

“Don’t you mean clonazepam?”

A 40-year-old woman with opioid use disorder
requesting detoxification from clonazolam
(novel/designer benzodiazepine)



Ximena A. Levander, MD

Addiction Medicine & General Internal Medicine Fellow

Oregon Health & Science University

NWIHB ECHO

Thursday May 21, 2020

Disclosures

I have no financial disclosures related to material covered in presentation

This case is from my 1st year of addiction medicine fellowship.

Details are recalled to best of my ability.

Learning Objectives

By conclusion participants should be able to:

1. Interpret a "negative" benzodiazepine urine drug screen and determine next steps for further confirmatory testing.
2. Recognize emergence of novel psychoactive substances (NPS) including novel benzodiazepines and the challenges of monitoring and reporting this rapidly changing drug-use landscape.

Case Presentation

On initial history

- 40-year-old woman – mildly tremulous and anxious
- Hx of OUD on methadone 110 mg daily for > 1 year
- ~3 months ago started taking clonazepam
- Went to her counselor ~2 months ago requesting “detox”
- UDS is “negative” for benzodiazepines on multiple occasions
- Ongoing difficulties trying to stop on her own
- Took “a bar” (alprazolam)
- She then had a “positive” UDS result
- Recommendation - admit for supervised benzo withdrawal

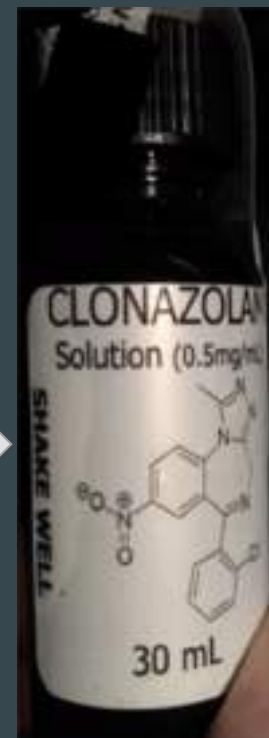
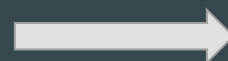
Clonazepam?

What is Clonazolam? Did you mean - clonazepam?

The image shows a screenshot of the UpToDate website. At the top left is the UpToDate logo. To its right is a search bar containing the text 'clonazolam' and a magnifying glass icon. Below the search bar is a blue navigation bar with the following items: 'Contents' with a dropdown arrow, 'Calculators', and 'Drug Interactions'. Below the navigation bar is a grey bar that says 'Showing results for clonazolam'. Underneath this is a row of filter buttons: 'All' (highlighted in blue), 'Adult', 'Pediatric', 'Patient', and 'Graphics'. Below the filters, the text 'Did you mean: [clonazepam](#)' is displayed. At the bottom of the page, a red-bordered box contains the message: 'No results were found containing clonazolam.'

Clonazepam - Novel Benzodiazepine

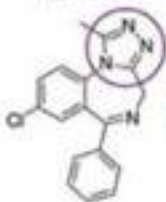
- Designer triazolobenzodiazepine
 - First synthesized in 1971
 - Never licensed for therapeutic use (anywhere)
 - First seen sold online starting in 2014
-
- Contents from this vial were analyzed from a case of clonazepam ingestion using LC/QTOF MS had 30-60 (0.2-0.4mg) doses



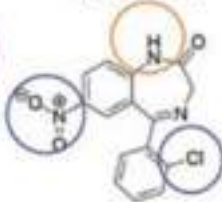
F1 Examples of benzodiazepines approved or not approved by FDA

Prescription (FDA-approved) Benzodiazepines

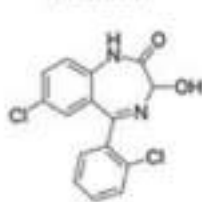
Alprazolam
(Xanax®)



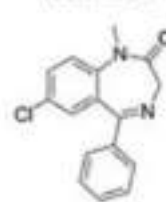
Clonazepam
(Klonopin®)



Lorazepam
(Ativan®)

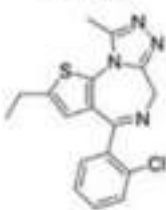


Diazepam
(Valium®)

