Welcome to Aisle 3: Kratom, Tianeptine, and Other Misused Oddities

Gabriella Schmit, PharmD and Megan Olson, PharmD PGY1
Pharmacy Residents - Aurora Health Care Metro, Inc.

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Disclosures

The planners and speakers have indicated that there are no relevant financial relationships with any ineligible companies to disclose.

Learning Objectives

At the end of this session, learners should be able to:

- Describe the mechanism of action and proposed clinical effects of kratom, tianeptine, phenibut, and nitrous oxide (“whippets”).
- Recognize clinical signs and symptoms of intoxication, withdrawal, and potential toxicity associated with each substance.
- Identify patterns of misuse, prevalence trends, and common sources of access for each substance, as well as factors contributing to rising popularity and online availability
- Discuss evidence-based management strategies for acute toxicity, withdrawal, and supportive care, including pharmacists’ roles in harm reduction

Outline

- Background
- Kratom
- Tianeptine
- Nitrous Oxide
- Phenibut
- Role of the Pharmacist

Abbreviation Key

- DEA: Drug Enforcement Agency
- ECG/EKG: Electrocardiogram
- FDA: Food and Drug Administration
- GABA: Gamma-Aminobutyric Acid
- IM: Intramuscularly
- IV: Intravenously
- LFTs: Liver Function Test
- MOA: Mechanism of action
- NMDA: N-methyl-D-aspartate
- PEA: Phenylethylamine
- TCA: Tricyclic Antidepressant
- T1/2: Half-life

Background

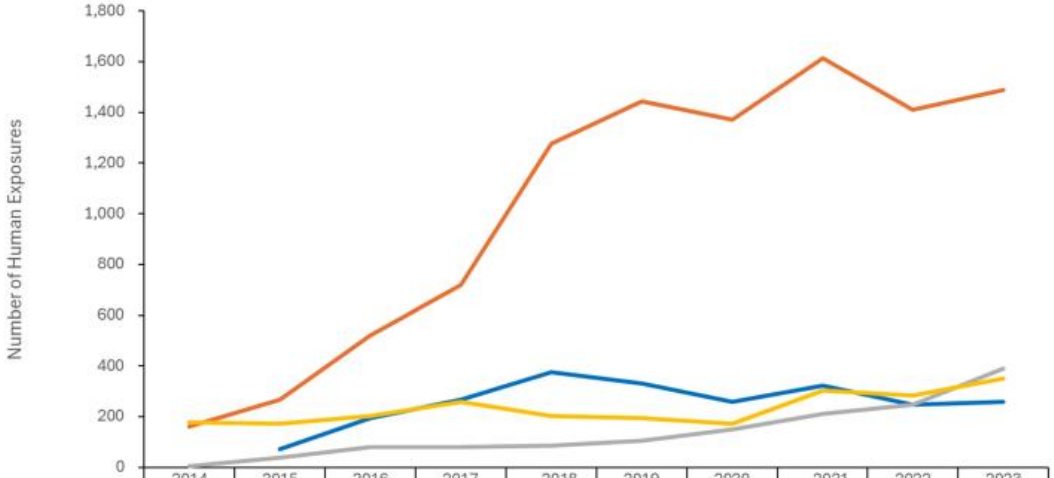
- Since 2013, there has been an increase in use of psychoactive substances in the United States
- Many of these agents mimic illicit substances or are used as "supplements" to stabilize mood, enhance cognitive function, or serve as sexual aids
- Despite rising in popularity, little is known to healthcare providers and the public regarding impacts of these substances

Mestas B. Tianeptine in the United States. *ToxTidbits - Maryland Poison Center*.
National Poison Data System® (NPDS) from America's Poison Centers®: 41st Annual Report. *Clinical Toxicology*.

