

# What are Gas Station Drugs, Their Dangerous Impacts, and Recovery Mechanisms from their Devastating Effects

**Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC**

**Clinical Associate Professor Emeritus**

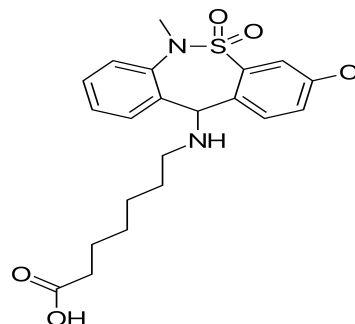
**Addiction Counselor Emeritus**

**Chemical Health Associates, Inc.**

[mernort@gmail.com](mailto:mernort@gmail.com)

**Maddie Marsh BS Psychology, Pharm.D. Candidate**

**University of Georgia College of Pharmacy**



1

## Disclosure

- I have no conflicts of interest to report and I intend to reference unlabeled/unapproved uses of drugs or products in my presentation.

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

2

2

## Learning Objectives

- Participants will:
- Develop a vocabulary of the current herbal and pharmaceutical drugs known as the gas station drugs;
- Gain an understanding of the pharmacodynamics and pharmacokinetics of Phenibut, Tianeptine, and Kratom;
- Comprehend the severe adverse drug effects of Phenibut, Tianeptine, and Kratom.

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

3

3



## Introduction: Gas Station Drugs

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

4

4

# What Are Gas Station Drugs?

The term "Gas Station Drugs" originally came from the DEA when describing locations where drug paraphernalia could be marketed through the internet, convenience stores or gas stations. Bath Salts, Spice, and synthetic cannabinoid products were being sold over the counter to adolescents and young adults.

Synthetic drugs are often labeled as "Not for human consumption" or "Potpourri" to avoid detection.

Seeing these labels on products that look like candy or snacks is almost a sure way to spot a synthetic substance.

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

5

5

# What Are Gas Station Drugs?

The reported harmful effects of synthetic substances range from nausea to drug-induced psychosis.

Due to the unpredictable nature of synthetic drugs and of human consumption of these drugs, the true effects of many of these drugs are unknown.

Many states have responded to synthetic drug abuse by passing laws banning certain synthetic cannabinoids and stimulants.

In 2015, most of these compounds were placed on the DEA Schedule 1 list and most thought that this problem had been resolved.....but wait.....

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

6

6

## What Are Gas Station Drugs?

- Beginning shortly after the changes in the law, new products began to be marketed through the internet, convenience stores and gas stations. This marketing episode was occurring as various states were legalizing the use of medical cannabis and CBD, so the products being introduced were being sold mostly unnoticed by local, state and federal officials.

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

8/26/21

7

7

## What Are Gas Station Drugs?

- A booming industry began manufacturing and marketing these "supplements" that mimic the effects of street legal and pharmaceutical drugs to anyone desperate or shameless enough to throw down a few bucks on products with names like Bullet Proof -- a so-called male enhancement pill that promises increased sexual performance -  
- Go Pillz for increased energy, focus, memory and a better mood, and Lazy Cakes Relaxation Brownies, a product whose mascot is a glassy-eyed brownie that smiles at you from the package like a chocolate Tommy Chong.

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

8/26/21

8

8



## What Are Gas Station Drugs?

- The drugs were promoted as sexual enhancers, nootropics or smart drugs, pain relievers, energizers, and mood stabilizers. The nootropics is a common term that will tag along with the compound responsible for the enhancement of mental performance. The energizers were herbal stimulants, sexual enhancers were herbal sex hormone precursors and the pain relievers are herbal opioid receptor agonists.
- Phenibut is a synthetic nootropic or smart drug, Tianeptine is a tricyclic antidepressant with pain management components, Kratom has both pain relieving and sexual enhancing properties, and ketamine is a synthetic pain reliever and antidepressant with psychosis side effects.

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

8/26/21

9

9

## What Are Gas Station Drugs?

- Several other drugs began to emerge into this “herbal market of gas station drugs” or nootropics during this time. Phenibut, tianeptine, kratom, and ketamine were being sold under various names on the internet, convenience stores, and gas stations.
- **Phenibut:** During 2009–2019, U.S. poison centers reported calls for 1,320 phenibut exposures from all 50 U.S. states and the District of Columbia.
- Graves JM, Dilley J, Kubsad S, Liebelt E. Notes from the Field: Phenibut Exposures Reported to Poison Centers — United States, 2009–2019. MMWR Morb Mortal Wkly Rep 2020;69:1227–1228. DOI: <http://dx.doi.org/10.15585/mmwr.mm6935a5external icon>.

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

8/26/21

10

10

## What Are Gas Station Drugs?

The number of cases increased sharply over the study period, particularly since 2015, when regional poison centers became able to use “phenibut” as a relevant term to capture exposures.

Phenibut exposures with known formulations most often involved solids (e.g., tablets) (65.1%) or powder (24.8%). Reported exposures were predominantly ingestions (93.2%), although 2.8% involved inhalation, and 4.0% involved other routes of exposure, including dermal.

Graves JM, Dilley J, Kubsad S, Liebelt E. Notes from the Field: Phenibut Exposures Reported to Poison Centers — United States, 2009–2019. MMWR Morb Mortal Wkly Rep 2020;69:1227–1228. DOI: [http://dx.doi.org/10.15585/mmwr.mm6935a5external icon](http://dx.doi.org/10.15585/mmwr.mm6935a5external_icon).

11 8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

11

## What Are Gas Station Drugs?

- Commonly reported adverse health effects included drowsiness or lethargy (29.0%), agitation (30.4%), tachycardia (21.9%), and confusion (21.3%).
- Coma was reported in 80 (6.2%) cases, including one involving an adolescent. In one half (49.6%) of cases, the exposure resulted in moderate effects (i.e., no long-term impairment).
- Major effects (i.e., life-threatening or resulting in significant disability or disfigurement) occurred in one in eight (12.6%) reported exposures, and three deaths were reported.
- Among exposures in which phenibut was the only drug or agent involved, 10.2% were associated with major effects, including one death.
- Graves JM, Dilley J, Kubsad S, Liebelt E. Notes from the Field: Phenibut Exposures Reported to Poison Centers — United States, 2009–2019. MMWR Morb Mortal Wkly Rep 2020;69:1227–1228. DOI: [http://dx.doi.org/10.15585/mmwr.mm6935a5external icon](http://dx.doi.org/10.15585/mmwr.mm6935a5external_icon).

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

12

12

## Phenibut and Drug Testing

- It is marketed for nootropic (neurocognitive enhancement), anxiolytic, and sedative effects, and trends **show** increasing use in the past few years. Of note, **phenibut** is not reliably detected on a typical **urine drug screen**.
- Because the US Food and Drug Administration (FDA) views phenibut as an amino acid, the substance is not regulated and is readily available from headshops and online retailers despite known risk of dependence, overdose, and withdrawal.
- Carrie Tamarelli, MD, Avinash Hosanagar, MD **Phenibut Use in a Patient Prescribed Gabapentinoids** *Pain Medicine*, Volume 22, Issue 3, March 2021, Pages 761–762, <https://doi.org/10.1093/pm/pnaa205>

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

8/26/21

13

13

## Phenibut and Drug Testing

- If someone was specifically being tested for the use of phenibut, which would be unlikely, it could show up for anywhere from four days to four weeks in a urine test. In a blood test, phenibut may show up for up to 80 hours after the last dose.
- While most screenings including a standard 5-panel screening won't test for phenibut, there is a rare chance that the use of phenibut could show up as a false positive for benzodiazepines.
- Ahuja, Tania; Mgbako, Ofale; Katzman, Caroline; Grossman, Allison. "[Phenibut \(β-Phenyl-γ-aminobutyric Acid\) Dependence and Management of Withdrawal: Emerging Nootropics of Abuse.](#)" National Center of Biotechnology Information. April 30, 2018. Accessed, July 17, 2021.

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

8/26/21

14

14



## Tianeptine

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

8/26/21

15

15

Figure 1. Structural differences between tianeptine and other substances.

