# Emerging Illicit Substances:
## What Clinicians Need to Know

JoAn Laes, MD, DFASAM, FACMT
Lewis Nelson, MD, MBA, DFASAM, FACMT
Jeanmarie Perrone, MD, FACMT
Cole Pueringer, MD
Daniel Sessions, MD, FASAM, FACMT, FAAEM
Alaina Steck, MD, FASAM, FACMT
Rachel Wightman, MD, FASAM, FACMT

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# Disclosure Information

- Dr. JoAn Laes: no disclosures
- Dr. Lewis Nelson: no disclosures
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- Dr. Alaina Steck: no disclosures
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# Learning Objectives

At the conclusion of this activity, attendees will be able to:

1. Describe epidemiological changes in the emerging illicit and unregulated drug supply.
2. Understand the pharmacology of emerging substances including:
   - **tianeptine**
   - **new synthetic opioids**
   - **bromazolam & other benzodiazepines**
   - **ketamine & other NMDA antagonists**
   - **medetomidine & other alpha-2 agonists**
3. Recognize the expected intoxication symptoms, withdrawal syndromes, and other potential harms associated with these emerging drugs.
4. Identify strategies for bedside clinical and laboratory evaluation of patients presenting intoxicated or in withdrawal in the context of an evolving drug supply.

# Background

Dr. Rachel Wightman, MD

# Drug Supply Surveillance

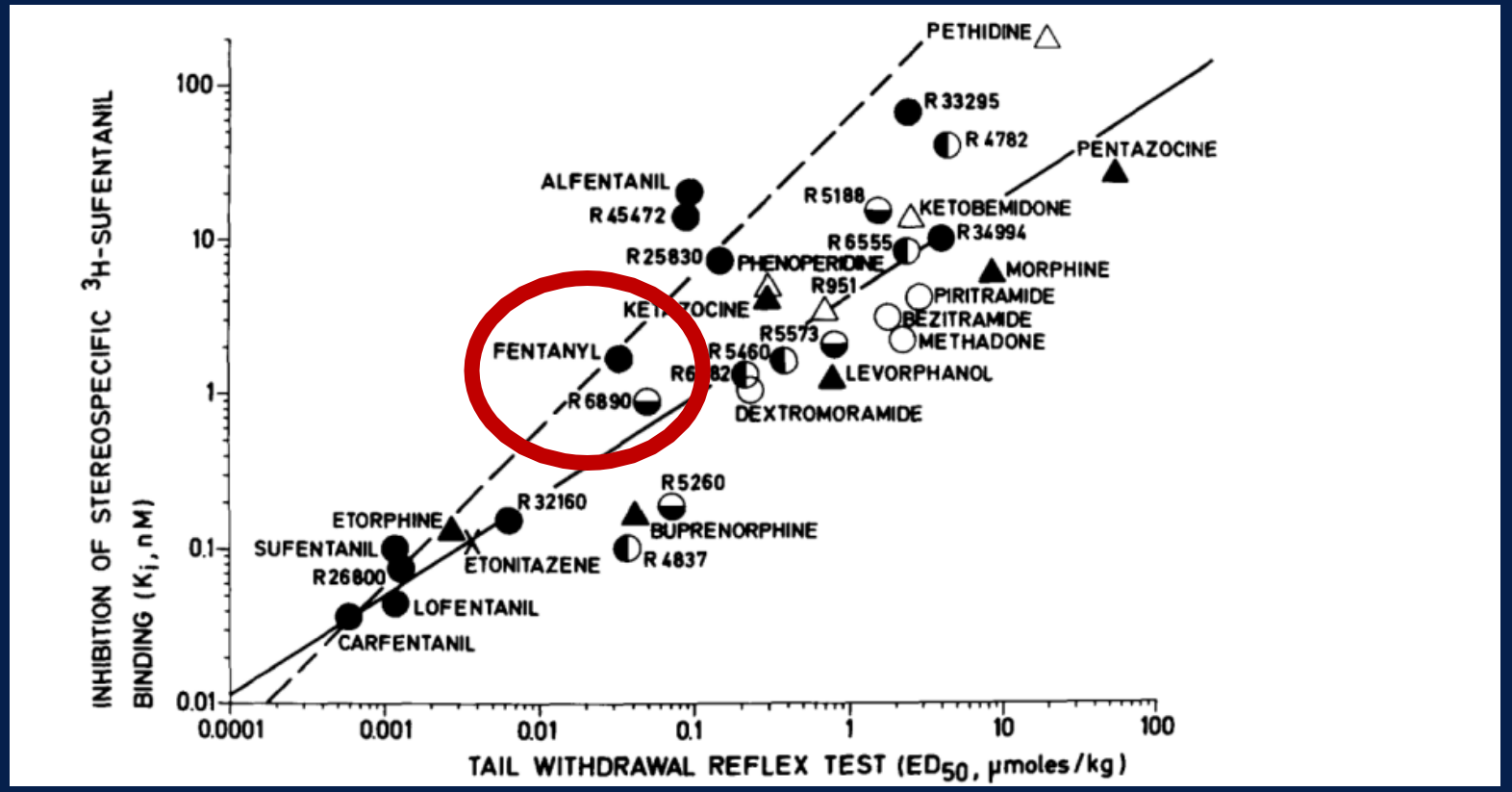
- Example sources:
  - Drug checking (NYC DOHMH, Toronto, DrugsData, MAADS, UNC)
  - Drug seizure data
  - Biospecimen samples
  - Post-mortem toxicology data (SUDORS, Medical Examiners)
  - Social media
  - Poison center reports
  - Wastewater
- Delays in testing and reporting methods are common

# Details Matter: Procedures & Methods

- How are the samples gathered? What is the scope? Is there secondary lab confirmation? What quantitative data is provided?
- Is there context around the samples tested?
- Understand the limitations. Examples:
  - Seizure data will often only report substances that are scheduled
  - What is the testing library?
  - What is the post-mortem testing algorithm?
  - Pills are harder to gather than powder
  - Cross contamination? (packaging, handling, health care, wastewater)

# Real World Example: R6890

- **R6890** (spirochlorphine) was recently detected in Rhode Island in seized fentanyl samples by forensic lab



# Implications for Clinical Care

| Clinical Issue | Implications |
| --- | --- |
| Overdose management | ▸ In-hospital testing takes time<br>▸ Local drug supply helps guide clinical toxidrome assessment |
| Withdrawal management | ▸ Novel BDZ withdrawal<br>▸ Detection window unknown for many substances |
| Treatment initiation (e.g., MOUD) | ▸ Use information to facilitate conversations and formulate treatment plans, especially relevant in cases of polysubstance use / exposure |

