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Psychiatry and Addictions Case Conference

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What Do I Need to Know About Synthetic Benzos in the Drug Supply

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SPEAKER DISCLOSURES

I have no conflicts of interest

PLANNER DISCLOSURES

The following series planners have no relevant conflicts of interest to disclose; other disclosures have been mitigated.

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OBJECTIVES

1. Define what synthetic benzodiazepines are and describe their pharmacology
2. Identify common synthetic benzos in circulation
3. Discuss current trends in the drug supply
4. Recognize the health risks and overdose potential of synthetic benzos
5. Discuss detection challenges

Definition

What are they?

Synthetic (or “designer”) benzodiazepines are benzodiazepine analogues that are typically not licensed medications (at least in certain countries).

They may be structurally similar to prescribed benzodiazepines or their metabolites, but were often originally developed as research chemicals and later exploited on the illicit market.

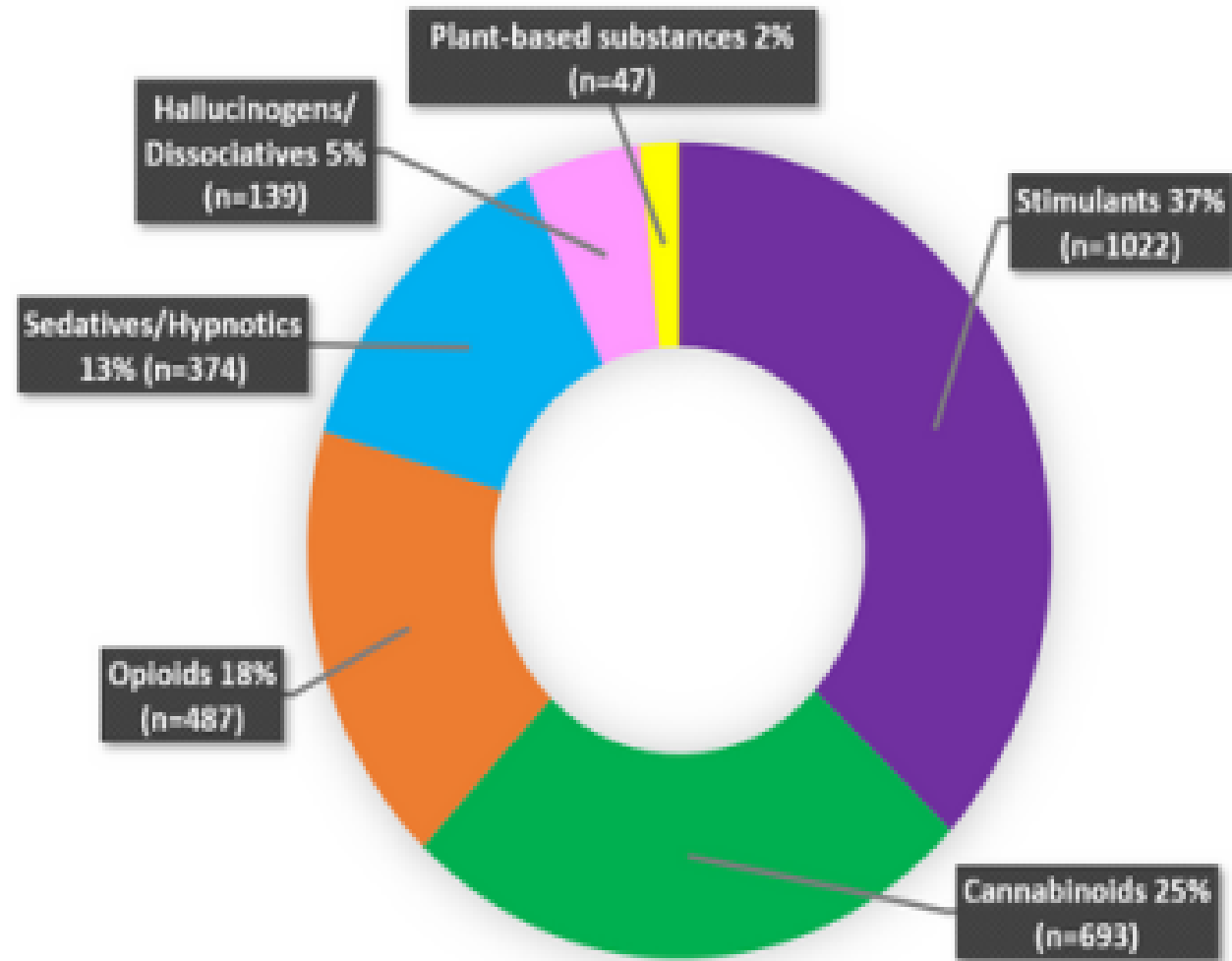


Figure 8: The distribution of NPS reported to the UNODC in the U.S. in 2013-2022, by effect group

Source: United Nations Office on Drugs and Crime (UNODC) [55]

