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CLINICAL RESEARCH

Opioid overdoses involving xylazine in emergency department patients: a multicenter study

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ABSTRACT

Introduction: Illicit opioids, consisting largely of fentanyl, novel synthetic opioids, and adulterants, are the primary cause of drug overdose fatality in the United States. Xylazine, an alpha-2 adrenergic agonist and veterinary tranquilizer, is being increasingly detected among decedents following illicit opioid overdose. Clinical outcomes in non-fatal overdose involving xylazine are unexplored. Therefore, among emergency department patients with illicit opioid overdose, we evaluated clinical outcome differences for patients with and without xylazine exposures.

Methods: This multicenter, prospective cohort study enrolled adult patients with opioid overdose who presented to one of nine United States emergency departments between 21 September 2020, and 17 August 2021. Patients with opioid overdose were screened and included if they tested positive for an illicit opioid (heroin, fentanyl, fentanyl analog, or novel synthetic opioid) or xylazine. Patient serum was analyzed *via* liquid chromatography quadrupole time-of-flight mass spectroscopy to detect current illicit opioids, novel synthetic opioids, xylazine and adulterants. Overdose severity surrogate outcomes were: (a) cardiac arrest requiring cardiopulmonary resuscitation (primary); and (b) coma within 4 h of arrival (secondary).

Results: Three hundred and twenty-one patients met inclusion criteria: 90 tested positive for xylazine and 231 were negative. The primary outcome occurred in 37 patients, and the secondary outcome occurred in 111 patients. Using multivariable regression analysis, patients positive for xylazine had significantly lower adjusted odds of cardiac arrest (adjusted OR 0.30, 95% CI 0.10–0.92) and coma (adjusted OR 0.52, 95% CI 0.29–0.94).

Conclusions: In this large multicenter cohort, cardiac arrest and coma in emergency department patients with illicit opioid overdose were significantly less severe in those testing positive for xylazine.

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Introduction

An unprecedented increase in United States (US) opioid overdose mortality has been observed since 2014, driven by the near ubiquitous presence of synthetic opioids in the illicit opioid supply [1–4]. Polypharmacy implicated deaths, which include combinations of opioids, stimulants, and benzodiazepines, have also surged [5–8]. Recently, xylazine has been reported in drug materials and overdose deaths linked to illicit fentanyl proliferation [9]. However, patient clinical outcomes following non-fatal illicit opioid overdose with the presence of xylazine have not been described.

Xylazine, a potent central alpha-2 adrenergic agonist used in veterinary medicine with ketamine or opioids, is used for large-animal anesthesia or pain management [10]. Xylazine is structurally related to clonidine (Figure 1), resulting in central nervous system (CNS) depressant effects (sedation) and cardiovascular side effects (bradycardia, hypotention, and cardiac arrest) [10]. By bolstering alpha-2 adrenergic receptor activity, xylazine decreases norepinephrine presynaptic release, subsequently decreasing an adrenergic physiologic response [10]. Animal studies using a mouse model have also demonstrated xylazine activity at mu-opioid receptors [11].

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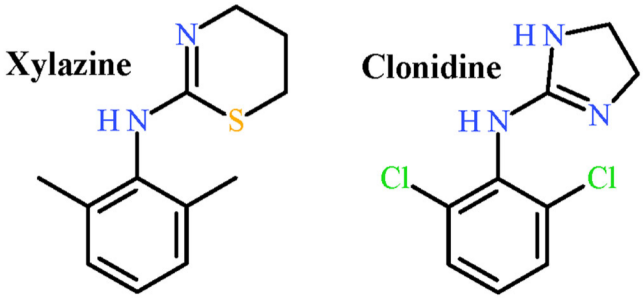

Figure 1. Chemical structures of xylazine and clonidine.

Over the last two decades, xylazine has emerged as an adulterant in the recreational drug supply (e.g., fentanyl, metamfetamine) [9,12]. Early xylazine detection in Puerto Rico describes patients using xylazine in combination with opioids or cocaine [13,14]. Recently, xylazine, known by its street-name "tranq," has been detected in urine, drug products and syringes with fentanyl and metamfetamine [15–17]. Xylazine has also been increasingly detected among overdose fatalities in post-mortem studies [18–22]. However, no studies have described clinical characteristics and outcomes for a prospective patient cohort exposed to opioids and xylazine.