# Surveillance Resources (see Appendix)

- **CDC SUDORS Dashboard**: National Drug Overdose Fatality Data Source
- **CSFRE NPS Discovery**: Drug and Forensic Toxicology Testing Results, Trend Reports, Emerging New Substances Data
- **Drug Overdose Toxico-Surveillance**: Emergency Department Overdose Biosurveillance Project conducted by the American College of Medical Toxicology in collaboration with CSFRE
- **National Forensic Laboratory Information System (NFLIS)**: Forensic Drug Chemistry Laboratory Data, Medical Examiner and Coroner Data, Toxicology Laboratory Data
- **National Drug Early Warning System (NDEWS)**: Collaboration between University of Florida, New York University, and Florida Atlantic University
- **Toronto Drug Checking Service**: Drug Checking Data Source- Key Findings, Updates, Testing Methods
- **New York State Dept. of Health Checking Service**: Drug Checking Data Source- Key Findings, Updates, Alerts
- **Drug Checking Programs in Pennsylvania: Philadelphia Dept. of Health Checking Service and PA Groundhogs Drug Checking Services**: in collaboration with CSFRE
- **Street Check**: Community Drug Checking
- **Erowid/Drugsdata.org**: Anonymous drug sample analysis data

# Case 1

Dr. Jeanmarie Perrone

# Case 1

- A 34-year-old woman with a history of opioid use disorder presents for help with opioid withdrawal symptoms.
- She has been using opioids intravenously for several years, but lately her withdrawal symptoms are significantly more severe
- Physical exam:
  - HR 80 bpm, BP 122/78 mmHg
  - myalgias, nausea, feels hot/cold
  - COWS 8

# Case 1

34-year-old woman OUD with acute withdrawal

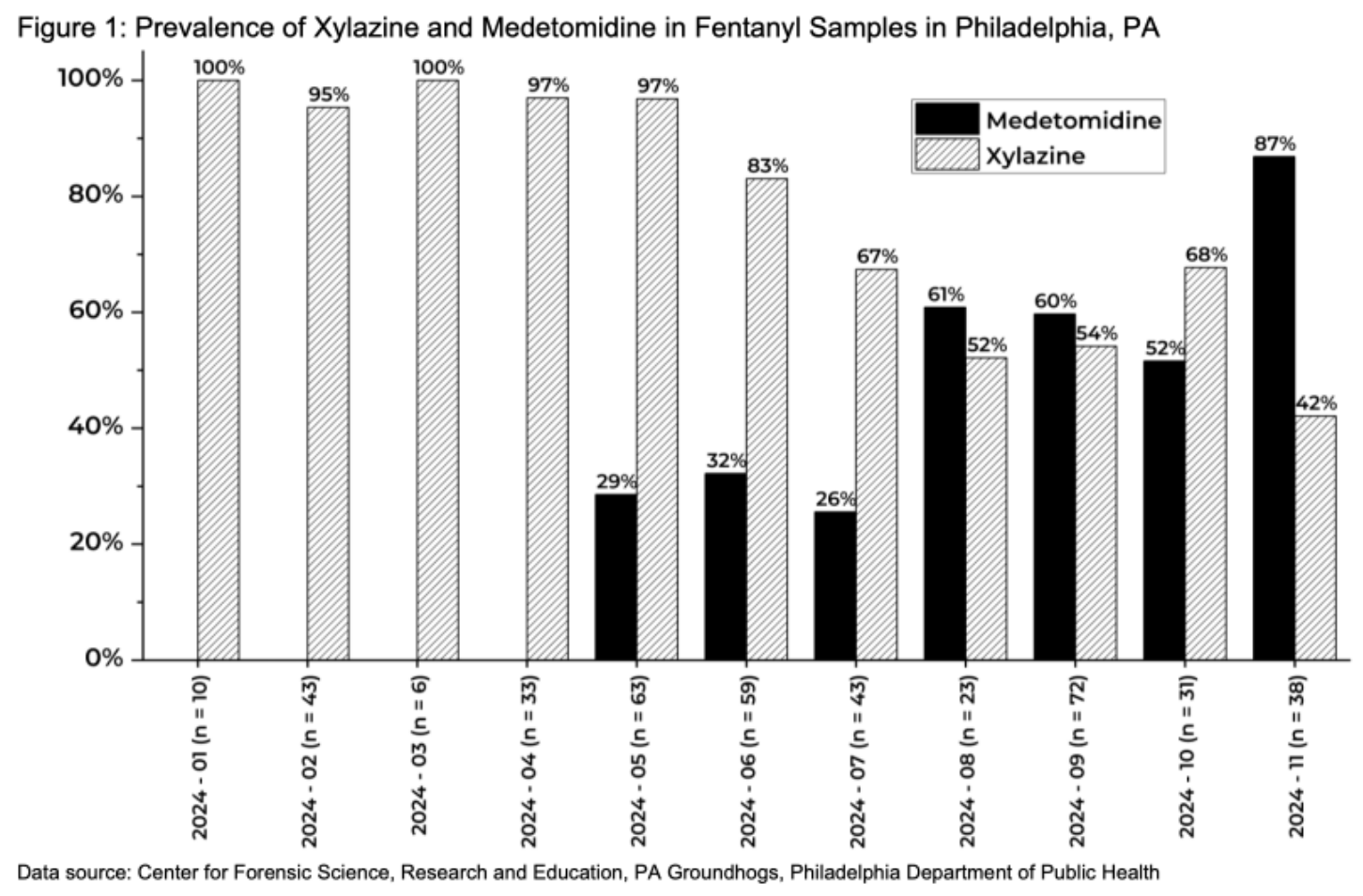
- Pt declines buprenorphine and opts for methadone
- 30mg methadone (PO) with improvement and resting comfortably awaiting transfer to rehab

2 hours later, the nurse asks you to re-evaluate her:

- BP 190/110mmHg, P 140/min, RR 20, T 99, pulse ox 100%
- Intermittent vomiting, diaphoresis, tremulousness, mydriasis, yawning
- COWS 24—“This is what has been happening, Doctor…”

