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Decreased Effectiveness of a Novel Opioid Withdrawal Protocol Following the Emergence of Medetomidine as a Fentanyl Adulterant

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Abstract: Background: Philadelphia has experienced a surge in illicit fentanyl adulterated with alpha-2 agonist sedatives. Initially, xylazine ("tranq") was the predominant adulterant, and a novel multimodal withdrawal protocol was effective at mitigating symptoms. However, since mid-2024, medetomidine—a more potent sedative—has largely supplanted xylazine. Clinicians have reported more severe, treatment-resistant opioid withdrawal during this transition. **Objectives**: To assess whether the previously effective withdrawal management protocol retained efficacy after the emergence of medetomidine as the primary fentanyl adulterant. **Methods**: We conducted a retrospective cohort study of patients receiving protocol-based opioid withdrawal treatment at two emergency departments in Philadelphia between September 2022 and March 2025. Patients were divided into the xylazine era (Sept 2022–July 2024) and medetomidine era (Aug 2024–Mar 2025). The primary outcome was change in Clinical Opioid Withdrawal Scale (COWS) score from pre- to post-treatment. Secondary outcomes included rates of discharge against medical advice (AMA) and ICU admission as well as the impact of a revised treatment protocol. **Results**: Among 1269 encounters with full data, 616 occurred during the xylazine era and 653 during the medetomidine era. Median COWS reduction was greater in the xylazine group (−9.0 vs −4.0 points, $p < 0.001$), with more patients achieving symptom relief (COWS ≤ 4: 65.6% vs 14.2%, $p < 0.001$). ICU admission occurred in 8.5% of xylazine-era patients and 16.8% of medetomidine-era patients ($p < 0.001$). Rates of AMA were higher during the medetomidine era as well (6.5% vs 3.6%) ($p=0.038$). Revision of treatment protocols showed promise. **Conclusions**: The protocol was significantly less effective during the medetomidine era, though a protocol change may be helping. Findings highlight the need to adapt withdrawal treatment protocols in response to changes in the illicit drug supply.

Keywords: opioid withdrawal; xylazine; medetomidine; OUD; fentanyl; adulterant; Philadelphia; Tranq Dope; Demon Dope

1. Introduction

Philadelphia remains at the leading edge of the opioid crisis, with high rates of fentanyl use and associated morbidity. In recent years, the local illicit opioid supply has been increasingly adulterated with potent sedatives, intensifying the clinical challenges associated with withdrawal management. [1] Xylazine—a veterinary alpha-2 adrenergic agonist—emerged in 2022 as a frequent fentanyl adulterant, becoming present in up to 99% of the publicly checked dope samples by 2023.[2] The combination of potent synthetic opioids and alpha-2 agonists wrought a series of challenges, including increasing reports of precipitated withdrawal, a serious and previously rare side effect when starting the medication buprenorphine. [3] This promoted the creation of emergency department (ED) protocols specifically tailored to manage the resulting complex withdrawal syndrome. [4]

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A multimodal opioid withdrawal treatment protocol was implemented at two Philadelphia EDs to address xylazine-associated withdrawal. This approach used multiple pharmacologic classes targeting distinct symptom domains: short-acting opioids (e.g., oxycodone, hydromorphone) for opioid cravings and bridging to partial agonists (low dose buprenorphine), ketamine for NMDA antagonism and analgesia, droperidol or olanzapine for anxiolytic and antiemetic effects, and alpha-2 agonists (tizanidine or guanfacine) for replacement the xylazine. In an early evaluation, the protocol produced a median COWS score reduction from 12 to 4, with only 3.9% of patients leaving AMA compared to a 10.7% historical baseline [4].

In mid-2024, toxicology surveillance and clinical observations indicated a shift in adulterants, with medetomidine supplanting xylazine as the dominant alpha-2 agonist in the local fentanyl supply [5]. Medetomidine, an alpha-2 agonist sedative up to 20 times more potent than xylazine [6,7], entered the fray, possibly as a result of the scheduling of xylazine as a controlled substance by the Commonwealth of Pennsylvania. [8] Clinicians noted increasingly severe and atypical withdrawal symptoms, including profound vomiting, hypertensive crises, tremor without clonus or seizure, hypoactive encephalopathy, and refractory symptoms to conventional treatment. These presentations often required ICU care and were poorly responsive to the previously successful xylazine-era protocol. Clinicians hypothesized that medetomidine-related withdrawal could mimic dexmedetomidine discontinuation syndrome, a well-documented phenomenon of sympathetic overactivity.[9]

This study evaluated whether the novel opioid withdrawal protocol maintained effectiveness during and after the transition from the xylazine era (XE) to the medetomidine era (ME) in Philadelphia. We compared outcomes from the xylazine and medetomidine eras, hypothesizing a significant decline in treatment efficacy and increased rates of severe clinical outcomes following the emergence of medetomidine.

2. Materials and Methods

2.1. Study Design and Setting

We conducted a retrospective cohort study at two urban EDs in Philadelphia, Pennsylvania, one academic and one community. The academic hospital, which sees approximately 76,000 visits annually, is a level 1 trauma center. The community hospital, which sees approximately 34,000 visits annually, is a stand-alone center 2.5 miles from the main hospital. Both sites serve large urban populations and care for a high volume of patients with opioid use disorder (OUD). Both hospitals were clinical sites for the retrospective analysis establishing evidence of order set efficacy, with the orders built into the electronic health record (EPIC Systems, Madison, WI). [4]

The study protocol adhered to STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for observational research, utilizing the guidelines prior to the development of the project. Institutional Review Board approval was obtained (IRB #1269), with a waiver of informed consent due to the retrospective nature and negligible risk of the study.

