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Widespread Distribution of Xylazine Detected Throughout the United States in Healthcare Patient Samples

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Objectives: Xylazine is a tranquilizer commonly added into the illicit drug supply and a likely contributor to overdoses because it does not respond to naloxone reversal. The objective of this study was to perform a retrospective data analysis on xylazine-positive samples collected from patients in various outpatient healthcare settings to illustrate geographic distribution and common copositive substances, which may also contribute to risk of adverse events.

Methods: Samples for which providers ordered testing for xylazine were subjected to enzymatic hydrolysis, extracted, and analyzed using liquid chromatography–tandem mass spectrometry. Retrospective analysis was performed on xylazine-positive samples collected from April 2021 to March 2022, to include geographic location and copositive substances.

Results: Xylazine was identified in 413 of 59,498 samples from adults aged 20–73 years and originated from 25 of the 39 states where xylazine testing was ordered. The most common routine substances detected with xylazine were fentanyl, buprenorphine, naloxone, cocaine, D-methamphetamine, and delta-9-tetrahydrocannabinol. The most common designer drugs detected included fentanyl analogs, isotonitazene, and designer benzodiazepines.

Conclusions: Xylazine is geographically spread throughout the United States, indicative of a wide incorporation into the illicit drug supply. These findings differ from previous studies in that these samples originated from healthcare providers in routine care settings, where other reports typically involve overdose deaths. This analysis illustrates that routine testing for xylazine in outpatient settings can afford providers the opportunity to educate individuals and adjust harm reduction measures to potentially mitigate overdose risk.

Key words: xylazine, designer drugs, substance use disorder, drug testing, overdose prevention

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Xylazine is an α_2-adrenergic agonist initially developed as an antihypertensive agent by Farbenfabriken Bayer AG (Leverkusen, Germany) in 1962, although severe hypotension and central nervous system (CNS) depression in early human clinical trials prevented its approval.[1] The drug was reintroduced in the late 1960s and early 1970s as a veterinary medication for sedation and analgesia[1] and is currently an unscheduled, approved drug by the US Food and Drug Administration for use as a sedative in horses, dogs, cats, deer, and elk.[2] Pharmacokinetic and pharmacodynamic data primarily exist in animal species, with human data currently sparse. Based solely on animal studies, characteristics of xylazine include high lipophilicity, an onset of action within minutes after intravenous administration, an elimination half-life of approximately 23–50 minutes, and extensive metabolism.[3] Xylazine has been shown to exhibit a wide range of mechanistic actions at various receptor sites, including α_2-adrenergic, α_1-adrenergic, cholinergic, serotonergic, dopaminergic, histaminergic, and opiate. This range of actions may potentially contribute to the toxidrome documented in human case reports to date: CNS depression, bradycardia, hypotension, hyperglycemia, and miosis.[3]

Xylazine has emerged as a drug of concern, predominantly as an adulterant in substances such as cocaine, heroin, and illicitly manufactured fentanyl.[3–5] The effects of adding xylazine to other substances is thought to be multifold, either as a bulking agent and/or to enhance the euphoric and sedative effects of pharmacologically similar drugs while attenuating the adverse effects and withdrawal of stimulant drugs. However, these interactions have not been formally evaluated in humans to date, and further research is needed to conclusively identify synergistic or potentiating effects, if any.[3] A review of published case reports indicates a trend of increasing xylazine detection in seized drug samples, toxicity cases, and overdose deaths.[3–7] Cases of nonmedical use initially emerged in the early 2000s in Puerto Rico as an adulterant in predominantly cocaine and heroin.[3,5] A literature review published in 2014 consisted of 42 cases over the span of 17 years, of which 51% of cases were fatal. Of the fatal cases, 94% involved other substances, with 41% involving fentanyl.[3] More recently, published studies have also documented a substantial increase in co-detection of xylazine with fentanyl.[6,8]

Given both the increased observance of xylazine with fentanyl and the overall increase in nonmedical fentanyl use rates, this study documents, for the first time in a widespread sampling of the outpatient setting, incidences of xylazine detection in routinely collected healthcare samples from throughout the United States.

METHODS

This retrospective cohort study was institutional review board approved (Pearl IRB #AG-08-01v2.0). From April 21, 2021, through March 29, 2022, 59,498 urine samples obtained from 39 states were evaluated for xylazine upon request of a healthcare provider as part of a larger Novel Psychoactive Substance profile. Xylazine was solvent extracted from hydrolyzed urine specimens within 96 hours of sample receipt and evaluated qualitatively by high-performance liquid chromatography–tandem mass spectrometry. The method was validated internally using standard industry criteria including, but not limited to specificity, sensitivity (limit of detection), stability, accuracy, precision, matrix interference, and carryover. The analytical cutoff was 10 ng/mL. Retrospective analysis was performed on positive samples to determine geospatial distribution of xylazine and common copositive substances.