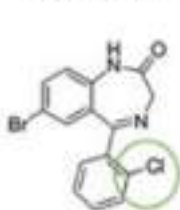


**Non (FDA-approved) Benzodiazepines
Approved in Other Countries**

Etizolam

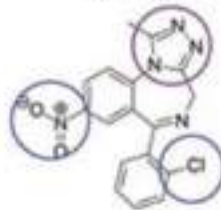


Phenazepam

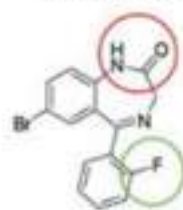


Designer Benzodiazepines

Clonazolam

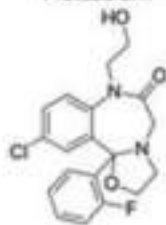


Flubromazepam

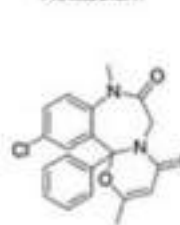


Atypical Designer Benzodiazepines

Flutazolam



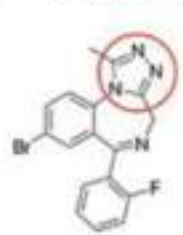
Ketazolam



Cloniprazepam



Flubromazolam



Case Presentation Continued

On further history

- Reports Clonazepam sold as “Research Chemicals” through Internet
- Currently taking between 1-2 “vials” a day of clonazepam
- Clear liquid, sips on the vial(s) throughout day
- No previous history of using benzodiazepines prior to 3 months ago
- One day had no access to clonazepam
- On this day needed 12 mg of alprazolam to stave off withdrawals

Concerns about Counterfeit Benzodiazepines

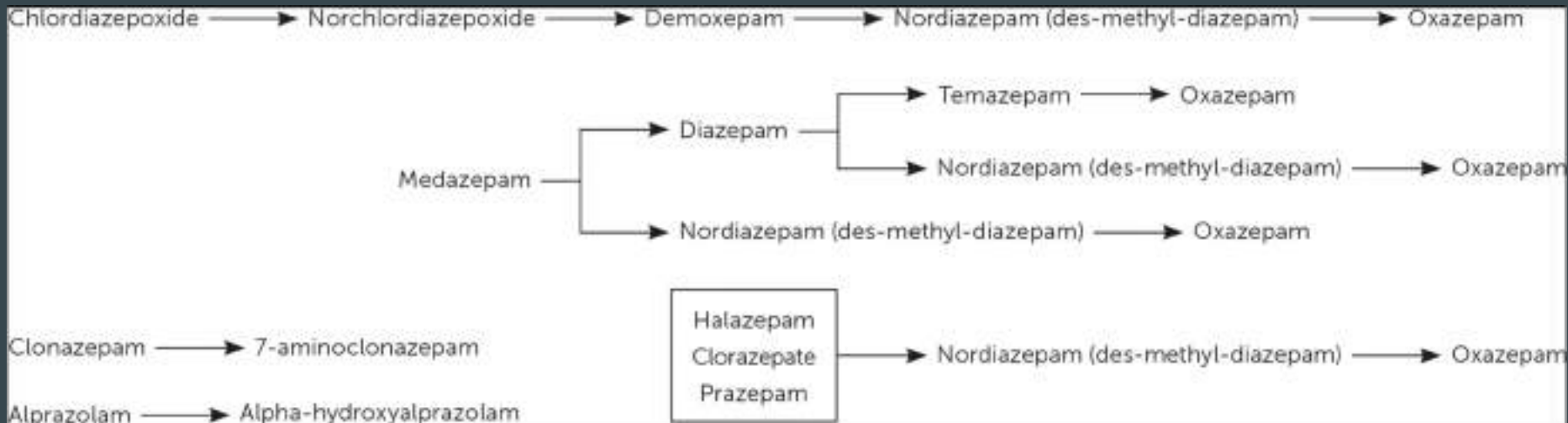
Can you tell the difference?



What happened with her UDS results?

Learning Objective #1: Interpret a "negative" benzodiazepine urine drug screen and determine next steps for further confirmatory testing.

Benzodiazepine Metabolism



Information from Valentine JL, Middleton R, Sparks C. Identification of urinary benzodiazepines and their metabolites: comparison of automated HPLC and GC-MS after immunoassay screening of clinical specimens. J Anal Toxicol. 1996;20(6):419.

