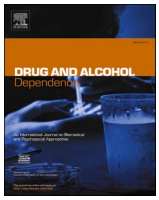
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Short communication

Assessing an ICD-10 code approach for estimating xylazine-involved overdose deaths in the United States

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ABSTRACT

Introduction: The prevalence of the veterinary sedative xylazine in US overdose deaths rose between 2018 and 2021. More updated estimates are limited, partially due to the lack of a dedicated ICD-10 code—a primary mechanism used to specify drugs implicated in overdose deaths in the US, including in the CDC WONDER system, which provides public data for download with a 6-month lag. For other emerging substances lacking dedicated codes, over time umbrella codes have come to *de facto* represent them, yet it has not been demonstrated if this has occurred for xylazine.

Methods: Overdose deaths in CDC WONDER involving T42.7 ("Antiepileptic and sedative-hypnotic drugs, unspecified") or T46.5 ("Other antihypertensive drugs, not elsewhere classified") were compared to two more specific, albeit delayed, sources: NVSS describing national trends in 2018–2021 and SUDORS describing state-level trends in 2020–2022. This CDC WONDER approach was also used to estimate trends in xylazine-involved deaths through 2024 Q1 by geography, race/ethnicity, substance co-involvement, and demographic categories.

Results: At the national level, concordance between CDC WONDER records and previous NVSS estimates improved after 2019 and became highly similar in 2021 (3480 vs 3468 deaths). Concordance was also high for estimates stratified by race, age, and region. At the state-level, across 49 state-year pairs, correlation between CDC WONDER and SUDORS was 0.97. Estimated xylazine-involved deaths doubled between 2021 and 2024 Q1, and estimated racial inequalities widened.

Discussion: T42.7 or T46.5, together, may have become the *de facto* coding scheme representing xylazine-involved deaths. This approach provides more up-to-date estimates, showing increasing prevalence and worsening racial inequalities in xylazine-involved deaths into 2024.

1. Introduction

The widespread proliferation of the veterinary α2-agonist xylazine in the illicit fentanyl supply of the United States (US) has been associated with numerous health risks (Friedman et al., 2022; Wightman et al., 2024; Rodríguez et al., 2008; Thompson et al., 2024; Jawa et al., 2024) and has been labeled an emerging threat by government officials (Gupta et al., 2023). Previous nationally-representative reports have documented rising xylazine prevalence among overdose deaths between 2018 and 2021 (Gupta et al., 2023; Spencer et al., 2023) and studies drawing on a subset of US states have shown further increases into 2022 (Cano et al., 2024; Kariisa, 2023). However, more updated trends are not currently publicly available, partially due to the lack of a dedicated or previously agreed upon code for xylazine in the tenth revision of the International Classification of Diseases (ICD-10).

ICD-10 codes are a primary mechanism used to track the specific drugs implicated in overdose deaths in the US. In particular they are the main way that substances are specified in the Center for Disease Control and Prevention (CDC) Wide-ranging ONline Data for Epidemiologic Research (WONDER) database (CDC, 2022), which is used by researchers, policymakers, and the public to access the most up-to-date federal death statistics. CDC WONDER generally makes overdose death statistics available on an approximately 6-month lag, due to inherent delays involved in overdose toxicology testing (Spencer, 2016).

While older drugs such as heroin and cocaine have bespoke ICD-10 codes (T40.1 "Heroin" and T40.5 "Cocaine," respectively), drugs of more recent importance often lack specific codes. However, for some of these substances, such as fentanyl and methamphetamine, over time

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they have become *de facto* represented by umbrella codes (T40.4 "Other synthetic narcotics" and T43.6 "Poisoning by, adverse effect of and underdosing of psychostimulants [not including cocaine]", respectively, in the case of these two substances). These broader codes have become widely understood to mainly represent these drugs of particular importance, although in a small number of cases they may also represent other similar substances (Han et al., 2021; Friedman and Shover, 2023).