Structure source: PubChem.

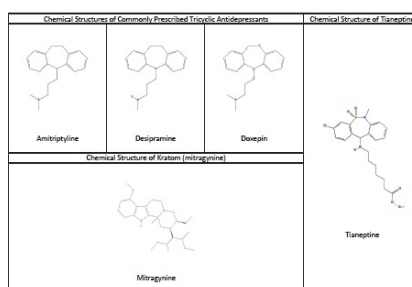
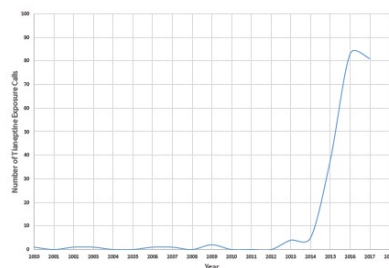


Figure 2. Tianeptine exposure calls to the National Poison Data System from 2000 through 2017. Graph based on Reference 6.



8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

16

16

## What Are Gas Station Drugs?

- **Tianeptine:** sold under the brand names **Stablon** and **Coaxil** among others, is a tricyclic antidepressant which is used mainly in the treatment of major depressive disorder, although it may also be used to treat anxiety, asthma, and irritable bowel syndrome;
- Tianeptine has antidepressant and anxiolytic effects with a relative lack of sedative, anticholinergic, and cardiovascular side effects.<sup>[7][10]</sup> It has been found to act as an atypical agonist of the μ-opioid receptor with clinically negligible effects on the δ- and κ-opioid receptors as do most tricyclic antidepressants

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

8/26/21

17

17

## What Are Gas Station Drugs?

- Tianeptine was discovered and patented by the French Society of Medical Research in the 1960s.
- Currently, tianeptine is approved in France and manufactured and marketed by Laboratories Servier SA; it is also marketed in a number of other European countries under the trade name Coaxil as well as in Asia (including Singapore) and Latin America as Stablon and Tatinol but it is not available in Australia, Canada, New Zealand, the United Kingdom, or the United States.

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

8/26/21

18

18

## What Are Gas Station Drugs?

- Tianeptine shows efficacy against serious depressive episodes (major depression), comparable to amitriptyline, imipramine and fluoxetine, but with significantly fewer side effects.
- It was shown to be more effective than maprotiline in a group of people with co-existing depression and anxiety.
- Tianeptine also displays significant anxiolytic properties and is useful in treating a spectrum of anxiety disorders including panic disorder, as evidenced by a study in which those administered 35% CO<sub>2</sub> gas (carbogen) on paroxetine or tianeptine therapy showed equivalent panic-blocking effects.

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

8/26/21

19

19

## What Are Gas Station Drugs?

- Tianeptine is an antidepressant drug that is not approved by the Food and Drug Administration (FDA).
- Clinical effects of tianeptine abuse and withdrawal can mimic opioid toxicity and withdrawal.
- Tianeptine is a substance that is not approved as a drug for any use, does not qualify as a dietary ingredient, is not an approved food additive, and is not generally recognized as safe.
- Any dietary supplement containing tianeptine is considered adulterated under the Federal Food, Drug, and Cosmetic Act, and therefore cannot be sold in the United States.

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

8/26/21

20

20

## What Are Gas Station Drugs?

- The CDC also reports tianeptine use as a possible emerging public health risk, as there was an increase in reports of adverse reactions to tianeptine in the United States.
- Notably, the number of tianeptine exposure calls reported by U.S. poison control centers increased from five in 2014 to 81 in 2017.
- There were 470 tianeptine-related adverse events reports submitted to the FDA's Adverse Events Reporting System (the agency's adverse event reporting system for drugs and biologics) and the Center for Food Safety and Applied Nutrition (CFSAN)
- El Zahran T, Schier J, Glidden E, et al. Characteristics of Tianeptine Exposures Reported to the National Poison Data System — United States, 2000–2017. MMWR Morb Mortal Wkly Rep 2018;67:815–818. DOI: [http://dx.doi.org/10.15585/mmwr.mm6730a2external icon](http://dx.doi.org/10.15585/mmwr.mm6730a2external%20icon)

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

8/26/21

21

21

## Drug Testing for Tianeptine

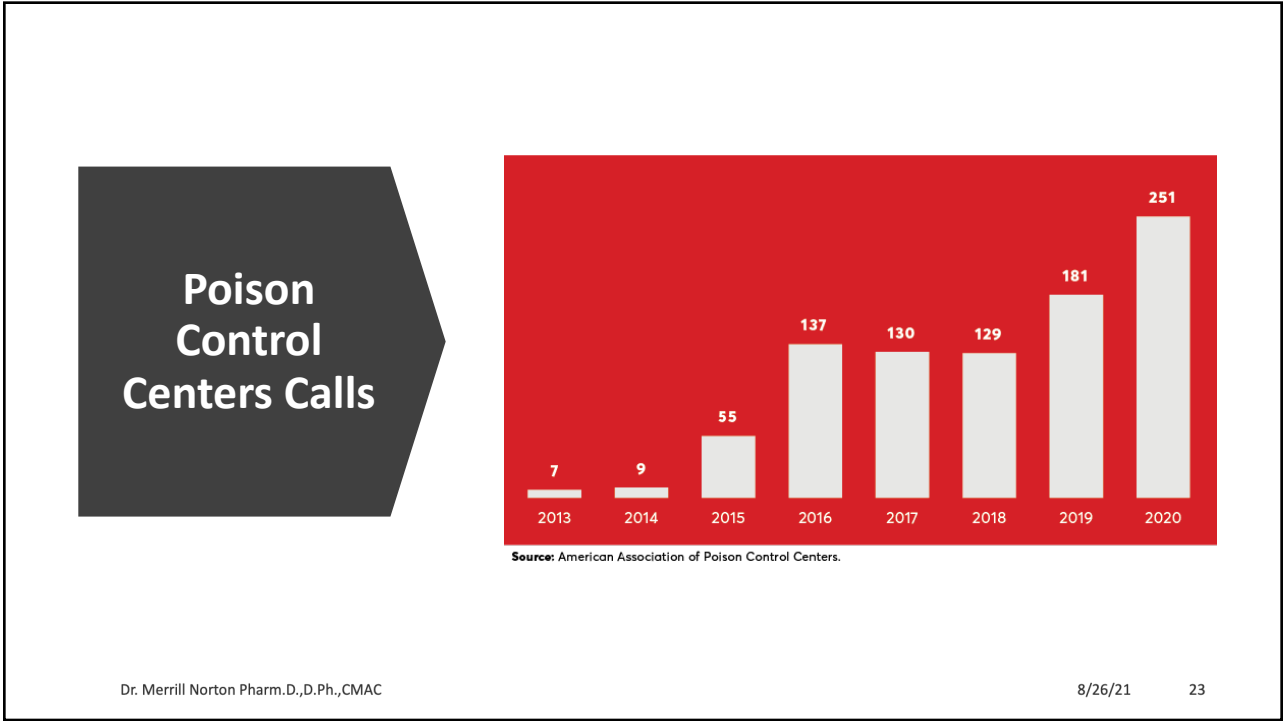
- As of September 2020, **only a blood assay is available that allows** for the detection of tianeptine; this sampling method is typically more expensive than urine testing, more invasive (particularly for weekly monitoring), and more difficult to obtain from those with a history of substance abuse.
- Tianeptine is rapidly cleared by the kidneys with a half life of 2.5 hours.
- **Drug testing for tianeptine** is not routinely available, but specialty-testing laboratories might have the capacity.

