



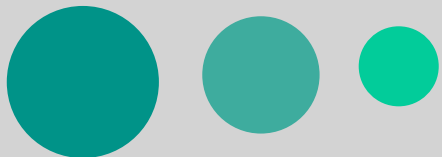
# Toxic Conundrums: A Review of Unique Toxicologic Encounters Within Kentucky Health-Systems

Jordan Woolum, PharmD, BCPS, DABAT

Clinical Toxicologist | UK HealthCare

Jay Adams, PharmD, DABAT

Clinical Operations Manager | Kentucky Poison Center



# Disclosures



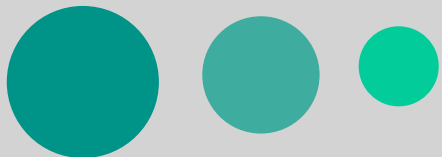
The authors of this presentation have no actual or potential disclosures to report related to this presentation.



# Abbreviations



- ABG/VBG: Arterial blood gas/Venous blood gas
- APAP: Acetaminophen
- ASA: Aspirin
- BPM: Beats per minute
- BZDs: Benzodiazepines
- CBC: Complete blood count
- CK: Creatinine kinase
- CMP: Comprehensive metabolic panel
- CT: Computed tomography
- CXR: Chest x ray
- EEG: Electroencephalogram
- EKG: Electrocardiogram
- EtOH: Ethanol
- GAD: General anxiety disorder
- Hx: History
- MDD: Major depressive disorder
- MRI: Magnetic resonance imaging
- NPDS: National Poison Data System
- PD: Pharmacodynamic
- PK: Pharmacokinetic
- WNL: Within normal limits
- YOA: Years-of-age



# Objectives



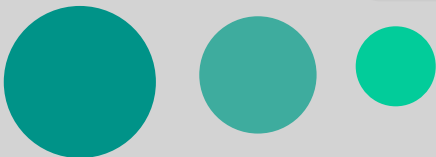
Describe new trends in recreational drug abuse



Review the toxicities and clinical management of select recreational substances



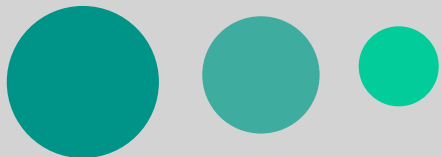
Review the many roles that regional poison centers occupy to help serve their communities



# Overdose Epidemiology



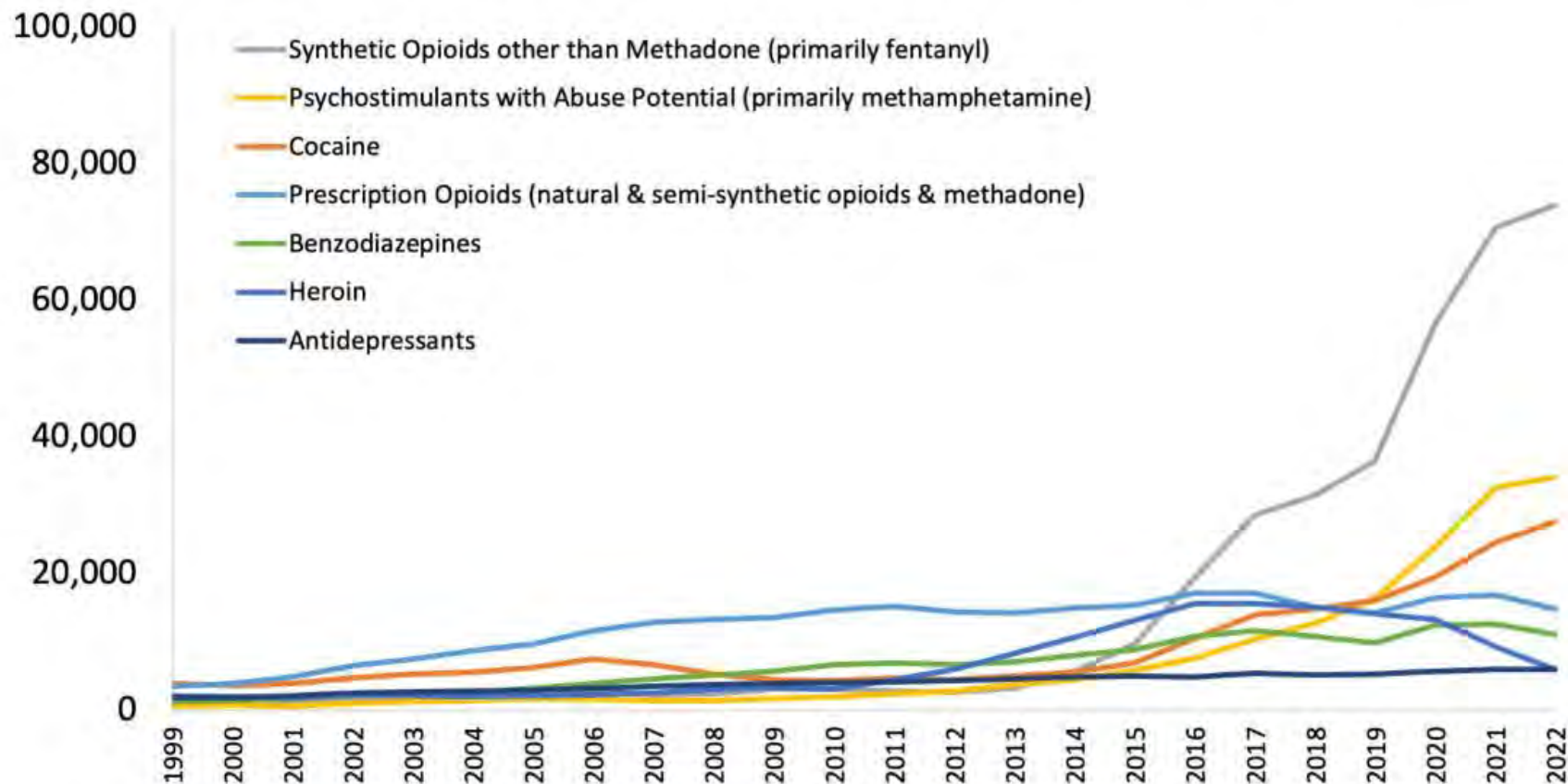
- Death from drug overdose remains the #1 cause of death for people aged 18-44 yoa
- Despite a nearly 24% decline for a 12-month period ending in September 2024, deaths still top 87,000
- **Death increases remain in 5 states; morbidity ≠ mortality**



# Drug Overdose Trends



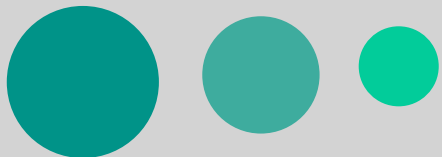
**Figure 2. U.S. Overdose Deaths\*, Select Drugs or Drug Categories, 1999-2022**



