

Emerging Illicit Substances

Clinical Recognition and Response

Xylazine, Medetomidine, Designer Benzodiazepines, Kratom

Agenda

Review clinical manifestations and management of:

1. Xylaxine
2. Medetomedine
4. Street benzos
5. Kratom
6. Nitazenes

Xylazine: What is Xylazine?



Veterinary sedative used in animals (e.g., horses)



Alpha-2 adrenergic agonist – causes sedation, hypotension



Used to extend opioid euphoria, especially fentanyl – gives it “legs”



Not reversed by naloxone

Xylazine: Where is it Found?

- Widespread in Northeast and Mid-Atlantic U.S.
- Frequently mixed into fentanyl without user knowledge
- Common street name: Tranq

• *References: NIDA, 2023;
ONDCP Emerging Threat
Report, 2024*

Xylazine: Clinical Effects

Acute: Sedation, bradycardia, hypotension

Chronic: Necrotic skin ulcers at and distant from injection sites

Withdrawal: Tachycardia, agitation – poorly studied

Xylazine: Management

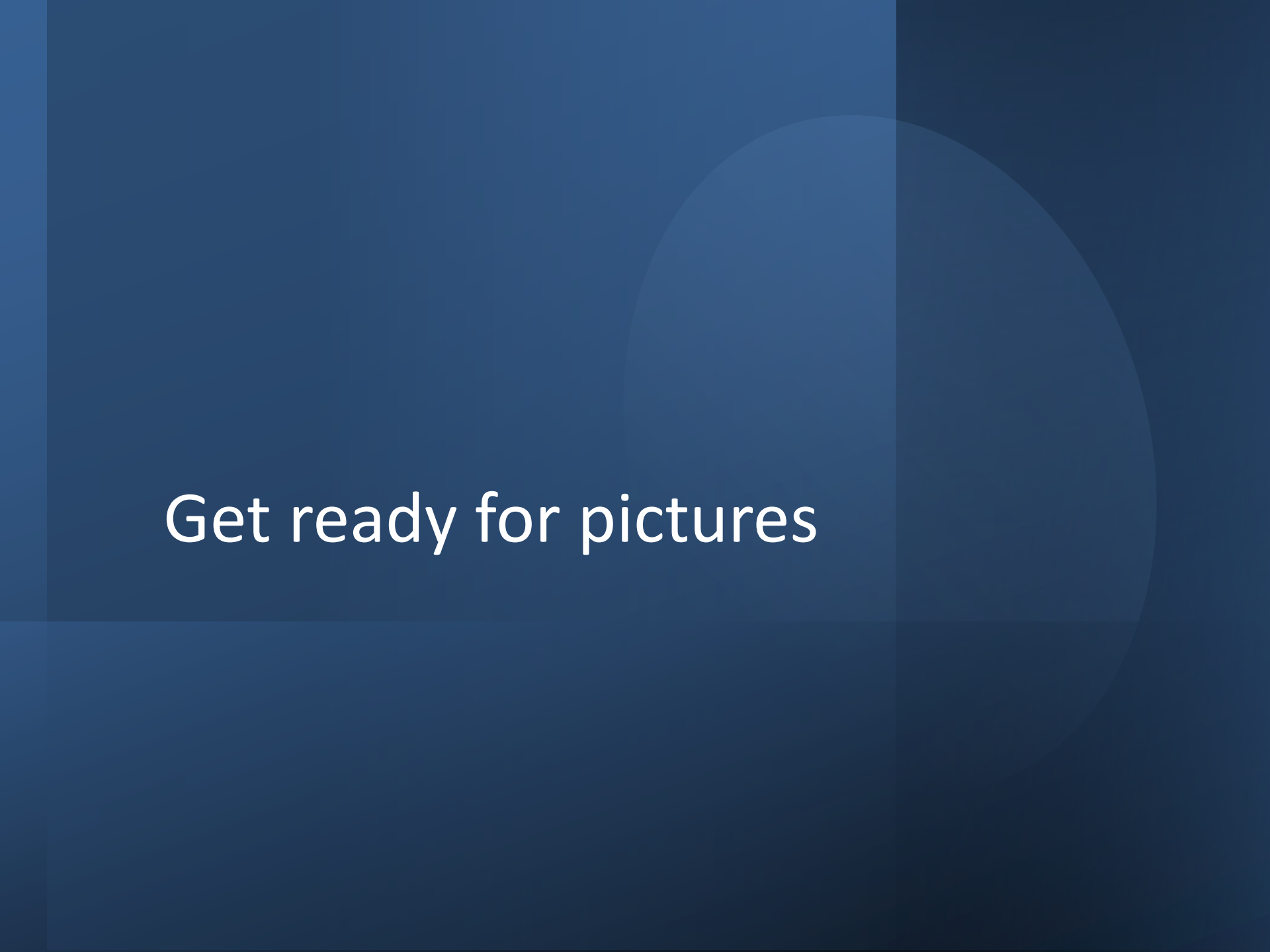
Supportive care: Airway, fluids, monitoring

