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Xylazine-Fentanyl Positivity and Concentration in Urine Drug Tests

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Abstract

IMPORTANCE The US opioid crisis is currently driven by illicitly manufactured fentanyl combined with an evolving mix of stimulants and adulterants, such as the veterinary sedative xylazine, which further complicate clinical and public health responses. Using urine drug testing (UDT) to understand changes in the geographic spread and relative concentration of xylazine over time may provide clarity on the changing dose of exposure for xylazine and future emerging adulterants.

OBJECTIVE To differentiate spatiotemporal trends in xylazine detection and relative concentration in UDT specimens from 2023 to 2025.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cross-sectional study analyzed UDT specimens collected from US patients (1 specimen per patient) aged 18 years or older from March 2023 and September 2025. Tests were ordered by behavioral health, primary care, or substance use treatment practitioners. If more than 1 specimen was provided by a patient during the study period, only the first specimen collected was included. Data were analyzed from June to September 2025.

EXPOSURE UDT specimens were analyzed for fentanyl and xylazine (primary exposure) using liquid chromatography with tandem mass spectrometry. Specimens were included in the study if fentanyl was detected.

MAIN OUTCOME AND MEASURES Differences in xylazine positivity by patient and practitioner characteristics, copositivity for other substances, and fentanyl concentration were assessed using logistic regression. Spatiotemporal trends in monthly percentages of xylazine positivity and concentration in UDT, stratified by East and West Census regions, are described.

RESULTS A total of 42 307 specimens (24 339 [57.52%] from male patients; 15 583 [36.83%] from patients aged 26-35 years) were analyzed. In both regions, xylazine detection increased between the first and last months (East: 8.52 percentage points [from 11.11% to 19.63%]; West 13.46 percentage points [from 0.0% to 13.46%]) while concentration decreased (East: −37.76 ng xylazine per 1 mg creatinine [from 61.77 to 24.00 ng xylazine per 1 mg creatinine]; West: −7.98 ng xylazine per 1 mg creatinine [from 28.62 to 20.64 ng xylazine per 1 mg creatinine]). Odds of xylazine detection were 79% lower in the West (AOR vs East, 0.21 [95% CI, 0.19 to 0.22]; $P < .001$), and 120% higher in samples with heroin positivity (AOR vs heroin negativity, 2.20 [95% CI, 2.07 to 2.35]; $P < .001$) or with higher fentanyl concentrations (AOR per 10-fold increase, 1.55 [95% CI, 1.53 to 1.57]; $P < .001$).

CONCLUSIONS AND RELEVANCE In this cross-sectional study of xylazine-fentanyl in UDT specimens, xylazine detection increased but concentration decreased over time. These findings suggest UDT complements existing drug surveillance and provides unique insights into emerging fentanyl adulterants.

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Key Points

Question How are the presence and concentration of xylazine with fentanyl changing in the US over time and region in the current phase of the opioid crisis?

Findings This cross-sectional study analyzed 42 307 fentanyl-positive urine drug testing (UDT) samples collected between March 2023 and September 2025 that were also tested for xylazine. In the East and West US, xylazine detection increased while concentration in UDT samples sharply decreased.

Meaning This cross-sectional study found that the concentration of xylazine in the US drug supply may be decreasing, but xylazine with fentanyl was still present and spreading.

+ Invited Commentary

+ Supplemental content

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Introduction

The opioid crisis persists as one of the most pressing public health challenges in the US.[1] Since 1999, nearly 1 million people have died of opioid overdoses.[1] The incidence of drug-related injuries, such as endocarditis and soft tissue wounds, is increasing and likely undercounted.[1-3] Opioid overdose fatalities have increased in 3 waves, largely tied to the opioid supply, first with prescription opioids, second with heroin and injection drug use, and third with fentanyl and synthetic opioids, excluding methadone. In the current fourth wave, the drug supply is characterized by an unpredictable mix of illicitly manufactured fentanyl, combined or co-used with stimulants (eg, methamphetamine, cocaine) and adulterants, such as xylazine.[1-6]

Xylazine, a veterinary sedative not approved for human use, has become a prevalent fentanyl additive throughout the US drug supply.[5,7] Xylazine was first detected in the early 2000s in Puerto Rico's heroin supply,[8,9] then in the Northeastern US in 2015.[7] Since 2019, xylazine mixed with opioids, also known as *tranq* or *tranq dope*, has been detected in all US states.[10] By the end of 2024, xylazine was detected in 38% of all fentanyl powder samples and over 12% of pills seized by the Drug Enforcement Administration, up from 23% and 7% in 2022, respectively.[10,11] Upstream manufacturers, producers, or distributors added xylazine to opioids, usually fentanyl, to increase drug supply volume as a cheap filler accessible through legitimate veterinary websites or international manufacturers and to prolong the sense of euphoria or high.[8-10,12] Despite increasing presence across the North American drug supply, not all people who use drugs containing xylazine are aware of or desire it.[13-15]

Information about the health effects of xylazine is also emerging. Xylazine-involved overdose mortality across the US increased by 5- to 10-fold between 2020 and 2021.[3] Xylazine is also associated with clinically complex soft tissue wounds among people who use drugs, which can become necrotic and result in amputations without early treatment.[16,17] Clinical guidance on treating xylazine-involved wounds and withdrawal is still developing.[2,17-22] and many people who use drugs, particularly those facing structural vulnerability and visible wounds, encounter barriers to care and stigma in health care settings.[11,12]