Gas Station Drugs

- Kratom, tianeptine, phenibut, and nitrous oxide are psychoactive substances often referred to as "gas station drugs"
- These substances are commonly sold in convenience stores, “vape” shops, and gas stations
- The sharp rise in use of these agents has caused significant concern in many parts of the country, prompting changes in legislature in several states

Trends in Use



	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Phenibut		72	195	267	375	330	258	323	247	258
Kratom	162	267	520	719	1,277	1,443	1,371	1,614	1,410	1,489
Tianeptine	6	38	81	80	86	105	151	210	246	389
Nitrous Oxide	179	173	204	259	202	195	173	303	283	351

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

National Poison Data System® (NPDS) from America's Poison Centers®: 41st Annual Report. *Clinical Toxicology*.

ADVOCATE HEALTH

Prevalence in Healthcare

Table B. 10-Year Prevalence of Healthcare Utilization and Medical Outcomes

	Healthcare evaluation		Hospital admission		More serious medical outcome	
	Total	%SS	Total	%SS	Total	%SS
Kratom	7,333	58.5%	3,343	45.3%	4,885	54.2%
Phenibut	2,032	59.9%	1,261	54.6%	1,425	56.1%
Nitrous oxide	1,493	68.8%	596	57.0%	889	63.0%
Tianeptine	1,190	71.3%	660	54.5%	847	61.4%

SS = Single substance exposure

More serious outcomes = moderate effect, major effect, and death

National Poison Data System® (NPDS) from America's Poison Centers®: 41st Annual Report. *Clinical Toxicology*.

ADVOCATE HEALTH

Kratom

ADVOCATE HEALTH

Kratom Background

- *Mitragyna speciose* is an herb consumed for its psychotropic effects
- Traditionally used in Southeast Asia as a part of folk medicine
- Close relative of the coffee plant
- Leaves of the tree are crushed then brewed in tea, ground into supplement powders or placed into capsules for oral consumption

DEA, DOJ. Kratom Drug Fact Sheet. Published online April 2020
Eastlack SC et al. Kratom—Pharmacology, Clinical Implications, and Outlook: A Comprehensive Review. *Pain and Therapy*

Kratom

- Advertised as:
  - Preventative for opioid withdrawal symptoms
  - Replacement for opioids
  - Treatment for polysubstance use to prevent withdrawal
  - Treatment for acute or chronic pain, depression, and/or anxiety
- Several names that vary based on geographic location
  - Herbal speedball, thom, thang, ketum
- Obtained from gas stations, supplement stores, "vape" shops

Reissig C, et al. *7-Hydroxymitragynine (7-OH): An Assessment of the Scientific Data and Toxicological Concerns around an Emerging Opioid Threat*. US Food and Drug Administration; 2025.
DEA, DOJ. Kratom Drug Fact Sheet. Published online April 2020.

Kratom Pharmacology

- Kratom is made of several psychoactive alkaloids but only two are predominant:
  - Mitragynine (MG)
  - 7-hydroxymitragynine (7-OH)
- Mitragynine and 7-OH target opioid receptors
  - 7-OH has 13x the affinity for opioid receptors than morphine
- Kratom powder contains a 4.5-fold higher content of 7-OH than naturally occurring Kratom leaves

Sanderson M, Rowe A. Kratom. *Canadian Medical Association Journal*. 2019
Stanciu C, et al. What Is the Kratom Overdose Risk? A Systematic Literature Review. *Current Addition Reports*.
Reissig C, et al. *7-Hydroxymitragynine (7-OH): An Assessment of the Scientific Data and Toxicological Concerns around an Emerging Opioid Threat*. US Food and Drug Administration; 2025.

