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Short communication

Manifestations of potential xylazine withdrawal: A retrospective cohort study with nested case series

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ABSTRACT

Purpose: The alpha$_2$-agonist xylazine is an increasingly common adulterant of illicitly manufactured fentanyl. A potential xylazine withdrawal syndrome (XWS) is poorly characterized. We assessed for XWS.
Methods: We conducted a retrospective cohort study of all hospitalized patients with urine GC-MS xylazine testing performed at three academic hospitals in Philadelphia, PA from 3/2022–2/2023. We used linear and logistic regression to compare peak systolic blood pressure, peak heart rate, and intensive care unit (ICU) admissions for patients with vs. without xylazine detected. Additionally, addiction specialist physicians assessed for candidate signs and symptoms of XWS (otherwise unexplained agitation, elevated blood pressure or heart rate, diaphoresis, tremor) using chart review.
Results: Of 121 xylazine tests, each among unique patients (mean age 44.6 years, 33.1 % female), 73 (60 %) were positive. Xylazine detection was not associated with differences in peak systolic blood pressure or heart rate, but was associated with lower odds of ICU admission (aOR 0.24, 95 % CI 0.09–0.60). Among 73 patients with xylazine detected, chart review determined 54 (74.0 %) did not have candidate signs of XWS, 12 (16.4 %) were indeterminate, and 5 (6.8 %) were excluded due to severe critical illness. Two patients (2.7 %) had otherwise unexplained blood pressure and heart rate elevation consistent with possible XWS. Co-occurring opioid, benzodiazepine, and alcohol withdrawal were common.
Conclusions: In a cohort of hospitalized patients, there was no association between xylazine detection and vital sign instability, xylazine detection was associated with lower ICU admission rate, and chart review did not detect distinct signs or symptoms of XWS.

1. Introduction

The alpha$_2$-agonist xylazine has emerged as a common adulterant in nonpharmaceutical opioid supplies across North America (Bowles et al., 2021; Kariisa et al., 2023). As xylazine detection has increased, clinicians and public health officials have raised concern about the possibility of physiologic dependence with a resulting xylazine withdrawal syndrome (XWS) (Ehrman-Dupre et al., 2022; Bettigole et al., 2022).

Xylazine is a potent alpha$_2$-adrenergic agonist that reduces norepinephrine and dopamine release in the central nervous system, resulting in sedation, muscle relaxation, and analgesia (D'Orazio et al., 2023a). Abrupt cession of the alpha$_2$-agonists clonidine and dexmedetomidine can lead to a withdrawal syndrome characterized by sympathetic hyperactivity (Glaess et al., 2020; Whelan et al., 2015; Pathan et al., 2021; Houston, 1981). In this context, some clinicians have suggested that xylazine withdrawal might involve elevations in blood pressure and

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heart rate (Ehrman-Dupre et al., 2022; Bettigole et al., 2022). People exposed to xylazine have described anxiety, depressed moods, and body aches during early abstinence, (Spadaro et al., 2022; Reed et al., 2022) and a case report attributed severe anxiety, restlessness, rigors, and dysphoria to possible XWS in a woman who required intensive care unit (ICU) management (Ehrman-Dupre et al., 2022). However, the incidence and clinical features of a potential XWS remain unclear (Perrone et al., 2024). Xylazine is almost always detected alongside fentanyl, and elevations in blood pressure, heart rate, anxiety, myalgias, and restlessness are also components of opioid withdrawal (Dunn and Strain, 2024).

The goal of this study was to identify and characterize the clinical features of a possible XWS to inform clinical management and care delivery. We used a retrospective cohort approach to compare systolic blood pressure, heart rate, and hospitalization outcomes among hospitalized patients with urine xylazine detected versus not detected. We paired this with chart review to assess for other potential signs or symptoms of a XWS.