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

8/26/21

22

22



23



24



## What Are Gas Station Drugs?

- Adverse Event Reporting System (CAERS). These reports included at least 458 serious cases, of which 55 involved death.
- In 2019, more than double the amount of tianeptine-related cases were reported to the FDA as compared to the yearly average for the period of 1998-2018.
- El Zahran T, Schier J, Glidden E, et al. Characteristics of Tianeptine Exposures Reported to the National Poison Data System — United States, 2000–2017. MMWR Morb Mortal Wkly Rep 2018;67:815–818.  
DOI: <http://dx.doi.org/10.15585/mmwr.mm6730a2external icon>

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

25

25

## What Are Gas Station Drugs?

- Kratom(*Mitragyna speciosa*), a plant native to Southeast Asia, contains the alkaloid mitragynine, which can produce stimulant effects in low doses and some opioid-like effects at higher doses when consumed.
- Use of kratom has recently increased in popularity in the United States, where it is usually marketed as a dietary or herbal supplement.
- Olsen EO, O'Donnell J, Mattson CL, Schier JG, Wilson N. *Notes from the Field: Unintentional Drug Overdose Deaths with Kratom Detected* — 27 States, July 2016–December 2017. MMWR Morb Mortal Wkly Rep 2019;68:326–327.  
DOI: <http://dx.doi.org/10.15585/mmwr.mm6814a2external icon>

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

26

26

## What Are Gas Station Drugs?

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

27

- Some studies suggest kratom has potential for dependence and abuse.
- As of April 2019, kratom was not scheduled as a controlled substance. However, since 2012, the Food and Drug Administration has taken a number of actions related to kratom, and in November 2017 issued a public health advisory\*; in addition, the Drug Enforcement Administration has identified kratom as a drug of concern.
- During 2011–2017, the national poison center reporting database documented 1,807 calls concerning reported exposure to kratom.
- To assess the impact of kratom, CDC analyzed data from the State Unintentional Drug Overdose Reporting System (SUDORS).
- Olsen EO, O'Donnell J, Mattson CL, Schier JG, Wilson N. *Notes from the Field: Unintentional Drug Overdose Deaths with Kratom Detected — 27 States, July 2016–December 2017*. MMWR Morb Mortal Wkly Rep 2019;68:326–327.  
DOI: <http://dx.doi.org/10.15585/mmwr.mm6814a2external icon>

27

## What Are Gas Station Drugs?

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

28

- Data on 27,338 overdose deaths that occurred during July 2016–December 2017 were entered into SUDORS, and 152 (0.56%) of these decedents tested positive for kratom on postmortem toxicology (kratom-positive).
- Postmortem toxicology testing protocols were not documented and varied among and within states.
- Kratom was determined to be a cause of death (i.e., kratom-involved) by a medical examiner or coroner for 91 (59.9%) of the 152 kratom-positive decedents, including seven for whom kratom was the only substance to test positive on postmortem toxicology, although the presence of additional substances cannot be ruled out .
- Olsen EO, O'Donnell J, Mattson CL, Schier JG, Wilson N. *Notes from the Field: Unintentional Drug Overdose Deaths with Kratom Detected — 27 States, July 2016–December 2017*. MMWR Morb Mortal Wkly Rep 2019;68:326–327.  
DOI: <http://dx.doi.org/10.15585/mmwr.mm6814a2external icon>

28

## What Are Gas Station Drugs?

8/26/21

In approximately 80% of kratom-positive and kratom-involved deaths in this analysis, the decedents had a history of substance misuse, and approximately 90% had no evidence that they were currently receiving medically supervised treatment for pain.

Postmortem toxicology testing detected multiple substances for almost all decedents

Olsen EO, O'Donnell J, Mattson CL, Schier JG, Wilson N. *Notes from the Field: Unintentional Drug Overdose Deaths with Kratom Detected — 27 States, July 2016–December 2017*. MMWR Morb Mortal Wkly Rep 2019;68:326–327.

DOI: <http://dx.doi.org/10.15585/mmwr.mm6814a2external>

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

29

29

## What Are Gas Station Drugs?

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

Fentanyl and fentanyl analogs were the most frequently identified co-occurring substances; any fentanyl was listed as a cause of death for 65.1% of kratom-positive decedents and 56.0% of kratom-involved decedents.

Heroin was the second most frequent substance listed as a cause of death (32.9% of kratom-positive decedents), followed by benzodiazepines (22.4%), prescription opioids (19.7%),\*\* and cocaine (18.4%).

Olsen EO, O'Donnell J, Mattson CL, Schier JG, Wilson N. *Notes from the Field: Unintentional Drug Overdose Deaths with Kratom Detected — 27 States, July 2016–December 2017*. MMWR Morb Mortal Wkly Rep 2019;68:326–327.

DOI: <http://dx.doi.org/10.15585/mmwr.mm6814a2external>

8/26/21

30

30

## Drug Testing for Kratom

- Quantitatively detects presence of Kratom (Mitragynine), an emerging drug of abuse, sold online and at "head shops" nationwide
- Redwood Labs has Advanced liquid chromatography - tandem mass spectrometry (LC-MS/MS) equipment provides definitive test results
- Labcorp Kratom screening analysis includes: mitragynine and 7-hydroxy-mitragynine at a threshold of 1.0 ng/mL.
- This test was developed and its performance characteristics determined by LabCorp. It has not been cleared or approved by the Food and Drug Administration.
- Premier Biotech is introducing the Premier Bio-Dip kratom drug screen, the first rapid urine test on the market to detect the key active compound Mitragynine at 150 ng/mL

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

8/26/21

31

31

## What Are Gas Station Drugs?

**Ketamine** is a dissociative anesthetic that has some hallucinogenic effects. It distorts perceptions of sight and sound and makes the user feel disconnected and not in control.

It is an injectable, short-acting anesthetic for use in humans and animals. It is referred to as a "dissociative anesthetic" because it makes patients feel detached from their pain and environment.

Ketamine can induce a state of sedation (feeling calm and relaxed), immobility, relief from pain, and amnesia (no memory of events while under the influence of the drug).

It is abused for its ability to produce dissociative sensations and hallucinations. Ketamine has also been used to facilitate sexual assault.

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

32

32

# What Are Gas Station Drugs?

Ketamine, along with the other “club drugs,” has become popular among teens and young adults at dance clubs and “raves.” Ketamine is manufactured commercially as a powder or liquid.

Powdered ketamine is also formed from pharmaceutical ketamine by evaporating the liquid using hot plates, warming trays, or microwave ovens, a process that results in the formation of crystals, which are then ground into powder.

Common street names include:

- Cat Tranquilizer, Cat Valium, Jet K, Kit Kat, Purple, Special K, Special La Coke, Super Acid, Super K, and Vitamin K

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

33

33

# What Are Gas Station Drugs?

Ketamine comes in a clear liquid and a white or off-white powder.

Powdered ketamine (100 milligrams to 200 milligrams) typically is packaged in small glass vials, small plastic bags, and capsules as well as paper, glassine, or aluminum foil folds.

Powdered ketamine is cut into lines known as bumps and snorted, or it is smoked, typically in marijuana or tobacco cigarettes. Liquid ketamine is injected or mixed into drinks.

Ketamine is found by itself or often in combination with MDMA, amphetamine, methamphetamine, or cocaine.

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

34

34

## What Are Gas Station Drugs?

Ketamine produces hallucinations. It distorts perceptions of sight and sound and makes the user feel disconnected and not in control.

A “Special K” trip is touted as better than that of LSD or PCP because its hallucinatory effects are relatively short in duration, lasting approximately 30 to 60 minutes as opposed to several hours.

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

35

35

## What Are Gas Station Drugs?

Slang for experiences related to Ketamine or effects of ketamine include:

“K-land” (refers to a mellow & colorful experience)

“K-hole” (refers to the out-of-body, near death experience)

“Baby food” (users sink in to blissful, infantile inertia)

“God” (users are convinced that they have met their maker)

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

36

36

## What Are Gas Station Drugs?

The onset of effects is rapid and often occurs within a few minutes of taking the drug, though taking it orally results in a slightly slower onset of effects.

Hallucinogen Persisting Perception Disorder (HPPD) has been reported several weeks after ketamine is used and may include experiencing the negative side effects that occurred while taking the drug initially.

Ketamine may also cause agitation, depression, cognitive difficulties, unconsciousness, and amnesia.