# Poison Center Data



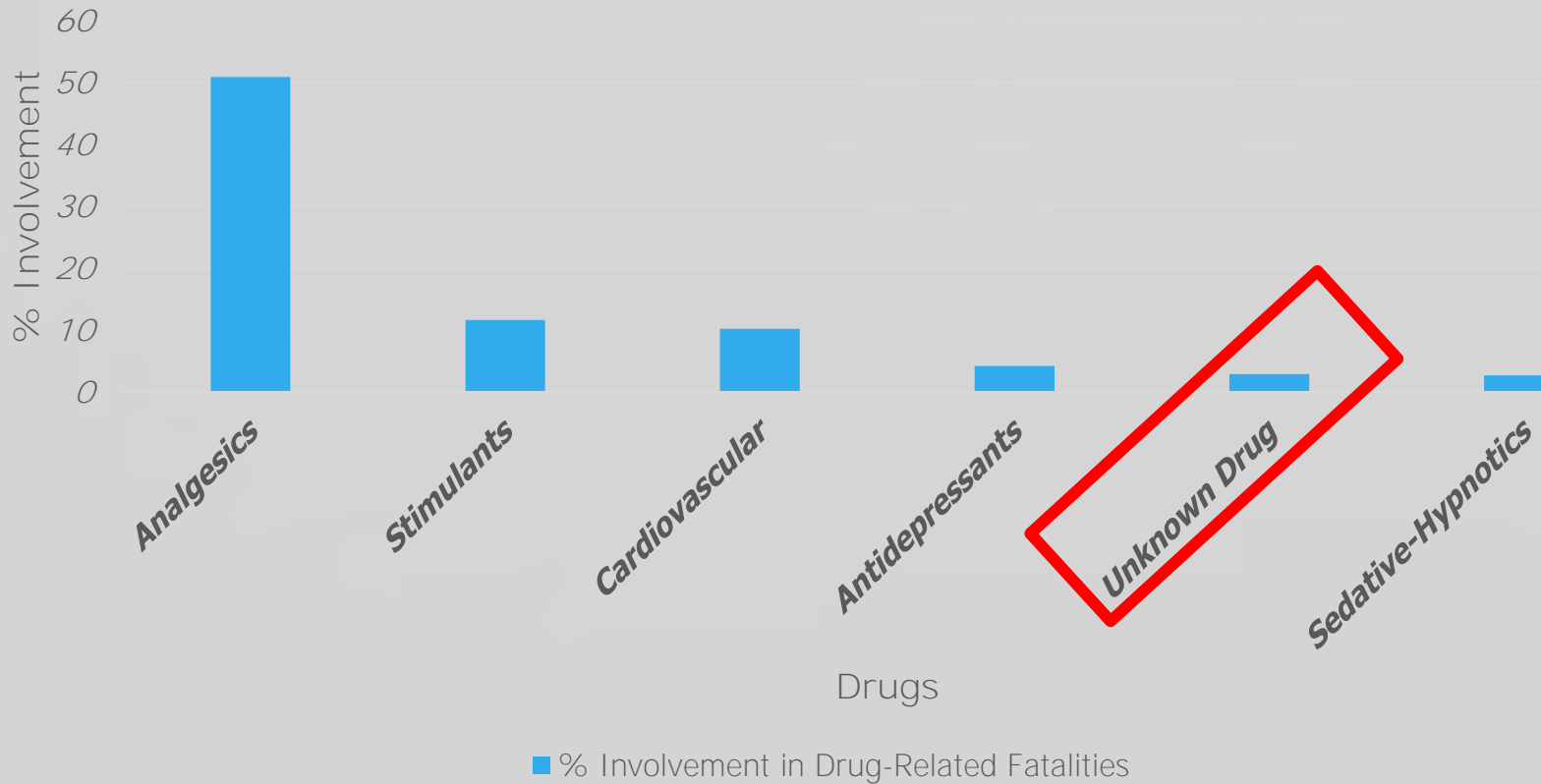
- Calls to United States (US) poison centers are uploaded every 8 minutes to the National Poison Data System (NPDS)
- US Poison centers recorded 2,080,659 exposure cases in 2023
- NPDS is monitored daily for emerging outbreaks
  - Diamond Shroomz detection in 2024



# 2023 Fatalities



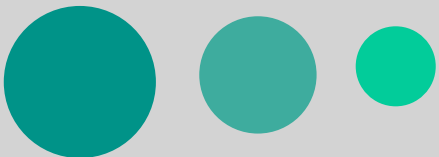
Drug-Related Fatalities (n = 2,700)



# Patient Case



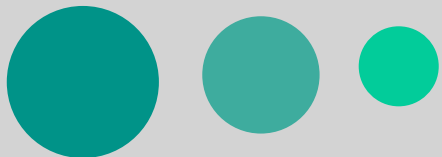
- History
  - 23 yo M presents to the ED with a chief complaint of paresthesia's after abusing a substance for the past 4 weeks. He reports worsening numbness and tingling in his distal extremities, with worse symptoms in his lower extremities compared to his upper.
- PMH
  - Substance abuse, GAD, MDD



# Patient Case



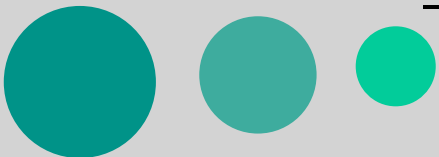
- Physical exam
  - Unremarkable otherwise
- Vitals
  - BP: 130/84
  - HR 107 bpm
  - RR: 17 bpm
  - O2 saturation: 98% on room air
  - Temperature: 98.9° F



# Patient Case



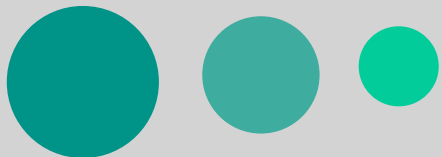
- Comprehensive metabolic panel
  - Within normal limits
- Complete blood count
  - White blood cells: 1.95 (4-10 x 10<sup>9</sup>/L)
  - Red blood cells: 2.3 (4.5-6.5 x 10<sup>12</sup>/L)
  - Hemoglobin: 5.9 (14-18 g/dL)
  - Hematocrit: 17.6 (42-50%)
  - Platelets: 125 (150-400 x 10<sup>9</sup>/L)
- Urine drug screen
  - Positive for THC



