cancer.gov/about-cancer/causes-prevention/risk/age



Medical Necessity

Criteria to establish medical necessity must be based on patient-specific elements identified during the clinical assessment and documented in the patient's medical record by the provider.

Documenting Medical Necessity

- Orders must be individualized
- Tests ordered and reasons for testing must be documented in the patient's medical record
- Risk assessment and stage of treatment should match testing frequency

Documenting How the Test Results Were Used

- Review of results and use in the treatment plan