2. Methods

2.1. Setting

This study included patients at three academic hospitals in Philadelphia from March 2022 to February 2023. During the study period, 98 % of opioids sampled by the Philadelphia Department of Public Health for community drug testing that contained fentanyl also contained xylazine, with average xylazine purity (percent xylazine by weight) of 34 % (range 0–65 %) (CFSRE, 2022, 2023). At study hospitals, opioid withdrawal was typically treated with a combination of methadone, clonidine, non-opioid adjuvants, and short-acting opioids (Thakrar, 2023). Urine xylazine was not included in standard urine toxicology testing but was ordered based on clinician discretion during routine clinical care, often alongside other urine drug testing. A University of Pennsylvania Institutional Review Board approved this study with a waiver of informed consent. We followed the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) reporting guidelines (von Elm et al., 2007) and guidelines for conducting case series (Kempen, 2011).

2.2. Study Participants

The study population comprised all ED or hospitalized adult patients who had xylazine testing performed during the study period with urine specimen collected within 48 hours of hospital presentation. A cut-off time of 48 hours was chosen because early work at the time suggested the detection time for xylazine in urine is less than two days from last use (Bird et al., 2025; Lin et al., 2024). More recent evidence in humans has found the median terminal half-life of xylazine in humans to be approximately 12 hours (range, 6–21 hours) (Lin et al., 2024) with mean predicted detection time 43.1 hours (range, 13.8–122.0) (Bird et al., 2025).

2.3. Measures

The exposure of interest was recent xylazine use, assessed using an in-house urine gas chromatography-mass spectrometry (GC-MS) assay with a lower limit of detection of 200 ng/ML.

The primary vital sign outcome was peak systolic blood pressure within the first 48 hours of hospitalization or by time of discharge, whichever occurred first. We chose systolic blood pressure because of reports of elevated systolic blood pressure in patients who abruptly stop clonidine therapy for hypertension (Reid et al., 1977). The 48-hour time frame was chosen because xylazine onset and elimination in animals occurs within minutes to hours (D'Orazio et al., 2023b) and because this time period captures onset of symptoms from withdrawal from other alpha$_2$ agonists in humans (Ram and Engelman, 1979; Flieller et al., 2019). A secondary vital sign outcome was peak heart rate in the same time period.

Hospital disposition outcomes included admission to an ICU, discharge from the ED (versus observation or hospital admission), and before medically advised (otherwise known as against medical advice) discharge.

2.4. Statistical analyses

We used unadjusted and adjusted linear regression for continuous outcomes and logistic regression for dichotomous outcomes. Covariates were chosen *a priori* based on prior research or clinical judgment suggesting they were confounders and were limited to those deemed most important to avoid overfitting. Linear regression models for vital sign outcomes adjusted for age, sex, Charlson comorbidity index, presence of either serum ethanol or urine benzodiazepines on toxicology testing, receipt of naloxone, receipt of clonidine, and admission to an ICU. Logistic regression for hospital disposition outcomes adjusted for age, sex, Charlson comorbidity index, presence of a serious injection-related infection (determined via diagnosis codes, see eTables 1 and 2), and hospital. We used Stata v16.0 (StataCorp LP) and two-sided statistical tests with a significance level of $P < 0.05$.

As sensitivity analyses, (1) we restricted our analytic sample to patients hospitalized for at least 48 hours, since onset of XWS might take up to 48 hours from last use and might not be detected in patients who left earlier; (2) we compared change in systolic blood pressure and heart rate from initial measurement to peak in the first 48 hours of hospitalization; and (3) we limited analyses only to patients with fentanyl or norfentanyl detected on urine drug testing.

2.5. Chart review

We paired the retrospective cohort analysis with chart review of xylazine positive cases (n = 73) to identify other potential characteristics of XWS.

Four addiction specialist physicians (APT, ML, JP, and SZ) developed a structured codebook and standardized chart abstraction tool to extract data from the electronic health record (EHR; Epic Systems Corporation) into a secure web platform (REDCap v12.5.4). After initial development, the four authors independently piloted the instrument on three cases, met to refine the instrument, then split the remaining cases for independent review with double coding.

Candidate signs and symptoms of XWS were based on prior literature (Ehrman-Dupre et al., 2022; Spadaro et al., 2022) and included: subjective reports or clinician-observed anxiety or agitation, systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg, heart rate > 90 BPM, diaphoresis, or tremor. After reviewing vital signs, laboratory results, the medication administration record, standardized withdrawal assessments, and all clinical notes, abstractors recorded the presence of any candidate XWS signs and symptoms along with other withdrawal syndromes or relevant conditions. Last, abstractors made a final assessment about a potential XWS syndrome by characterizing each case as: (1) expected clinical course (any candidate XWS signs and symptoms present fully explained by other conditions), (2) indeterminate for XWS (administered medications could have masked or other conditions may have caused candidate XWS signs and symptoms), or (3) potential XWS (otherwise unexplained candidate signs & symptoms of XWS).