Kratom Pharmacology

- Proposed mechanism of action:
  - Both alkaloids exhibit partial agonism at mu-opioid receptors
  - MG stimulates alpha-2 adrenergic receptors
- Kratom users can expect to experience full effects within 30-60 minutes of ingestion
- T1/2: ~5-7 hours
- Kratom may inhibit CYP3A4, CYP2D6, and CYP1A2 enzymes

Warner ML, et al. The pharmacology and toxicology of kratom: from traditional herb to drug of abuse. *International Journal of Legal Medicine*. 2015.
Eastlack SC et al. Kratom—Pharmacology, Clinical Implications, and Outlook: A Comprehensive Review. *Pain and Therapy*

Kratom Clinical Effects

- Kratom's effects are dose dependent
  - Stimulant effects: 1-5 g of raw leaves
  - Sedative effects: 5-15 g of raw leaves
- Products are unregulated with highly variable alkaloid content
- Daily users of kratom are likely to experience tolerance and even withdrawal

Sanderson M, Rowe A. Kratom. *Canadian Medical Association Journal*. 2019
Stanciu C, et al. What Is the Kratom Overdose Risk? A Systematic Literature Review. *Current Addition Reports*.
U.S. Food and Drug Administration. FDA and Kratom. U.S. Food and Drug Administration. 2019.

Kratom Toxicity

Clinical signs and symptoms:

- Agitation
- Tachycardia
- Drowsiness
- Nausea/Vomiting
- Hallucinations/psychosis
- Seizures

- Toxicity seems to occur at doses greater than 8 g, but is patient dependent
- Observational reports note more patients exhibit more adrenergic effects than opioid-like effects

Stanciu C, et al. What Is the Kratom Overdose Risk? A Systematic Literature Review. *Current Addition Reports*.

Kratom Management

- Treatment for acute toxicity
  - No formal guidance exists
  - Focus on supportive care and symptom directed management
- Treatment for withdrawal
  - Similar to opioid withdrawal, some efficacy with buprenorphine-naloxone
- Monitoring:
  - LFTs, EKG, acute pulmonary edema, seizure-like activity

Stanciu C, et al. What Is the Kratom Overdose Risk? A Systematic Literature Review. *Current Addition Reports*.

Supportive Care

- Goal of supportive care is to protect essential organ function and prevent further complications

- Evaluate the following measures for toxicologic emergencies:
  - Airway and/or Antidotes
  - Breathing
  - Circulation
  - Decontamination
  - Elimination

Nelson LS, Goldfrank LR. *Goldfrank's Toxicologic Emergencies*. 11th ed. New York Mcgraw-Hill Education; 2019.
Emergency Management of Poisoning. *Haddad and Winchester's Clinical Management of Poisoning and Drug Overdose*.2007.

Kratom Management

- Naloxone may be a suitable agent for Kratom management
- 2018 Case Report by Overbeek and colleagues
  - 38 year-old female with a past medical history of polysubstance use and depression presented with decreased respiratory drive and altered mental status
  - She had a history of Kratom use from a previous hospitalization
    - Confirmed via gas chromatography/mass spectrometry
  - She was given a total of 0.8 mg of naloxone

Overbeek D, Abraham J, Munzer B. Kratom (Mitragynine) Ingestion Requiring Naloxone Reversal. *Clinical Practice and Cases in Emergency Medicine*. 2019

Assessment Question #1

Kratom is commonly misused through which of the following formulations? Select all that apply.

a. Herbal Tea
b. Capsules
c. Injections
d. Inhalation
e. Powder supplements

Tianeptine

ADVOCATE HEALTH

Tianeptine Background

- Classified as an atypical TCA in European, Latin American, and Asian countries where it is approved for anxiety and major depressive disorder (MDD)
- Elixirs or oral capsules sold as supplements
  - Marketed as a "smart drug" or nootropic that enhances cognitive function
  - Allegedly used to manage opioid consumption, mitigate withdrawal symptoms, and reduce cravings

Spyres M, Kent J. *The ToxIC NOSE (Novel Opioid and Stimulant Exposure) Report #15 from ToxIC's Rapid Response Program for Emerging Drugs*. Toxicology Investigators Consortium; 2024.
Smith KE, Rogers JM, Strickland JC, Epstein DH. When an obscurity becomes trend: social-media descriptions of tianeptine use and associated atypical drug use. *The American Journal of Drug and Alcohol Abuse*. 2021

Tianeptine

- In countries where it is approved, the typical dose to treat depression is 12.5 mg PO three times daily
- Case reports highlight that US consumers of tianeptine are ingesting 1.3 to 250x the approved daily dose
  - Equates to 50-10,000 mg daily
- Obtained at convenience stores, gas stations, and through online retailers
- Marketed under the names:
  - ZaZa, Neptune's Fix, Tianaa Red, Pegasus, Gas-Station Heroin

FDA. FDA warns consumers not to purchase or use any tianeptine product. Published 2026.