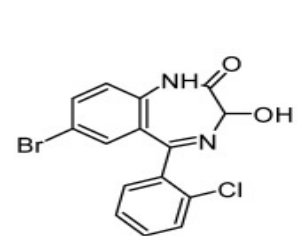
Pharmacology

Like traditional benzodiazepines, they act as positive allosteric modulators of GABA-A receptors in the CNS, enhancing the inhibitory effect of GABA. This yields the classic benzodiazepine effects: anxiolysis, sedation/hypnosis, muscle relaxation, anti-seizure activity, and amnesia.

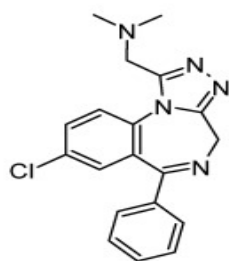
Potency & kinetics

- Many designer benzos exhibit high potency and variable half-lives.
- Because most were never formally tested in humans, their pharmacokinetics are not well characterized. This unpredictability can make their clinical effects dangerous, as small dose differences may lead to disproportionate sedation.

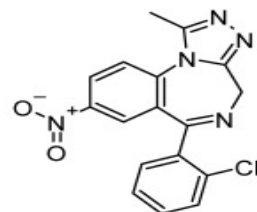
Common Synthetic Benzos in Circulation



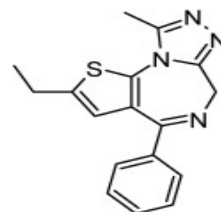
3-Hydroxyphenazepam



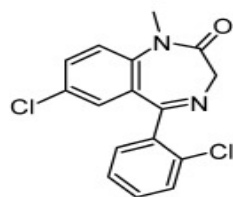
Adinazolam



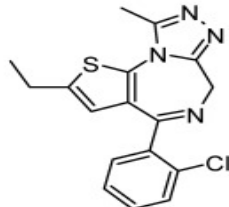
Clonazepam



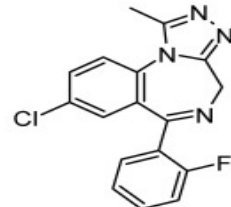
Deschloroetizolam



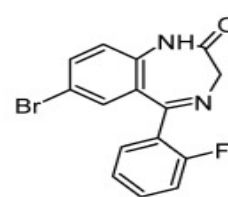
Diclazepam



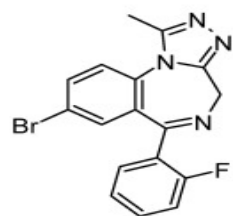
Etizolam



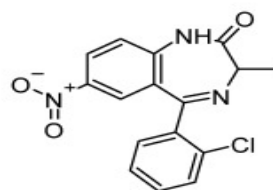
Flualprazolam



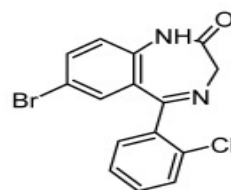
Flubromazepam



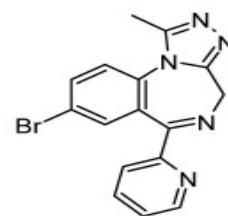
Flubromazolam



Meclonazepam



Phenazepam



Pyrazolam



Real Xanax (left) and counterfeit Xanax (right)