Major gaps remain in our understanding of the epidemiology of xylazine. First, little is known about the geographic spread of xylazine across the country, partly because few data sources systematically track xylazine exposure among people who use drugs. Second, little is known about the concentrations of xylazine in drugs relative to fentanyl or other substances.[8,23,24] Understanding relative xylazine concentrations may provide some clues into xylazine dose of exposure and toxic effects. A prior report[25] measured xylazine positivity rates by US Census region in urine drug testing (UDT) samples, but this report represents 1 year of data (2023-2024) and does not explore xylazine concentrations or use multivariate modeling approaches that adjust for potential confounders.

Analyzing results of UDT specimens, biologically verified assessments of the drug analytes and metabolites excreted by an individual, is one way to understand patient exposure to emerging substances.[25-27] Specimens collected in health care settings and during drug treatment provide insights about the substances and metabolites of substances a patient used and at what concentrations they are present.[23,26-29] Thus, UDT results represent a measure of an individual's recent exposure to a range of psychoactive substances. Given the lack of information about changes in xylazine exposure, the purpose of this study is to describe spatiotemporal trends in the prevalence of xylazine in combination with fentanyl and the concentration of xylazine in UDT samples.

Methods

This cross-sectional study was reviewed and determined as non–human participants research involving the use of existing deidentified data by the institutional review board at Johns Hopkins Bloomberg School of Public Health. Data collection and analysis protocols from Millennium Health were approved by the Aspire independent review board, which waived the informed consent

requirement because the study used deidentified data. This study is reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

In this retrospective cross-sectional study, we analyzed UDT results from patient specimens collected by Millennium Health and tested for xylazine between March 2023 and September 2025. Millennium Health is a specialty laboratory that serves a broad array of clinical settings, including office-based, specialty outpatient, and inpatient substance use disorder treatment settings. UDT were ordered for patients in the care of clinicians in behavioral health, primary care, or substance use treatment settings. Specimens were obtained from patients aged 18 years or older and analyzed by a specialized liquid chromatography–tandem mass spectrometry (LC-MS/MS) laboratory, a method used by Millennium Health that is certified by the Clinical Laboratory Improvement Amendments and accredited by the College of American Pathologists for high-complexity testing.[30] Millennium Health added xylazine to their testing panel in March 2023. The analytes of interest in this study (xylazine, fentanyl, methamphetamine, cocaine, and heroin) were selected to understand the prevalence and concentration of xylazine with fentanyl over time and substances that people who use drugs may co-use with xylazine.

For patients who provided more than 1 UDT specimen in the study period, we kept only results from the first specimen. The American Society of Addiction Medicine recommends testing more frequently at the beginning of treatment, at least weekly, until a patient becomes more stable.[31] The terminal half-life of xylazine is approximately 12 hours,[32] so the first specimen analyzed would have the highest metabolite concentration for xylazine. Specimens were limited to samples positive for both fentanyl and xylazine, as only 0.2% of specimens that were positive for xylazine were not also positive for fentanyl. Hereafter, *xylazine positivity* refers to xylazine detection in samples where fentanyl was also detected. Specimens and patients with any missing data were excluded from the analytic dataset.

Statistical Analysis

First, we calculated descriptive statistics of patient, treatment clinician, and sample characteristics. Patient characteristics included age group (18-25, 26-35, 36-45, 46-55, ≥55 years) and sex (female, male). Treatment setting characteristics included the type of health care setting of clinician who requested a UDT (behavioral health, primary care, substance use treatment), and testing region based on state (Western [Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, Wyoming] vs Eastern US [all other states in the South, Midwest, and Northeast Census regions]).[33,34] UDT sample characteristics included other copositive substances (methamphetamine [positive, negative], heroin [positive, negative], cocaine [positive, negative]), and fentanyl concentration (continuous, log-normalized; nanograms per milligram of creatinine). Descriptive statistics were stratified by region and xylazine positivity (positive, negative). To understand xylazine positivity over time, we calculated the percentage of xylazine-positive samples per month by region.

Next, to understand the relative concentration of xylazine by time and region, we calculated the median normalized concentration of xylazine in xylazine-positive samples in a given month and region. Normalization is the process of comparing the amount of analyte (xylazine) to amount of creatinine, which helps account for the hydration level of a urine sample. It is expressed as the analyte volume (nanograms per milliliter) divided by the creatinine volume (milligrams per milliliter) which gives nanograms xylazine analyte per 1 mg of creatinine. As a supplemental analysis to understand state-by-state variation, we calculated the monthly mean xylazine concentration over time in 9 states (Arizona, California, Indiana, Kentucky, Louisiana, Maryland, Minnesota, Ohio, Washington).

Finally, we constructed multivariable logistic regression models to understand differences in xylazine positivity by patient, clinician, and specimen characteristics. The outcome variable for all models was xylazine positivity (positive, negative). The primary covariate of interest was region.