Given the lack of a dedicated ICD-10 code, deaths involving xylazine have largely been tracked using other data sources, such as free text searches in the National Vital Statistics System (NVSS) (Spencer et al., 2023), or the CDC's State Unintentional Drug Overdose Reporting System (SUDORS) (Kariisa, 2023). Both systems leverage more detailed underlying records; however, neither allows the public to use data queries to access continuously updated records, which is a primary advantage of CDC WONDER.

Although there is currently no agreed upon standard set of ICD-10 codes for xylazine, in a recent viewpoint, Gupta et al. used two codes—T42.7 ("Antiepileptic and sedative-hypnotic drugs, unspecified") or T46.5 ("Other antihypertensive drugs, not elsewhere classified")—to represent national xylazine deaths (Gupta et al., 2023). If these codes prove to reliably represent xylazine-involved deaths, there would be numerous potential advantages for producing timely statistics. However, in addition to xylazine, these codes may also represent deaths from other medications, such as levetiracetam or gabapentin, which may bias results (Spencer et al., 2023; Cano et al., 2024). Therefore, further assessment is warranted to see how death rates from these ICD-10 codes compare against other more specific, albeit delayed, sources of data.

Additionally, in order to illustrate the possible utility of this approach, the method was used to estimate detailed trends in xylazine-involved deaths through March 2024 by geography, race/ethnicity, substance co-involvement, and demographic categories.

2. Methods

The CDC WONDER platform was used to estimate overdose deaths involving the T42.7 or T46.5 multiple cause of death ICD-10 codes, from January 2018-March 2024 (CDC, 2022). Overdose deaths were defined as those corresponding to underlying cause of death codes X40–X44 (unintentional), X60–X64 (suicide), X85 (homicide), and Y10–Y14 (undetermined intent). 95 % uncertainty intervals were estimated assuming a Poisson distribution. Data from 2023 and 2024 are provisional and may be updated in final numbers. Estimates from January-March (Q1) 2024 were annualized to reflect full year totals should Q1 death rates persist. Race/ethnicity categories were used as defined in the underlying data. See supplemental methods for more details on data preparation. Rates per 100,000 were calculated using population estimates from CDC WONDER.

Xylazine-involved deaths estimated using the ICD-10 code based approach described above were compared to two more specific, albeit delayed, sources describing national and state-level trends in xylazine deaths: NVSS and SUDORS. NVSS data were available from a report published by Spencer et al., which examined free text fields on all death certificates in the system to describe xylazine deaths between 2018 and 2021 by year, race, age, and region (Spencer et al., 2023). A publicly available SUDORS database was used to assess annual counts of xylazine-involved deaths between 2020 and 2022 for 29 participating states (Kariisa, 2023). State-level concordance between deaths estimated via CDC WONDER and xylazine deaths reported in the SUDORS system was assessed using a Pearson correlation coefficient and a bivariate linear regression, with the intercept fixed at 0 (allowing for the slope to represent the average ratio of the magnitude between the two data sources).

This study was deemed exempt from review and informed consent by the University of California, San Diego Institutional Review Board as it uses only publicly available, de-identified records.

3. Results

At the national level, overdose deaths coded with either T42.7 or T46.5 in CDC WONDER initially overestimated xylazine deaths according to NVSS in 2018 (with 260 vs 110 deaths, respectively) and 2019 (728 vs 627 deaths) (Fig. 1A). However, the two measures converged considerably in 2020 (1611 vs 1499 deaths) and became highly similar in 2021 (3480 vs 3468 deaths). Concordance by race, age, and region in 2021 was also high (Fig. 1A).

State-level concordance between deaths in CDC WONDER coded with T42.7 and T46.5, and xylazine deaths in the SUDORS system, is shown in Fig. 1B. The overall correlation across the n = 49 observed state-year pairs was 0.970. Across these 49 paired data points, a regression model predicting CDC WONDER-derived xylazine death rates using SUDORS xylazine death rates as an explanatory variable, with an intercept fixed at 0, showed a slope of 0.854 (95 % CI: 0.802 – 0.906), and an adjusted R squared of 0.955. This means that CDC WONDER tended to underestimate trends from SUDORS by about 15 %, but the overall predictive power was quite high, with about 95 % of variation explained.