Two temporal cohorts were defined using August 1, 2024, as a transition point based on public health data identifying a shift from xylazine to medetomidine as the dominant fentanyl adulterant [5]. The xylazine-era cohort included encounters from September 1, 2022, when the order set debuted, to July 31, 2024. The medetomidine-era cohort included encounters from August 1, 2024, to March 31, 2025.

On February 11, 2025, in response to local trends, the order sets were updated to address medetomidine adulteration. Doses of short acting opioids were doubled (oxycodone 10 mg > 20 mg, hydromorphone 2mg > 4 mg) and clonidine was added due to the rates of hypertensive crises (0.3 mg orally and 0.3 mg transdermal). Education about this change was made to staff during the standing faculty meeting and resident didactics as well as through virtual/asynchronous communication. While this period still represents part of the ME, given this defined change, it was analyzed both wholly and as a subgroup.

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2.2. Population

This study included adult patients (≥18 years) treated in the ED, who received medications from the withdrawal protocol during the study period (September 1, 2022 – March 31, 2025). This represents the total cohort and includes all patients who were present on the database report.

The final cohort, are those from the total who had both pre- and post-treatment COWS scores and a disposition documented in their charts. Exclusion criteria included missing outcome data, pregnancy, and active enrollment in methadone or buprenorphine maintenance therapy.

Detection of xylazine and medetomidine exposure in humans is difficult and not performed routinely. Due to the conjoined nature of opioids and alpha-2 agonists in Philadelphia, fentanyl urine toxicology testing is used as a marker of street "dope" exposure. Adulterant classification was therefore based on temporal trends rather than individual toxicology testing, which was unavailable in the ED setting, aside from fentanyl testing.

2.3. Exposure Classification

Era classification was based on date of presentation and the predominant local adulterant as identified through citywide drug surveillance. Xylazine predominated before August 1, 2024, while medetomidine became the dominant adulterant thereafter. A subgroup analysis of patients treated after a protocol revision on February 11, 2025, was also performed.

2.4. Outcomes

The primary outcome was change in Clinical Opioid Withdrawal Scale (COWS) score from pre- to post-treatment. COWS is a multi-item scale used as the standardized means of assessing withdrawal severity in the United States. [10] Notably, there are not standardized withdrawal severity tools for alpha-2 agonist withdrawal. [11] In their absence, given that anxiety, and vital sign abnormalities are included in COWS, this was used as the sole criterion for fentanyl, xylazine and medetomidine withdrawal. Secondary outcomes included: (1) percentage of patients with COWS ≤ 4 post-treatment (which signifies no longer classifying as having withdrawal); (2) disposition from the ED, including AMA discharge, hospital admission, and ICU transfer; and (3) occurrence of serious adverse events during ED care.

The primary outcome was change in COWS score from pre-treatment to post-treatment. Secondary outcomes included the percentage of patients with post-treatment COWS scores ≤4 (defined as symptom resolution), ED disposition (including discharge, AMA, and ICU admission).

2.5. Measurements and Analysis

Data for this study was obtained by an automated database report. This report contains visit demographics, chief complaint and diagnostic data (urine fentanyl screen results), pre- and post-treatment COWS scores and disposition data.

Statistical analysis was performed using R statistical software (R Core Team, 2023). Descriptive statistics were calculated utilizing demographic information documented in the codebook including standard deviations for non-parametric data.

Continuous variables were summarized as medians with interquartile ranges and compared using Mann–Whitney U and Wilcoxon signed-rank tests. Categorical variables were reported as frequencies and compared using chi-square tests. A two-sided p-value < 0.05 was considered statistically significant. Monthly COWS trends and responder rates were graphed with key inflection points noted.

3. Results

3.1. Patient Characteristics

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A total of 1269 patient encounters met inclusion criteria, out of 1980 total encounters having received medications from the protocol during the period. Of the final cohort, 616 encounters were in the xylazine-era cohort (September 2022 – July 2024) and 653 in the medetomidine-era cohort (August 2024 – March 2025). The two cohorts were similar in demographic makeup both in their total and final cohort forms. The mean age was 39.8 years in the XE and 40.8 years in the medetomidine era, which was statistically but not practically different. Over 35% of patients in the xylazine cohort and 36.0% in the medetomidine cohort were female. Full demographics data, including race/ethnicity is included in Table 1. Aside from age, no other demographic categories were different between cohorts.

Table 1. Demographic Characteristics by Era and Cohort.

Characteristic	Xylazine Era (Total, N=1160)	Medetomidine Era (Total, N=820)	Xylazine Era (Final, N=616)	Medetomidine Era (Final, N=653)	p-value (Total, Final)
Age, mean ± SD	39.8 ± 9.2	40.8 ± 9.7	39.5 ± 9.2	40.9 ± 10.1	p=0.024, p=0.008
Female, n (%)	408 (35.2%)	295 (36.0%)	212 (34.4%)	239 (36.6%)	p=0.749, p=0.477
Male, n (%)	752 (64.8%)	525 (64.0%)	404 (65.6%)	414 (63.4%)	
White or Caucasian, n (%)	885 (76.3%)	638 (77.8%)	464 (75.3%)	507 (77.6%)	p=0.464, p=0.292
Black or African American, n (%)	122 (10.5%)	97 (11.8%)	69 (11.2%)	71 (10.9%)	p=0.399, p=0.715
Hispanic/Latino, n (%)	0 (0.0%)	0 (0.0%)	65 (10.6%)	49 (7.5%)	
Two or More Races, n (%)	13 (1.1%)	4 (0.5%)	6 (1.0%)	4 (0.6%)	p=0.209, p=0.556
Asian, n (%)	3 (0.3%)	2 (0.2%)	1 (0.2%)	2 (0.3%)	
American Indian or Alaska Native, n (%)	3 (0.3%)	1 (0.1%)	2 (0.3%)	1 (0.2%)	p=0.874, p=1.000
Other / Unknown, n (%)	0 (0.0%)	0 (0.0%)	8 (1.3%)	18 (2.8%)	
Positive Urine Fentanyl Screen, n (%)	893 (97.0%)	668 (98.4%)	515 (96.6%)	548 (98.4%)	p=0.098
Missing Urine Fentanyl Screen	239 (20.6%)	141 (17.2%)	83 (13.5%)	96 (14.7%)	