Here, we investigate the effect of xylazine on clinical outcomes of emergency department (ED) patients who presented with suspected illicit opioid overdose. We performed blinded toxicological analyses and compared clinical outcomes *via* medical chart abstraction. We hypothesized that xylazine would be associated with worse clinical outcomes, most importantly cardiac arrest, and coma.

Methods

This multicenter, prospective cohort study enrolled consecutive patients with suspected opioid overdose who presented to a participating ED between 21 September 2020 and 17 August 2021. Participating institutions were a subset of the Toxicology Investigators Consortium (ToxIC), which is an existing network of 48 US hospitals in 30 US cities [23]. Nine EDs participated across 7 states: California, Oregon, Michigan, Missouri, Pennsylvania, New York, and New Jersey. A central institutional review board (Western IRB) provided approval and a waiver of informed consent.

Inclusion/exclusion criteria

Patients at least 18 years old and who presented to the ED with suspected opioid overdose between 21 September 2020 and 17 August 2021 were screened for study eligibility. Patients were eligible for study inclusion if they (1) had opioid toxicity based on chief complaint or discharge diagnosis; (2) received naloxone for overdose treatment in the ED; or (3) had self-reported opioid use resulting in an ED visit for an overdose. Patients who presented with trauma, in custody of law enforcement, or without waste specimens were excluded. Of those eligible for study inclusion, only patients testing positive for illicit opioids or xylazine were included in the final cohort. An illicit opioid included heroin, fentanyl, fentanyl analogs, nitazene analogs, or other new synthetic opioids.

Toxicological analyses

Waste clinical specimens were collected as directed by site investigators and ToxIC staff. Serum and/or blood samples drawn in heparinized tubes obtained as part of routine clinical care were collected, de-identified, and stored at −80 °C until sent to the Center for Forensic Science Research and Education (CFSRE) for analysis. Qualitative molecular identification consisted of liquid chromatography quadrupole time-of-flight mass spectrometry (LC-QTOF-MS) analysis with secondary analysis by liquid chromatography tandem quadrupole mass spectrometry (LC-QqQ-MS), when necessary. Current CFSRE toxicology testing contains over 900 drugs, including therapeutics, traditional illicit drugs, novel psychoactive substances, adulterants, and other compounds. This methodology has been previously validated [24] and the molecular battery is frequently updated, as drugs in this dynamic market change frequently. Illicit opioids of interest were fentanyl, fentanyl analogs (e.g., acetylfentanyl, furanylfentanyl, carfentanil, para-fluorofentanyl), nitazene analogs (e.g., isotonitazene, metonitazene), and other new synthetic opioids (e.g., brorphine, 2-methyl AP-237), as well as previously prevalent synthetic opioids (e.g., AH-7921, MT-45, U-47700) [5]. The limit of detection for both xylazine and fentanyl was 0.1 μg/L.

Biological samples were de-identified with a code linking the patient's sample to the corresponding ToxIC site clinical data entry. Toxicological analyses were blinded to clinical outcomes. Results were summarized and sent to the principal investigator for linkage to clinical data for analysis. Patients were then categorized into those testing positive (i.e., xylazine group) or negative (i.e., controls) for xylazine based on LC-QTOF-MS and/or LC-QqQ-MS.

Definitions

An illicit opioid was defined as heroin, fentanyl, fentanyl analogs, nitazene analogs, or other new synthetic opioids. Patients testing positive for prescription opioids (e.g., oxycodone, methadone) without xylazine were not included in the study cohort.

Cardiovascular adverse events were defined as a ventricular arrhythmia, intraventricular conduction delay, QT prolongation, documented cardiac arrest, elevated troponin, or bradycardia (<50 beats per minute at any time). Troponin was considered elevated if above the upper limit of normal for the given hospital's reference range.

Individual sites were grouped into three regions: West (California, Oregon), Central (Michigan, Missouri), and East (Pennsylvania, New York, New Jersey).