# Case 1 Discussion

# Recent Drug-Checking Trends in Philadelphia

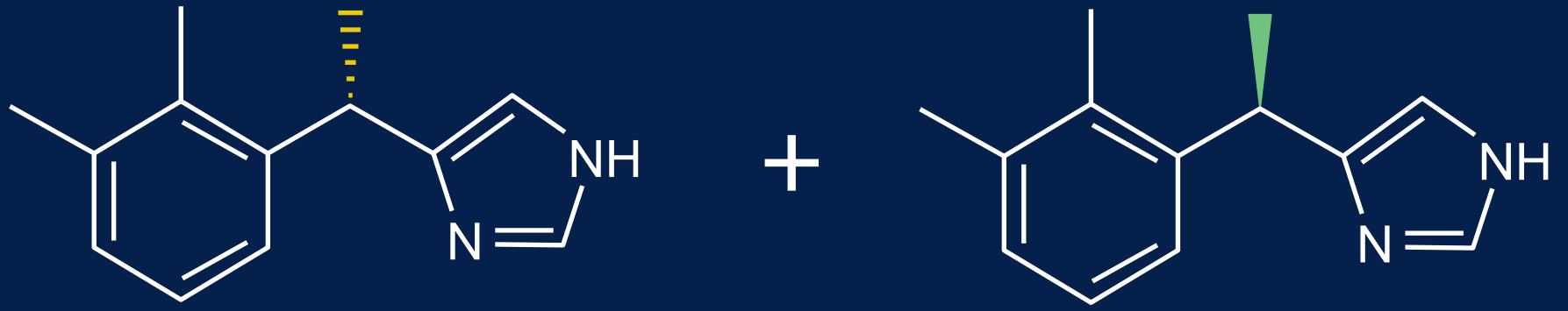



- Quantity of medetomidine in individual bags ranged from **1,000 – 10,000mcg**
  - compare to therapeutic dexmedetomidine doses, **1.5 mcg/kg/hr drip**
- Tetracaine, lidocaine, diphenhydramine, caffeine also frequently encountered
- Fentanyl concentration remains the same at ~13,000mcg/bag

*Philadelphia Dept. of Public Health HAN 00444A (2024)*

# What is Medetomidine?

racemic mixture of dexmedetomidine + levomedetomidine




**dex**medetomidine

$\alpha_2$:$\alpha_1$ selectivity: **1620**:1

(clonidine $\alpha_2$:$\alpha_1$ **220**:1)
(xylazine $\alpha_2$:$\alpha_1$ **160**:1)

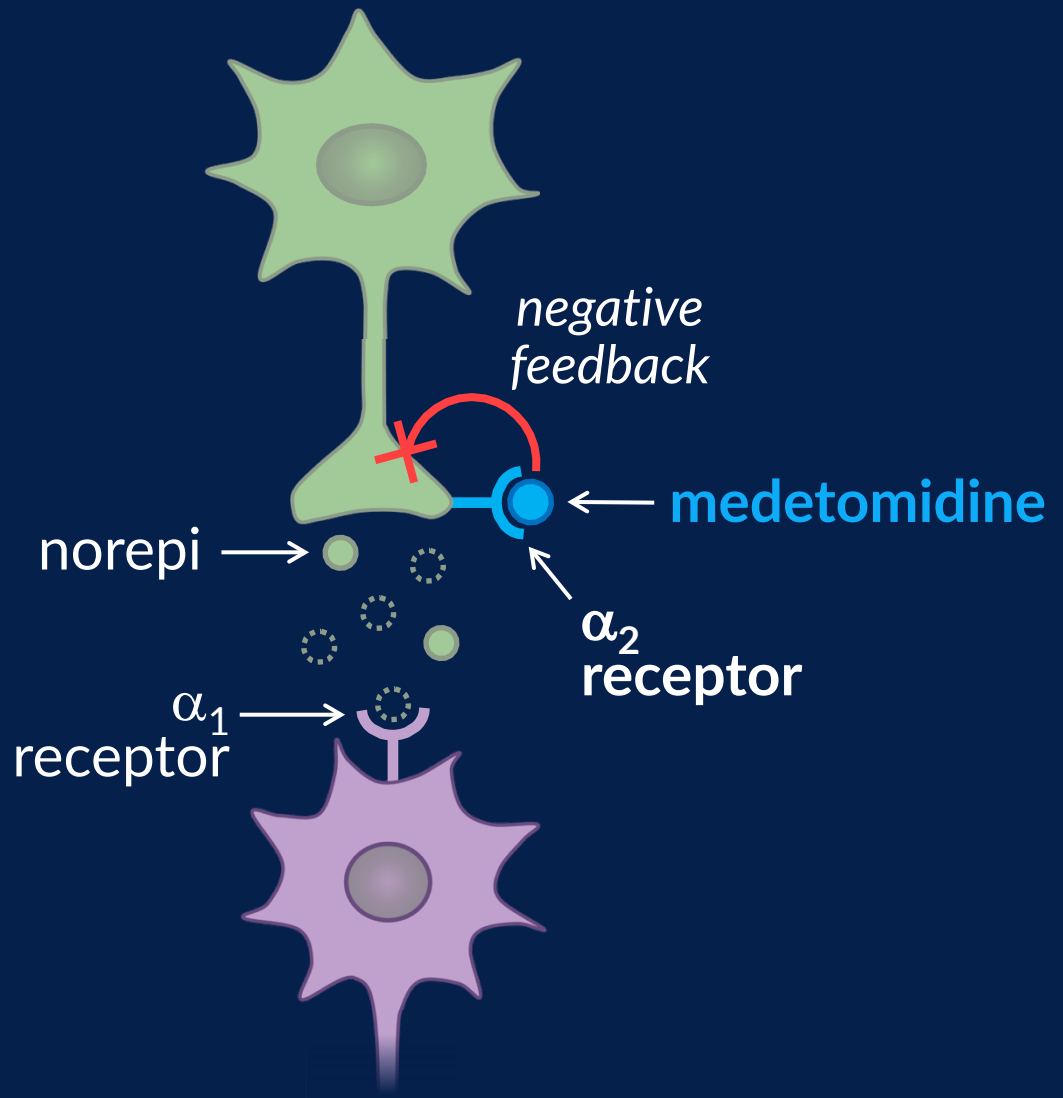
**levo**medetomidine

*(inactive)*

*de Andrade HP, et al. (ACS Chem Neurosci 2024); Gertler R, Brown HC, Mitchell DH, Silvius EN (Bayl Univ Med Cent 2001)*

# What is Medetomidine?

- **dex**medetomidine (Precedex®)
- **medetomidine** used for veterinary sedation & analgesia (Domitor®)
  - bradycardia in animals
  - 2024 overdose cluster in Philly and Chicago: bradycardia and hypotension



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# Evaluation of dexmedetomidine withdrawal in critically ill adults

Sophia Pathan, PharmD, BCPS [a,1,*], Justin B. Kaplan, PharmD, BCCCP [b], Katarzyna Adamczyk, PharmD, BCCCP [b], Stephanie H. Chiu, MPH [c], Chirag V. Shah, MD, MSCE [d]

[a] Department of Pharmacy, The Johns Hopkins Hospital, United States of America
[b] Department of Pharmacy, Atlantic Health System, United States of America
[c] Atlantic Center for Research, Atlantic Health System, United States of America
[d] Department of Medicine, Atlantic Health System, United States of America

Table 3. DEX Withdrawal Characteristics.[a]

| Withdrawal symptom | Withdrawal (n = 50) | No Withdrawal (n = 115) | *p*-value |
|---|---|---|---|
| Tachycardia | 36 (72%) | 23 (20%) | <0.001 |
| Hypertension | 37 (74%) | 15 (13.04%) | <0.001 |
| Agitation | 21 (42%) | 12 (10.53%) | <0.001 |
| Nausea and/or Vomiting | 19 (38%) | 10 (8.7%) | <0.001 |

Pathan S, et al: Evaluation of dexmedetomidine withdrawal in critically ill adults. Journal of Critical Care 2021; 62:19-24.
Bouajram RH, Bhatt K, Croci et al: Incidence of Dexmedetomidine Withdrawal in Adult Critically Ill Patients: A Pilot Study. Crit Care Explor. 2019 9;1.