Notably, xylazine is well known to be associated with severe skin ulceration and eventual infection. [11] The chief complaints of all presentations are shown in Table 2. They have been simplified for categorization sake, please see Appendix A for a full list of chief complaints and which categories they were placed. It is therefore quite telling that rates of visit for skin and soft tissue visit fell from 32.1% to 15.2% ($p < 0.001$) between the eras and that volume was made up for with a commensurate rise in visits purely for opioid withdrawal (10.5% to 25.6%, $p < 0.001$).

Table 2. Chief Complaints of Presentations between the Xylazine and Medetomidine eras.

Chief Complaint Category	Xylazine Era (n)	Xylazine Era (%)	Medetomidine Era (n)	Medetomidine Era (%)	p-value
General Medical/Other	603	52.0%	440	53.7%	0.490
Skin/Soft Tissue Infection	372	32.1%	125	15.2%	< 0.001
Opioid Withdrawal	122	10.5%	210	25.6%	< 0.001

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Trauma	63	5.4%	45	5.5%	1.000

Note: p-values reflect chi-square comparisons of category frequency by era. Categories were formed based on clinical similarity.

At presentation, median initial COWS scores were higher in the medetomidine cohort (16.0, IQR 12–20) than in the xylazine cohort (13.0, IQR 10–17), which was statistically significant ($p < 0.001$). Of note, there were also significantly more presentations per month in the medetomidine era than in the XE. See full COWS score and encounter details in Table 3.

Table 3. Withdrawal Severity and Treatment Response by Era.

Outcome Metric	Xylazine Era (n=616)	Medetomidine Era (n=653)	p-value
Mean ED Encounters per Month	50.4	102.5	<0.001
Median Pre-Treatment COWS	13.0	16.0	<0.001
Median Post-Treatment COWS	3.0	12.0	<0.001
Median COWS Reduction (Δ)	9.0	4.0	<0.001
Mean COWS Reduction ± SD	8.77 ± 7.43	4.58 ± 7.71	
% Achieving COWS ≤ 4	65.6%	14.2%	<0.001

3.2. Withdrawal Treatment and COWS Outcomes

The primary outcome of withdrawal severity improvement, measured by the change in COWS, differed markedly between the two eras. Figure 1 illustrates the COWS scores before and after treatment for each cohort (median and IQR). In the XE cohort, withdrawal scores improved substantially with protocol treatment. The median COWS decreased from 13.0 (IQR 10–17) on arrival to 16.0 (IQR 1–6) after treatment, a median reduction of –9 points ($p < 0.001$ for within-cohort pre/post comparison). This confirms the efficacy of the protocol in mitigating withdrawal signs and symptoms in the XE, consistent with previously published outcomes [2].

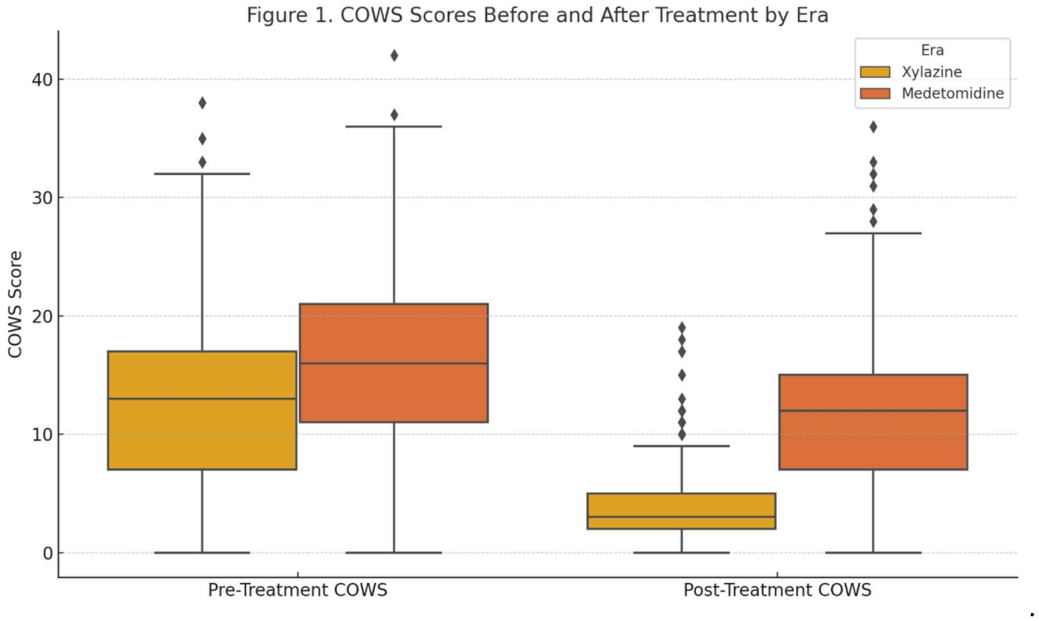

Figure 1. COWS Scores Before and After Treatment by Era.