Tianeptine Pharmacology

- Proposed mechanism of action:
  - Full mu-opioid and weak delta-opioid receptor agonism
  - Stabilizes glutaminergic activity and opposes NMDA receptors
  - Proposed to stimulate serotonin reuptake
- When taken orally, 99% bioavailability within 1 hour of ingestion
- Highly protein bound
- T1/2: ~2.5 hours

NatMed Pro - Tianeptine. Natural Medicines. Published 2026.

Tianeptine Presentation

Opioid Toxicity	Tianeptine Toxicity	Serotonin Syndrome
Decreased Respiratory Drive	**Agitation**	Agitation
Bradycardia	Nausea/Vomiting	Tremor
Cyanosis	**Diaphoresis**	Clonus
Miosis	**Tachycardia**	Diaphoresis
Decreased Bowel Sounds	**Hypertension**	Tachycardia
Sedation	**Tremor**	Hypertension
Coma	**Decreased Respiratory Drive**	Mydriasis
Death	**Sedation**	Hyperactive Bowel Sounds
	Death	

Zahran TE. Characteristics of Tianeptine Exposures Reported to the National Poison Data System — United States, 2000–2017. *MMWR Morbidity and Mortality Weekly Report*. 2018
ToxTalks:Substances of Use and Misuse Highlights from the Field. Blue Ridge Poison Center; 2023.
National Poison Data System® (NPDS) from America's Poison Centers®: 41st Annual Report. *Clinical Toxicology*.

ADVOCATE HEALTH

Tianeptine Withdrawal

- "Classic" withdrawal symptoms
  - Agitation
  - Tachycardia
  - Nausea
  - Vomiting
  - Diarrhea
  - Tremors
  - Diaphoresis
  - Hypertension

Zahran TE. Characteristics of Tianeptine Exposures Reported to the National Poison Data System — United States, 2000–2017.*MMWR Morbidity and Mortality Weekly Report*. 2018
ToxTalks:Substances of Use and Misuse Highlights from the Field. Blue Ridge Poison Center; 2023.
National Poison Data System® (NPDS) from America's Poison Centers®: 41st Annual Report. *Clinical Toxicology*.
Health Alert: Tianeptine or "Gas Station Heroin." New Jersey Department of Health; 2025.

ADVOCATE HEALTH

Tianeptine Toxicity Management

Acute Toxicity:

- Reasonable to use naloxone due to mechanism of action
- Supportive care (fluids, benzodiazepines, etc.)
- Monitoring:
  - EKG changes

Chronic Toxicity:

- Involve addiction medicine or toxicologists
- Some case reports of successful taper with buprenorphine use

Logan B, Labay L, Mohr A, Browne T. Emerging Drug Alert: Tianeptine. Center for Forensic Research and Education. February 2024.
Ari M, Öztürk M, Oktar S. Amitriptyline and tianeptine poisoning treated by naloxone. *Human and Experimental Toxicology*. 2010.