Other covariates included patient age group, sex, clinician specialty group, other copositive substances, and log-normalized fentanyl concentration in the sample. To test for potential association modification of xylazine positivity within each region, we constructed separate models that used only regional samples. The second model used samples from patients in the East region, and the third model used samples from patients in the West. Specimen characteristics were the primary variables of interest, and we adjusted for patient demographics and clinician settings.

P values were 2-sided and statistical significance was set at $P < .05$. Analyses were completed in R Studio version 4.4 (R Project for Statistical Computing). Data were analyzed from June to September 2025.

Results

The study sample included the first specimen tested for xylazine and fentanyl from 42 307 patients (24 339 [57.52%] male; 15 583 [36.83%] aged 26-35 years) (**Table**). Among all samples, most were collected from the Western region (24 135 samples [57.05%]) and substance use treatment settings (36 059 samples [85.23%]) and were copositive for methamphetamine (27 169 samples [64.21%]). Of all samples, 7156 (16.91%) were positive for xylazine. Demographic patterns in patients with xylazine-positive samples were similar to those in the entire UDT sample. Most xylazine-positive samples were found in the Eastern region (4809 samples [67.20%]), patients aged 36 to 45 years (2601 samples [36.34%]), and male patients (4100 samples [57.29%]) and were requested by substance use treatment practitioners (6354 samples [88.79%]) and copositive for methamphetamine (4454 samples [62.24%]). The higher proportion of male patients in the sample is consistent with demographics from national public health surveillance of people who inject drugs.[35] Descriptive distributions of xylazine positivity by individual characteristics were similar within regions.

Table. Characteristics of People With vs Without Xylazine Detected in Fentanyl-Positive Urine Drug Testing Samples in the US, 2023-2025

	Patients, No. (%)						
	Full sample			East (n = 18 172 [42.95%])		West (n = 24 135 [57.05%])	
Characteristic	Total	Xylazine negative	Xylazine positive	Xylazine negative	Xylazine positive	Xylazine negative	Xylazine positive
Total	42 307 (100)	35 151 (83.08)	7156 (16.91)	13 363 (73.53)	4809 (26.46)	21 788 (90.27)	2347 (9.72)
Age group, y							
18-25	3952 (9.34)	3429 (9.75)	523 (7.31)	1635 (12.23)	364 (7.56)	1794 (8.23)	159 (6.77)
26-35	15 583 (36.83)	13 008 (37)	2575 (35.98)	4820 (36.06)	1727 (35.91)	8188 (37.58)	848 (36.13)
36-45	14 105 (33.33)	11 504 (32.72)	2601 (36.34)	4225 (31.61)	1723 (35.82)	7279 (33.41)	878 (37.41)
46-55	5572 (13.17)	4583 (13.03)	989 (13.82)	1721 (12.87)	657 (13.66)	2862 (13.13)	332 (14.14)
≥55	3095 (7.31)	2627 (7.47)	468 (6.53)	962 (7.19)	338 (7.02)	1665 (7.64)	130 (5.53)
Sex							
Female	17 968 (42.47)	14 912 (42.42)	3056 (42.71)	5870 (43.92)	2059 (42.81)	9042 (41.49)	997 (42.47)
Male	24 339 (57.52)	20 239 (57.57)	4100 (57.29)	7493 (56.07)	2750 (57.18)	12 746 (58.5)	1350 (57.52)
Requesting clinician type							
Behavioral health	4593 (10.85)	4017 (11.42)	576 (8.04)	1573 (11.77)	447 (9.29)	2444 (11.21)	129 (5.49)
Primary care	1655 (3.91)	1429 (4.06)	226 (3.15)	701 (5.24)	176 (3.65)	728 (3.34)	50 (2.13)
Substance use treatment	36 059 (85.23)	29 705 (84.51)	6354 (88.79)	11 089 (82.98)	4186 (87.04)	18 616 (85.44)	2168 (92.37)
Copositive substances							
Methamphetamine	27 169 (64.21)	22 715 (64.62)	4454 (62.24)	5612 (41.99)	2311 (48.05)	17 103 (78.49)	2143 (91.31)
Heroin	2068 (4.88)	1226 (3.48)	842 (11.76)	473 (3.53)	761 (15.82)	753 (3.45)	81 (3.45)
Cocaine	10 831 (25.60)	7834 (22.28)	2997 (41.88)	4646 (34.76)	2457 (51.09)	3188 (14.63)	540 (23.01)

Trends Analyses

Percentage Xylazine Positivity

Trends analyses showed variations in the percentages of UDT samples that were positive for xylazine over time, with notable differences by region (**Figure 1**). The monthly percentages of xylazine-positive tests were higher in the East than the West for the entire study period. Percentages of xylazine positivity by region are in eTable 2 in Supplement 1. Xylazine copositivity in the Eastern region ranged from 11.11% to 42.31% during the study period, while xylazine copositivity in the West ranged from 0.00% to 19.86%.

Xylazine positivity increased through the study period for both regions. Between the first and last months of the study period, xylazine detection in the East increased by 8.52 percentage points (from 11.11% to 19.63%) and in the West by 13.46 percentage points (from 0.0% to 13.46%). The percentage of xylazine-positive tests in the East increased sharply 2 separate times, once between March and April 2023 (from 11.11% to 25.42%; 14.30 percentage points) and again between November and December 2024 (from 31.24% to 42.31%; 11.07 percentage points), when it peaked, then dropped each month from December 2024 to March 2025 for a total −21.24–percentage point decrease (from 42.31% to 21.07%).