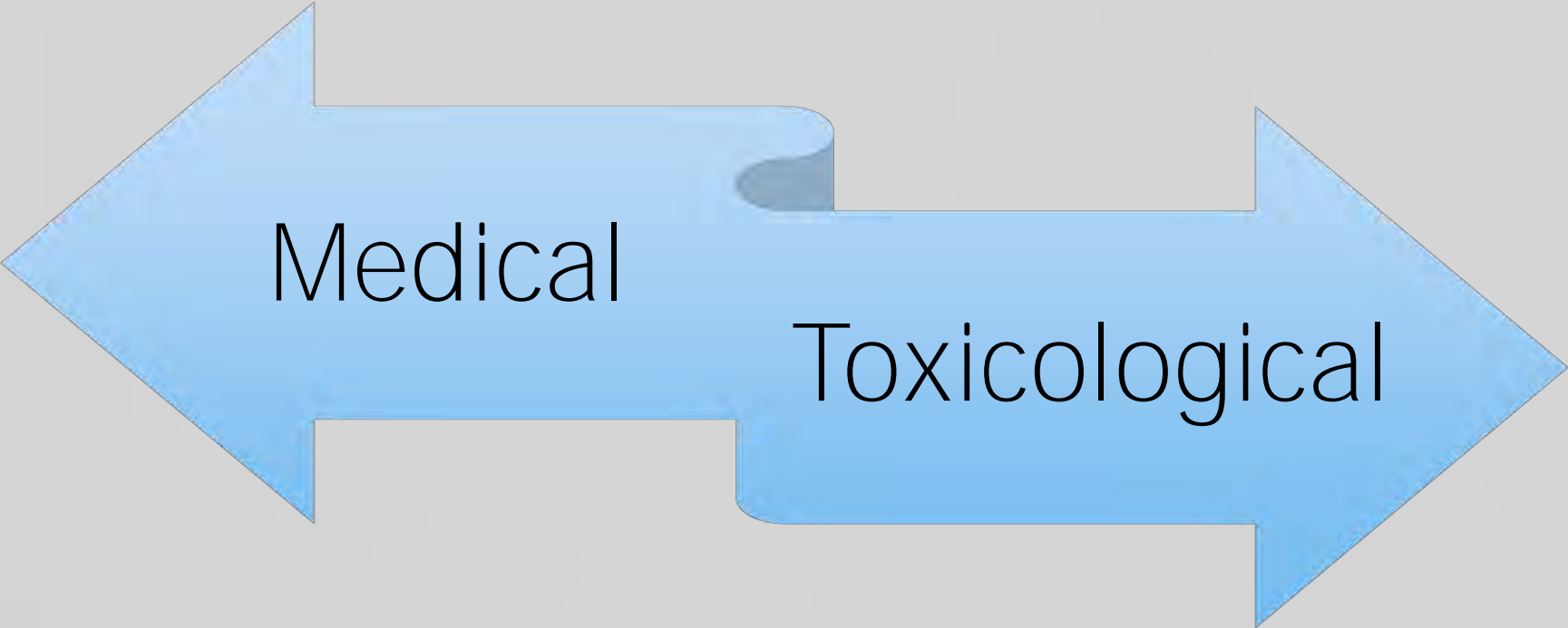
# Patient Case



- Due to the substance that the patient was reported **abusing, some additional labs were ordered...**
  - Vitamin B<sub>12</sub>: **< 150** (normal 180-914 pg/mL)
  - Serum homocysteine: **178.2** (normal 6-15  $\mu$ /L )
  - Folic acid: **> 24.8** (normal > 5.8 ng/mL)
  - Serum methylmalonic acid: **1145** (normal > 0-378 nmol/L)



# Patient Case



Differential?!

# Concerning Trends Persist: Abuse

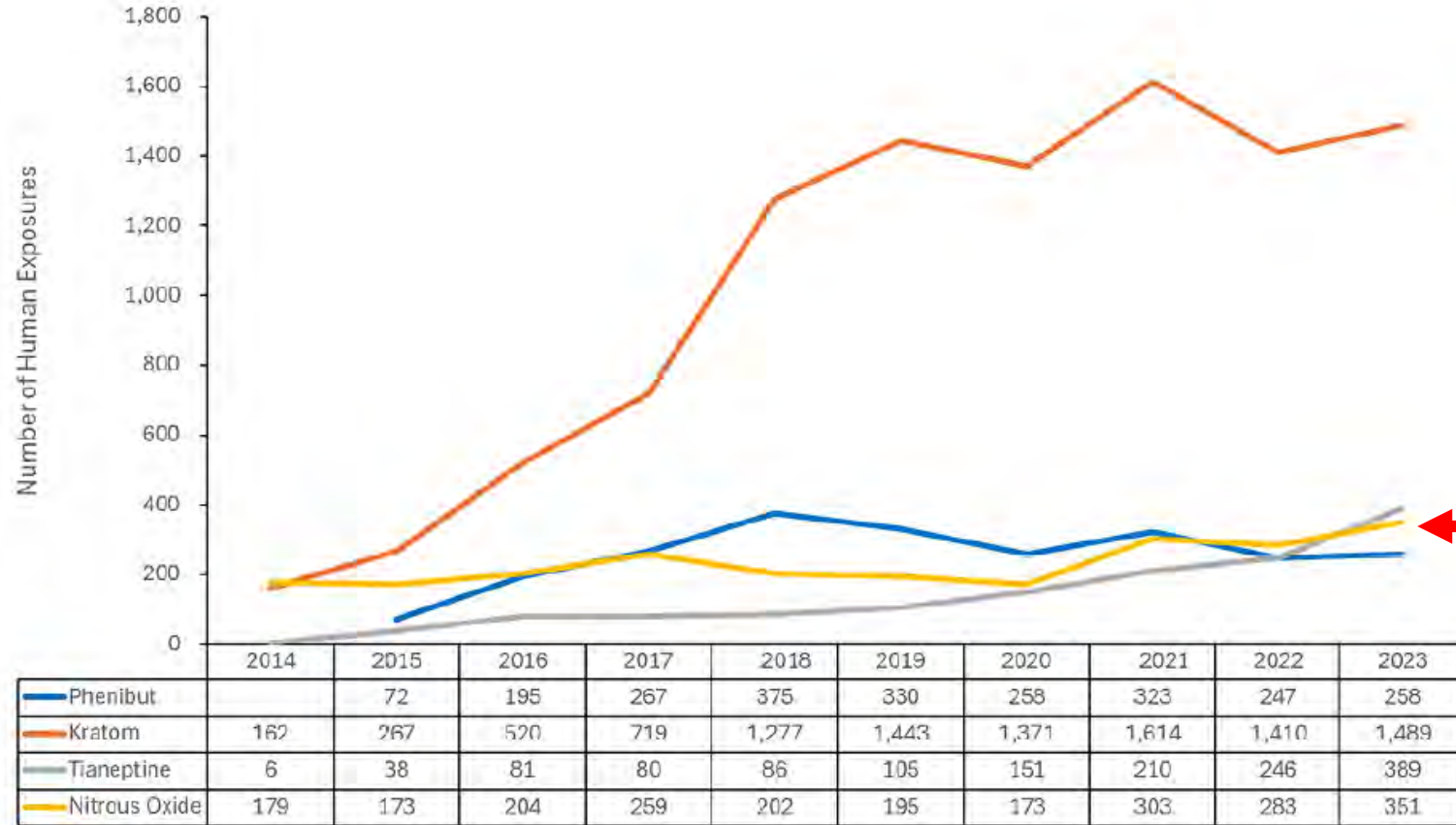
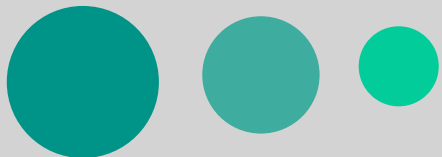


Figure 6. Kratom, Tianeptine, Phenibut, and Nitrous Oxide Exposures Reported to US Poison Centers by Year, 2014-2023

# Nitrous Oxide (N<sub>2</sub>O)



- "Laughing gas" or "whippets"
- Used medicinally as an inhalational anesthetic; abused for euphoric effects
- Common propellant in supermarket-bought whipped cream canisters and cartridges
- Sold in a variety of different formulations; no common lab method for detection