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

37

37

## What Are Gas Station Drugs?

A couple of minutes after taking the drug, the user may experience an increase in heart rate and blood pressure that gradually decreases over the next 10 to 20 minutes. Ketamine can make users unresponsive to stimuli. When in this state, users experience:

- Involuntarily rapid eye movement, dilated pupils, salivation, tear secretions, and stiffening of the muscles. This drug can also cause nausea.

An overdose can cause unconsciousness and dangerously slowed breathing.

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

38

38

## What Are Gas Station Drugs?

The anesthetic drug ketamine has been shown, in low doses, to have a rapid effect on difficult-to-treat depression.

Researchers now report that they have identified a key target for the drug: specific serotonin receptors in the brain. Their findings give hope of new, effective antidepressants.

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

39

39

## What Are Gas Station Drugs?

The U.S. Food and Drug Administration today approved Spravato (esketamine) nasal spray, in conjunction with an oral antidepressant, for the treatment of depression in adults who have tried other antidepressant medicines but have not benefited from them (treatment-resistant depression).

Because of the risk of serious adverse outcomes resulting from sedation and dissociation caused by Spravato administration, and the potential for abuse and misuse of the drug, it is only available through a restricted distribution system, under a Risk Evaluation and Mitigation Strategy (REMS).

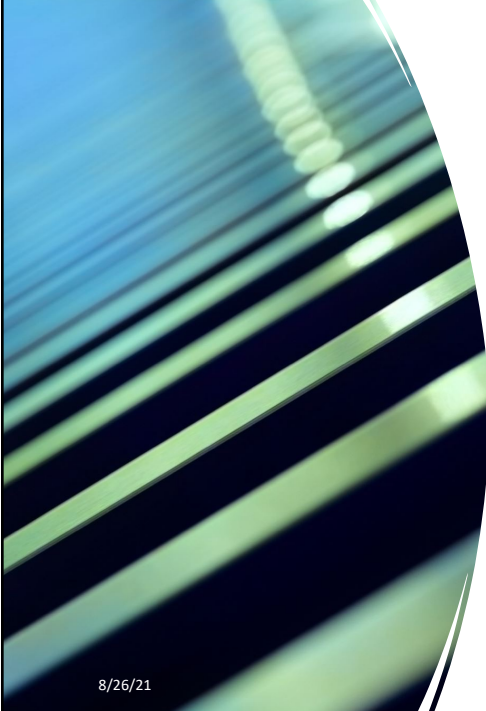
8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

40

40





## Other Gas Station Drugs

---

**Imodium (Loperamide):** Overdose deaths reported.

---

**Dextromethorphan (DMX):** DXM abuse is responsible for some 6,000 emergency room visits each year, almost half of which are among patients between the ages of 12 and 25.

---

**Caffeine Pills:** one tablespoon of caffeine power, or 10,000 milligrams, can be fatal for an adult. Even in lower doses it can cause dehydration, panic attacks, and heart irregularities.

---

**Herbal Diet Pills:** substance use disorders common.

---

**Laxatives:** eating disorders used to control weight.

---

**Benadryl (diphenhydramine):** can put people in a lucid, dreamy state when taken in high doses.

8/26/21 Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC 41

41

## Coming to a Gas Station Soon

<ul style="list-style-type: none"> <li>• Fastin-XR</li> <li>• Hi-Tech Pharmaceuticals: Contained methysynephrine, a stimulant used to improve oxygen exchange.</li> <li>• NeuroPill</li> <li>• Cognitive Nutrition: Contained piracetam, purported to improve cognitive function.</li> <li>• NoöCamilon</li> <li>• LifeLink: Contained picamilon, a drug prescribed in other countries for neurological conditions.</li> <li>• Green Stinger</li> <li>• Schwartz Laboratories: Contained acacia rigidula, a plant used in some weight-loss supplements.</li> <li>• Friction</li> <li>• VPX/Bang Energy: Contained isopropylloctopamine, a stimulant also known as deterenol.</li> </ul>	<ul style="list-style-type: none"> <li>• pH Balancer Plus</li> <li>• American Nutraceuticals: Contained cesium chloride, a substance promoted as an alternative cancer treatment.</li> <li>• Milletov-X</li> <li>• Millecor: Contained DMHA, a stimulant marketed for weight loss and athletic performance.</li> <li>• Thermosculpt Original</li> <li>• Designed by Dean: Contained BMPEA, a synthetic substitute for amphetamine.</li> <li>• Adipropen Ultra</li> <li>• 8 Weeks Out: Contained DMAA, an amphetamine derivative.</li> <li>• Anesthetized</li> <li>• Blackstone Labs: Contained phenibut, used in Russia as an anti-anxiety medication.</li> </ul>
---	---

8/26/21 Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC 42

42



8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

43

43

## Questions To Be Answered About Ketamine and Kratom

What is Kratom?

What are the signs and symptoms  
of a Kratom overdose?

What are the medical uses of  
Ketamine?

What are the signs and symptoms  
of a Ketamine intoxication?

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

44

44

## Introduction: Kratom



8/26/21

Dr. Merrill Norton Pharm.D., D.Ph., CMAC

45

45

## Kratom

Kratom is a tropical tree (*Mitragyna speciosa*) native to Southeast Asia, used traditionally to combat fatigue and improve work productivity among farm populations in Southeast Asia

- Has recently become popular as a novel psychoactive substance in Western countries (Cinosi et al, 2015).
- FDA is concerned that kratom, which affects the same opioid brain receptors as morphine, appears to have properties that expose users to the risks of addiction, abuse, and dependence
- Currently, there are no FDA-approved uses for kratom, and the agency has received concerning reports about its safety

46

# Mitragyna Speciosa

## Used in:

- Malaysia
- Thailand
- Indonesia

## Local names:

- Ithang
- Biak Biak
- Ketum
- Kakuam

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

47

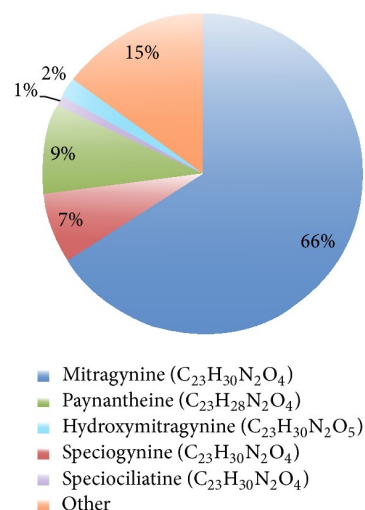
47



48

## Kratom Extract Composition

- Kratom preparations contain varying amounts of several phytochemicals, making their pharmacological and toxicological evaluation unique and difficult.
- More than 20 alkaloids in kratom have been identified in the laboratory.
- Mitragynine is classified as a kappa-opioid receptor agonist and is roughly 13 times more potent than morphine.**
- Mitragynine/OH-mitragynine thought to be responsible for the opioid-like effects.



Source: Cinosi E.; Martinotti; et al. Following "the Roots" of Kratom (*Mitragyna speciosa*): The Evolution of an Enhancer from a Traditional Use to Increase Work and Productivity in Southeast Asia to a Recreational Psychoactive Drug in Western Countries; Biomed Res Int. 2015; 2015: 968786

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

49

49

## Kratom

Also known as biak-biak, ketum, kakuum, thang, thom

- Mitragyna speciosa*



Mitragynine



7- hydroxymitragynine

- Uses
  - Opioid/heroin withdrawal
  - Chronic pain
  - Depression/anxiety



Rech MA et al. Pharmacotherapy. 2015;35(2):189-97.  
 Pantano F et al. Int J Mol Sci. 2016;17(4):580.  
 Available at:  
[https://farm4.staticflickr.com/3903/32946904495\\_c77444a965\\_b.jpg](https://farm4.staticflickr.com/3903/32946904495_c77444a965_b.jpg) Accessed 2 Mar 2018.