DEA

United States Drug Enforcement
Administration

September 25, 2023

Five Synthetic Benzodiazepine Drugs Deemed Imminent Hazard to Public Safety

DEA's Diversion Control Division

On July 26, 2023, DEA temporarily scheduled five synthetic benzodiazepine substances – etizolam, flualprazolam, clonazepam, flubromazolam, and diclazepam – in schedule I of the Controlled Substances Act (CSA). Individuals who handle these substances will now be subject to regulatory controls, as well as to administrative, civil, and criminal sanctions applicable to schedule I controlled substances under the CSA.

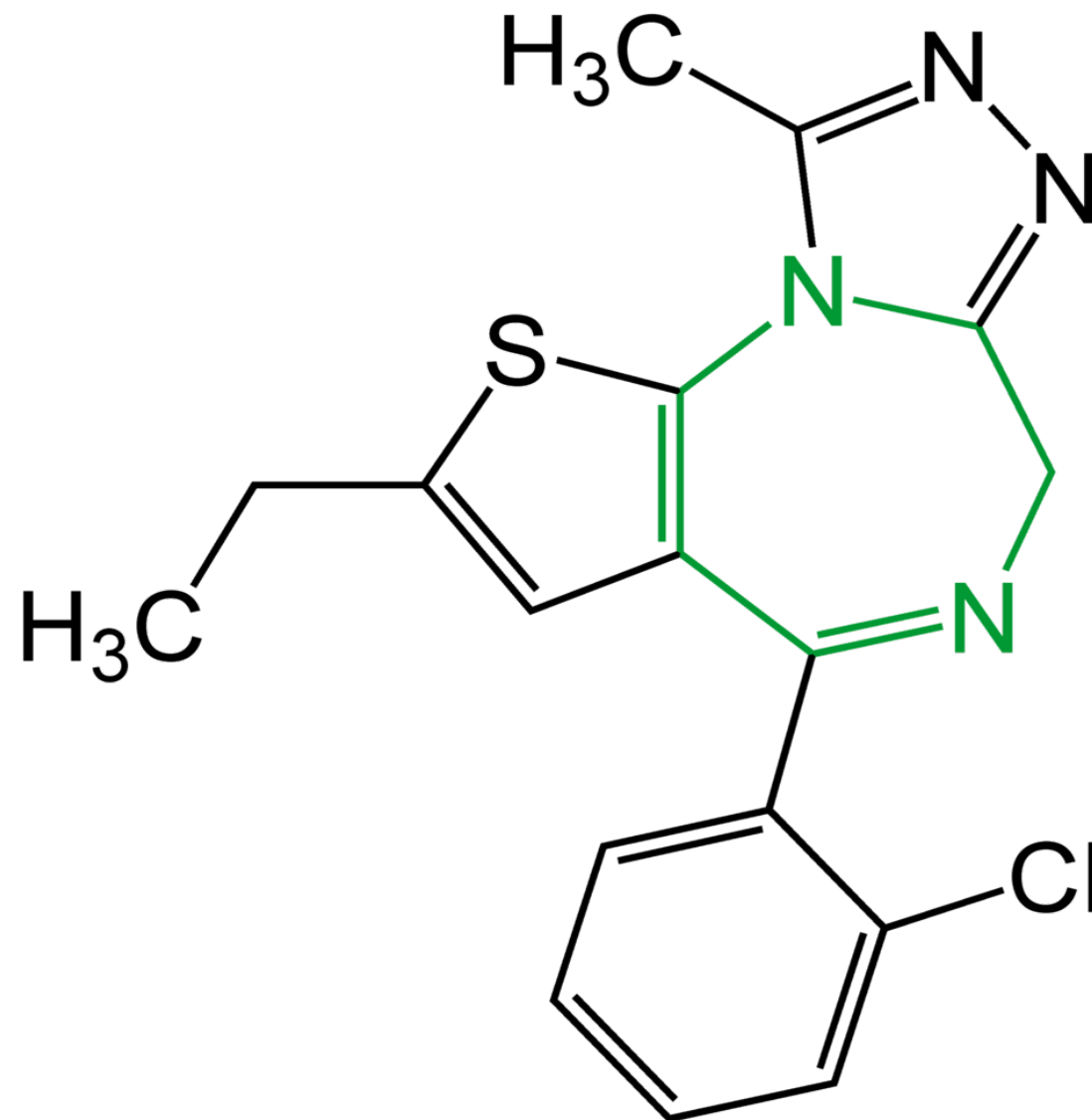
The dramatic increase in trafficking and abuse associated with these substances, also known as “designer benzodiazepines,” has become a national public health concern in recent years. According to the Centers for Disease Control and Prevention, benzodiazepines were involved in 12,499 overdose deaths in the United States between 2019 and 2021.