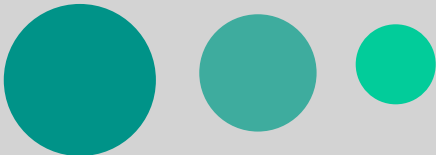
# Nitrous Oxide



## EXHIBITION OF THE LAUGHING GAS.

THE Nitrous Oxide, or Laughing Gas, was discovered by Dr. Priestly, who produced it by abstracting a part of the Oxygen from the Nitric Oxide. It is composed of equivalent parts of Oxygen and Nitrogen. Before the time of Sir Humphry Davy, it was considered irrespirable: but by some very interesting experiments, he proved this opinion to be incorrect; he also wrote a work, entitled, "Researches on the Nitrous Oxide." It is named Laughing Gas on account of the very exhilarating emotions produced in those who respire it for a short time: laughing, dancing, jumping, acting, reciting, and (last but not least) fighting are amongst the prominent effects displayed by persons under its influence. The Febrile Miasma depresses and terrifies the mind as much as the Nitrous Oxide raises and enlivens it. The easiest way of making it is to dissolve Crystals of the Nitrate of Ammonia in a retort, over a strong flame; after the atmospheric air has passed away, the Gas will be given off in great abundance, and may be collected in bladders, or a gasometer, for use. Sulphur, Phosphorus, red hot Charcoal, or a Taper, will burn with great brilliance when immersed in Nitrous Oxide.

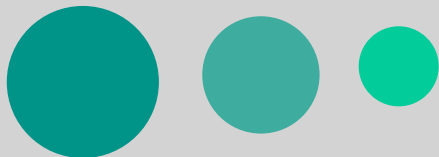
Engraved and Printed at the Exhibition - - H. & A. HILL, Printers, Castle Green, Bristol.



# Nitrous Oxide



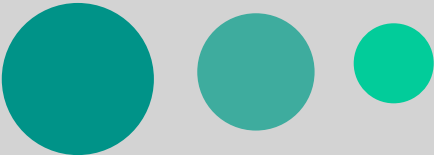
- Reports to poison centers for nitrous oxide (N<sub>2</sub>O) exposures doubled between 2014-2023
- True abuse estimate likely not correctly represented; >500,000 patients 12 yoa+
- 51.5% of exposures reported experienced a "serious medical outcome"
  - 33.1% of cases require hospital admission



# Nitrous Oxide Abuse



**Florida woman's family files lawsuit seeking to halt sales of Galaxy Gas and other nitrous oxide after her death**

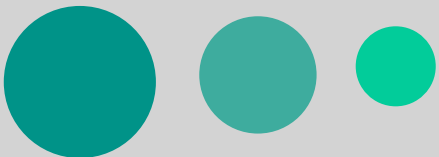


# Nitrous Oxide Abuse



“We walk into the president's chambers (at the fraternity) ... and there’s three dudes carrying, like, Butane tanks,” Hurley said. “And they're going, ‘keep going, keep going, keep going!’” as a student huffed the gas. Hurley says he witnessed the student pass out for several seconds; and he met a woman later in the evening who was also huffing, which illustrated to him the behavior wasn't contained to a single group of students or fraternity.

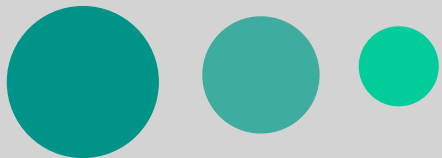
**Community Notice issued as campus health officials warn of mouth and throat injuries due to inhalant abuse**



# Patient Case



What symptoms are related to both the acute and chronic use of nitrous oxide?



# Pathophysiology of N<sub>2</sub>O



- 35x more soluble in blood than O<sub>2</sub>
- Any compliant air-containing space increases in size
  - Bowel perforation, tympanic membrane rupture
- Valsalva maneuver places additional strain on lungs
  - Pneumothorax, laryngeal trauma
- Consider impurities in preparation or other inhalants