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

50

50

## Kratom Pharmacology

Mitragynine

Structurally similar to some  
hallucinogens

No hallucinogenic activity or effects

Acts on opioid receptors

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

51

51



8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

52

52



8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

53

53

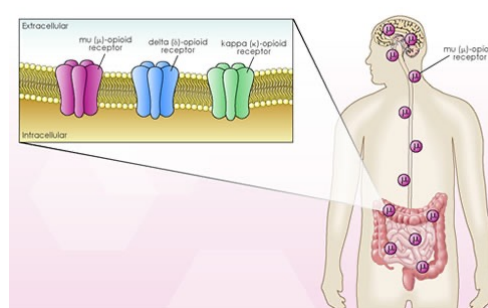
## Pharmacologic Properties of Kratom

- Partial mu receptor agonist
- Delta receptor agonist
- Kappa receptor agonist

Analgesia

Sedation

Euphoria



Stimulant Properties

Pantano F et al. Int J Mol Sci. 2016;17(4):580.  
 White CM. Am J Health Syst Pharm. 2018;75(5):261-67.  
 Opioid Analgesics. The Opioid Receptors. Available at:  
<http://opioidanalgesics.blogspot.com/2011/03/opioid-receptors.html>. Accessed 1 Mar 2018.

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

54

54



# Kratom

Seems to be a stimulant in lower doses

- Mitragynine

Seems to be sedative in higher doses

- 7 hydroxymitragynine

Often produces a mixed effect

Onset 5 t o 10 minutes

Duration several hours

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

55

55



8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

56

56



# Kratom: How Used

Capsules

Pills

Extract

Leaves

- Chewed
- Brewed as tea
- Smoked

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

57

57

## Kratom: Effects

The effects of kratom in humans are dose-dependent:

- Small doses produce stimulatory effects resembling the stimulant effect of drugs such as cocaine or amphetamines.
- Larger dosages associated with sedative-narcotic, pain reducing effects that resemble drugs such as opiates.
- Regular kratom use is associated with addictive disorders, as evidenced by craving and compulsive use. Opioid withdrawal symptoms upon cessation.



**SOURCE:** Prozialeck W. C., Jivan J. K., Andurkar S. V. Pharmacology of Kratom: an emerging botanical agent with stimulant, analgesic and opioid-like effects. Journal of the American Osteopathic Association. 2012;112(12):792-799; Singh, 2014; Suwanlert, 1975; Ahmad and Aziz, 2012; Vicknasingam et al., 2010; Singh et al., 2014

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

58

58

- It's only been studied in-depth in animals. However, based on the research conducted thus far, it's believed that the primary alkaloid found in kratom, mitragynine, has a half-life of around 23 hours.
- When someone takes kratom, the effects usually begin around 10 to 15 minutes later.
- A dosage of four to five grams generally leads to somewhat potent effects that last for about two hours, while seven to eight grams lead to longer effects.
- The peak effects of using kratom are believed to be around 1.5 to 2.5 hours after someone takes it.

## Half-Life of Kratom

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

59

59

## Kratom Oil

- Kratom is a tree-like plant in the same botanical family as the coffee tree and gardenia (Rubiaceae), native to Southeast Asia.
- Kratom has been used for centuries in Thailand, Malaysia, and Indonesia to combat fatigue and, empirically, to treat pain and opioid withdrawal symptoms.
- Effects are reported to be dose-dependent. Doses of 1-5 g have a stimulant effect and increase energy. Moderate to high doses (5-15 g) have opioid-like effects, including euphoria. Doses > 15 g can cause extreme sedation and stupor, similar to opioids.



8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

60

60

# Kratom

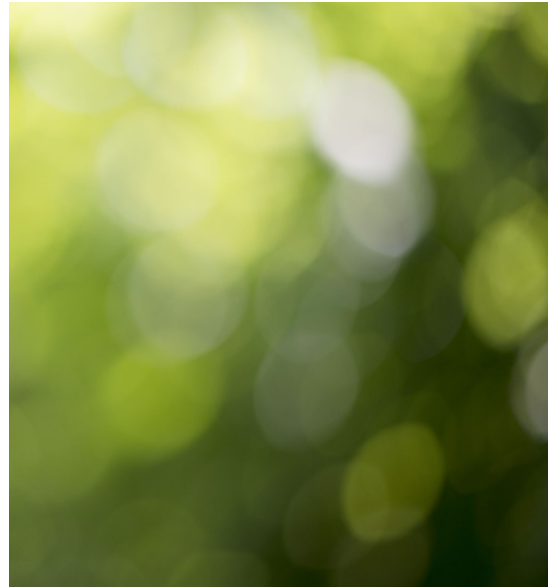
Kratom is currently legal in most states.

Acute adverse effects include

- anxiety                      - sedation                      -itching
- irritability                - nausea
- aggression               - constipation

Common presentations of overdose include palpitations and seizures.

Withdrawal symptoms include myalgia, insomnia, fatigue, and chest discomfort.



8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

61

61

## Kratom Side Effects

### Short term (immediate)

- Dry mouth
- Increased or decrease urination
- Loss of appetite
- Nausea and/or vomiting

### Side effects

- Anorexia/weight loss
- Depression
- Addiction

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

62

62



•Kratom is often described as producing simultaneous, contradictory effects- both an opiate-like sedation and coca-like stimulation. The stimulating effects tend to predominate at low dose levels, which may cause alertness, energy, and mild euphoria. Higher level doses are usually more tranquilizing, causing an opiate-like dreamy effect. Excessive doses can cause severe nausea. As with opium, it is known for causing constipation, and is sometimes used as a treatment for diarrhea.

#### Onset

•When taken orally, the effects of kratom usually become noticeable in 15-20 minutes and clearly apparent in 30-60 minutes. Strong doses tend to have a more quicker, more dramatic onset.

#### Duration

•A moderate dose of kratom may cause strong effects that last 2-4 hours, with residual effects lasting hours longer.

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

63

63

# Krat



•Some visual effects have been reported, including both open-eye and closed-eye effects. Effects reported include wavering, shifting, and strobing in the visual field. There was also some patterning with eyes closed, as well as increased closed-eye visualizations.

#### PROBLEMS

•Kratom is not known to be toxic, but can cause unpleasant symptoms at high doses such as nausea and vomiting. Regular use can lead to physical dependency. Kratom use can cause constipation similar to that caused by opiates. Chronic heavy use is reported to cause darkening of skin, insomnia, dry mouth, and anorexia.

#### Addiction Potential

•There are reports of physical dependency after frequent, heavy kratom use. Individuals who use it regularly or in large doses may have trouble quitting. Withdrawal symptoms include irritability, yawning, diarrhea, runny nose, and pain in the joints or muscles.

•<http://www.bing.com/videos/search?q=You+Tube+Kratom&view=detail&mid=EC48A0AFEDFBEA20762AEC48A0AFEDFBEA20762A&first=0&FORM=LKVR16>

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

64

64

## Kratom Online Ad

<http://www.ethnobotanicals.com/Kratom.html>

- **Kratom Super Powder**

If you want the best of the best, as only the first Kratom supplier in the world can deliver, our Super Powder Kratom is of unrivalled potency. No need to shop around for blue light specials on garbage quality "kratom." We can guarantee that our Super Powder Kratom is the highest quality Kratom you can find anywhere! And at a great price. This powdered *Mitragyna speciosa* leaf is high alkaloid like the previous product but has it's own unique mix of alkaloids. It is superior to the young, cultivated leaf material which copycat sellers have tried to sell, and of course to the altogether fake "kratom" which other copycats have tried to offer. Our Kratom Super Powders are very, very fine powder, not crushed with stem bits as found elsewhere. Always in stock and ships to you TODAY! (M-F)  
You will love this material for your research!

25 grams / \$35.95  
50 grams; \$69.95  
100 grams / \$134.95

Ships SAME-DAY if ordered by 3 PM central!



Product not available to Australia, Denmark, Finland, Malaysia, Myanmar, New Zealand, Norway, Romania, Thailand.

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

65

65

## Management of Toxicity

ABCs

Gastric decontamination

Naloxone for respiratory depression

Antidotes for co-ingestions

Supportive care

- Antiemetics
- Antihistamines
- Bowel regimen

Rech MA et al. *Pharmacotherapy*. 2015;35(2):189-97.  
Pantano F et al. *Int J Mol Sci*. 2016;17(4):580.  
White CM. *Am J Health Syst Pharm*. 2018;75(5):261-67.

