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INTRODUCTION

- **Prescription benzodiazepine misuse** is a well-established public health challenge¹
- **“Designer” benzodiazepines** represent a **novel class of synthetic benzodiazepine compounds (e.g., bromazolam)** which may be **obtained without a prescription**²

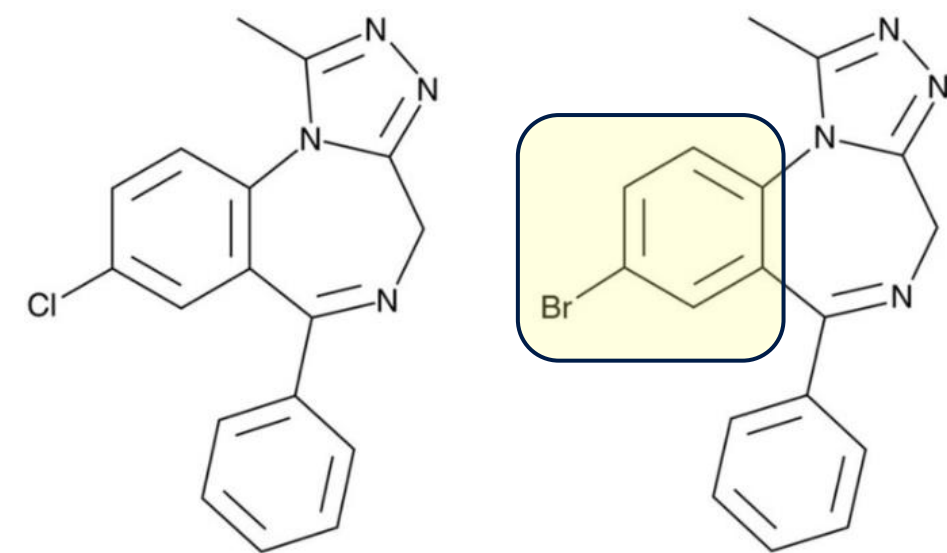


Figure 1: Chemical structure of alprazolam (left) versus bromazolam (right) with highlighted changes.³

- Most designer benzodiazepines are **purchased from online retailers**, including those on the dark web
- Limitations in testing methods **may affect detection of designer benzodiazepines** in clinical samples

EMERGENCY DEPT. EVALUATION

- **22-year-old male** with a history of cannabis and alcohol use presented to the ED for evaluation of an initial complaint of chest pain
 - Vital signs: **Significant tachycardia** and **hypertension**
- Patient reported using **bromazolam**, a **synthetic triazolobenzodiazepine purchased online**, daily for at least the last month
 - Collateral information from his parents confirmed the **recent cessation of bromazolam use** and a lack of recent alcohol use
 - Patient experienced auditory hallucinations and odd dreams during the 24 hours prior to presentation
- Diagnostic testing:
 - Urine drug screen was positive for tetrahydrocannabinol, **but negative for benzodiazepines**
 - ECG demonstrated sinus tachycardia without ischemia
- During further ED evaluation, the patient became **increasingly agitated with worsening auditory, visual, and tactile hallucinations**
 - **Required sedation and intubation** due to ongoing agitation and was admitted to the medical ICU for further management

TREATMENT COURSE

ICU Admission	<ul style="list-style-type: none"> • Following admission, remained intubated on a propofol infusion • Intravenous phenobarbital was utilized for neuroprotection due to concern for severe benzodiazepine withdrawal • After 24 hours, dexmedetomidine was initiated to allow for slow propofol weaning • Transitioned to CIWA protocol with lorazepam for monitoring and treatment of additional symptoms
General Medical Floor	<ul style="list-style-type: none"> • Reported ongoing auditory/visual hallucinations consistent with delirium in the setting of benzodiazepine withdrawal • Symptoms managed with as-needed quetiapine • Psychiatry and Social Work consultation recommended connection with substance use assessment and treatment
Outpatient Care	<ul style="list-style-type: none"> • Further behavioral health assessment identified a history of social anxiety with use of cannabis and benzodiazepines to self-manage anxiety symptoms • Pharmacologic treatment started with bupirone to address anxiety, plus outpatient psychotherapy • To date, the patient has not required re-hospitalization for substance use or psychiatric concerns

DESIGNER BENZODIAZEPINE TRENDS

- Designer benzodiazepines are derived from **currently or formerly licensed benzodiazepines** through the process of **structural modification**²
- Timeline of notification to the EU Early Warning System from 2016-2019⁴:

2016	Cloniprazepam, flunitrazolam, 4-chlorodiazepam, bromazolam
2017	Norfludiazepam, thionordiazepam
2018	Methylclonazepam, flucotizolam, tofisopam, clobromazolam
2019	Bentazepam, cinazepam

- Resultant substances retain pharmacological effects similar to licensed products, by **potency, half-life, and purity** may vary significantly
- Demonstrated effects may include **anxiolysis, amnesia, and sedation**⁵

DETECTION AND LEGAL ISSUES

- **Detection considerations**⁵:
 - Commercially available immunochemical assays **retain cross-reactivity** with many current designer benzodiazepines
 - Detection challenges arise when **drug metabolites are not identified** through standard testing practices
 - **Early warning systems** exist through the United Nations and the European Monitoring Centre for Drugs and Drug Addiction – but **the US lacks a centralized reporting system** for real-time monitoring
- **Legal issues**:
 - Bromazolam was involved in **over 2,900 law enforcement seizures in 2023**, which represents a marked increase from prior years⁶
 - Tested bromazolam samples often contain contaminants, including **fentanyl** and **other opioids**
 - The United States Drug Enforcement Administration has **temporarily scheduled five designer benzodiazepines under schedule I** of the Controlled Substances Act⁷

September 25, 2023

Five Synthetic Benzodiazepine Drugs Deemed Imminent Hazard to Public Safety

DEA's Diversion Control Division

LEARNING POINTS

- **Designer benzodiazepines** represent a **novel class of psychoactive substances** with **variable clinical effects** similar to currently available prescription benzodiazepines
- Limitations in commercial testing methods, including **challenges detecting drug metabolites**, may negatively impact designer product identification in clinical samples
- The **legal landscape** surrounding designer benzodiazepines continues to evolve with **recent DEA regulations** and **changes in drug scheduling**

References available via QR code:



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