Data collection

Medical record data included age, sex, past medical and psychiatric comorbidities, suspected opioid name, treatment rendered (including dose, amount, route, and duration of

naloxone administration), and outcome, including the presence or absence of any organ system toxicity. Data were collected and entered in a secure, web-based software platform (Research Electronic Data Capture [RedCap]) by a trained research assistant or site investigator/toxicologist.

Outcomes

The primary outcome of cardiac arrest was defined as loss of pulse requiring cardiopulmonary resuscitation (CPR), as documented in the medical chart. The secondary outcome of coma was defined as unarousable unresponsiveness or the phrase "coma" at any time within the first 4 h of ED arrival based on medical chart documentation. Adjudication of outcomes was performed independently by each ToxIC site investigator.

Data analysis

Descriptive statistics are reported as medians with interquartile ranges and percentages. Categorical variables were evaluated using the Chi-squared test and Fisher's exact test (when appropriate). Continuous variables were compared *via* Student's *T*-test. Clinical variables included age, sex, race/ethnicity, psychiatric history, initial blood pressure, total naloxone dose administered, and the presence of xylazine. Multivariable logistic regression analysis was used to estimate the association between the explanatory variable (xylazine) and study outcomes when controlling for confounders. Data are reported as point estimates with corresponding 95% confidence intervals. Data analysis was performed on Stata/SE (version 16.1; College Station, TX).

Data management and quality

Site-specific medical record data were abstracted into a RedCap data collection platform without patient identifiers. Patient data were linked to corresponding biological specimens. ToxIC registry data quality assurance is maintained in accordance with current best-practices [25] including database logical checks, pilot testing, procedure manuals, quality assurance personnel, paperless e-forms, automated data cleaning, data tracking, secure encryption, and data abstractor training [26]. RedCap platform quality assurance confirmed that >90% of pertinent data fields were completed.

Results

Figure 2 shows study patient selection. During the study period, 1,006 patients were screened for eligibility and 395 patients were enrolled. 321 patients (81.3%) were identified with at least one illicit opioid of interest or xylazine present in toxicology samples. Of these patients, 90 patients (28.0%) tested positive for xylazine and 231(72.0%) tested positive for an illicit opioid without xylazine. Among patients without xylazine, 16% had heroin detected, 93.5% had fentanyl detected, 13.9% had other fentanyl analogs detected and 3.0% had a novel synthetic opioid detected. Among patients with xylazine, 25.5% had heroin detected, 98.9% had fentanyl detected, 32.2% had other fentanyl analogs detected and 2.2% had a novel synthetic opioid detected (Table 1). Only one patient tested positive for xylazine without an illicit opioid. This patient tested positive for a prescription opioid (methadone).

Overall, most patients were male (69.5%). The median (IQR) age was 39 (30–50) years. Psychiatric illness was prevalent and relatively evenly distributed among patients with and without xylazine. Baseline characteristics were similar

