



Polysubstance Overdose Response Action Guide

Updated June 16, 2025

This publication is supported by the Centers for Disease Control and Prevention (CDC) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award totaling \$17,000,000, with 100 percent funded by CDC/HHS. A portion of this funding supported the project described above. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement by, CDC/HHS, the U.S. Government, or the CDC Foundation.

The unregulated illicit drug supply is becoming increasingly unpredictable, with more substances being mixed — often without an individual’s knowledge. This has exacerbated the opioid overdose epidemic and complicated response efforts. This guide outlines the common adulterants found in opioids and stimulants, along with compassionate overdose and overamping (stimulate drug overdose) response guidance for the adulterant.

Best Practices for Polysubstance Overdose Response

- **Call 911 immediately.** Encourage the individual to seek follow-up medical care.
- **Prioritize breathing.** Respiration over response.
- **Compassionate response.** 3 or 4 mg naloxone is best; too much naloxone can invoke precipitated withdrawal.¹ Wait 2-3 minutes for the naloxone to take effect before administering another dose.²
- **Standard overdose kits should include:**
 - Naloxone
 - CPR mask or barrier
 - Gloves
- **Offer harm reduction tools:**
 - Additional naloxone
 - Fentanyl and xylazine test strips
- **Advanced tools (if trained and budget allows):**
 - Pulse oxygen monitor
 - Artificial Manual Breathing Unit (AMBU) bag
 - Recreational oxygen cans or tanks³
 - Oropharyngeal (OPA)/nasopharyngeal (NPA) airways⁴

Nitazenes

Nitazenes are a highly potent synthetic opioid and often found alongside other opioids in the unregulated drug supply. According to emergency services (EMS) data from January 2023 to April 2025, 99.4% of nonfatal and 0.6% of fatal overdoses were linked to nitazenes.⁵ Opioid and synthetic opioid overdose brings the focus to patient responsiveness. If a suspected overdose occurs where synthetic opioids may be present, follow these best practices:

- Check for responsiveness (call to them, sternum rub)
- Check for breathing
- Check for skin color changes (blue/gray on light skin or gray/purple on darker skin)
- Administer naloxone
- Call 911
- Begin rescue breaths
- Recovery Position (see Figure 2)

¹ A Call for Compassionate Opioid Overdose Response. <https://www.sciencedirect.com/science/article/pii/S0955395924002718?via%3Dihub>. Accessed June 16, 2025.

² 5 Things to Know About Naloxone. <https://www.cdc.gov/overdose-prevention/reversing-overdose/about-naloxone.html>. Accessed June 16, 2025.

³ Comprehensive Overdose Response with Oxygen. <https://pqwchc.org/wp-content/uploads/Report-Comprehensive-Overdose-Response-with-Oxygen-Training-for-Shelter-Providers-in-Toronto.pdf>. Accessed June 16, 2025.

⁴ Atanelov Z, Aina T, Smith T, et al. Nasopharyngeal Airway. [Updated 2024 Jan 30]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK513220/>

⁵ National Drug Early Warning System. https://ndews.org/wordpress/files/2025/05/5.2.25_NDEWS-2025-nitazene-overdoses.pdf. Accessed June 16, 2025.

- If no response after 2-3 minutes, administer another dose of naloxone¹

Sedatives (e.g., Xylazine, Medetomidine)

Sedatives like xylazine and medetomidine are nonopioid sedatives used for muscle relaxation and as an anesthetic in veterinary medicine. Among 21 jurisdictions, the monthly percentage of fentanyl involved deaths with xylazine detected increased 276% from January 2019 (2.9%) to June 2022 (10.9%).⁶ Xylazine and Medetomidine cause prolonged sedation, respiratory depression, skin ulcerations and physiological depression.⁷ These substances can complicate opioid withdrawal and opioid overdose. Naloxone has no effect on reversing the effects of xylazine or medetomidine. The response prioritizes positioning the individual to maintain an open airway (see Figure 1) and focusing on the person breathing. If a suspected overdose occurs where sedatives may be present, follow these best practices:

- Check for breathing
- Check for skin color changes (blue/gray on light skin or gray/purple on darker skin)
- Check for responsiveness (call to them, sternum rub)
- Administer naloxone (for possible opioid combination)
- Call 911
- Begin rescue breaths
- Recovery Position (see Figure 2)
- For more on wound care associated with xylazine, refer to [Jefferson University's Xylazine Interventions](#).



Figure 1. Keeping the Airway Clear



Figure 2. Recovery Position

Local Anesthetics (e.g., Lidocaine, Diphenhydramine)

Local anesthetics are often found in combination with illicit substances and may delay response or cause other health symptoms that may impact rescue efforts. If a suspected overdose occurs where local anesthetics may be present, the response is the same as for sedatives — prioritize breathing and ensure airway support.

Stimulants (e.g., Cocaine, Methamphetamine)

Stimulant use can lead to an overdose known as “overamping.” Overamping can cause rapid heart rate, chest pain, difficulty breathing, elevated body temperature, anxiety or psychosis. Signs of overamping and stimulant use include dilated pupils, tremors, dizziness, confusion, rapid breathing, excessive sweating and nausea/vomiting. Response steps can vary from supportive care and rest to medical or medication intervention. If overamping is suspected, 911 should be called. While waiting for EMS, keep the patient cool, oxygenated and safe.

Synthetic Cannabinoids

Synthetic cannabinoids, often combined with many chemicals, can cause a variety of symptoms like mood swings, euphoria, intense anxiety, intense withdrawal and even heart attacks or strokes. An “overdose” with synthetic cannabinoids can resemble an opioid overdose due to decreased responsiveness; however, naloxone may not work in this scenario. Supportive care with reassurance, reorientation, monitoring of vital signs, responding to seizures and administration of oxygen may be needed.

⁶ Kariisa M, O'Donnell J, Kumar S, Mattson CL, Goldberger BA. Illicitly Manufactured Fentanyl—Involved Overdose Deaths with Detected Xylazine — United States, January 2019–June 2022. *MMWR Morb Mortal Wkly Rep* 2023;72:721–727. DOI: <http://dx.doi.org/10.15585/mmwr.mm7226a4>

⁷ Papudesi BN, Malayala SV, Regina AC. Xylazine Toxicity. [Updated 2023 Jul 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK594271/>