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A large majority of XE patients achieved a post-treatment COWS score of < 5 (65.6%, indicating relief from withdrawal). In contrast, the ME cohort experienced more modest improvements. The median COWS in this group was 16.0 (IQR 12–20) before treatment and 12.0 (IQR 8–16) post-treatment, for a median reduction of only –4 points. While this reduction was still statistically significant compared to pre-treatment scores ($p = 0.013$), the magnitude of improvement was clearly smaller. Only 14.2% during the ME attained a post-treatment COWS < 5 ($p < 0.001$ vs XE). The between-cohort comparison of ΔCOWS was highly significant ($p < 0.001$), indicating that the protocol's effectiveness in reducing objective withdrawal scores was significantly blunted in the ME. See Figure 2 for monthly median COWS scores (pre- and post-treatment).

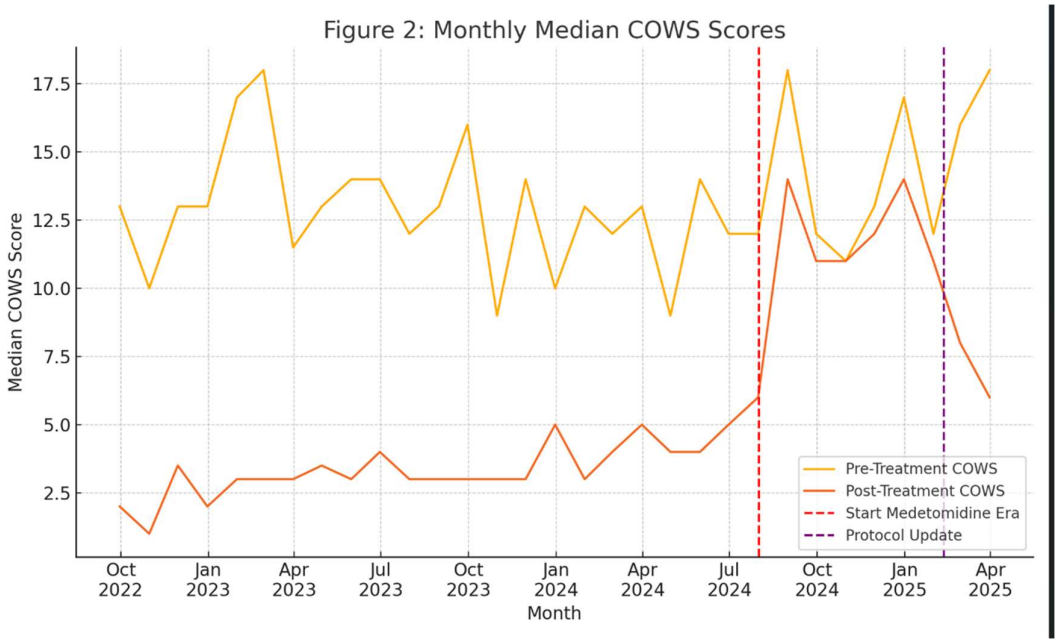
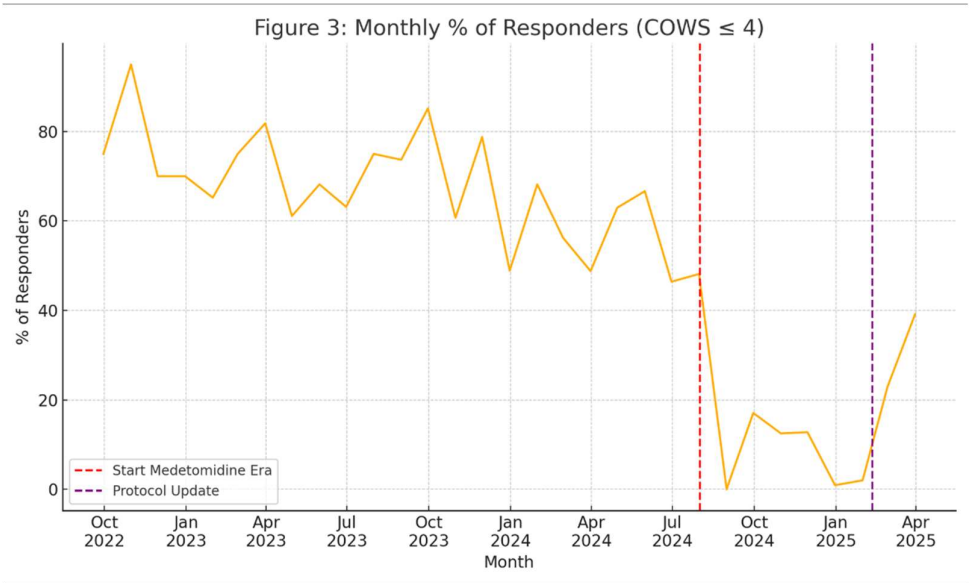


Figure 3 shows the % of patients who achieved a COWS score of 5 or lower (defined as no longer demonstrating symptoms of withdrawal), showing the dramatic change from XE to ME, starting in the months preceding the change in adulteration.



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To account for any baseline differences, we performed a two-way analysis of variance on COWS scores with time (pre vs post) and era as factors. This analysis demonstrated a significant interaction effect ($p < 0.001$), corroborating that the improvement in COWS over time depended on which era (XE vs ME). In essence, patients in the ME did not respond as robustly to the standardized regimen as those in the XE did.