Benzodiazepine Urine Drug Screen

1. Immunoassay (POC screening)
 - a. False-negative
 - b. False-positive
2. Confirmatory LC/GC-MS
3. Send-off to specialized lab for designer drug panel

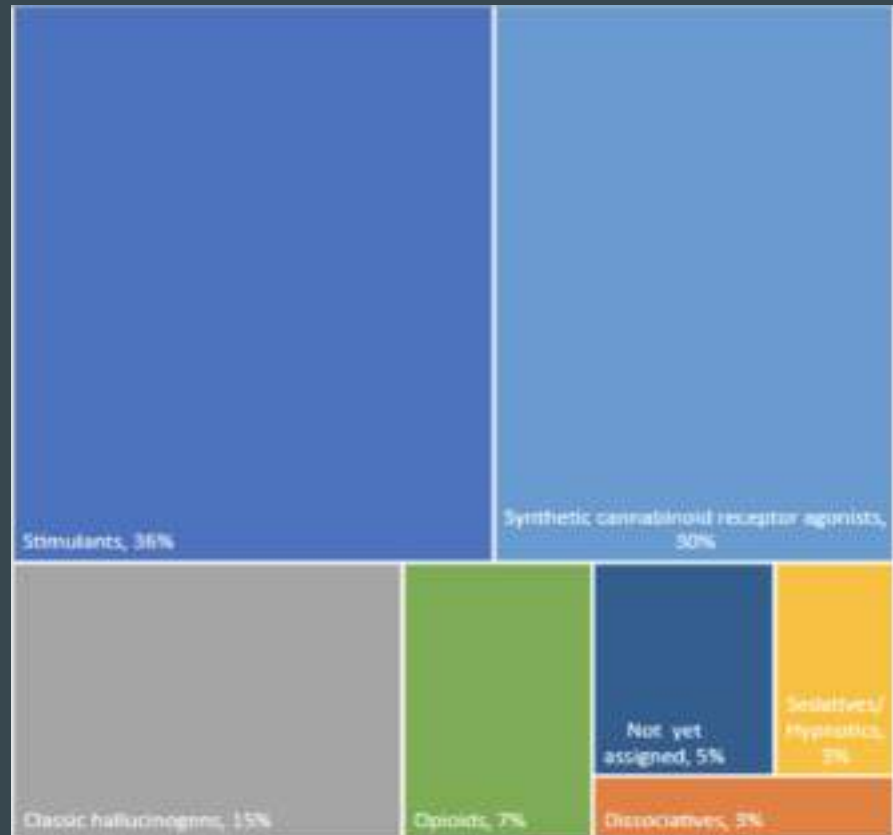


Novel Psychotropic Substances (NPS) & Novel Benzodiazepines

Learning Objective #2: Recognize the emergence of novel psychoactive substances (NPS) including novel benzodiazepines and the challenges of monitoring and reporting this rapidly changing drug-use landscape.

What is a Novel Psychotropic Substance?

- Not controlled under UN drug control conventions
- Similar threats to health
- Many categories of substances
- Marketed as “legal” replacements for illicit drugs
- Large number of new substances – development and distribution
- Significant diversity of substances
- Challenging to monitor
- Challenging to develop effective and timely responses



Challenges Monitoring NPS



European Monitoring Centre
for Drugs and Drug Addiction

 **EUROPOL**



OAS | CICAD



UNODC

United Nations Office on Drugs and Crime

NFALS

DEA DIVERSION CONTROL DIVISION

NATIONAL FORENSIC LABORATORY
INFORMATION SYSTEM

**REPORT ON DRUG
USE IN THE AMERICAS
2019**



NDEWS *National Drug Early Warning System*

Funded at the Center for Substance Abuse Research by the National Institute on Drug Abuse

Emergence of Novel Benzodiazepines

- “Classical” benzodiazepines - where do synthetic benzos fit?
 - Schedule 4 - UN 1971 Convention
 - Schedule IV - US Controlled Substances Act





Erin Artigiani via NDEWS Network <ndews@discoursemail.com>

Mon, 5/16, 1:42 PM

Re: Erin Lovander

5 Reply



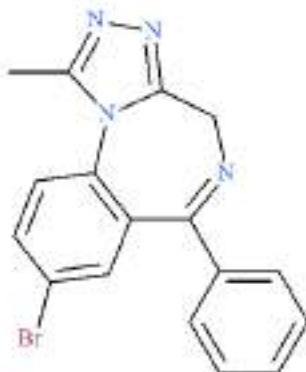
erartigiani NDEWS Staff

May 17

Bromazolam

Bromazolam: Announcement of Newly Identified Novel Psychoactive Substance (NPS) in the United States

NMS Labs, in collaboration with the Center for Forensic Science Research and Education (CFSRE) at the Fredric Rindert Family Foundation and the Organized Crime Drug Enforcement Task Force (OCDETF) at the United States Department of Justice (DOJ), has received funding from the Centers for Disease Control and Prevention (CDC) to develop systems for the early identification and notification of Novel Psychoactive Substances (NPS) in the drug supply within the United States. The goal of the program is the early identification of NPS in seized drug and/or forensic toxicology casework samples using various analytical techniques. Information about these programs and an archive of newly reported substances can be found on the following website: www.npsdiscovery.org



