Millennium Health Signals Report™

Zeroing in on Xylazine:

The First 100 Days After U.S. Emerging Threat Designation

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Background

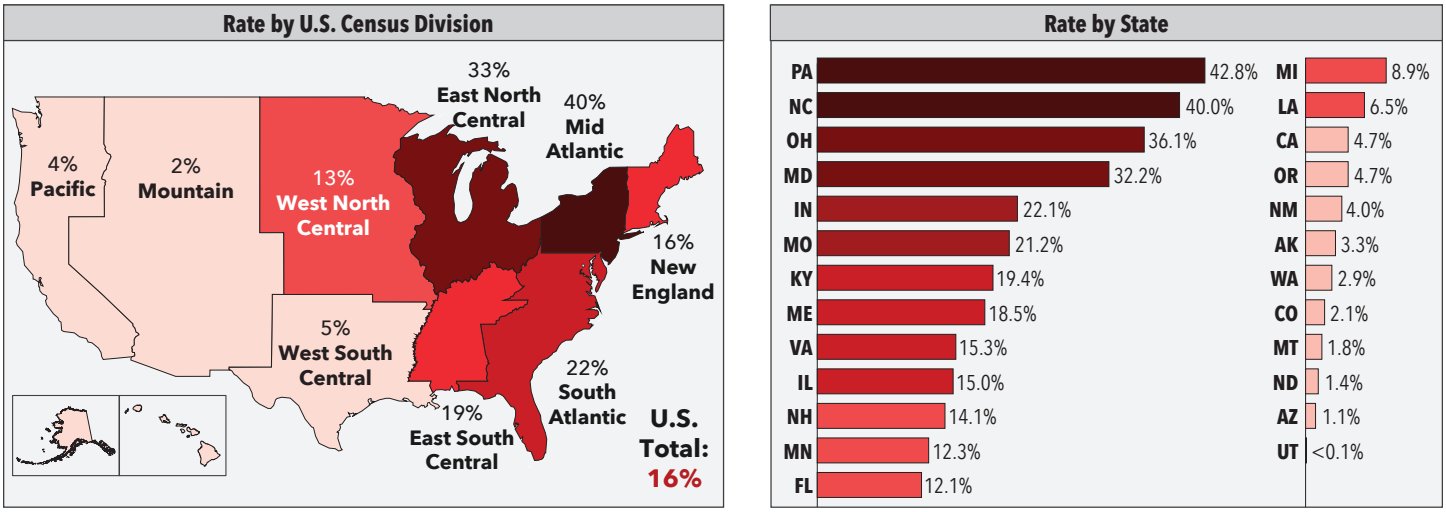
Xylazine, also known as "tranq," is a powerful, non-opioid, veterinary tranquilizer that is not approved for human use. Similar to clonidine in structure and action, xylazine produces marked sedation, muscle relaxation, and potentially dangerous reductions in heart rate and blood pressure.[1] Withdrawal symptoms and severe skin ulcers and abscesses may also emerge with repeated use.[1]

Xylazine has worsened the nation's ongoing overdose epidemic. The Drug Enforcement Administration (DEA) reported that xylazine identifications and xylazine-associated deaths rose in all U.S. census regions between 2020 and 2021.[2] Reportedly added to prolong and enhance the euphoric effects of illicit fentanyl, nearly 100% of xylazine-associated deaths also involved illicitly manufactured fentanyl or fentanyl analogues.[2,3]

Given their public health impacts, the Biden Administration designated fentanyl adulterated or associated with xylazine as an emerging threat to the nation on April 12th, 2023.[4]

This Millennium Health Signals Report reflects our commitment to share timely information about current drug use trends to support clinicians and communities. Consistent with the above, our analysis of more than 160,000 definitive urine drug test (UDT) results from over 73,000 unique patients revealed that nearly all xylazine-positive urine specimens also contained fentanyl. Therefore, we evaluated the prevalence of xylazine among those who have also used fentanyl across the U.S. (Figure 1) and provide insight into xylazine-associated polysubstance use in the 100 days following the national emerging threat designation (Figure 2).

Figure 1. Geographical Analysis of Xylazine Detection in Fentanyl-Positive Specimens



Xylazine urine drug test (UDT) positivity rate in fentanyl-positive specimens by U.S. Census Division (left) and state (right). Logistic generalized estimating equation (GEE) regression models were fit with xylazine detection via LC-MS/MS as the dependent variable. Sex, age (discrete variable), specialty of the referring clinician, payer group and U.S. Census Division (left) or state (right) were treated as model covariates. States listed on the right were restricted to those with 50 or more fentanyl-positive results for accurate xylazine positivity rate estimation. All data were derived from clinician-ordered testing for xylazine on specimens collected between April 12th and July 20th, 2023.