Etizolam

- Used as a prescription anxiolytic in some countries but not approved in the US.
- On the illicit market, it has been found in powder or counterfeit pill form.
- It is roughly 6–8 times more potent than diazepam, and has a short to intermediate half-life (~3–6 hours).
- Etizolam was one of the earliest designer benzos to appear and contributed to many overdose deaths in the late 2010s.

Etizolam

The green-highlighted diazepine ring is a core feature shared with traditional benzodiazepines.



Flubromazolam

- An extremely potent triazolo-benzodiazepine (analogue of triazolam/flubromazepam).
- Recreational user reports note heavy sedation and amnesia as defining effects. Even microgram doses can induce profound hypnosis.
- It has a long duration: effects last 3–6 hours with after-effects up to 14 hours.
- Cases of flubromazolam overdose document deep coma, respiratory depression, and prolonged CNS depression.

<https://www.dea.gov/stories/2023/2023-09/2023-09-25/five-synthetic-benzodiazepine-drugs-deemed-imminent-hazard-public#:~:text=On%20July%2026%2C%202023%2C%20DEA,controlled%20substances%20under%20the%20CSA>

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Edinoff AN, Nix CA, Odisho AS, Babin CP, Derouen AG, Lutfallah SC, Cornett EM, Murnane KS, Kaye AM, Kaye AD. Novel Designer Benzodiazepines: Comprehensive Review of Evolving Clinical and Adverse Effects. *Neurol Int.* 2022 Aug 22;14(3):648-663. doi: 10.3390/neurolint14030053. PMID: 35997362; PMCID: PMC9397074.

Clonazolam



- A triazolo-analog of clonazepam, notable for its high potency. It's reported to be over twice as potent as alprazolam.
- Clonazolam often causes pronounced sedation and memory loss; users describe rapid development of tolerance and severe withdrawal symptoms upon cessation.
- It has no medical use and has been involved in numerous impaired driving and overdose cases.
- Poison center data (2014–2017) identified clonazolam as a frequent culprit in designer benzo exposures, with 36% of such cases requiring hospital admission.

Flualprazolam

- A fluorinated analog of alprazolam. Emerged around 2018–2019 and quickly became common in forensic detections.
- Effects are similar to alprazolam (anxiolytic, sedative) but potency is slightly higher.
- Flualprazolam was linked to multiple overdose fatalities leading to its international control in 2020.
- Often found in counterfeit Xanax bars or pressed tablets.