BROMAZOLAM

Bromazolam is classified as a novel benzodiazepine. Limited peer reviewed literature is available describing bromazolam. Confirmatory data for its activity and potency have not been reported. Benzodiazepines are central nervous system depressants. Novel benzodiazepines, often pirated from early drug discovery or pharmaceutical studies, have appeared on novel and illicit drug markets in recent years. These substances have caused adverse events, as described in the literature, fatalities linked to novel benzodiazepine use have occurred, commonly when used in combination with other depressants (e.g. opioids and alcohol). Bromazolam is structurally similar to traditional benzodiazepines, including alprazolam (replacing the chlorine with a bromine) and bromazepam (addition of triazole ring). Alprazolam and bromazepam are Schedule IV substances in the United States; bromazolam is not explicitly scheduled. To date, bromazolam has been identified in at least one blood sample from a forensic toxicology case.

Online Forums - Bluelight

BLUELIGHT



Forums > Recovery Support > Health and Recovery >

Detox 4 day clonazepam binge, don't know what to do

disheveledfiend · Sep 23, 2019



disheveledfiend

Greenlighter

Joined: Sep 5, 2019

Messages: 11

Sep 23, 2019

< #1

I had made a horrible decision to give this drug another go, and make responsible and educated decisions surrounding it or so I had thought. Well for the millionth time you guys are gonna have to hear another clam horror story, I'm sorry but I need help with this. It was 4 days straight of near constant redosing, the last dose being yesterday, 9/23, at about 7am. I believe I went through at least 5mg to myself during this unintended binge, redosing when I felt myself coming down. I had laid doses down on blotter .5mg per tab. I thought the whole vial was underdosed but really I was just barred out. I no longer have these tabs, except 1 I found on my couch that might not even be active.

so right now I have no idea what to do, I didn't know tolerance builds over a matter of days with this drug, I had assumed I'd simply have my fun and be on my way. Well, I had my fun but now I'm going to have to pay for it in horrendous withdrawals. constant stage 2 hypertension, splitting headache, brain zaps, horrible anxiety, irritability, a fear and a feeling of going into absence seizures, insomnia, fucking etc. just read the wiki page on symptoms of benzo wd, I got pr much all of it at random intervals, from 4 days of use, ridiculous.

I have maybe 25 600mgs Neurontin left, 3 1/2 suboxone and plenty of 300mg quetiapines which I haven't yet used due to fear of seizures. a couple metoprolols some vyvanse, I'm sure most of this has zero application to help me feel better but maybe you guys know something I don't. I've only utilized the Neurontin so far, 1.5gs, as an anxiolytic and anticonvulsant, the efficacy of the latter for this application is questionable though.

can anyone tell me what to expect these next few days? how realistic is the possibility of a seizure? will this WD last for weeks without a proper taper? can I sleep without going into a coma or convulsions? any inputs appreciated.

Online Forums - Reddit

 [r/researchchemicals](#) · Posted by [u/morethanafewchanges](#) 17 hours ago

Hello. I'm an idiot who took clonazepam. People who are experienced with this... can you shed some light on the situation?

Hi guys. I'll keep it short and sweet.

Saturday night I took .48mg of clonazepam

Sunday I took .44mg of clonazepam

Monday I took .22 of clonazepam

Today I took .05mg of clonazepam.

Am I going to feel like shit tomorrow? Luckily I can stop myself but I'm scared of the anxiety that awaits me tomorrow. I know this is child's play compared to what other people have to deal with and for that I feel lucky but I want some input by someone who knows what I'm in for... am I in for anything? I've had a headache today but other than that (and anxiety) I feel alright. I've already gotten rid of the clonazepam and don't plan on taking anymore. Luckily I saw that it had claws after a few days and got my head right, but I'm nervous.









Can anyone shed some light on my situation/day tomorrow? It would be much appreciated...