Examining the breakdown of deaths from T42.7 and T46.5 shows a shifting pattern over time (Supplemental Figure 1). In 2019 and 2020, the majority of all deaths from either cause were coded as T46.5 "Other antihypertensive drugs, not elsewhere classified". Deaths identified with this ICD-10 code increased from 112 in 2018, to 460 in 2019, and to 1208 in 2020, showing a rapid rise, unlikely to be due to increasing deaths from another substance besides xylazine. After 2020, T42.7 "Antiepileptic and sedative-hypnotic drugs, unspecified" became the most common code, and between 2022 and 2024 it represented over 96 % of the total deaths from either code (Supplemental Figure 1).

Estimates leveraging this ICD-10 code based method are shown in Fig. 2 and Supplemental Table 1. The national xylazine-involved overdose death rate was estimated to have increased steadily during the study period and double between 2021 (1.05 per 100,000; 95 % CI: 1.01–1.08) and Q1 2024 (2.11; 2.06–2.16). Rates in 2023 were estimated to be higher among men (2.73 per 100,000; 95 % CI: 2.65–2.81) than women (1.07; 1.02–1.12), and the highest among the 35–44 (4.06; 3.88–4.26) and 45–54 (3.35; 3.18–3.53) age groups. During the study period the estimated rate among Black and African Americans overtook that of other groups, reaching 3.31 per 100,000 (95 %CI: 3.13–3.48) in 2023, representing 1.75 (95 %CI: 1.66–1.84) times the estimated national average. In 2023, fentanyl, cocaine, and methamphetamine were co-involved in 96 % (95 %CI: 93 %-98 %), 38 % (36 %-39 %) and 23 % (22 %-24 %) of estimated xylazine-involved overdose deaths, respectively. By 2023, all census divisions were affected by xylazine-involved overdose mortality; the Middle Atlantic (5.83 per 100,000; 95 % CI: 5.6–6.07) and New England (4.48, 4.15–4.83), had the highest estimated rates, while the Pacific had the lowest (0.31, 0.26–0.36). The states with the highest estimated death rates were Vermont, Pennsylvania, Connecticut, West Virginia, and New York. In 2023, 38 states had at least 10 estimated xylazine-involved overdose deaths, the minimum required for reporting a rate in the CDC WONDER system.

4. Discussion

By 2021, a high concordance was observed at the national level between estimates of xylazine-involved overdose deaths in the CDC WONDER system (using the T42.7 or T46.5 ICD-10 codes) and those of the NVSS system. At the state-level, compared to the SUDORS system, the ICD-10 code based approach somewhat underestimated xylazine-involved death rates, however still showed a high predictive power and correlation. It is important to note that there are underlying differences between CDC WONDER, the NVSS system, and SUDORS, and identical results would not be expected (see supplement). Instead, each of these methods represents a signal from a slightly different set of populations, measured in slightly different ways, yet which should all be