# An Emerging Entity: Medetomidine Withdrawal Syndrome

| Characteristic | Jefferson | Penn | Temple | Total |
|---|---|---|---|---|
| Number of Patients | 55 | 48 | 62 | **165** |
| Maximum HR (median & IQR) | 144 (125 – 155) | 136 (118 – 156) | 148 (140 – 157) | **145 (132 – 156)** |
| Maximum systolic BP (median & IQR) | 191 (172 – 211) | 196 (171 – 224) | 200 (185 – 215) | **195 (175 – 215)** |
| Maximum diastolic BP (median & IQR) | 111 (103 – 123) | 127 (109 – 137) | 131 (119 – 143) | **122 (109 – 136)** |
| Treated with dexmedetomidine | 51 (93%) | 35 (73%) | 51 (82%) | **137 (83%)** |
| Intubated | 12 (22%) | 11 (23%) | 16 (26%) | **39 (23%)** |
| Admitted to ICU | 49 (89%) | 44 (92%) | 57 (92%) | **150 (90%)** |
| **Disposition** | | | | |
| Home | 15 (27%) | 28 (58%) | 32 (52%) | **75 (45%)** |
| Patient-Directed Discharge | 14 (26%) | 13 (27%) | 25 (40%) | **52 (32%)** |
| Residential Drug Treatment | 14 (26%) | 7 (15%) | 0 (0%) | **21 (13%)** |
| Law Enforcement Custody | 12 (22%) | 0 (0%) | 5 (8%) | **17 (10%)** |

# An Emerging Entity: Medetomidine Withdrawal Syndrome

- 100 – 200x more potent $\alpha_2$ agonist than xylazine
- overdose: bradycardia, +/- hypotension
- **withdrawal**: tachycardia, hypertension, nausea/vomiting, tremors, variable AMS
- complications: PRES, MI

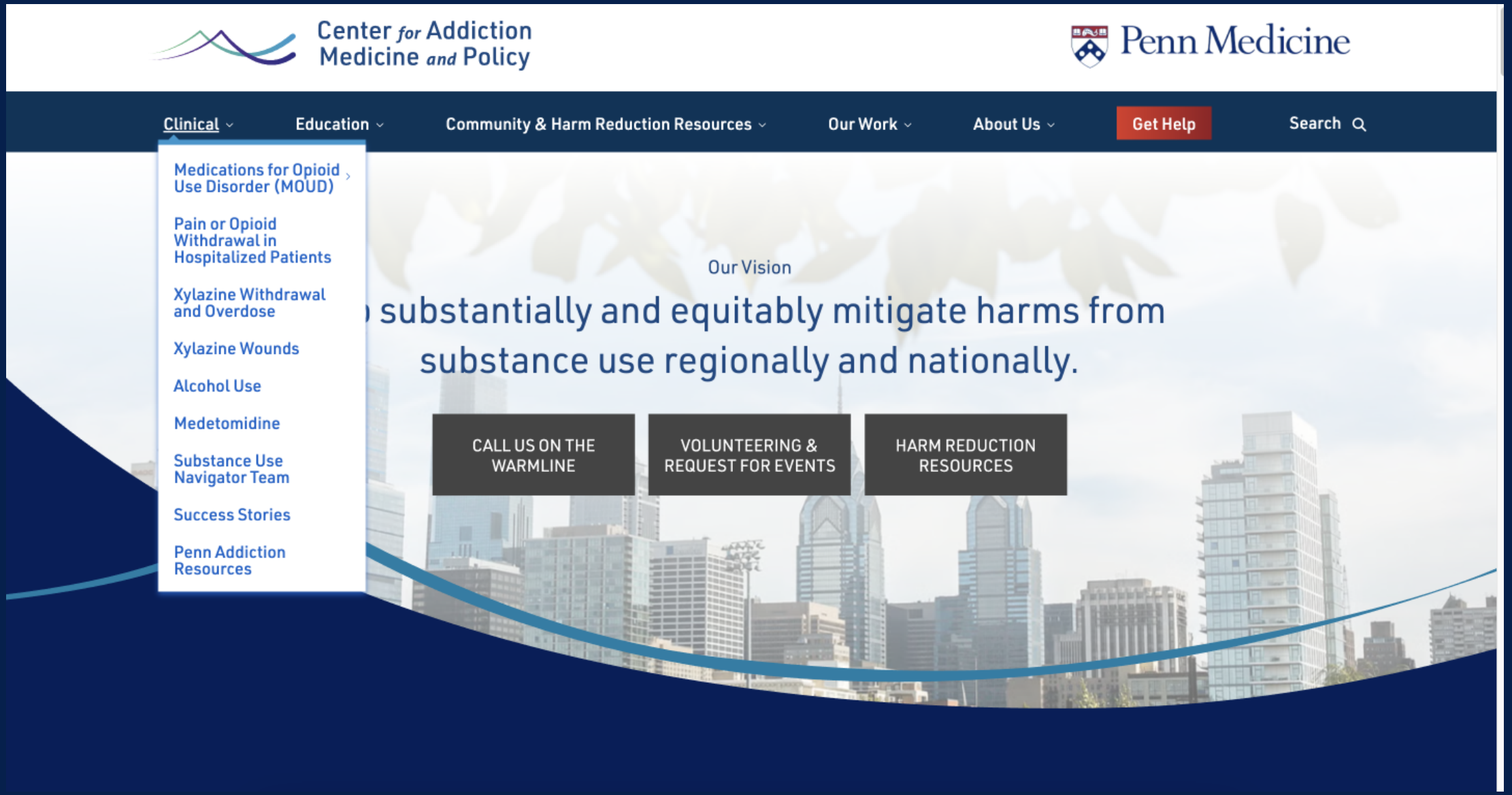
Our response:

- developed ICU guideline → ED guideline to prevent ICU upgrades
- ordersets to include higher doses alpha-2 agonists
- https://penncamp.org/medetomidine/