Tianeptine Toxicity Management

- Systematic Review and Exploratory Analysis by Parnia et al
  - 1,582 records screened → 25 studies included
  - Of 52 cases, overdose occurred in 34.62% of cases
    - Naloxone reversed symptoms in 17.31% of treated cases
- Naloxone
  - Mechanism of action: competitive antagonist of mu, delta, and kappa opioid receptors
  - Dosing dependent on route
    - Nasal Spray: 4 mg (1 spray) every 2-3 minutes
    - IV: 0.4 mg to 2 mg every 2 to 3 min
  - Rapid onset of action
  - T1/2: ~1 hour

Parnia S, et al. Gas station heroin- tianeptine and its impact: a systematic review and exploratory analysis. *BMC Public Health*

Assessment Question #2

What is the mechanism through which tianeptine exerts euphoric effects?

a. Full gamma, delta, and mu opioid antagonism
b. Selective serotonin receptor inhibition
c. Full mu opioid agonism, partial delta opioid agonism
d. Serotonin norepinephrine receptor inhibition

Nitrous Oxide

ADVOCATE HEALTH

Nitrous Oxide Background

- Also known as "whippets" or "laughing gas"
- Long-term established use for pain control in medical and dental procedures
  - Anesthetic and analgesic properties
- Used in food industry for items such as whipped cream canisters
- Misused for euphoric and hallucinogenic effects
- Legal to obtain in the US due to its legitimate uses
  - More states are creating laws to decrease recreational use

Sanders RD, Weimann J, Maze M, Warner DS, Warner MA, eds. Biologic effects of nitrous oxide: a mechanistic and toxicologic review. *Anesthesiology*. 2008

Nitrous Oxide Pharmacology

- Anesthetic MOA:
  - Non-competitive NMDA inhibition in central nervous system
- Analgesic MOA:
  - Release of endogenous opioids that act on opioid receptors
- Absorbed through alveoli and has low blood solubility
- Onset within 2-5 minutes and half-life ~5 minutes
- Rapid onset and quick offset can lead to repeat use

Sanders RD, Weimann J, Maze M, Warner DS, Warner MA, eds. Biologic effects of nitrous oxide: a mechanistic and toxicologic review. *Anesthesiology*. 2008

Nitrous Oxide Use

- Recreationally obtained as small, pressurized canisters or “whippets”
- Often containing up to 8 g of nearly 100% nitrous oxide
  - In medical setting, it is an inhaled mixture that also contains 30-70% oxygen
- Gas from canister is typically released into a balloon for inhalation or inhaled directly from canister
  - Gas is released at -40 to -55 degrees Celsius
  - Can lead to cold burns if directly exposed

Riccò M, Ferraro P, Corrado S, Bottazzoli M, Marchesi F. Nitrous Oxide Inhalant Abuse: Preliminary Results from a Cross-Sectional Study on Knowledge, Attitudes, and Practices of Italian Physicians (2023). *Medicina (Kaunas)*. 2023

Nitrous Oxide Acute Toxicity

- Diagnosing toxicity may be difficult
  - Relies on presentation, patient history, exclusion of other causes

- Symptoms of acute toxicity:
  - Slurred speech
  - Dizziness
  - Drowsiness
  - Lack of coordination
  - Cognitive impairment
  - Hallucinations

- Acute complications:
  - Frost bite
  - Lung collapse
  - Seizures
  - Hypoxemia leading to hypoxia
  - Death with high concentrations

De Halleux C, Juurlink DN. Diagnosis and management of toxicity associated with the recreational use of nitrous oxide. *CMAJ*. 2023

Nitrous Oxide Acute Toxicity

- There is no guideline for treatment of acute toxicity
  - Acute symptoms not considered to be extremely dangerous
- Management typically involves supportive care to treat symptoms
- Patients more likely to present due to an acute complication
  - Management involves treatment of associated complication

De Halleux C, Juurlink DN. Diagnosis and management of toxicity associated with the recreational use of nitrous oxide. *CMAJ*. 2023