3.3. Secondary Outcomes: Subgroup, Disposition and Adverse Events

To assess the impact of the revised withdrawal protocol introduced on February 11, 2025, we performed a subgroup analysis of ME encounters before and after the protocol change. Among the 653 encounters in the ME, 174 (26.6%) occurred after the updated protocol was implemented. Patients in this subgroup showed modestly greater improvement in COWS scores compared to those treated earlier in the medetomidine era: median reduction in COWS was −6.0 (IQR: −9 to −3) post-revision vs −4.0 (IQR: −6 to −2) pre-revision ($p < 0.001$). Additionally, the proportion of patients achieving post-treatment COWS ≤4 increased from 11.0% to 21.1% after the protocol update ($p = 0.003$). While still substantially lower than XE outcomes, these findings suggest partial restoration of protocol efficacy following the revision.

We also examined clinical outcomes beyond COWS scores, studying dispositions. See Table 4. Disposition from the ED differed between the two eras in several notable ways. The incidence of patients leaving against medical advice (AMA) was higher in the medetomidine cohort (6.5%) than in the xylazine cohort (3.6%), though the difference was only mildly statistically significant ($p = 0.038$). More notably, ICU-level admission occurred more frequently in the medetomidine cohort: 88 (18.4% of admissions) ME patients were admitted to the ICU from the ED, compared to 35 patients in the xylazine cohort (8.5% of admissions, $p < 0.001$). Adverse events were infrequent, and no serious adverse events were documented in either group.

In the subgroup analysis that separated the ME into before and after withdrawal protocols were changed, ICU and overall admission rates remained high (16.8%, 75.3%), although ICU rates were slightly but not significantly reduced compared to the pre protocol change ME period (18.4%, $p = 0.107$). AMA rates slightly improved after protocol change, did not significantly change either. See Figures 2 and 3 for monthly trends.

Table 4. Emergency Department Disposition by Era (including Post-Protocol Change Cohort).

ED Disposition	Xylazine Era (N=616)	Medetomidine Era Before Protocol Change (BPC) (N=479)	Medetomidine Era After Protocol Change (APC) (N=174)	p-value (XE vs. BPC, BPC vs. APC)
Admit	410 (66.6%)	348 (72.7%)	131 (75.3%)	0.036, 0.566
ICU Admission	35 (8.5%)	88 (18.4%)	22 (16.8%)	< 0.001, 0.107
Discharge	182 (29.5%)	99 (20.7%)	33 (19.0%)	0.001, 0.712
AMA	22 (3.6%)	31 (6.5%)	9 (5.2%)	0.038, 0.669
Transfer to Another Facility for Eval	2 (0.3%)	1 (0.2%)	1 (0.6%)	1.000, 1.000

Hospital admissions for continued withdrawal management were more frequent in the ME. In the xylazine-era, nearly 30% of patients could be discharged home or to a treatment program after ED management. In contrast, in the medetomidine-era cohort, only around 20% were discharged from the ED, while a significantly higher proportion (~75%) required inpatient admission for ongoing care of withdrawal, including almost double the amount who needed ICU care.

Regarding adverse events, the protocol was generally well-tolerated in both groups, with no serious adverse events directly attributable to the medications. There were zero instances of respiratory arrest or cardiac arrest due to the treatment in either era.

4. Discussion

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This study demonstrates that the emergence of medetomidine as an adulterant in illicit fentanyl coincided with a marked decline in the effectiveness of a novel opioid withdrawal management protocol developed during the XE. In the era when fentanyl was co-adulterated with xylazine (September 2022–July 2024), the protocol reliably reduced withdrawal severity, whereas during the ME (August 2024–March 2025) we observed significantly smaller improvements in COWS scores. Concurrently, ME patients saw higher rates of intensive care unit (ICU) admission for withdrawal-related complications and more patients leaving the emergency department against medical advice (AMA).

These disparities suggest that medetomidine adulteration introduced additional clinical challenges not adequately addressed by a protocol originally tailored to manage opioid withdrawal with another potent alpha-2 agonist (xylazine) as the primary adulterant. Xylazine, a veterinary alpha-2 agonist sedative, rose to prominence as a fentanyl adulterant in the mid-2010s and early 2020s. By 2019–2022, xylazine was detected in approximately 2.9–10.9% of fentanyl-involved overdose deaths in the United States[12]. Clinicians recognized that xylazine's presence complicates opioid overdoses because its central sedative effects (hypoventilation, bradycardia) are not reversed by naloxone[12]. Medetomidine — a pharmacologically similar, though more potent alpha-2 agonist — has rapidly followed as a new adulterant over the past two years[13]. The first confirmed cases of medetomidine exposure in U.S. overdose patients were reported in late 2023 in a CDC surveillance brief[13], which called for heightened toxicologic screening and clinical awareness of this emerging adulterant[13]. Shortly thereafter, public health alerts in early 2024 announced the detection of medetomidine in local fentanyl supplies in Philadelphia and New York[14, 15]. These alerts noted that medetomidine was identified in street "dope" samples alongside fentanyl and xylazine [14], and described overdose clusters involving profound sedation unresponsive to naloxone[14-15].

Forensic drug surveillance from mid-2024 further documented medetomidine's proliferation, being identified in opioid samples across multiple states[16]. Medetomidine was almost invariably found in combination with xylazine[16], indicating a shift to an increasingly dynamic supply pattern in which fentanyl is co-mixed with multiple sedatives. This context likely contributed to the challenging clinical presentations observed during the ME. Patients were effectively exposed to two synergistic α_2-agonists (medetomidine plus xylazine) alongside fentanyl, a combination expected to produce more profound and prolonged CNS depression than either sedative alone[16]. It is plausible that illicit suppliers introduced medetomidine as a more potent or longer-acting replacement for xylazine once awareness and regulation of xylazine increased, thereby sustaining the enhanced sedative "kick" of adulterated fentanyl.