In the West, xylazine positivity increased gradually and more consistently, and peaked at approximately the same time as the Eastern region. Xylazine positivity increased from 0.00% in March 2023 to 7.90% in May 2024. Between May 2024 and August 2024, xylazine positivity increased 11.96 percentage points, to 19.86%. Xylazine positivity then decreased through March 2025 to 6.43%, until it increased through the remainder of the study period to 13.46% by August 2025.

Concentration

Normalized concentration of xylazine in UDT specimens also showed regional differences and decreasing trends over the study period, with concentrations peaking in both regions early in the study period (**Figure 2**; eTable 3 in Supplement 1). Xylazine concentration was consistently higher in the East (median [IQR], 97.01 [67.07-136.25] ng xylazine per 1 mg creatinine) compared with the West (median [IQR], 29.17 [25.17-39.06] ng xylazine per 1 mg creatinine).

Concentrations in both regions peaked shortly after the study period began, then declined in the remainder of the study period. Xylazine concentration peaked in the Eastern region in April 2023, at 254.79 ng xylazine per 1 mg creatinine, then fell to 114.16 ng xylazine per mg creatinine (change, −140.63 ng xylazine per 1 mg creatinine) by July 2023. In the West, xylazine concentration peaked at 92.92 ng xylazine per 1 mg creatinine in May 2023, then dropped to 23.15 ng xylazine per 1 mg creatinine by July 2023 (change, −69.77 ng xylazine per 1 mg creatinine). The difference in xylazine

Figure 1. Line Graph of Positivity of Xylazine in Urine Drug Testing Samples With Fentanyl by US Region and Month, 2023-2025

Specimens include each patient's first urine drug testing specimen in the study period that was tested for xylazine.

concentration in the first and last months of the study period was −37.76 ng xylazine per 1 mg creatinine in the East (March 2023: 61.77 ng xylazine per 1 mg creatinine; September 2025: 24.00 ng xylazine per 1 mg creatinine), and −7.98 ng xylazine per 1 mg creatinine in the West (April 2024: 28.62 ng xylazine per 1 mg creatinine; September 2025: 20.64 ng xylazine per 1 mg creatinine). Supplemental analyses of state-level xylazine concentration trends are in the eFigure in Supplement 1.

Xylazine Positivity Models

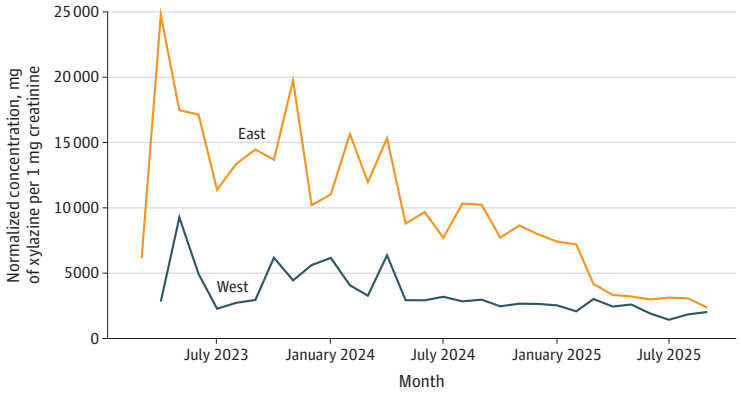
Logistic regression models showed additional differences in xylazine positivity by patient demographics, region, and copositive substances. Unadjusted odds ratios are in eTable 1 in Supplement 1. In adjusted models, odds of xylazine detection were significantly higher in patients aged 36 to 55 years compared with patients aged 18 to 25 years (eg, 36-45: adjusted odds ratio [AOR], 1.21 [95% CI, 1.08-1.35]; $P = .01$) and male patients compared with female patients (AOR, 1.16 [95% CI, 1.09-1.23]; $P = .001$). Odds of xylazine detection were significantly lower in specimens from the West than in the East (AOR, 0.21 [95% CI, 0.19-0.22]; $P < .001$) and in tests requested by behavioral health practitioners (AOR, 0.78 [95% CI, 0.70-0.86]; $P < .001$) and primary care physicians (AOR, 0.81 [95% CI, 0.68-0.95]; $P = .009$) vs tests requested by substance use treatment practitioners.

Adjusted odds of xylazine detection were also significantly higher in specimens that also contained methamphetamine, cocaine, or heroin, with heroin having the highest odds of xylazine positivity (AOR vs no heroin detected, 2.2X [95% CI, 2.07-2.35]; $P < .001$). Odds of xylazine detection also increased with fentanyl concentration. For every 10-fold increase in fentanyl concentration, odds of xylazine detection were 55% higher (AOR, 1.55 [95% CI, 1.53-1.57]; $P < .001$).