RESULTS

Xylazine was detected in 413 of 59,498 samples from adults, aged 20–73 years, during the study period, with positive samples originating from 25 of 39 states where providers ordered testing (Fig. 1). In the xylazine-positive samples, fentanyl was the most detected copositive analyte (96%). When considering traditional toxicology tests, other notable copositive drugs/classes include buprenorphine (48.9%), nicotine metabolites (48.9%), cocaine (44.7%), naloxone (37.7%), D-methamphetamine (33.6%), and delta-9-tetrahydrocannabinol (THC 25.9%), among others. When further testing for designer drugs was ordered, the opioids were most often detected, with fluorofentanyl (54.9%), despropionyl fluorofentanyl (31.4%), benzylfentanyl (7.9%), and a metabolite of isotonitazene (4-hydroxynitazene, 5.3%) most frequently detected. The two most frequently detected designer benzodiazepines were metabolites of etizolam and clonazolam (Table 1). Other designer drugs were detected in fewer than 5% of samples, including synthetic cathinones, cannabinoids, and hallucinogens.

Sample positivity is based on what analytes were ordered and tested; not all samples may have been tested for all classes. Percent positivity is based on number of xylazine-positive samples. Other analytes were detected with decreasing prevalence. The most indicated prescribed drugs from test requisitions for this cohort are buprenorphine (48.1%), naloxone (39.2%), alprazolam (3.6%), gabapentin (3.1%), clonidine (2.6%), methadone (2.4%), quetiapine (2.4%), oxycodone (1.9%), cyclobenzaprine (1.6%), and amphetamine (1.4%). Of note, more than one medication may be listed as prescribed, and not all requisitions include prescription drug information.

DISCUSSION

Although published case reports regarding nonmedical use of xylazine were published as early as the 1980s, adverse effects, including overdose, secondary to use or exposure, have become increasingly reported in the past few years.[9] Updated data from the 2019 State Unintentional Drug Overdose Reporting System reveal an alarmingly steep increase of xylazine cases with 1,357 overdose deaths reported over the span of one year, approximately 3% of all overdose deaths in that year in the continental United States.[4] Of the cases in which xylazine was detected, 39% listed xylazine on the death certificate as a contributing cause of death.[6] The data also show evidence of a shift to illicitly manufactured fentanyl as the predominant coinvolved drug as fentanyl was detected in approximately 99% of all xylazine overdoses.[3,4] The progressing trends in the State Unintentional Drug Overdose Reporting System data are supported by published data from individual locales, such as Connecticut and Texas, which reflect the increasing prevalence of xylazine.[6,7] The permeation of xylazine into the US drug supply has also been documented in Pennsylvania, which revealed a growing trend of xylazine detection in polydrug

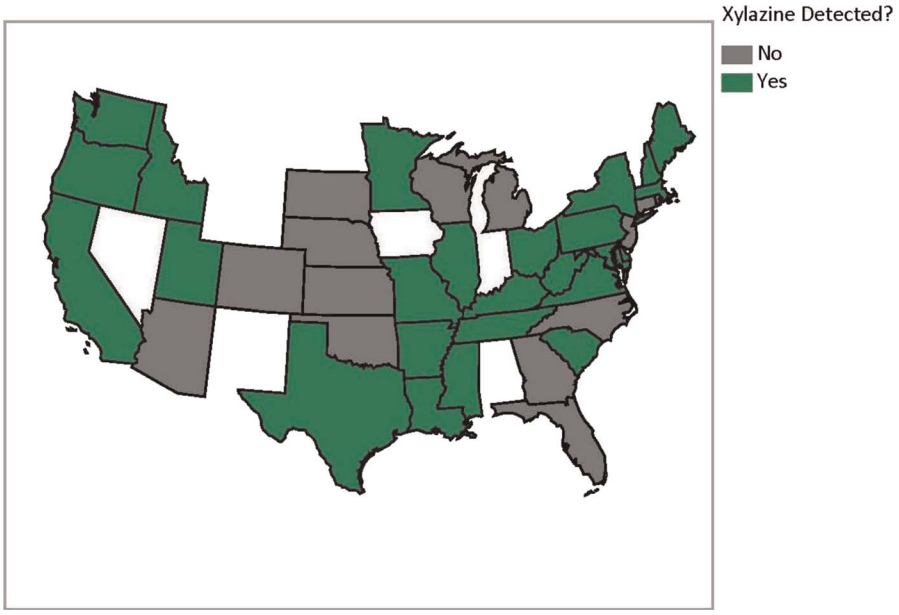

FIGURE 1. States where xylazine testing has been ordered and detection status.

