

# Xylazine appears to worsen the life-threatening effects of opioids in rats

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A new study in rats suggests that xylazine, the active ingredient in a non-opioid veterinary tranquilizer not approved for human use, can worsen the life-threatening effects of opioids.

The findings imply that when used in combination with opioid drugs

such as [fentanyl](#) and [heroin](#), xylazine may damage the ability of the brain to get enough oxygen, which is one of the most dangerous effects of opioid drugs and can lead to death. The study, published in *Psychopharmacology*, was led by researchers at the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health.

Research has shown xylazine is often added to illicit opioids, including fentanyl, and that xylazine has been increasingly detected in the illicit opioid supply. While some people knowingly use fentanyl and xylazine in combination, many people do not know if the drugs they plan to use contain fentanyl, xylazine, or both. This combination can be extremely dangerous, and in April 2023, the U.S. government declared fentanyl adulterated or associated with xylazine as an [emerging drug threat](#).

"Drug mixtures containing both xylazine and opioids such as fentanyl demonstrate how rapidly the drug supply can change, and how dangerous products can proliferate despite rampant [overdose](#) deaths," said Nora Volkow, M.D., director of NIDA.

"Understanding the mechanisms behind how xylazine contributes to drug overdoses is essential to enable us to develop interventions that can reverse overdoses and save lives. In the meantime, naloxone, an opioid overdose reversal medication, should always be administered in the event of an overdose because xylazine is most often combined with opioids such as fentanyl."

Xylazine is known to cause sedation and dangerously slow breathing, heart rate, and [low blood pressure](#) in people. The harms of xylazine and risk of fatal overdose are also known to increase when it is used in combination with other central nervous system depressants like alcohol, benzodiazepines, and opioids like fentanyl or heroin. However, the mechanisms underlying the effects of xylazine and its interaction with opioid drugs are largely unknown. In this study, a research team led by

the NIDA Intramural Research Program conducted a series of experiments in rats to better understand the effects of xylazine as an adulterant to fentanyl and heroin.

For the first stage of the study, xylazine was administered on its own, and in different doses, to assess the effects of xylazine on movement, temperature, and oxygen levels in the brain. Even with low doses of xylazine, researchers observed known effects of the drug, including sedation, muscle relaxation, and decreased body temperature.

Researchers also observed a modest decrease in brain oxygen levels, which was long-lasting, and dose-dependent, meaning the decrease in oxygen levels in the brain was stronger when more xylazine was administered.

In the second phase of the study, either fentanyl or heroin was administered to examine the changes in levels of oxygen in the brain after being exposed to these drugs. Researchers then compared the effects between the combination of either fentanyl and xylazine or heroin and xylazine. In contrast to the modest and prolonged decreases in brain oxygen levels observed with xylazine, administering fentanyl or heroin on their own generated an initial rapid and strong decrease in brain oxygen levels, resulting from slowed breathing. This was followed by a slower and more prolonged brain oxygen increase.

However, when the xylazine-fentanyl mixture or the xylazine-heroin mixture were administered, the rebounding increase in oxygen to the brain was eliminated, and the brain [oxygen levels](#) therefore remained lower for a longer period compared to fentanyl or heroin alone. In addition, the xylazine-heroin mixture resulted in a much stronger and more prolonged initial decrease in brain oxygen compared to heroin alone.

These findings suggest that the addition of xylazine to fentanyl or heroin

disrupts the mechanism that the [brain](#) uses to counteract a rapid loss of oxygen after being exposed to [opioid drugs](#). The authors therefore hypothesize that xylazine is contributing to overdose deaths involving opioids.

"The risks that people face from a drug contaminated with fentanyl are very concerning, and this study provides evidence to suggest that the addition of xylazine is exacerbating those risks," said Eugene A. Kiyatkin, M.D., Ph.D., lead author on the paper and senior associate scientist in the NIDA Behavioral Neuroscience Branch. "Further research is needed to explore how these observations may apply in humans, and to continue to parse the complex role of illicit drug combinations with xylazine and risk of overdose."

The United States has experienced a massive change in its illicit drug supply over the past several years, most notably through the rapid expansion of illicit fentanyl, a cheap, very potent synthetic [opioid](#) drug. There has been a corresponding dramatic increase in overdose deaths, which have now plateaued at more than 100,000 people dying in the U.S. annually.

**More information:** S Choi, MR Irwin, & E Kiyatkin. Xylazine effects on opioid-induced brain hypoxia, *Psychopharmacology* (2023). [DOI: 10.1007/s00213-023-06390-y](https://doi.org/10.1007/s00213-023-06390-y) , [link.springer.com/article/10.1 ... 7/s00213-023-06390-y](https://link.springer.com/article/10.1007/s00213-023-06390-y)

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