Diclazepam

- Also known as chlorodiazepam, a designer analog of diazepam
- It's a long-acting benzodiazepine with similar effects to diazepam but roughly 10x more potent
- It was sold online as a “legal” sedative in the 2010s

Bromazolam

- A relatively newer analog (structurally similar to alprazolam, with a bromine substitution). Bromazolam has recently surged in prevalence as earlier analogs became controlled.
- In Scotland, bromazolam replaced etizolam as the most common street benzo after 2021.
- Potency is in the same range as alprazolam or higher.
- U.S. reports in 2023 indicate bromazolam is now frequently detected in illicit “Xanax” pills post-DEA scheduling of others.

Trends in Drug Supply

Designer benzodiazepines began appearing in the illicit drug market in the early 2010s, then surged after 2018, peaking in 2021.

2020	2021	2022	2023
Eutylone (739)	Fluorofentanyl (2,060)	Fluorofentanyl (2,308)	Fluorofentanyl (1,103)
MDMB-4en-PINACA (634)	para-Fluorofentanyl (1,428)	para-Fluorofentanyl (755)	Bromazolam (388)
5F-MDMB-PICA (471)	Eutylone (678)	Clonazolam (261)	para-Fluorofentanyl (345)
Acetyl fentanyl (428)	Clonazolam (666)	MDMB-4en-PINACA (246)	MDMB-4en-PINACA (272)
Etizolam (384)	MDMB-4en-PINACA (470)	Acetyl fentanyl (228)	Acetyl fentanyl (269)

Cannabinoids Opioids Benzodiazepines Stimulants

Table 2: Five most commonly detected novel psychoactive substances in PA in 2020-2023

Source: U.S. Drug Enforcement Administration, Diversion Control Division [56]

Note: Number in parenthesis indicates total number of drug samples for a specific drug in a given year.