Geographic Differences

Models of samples within the East and Western regions showed similarities in odds of xylazine detection, with some specimen characteristics as potential effect modifiers (**Figure 3**). Compared with UDTs negative for methamphetamine, xylazine detection was more likely to be detected in UDTs with methamphetamine and fentanyl in the East (AOR, 1.19 [95% CI, 1.10-1.29]; $P < .001$) and in the West (AOR, 1.76 [95% CI, 1.51-2.05]; $P < .001$). Compared with UDTs negative for heroin, odds of xylazine detection with in tests positive for heroin were almost double in the East (AOR, 2.56 [95% CI, 2.36-2.78]; $P < .001$) compared with the West (AOR, 1.56 [95% CI, 1.39-1.75]; $P < .001$). Odds of xylazine detection with higher concentrations of fentanyl and codetection with cocaine were similar between regions.

Figure 2. Line Graph of Normalized Median Xylazine Concentration in Urine Drug Testing Specimens by US Region, 2023-2025



Specimens include each patient's first urine drug testing specimen in the study period that was tested for xylazine.

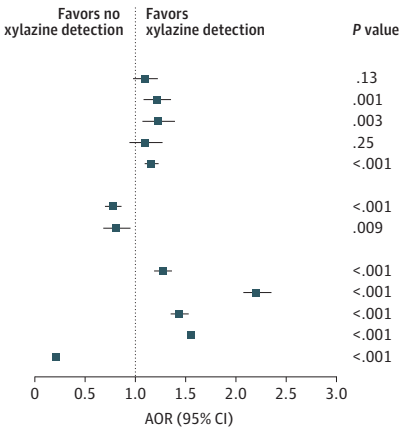
Discussion

In this cross-sectional study, we used a national sample of UDT results from adult patients receiving care in primary care, behavioral health, or substance use treatment settings to describe trends in xylazine exposure and relative xylazine concentration in 2023 to 2025 and by US region. In this sample, the monthly percentage of xylazine-positive samples increased over the study period.

Figure 3. Adjusted Odds Ratios (AORs) of Xylazine Detection in Fentanyl-Positive Urine Drug Samples by Region, Patient Demographics, Treatment Facility Type, and Drug Copositivity

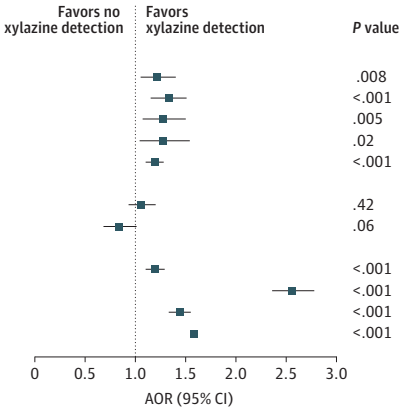
A Full sample

Source	AOR (95% CI)	*P* value
Age, y (vs 18-25)		
26-35	1.09 (0.98-1.22)	.13
36-45	1.21 (1.08-1.35)	.001
46-55	1.22 (1.07-1.39)	.003
≥55	1.09 (0.94-1.27)	.25
Female (vs male)	1.16 (1.09-1.23)	<.001
Requesting clinician type (vs substance use treatment)		
Behavioral health	0.78 (0.70-0.86)	<.001
Primary care physician	0.81 (0.68-0.95)	.009
Additional positive results		
Methamphetamine	1.27 (1.19-1.36)	<.001
Heroin	2.20 (2.07-2.35)	<.001
Cocaine	1.44 (1.35-1.53)	<.001
Log (fentanyl concentration)	1.55 (1.53-1.57)	<.001
West (vs East)	0.21 (0.19-0.22)	<.001



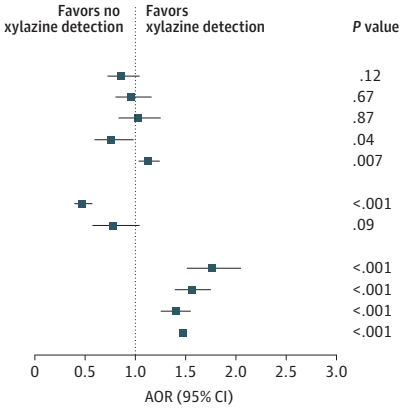
B East

Source	AOR (95% CI)	*P* value
Age, y (vs 18-25)		
26-35	1.21 (1.05-1.40)	.008
36-45	1.33 (1.15-1.54)	<.001
46-55	1.27 (1.07-1.50)	.005
≥55	1.27 (1.04-1.54)	.02
Female (vs male)	1.19 (1.10-1.28)	<.001
Requesting clinician type (vs substance use treatment)		
Behavioral health	1.05 (0.93-1.20)	.42
Primary care physician	0.83 (0.68-1.01)	.06
Additional positive results		
Methamphetamine	1.19 (1.10-1.29)	<.001
Heroin	2.56 (2.36-2.78)	<.001
Cocaine	1.44 (1.33-1.55)	<.001
Log (fentanyl concentration)	1.58 (1.55-1.61)	<.001



C West

Source	AOR (95% CI)	*P* value
Age, y (vs 18-25)		
26-35	0.86 (0.72-1.04)	.12
36-45	0.96 (0.80-1.16)	.67
46-55	1.02 (0.83-1.25)	.87
≥55	0.76 (0.59-0.98)	.04
Female (vs male)	1.13 (1.03-1.24)	.007
Requesting clinician type (vs substance use treatment)		
Behavioral health	0.47 (0.39-0.57)	<.001
Primary care physician	0.77 (0.57-1.04)	.09
Additional positive results		
Methamphetamine	1.76 (1.51-2.05)	<.001
Heroin	1.56 (1.39-1.75)	<.001
Cocaine	1.40 (1.25-1.55)	<.001
Log (fentanyl concentration)	1.47 (1.44-1.51)	<.001



Monthly xylazine concentration in UDT samples peaked early in 2023, then decreased over the study period. We found xylazine detection was highest in the East, but had the greatest net increase in the West. Key findings from this study are that xylazine exposure increased differentially between regions and that concentration declined in the US in the last 2 years of the study period.