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

66

66

## Kratom & E-Cigarettes

- **Kratomite**

Adventure Industries' Kratomite is the world's first electronic cigarette to deliver Kratom, a medicinal herb known for its concentration of alkaloids, according to the company. Kratom interacts with opioid receptors, which may offer users relaxing sensations. Unlike tobacco-alternative electronic cigarettes, Kratomite is a personal vaporizer that uses a proprietary, herbal-infused formula, said the maker.

**Adventure Industries**

Pembroke Park, Fla.

(800) 999-2483, ext. 1287

[sales@adventureindustries.com](mailto:sales@adventureindustries.com)



8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

67

67

## No “Typical” Clinical Presentation

- Low-moderate usage: 1-5 grams/day
  - Users report some stimulant and mild opioid-like effects
- Heavy usage: greater than 5 grams/day
  - 10-15 grams/day- more severe opioid-like effects seen
- Neurologic effects more common in laced batches or when combined with co-ingestions  
i.e. “Krypton,” “4x100”

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

### Opioid-Induced Side Effects

- |  |   |
|--|---|
| <ul style="list-style-type: none"> <li>• Common side effects               <ul style="list-style-type: none"> <li>– Constipation</li> <li>– Nausea</li> <li>– Sedation</li> <li>– Confusion</li> <li>– Hallucination</li> <li>– Sweats</li> <li>– Dry mouth</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>• Uncommon side effects               <ul style="list-style-type: none"> <li>– Urinary retention</li> <li>– Pruritis</li> <li>– Delirium</li> <li>– Myoclonus</li> <li>– Hyperalgesia</li> <li>– Seizures</li> <li>– Respiratory depression</li> </ul> </li> </ul> |
|--|---|

Pantano F et al. Int J Mol Sci. 2016;17(4):580.  
 White CM. Am J Health Syst Pharm. 2018;75(5):261-67.  
 Levy MH. Management of Opioid-Induced Side Effects. Available at:  
<https://www.medscape.org/viewarticle/573016>. Accessed 2 Mar 2018.

68

# Kratom & Opioid Treatment

Currently used for heroin and methadone dependence in some countries

- New Zealand
- Thailand

Used in detox to manage withdrawal symptoms from opioids

Millenium Labs announced test Aug. 2012

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

69

69

## Kratom & Opioid Treatment

- [www.bluelight.ru](http://www.bluelight.ru)
  - Forum with much Kratom info
  - Participants using Kratom to wean off of oxy, heroin, Bup, etc.
  - Majority unable to wean off of Kratom
  - Descriptions of withdrawal
  - Descriptions of how to prepare & dosage
  - Descriptions of which to buy and where

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

8/26/21

70

70

## Kratom Timeline

1996-1997: Rat studies show kratom's pain and gastric motility inhibition properties and its reversal by naloxone

2016: DEA announces plans to make mitragynine a Schedule I substance but received extensive backlash during a comment period

2017: Vermont, Wisconsin, Indiana, Arkansas, Tennessee, Alabama ban its use. Arizona and Massachusetts have pending legislation

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

Yusoff NHM et al. Behav Brain Res 2017;332:1-6.  
Gottlieb S. FDA Statement 2017 Nov 14.

71

71

## Kratom Timeline

Feb 2018:

- FDA analysis concludes that kratom contains the same chemicals found in opioids
- Multistate outbreak of Salmonella infection linked to kratom consumption
- FDA oversees recall and destruction of kratom products
- DEA declares kratom an opioid like drug. It is classified as a Drug and Chemical of Concern

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

Gottlieb S. FDA Statement 2017 Nov 14.  
FDA News Release. 21 Feb 2018.

72

72



## Use of Kratom in the US

- An anonymous online survey was conducted in October 2016 of 10,000 current kratom users through available social media and from the American Kratom Association (<https://speciosa.org/home/>)
- 8,049 respondents completed the survey.
- Findings:
  - Kratom was primarily used by a middle-aged (31-50 years) males (56.91%) with income \$35,000 or higher with private insurance (61.31%).
  - Kratom was used to self-treat pain (68%) and emotional or mental conditions (66%) and for withdrawal symptoms associated with prescription opioid use.
  - Subjects reported dose-dependent nausea and constipation with high doses (5g) and with and frequent dosing (Q22 doses/wk).

SOURCE: Grundmann O. Patterns of kratom use and health impact in the US: results from an online survey. Drug Alcohol Depend. 2017; 175(5):63Y70.

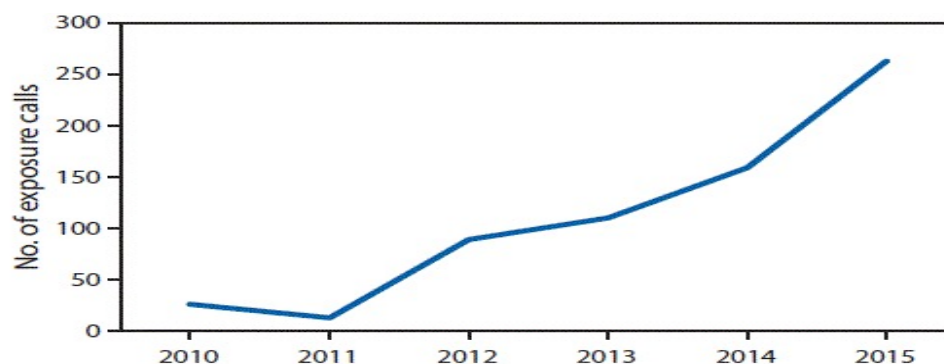
8/26/21

73

73

## Number of Kratom-related Reported Exposure Calls to Poison Centers in the US

National Poison Data System - United States and Puerto Rico January 2010–December 2015



SOURCE: Anwar M, Law R, Schier J. Notes from the Field. Kratom (*Mitragyna speciosa*) Exposures Reported to Poison Centers — United States, 2010–2015. MMWR Morb Mortal Wkly Rep 2016;65:748–749. DOI: <http://dx.doi.org/10.15585/mmwr.mm6529a4>  
Dr. Merrill Norton Pharm.D., D.Ph., CMAC

8/26/21

74

74

## Fatal Overdoses Involving Kratom

From July 2016 to June 2017, 25 fatal overdoses involving kratom across 8 CDC SUDORS states were identified

States	ME	NH	NM	OH	PA	RI	WV	WI	Total
Opioid overdose deaths	301	402	322	4,534	3,231	265	844	825	10,724
Deaths involving kratom	4	2	1	3	8	1	5	1	25
Percent involving kratom	1.3%	0.5%	0.3%	0.07%	0.25%	0.4%	0.6%	0.1%	0.23%

Caution: testing of kratom is not uniform thus these numbers are underestimates

Source: CDC SUDORS Overdose Death Data

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

75

In 2017, the Food and Drug Administration (FDA) began issuing a series of warnings about kratom and has now identified at least 44 deaths related to its use.

Most kratom associated deaths appeared to have resulted from adulterated products or taking kratom along with other potent substances.

75

## Kratom Concerns

- Kratom has gained popularity for its euphoric effects and is being popularized as a safe herbal product capable of giving a "legal" high (Swogger *et al.*, 2015), and as an alternative to other sedative and stimulant type drugs (Warner *et al.*, 2016).
- Reports of physical dependence on kratom in Western nations emerge from case reports from the UK (Boyer *et al.*, 2008, McWhirter and Morris, 2010), Germany (Kapp *et al.*, 2011) and the US (Dorman *et al.*, 2014, Nelsen *et al.*, 2010, Forrester, 2013, Sheleg and Collins, 2011).
- It can be surmised that given the large and growing number of internet purchase sites for kratom (cited in Cinosi *et al.*, 2015), addiction to kratom is also likely to be growing in the Western countries.
- No treatment specific for kratom addiction available
- One case of NAS in an infant whose mother was a kratom user and who responded to opioid treatment.