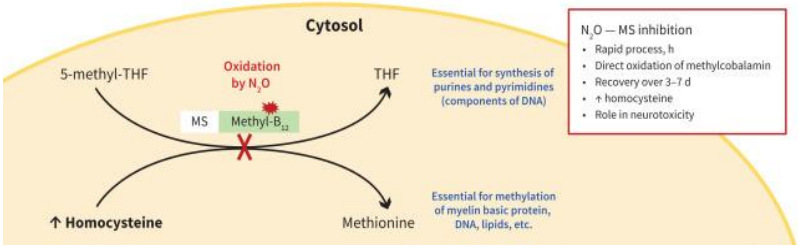
Nitrous Oxide Chronic Toxicity

- Complications of chronic abuse:
  - Anemia
  - Neuropathy
  - Paralysis
  - Cerebrovascular events
  - Thromboembolic events
- Result of vitamin B12 deficiency, primarily causing neurologic and hematologic complications
- A study of 76 chronic users with neurological complications:
  - Median duration of nitrous oxide use was 8 months
  - Median exposure was 25 canisters per day (200 g N2O)

De Halleux C, Juurlink DN. Diagnosis and management of toxicity associated with the recreational use of nitrous oxide. *CMAJ*. 2023

Nitrous Oxide Chronic Toxicity

- Mechanism of chronic complications:
  - Irreversibly oxidizes methylcobalamin, an important coenzyme for methionine synthesis
  - Results in increased homocysteine and decreased methionine
  - Methionine is important for myelin synthesis and a decrease leads to neurotoxicity
  - Interferes with DNA synthesis in hematopoietic cells



De Halleux C, Juurlink DN. Diagnosis and management of toxicity associated with the recreational use of nitrous oxide. *CMAJ*. 2023

ADVOCATE HEALTH

Nitrous Oxide Chronic Toxicity

- Treatment for chronic toxicity:
  - Immediate discontinuation of nitrous oxide
  - Cobalamin 1000 mcg IM daily for 1-2 weeks followed by 1000 mcg IM weekly until resolution of symptoms
  - Methionine 1 g orally three times daily for 4-6 weeks or until significant improvement of symptoms

De Halleux C, Juurlink DN. Diagnosis and management of toxicity associated with the recreational use of nitrous oxide. *CMAJ*. 2023

Assessment Question #3

Which of the following are acute complications associated with nitrous oxide abuse? Select all that apply.

a. Seizure
b. Hypoxemia
c. Coagulopathy
d. Frost bite

Phenibut

ADVOCATE HEALTH

Phenibut Background

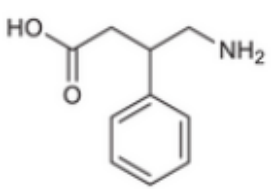
- Historically used by Soviet military personnel an anxiolytic and nootropic
- Current recreational uses include:
  - Cognitive performance enhancement
  - Treatment of anxiety and insomnia
  - Alcohol and benzodiazepine withdrawal
  - Increase libido
  - Euphoria
- Legal in the US, but not FDA approved

Gurley BJ, Koturbash I. Phenibut: A drug with one too many "buts". *Basic Clin Pharmacol Toxicol*. 2024

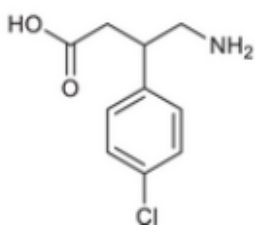
Phenibut Pharmacology

- Structurally similar to baclofen
  - Baclofen is 30x more potent
- MOA:
  - GABA-B and some GABA-A agonism
  - Stimulates dopamine receptors
  - Antagonizes beta-PEA
- Onset: 2-4 hours
- Half-life: ~5 hours

a) Phenibut



b) Baclofen



Penzak SR, Bulloch M. Phenibut: review and pharmacologic approaches to treating withdrawal. *J Clin Pharmacol*. 2024

Phenibut Use

- Exposure most commonly via ingestion, however some reports of inhalation
- Available as capsules, solution, powder, and large crystals
  - Many users report obtaining from online retailers
- Effects are dose dependent
- Therapeutic dose: 250-750 mg daily
  - Doses > 2 g per day associated with toxicity

Gurley BJ, Koturbash I. Phenibut: A drug with one too many "buts". *Basic Clin Pharmacol Toxicol*. 2024