There could be several reasons for changes in xylazine detection and concentration. Upstream actors who manufacture or distribute unregulated opioids may have decreased the amount of xylazine in a particular recipe or mix in response to reported negative effects, such as soft tissue wounds and extended sedation.[13,14,36] Additionally, xylazine supply may be constrained, given new state scheduling laws[37] and restrictions from veterinary pharmaceutical companies.[38] More recent increases in medetomidine in the illicit opioid supply suggest that upstream actors have also begun to substitute analogous xylazine substances that are introducing new public health concerns.[39] Understanding market forces that shape the availability and cost of xylazine and other veterinary adulterants, such as medetomidine, is an important topic for further study.

One notable finding was the regional changes in xylazine positivity and concentration by region over time. Xylazine positivity in the East only increased 8.52 percentage points compared with 11.96 percentage points in the West. However, xylazine concentration continued to decline in both regions, suggesting that the mix or cocktail and/or co-use of substances with fentanyl remained largely regional and variable over time. These findings are consistent with a 2025 study of fentanyl samples from Los Angeles, California, in which xylazine detection in fentanyl samples increased between 2023 and 2025, but concentration was relatively low, and samples often contained other substances, such as lidocaine.[40] Future research should continue to study changing concentrations of xylazine and emerging adulterants in fentanyl markets within regional drug supplies over time.

There are multiple implications for clinical and public health practice from our study. First, it is imperative that surveillance data and clinical guidelines about new adulterants are gathered and shared efficiently among public health surveillance systems, people who use drugs, and their health care practitioners to meet the challenge of novel adulterants and the evolving opioid supply. Xylazine has been present in the illicit drug supply since the early 2010s,[9] but it was not widely detected through existing surveillance methods until recently. Clinical guidance to treat xylazine-related health needs has required rapid development with only limited available information about its prevalence and physiological effects.[41]

Second, our study suggests that UDT can viably track the presence and concentration of emerging substances of concern in the illicit drug supply. Unlike existing surveillance systems, such as State Unintentional Drug Overdose Reporting System,[5,42] UDT tracking does not require mortality to identify a potential new substance that may be of concern. A prior study confirmed that UDT data could be used to detect trends in overdose deaths earlier than provisional drug overdose data.[29] Additionally, UDT xylazine detection was consistent with other sources[10] and offered additional insight into patient exposure to substances while actively seeking drug treatment. As suggested in our study, UDT can also be used to approximate xylazine dose of exposure, which is not currently available in any other existing drug surveillance method on a national scale. Future regional and national drug supply monitoring efforts should explore integrating UDT results into regional and national drug supply monitoring as a complement to community drug checking and other drug surveillance data sources.

Limitations

This study has limitations. First, our sample is limited to patients receiving substance use treatment from primary care, behavioral health, or substance use treatment practitioners who use services from Millennium Health. The population of people contributing UDT samples in health care settings is not generalizable to the population of people who use drugs in community settings. Second, xylazine detection and concentrations could vary based on the time a patient last used drugs. Third, this study does not include other emerging substances, namely medetomidine, which may be

replacing xylazine in the drug supply. Medetomidine was not on the analyte panel at Millennium Health at the time of the study, but further investigation of medetomidine detection relative to xylazine detection is warranted.

Conclusions

In this cross-sectional study, we used UDT specimens to understand trends and regional differences in xylazine detection and concentration. Xylazine exposure increased moderately in the East but more substantially in the West, while concentration decreased nationally. There is an urgent need for more robust and immediate information to inform clinical and harm reduction responses to health hazards emerging within the illicit drug supply.[43] This study shows the unique utility of UDT results as part of a comprehensive strategy for monitoring evolving and emerging drug threats.

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REFERENCES

1. Centers for Disease Control and Prevention. Understanding the opioid overdose epidemic. Updated November 1, 2024. Accessed December 3, 2024. https://www.cdc.gov/overdose-prevention/about/understanding-the-opioid-overdose-epidemic.html

2. Alexander RS, Canver BR, Sue KL, Morford KL. Xylazine and overdoses: trends, concerns, and recommendations. *Am J Public Health*. 2022;112(8):1212-1216. doi:10.2105/AJPH.2022.306881

3. Escobar S, MacKinnon NJ, Ambade P, Hoffman Z, Cuadros DF. Spatiotemporal analysis of substance use disorder mortality in the United States: an observational study of emerging hotspots and vulnerable populations (2005-2020). *Lancet Reg Health Am*. 2025;45:101075. doi:10.1016/j.lana.2025.101075