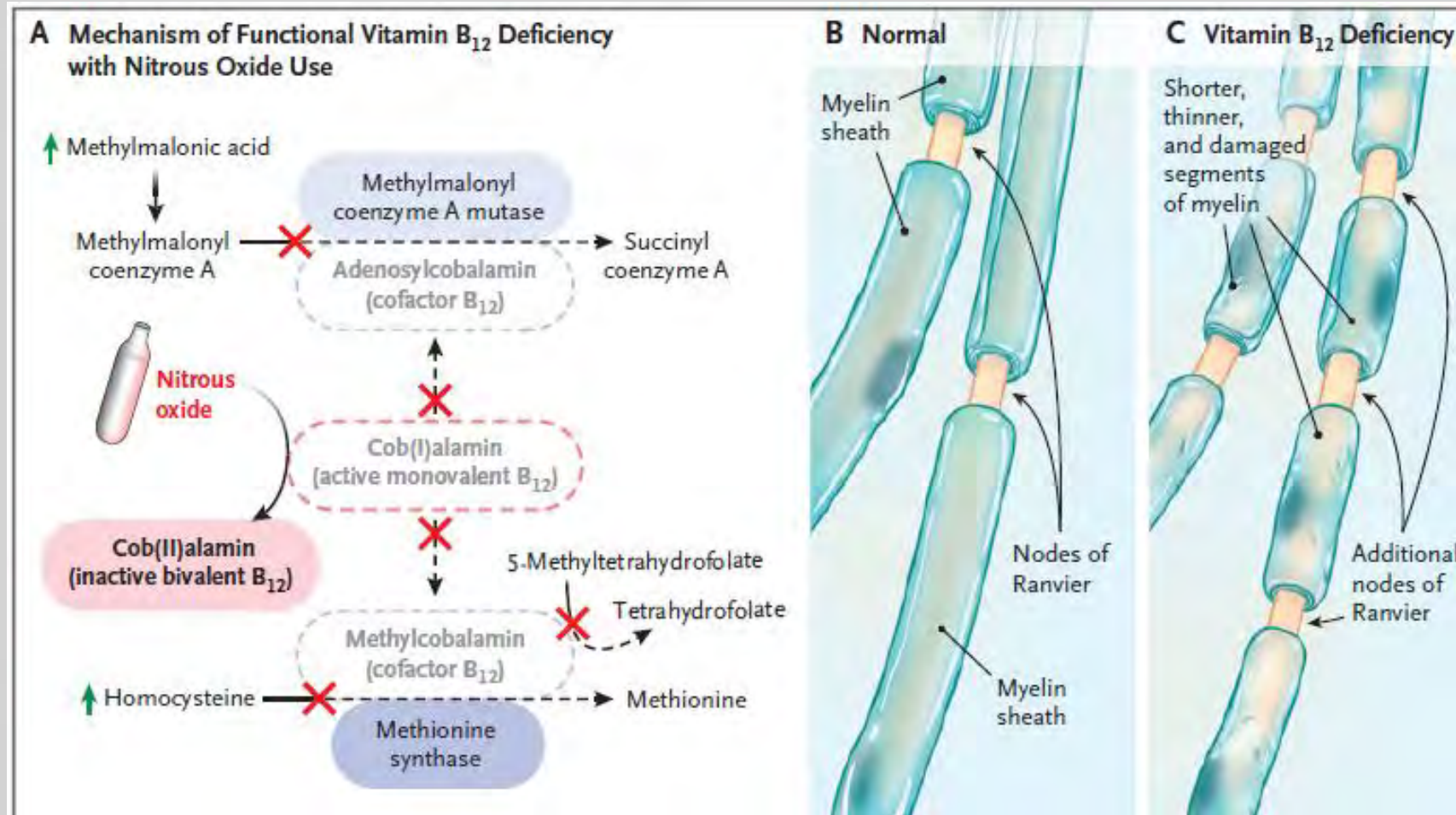
# Pathophysiology of N<sub>2</sub>O



- NMDA antagonism, dopaminergic agonism, and  $\kappa$ -opioid receptor agonism contribute to euphoria and analgesia
- Chronic use associated with disabling polyneuropathy
  - Sensorimotor neuropathy
  - Numbness/paresthesia
  - Weakness
- Neuropathy may take months to develop; associated with oxidation of cobalt in vitamin B<sub>12</sub>, inactivating it



# Pathophysiology of N<sub>2</sub>O

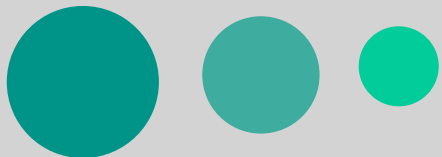


# Clinical Effects of N<sub>2</sub>O



- Acute
  - Lethargy, intoxication, asphyxiation, skin discoloration
- Death not generally due to a direct N<sub>2</sub>O effect

Top 10 Reported Symptoms to Poison Centers	
Headache*	Tachycardia
Vomiting	Other- Neurological
Nausea	Numbness*
Ataxia*	Confusion
Dizziness/Vertigo	Other - Miscellaneous



# Clinical Effects of N<sub>2</sub>O



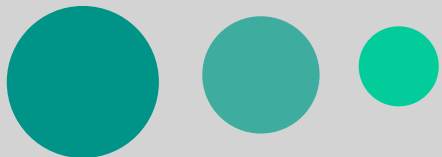
- Chronic
  - Myeloneuropathy involving posterior columns of the spinal cord
    - Numbness, tingling of extremities
    - Weakness, diminished sensation
    - Bowel/urinary incontinence
- Bone marrow suppression
  - Leukopenia, thrombocytopenia
- Manifestations strongly resemble B<sub>12</sub> deficiency
  - Pernicious (megaloblastic) anemia



# Differential Diagnosis & Workup



- Routine urine toxicology tests are unlikely to identify N<sub>2</sub>O
- Labs that are generally helpful
  - CMP
  - VBG/ABG
  - Methemoglobin & Carboxyhemoglobin (?)
  - CBC
  - [Methylmalonic acid, homocysteine, vitamin B<sub>12</sub>]
- EKG, CXR, Head CT/MRI



# Differential Diagnosis & Workup



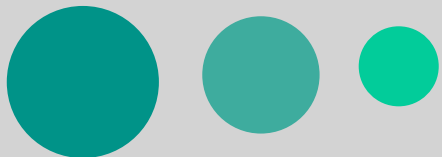
- Hx of inhalant abuse
  - Volatile hydrocarbons, alkyl nitrites, toluene
- Megaloblastic anemia
  - Chronic EtOH abuse, folate antagonists (phenytoin, sulfamethoxazole, valproate, metformin, proton pump inhibitors), B<sub>12</sub> deficiency
- Toxic neuropathy
  - Copper deficiency (zinc excess), arsenic, thallium, vinca alkaloids, *n*-Hexane, organophosphates
- When you hear hoof beats, think horses, not zebras



# Treatment



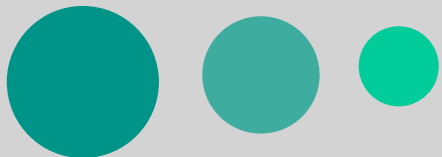
- Don't reinvent the wheel – ABCs
- Consider early consultation with a poison center or medical toxicologist
- Be prepared to treat concurrent hemoglobinopathies, cardiac dysrhythmias, frostbite (?)
- Neuropathy treatment – abstinence + vitamin B<sub>12</sub>
  - Vitamin B<sub>12</sub> 1mg IM daily x 7 days | 1 mg IM weekly x 4-9 weeks | monthly until resolution
  - Methionine 3g daily + 30 mg IV folic acid



# Interim Summary



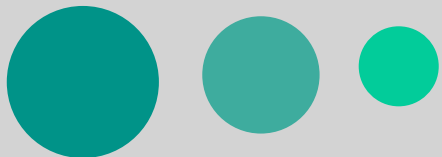
- Nitrous oxide abuse persists, at an increasing rate.
- Acute exposures produce sedation and euphoria.
  - Headache and ataxia are the most common ADRs reported.
  - Death likely due to hypoxia or trauma related to inhalation.
- Chronic toxicity is associated with significant peripheral neuropathy and megaloblastic anemia.
  - Treatment consists of vitamin B12, methionine, and folic acid.



# Patient Case #2



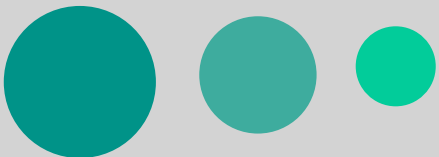
- History
  - 28 yo M was brought into the ED by family with a chief complaint of altered mental status. The family reports the patient has been taking a substance that **he bought from “the local herb shop” for the last year “to get high”**. The family reports the patient has been taking 20 pills a day for the last year.
- Physical exam
  - Altered, confused (GCS 12), agitated, diaphoretic, **“high” per family**



# Patient Case #2



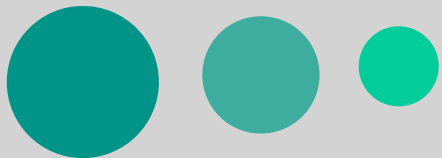
- Vitals
  - BP: 150/68
  - HR: 111 bpm
  - RR: 22
  - O2 saturation: 96% on room air
  - Temperature 100.9°F
- CMP and CBC WNL
- EKG intervals: QRS 97 ms, QTc 470 ms



# Patient Case #2



Differential?!