*Connell AR, et al. (J Ocul Pharmacol Ther 2022)*

# Current Insights into Management Strategies

- Backbone remains **aggressive opioid withdrawal management**
  - methadone PO or IV if not tolerating PO
  - scheduled short-acting oxycodone or hydromorphone PO
  - hydromorphone IVP prn
- **$\alpha_2$ agonist therapies:**
  - clonidine PO (up to 0.3mg) or patch
  - **dexmedetomidine: consider boluses, "max" 1.5 mcg/kg/hr drip**
- management of agitation / delirium:
  - ketamine PO, IV, or drip
  - olanzapine
- phenobarbital / benzos
  - BDZ may worsen delirium
  - PHB preferred if needed for sedation (not routinely indicated unless concomitant BDZ/EtOH withdrawal)
- management of HTN / tachycardia as needed (CCB, beta-blockers)




PennCAMP.org

# Medetomidine: Take-Aways

- a potent, highly-selective **alpha-2 receptor agonist**
  - quantity detected in seized samples in orders of magnitude higher than doses of dexmedetomidine provided clinically
  - sedation, bradycardia, and hypotension in overdose
- **emerging medetomidine withdrawal syndrome**
  - agitation, tachycardia, and hypertension
  - difficult to manage, requires multi-modal approach
  - ongoing response, surveillance, evolving clinical management guidelines

PennCAMP.org

# Case 2

Dr. JoAn Laes
Dr. Lewis Nelson

# Case 2

- A 36-year-old man injects an unknown substance to obtain euphoric effects.
  - unresponsive within 30 minutes
- Physical exam:  miosis, sedation, respiratory rate 6 breaths / min
- UDS (immunoassay):
  - *negative*: opiates, tricyclics, amphetamine, cocaine, phenobarbital
  - *positive*: benzodiazepines
- Receives naloxone 0.4mg IV → wakes but remains drowsy

# Case 2 Discussion

What novel substances are on your differential?

# Tianeptine

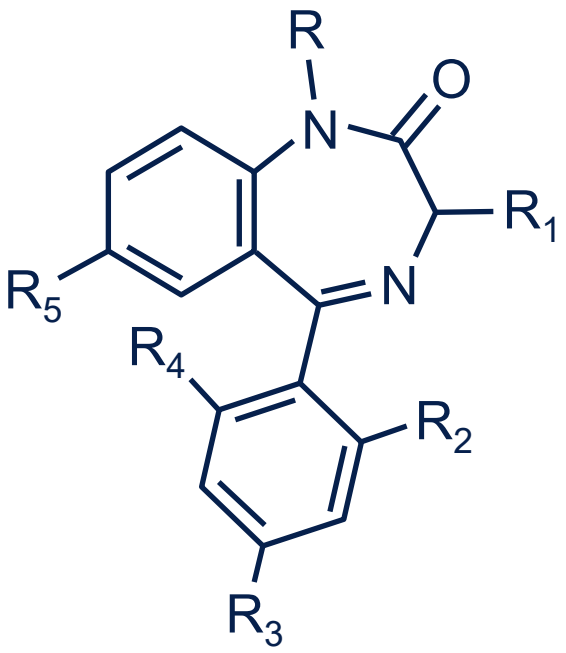
- atypical tricyclic antidepressant (TCA)
  - enhancement of serotonin reuptake
  - agonist activity at μ opioid receptor
- "gas station heroin"
  - increase 2014 → 2017
  - co-exposures common (phenibut, 31%; also EtOH, BDZ, & other opioids)
- withdrawal syndrome
- lab testing: *negative TCA assay*

# Tianeptine Management

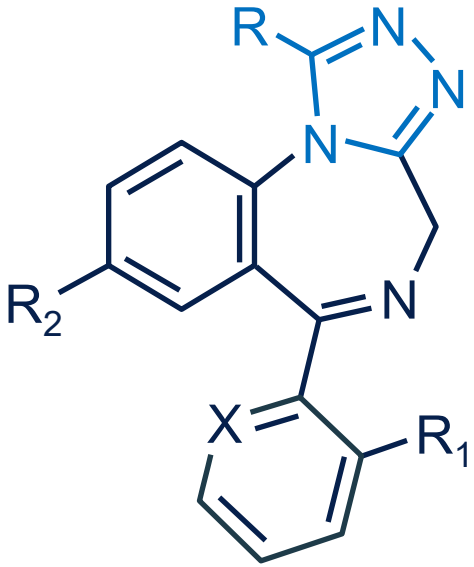
- intoxication
  - tolerance reported
  - symptomatic & supportive
  - partial response to naloxone
- withdrawal
  - case reports: buprenorphine
  - symptomatic: fluids, anti-emetics


*El Zahran T, et al. (MMWR 2018); Farsani A, Reyes C (Cureus 2024); Rawal VY, et al. (J Addict Dis 2025)*