4. Midgette G, Reuter P. The dynamics of US drug markets. 2024. Accessed December 18, 2025. https://www.brookings.edu/wp-content/uploads/2024/11/FP-20241127-drug-markets-midgette-reuter.pdf

5. Kariisa M, O'Donnell J, Kumar S, Mattson CL, Goldberger BA. Illicitly manufactured fentanyl-involved overdose deaths with detected xylazine—United States, January 2019-June 2022. *MMWR Morb Mortal Wkly Rep*. 2023;72(26):721-727. doi:10.15585/mmwr.mm7226a4

6. Ciccarone D. The Donovan Memorial Lecture: 'fentanyl-plus': a new era of fentanyl polydrug combinations in the North American overdose crisis. *J Med Toxicol*. 2026;22(1):49-62. doi:10.1007/s13181-025-01104-6

7. Friedman J, Montero F, Bourgois P, et al. Xylazine spreads across the US: a growing component of the increasingly synthetic and polysubstance overdose crisis. *Drug Alcohol Depend*. 2022;233:109380. doi:10.1016/j.drugalcdep.2022.109380

8. Ruiz-Colón K, Chavez-Arias C, Díaz-Alcalá JE, Martínez MA. Xylazine intoxication in humans and its importance as an emerging adulterant in abused drugs: a comprehensive review of the literature. *Forensic Sci Int*. 2014;240:1-8. doi:10.1016/j.forsciint.2014.03.015

9. Torruella RA. Xylazine (veterinary sedative) use in Puerto Rico. *Subst Abuse Treat Prev Policy*. 2011;6(1):7. doi:10.1186/1747-597X-6-7

10. Drug Enforcement Administration. 2025 National Drug Threat Assessment. Published May 2025. Accessed December 18, 2025. https://www.dea.gov/sites/default/files/2025-07/2025NationalDrugThreatAssessment.pdf

11. Drug Enforcement Administration. Xylazine information. Updated October 30, 2024. Accessed December 10, 2025. https://www.dea.gov/xylazine-information

12. Friedman JR, González Montoya A, Ruiz C, et al. The Detection of xylazine in Tijuana, Mexico: triangulating drug checking and clinical urine testing data. *J Addict Med*. 2026;20(1):22-25. doi:10.1097/ADM.0000000000001474

13. German D, Genberg B, Sugarman O, et al. Reported xylazine exposure highly associated with overdose outcomes in a rapid community assessment among people who inject drugs in Baltimore. *Harm Reduct J*. 2024;21(1):18. doi:10.1186/s12954-024-00940-z

14. Heidari O, Sugarman OK, Winiker AK, et al. Personal experiences with xylazine and behavior change: a qualitative content analysis of Reddit posts. *J Addict Med*. 2025;19(2):135-142. doi:10.1097/ADM.0000000000001383

15. Spadaro A, O'Connor K, Lakamana S, et al. Self-reported Xylazine experiences: a mixed-methods study of Reddit subscribers. *J Addict Med*. 2023;17(6):691-694. doi:10.1097/ADM.0000000000001216

16. Drug Enforcement Administration. The growing threat of xylazine and its mixture with illicit drugs. Published October 2022. Accessed December 10, 2025. https://www.dea.gov/sites/default/files/2022-12/The%20Growing%20Threat%20of%20Xylazine%20and%20its%20Mixture%20with%20Illicit%20Drugs.pdf

17. Sue KL, Hawk K. Clinical considerations for the management of xylazine overdoses and xylazine-related wounds. *Addiction*. 2024;119(4):606-608. doi:10.1111/add.16388

18. Owusu-Antwi P, Atodaria P, Appiah-Kubi E, Shah Z, Garcia EM. Management of xylazine toxicity, overdose, dependence, and withdrawal: a systematic review. *Am J Addict*. 2025;34(6):589-602. doi:10.1111/ajad.70051

19. Johnsen P, Morway GR, Jackson A, et al. The management of upper-extremity xylazine-associated wounds. *J Hand Surg Am*. 2025;50(3):331-339. doi:10.1016/j.jhsa.2024.11.017

20. Lutz L, McFadden R, Xu L, et al. Wound characteristics among patients exposed to xylazine. *JAMA Dermatol*. 2025;161(1):75-80. doi:10.1001/jamadermatol.2024.4253

21. Jawa R, Ismail S, Shang M, et al. Drug use practices and wound care experiences in the age of xylazine adulteration. *Drug Alcohol Depend*. 2024;263:112390. doi:10.1016/j.drugalcdep.2024.112390

22. Department of Public Health: City of Philadelphia. Recommendations for caring for individuals with xylazine-associated wounds. Published January 8, 2024. Accessed December 10, 2025. https://hip.phila.gov/document/4148/Recommendations_for_Caring_for_People_with_Xylazine-Associated_Wounds_1.12.pdf/

23. Leal Lopez A, Tamama K. Xylazine detection in urine of fentanyl-positive patients from a single academic center. *Clin Toxicol (Phila)*. 2025;63(10):706-716. doi:10.1080/15563650.2025.2529016

24. Crews BO. Recent advances in the identification and quantification of xylazine and medetomidine in biological specimens. *Bioanalysis*. 2025;17(20):1295-1303. doi:10.1080/17576180.2025.2572959