Charts with disagreement by double-coding on the final assessment (n = 15, 21 %) were coded by a third assessor blinded to initial assessments. The final determination was made based on agreement from two reviewers.

3. Results

There were 128 hospitalizations with urine xylazine testing performed, each from a unique patient. Seven patients were excluded due to urine specimens collected more than 48 hours after presenting to the ED, none of whom had xylazine detected. In the final cohort of 121 patients, mean age was 44.2 years (SD 1.1); 34 % were female; 31 % self-identified as non-Hispanic Black, 59 % as non-Hispanic White, and 4 % as Hispanic; and 60 % had xylazine detected (Table 1). Among patients with xylazine detected, 96 % had fentanyl and/or norfentanyl detected in urine.

Table 1
Patient Characteristics.

	No. (%)		
	All	**Xylazine Not Detected**	**Xylazine Detected**
Patient characteristics	*n = 121*	*n = 48 (39.7)*	*n = 73 (60.3)*
Age, mean (SD)	44.6 (1.1)	51.0 (2.1)	40.4 (1.1)
Female	40 (33.1)	14 (29.2)	26 (35.6)
Race/Ethnicity			
Black (non-Hispanic or Latino)	37 (30.5)	24 (50.0)	13 (17.8)
White (non-Hispanic or Latino)	69 (57.0)	20 (41.7)	49 (67.1)
Other (non-Hispanic or Latino)	9 (7.4)	3 (6.3)	6 (8.2)
Hispanic or Latino ethnicity	5 (4.1)	4 (8.3)	4 (5.5)
Missing	1 (0.8)	1 (2.1)	1 (1.4)
Health insurance			
Medicaid	91 (75.2)	33 (68.8)	58 (79.5)
Medicare	12 (9.9)	10 (20.8)	2 (2.7)
Private	14 (11.6)	4 (8.3)	10 (13.7)
Uninsured	4 (3.3)	1 (2.1)	3 (4.1)
ED visit in study health system in prior 30 days	30 (24.8)	10 (20.8)	20 (27.4)
Charlson Comorbidity Index	1.3 (2.1)	1.7 (2.4)	0.9 (1.9)
Time from ED arrival to urine collection, hours	9.3 (10.2)	10.8 (11.8)	8.2 (9.0)
Other drugs detected*			
Fentanyl and/or norfentanyl (urine)	102 (84.3)	32 (66.7)	70 (95.9)
Methadone or buprenorphine (urine)	16 (13.2)	2 (4.2)	14 (20.5)
Other opioids** (urine)	42 (34.7)	12 (25.0)	30 (41.1)
Benzodiazepines (urine)	54 (44.6)	18 (37.5)	36 (49.3)
Amphetamines (urine)	23 (19.0)	11 (22.9)	12 (16.4)
Cocaine (urine)	5 (4.1)	3 (6.3)	2 (2.7)
Alcohol (urine or serum)	11 (9.1)	8 (16.7)	3 (4.1)
Received naloxone by EMS or in the ED	13 (10.7)	7 (14.6)	6 (8.2)
Received clonidine	51 (42.1)	12 (25.0)	39 (53.4)
ICU admission	39 (32.2)	24 (50.0)	15 (20.5)
Serious injection-related infection	13 (10.7)	3 (6.3)	10 (27.4)
Hospital			
Hospital A	35 (28.9)	11 (22.9)	24 (32.9)
Hospital B	82 (67.8)	36 (75.0)	46 (63.0)
Hospital C	4 (3.3)	1 (2.1)	3 (4.1)

* Non-exclusive categories
** Includes oxycodone, codeine, hydrocodone, dihydrocodeine, hydromorphone, morphine, acetylmorphine, oxymorphone, and tramadol

3.1. Vital signs

In unadjusted and fully adjusted models, there was no detected association between urine xylazine and peak systolic blood pressure or peak heart rate (Table 2). There was also no detected difference between xylazine detection and elevated heart rate or blood pressure in adjusted models from the three sensitivity analyses (eTables 2–4). These sensitivity analyses restricted to hospitalizations lasting at least 48 hours, examined change in systolic blood pressure and heart rate between initial and peak readings, and limited the sample to the subset of patients with fentanyl or norfentanyl detected in urine.