Medetomidine's pharmacologic properties help explain why its presence undermined our withdrawal protocol's effectiveness. Medetomidine is a veterinary alpha-2 agonist sedative that is substantially more potent than xylazine, though most animal studies cite estimates of 10-20x greater potency [6,7], one clinical report estimates it to be on the order of 200 times more potent [17]. Pharmacodynamically, medetomidine produces similar effects to xylazine – including sedation, analgesia, bradycardia, and hypotension[18] – but tends to have a longer duration of action[17,19]. Critically, medetomidine's CNS depressant effects are not reversed by the opioid antagonist naloxone[13, 17]. Thus, an opioid user co-exposed to medetomidine may remain heavily sedated even after naloxone administration. A CDC case series documented exactly this scenario: patients with fentanyl–medetomidine exposure presented with prolonged unresponsiveness and hypotension that was unresponsive to naloxone[13]. Frontline clinicians have similarly been cautioned to suspect medetomidine or other α_2-agonists when an apparent opioid overdose victim fails to awaken after naloxone[17]. In our cohort, these pharmacologic effects likely contributed to the increased number of ED visits for withdrawal, as well as the increased need for ICU-level care during the ME, as patients often suffered more severe withdrawal, requiring higher intensity care.

In contrast to xylazine, which is notorious for causing necrotic skin ulcers in chronic users[20], medetomidine has not been linked to such tissue injury. Its chief hazards are systemic, exerting powerful neurodepressive effects that complicate both overdose resuscitation and withdrawal

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management. This is notable given the decreased number of visits related to skin and soft tissue infections in the ME.

Another key consideration is the potential for medetomidine to cause physiological dependence and a withdrawal syndrome, compounding the challenge of opioid withdrawal. Chronic exposure to alpha-2 agonists can induce adaptive changes; abrupt cessation precipitates a rebound hyperadrenergic state. In the critical care literature, prolonged infusions of dexmedetomidine (the active enantiomer of medetomidine) have been shown to produce significant withdrawal symptoms upon discontinuation[21]. A recent meta-analysis reported that over one-third of patients developed hypertension and tachycardia after stopping long-term dexmedetomidine, and it advocated gradual weaning or adjunctive clonidine to mitigate such withdrawal effects[21]. By analogy, individuals using medetomidine-adulterated opioids regularly may develop dependence on this sedative. When they present to the ED in opioid withdrawal (having not used for several hours), they plausibly could simultaneously be in medetomidine withdrawal.

This scenario would likely manifest as severe autonomic hyperactivity (anxiety, vomiting, tremors, hypertension, tachycardia) that overlaps with opioid withdrawal but does not fully respond to opioid agonist therapy, which is exactly what we found evidence to support. Indeed, health officials have noted that frequent xylazine users experience a distinct withdrawal syndrome (irritability, anxiety, palpitations, and elevated blood pressure) when xylazine is discontinued[20]. It is likely that medetomidine causes a similar withdrawal phenomenon. Unrecognized alpha-2 agonist withdrawal in our medetomidine-era patients is likely therefore a key factor in the blunted COWS score improvements – since certain withdrawal signs (e.g., tachycardia, diaphoresis, agitation) could persist due to persistent autonomic activation.

After appreciating these issues, we modified our ED withdrawal protocol in February 2025 to better address medetomidine co-exposure. Although detailed outcomes of the new protocol are beyond the scope of this discussion, and will be published separately, we observed clear improvements following its implementation: withdrawal-symptom relief rates began to rise, and ICU admission and AMA discharge rates declined relative to earlier in the medetomidine era. The protocol revisions included measures to counteract medetomidine withdrawal, such as more aggressive management of autonomic symptoms by use of clonidine and sympatholysis with higher doses of short acting opioids. Clonidine is a more potent oral alpha-2 agonist than tizanidine or guanfacine, up to 50 times more vasoactive. [21] In essence, we attempted to pharmacologically bridge the sudden loss of alpha-2 agonist input – an approach analogous to using clonidine to taper patients off dexmedetomidine or xylazine[22].

The partial restoration of efficacy supports the notion that more aggressive management may improve outcomes. However, even with these adjustments, medetomidine-era outcomes did not return fully to the baseline seen in the xylazine era, indicating that significant challenges remain. Patients with medetomidine exposure may require prolonged observation, higher levels of care to completely normalize their withdrawal trajectory. Further work is needed to determine optimal strategies for managing withdrawal in the context of medetomidine and similar sedative adulterants. Overall, our findings highlight the necessity for clinicians to rapidly adapt withdrawal management protocols in response to changes in the adulterant profile of illicit opioids as well as the importance of community based drug testing programs. A protocol that was effective for “tranq dope” (fentanyl + xylazine) had to be recalibrated for what some have termed “demon dope” (fentanyl + xylazine + medetomidine). Frontline providers should maintain a high index of suspicion for atypical sedative co-intoxication in opioid users – especially if a patient exhibits deeper-than-expected sedation, bradycardia, hypotension or withdrawal symptoms that are unusually refractory to standard treatment (with associated hypertension, tachycardia and sympathetic activation). In such cases, early use of adjunct therapies (targeted at the sedative component) and a low threshold for intensive monitoring may be warranted. These conclusions align with emerging guidance urging emergency and critical care providers to recognize and manage polysubstance opioid withdrawal, including the effects of alpha-2 agonist adulterants[17]. By integrating clinical findings with public health

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intelligence on drug-supply trends, healthcare systems can better prepare for and respond to the next evolution of the opioid crisis.