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

8/26/21

76

76

## International Status of Kratom

### Kratom is restricted or illegal in:

Australia	Lithuania	Romania
Denmark	Myanmar	South Korea
Finland	Malaysia	Sweden
Israel	Poland	Thailand
United Kingdom		

Scheduling under consideration in U.S.

On November 14, 2017, the FDA issued a public health advisory related to mounting concerns regarding the risks associated with kratom and reported deaths with use.

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

77

77

## Legality of Kratom in Georgia

- Kratom is legal. There was a bill to ban it; however, it did not pass; Georgia was the third state to pass the Kratom Consumer Protection Act;
- Kratom Consumer Protection Act:
- The act concerns itself with appropriate packaging, standards for recommended dosages, and age (18) allowing for possession and purchase;
- Removed from the Dangerous Drug List;
- Continued Efforts to change legal status are underway.

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

78

78

## Drug Testing for Kratom

- Quantitatively detects presence of Kratom (Mitragynine), an emerging drug of abuse, sold online and at "head shops" nationwide
- Redwood Labs has Advanced liquid chromatography - tandem mass spectrometry (LC-MS/MS) equipment provides definitive test results
- Labcorp Kratom screening analysis includes: mitragynine and 7-hydroxy-mitragynine at a threshold of 1.0 ng/mL.
- This test was developed and its performance characteristics determined by LabCorp. It has not been cleared or approved by the Food and Drug Administration.
- Premier Biotech is introducing the Premier Bio-Dip kratom drug screen, the first rapid urine test on the market to detect the key active compound Mitragynine at 150 ng/mL

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

8/26/21

79

79

- One of the biggest reasons that many people decide to use kratom, especially as opposed to other opioids and substances, is that they believe it won't show up on drug tests.
- Kratom doesn't show up on many standard drug tests like the SAMHSA-5, but some kratom alkaloids can be detectable on certain drug tests, such as urine or blood tests.
- Because blood tests provide a shorter detection window for substances and are more invasive, it's more likely that a urine test would be conducted.
- There is a specific kratom drug test called the kratom 10-panel drug test that can be given as well.

## Drug Testing of Kratom

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

80

80

# Kratom and Drug Testing

Some kratom alkaloids may show up in drug tests specific to kratom testing.

A blood test can show blood concentration levels of kratom and it is easily detectable in the blood.

Hair testing has not shown any evidence of reliability.

A saliva test could identify certain metabolites of kratom.

Meireles V, Rosado T, Barroso M, et al. *Mitragyna speciosa*: Clinical, Toxicological Aspects and Analysis in Biological and Non-Biological Samples. *Medicines (Basel)*. 2019;6(1):35. Published 2019 Mar 4. doi:10.3390/medicines6010035

8/26/21

81

81

## Drug Testing Kratom (Advertisement)

- Introducing the Premier Bio-Dip kratom drug screen, the first rapid urine test on the market to detect the key active compound Mitragynine at 150 ng/mL.
- **Kratom (Mitragynine) Single-Dip**
  - Detects mitragynine in human urine at a cutoff level of 150 ng/mL, the lowest on the market!
  - 100% sensitive to both active compounds in the leaves: mitragynine and 7-OH-mitragynine
  - Hermetically sealed and flood proof, even while submerged in the sample
  - Easy to use and interpret with 60 minute result stability
  - Negative results as soon as lines appear which is usually within 1 minute after test initiation

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

82

82

## Conclusions

- Kratom is a recognized emerging public health threat (*MMWR. July 29, 2016;65(29):748Y749*)
- People need to understand that “legal” and “available” are not the same as “safe.”
- In the West, kratom has been valued for its analgesic effects and to aid in managing opioid withdrawal. However, some of these individual attempts have resulted in cases of toxicity and fatalities.
- Physicians should be aware of these herbal supplements and potential toxicity or withdrawal effects in patients including in newborns which cannot be picked up by the standard toxicology screen (*Davidson et al, 2018*).
- Preventionists should be aware of this drug and work with their communities raising awareness, providing education about effects and risks.

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

8/26/21

83

83

## Tianeptine

- Sold under names such as Stablon, Tatinol, Tianaa, or Coaxil
- Not FDA approved



84



**Availability in the U.S.**

- Online – many websites
- Not regulated by the FDA

85

Dr. Merrill Norton Pharm.D., D.Ph., CMAc

**What is Tianeptine ?**

- Tianeptine was discovered and patented by the French Society of Medical Research in the 1960s.
- Currently, tianeptine is approved in France and manufactured and marketed by Laboratories Servier SA; it is also marketed in a number of other European countries under the trade name Coaxil as well as in Asia (including Singapore) and Latin America as Stablon and Tatinol
- It is not available in Australia, Canada, New Zealand, the United Kingdom, or the United States

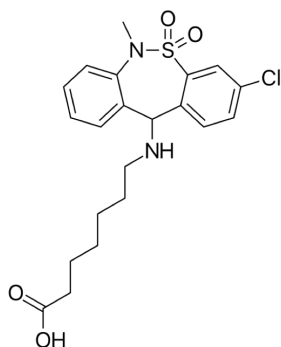
86

## Approval by country

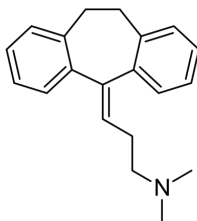
- **Approved for treatment of anxiety and depression: a few countries in Europe, Asia, and Latin America**
- **Not approved by FDA in U.S.**
  - **Classified as a controlled substance: Michigan**
- **Withdrawn from market: Georgia**
- **Classified as controlled substance: Russia, Armenia, Ukraine**

87

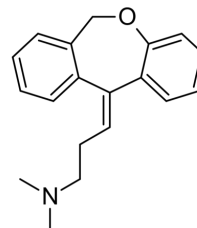
## Tianeptine is a Tricyclic Antidepressant???



Tianeptine



Amitriptyline



Doxepin

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

88

88



## How Does Tianeptine Work?

Tianeptine is prescribed for the treatment of depression and anxiety, which makes sense since it has a similar tricyclic backbone to other well-known antidepressants. But there was something weird about this antidepressant, it didn't seem to work like the others.

What was different? For one, it seemed to work *a lot* faster than most antidepressants. Patients reported improved symptoms within days instead of weeks. Another big difference is that it didn't seem to work by blocking monoamine reuptake transporters. So, no SSRI or SNRI effects. But patients liked it nonetheless. It seemed to help with depression, reduced anxiety, improved PTSD symptoms, and relieved irritable bowel symptoms.

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

89

89

## How Does Tianeptine Work?

Scientists were perplexed as to how this drug worked. There was some evidence that it affected glutamate neurotransmission, and some that it worked on adenosine receptors.

Or, maybe it worked through dopamine or by doing the opposite of SSRIs – enhancing the reuptake of serotonin? Nobody really seemed to know why this drug had antidepressant effects.

Then in 2014, researchers looking for the mechanism of the drug's action screened it for binding and activity at a variety of different receptors. What they found was that tianeptine was a mu agonist; an effect that might actually be behind its antidepressant effect.

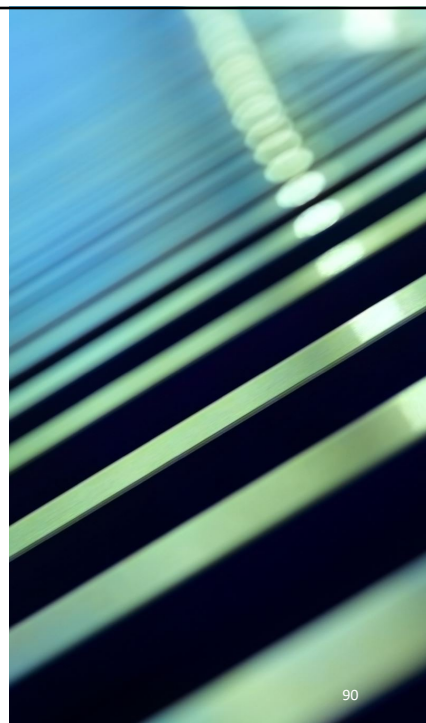
That's right, tianeptine worked as an agonist at the same receptor in the brain as heroin, fentanyl, and oxycodone. No wonder patients liked it.