# Concerning Trends Persist: Withdrawal

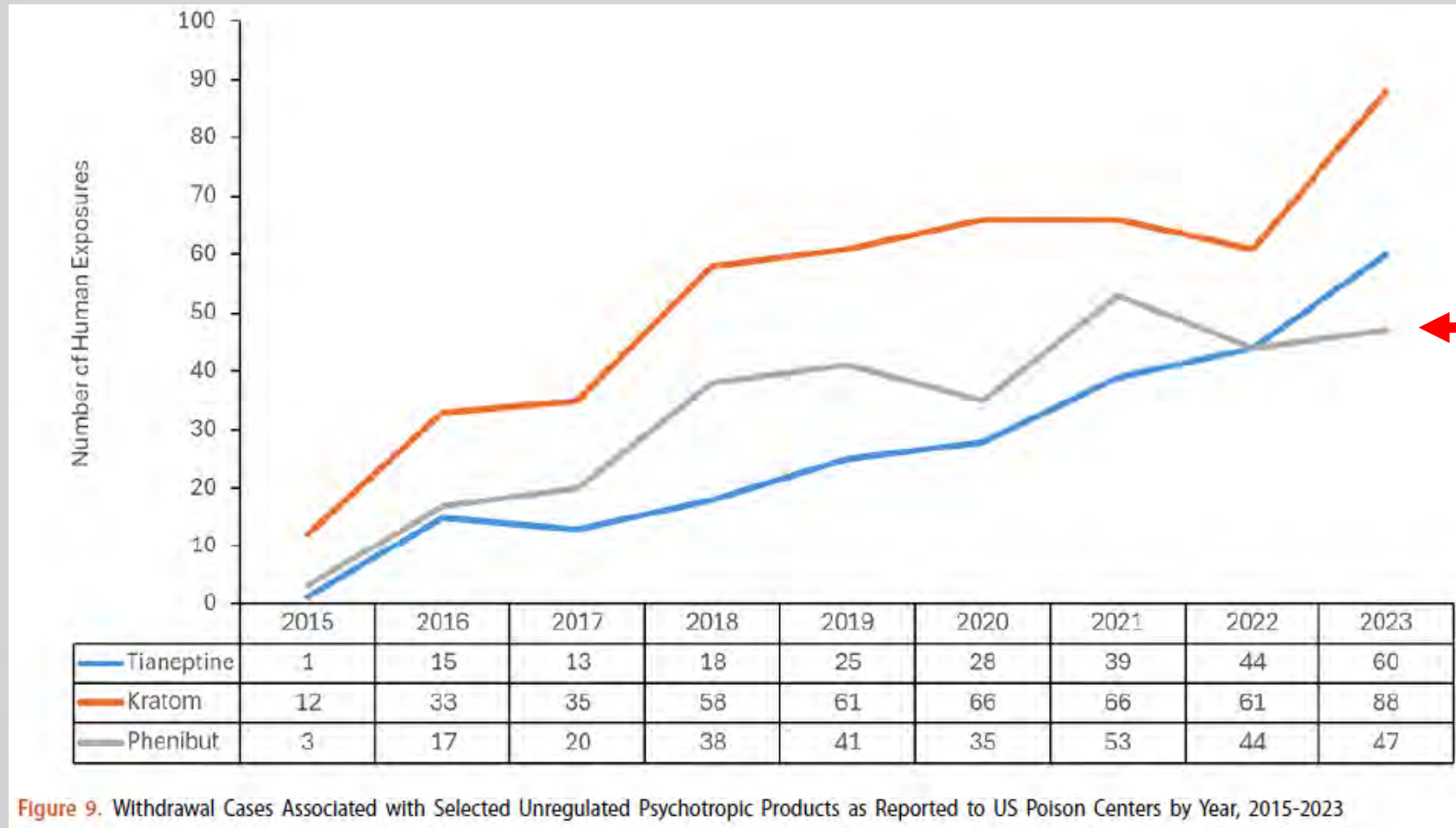


Figure 9. Withdrawal Cases Associated with Selected Unregulated Psychotropic Products as Reported to US Poison Centers by Year, 2015-2023

# Phenibut



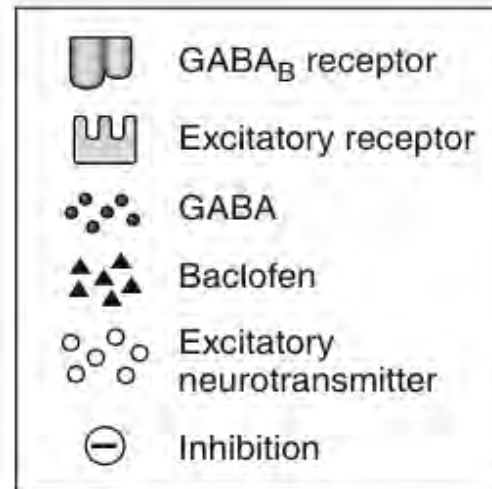
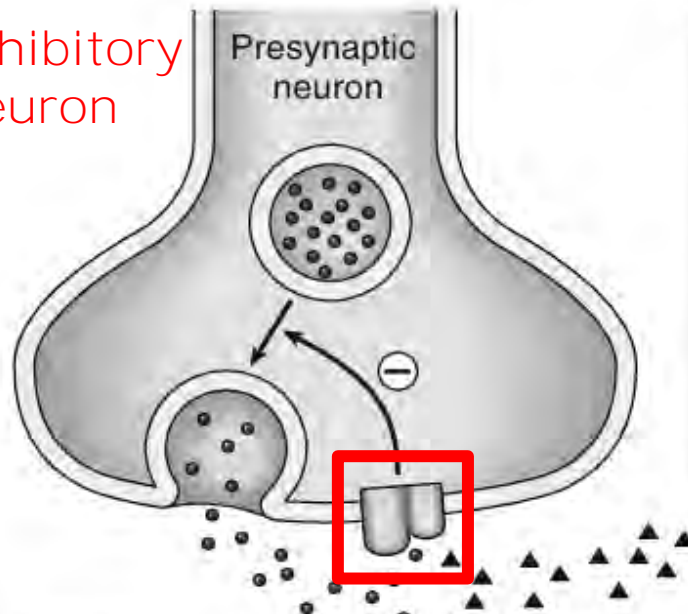
- Developed in Russia in the 1960s for use as an antianxiety medication and possible cognitive enhancer
- Structurally similar to baclofen; GABA-B agonist
- Used in the United States for a variety of indications: anxiety, sleep, relaxation
- Available in a myriad of stores and online platforms; unregulated



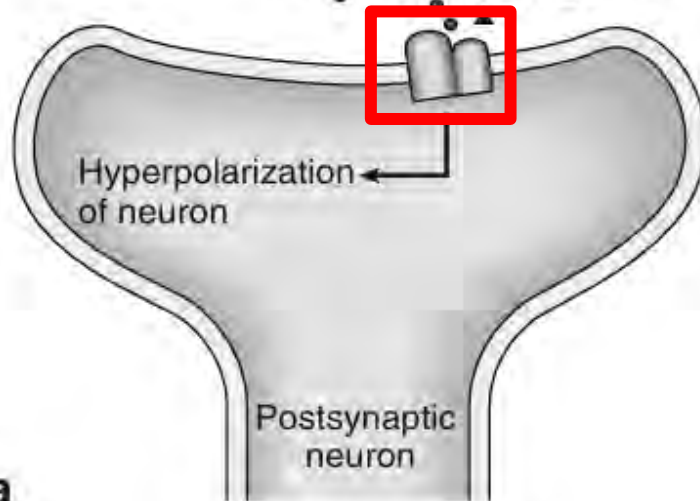
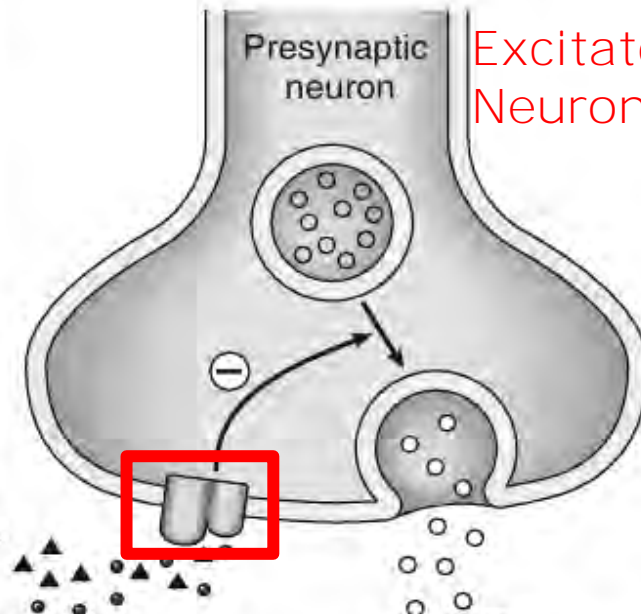
# Phenibut Pharmacology