3.2. Hospital disposition

Xylazine in urine was associated with lower odds of ICU admission in both unadjusted (OR 0.26, 95 % CI 0.12–0.58) and adjusted models (aOR 0.24, 95 % CI 0.09–0.60) (Table 2). There was no association found in adjusted analyses between xylazine and discharge from the ED or before medically advised discharge.

3.3. Clinical course of withdrawal for patients with xylazine detected in urine

Candidate signs and symptoms of a potential XWS were observed frequently among the 73 patients with xylazine detected, including elevated blood pressure and heart rates, anxiety or restlessness, diaphoresis, or tremor (eTable 2). However, reviewers frequently attributed these signs to other causes.

Fifty-four patients (74.0 %) had an expected clinical course without distinct features of a potential XWS (eFigure). Of these, 31 showed typical signs and symptoms of opioid withdrawal without unrelated or unexpectedly severe symptoms, 15 had concurrent benzodiazepine or alcohol withdrawal with opioid withdrawal, and 8 had no withdrawal documented in the EHR.

Among the 73 patients with xylazine detected, 12 (16.4 %) had a clinical course indeterminate for potential XWS in the context of co-occurring conditions. Five had mild, asymptomatic, isolated blood pressure elevation and four had anxiety and restlessness despite some opioid withdrawal treatment; three had agitated delirium after recent use of stimulants or synthetic cannabinoids.

Two of 73 patients (2.7 %) were deemed to have a clinical course suggestive of possible XWS. The first was a woman with fentanyl, xylazine, and cocaine detected in urine who was admitted for osteomyelitis of a finger; she developed asymptomatic blood pressure elevation and tachycardia without other objective signs of opioid withdrawal. The second was a woman with a history of supra-ventricular tachycardia, OUD, and prior benzodiazepine use disorder who denied recent benzodiazepine use and who was admitted for xylazine-associated wounds; she developed tachycardia with mild asymptomatic blood pressure elevation in the context of mild opioid and/or benzodiazepine withdrawal. See eFigure for additional details.

Five patients could not be assessed for XWS because of critical illness requiring mechanical ventilation and/or sedation. No patients required ICU admission specifically for withdrawal management.

4. Discussion

In a cohort of hospitalized patients with urine testing performed for xylazine, there was no detected association between xylazine detection and subsequent systolic blood pressure elevation or tachycardia, but xylazine detection was associated with a lower rate of ICU admission. Among patients with xylazine detected, chart review by addiction specialist physicians was unable to identify distinct signs of XWS in most patients. This is among the first studies to compare vital signs and hospital outcomes between patients with and without xylazine and to assess for potential XWS in a cohort with confirmed xylazine exposure.

Table 2
Vital sign & hospital disposition outcomes, by urine xylazine result.

	Peak systolic blood pressure & heart rate in the first 48 h of admission (or by discharge, if sooner)								
	Systolic blood pressure, mmHg			Heart rate, beats per minute					
	Mean (SD)	Unadjusted mean difference (95 % CI)	Adjusted mean difference (95 % CI)*	Mean (SD)	Unadjusted mean difference (95 % CI)	Adjusted mean difference (95 % CI)*			
Xylazine									
Not detected (n = 48)	163.1 (27.2)	ref.	ref.	92.9 (9.8)	ref.	ref.			
Detected (n = 73)	152.7 (22.5)	−10.4 (−19.4, −1.4)	−1.2 (−10.6, 8.2)	88.1 (15.6)	−4.8 (−9.8, 0.2)	−5.3 (−11.0, 0.5)			
	Hospital disposition outcomes								
	Admission to an ICU			**Discharged from the ED**			**Discharged before medically advised**		
	n (%)	OR (95 % CI)	aOR (95 % CI)**	n (%)	OR (95 % CI)	aOR (95 % CI)**	n (%)	OR (95 % CI)	aOR (95 % CI)**
Xylazine									
Not detected (n = 48)	24 (50.0)	ref.	ref.	11 (22.9)	ref.	ref.	9 (18.8)	ref.	ref.
Detected (n = 73)	15 (20.5)	0.26 (0.12, 0.58)	0.24 (0.09, 0.60)	22 (30.1)	1.45 (0.63, 3.36)	1.89 (0.65, 5.47)	26 (35.6)	2.40 (1.01, 5.71)	1.87 (0.71, 4.90)