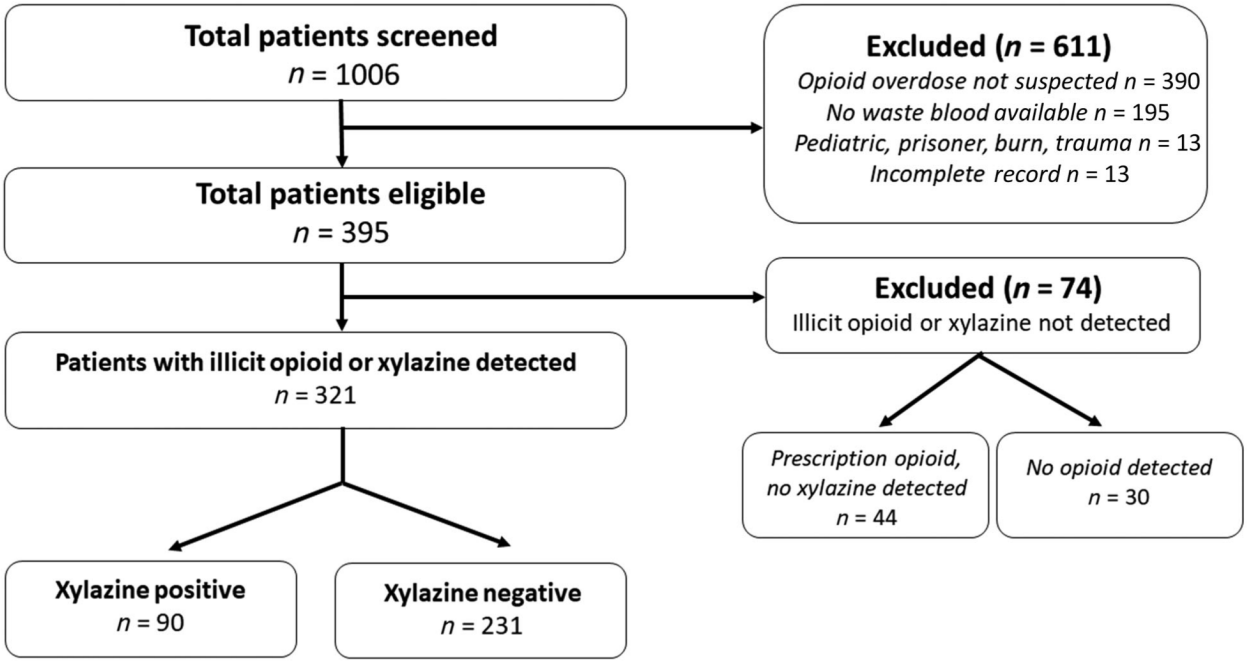

Figure 2. Patient eligibility and enrollment.

Table 1. Demographic characteristics of xylazine and control cohorts.

Demographic variables	Xylazine ($n = 90$)	Xylazine absent ($n = 231$)
Male (%)	69 (76.7%)	154 (66.7%)
Age; median (IQR)	41 (32–53)	38 (30–50)
Psychiatric history		
Any	58 (64.4%)	138 (59.7%)
Anxiety	19 (21.1%)	34 (14.7%)
Attention deficit hyperactivity disorder	4 (4.4%)	10 (4.3%)
Bipolar	9 (10%)	25 (10.8%)
Depression	17 (18.9%)	55 (23.9%)
Post-traumatic stress disorder	4 (4.4%)	12 (5.2%)
Schizophrenia	4 (4.4%)	10 (4.3%)
Geographic Region		
East (PA, NY, NJ)	63	127
Central (MI, MO)	26	74
West (CA, OR)	1	30
Naloxone		
Received any naloxone (%)	70 (77.8%)	195 (84.4%)
Initial naloxone dose mg; median (IQR)	2 (0.875–4)	2 (2–4)
Total naloxone dose mg; median (IQR)	3.6 (1.3–4.1)	2.8 (2–4.1)
Number of naloxone doses; median (IQR)	2 (1–3); range 1–5	1 (1–2); range 1–9
Repeat naloxone received (%)*	39 (43.3%)	96 (41.5%)
Initial ED vital signs		
SBP; median (IQR)	132 (114–150)	130 (118–145)
DBP; median (IQR)	84 (68–98)	84 (70–95)
HR ED; median (IQR)	95 (81–108)	98 (84–112)
RR ED; median (IQR)	18 (14–20)	18 (15–20)
Opioid analytes detected **		
Heroin	23 (25.5%)	37 (16%)
Fentanyl	89 (98.9%)	216 (93.5%)
Other fentanyl analogs	29 (32.2%)	32 (13.9%)
Novel synthetic opioids	2 (2.2%)	7 (3.0%)

Abbreviations. IQR, interquartile range; PA, Pennsylvania; NY, New York; NJ, New Jersey; MI, Michigan; MO, Missouri; CA, California; OR, Oregon; ED, emergency department; DBP, diastolic blood pressure; SBP, systolic blood pressure; HR, heart rate; RR, respiratory rate.
*Percentage of entire cohort.
**Samples tested for all potential analytes. Single sample may have multiple analytes and percent totals may exceed 100%.

between groups, but xylazine was more prevalent in samples from the East (Table 1).

Most patients (82.6%) were treated with naloxone and received a median initial 2 mg dose. Table 1 describes naloxone administration in patients with and without xylazine detected. A large patient minority (42.1%) in both groups required multiple doses of naloxone.