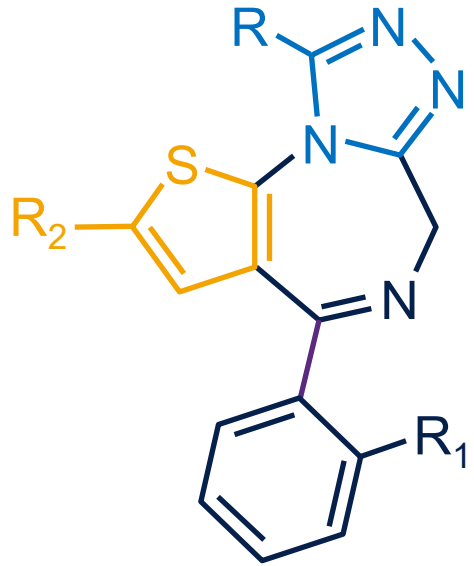
# Novel Benzodiazepines




1,4-benzodiazepine



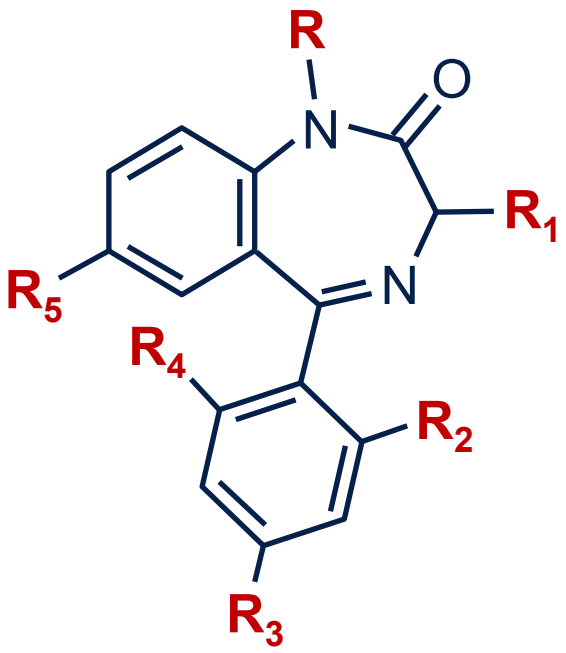

triazolobenzodiazepine



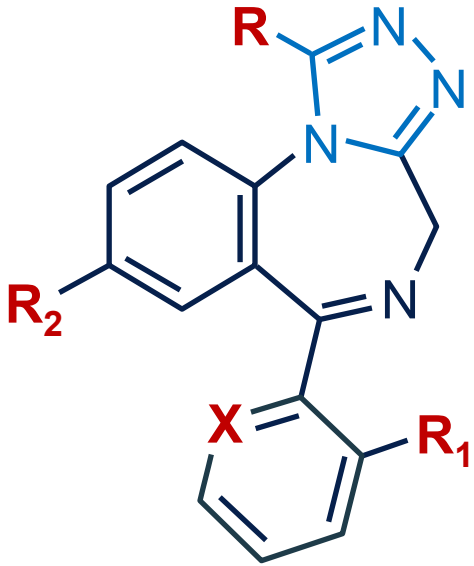

thienotriazolobenzodiazepine

examples of core structures

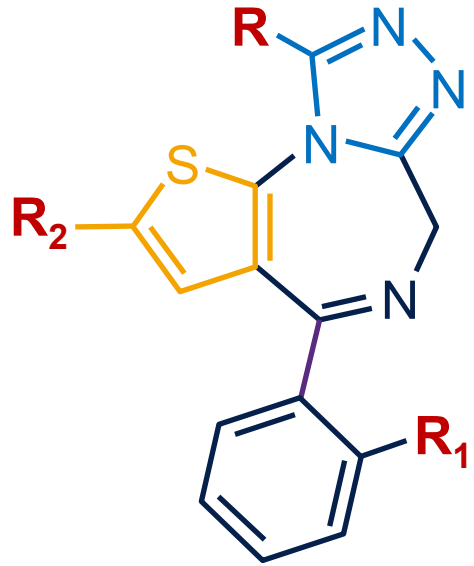
# Novel BDZ: Manipulate Side Chains




1,4-benzodiazepine



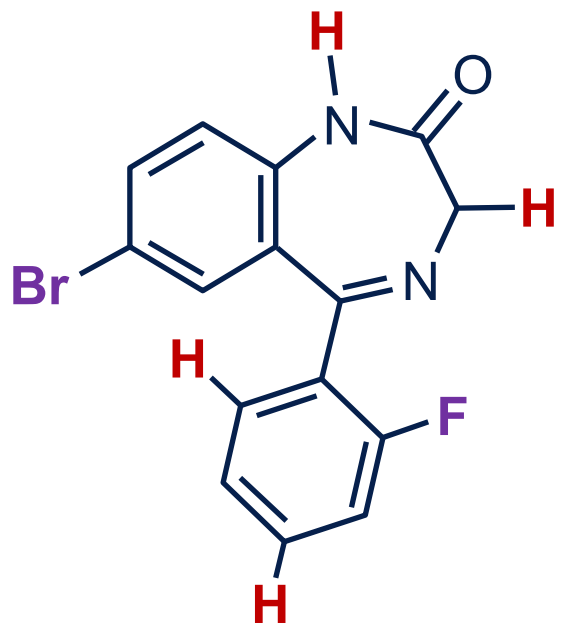

triazolobenzodiazepine



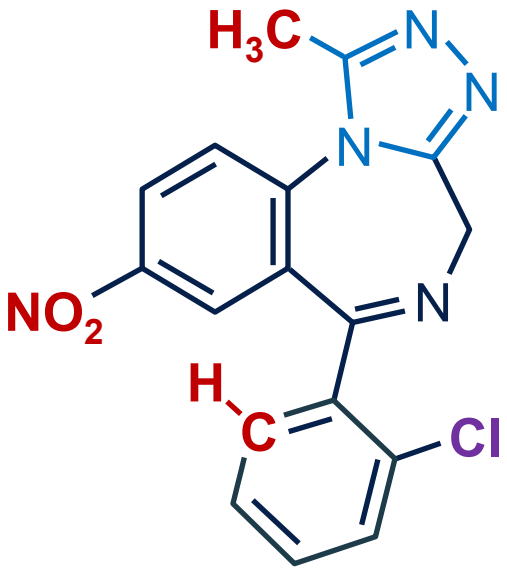

thienotriazolobenzodiazepine

functional group modifications affect pharmacokinetic properties

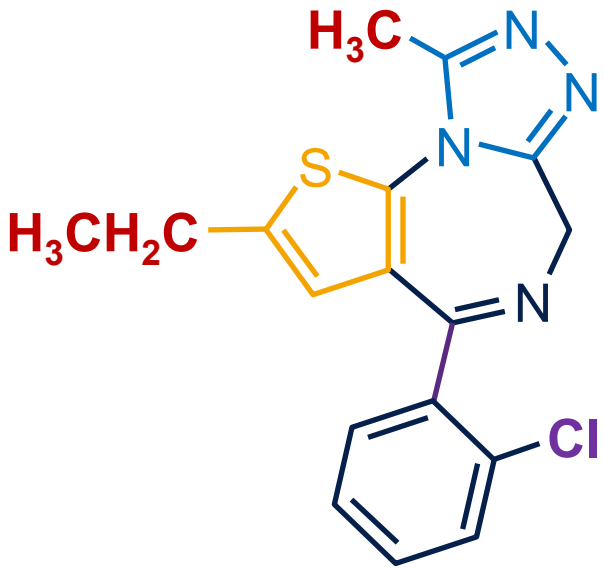
# Result: Novel ("Designer") BDZ




flubromazepam



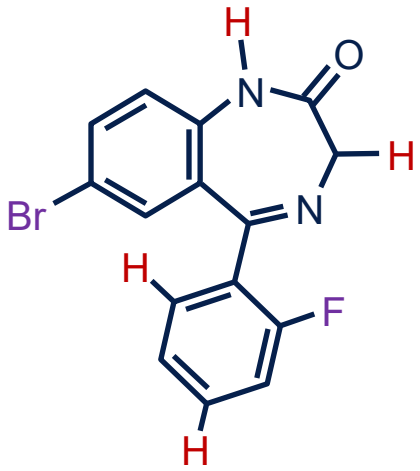

clonazolam



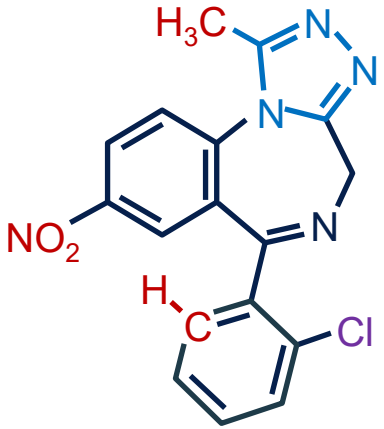

etizolam

many possible permutations

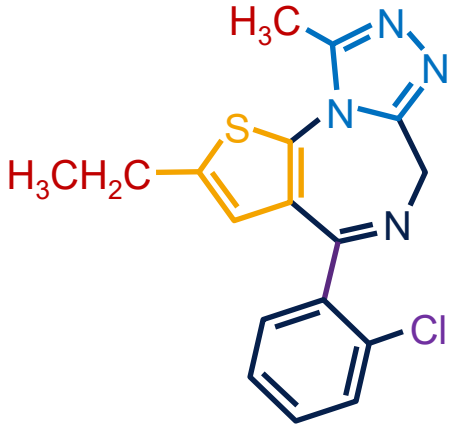
# A Few Other Examples




**flubro**mazepam
4-chloro**diazepam**
methyl**clonazepam**
phen**azepam**




**clon**a**zolam**
brom**azolam**
flu**alprazolam**
flunitr**azolam**




**et**i**zolam**
met**izolam**
deschloro**etizolam**
fluclo**tizolam**

# Novel Benzodiazepine Surveillance

drug seizures and undercover purchases

| 2010-2015 | 2018 | 2019 | 2021 |
| --- | --- | --- | --- |
| **Appearance of non-medical benzodiazepines** | **#2391 seizures/purchases** | **#6194 seizures/purchases** | **2021: Etizolam**<br>**2022: Etizolam, flualprazolam, clonazolam, flubromasolam, diclazepam**<br>**2022/2023: bromazolam** |

# Novel Benzodiazepine Testing

Immunoassay detected:

flubromazolam

flualprazolam