TABLE 1. Copositivity From Traditional Toxicology Testing and Designer Drug Testing of Xylazine-Positive Samples (≥5% Positivity Only)

Compounds Detected Through Routine Testing in 413 Xylazine-Positive Samples	n	% Copositive
Fentanyl	396	95.8%
Buprenorphine	202	48.9%
Cotinine (nicotine metabolite)	202	48.9%
Cocaine	185	44.7%
Naloxone	156	37.7%
Methamphetamine*	141	34.0%
D-methamphetamine†	139	33.6%
THC	107	25.9%
Morphine	64	15.4%
Heroin	56	13.5%
Gabapentin	55	13.3%
Tramadol	49	11.8%
Ethyl glucuronide/ethyl sulfate (ethanol metabolites)	38	9.2%
Methadone	31	7.5%
Nordiazepam/oxazepam/temazepam	25	6.0%
Alprazolam	24	5.8%
Clonazepam	21	5.0%
Compounds Detected Through Enhanced, Designer Drug Testing in 413 Xylazine-Positive Samples	**n**	**% Copositive**
Fluorofentanyl‡	227	54.9%
Despropionyl fluorofentanyl‡	130	31.4%
Benzylfentanyl‡	33	7.9%
alpha-Hydroxyetizolam§	30	7.2%
8-Aminoclonazolam§	28	6.7%
4-Hydroxynitazene‡	22	5.3%

*Nonspecific methamphetamine test.
†Portion of 141 methamphetamine samples confirmed as D-methamphetamine.
‡Designer opioid.
§Designer benzodiazepine.

seizures by the Drug Enforcement Administration: 0% in 2013, 5% in 2015, 9% in 2017, and 25% in 2019.[5]

Our findings demonstrate similar copositivity with other published reports as well as demonstrate that use of xylazine, whether intended or unintended, is not specific to a single region of the United States.[10–12] The actual distribution is likely underrepresented as testing for xylazine was only performed when judged medically necessary by the ordering provider, which is an important limitation of this study. We agree with the notion put forth by Alexander et al.[10] that current surveillance on use of xylazine is limited and feel that integration of results from ambulatory patients indicating use, such as those included in our data set, should be better utilized to monitor the components of the current drug supply. The availability of xylazine testing in the ambulatory population affords providers the opportunity to proactively adjust harm reduction strategies in individuals who test positive.

CONCLUSIONS

Based on this analysis of samples from the US healthcare system, xylazine is likely widespread in the US illicit drug supply, with samples detected throughout the country. It was frequently detected with other drugs, which are known to cause CNS depression, particularly fentanyl, but including other opioids and benzodiazepines, among others. This information is useful to various stakeholders, health policy agencies, public health officials, healthcare providers, and the general populace to better inform harm-reduction strategies, as it is known that xylazine is not reversible by naloxone and can potentiate CNS and respiratory depression caused by concurrently ingested opioids and benzodiazepines.

REFERENCES

1. Greene SA, Thurmon JC. Xylazine—a review of its pharmacology and use in veterinary medicine. *J Vet Pharmacol Ther*. 1988;11(4):295–313.
2. US Food and Drug Administration. Animal Drugs @ FDA. Available at: http://animaldrugsatfda.fda.gov/adafda/views/#/search. Updated April 2022.
3. Ruiz-Colón K, Chavez-Arias C, Díaz-Alcalá JE, et al. Xylazine intoxication in humans and its importance as an emerging adulterant in abused drugs: a comprehensive review of the literature. *Forensic Sci Int*. 2014;240:1–8.
4. Kariisa M, Patel P, Smith H, et al. Notes from the field: xylazine detection and involvement in drug overdose deaths—United States, 2019. *MMWR Morb Mortal Wkly Rep*. 2021;70(37):1300–1302.
5. Johnson J, Pizzicato L, Johnson C, et al. Increasing presence of xylazine in heroin and/or fentanyl deaths, Philadelphia, Pennsylvania, 2010–2019. *Inj Prev*. 2021;27(4):395–398.
6. Nunez J, DeJoseph ME, Gill JR. Xylazine, a veterinary tranquilizer, detected in 42 accidental fentanyl intoxication deaths. *Am J Forensic Med Pathol*. 2021;42(1):9–11.
7. Forrester MB. Xylazine exposures reported to Texas poison centers. *J Emerg Med*. 2016;51(4):389–393.
8. Chhabra N, Mir M, Hua MJ, et al. Notes from the field: xylazine-related deaths—Cook County, Illinois, 2017–2021. *MMWR Morb Mortal Wkly Rep*. 2022;71(13):503–504.
9. Gallanosa AG, Spyker DA, Shipe JR, et al. Human xylazine overdose: a comparative review with clonidine, phenothiazines, and tricyclic antidepressants. *Clin Toxicol*. 1981;18(6):663–678.
10. Alexander RS, Canver BR, Sue KL, et al. Xylazine and overdoses: trends, concerns, and recommendations. *Am J Public Health*. 2022;112(8):1212–1216.
11. Friedman J, Montero F, Bourgois P, et al. Xylazine spreads across the US: a growing component of the increasingly synthetic and polysubstance overdose crisis. *Drug Alcohol Depend*. 2022;233:109380.
12. Kacinko SL, Mohr ALA, Logan BK, et al. Xylazine: pharmacology review and prevalence and drug combinations in forensic toxicology casework. *J Anal Toxicol*. 2022;46(8):911–917.