Online Forums - Reddit

R/RESEARCHCHEMICALS / MODERATORS

Moderators of r/researchchemicals

Search for a user

	libertas	9 years ago
	roionsteroids	6 years ago
	Borax	3 years ago
	cyrillo	3 years ago
	Flying_Dutchmann	3 years ago
	DrugsAMA	2 years ago
	phagemasterflex	2 years ago
	BotTerminator	3 days ago







r/researchchemicals

68.3k
Members

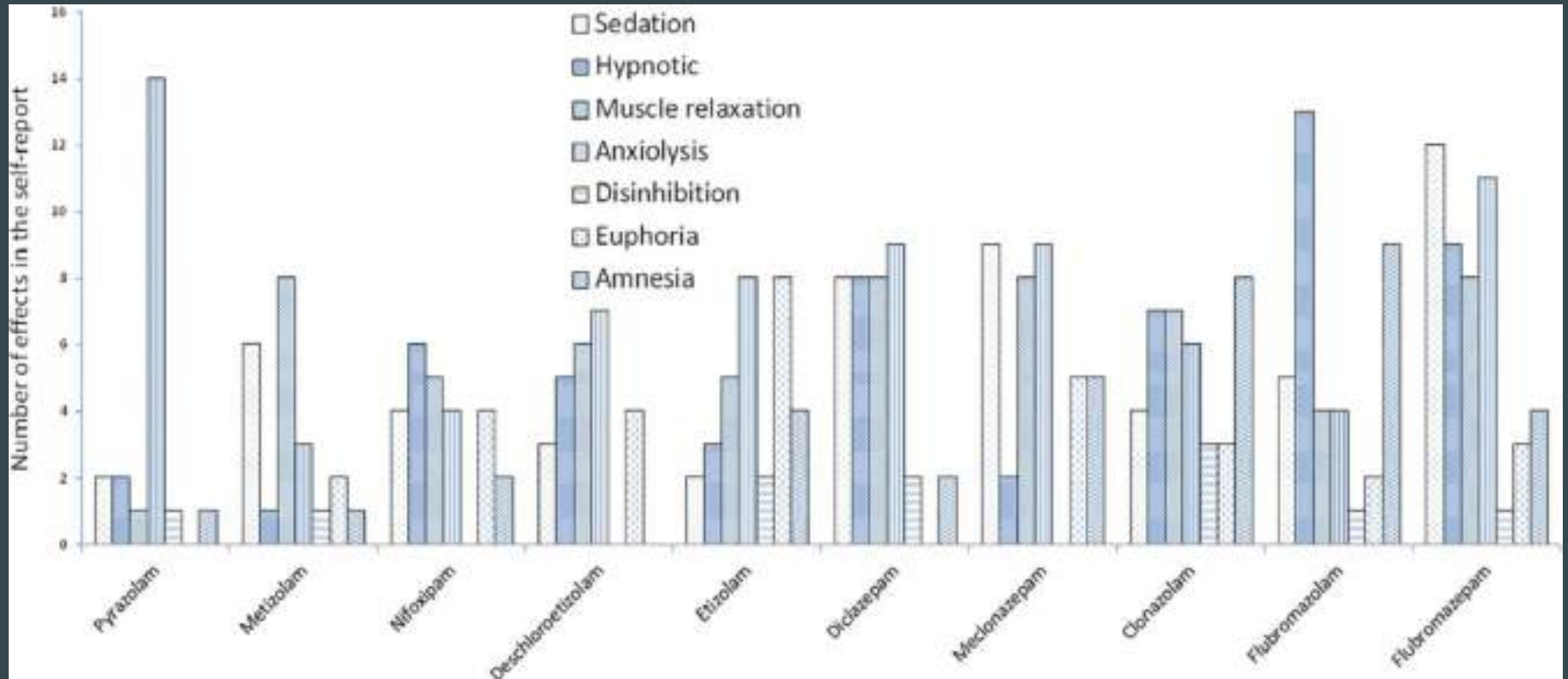
326
Online

Feb 8, 2010
Cake Day

A dedicated subreddit for the discussion of synthetic psychoactive research chemicals. Strictly no sourcing.

-  teardedqueen 7 points - 17 hours ago
You're going to be fine... It's no different than taking any other benzo for 4 days. No reason to freak out.
And there is nothing wrong with taking Clam as long as it's done responsibly after researching it just like any other benzo.
-  speedy_re 4 points - 17 hours ago
You should be fine. Might have a little rebound anxiety but nothing major.
-  Setap 3 points - 13 hours ago
ezpz dude you're fine, just sttttoopp now while you're way ahead man and only use once a week TOPS.
-  Sp4c3m4n819 1 point - 16 hours ago
Shouldn't be an issue. I've taken etizolam for two months straight before and quit with only some anxiety but no wd
I think I'm going to be in the minority for that though. I was using maybe a mg a day usually .5 but some people develop dependency in only a couple weeks.
4 days shouldn't be an issue tbh. Don't stress it

Patient Symptoms – Study of Online Trip Reports





Thank you!

@ximenalevander



levander@ohsu.edu

Finley at Powell Butte with Mt. Hood in the Background