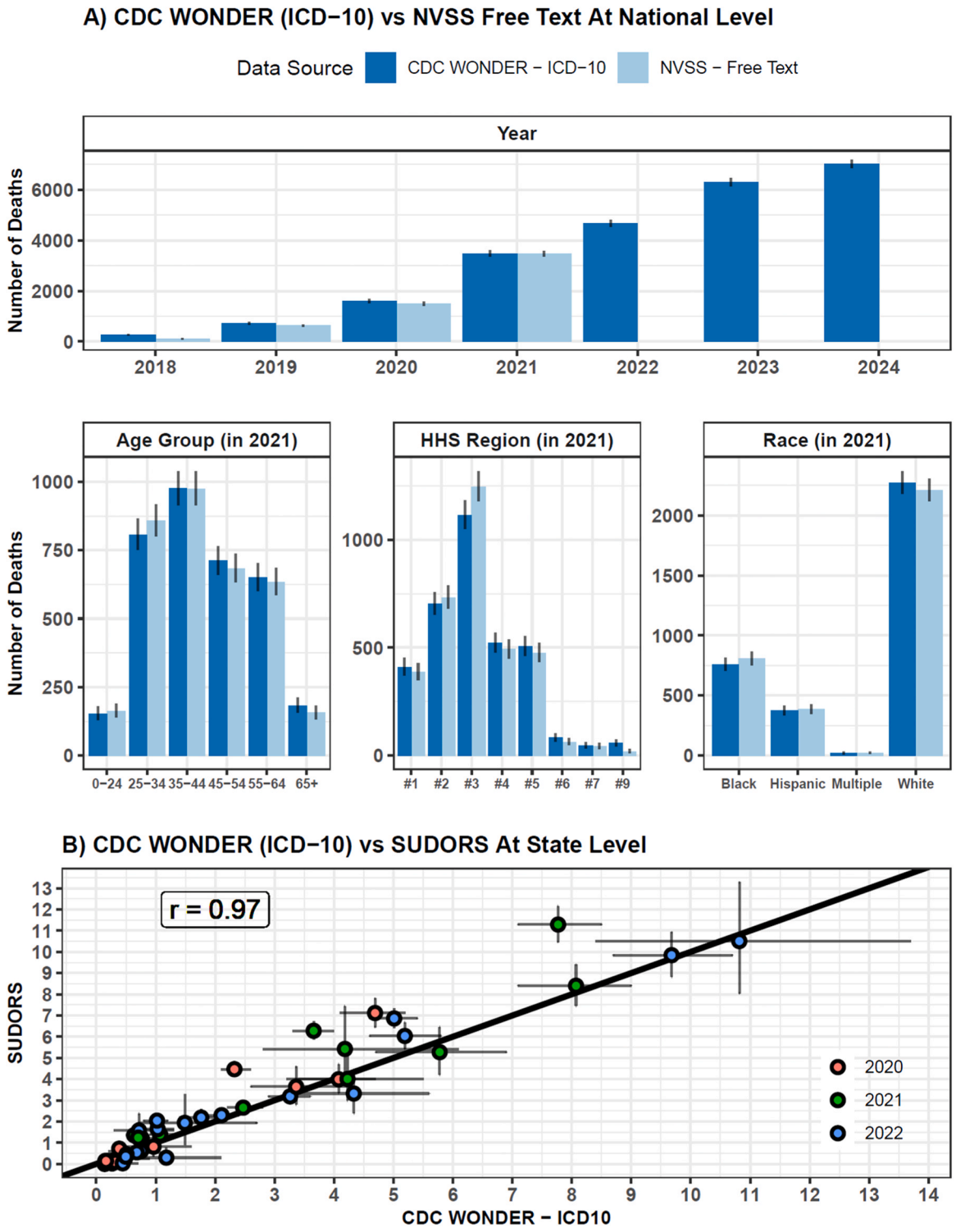


Fig. 1. Comparing Xylazine Overdose Deaths Using ICD-10 Codes, SUDORS, and NVSS Free Text A) Results from the CDC-WONDER ICD-10 code based approach are compared to published results from NVSS by year, race, age group, and HHS region. Data for race, age group, and HHS region are only shown for 2021, as it was the latest year of data available in the NVSS comparison dataset. 95 % uncertainty intervals were estimated using a Poisson distribution and are shown with vertical bars. Data from 2023 and 2024 are provisional and may change in final numbers. Numbers from 2024 represent annual equivalents based on data from January-March only. HHS regions include: #1 (CT, ME, MA, NH, RI, VT), #2 (NJ, NY), #3 (DE, DC, MD, PA, VA, WV), #4 (AL, FL, GA, KY, MS, NC, SC, TN), #5 (IL, IN, MI, MN, OH, WI), #6 (AR, LA, NM, OK, TX), #7 (IA, KS, MO, NE), #9 (AZ, CA, HI, NV). B) State-level estimates are compared between CDC WONDER and SUDORS. Each point represents data from a particular state and year for which data from both sources was available (n = 49). On both the x and y-axis, estimated annual xylazine-involved overdose mortality rates are shown. SUDORS data are limited to 29 participating jurisdictions. CDC WONDER data are limited to jurisdictions with at least 10 deaths occurring per year. Point color indicates year. 95 % uncertainty intervals for both measures are shown with vertical and horizontal bars. Uncertainty intervals for CDC WONDER data were available directly from the platform. Uncertainty intervals for SUDORS data were estimated using a Poisson distribution. A line of equality is shown in black. The overall correlation coefficient across the n = 49 observed pairs of datapoints was r = 0.97. All CDC WONDER and SUDORS data shown here are finalized (not provisional).