Cardiovascular-related clinical outcomes were uncommon and did not differ between patients who did and did not have xylazine detected (Table 2). Xylazine-negative patients were more likely to have cardiac arrest compared to xylazine-positive patients: 33 patients (14.3%) without xylazine compared to four patients with xylazine [(4.4%), $P = 0.013$; 95% CI −0.16, 0.036)]. The 95% confidence interval is –0.16 to –0.036.

Coma was documented in 24 (26.7%) xylazine-positive patients within 4 h and persisted in 12 patients (13.3%) beyond 4 h. In contrast, coma was documented in 87 (37.7%) xylazine-negative patients within 4 h and persisted beyond 4 h in 35 patients (15.2%). However, there was no significant difference in early or late coma rates among those with and without xylazine (Table 2).

Most patients were discharged from the ED (59 [65.5%] xylazine-positive, vs. 147 [63.6%] xylazine-negative patients). One xylazine-positive patient (1.1%) died, compared with five (2.16%) xylazine-negative patients. The proportion of patients discharged from the ED, admitted patient average length-of-stay, and mortality rates were not significantly different between the xylazine-positive and xylazine-negative groups.

Table 3 shows multivariate logistic regression modeling results for patients developing coma within 4 h of ED arrival. After controlling for age group, sex, race, prior psychiatric history, initial blood pressure and naloxone administration, xylazine exposure was associated with a significantly lower odds of developing coma within 4 h of ED arrival (OR = 0.52, 95% confidence interval: 0.29 − 0.94). Blacks/African Americans (OR = 1.95, CI: 1.01–3.74), unknown race (OR = 3.64, CI: 1.63–8.16), and receiving naloxone (OR = 2.48, CI: 1.29–4.79) were associated with significantly higher odds of coma within 4 h of ED arrival.

Table 4 shows multivariate logistic regression modeling results for patients with cardiac arrest. After controlling for age group, sex, race, prior psychiatric history, initial blood pressure and administration of naloxone, xylazine exposure was associated with a significantly lower odds of cardiac arrest (OR = 0.30, 95% confidence interval: 0.10 − 0.92). Black/African American race (OR = 0.23, CI: 0.06–0.84) was also associated with lower odds of cardiac arrest.

Discussion

In this large multicenter study analyzing xylazine overdose severity in ED patients, our primary finding was that clinical

Table 2. Clinical outcomes in xylazine vs. control patients.

Clinical outcome variables	Xylazine ($n = 90$)	Xylazine absent ($n = 231$)	*P*-Value
Cardiovascular outcomes			
Received CPR	4 (4.4%)	33 (14.3%)	**0.013**
Bradycardia	2 (2.2%)	4 (1.7%)	0.77
Pulmonary outcomes			
Intubated within 4 h	2 (2.2%)	13 (5.6%)	0.193
Non-invasive positive pressure within 4 h	1 (1.1%)	4 (1.7%)	0.689
Any ventilatory support within 4 h	3 (3.3%)	17 (7.4%)	0.182
Intubated after 4 h	2 (2.2%)	11 (4.8%)	0.298
Non-invasive positive pressure after 4 h	2 (2.2%)	2 (0.9%)	0.327
Any ventilatory support after 4 h	4 (4.4%)	13 (5.6%)	0.67
Central nervous system outcomes			
Coma within 4 h	24 (26.7%)	87 (37.7%)	0.063
Coma after 4 h	12 (13.3%)	35 (15.2%)	0.682
Overall outcomes			
Death	1 (1.1%)	5 (2.16%)	0.528
Discharged from the ED	59 (65.6%)	147 (63.6%)	0.528
ICU Admissions	11 (12.2%)	39 (16.9%)	0.30
Miscellaneous			
Length of hospitalization (h); median (IQR)	10 (5–28)	9 (5–36)	0.806
Total naloxone dose (mg)	3.68 (1.3–4.05)	2.8 (2–4.1)	0.448

Abbreviations: IQR, interquartile range; CPR, cardiopulmonary resuscitation; ED, emergency department; ICU, intensive care unit. The bold values indicate variables that are statistically significant ($P < 0.05$).
*Percentage of entire cohort.

Table 3. Modelling xylazine as an independent predictor of coma.