5. Limitations

This study has several limitations. First, as a retrospective analysis, it is inherently subject to confounding, selection bias, and limited generalizability beyond the two emergency departments studied. While both institutions serve a high volume of individuals with opioid use disorder in Philadelphia, the findings may not reflect experiences in other regions or healthcare systems.

Second, not all patients receiving withdrawal protocol treatment during the study period could be analyzed due to missing data. Specifically, patients lacking either pre- or post-treatment COWS scores or documented ED disposition were excluded from the final cohort. This may have introduced bias if these excluded encounters differed systematically from those included.

Third, individual toxicologic confirmation of xylazine or medetomidine exposure was not available. Neither compound is included in routine clinical toxicology screening, and their detection requires specialized analytical techniques that were not performed in real-time ED care. Era classification was therefore inferred based on temporal association with drug-supply trends reported by public health surveillance, which may misclassify some cases—especially during transition months.

Fourth, chief complaint data relied on structured text documentation, which introduces limitations in symptom categorization. Complaints related to opioid withdrawal may have been inconsistently documented or underreported if patients presented with overlapping symptoms such as vomiting or altered mental status. As a result, the frequency of opioid withdrawal presentations may be underrepresented in our analysis.

Additionally, the Clinical Opiate Withdrawal Scale (COWS) was the sole tool used to assess withdrawal severity, though it was developed for opioid withdrawal and may not fully capture the autonomic or neuropsychiatric features of α_2-agonist withdrawal. There are currently no validated tools for medetomidine or xylazine withdrawal, and this likely underestimates the true symptom burden in such patients.

Finally, while the protocol revision in February 2025 showed promising improvements, this subgroup had limited follow-up time, and further data are needed to confirm its long-term effectiveness and safety in the context of medetomidine exposure.

6. Conclusions

In summary, this retrospective cohort analysis found that our opioid withdrawal protocol was significantly less effective during the period when fentanyl was adulterated with medetomidine, compared to the earlier xylazine-dominant era. Patients in the medetomidine era experienced poorer withdrawal symptom relief and higher rates of ICU admission and AMA disposition, indicating more severe and complex withdrawal presentations. Implementation of a revised protocol (in February 2025), which incorporated adjustments to address medetomidine's α_2-agonist effects, was associated with partial restoration of efficacy. This suggests that adapting treatment strategies to account for medetomidine co-exposure can mitigate some of the negative impact.

However, even after protocol changes, medetomidine-exposed patients remained more difficult to treat than those in the xylazine era, underscoring the formidable challenge posed by this new adulterant. For medical practice, these findings highlight the importance of dynamic protocol revisions in the face of an evolving drug supply. Standard opioid-centric withdrawal management approaches may fail when confronted with novel adulterants that produce additional non-opioid pharmacologic effects (such as profound sedation or autonomic instability). Clinicians should be alert to regional drug trends and be prepared to modify withdrawal treatment plans accordingly.

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Looking ahead, enhanced surveillance of illicit drugs is crucial for early identification of emerging adulterants. Timely toxicological analysis of overdose cases and drug samples, coupled with rapid information-sharing through public health alerts, will enable clinicians to anticipate changes in withdrawal patient presentations[13]. Future research should focus on developing tailored withdrawal protocols for multi-substance exposures. This includes investigating optimal management of alpha-2 agonist withdrawal in patients with OUD– such as the role of clonidine or other sympatholytics in treating medetomidine/xylazine withdrawal – and determining best practices to reduce ICU utilization and prevent AMA dispositions in these complex cases. In conclusion, a proactive, evidence-based approach to new opioid adulterants is needed to maintain effective withdrawal care. Ongoing collaboration between clinicians, addiction medicine and toxicology experts, as well as public health authorities, will be essential to stay ahead of emerging trends and to safeguard the outcomes of patients with opioid use disorder.

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Abbreviations

The following abbreviations are used in this manuscript:

ED	Emergency Department
ME	Medetomidine Era
XE	Xylazine Era
OUD	Opioid Use Disorder
COWS	Clinical Opioid Withdrawal Scale
MDPI	Multidisciplinary Digital Publishing Institute
DOAJ	Directory of open access journals

Appendix A

Appendix A. Categorization of Chief Complaints by Assigned Presentation Category

Chief Complaint	Assigned Category
ABDOMINAL INJURY	Trauma
ABDOMINAL PAIN	General Medical/Other
ABNORMAL LAB	General Medical/Other
ABRASION	Trauma
ABSCESS	Skin/Soft Tissue Infection
ABSCESS DRAINAGE	Skin/Soft Tissue Infection
ALCOHOL INTOXICATION	General Medical/Other
ALTERED MENTAL STATUS	General Medical/Other
ANGIOEDEMA	General Medical/Other
ANKLE PAIN	General Medical/Other
ANXIETY	General Medical/Other
ARM INJURY	General Medical/Other
ARM PAIN	General Medical/Other