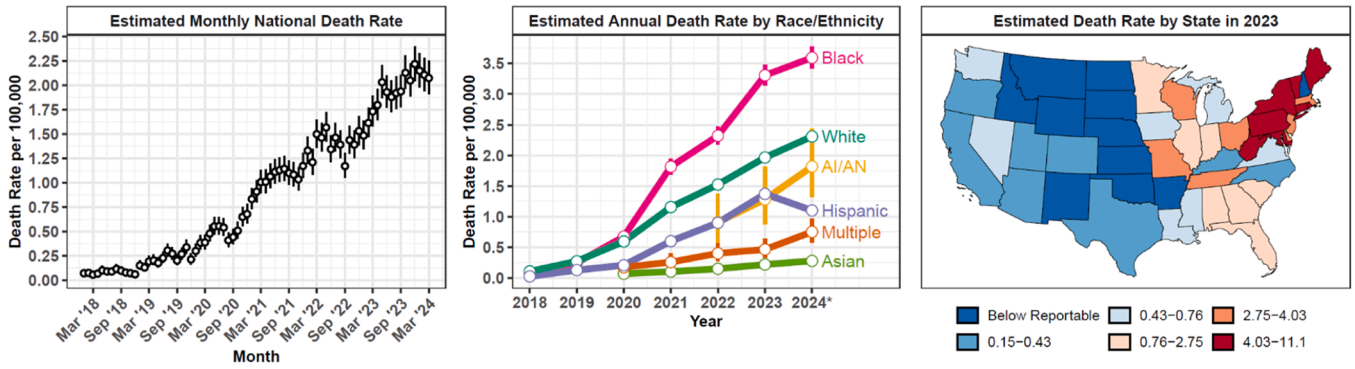


Fig. 2. Estimates of National Xylazine-Involved Overdose Deaths Using CDC Wonder ICD-10 Code Approach Overall, this figure shows high-level trends in estimated xylazine-involved overdose mortality by key dimensions including time, race/ethnicity, and state. Left. National-level estimates of xylazine-involved overdose deaths per 100,000 are shown by month with 95 % uncertainty intervals. Middle. National-level estimates of xylazine-involved overdose deaths per 100,000 are shown by race/ethnicity and year, with 95 % uncertainty intervals. Right. Estimates of xylazine-involved overdose deaths per 100,000 in 2023 are shown by state. 95 % uncertainty intervals were estimated using a Poisson distribution, as they are not directly available for all estimated quantities in CDC WONDER (e.g. when stratifying data by month). Data from 2023 and 2024 are provisional and may change in final numbers. *Numbers from 2024 shown in the middle panel represent annualized values based on data from January-March only.

roughly comparable in terms of big picture results. Therefore, rather than a formal validation study (which is not possible to conduct with publicly available data at this time), this analysis seeks to establish if these various methods of representing xylazine-overdose deaths are roughly compatible—and it concludes that they likely are, at least after 2019. A formal validation study—most feasibly conducted by government researchers with access to fully linked records—would represent an important next step in conclusively establishing a *de facto* ICD-10 code for xylazine-involved deaths.

The breakdown of deaths between these two codes (T42.7 and T46.5) suggests that both were likely initially used to code for xylazine-involved deaths between 2018 and 2021, with T46.5 predominating in 2019 and 2020. After 2021, T42.7 appears to have become the default code for this purpose, with deaths corresponding to T46.5 dropping to very low levels. This suggests that moving forward, using T42.7 as the primary code for xylazine may be sufficient. Nevertheless, historical analyses including data from before 2022 should likely also use T46.5. The historical reasons for the shift from T46.5 to T42.7 may relate to customs and habits among medical examiners, however this represents an important area for further study.