Variable name	aOR	95% CI
Xylazine	**0.52**	**0.29–0.94**
Age category		
18–29 years old	REF	REF
30–39 years old	1.52	0.73–3.17
40–50 years old	0.92	0.41–2.05
50+ years old	1.54	0.69–3.45
Sex		
Female	REF	REF
Male	1.49	0.84–2.64
Race category		
Non-Hispanic White	REF	REF
Black/African American	**1.95**	**1.01–3.74**
Asian	1.00	–
Hispanic	0.51	0.15–1.67
Other/Native American/Hawaiian/mixed race	2.54	0.72–8.91
Race - unknown	**3.64**	**1.63–8.16**
Prior psychiatric history	0.87	0.49–1.56
Initial ED blood pressure	0.99	0.97–1.00
Received naloxone	**2.48**	**1.29–4.79**

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; ED, emergency department; REF, reference category. Variables in **bold** were statistically significant.

Table 4. Modelling xylazine as an independent predictor of cardiac arrest.

Variable name	aOR	95% CI
Xylazine	**0.30**	**0.10–0.92**
Age category		
18–29 years old	REF	REF
30–39 years old	1.41	0.57–3.50
40–50 years old	0.78	0.26–2.35
50+ years old	0.56	0.15–2.03
Sex		
Female	REF	REF
Male	0.68	0.32–1.44
Race category		
Non-Hispanic White	REF	REF
Black/African American	**0.23**	**0.06–0.84**
Asian	1.00	–
Hispanic	1.63	0.51–5.23
Other/Native American/Hawaiian/mixed race	1.10	0.21–5.69
Race unknown	0.80	0.24–2.67
Prior psychiatric history	1.93	0.92–4.05
Received naloxone	1.37	0.52–3.61

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; ED, emergency department; REF, reference category. Variables in **bold** were statistically significant.

outcomes for ED patients with illicit opioid overdose were significantly less severe in those testing positive for xylazine compared to those testing negative for xylazine. Additionally, high rates of cardiac arrest (11.5% of patients analyzed) and high total naloxone requirements (3.68 mg xylazine vs. 2.8 mg non-xylazine) were observed. Importantly, almost all xylazine patients had fentanyl/fentanyl analogs detected rather than heroin. These findings are consistent with recent reports describing a strong association between xylazine detection and fentanyl analogs in the illicit drug supply [9,17,21,22].

Our findings of lower odds of cardiac arrest and coma among xylazine-adulterated opioid overdoses are consistent with and build upon prior studies. Previously, commonly described xylazine overdose clinical effects included CNS depression, bradycardia, and hypotension [10,27,28]. Xylazine overdose case reports have described respiratory depression, hyperglycemia, and hypotonia [27,29]. With supportive treatment, most patients recover from xylazine intoxication [27]. In our study, the mortality rate overall was low, and most patients in both groups were discharged from the ED. Both groups had similar initial ED vital signs, and there was no difference in rates of bradycardia. These findings may be explained by the increasing presence of adulterants, contaminants, and other substances in illicit opioids.

In the present study, there remains a question of whether xylazine was an adulterant or desired component of the illicit opioid supply. Adulterants are pharmacologically active substances added to mirror or enhance specific drug effects [30] and have been well-described in illicit drug supply studies. Adulterants in heroin have included scopolamine [31] and quinine [32,33], and more recently clenbuterol [34,35] and

novel synthetic opioids [36,37]. Recent reports have described the adulterant role of xylazine as one that improves and prolongs opioid-associated euphoria [9].

The explanation for the findings associated with xylazine-adulterated opioids remains elusive. Xylazine does not cause the same degree of respiratory depression as opioids, especially fentanyl. It is possible that a drug sample containing both xylazine and an opioid may result in exposure to a lower opioid concentration. Alternatively, other adulterants, contaminants, or novel psychoactive substances in patients' illicit opioid products may account for lower cardiac arrest and high ED discharge rates. Finally, it is possible that patients without xylazine exposure were exposed to higher total opioid amounts.

Despite similar mortality rates between groups, the xylazine group had significantly lower adjusted odds of cardiac arrest. Cardiac arrest following opioid overdose is mechanistically preceded by respiratory arrest, leading to hypercarbia, respiratory acidosis, and cardiovascular collapse. In pre-hospital settings, CPR initiation may be triggered by bystanders or emergency medical services for an apneic patient. Respiratory depression from xylazine is markedly less severe than that from opioids. Thus, the xylazine group may have had decreased risk of severe respiratory depression, and account for the lower odds of cardiac arrest.