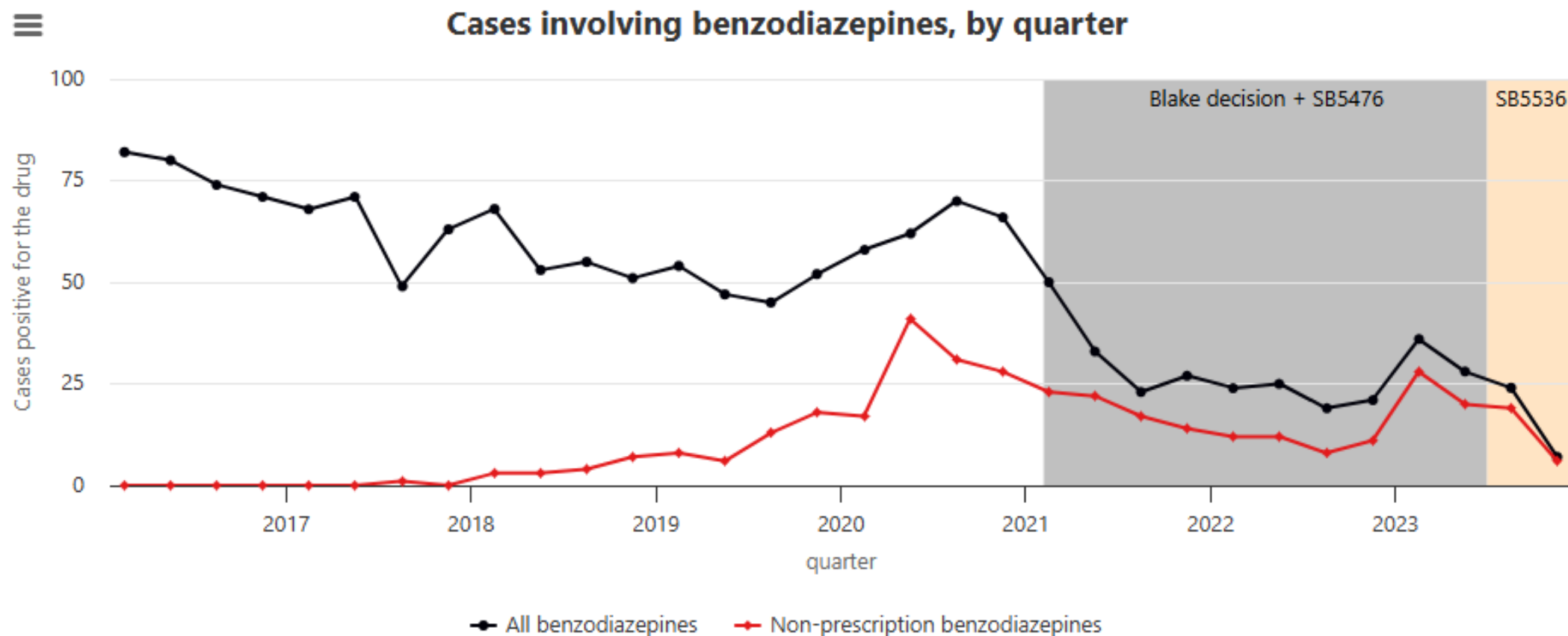
Trends in Drug Supply

- The U.S. DEA's National Forensic Lab system reported that the number of synthetic benzo undercover purchases more than doubled from 2018 to 2019 (rising from 2,391 to 6,194).
- In Pennsylvania, designer benzos were detected in 59 overdose fatalities in 2022, climbing to 147 deaths in the first half of 2023 alone.

Geographic Prevalence & Market Data

- United States Hotspots?
- Pennsylvania has consistently reported a high incidence, 57% of ED patients with illicit benzos detected were from PA. The same study found 14.9% of patients with suspected opioid overdose across four states had co-exposure to illicit benzodiazepines (most commonly clonazepam and etizolam).

Washington State



Analysis by UW ADAl. For data sources, see text or adai.uw.edu/WAdata

Data source: Forensic Laboratory Services Bureau, Washington State Patrol. 2021 counts and onward are impacted by the 2/25/2021 *Washington State v Blake* decision. The most recent quarter always represents an undercount.

Online/Dark Web Market



Why Are Designer Benzos Emerging in the Illicit Market?

- Legal Evasion
- High Demand
- Cheap Production
- User Appeal
- Detection Avoidance

Health Risks and Toxicity

- **CNS Depression:** All benzodiazepines, traditional or synthetic, are central nervous system depressants.
- **Respiratory Depression:** Synthetic benzos - ↑ potency → respiratory failure in some instances.
- **Overdose and Toxicity:** The margin of safety is narrower with designer benzos. Users may not realize how strong a dose they've taken. Accidental overdose is common, especially when taking pressed pills of unknown content.

Health Risks and Toxicity

- **Amnesia & Behavioral Risks:** Synthetic benzos often induce profound memory gaps. Flubromazepam and clonazepam are notably amnestic, ranking among the most amnesia-producing in user reports.
- **Dependency & Withdrawal:** There is concern that certain designer benzos may cause more intense dependence and harder withdrawal than traditional ones.
- **Overdose Fatality:** Fatal outcomes do occur, especially when the benzo is extremely potent or mixed with others. Many overdose deaths involving designer benzos also involve opioids, but in some cases the benzo was a primary contributor.

“Benzo-Dope”



ONE HIT OF BENZO DOPE
CAN KILL YOU



‘BENZO-DOPE’ REPLACING
FENTANYL ON THE STREETS

“Benzo-Dope”

- One U.S. toxicology study found illicit benzos in ~15% of suspected opioid overdose ED patients
- Naloxone limitation!!!

Laboratory Detection Challenges

- Urine drug screens for benzodiazepines use immunoassays targeting common benzo metabolites (like oxazepam). Many synthetic benzos do not cross-react with these assays.
- Specialized Toxicology Testing: (GC-MS or LC-MS/MS)
- Resource Constraints!
- Continuous Evolution: A major issue is that analytical methods must keep up with new compounds.

A high clinical suspicion might be your best tool!

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Thank you!!