These results suggest that these two ICD-10 codes, together, may have become the *de facto* coding scheme used to represent xylazine-involved deaths, similar to other umbrella codes that have taken on a similar role for fentanyl and methamphetamine. This could allow researchers, policymakers, and the public to assess xylazine-involved death trends in CDC WONDER by race, geography, age, sex, and other dimensions, with an approximately 6-month lag. Rather than replacing analyses relying on more detailed systems—such as SUDORS or free text in the NVSS system—the ICD-10 code based approach may simply provide a method of measuring xylazine-involved deaths in a more rapid and publicly transparent fashion.

The small—and likely stable—number of annual deaths represented by these codes involving levetiracetam, gabapentin, or other non-xylazine agents appear to have a minimal effect on the total number of deaths after 2019. However, ongoing validation against subsequently released NVSS and SUDORS records would be valuable, to confirm that these data sources continue to be roughly comparable.

Even if a *de facto* set of ICD-10 codes for xylazine is established, numerous challenges remain for tracking xylazine-involved deaths. Given limited testing, the death tolls shown here—using any of the data sources available—almost certainly represent underestimates of the true spread of xylazine (Gupta et al., 2023; Spencer et al., 2023). Xylazine also has a short half-life, and—although the pharmacokinetics in humans are imperfectly understood—this may limit the detection of the drug in toxicological testing (Ruiz-Colón et al., 2014).

Given the limitations of the CDC WONDER public-facing query system, it is possible to generate counts of deaths involving two specific substances (e.g. deaths involving xylazine and fentanyl) but not specifically delineate groups of deaths involving 3 + substances (e.g. xylazine, fentanyl, and cocaine), or deaths involving 2 substances but excluding a third substance (e.g. xylazine and cocaine, but not fentanyl). This limits the degree to which polysubstance patterns can be detailed using this approach. More nuanced assessments of clusters of drugs involved in xylazine-positive deaths could be accomplished via SUDORS or other more detailed death data sources.

Xylazine is also only one of numerous novel substances of concern emerging in the US illicit drug supply, which are spreading rapidly, and lack dedicated ICD-10 codes. Across each of these substances of novel importance, more flexible and transparent systems are needed to track the diverse substances increasingly involved in overdose deaths and provide results to the public in a rapid and transparent fashion.

Leveraging this method also provides insights into recent trends in the spread of xylazine. The prevalence of xylazine-involved overdose deaths has continued to rise sharply in recent years. Although the Northeast remains the most affected region, as xylazine continues to advance from East to West across the nation (Friedman et al., 2021), it is now present in all major US regions, and the vast majority of states. Racial inequalities in xylazine-involved overdose mortality have also risen sharply—with Black and African Americans almost twice as affected as the national average by 2023—which warrants tailored interventions to reduce inequalities directly (Friedman et al., 2024). Similar inequalities are also present for Black and African Americans among total and fentanyl-involved overdose death rates (Friedman et al., 2024), with inequalities among xylazine deaths mimicking national trends. Nevertheless, differences in patterns of inequalities do exist; for instance, at the national level, American Indian and Alaska Native populations have the highest overdose deaths rates of any major racial/ethnic group, whereas they are less affected than the national average for xylazine-involved overdose deaths (Friedman et al., 2024). A significant portion of trends in xylazine-involved deaths are likely explained by trends in fentanyl deaths, given the tight ecological link between fentanyl and xylazine (Friedman et al., 2021). Nevertheless, with fentanyl-involved deaths decreasing nationally, and xylazine increasingly spreading West across the US, further detailed studies will be required to parse apart these competing dynamics contributing to overall xylazine-involved deaths numbers.

CRediT authorship contribution statement

Joseph Friedman: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization

Declaration of Competing Interest

The author declares 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.2025.112781.

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