Naloxone only treats co-ingested opioids – but administer!
Xylazine is most frequently found mixed with fentanyl

Wound care: Debridement, antibiotics, surgical referral

Skin ulcers

- Often start as dark purple blisters with irregular borders, which coalesce and harden into a dry eschar, sometimes opening into deep ulcers
- Commonly located on the extensor surfaces of the extremities

The background is a solid dark blue. A large, lighter blue circle is positioned on the right side, partially cut off by the edge. A vertical line of a slightly different shade of blue runs from the top to the bottom of the frame, intersecting the circle.

Get ready for pictures



Skin ulcers



Skin ulcers

Occur at sites of injection but also at sites from injection and even among individuals who smoke, do not inject

Wound management

May need to occur primarily outside of a health care setting due to limited transportation options and/or distrust of healthcare system

1. Clean (normal saline or generic wound washes)
2. Debride as necessary (medihoney, silver sulfadiazine)
3. Other topicals to preserve intact periwound tissue
4. Primary dressing (if wet wound: oil-emulsion like Adaptic. If dry wound: petroleum-based like xeroform)
5. Secondary dressing (e.g., gauze) and secure

Xylazine: Testing and Detection

Not detected by standard drug screens

Requires GC-MS or LC-MS/MS testing

Often identified postmortem or in research settings

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GOOD NEWS

BAD NEWS

Medetomidine

Veterinary sedative like xylazine, but about 200 times more potent

Racemic mixture of dexmedetomidine (Precedex) and levomedetomidine

Alpha-2 adrenergic agonist – CNS depression, bradycardia

Illicit use as an adulterant in fentanyl

Medetomidine: Where is it Found?

- Detected in U.S. and Canadian fentanyl supplies
- Often co-present with xylazine and opioids
- Increasing in Northeast U.S. and Toronto area

Medetomidine: Clinical Effects

- Profound sedation, bradycardia, respiratory depression
- Non-responsive to naloxone – but give it anyway!

Management of Intoxication

Airway support, fluids, vital monitoring

No human-approved reversal; atipamezole used in animals

Suspect in overdoses unresponsive to naloxone

Management of Withdrawal

Emerging Literature

Case series of 11 patients from Temple University

- **All patients** had sinus bradycardia without other conduction abnormalities
- Hypotension was uncommon, only seen in 18% of cases
- In the cases involving hypotension, **vasopressors were not required**, and blood pressure normalized with IV fluids alone
- After reversal of hypoxia and respiratory depression, patients were noted to be **persistently bradycardic** with sustained heart rates below 50bpm
- All patients tested positive for fentanyl, medetomidine, and xylazine
- Duration of bradycardia lasted from 1.5 h to 31.9 h (median 3.4 h [IQR: 2.7–9.3 h])



Notes from the Field: Severe Medetomidine Withdrawal Syndrome in Patients Using Illegally Manufactured Opioids — Pittsburgh, Pennsylvania, October 2024–March 2025

Weekly / May 1, 2025 / 74(15);269–271

[Print](#)

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Summary

Article Metrics

Withdrawal

- Case study of 23 adult patients, all fentanyl users
- All used the same source, all who were tested, tested positive for medetomidine as well
- Presented with tremulousness, agitation, diaphoresis, tachycardia, and significant hypertension.
- Most required dexmedetomidine infusion and intensive care unit–level management.

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ORIGINAL RESEARCH

Severe Fentanyl Withdrawal Associated With Medetomidine Adulteration: A Multicenter Study From Philadelphia, PA

 London, Kory S. MD; Huo, Samantha MD; Murphy, Lauren MD; Warrick-Stone, TaReva DO; Goodstein, Dennis PharmD; Montesi, Maeve PA; Carter, Meg MD; Butt, Sabrina MD; Alexander, Karen PhD, RN; Satz, Wayne MD; Tasillo, Abriana MD; Xu, Lin MS; Arora, Maya BS; Casey, Emily PharmD; McKeever, Rita MD; Lowenstein, Margaret MD, MPhil, MSHP; Durney, Philip MD; Hart, Brendan MD, PhD; Perrone, Jeanmarie MD

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Journal of Addiction Medicine ():10.1097/ADM.0000000000001560, August 1, 2025. | DOI: 10.1097/ADM.0000000000001560

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Rel

Data

- 209 patients
- Intensive care unit (ICU) admission occurred in 77.5%, with 20.1% requiring intubation.
- Symptoms were often refractory to traditional opioid withdrawal management, and patients suffered from severe withdrawal, with a median maximum recorded Clinical Opiate Withdrawal Score (COWS) score of 23.
- 73.7% received dexmedetomidine infusion.
- Severe complications included encephalopathy (35.4%), myocardial injury (28.7%), and rarely seizures (5%).