flubromazepam

nitrazepam

clonazolam

etizolam

*Puzyrenko A, et al. (J Analytical Toxicol 2022)*

# Novel Benzodiazepine Management

- intoxication
  - supportive care
- withdrawal
  - scales: CIWA-A, CIWA-B, RASS
  - medications: GABA-ergic agents, adjuncts

*Puzyrenko A, et al. (J Analytical Toxicol 2022)*

# Tianeptine & Novel BDZ: Take-Aways

- tianeptine (an atypical TCA)
  - **serotonergic and opioid effects** → partial response to naloxone
  - co-ingestants common, may muddy the clinical picture
  - consider buprenorphine for withdrawal
  - not detected by TCA immunoassay
- novel benzodiazepines
  - dozens available, varying potency and duration of action
  - pharmacokinetics not well defined
  - only some are detected by BDZ immunoassay

# Case 3

Dr. Cole Pueringer
Dr. Alaina Steck

# Case 3

- A 19-year-old male with no significant PMH insufflates what he believes to be ketamine, but shortly after taking it, he “suddenly felt very drunk.”
- Approximately 4 hours later, he presents with drowsiness, severe incoordination (several falls) and dysarthria.
- Vitals: T 36.7 ° C, HR 107 bpm, BP 194/110 mmHg
- Neuro exam:
  - GCS 13 (disorientated, drowsy), mydriasis
  - “severe cerebellar ataxia,” coarse nystagmus, dysdiadochokinesis
  - normal symmetrical limb reflexes, no Babinski

# Case 3 Discussion

If not ketamine, what could this be?

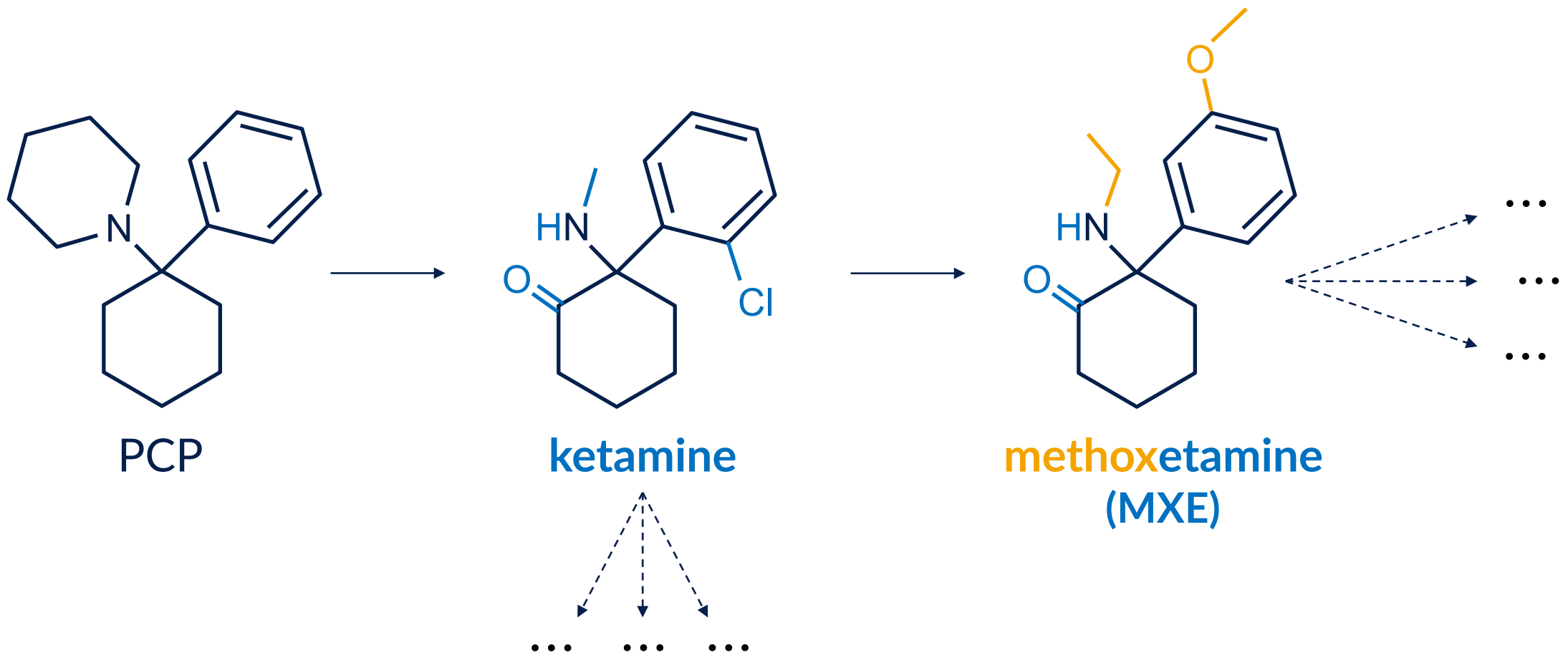
Notable features:

- fairly rapid onset of symptoms
- hypertension, tachycardia, normothermia

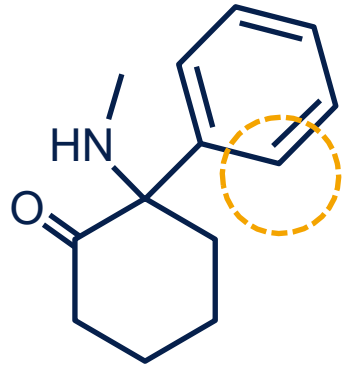
Additional information:

- labs notable for leukocytosis (19.8 × $10^9$/L) and mildly elevated CK (701 U/L), otherwise WNL
- EKG: normal

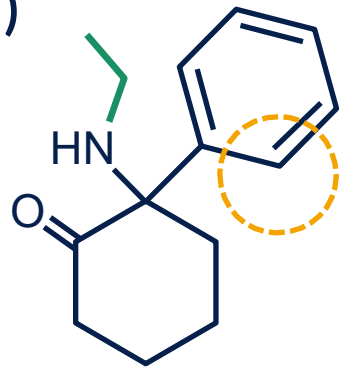
# Ketamine Analogs (Arylcyclohexamines)



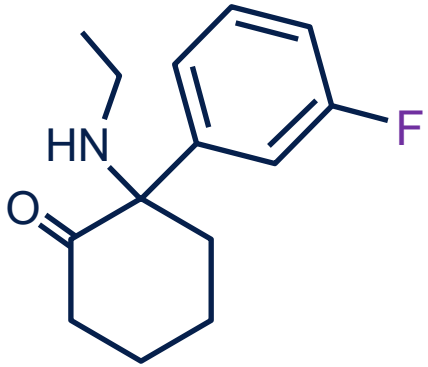
# Ketamine Analogs: Examples



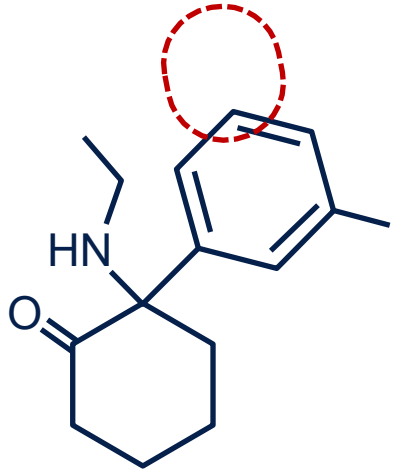

deschloroketamine
(DXE, DCK, 2'-oxo-PCM)




N-ethyldeschloroketamine
(2-oxo-PCE, O-PCE)




fluorexetamine
(3-FXE)




deoxymethoxetamine
(DMXE)

# Mechanism of Action and Clinical Effects

- All **antagonize the NMDA receptor** (glutamate), producing:
  - dissociation
  - memory deficits with long-term use

- Involvement of other neurotransmitter systems?
  - 5-HT receptors, SERT
  - may account for reports of agitation, hyperthermia, and urologic complications
    - although touted as a “bladder friendly” alternative to ketamine, case reports of MXE-associated cystitis exist

# Distinctions Among Analogs

- as compared to ketamine, **MXE has**:
  - **delay in onset**
  - **longer duration of action**
  - “near-death experience”

- rodent studies of multiple analogs show:
  - same reinforcing effects as ketamine
  - consistent findings regarding memory deficits
  - mixed data on bladder effects

# Pharmacokinetics of Ketamine Analogs

| Analyte | *In vitro* hepatic stability | |
|---|---|---|
| | *in vitro* T½ [min] (Eq. 2) | $CL'_{int}$ [mL/min/kg] (Eq. 3) |
| Ketamine | 15.1 ± 0.8 | 41.3 ± 2.1 |
| NK | 72.6 ± 2.9 | 8.6 ± 0.3 |
| 2FDCK | 69.1 ± 13.1 | 9.2 ± 1.7 |
| MXE | 99.2 ± 4.5 | 6.3 ± 0.3 |
| DCK | $N/A_A$ | N/A |

all hepatically metabolized

analogs: longer half-lives (decreased clearance)

Predicted partitioning coefficients and measured protein binding for ketamine and four ketamine analogues. The unbound fraction ($f_u$) is shown as mean ± std. dev. values (n = 6).

| Analyte | Predicted logP | $f_u$ (Eq. 1) |
|---|---|---|
| Ketamine | 3.35 | 0.54 ± 0.08 |
| NK | 2.91 | 0.60 ± 0.03 |
| 2FDCK | 2.89 | 0.79 ± 0.10 |
| MXE | 2.94 | 0.73 ± 0.03 |
| DCK | 2.74 | 0.84 ± 0.04 |

NK: norketamine; 2FDCK: 2-fluoro-deschloroketamine, MXE: methoxetamine, DCK: deschloroketamine.

ketamine: most lipophilic, highest protein binding

analogs: less lipophilic but higher free fraction of drug available to diffuse into CNS

final metabolic fate and drug potency is still difficult to predict

*Davidsen AB, et al. (J Pharm Biomed Anal 2020)*

# Testing: Cross-Reactivity with PCP on UDS

| Compound | Detectable with GC/MS | PCP immunoassay (IA) cross-reactivity |
|---|---|---|
| ketamine | Yes | not detected in any PCP IA evaluated |
| 3-methoxy-phencyclidine (3-MeO-PCP) | Yes | varied widely between different IA's (1 – 143%) |
| 4-methoxy-phencyclidine (4-MeO-PCP) | Yes | varied widely between different IA's (1 – 143%) |
| Methoxetamine (MXE) | Yes | most IA's had very weak cross-reactivity (<1%)<br>a few IA's had moderate cross-reactivity |
| deschloro-N-ethylketamine (O-PCE, 2-oxo-PCE) | ?? | varied widely between different IA's |
| 3-methoxy-eticyclidine (3-MeO-PCE) | Yes | varied widely between different IA's |

*Gomila I, et al. (J Anal Toxciol 2019)*

# Ketamine Analogs: Take-Aways

- **NMDA receptor antagonists** with varying (suspected) involvement of serotonergic system
  - typical dissociative effects, but vary in intensity, onset, and duration
  - +/- serotonergic effects (agitation, hyperthermia)
- Highly variable pharmacokinetics
- Not reliably detected by PCP immunoassays

# Emerging Substances: Overall Summary

1. There are many available surveillance resources for changing drug supply; know the limitations.
2. Medetomidine: is >100x more potent than xylazine. Withdrawal management relies on multi-modal approaches including clonidine and dexmedetomidine and opioid withdrawal treatment.
3. Tianeptine: an atypical TCA that also has opioid agonist effects. Partial response to naloxone in overdose, may respond to buprenorphine for withdrawal management.
4. Novel benzodiazepines: +/- cross-reactivity on immunoassays; withdrawal management with GABAergic agents.
5. Ketamine analogs: exhibit full spectrum of clinical effects, long-term toxicity remains undefined. Unreliable detection on immunoassays.

# Emerging Illicit Substances:
## What Clinicians Need to Know

**Thank you!**

**Questions?**