* Models adjusted for age, sex, Charlson comorbidity index, the presence of alcohol or benzodiazepines on toxicology testing, receipt of naloxone, receipt of clonidine, and admission to an intensive care unit

** Models adjusted for age, sex, Charlson comorbidity index, presence of a serious injection-related infection, and study hospital

Together, the absence of an association between xylazine and blood pressure or heart rate elevation, along with the finding that patients with xylazine had lower odds of ICU admission, suggest that management of fentanyl-xylazine withdrawal likely does not require an ICU. The lower rate of ICU admission among patients with xylazine detected could reflect attenuation of opioid withdrawal due to the presence of xylazine (Sadek et al., 2024). Alternatively, it could be attributed to bias in testing if ICU patients were more likely to have xylazine testing ordered or unmeasured confounding. Regardless, the absence of clinically significant adrenergic hyperactivity in this cohort might inform resource allocation as xylazine detection increases.

Chart review did not identify other signs or symptoms of XWS among patients with confirmed xylazine exposure. We offer three potential explanations for this null finding. First, it may reflect the challenge of distinguishing xylazine withdrawal from co-occurring fentanyl, benzodiazepine, or alcohol withdrawal syndromes (Thakrar, 2023; Englander et al., 2024; Thakrar and Kleinman, 2022). Second, XWS may predominantly feature subjective symptoms like anxiety that are not well-characterized with chart review (Spadaro et al., 2023). Third, xylazine may not lead to physiologic dependence with a resulting withdrawal syndrome. Ultimately, whether individual symptoms are caused by fentanyl or xylazine, clinical experience suggests that patients using fentanyl-xylazine might benefit from early, multimodal withdrawal management (London et al., 2024).

Strengths of this study include the use of GC-MS xylazine testing and its setting in Philadelphia, where chronic xylazine exposure is common. This study also has several limitations. First, it was a retrospective study that relied on documentation during routine clinical care; this could have introduced bias in who had xylazine testing ordered, inaccuracies in withdrawal assessments, and/or inconsistencies in documentation. Second, we identified candidate XWS signs based on published reports; there may be clinical manifestations we missed. Third, this study could have been underpowered to detect differences in blood pressure or heart rate. Fourth, chart review did not examine patients without xylazine detected. Fifth, xylazine testing was performed using a qualitative approach, so we could not assess for differences by urine xylazine concentration. Last, this study did not include a qualitative assessment of patient experiences withdrawing from fentanyl-xylazine.

5. Conclusions

In a cohort of ED and hospitalized patients, there was no association between xylazine detection and elevations in systolic blood pressure or heart rate. Xylazine detection was associated with lower odds of ICU admission. Although signs and symptoms of potential XWS were common, chart reviewers could not distinguish these from other co-occurring withdrawal syndromes.

Contributors

Study concept and design: AT, JP, ML. Acquisition of the data: AT, MHD, RB, NR, LX. Analysis and interpretation of the data: AT, SZ, PC, JP, ML. Drafting of the manuscript: AT. Critical revision of the manuscript for important intellectual content: SZ, PC, AS, MHD, RB, NR, LX, JP, ML.

CRediT authorship contribution statement

Bhatia Ranvir: Investigation, Data curation. **Davis M Holliday:** Writing – review & editing, Investigation, Data curation. **Xu Lin:** Investigation, Data curation. **Rohacs Natasa:** Investigation, Data curation. **Lowenstein Margaret:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Perrone Jeanmarie:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Thakrar Ashish Prakash:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Christine Paul J.:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Zwiebel Samantha J.:** Writing – review & editing, Methodology, Investigation, Formal analysis, Conceptualization. **Spadaro Anthony:** Writing – review & editing, Conceptualization.

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Conflict of Interest

No conflicts declared.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2025.112681.

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