In sum:

Opioids for opioid withdrawal

Alpha-2 agonists (clonidine/tizanidine if taking PO. May need dexmedetomidine if critically ill)

Antiemetics

Antihypertensives if not responsive to the above

Medetomidine: Testing and Detection

- Not detected on standard tox screens
- Identified via LC-MS/MS in specialty labs

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Designer Benzodiazepines: What Are They?

- Novel benzos synthesized to evade regulation
- Often more potent than pharmaceutical benzos
- Examples: Etizolam, Flubromazolam, Clonazolam

Designer Benzodiazepines: Where Are They Found?

- Online markets, pressed into counterfeit pills
- Frequent in fake Xanax, Valium
- Detected in overdose deaths and impaired driving cases

Designer Benzodiazepines: Clinical Effects

- Sedation, amnesia, respiratory depression
- Longer half-lives → prolonged intoxication
- Withdrawal can be severe, including seizures

Designer Benzodiazepines: Management

- Supportive care: Monitor airway and vitals
- Flumazenil rarely used due to seizure risk
- Long-acting benzodiazepines (diazepam) used for tapering in withdrawal or phenobarbital

Designer Benzodiazepines: Testing and Detection

- Not detected by standard UDS panels
- LC-MS/MS needed to identify specific analogs
- High false-negative rate in clinical settings

At Pres



Kratom: Where is it Found?

- [Herbal substance from *Mitragyna speciosa*](#)
- A tropical evergreen tree native to Southeast Asia.
- Used traditionally for centuries as an herbal remedy, often brewed as a tea, particularly in countries like Thailand, Indonesia, Malaysia, and Myanmar.

Native kratom leaf material contains more than 50 bioactive alkaloids

Up to 2% mitragynine by weight.

- Mitragynine weekly binds mu-opioid receptor (partial agonist)
- Agonist at adrenergic receptors
- Some serotonergic, dopaminergic, and adenosinergic activity
- Stimulant at low dose, sedative at high dose
- Metabolizes to 7-hydroxymitragynine

7-hydroxymitragynine

- Highly selective mu opioid agonist with a binding affinity 14-22 times that of morphine
- IMAGE



An estimated 1.9 million Americans reported using kratom in the previous year

Rossheim et al *American Journal of Public Health* 2024

Used for

- chronic pain
- Opioid withdrawal
- Euphoria
- Anxiety/depression/fatigue

Kratom: Where is it Found?

- Sold online, head shops, gas stations
- Legal in most U.S. states, unregulated labeling
- Often marketed as supplement or tea

What is difference

- kratom extract products created via extraction of kratom leaves using organic solvents. This enrichment process can increase the mitragynine concentration to 40% or higher in such products
- formulation of concentrated kratom extracts as capsules, tablets, liquid shots or gummies circumvents kratom's natural self-limiting qualities (e.g. unpleasant taste) and reduces the volume of product needed to achieve an effect
- Grundmann et al Addiction 2023

Kratom: Clinical Effects

- Low dose: stimulation, alertness
- High dose: sedation, nausea, respiratory depression
- Chronic use: dependence, withdrawal (irritability, insomnia)

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CASE REPORT

A Case of 7-OH Mitragynine Use Requiring Inpatient Medically Managed Withdrawal

 Wightman, Rachel S. MD; Hu, David MD

[Author Information](#) ✓

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Abstract

Kratom: Testing and Detection

- Not included in standard drug screens
- Specialty tests detect mitragynine
- Users may not disclose use unless asked

Kratom: Management

- Supportive care for intoxication
- Clonidine or buprenorphine for withdrawal (off-label)
- Counseling, gradual tapering if used chronically

Nitazines (Etonitazene, isotonitazene, clonitazene)

- Highly potent opioid
- Originate in China
- Mixed in w heroin, fentanyl, designer bzos
- Mostly in Europe for now, though present in the US
- About 5x as potent as fentanyl
- Can be reversed by naloxone
- Unclear how much is in the US due to limited testing

Take-Home Messages

- Many emerging substances are not detected by standard tox screens
- Naloxone is ineffective for non-opioids like xylazine and medetomidine – but use it anyway!
- Consider these substances in atypical overdose presentations