25. Millenium Health. Xylazine spreads west in year following emerging threat designation. Published July 2024. Accessed September 20, 2024. https://www.millenniumhealth.com/wp-content/uploads/2024/07/Xylazine-Signals-Alert.pdf

26. Millennium Health. Zeroing in on Xylazine: The First 100 Days after U.S. Emerging Threat Designation. Published 2023. Accessed September 20, 2024. https://resource.millenniumhealth.com/signalsreportxylazine

27. Whitley P, LaRue L, Fernandez SA, Passik SD, Dawson E, Jackson RD. Analysis of urine drug test results from substance use disorder treatment practices and overdose mortality rates, 2013-2020. *JAMA Netw Open*. 2022;5(6):e2215425. doi:10.1001/jamanetworkopen.2022.15425

28. Huhn AS, Whitley P, Bolin BL, Dunn KE. Fentanyl, heroin, methamphetamine, and cocaine analyte concentrations in urine drug testing specimens. *JAMA Netw Open*. 2024;7(10):e2441063. doi:10.1001/jamanetworkopen.2024.41063

29. Myers JV, Marks C, Kim J, et al. Generating timely estimates of overdose deaths for the US using urine drug test data. *JAMA Netw Open*. 2025;8(6):e2514402. doi:10.1001/jamanetworkopen.2025.14402

30. Millennium Health. Drug testing laboratory. Accessed December 19, 2025. https://www.millenniumhealth.com/for-clinicians/our-laboratory/

31. Jarvis M, Williams J, Hurford M, et al. Appropriate Use of Drug Testing in Clinical Addiction Medicine. *J Addict Med*. 2017;11(3):163-173. doi:10.1097/ADM.0000000000000323

32. Lin Y, Farnsworth CW, Azimi V, Liss DB, Mullins ME, Crews BO. Xylazine pharmacokinetics in patients testing positive for fentanyl and xylazine. *Clin Chem*. 2025;71(2):266-273. doi:10.1093/clinchem/hvae163

33. Centers for Disease Control and Prevention. Geographic division or region. Updated July 30, 2024. Accessed April 14, 2026. https://www.cdc.gov/nchs/hus/sources-definitions/geographic-region.htm

34. US Census Bureau. Census regions and divisions of the United States. Accessed April 14, 2026. https://www2.census.gov/geo/pdfs/maps-data/maps/reference/us_regdiv.pdf

35. Centers for Disease Control and Prevention. HIV risk, prevention, and testing behaviors among persons who inject drugs. Published March 31, 2026. Accessed April 15, 2026. https://www.cdc.gov/hiv-data/nhbs/hiv-risk-prevention-testing-pwid.html

36. Sibley AL, Miller CW, Joniak-Grant E, et al. A brick to a bundle: a qualitative study of behavioral responses to xylazine adulteration. *Int J Drug Policy*. 2025;145:105017. doi:10.1016/j.drugpo.2025.105017

37. Sugarman OK, Shah H, Whaley S, McCourt A, Saloner B, Bandara S. A content analysis of legal policy responses to xylazine in the illicit drug supply in the United States. *Int J Drug Policy*. 2024;129:104472. doi:10.1016/j.drugpo.2024.104472

38. Avilucea I. New drug emerges in Philly's drug supply as xylazine use falls. *Axios*. April 3, 2025. Accessed December 18, 2025. https://www.axios.com/local/philadelphia/2025/04/03/xylazine-decline-new-drug-philly-medetomidine

39. Huo S, Perrone J. The shifting landscape of a fentanyl adulterant: moving from xylazine to medetomidine. *J Addict Med*. Published online September 24, 2025. doi:10.1097/ADM.0000000000001592

40. Friedman J, Molina CA, Koncsol AJ, et al. Xylazine prevalence and concentration in the Los Angeles fentanyl market, 2023-2025. *Drug Alcohol Depend Rep*. 2025;16:100364. doi:10.1016/j.dadr.2025.100364

41. Gupta R, Holtgrave DR, Ashburn MA. Xylazine—medical and public health imperatives. *N Engl J Med*. 2023;388(24):2209-2212. doi:10.1056/NEJMp2303120

42. Centers for Disease Control and Prevention. SUDORS Dashboard: fatal drug overdose data. Updated December 3, 2025. Accessed December 10, 2025. https://www.cdc.gov/overdose-prevention/data-research/facts-stats/sudors-dashboard-fatal-overdose-data.html

43. Ashburn MA, Holtgrave DR, Baum RJ, Gupta R. Establishing an approach for designation of evolving and emerging drug threats. *Health Secur*. 2023;21(3):239-241. doi:10.1089/hs.2022.0150

SUPPLEMENT 1.

eTable 1. Unadjusted odds ratios of fentanyl-xylazine co-positivity

eTable 2. Percent of xylazine positivity in fentanyl-positive urine drug tests by U.S. region, March 2023-September 2025

eFigure. Monthly mean xylazine concentration in urine drug testing samples that were positive for xylazine and fentanyl in nine select states

eTable 3. Median normalized xylazine concentration (mg xylazine/ng creatinine) in urine drug samples in the U.S. by region, March 2023-September 2025

SUPPLEMENT 2.

Data Sharing Statement