Phenibut Toxicity

- Symptoms of acute toxicity:
  - Drowsiness
  - Agitation
  - Delirium
  - Psychosis
  - Mydriasis
  - Hypothermia
  - Tachycardia or bradycardia
- Treatment for acute toxicity largely relies on symptom management and supportive care
  - Symptoms typically resolve after hours to days

Gurley BJ, Koturbash I. Phenibut: A drug with one too many "buts". *Basic Clin Pharmacol Toxicol*. 2024

Phenibut Withdrawal

- Chronic abuse can lead to dependence and severe withdrawal if use is discontinued
- Symptoms of withdrawal:
  - Insomnia
  - Anger
  - Psychomotor agitation
  - Anxiety
  - Tremors
  - Palpitations
  - Hallucinations

Penzak SR, Bulloch M. Phenibut: review and pharmacologic approaches to treating withdrawal. *J Clin Pharmacol*. 2024

Phenibut Withdrawal

- A systematic review of phenibut withdrawal cases was performed
  - All cases involved male patients with a median age of 30 years old
  - The median daily phenibut dose prior to withdrawal was 10 g
  - The shortest duration of use prior to experiencing withdrawal was 1 week
  - Withdrawal symptoms could occur as quickly as 2 hours after last dose
- Withdrawal was reported to require therapeutic intervention in 95.7% of cases

Feldman R, Autry B, Dukes J, et al. A systematic review of phenibut withdrawal focusing on complications, therapeutic approaches, and single substance versus polysubstance withdrawal. *Clinical Toxicology*. 2023

Phenibut Withdrawal

- Treatment for phenibut withdrawal:
  - Baclofen taper
    - Duration of taper depends on severity of patients chronic abuse
  - Benzodiazepines
  - Phenobarbital
- Combinations of these drugs have also been used
  - Systemic review reported 76% of patients required 2 drugs to manage symptoms

Penzak SR, Bulloch M. Phenibut: review and pharmacologic approaches to treating withdrawal. *J Clin Pharmacol*. 2024

Assessment Question #4

Which of the following is considered appropriate treatment for acute phenibut toxicity?

a. Naloxone
b. Vitamin B12 supplementation
c. Supportive care
d. Flumazenil

The Pharmacist's Role

- In 2025, ASHP published a formal statement on the Pharmacist's Role in Substance Use Disorder:

  "Pharmacists are uniquely positioned to support prevention, treatment, recovery, and harm reduction across all healthcare settings. With their accessibility, medication expertise, and trusted role in communities, pharmacists play a vital role in addressing gaps in care, reducing stigma, and improving patient outcomes"

Jorgenson T, Tran TH, Bratberg J. ASHP Statement on the Pharmacist's Role in Substance Use Disorder Prevention, Treatment, and Recovery. *American Journal of Health-System Pharmacy*. February 2026

The Pharmacist's Role

- Pharmacists as medication experts are uniquely qualified to help guide care in toxicologic emergencies
- Pharmacists not only guide toxicity management, but also hold roles in education, protocol development, formulary management, and poison center collaboration
- It is important for pharmacists to be aware of current trends in recreational drug use

Routsolias JC, Renee Petzel Gimbar, Zell-Kanter M. Clinical Pharmacists: Essential During a Poison Outbreak. *Journal of medical toxicology*. 2020
Jorgenson T, Tran TH, Bratberg J. ASHP Statement on the Pharmacist's Role in Substance Use Disorder Prevention, Treatment, andRecovery. *American Journal of Health-System Pharmacy*. February 2026

Summary/Conclusion

- There is an increase in use of ‘gas station drugs’ such as kratom, tianeptine, nitrous oxide, and phenibut across the United States due to their psychoactive effects
- This increase in use can result in more toxicological emergencies or withdrawal syndromes presenting for care
- Supportive care is a key element to providing care to the acutely intoxicated patient
- It is important to understand the pharmacist’s unique role in the care of these patients

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Questions?

Gabriella Schmit
Gabriella.Schmit@aah.org

Megan Olson
Megan.Olson2@aah.org