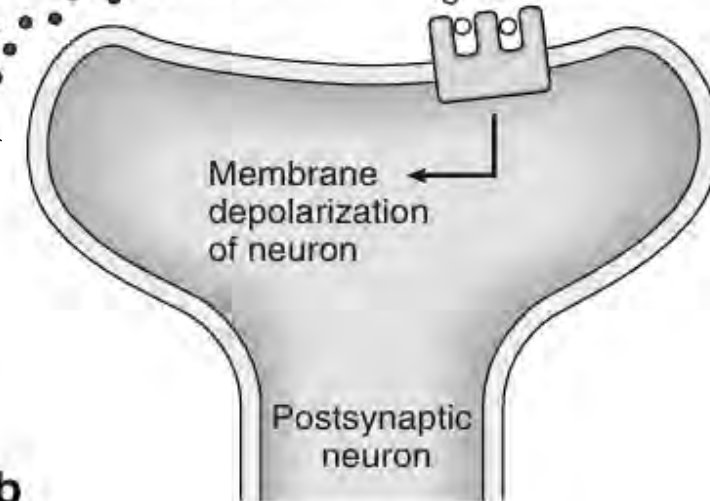
Inhibitory Neuron



Excitatory Neuron



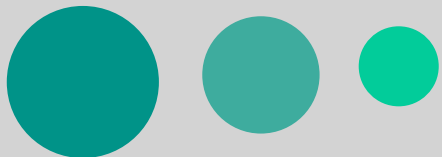
Net Results:  
1. Hyperpolarization of post-synaptic neuron  
2. Inhibition of neurotransmitter release from the pre-synaptic neuron



# Phenibut Pharmacology



- Additional mechanisms of action may include enhanced dopaminergic neurotransmission, and GABA-A agonism
- Reference dosing range is 250-500mg TID
- Considered a supplement in US markets with wide availability
- Acute doses of 1-1.5 g potentially toxic; chronic use of 1 g+ daily may lead to severe withdrawal

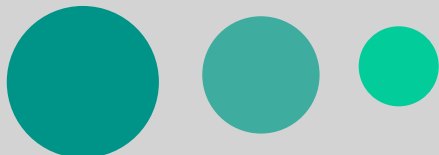


# Phenibut Supplement Variations



**Table 1.** Information provided on the label and corresponding measured quantities of phenibut in selected supplements.

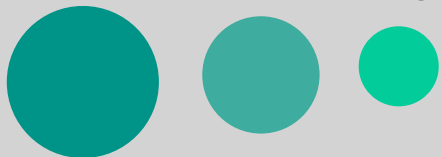
Code for supplement product*	Declared ingredient on label meeting inclusion criteria	Number of other ingredients on label	Recommended serving size on label	Quantity declared on label of phenibut per serving size, mg	Maximum recommended daily dose per label	Measured Phenibut per serving size, mg (SD)	
						From purchase before FDA warning	From purchase after FDA warning
Product A	4-amino-3-phenylbutyric acid (phenibut)	13	1 scoop (14 g)	NP	NP	487 (33)	1164 (81)
Product B	phenibut	6	1 capsule (500 mg)	500 <sup>a</sup>	4 capsules (2,000 mg)	484 (89)	425 (44)
Product C	phenibut	6	1 capsule	200 <sup>a</sup>	NP	<LoD	21 (2)
Product D	phenibut	19	2 capsules	NP	2 capsules	<LoD	198 (29)



# Phenibut Toxicology: Overdose



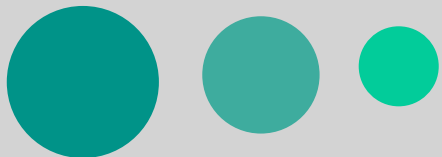
- Ingestions largely mimic baclofen exposure
  - Headache, N/V, dizziness, hyporeflexia
  - Lethargy, bradycardia, hypotension
  - Coma, seizures, agitated delirium, paradoxical "excited" state
- Observational studies identify seizures in 17% cases; delirium in 35% | pupillary responses mixed
- Baclofen is a known brain-death mimic in large overdoses, potential crossover with phenibut?



# Phenibut Toxicology: Withdrawal




- Removal of inhibitory "tone" promotes "excitation"
- In heavy users, withdrawal syndrome may develop rapidly after an acute exposure
- Large systematic review of published cases:
  - Median time from cessation to withdrawal: 2 days w/ mean daily dose 2.43 g
  - 88% required admission; 50% required ICU level treatment



# Phenibut Toxicology: Withdrawal

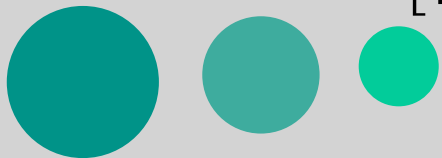


- Symptoms: initial insomnia, irritability, diaphoresis
- Withdrawal course very similar to baclofen and other sedative-hypnotics and/or ethanol
  - Clonus, rigidity, AMS, hallucinations, seizures
  - Hyperthermia, brady/tachycardia, rhabdomyolysis
  - Respiratory depression, death (?)
- Be wary of co-dependency on other substances (up to 45%!)  


# Differential Diagnosis & Workup



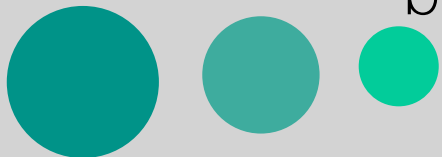
- Overdose may resemble sedative/hypnotic ingestions & ethanol
- Withdrawal differential is broad: sedative/hypnotic withdrawal, EtOH withdrawal, serotonin syndrome, sympathomimetics, NMS, infection
- Labs/exams often forgotten: CK, APAP/ASA, [EtOH], EKG, EEG (?)