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ARM SWELLING	General Medical/Other
ASSAULT	General Medical/Other
ASTHMA	General Medical/Other
BACK PAIN	Trauma
BLACK OR BLOODY STOOL	General Medical/Other
BLOOD INFECTION	General Medical/Other
BURN	General Medical/Other
CAST CHECK	General Medical/Other
CELLULITIS	Skin/Soft Tissue Infection
CHEST PAIN	General Medical/Other
CHEST TIGHTNESS	General Medical/Other
CHILLS	General Medical/Other
COLD EXPOSURE	General Medical/Other
CONSTIPATION	General Medical/Other
COUGH	General Medical/Other
COUGHING UP BLOOD	General Medical/Other
CYST	General Medical/Other
DEBRIDEMENT	General Medical/Other
DENTAL PAIN	General Medical/Other
DEPRESSION	General Medical/Other
DETOX	General Medical/Other
DIALYSIS TREATMENT	General Medical/Other
DIARRHEA	General Medical/Other
DIFFICULTY WALKING	General Medical/Other
DIZZINESS	General Medical/Other
DRUG OVERDOSE	General Medical/Other
DRUG PROBLEM	General Medical/Other
DYSURIA	General Medical/Other
EARACHE	General Medical/Other
ELBOW PAIN	General Medical/Other
ENDOCARDITIS	General Medical/Other
EXTREMITY WEAKNESS	General Medical/Other
EYE DRAINAGE	General Medical/Other
EYE INFECTION	General Medical/Other
EYE PAIN	General Medical/Other
EYE PROBLEM	General Medical/Other
EYE TRAUMA	General Medical/Other
FACIAL SWELLING	General Medical/Other
FAILURE TO THRIVE	General Medical/Other
FALL	Trauma
FEVER	General Medical/Other
FINGER INJURY	General Medical/Other
FINGER PAIN	General Medical/Other
FLANK PAIN	General Medical/Other
FLU SYMPTOMS	General Medical/Other
FOOT BLISTER	General Medical/Other
FOOT INJURY	General Medical/Other
FOOT PAIN	General Medical/Other
FOOT SWELLING	General Medical/Other
FOOT WOUND CHECK	General Medical/Other

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FOREIGN BODY	General Medical/Other
FOREIGN BODY IN SKIN	General Medical/Other
FROSTBITE	General Medical/Other
GENERALIZED BODY ACHES	General Medical/Other
GENITAL WARTS	General Medical/Other
GROIN PAIN	General Medical/Other
GROIN SWELLING	General Medical/Other
GUN SHOT WOUND	General Medical/Other
HAND INFECTION	General Medical/Other
HAND INJURY	General Medical/Other
HAND PAIN	General Medical/Other
HEAD LICE	General Medical/Other
HEADACHE	General Medical/Other
HERNIA	General Medical/Other
HIP PAIN	General Medical/Other
HOMELESS	General Medical/Other
HYPERGLYCEMIA	General Medical/Other
HYPERTENSION	General Medical/Other
HYPOGLYCEMIA	General Medical/Other
INFECTION	Skin/Soft Tissue Infection
INGESTION	General Medical/Other
INTOXICATED	General Medical/Other
JAW PAIN	General Medical/Other
JOINT SWELLING	General Medical/Other
KNEE INJURY	General Medical/Other
KNEE PAIN	General Medical/Other
LEG INJURY	Trauma
LEG PAIN	General Medical/Other
LEG PROBLEM	General Medical/Other
LEG SWELLING	General Medical/Other
MEDICAL COMPLAINT	General Medical/Other
MEDICATION REFILL	General Medical/Other
MOTOR VEHICLE VS PEDESTRIAN	General Medical/Other
MOTOR VEHICLE CRASH	General Medical/Other
MRSA	General Medical/Other
MULTIPLE SCLEROSIS	General Medical/Other
NASAL CONGESTION	General Medical/Other
NAUSEA	General Medical/Other
NECK INJURY	General Medical/Other
NECK PAIN	General Medical/Other
NUMBNESS	General Medical/Other
OPEN WOUND	General Medical/Other
OSTEOMYELITIS	General Medical/Other
OTHER	General Medical/Other
PAIN	General Medical/Other
PAIN WITH BREATHING	General Medical/Other
PALPITATIONS	General Medical/Other
PNEUMONIA	General Medical/Other
POOR APPETITE	General Medical/Other
POST-OP PROBLEM	General Medical/Other

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PREGNANCY PROBLEM	General Medical/Other
PSYCHIATRIC EVALUATION	General Medical/Other
RAPID HEART RATE	General Medical/Other
RASH	General Medical/Other
RECURRENT SKIN INFECTIONS	General Medical/Other
RESPIRATORY DISTRESS	General Medical/Other
RIB INJURY	General Medical/Other
RING REMOVAL	General Medical/Other
RULE OUT STROKE	General Medical/Other
SEIZURES	General Medical/Other
SEPSIS OUTREACH	General Medical/Other
SEXUAL ASSAULT	General Medical/Other
SHORTNESS OF BREATH	General Medical/Other
SHOULDER PAIN	General Medical/Other
SINUSITIS	General Medical/Other
SKIN PROBLEM	General Medical/Other
SOCIAL DETERMINANTS SCREENING	General Medical/Other
SORE THROAT	General Medical/Other
SPASMS	General Medical/Other
STAB WOUND	General Medical/Other
STROKE ALERT	General Medical/Other
SUICIDAL	General Medical/Other
SUICIDE ATTEMPT	General Medical/Other
SWELLING	General Medical/Other
SWELLING HEAD/NECK	General Medical/Other
SYNCOPE	General Medical/Other
TRAUMA	General Medical/Other
URI	General Medical/Other
URINARY PROBLEM	General Medical/Other
VAGINAL BLEEDING	General Medical/Other
VAGINAL BLEEDING - PREGNANT	General Medical/Other
VASCULAR ACCESS PROBLEM	General Medical/Other
VENOUS THROMBOSIS	General Medical/Other
VOMITING	General Medical/Other
VOMITING BLOOD	General Medical/Other
WEAKNESS - GENERALIZED	General Medical/Other
WELLNESS VISIT	General Medical/Other
WITHDRAWAL	Opioid Withdrawal
WOUND CARE	General Medical/Other
WOUND CHECK	Skin/Soft Tissue Infection
WOUND DEHISCENCE	General Medical/Other
WOUND INFECTION	Skin/Soft Tissue Infection
WRIST PAIN	General Medical/Other

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