Patients with detectable xylazine and an illicit opioid had approximately half the rate of coma within 4 h of ED arrival. Due to the alpha-2 adrenergic agonist effects of xylazine, we hypothesized that the xylazine group would have a higher likelihood of developing early coma. Several factors may contribute to these results. The amount of xylazine contained in a sample may cause mild clinical CNS effects. Most case reports of xylazine exposure associated with hemodynamic or severe CNS depression/coma have described large, single-agent exposures. Also, the combination of insufficient xylazine and decreased total opioid concentration may have led to lower overall rates of coma.

Interestingly, all patients had relatively high total naloxone requirements (3.68 mg xylazine vs. 2.8 mg non-xylazine), but there was no significant difference in initial or total naloxone doses received between the groups. We hypothesized that patients in the illicit opioid only group might receive a higher total naloxone dose or more frequent repeat naloxone dosing, due to the opioid dose received or high potency of fentanyl/nitazene analogs. Again, the presence of other adulterants or contaminants may have limited the patient's total opioid exposure. Alternatively, patients in the xylazine-opioid group may have received more naloxone due to mild xylazine-related CNS depression, which could be mistaken for opioid-related CNS depression. If ED clinicians are titrating naloxone to reverse CNS depression, frequent repeat dosing may result.

Finally, there was no association between the xylazine group and ED length-of-stay or hospital admission. Most patients in both groups were discharged from the ED. Several clinical care factors may explain this finding. The relative concentration of xylazine in a drug sample and subsequently small hemodynamic or CNS changes are easily managed with ED resuscitation, such as intravenous fluids, and standard ED observation times. Also, because xylazine is an increasingly prevalent adulterant, ED clinician disposition decision-making is likely guided by opioid and naloxone pharmacokinetic knowledge, and without consideration to monitor for the potential clinical effects of xylazine. Because the human half-life of xylazine is not known, it is difficult to assess if the pharmacokinetics are related to patient length-of-stay.

Limitations of the present study require some consideration. Waste clinical specimens were not available for a large proportion of patients screened, leading to a large number of exclusions; this likely contributed to a higher overall overdose severity for patients included. Many screened patients did not have blood samples obtained in the ED, and patients who had blood work performed may represent a skewed overdose population. Blood sampling provided qualitative detection only; because quantitative serum concentrations were not measured, and opioid concentrations were not adjusted for, it is fraught to infer causality. Additionally, we do not know the relative timing of substance use; therefore, it is possible, though unlikely, that the presence of xylazine represented a prior drug exposure.

Because this study focused on ED patients, pre-hospital fatalities which were pronounced in the field were not examined; however, there were many cardiac arrests in the field which were successfully resuscitated and survived to hospital discharge. Lastly, given the severity of the US opioid epidemic, the study regions may limit generalizability especially to international locations. All participating ToxIC sites were located in large cities, and findings may not be applicable to rural communities.

Future studies should focus on measuring illicit opioid and xylazine serum concentrations to evaluate if relative serum concentrations of opioids, xylazine or other adulterants predict clinical effects and patient outcomes. Additionally, antidotal naloxone use to reverse xylazine toxicity is theoretically plausible [38] but its efficacy is understudied.

Conclusions

In summary, in this large multicenter cohort study, ED patients with illicit opioid overdose testing positive for xylazine had significantly lower odds of cardiac arrest and coma. Confirmed illicit opioids consisted mostly of fentanyl and fentanyl analogs, rather than heroin. Overall rates of cardiac arrest and total naloxone dosing following acute opioid overdose were relatively high, consistent with the high prevalence of potent fentanyl and fentanyl analogs detected.

Author contributions

AFM, ML, KA, JB, AJK, BKL and PW conceptualized the study. AFM was primarily responsible for funding acquisition. AJK, BKL and SEW were responsible for toxicologic specimen data analysis and acquisition, while KA, AFM and the ToxIC study group were responsible for clinical data acquisition. JSL, ML, CVT and AFM conducted formal data analysis. JSL and ML wrote the original manuscript draft, and all authors were responsible for manuscript review and editing.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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