# Phenibut Management: Overdose



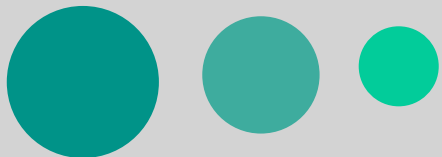
- Acute ingestions best managed with aggressive supportive care
  - ABCs
  - Support "appropriate" hemodynamics with short-acting agents
- Seizures – BZDs | Other GABA-A agonists
  - Succinylcholine > rocuronium if possible
- Adequate hydration if concerned for rhabdomyolysis | brain death mimic!



# Patient Case #2



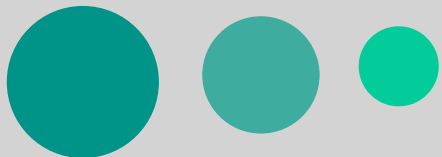
Drawing on knowledge of other withdrawal states, what options do you think are available to use to manage this withdrawal state?



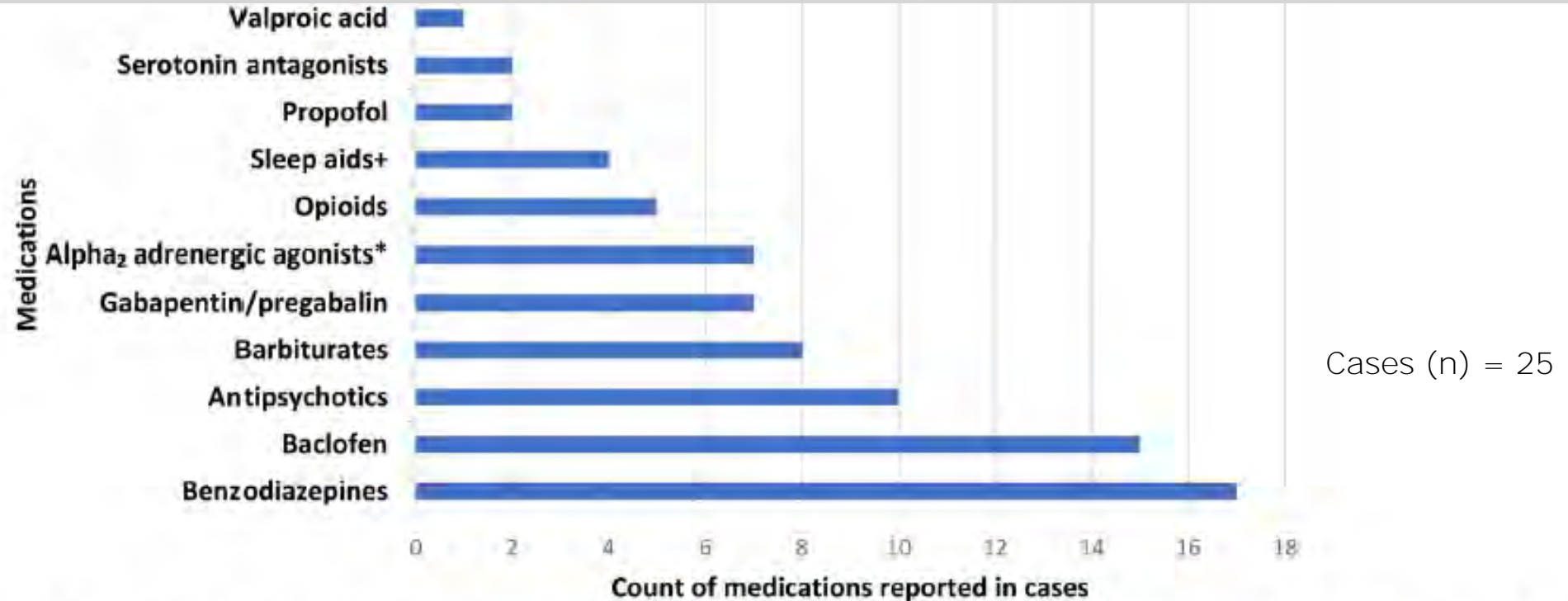
# Phenibut Management: Withdrawal



- No standard for withdrawal assessment exists
  - CIWA/CIWA-AR employed most (28%)
- Initial stabilization with BZDs appropriate
- Transition to an oral baclofen regimen is most commonly reported, though regimens vary
- No standardized approach



# Phenibut Management: Withdrawal



**Figure 2.** Medications used in the management of phenibut withdrawal symptoms. \*Alpha<sub>2</sub> adrenergic agonists were used in six cases; however, one case used both clonidine and dexmedetomidine, bringing the total count of alpha<sub>2</sub> adrenergic agonist use to seven. +Sleep aids include anticholinergics, melatonin, and ramelteon.



# Phenibut Management: Withdrawal



- Baclofen attractive given PK/PD similarities
- Median daily dose 30 mg | median max dose 60 mg | durations 7-14 days

**Table 2.** Baclofen treatment regimens.

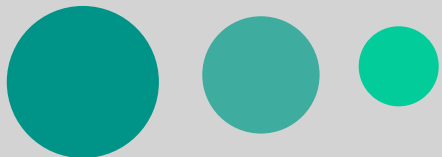
[Citation]	Starting doses (mg/day)	Max doses (mg/day)	Taper strategy	Taper duration (days)	Cross taper <sup>a</sup>
[27]	15	15	Yes	7	No
[19]	100	105	Yes	365	No
[20]	15	15	Yes	5	No
[9]	30	90	Yes	63	No
[21]	45	45	Yes	28	No
[23]	30	60	Yes	12	No
[28]	40	40	No	5	No
[14]	30	30	Cross taper with phenibut	8	Yes
[16]	30	120	Unknown lost to follow up	Unknown lost to follow up	No
[15]	15	60	Cross taper with phenibut	147	Yes
[7]	15	15	Yes	5	No
[12]	130	130	Yes	15	No
[18]	Not reported	Not reported	Unknown lost to follow up	Unknown lost to follow up	No
[8]	15	60	Yes	280	No
[30]	60	60	Unknown lost to follow up	Unknown lost to follow up	No

<sup>a</sup>A cross taper was defined as a gradual down titration of phenibut dose with concurrent initiation of baclofen.

# Poison Center's Role



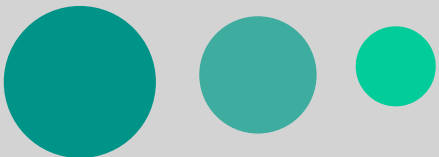
- 1-800-222-1222 | Available 24/7/365
- Not limited to lay people, can facilitate appropriate triage and management of poisoned patients in healthcare facilities
- May forward calls to a medical or clinical toxicologist for advanced recommendations
- Calls help inform current epidemiological trends!



# Summary



- Though headway in drug overdose has been made, work remains, with new drugs of abuse emerging.
- Nitrous oxide and phenibut are largely unregulated products, available for purchase from a multitude of locations.
- Care is largely supportive. Specific antidotes are available in some cases.
- The poison center is a free resource that can be utilized if questions arise.





# Toxic Conundrums: A Review of Unique Toxicologic Encounters Within Kentucky Health-Systems

Jordan Woolum, PharmD, BCPS, DABAT

Clinical Toxicologist | UK HealthCare

Jay Adams, PharmD, DABAT

Clinical Operations Manager | Kentucky Poison Center