Key Findings for Geographical Analysis of Xylazine Detection in Fentanyl-Positive Specimens

- Nationally, over 99% of xylazine-positive specimens also contained fentanyl; 16% of fentanyl-positive specimens contained xylazine (above, left)
- Xylazine use among those who use fentanyl varies substantially across the U.S.; the highest rates of xylazine use were in the Mid-Atlantic and East North Central divisions and the lowest were in the Pacific and Mountain divisions (above, left)
- Xylazine was detected in 34 states during the 100 days following the emerging threat designation
- Among the 25 states with at least 50 fentanyl-positive results during the analyzed period, more than half had xylazine positivity rates over 12% (above, right)
- Pennsylvania, North Carolina, and Ohio had the highest xylazine positivity rates nationally (above, right)
- California, Oregon, New Mexico, and Alaska had the highest rates of xylazine use (approximately 3-5%) among those who also use fentanyl in the West (above, right)

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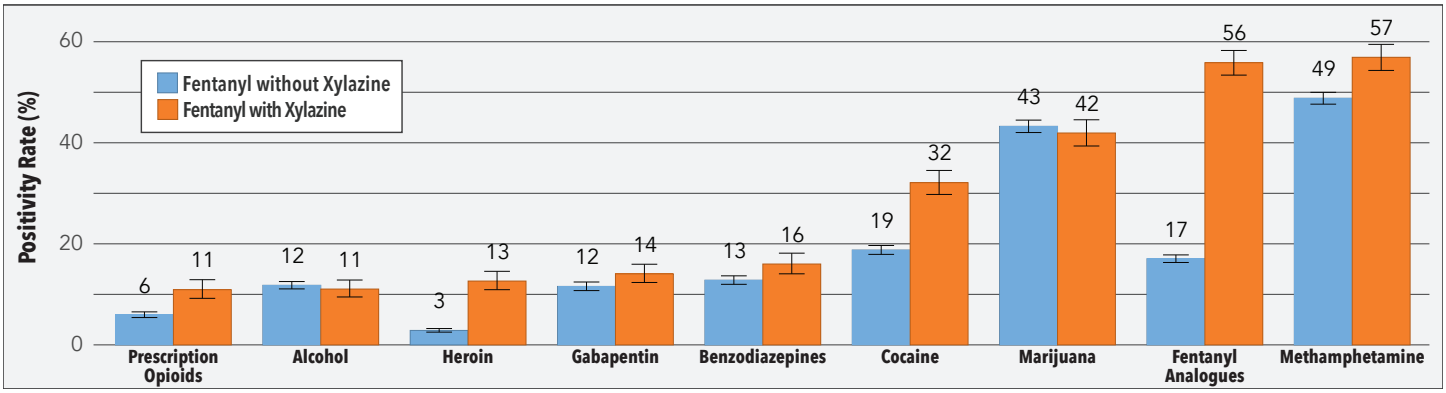
Figure 2. Drug Detection in Fentanyl-Positive Specimens With and Without Xylazine



Adjusted marginal probability of urine drug test (UDT) positivity for 9 illicit or non-prescribed drugs/drug classes in fentanyl-positive specimens that were negative (light blue) or positive (orange) for xylazine. Logistic generalized estimating equation (GEE) regression models were fit with Illicit and/or non-prescribed drug detection as the dependent variable. Xylazine detection (positive or negative) was treated as the main factor of interest. Sex, age (discrete variable), specialty of the referring clinician, payor group and U.S. Census Division were treated as model covariates. Prescription Opioids includes hydrocodone, hydromorphone, oxycodone, oxymorphone and tramadol. Benzodiazepines includes both illicit (clonazolam, etizolam, flualprazolam, flubromazolam) and prescription drugs (alprazolam, clonazepam, lorazepam, diazepam, oxazepam, temazepam). Fentanyl Analogues includes carfentanil, parafluorofentanyl and acrylfentanyl.

Key Findings for Drug Detection in Fentanyl-Positive Specimens With and Without Xylazine

- Polysubstance use is very common among people who use fentanyl, regardless of whether they have used xylazine
- Polysubstance use was significantly higher among those using fentanyl with xylazine (■) compared to those who had used fentanyl but not xylazine (■); the only exceptions were alcohol and marijuana
- Over 10% of those who used xylazine (■) had also taken other sedating drugs (alcohol, gabapentin, benzodiazepines) that, like xylazine, do not respond to naloxone

Conclusions

The findings in this Signals Report suggest that xylazine and fentanyl use are closely intertwined, as fentanyl was found in nearly every xylazine-positive urine specimen. This is consistent with reports that xylazine is often found in drug mixtures that contain fentanyl and/or other illicit substances.[2] In tandem, these drugs increase overdose risk, complicate overdose response efforts, and are likely to enhance clinical complexity, making opioid use disorder treatment more challenging.[1]

Xylazine was detected in every region of the country but rates of xylazine use vary substantially across regions and states. **Although xylazine use among those who use fentanyl is currently concentrated in the East, a 2022 DEA report suggested that xylazine appears to be following the same East-to-West path as fentanyl.**[2] Increased awareness of the threats posed by xylazine is needed among clinicians and public health officials across the U.S. and geographical changes in xylazine use should be monitored closely with timely and reliable sources of surveillance data, like UDT.

As in Volume 5 of the Millennium Health Signals Report, these results show that fentanyl use is generally associated with high rates of polysubstance use. The current findings further suggest that polysubstance use is even higher among those who have used fentanyl and xylazine, especially for stimulants and opioids.

The combined use of xylazine with other sedating drugs like benzodiazepines, alcohol, and gabapentin is especially concerning because their effects are not reversed by naloxone and, when taken together, may cause profound sedation that increases risk for personal injury, victimization, and fatal overdose.[5]

We will continue to follow trends in xylazine use and changes in patterns of polysubstance use to inform clinicians, researchers, public health officials, and the public as part of our commitment to improve patient care and lessen the toll of substance use in our communities.

Methods: View our full methods at millenniumhealth.com/signalsreport/methods

References:

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