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

90

90



# What's the Problem With Tianeptine?

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

91

91

## History and Background of Tianeptine

- Tianeptine abuse and dependence has become a cause for concern in approved markets with recent emergence in the United States.
- Psychiatrists should be aware of a potentially fatal opiate-like withdrawal in the absence of positive urine drug screens or cases where withdrawal does not follow expected patterns.
- Tianeptine users should be educated regarding risk associated with this drug.
- Without further intervention, additional cases should be anticipated.
- Lauhan R, Hsu A, Alam A, Beizai K. Tianeptine Abuse and Dependence: Case Report and Literature Review. Psychosomatics. 2018 Nov;59(6):547-553. doi: 10.1016/j.psych.2018.07.006. Epub 2018 Jul 19. PMID: 30149933.

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

92

92

## What's the Problem with Tianeptine?

While there had been a few reports of tianeptine abuse prior to 2014, it was after the publication that it was a mu agonist that cases really started to mount; yes drug dealers read the scientific literature.

In 2016, a 27-yo-male overdosed on tianeptine with predictable mu opioid effects: small pupils, slow respirations, and coma ([AJRCCM 2016](#)).

Equally predictable, he woke up after 0.4 mg naloxone (he required another dose a few hours later). In 2017, a 36-year-old in Virginia injected tianeptine with similar results. I mentioned at the start that we have seen an increasing number of cases.

Tox & Hound. Tox and Hound – Not For Human Consumption. *EMCrit Blog*. Published on February 4, 2019. Accessed on June 3rd 2021. Available at [<https://emcrit.org/toxhound/not-for-human-consumption/>].

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

93

93

## What's the Problem with Tianeptine?

All of these were similar to the case reports. Patients using tianeptine as a drug of abuse present with a classic opioid toxidrome.

And my poison center is not alone. Since 2014 there has been a dramatic increase in calls to poison centers regarding tianeptine.<sup>8,9</sup>

Tianeptine abusers who abruptly stop can also develop a withdrawal syndrome similar to opioid abstiners.<sup>10</sup>

And, sadly, tianeptine abuse also seems to carry the same neonatal risks as opioids – there is a reported case of neonatal abstinence syndrome from tianeptine.<sup>11</sup>

Tox & Hound. Tox and Hound – Not For Human Consumption. *EMCrit Blog*. Published on February 4, 2019. Accessed on June 3rd 2021. Available at [<https://emcrit.org/toxhound/not-for-human-consumption/>].

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

94

94



## What's the Problem with Tianeptine?

What about the other TCA effects? Do patients who overdose on this get a prolonged QRS and QTc, do they seize, do they get anticholinergic?

Those are great questions. I am so glad you asked.

The short answer is NO, this has not been reported. Although it shares a TCA structure, this drug appears not to have the sodium channel blocking effects (wide QRS), potassium channel blocking effects (prolonged QTc), anticholinergic effects, or proconvulsant effects.

*It should be said with caution*, however, that there are very few cases of overdose in the literature to date. It is possible that these effects could occur in larger doses.

Tox & Hound. Tox and Hound – Not For Human Consumption. *EMCrit Blog*. Published on February 4, 2019. Accessed on June 3rd 2021. Available at [<https://emcrit.org/toxhound/not-for-human-consumption/>].

8/26/21

Dr. Merrill Norton Pharm.D., D.Ph., CMAQ

95

95

## Toxicity

An overdose of tianeptine can lead to opioid-like effects and lead to respiratory failure and death, due to its direct effect on the *mu* opioid receptor.

In addition, cardiotoxicity can result from an overdose of this medication.

Over 1000 drug to drug interactions;

Exercise caution with grapefruit products. Grapefruit inhibits CYP3A4 metabolism, which may increase the serum concentration of tianeptine.

Exercise caution with St. John's Wort. This herb induces CYP3A metabolism, which may reduce serum levels of tianeptine.

<https://go.drugbank.com/drugs/DB09289>

8/26/21

Dr. Merrill Norton Pharm.D., D.Ph., CMAQ

96

96

## Treatment Aspects of Tianeptine

Tianeptine Intoxication

Tianeptine Withdrawal

Tianeptine Detoxification

Tianeptine Overdose

Tianeptine Addiction

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

97

97

## Tianeptine Intoxication

Nausea

Vomiting

Diarrhea

Tachycardia

Hypertension

Mydriasis or  
miosis

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

98

98



## Treatment Aspects of Tianeptine

Tianeptine Intoxication

Tianeptine Withdrawal

Tianeptine Detoxification

Tianeptine Overdose

Tianeptine Addiction

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

99

99

## Tianeptine Intoxication Management

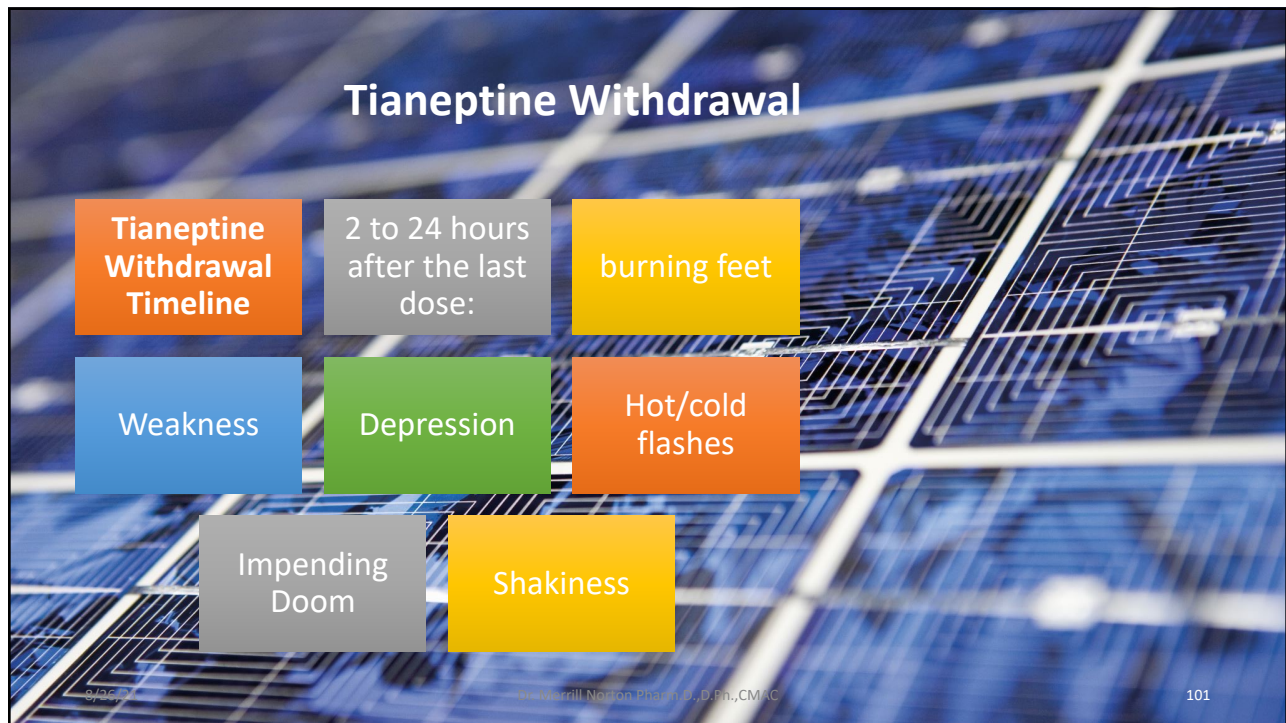
- Airway management
  - [Intubation](#) if necessary
- Oxygen for hypoxia
- [Naloxone](#) has been successfully used to treat at least one case in the literature but data is limited<sup>[3]</sup>
- [Benzodiazepines](#) for agitation
- Depends on severity of toxicity
  - Admit to floor vs ICU

8/26/21

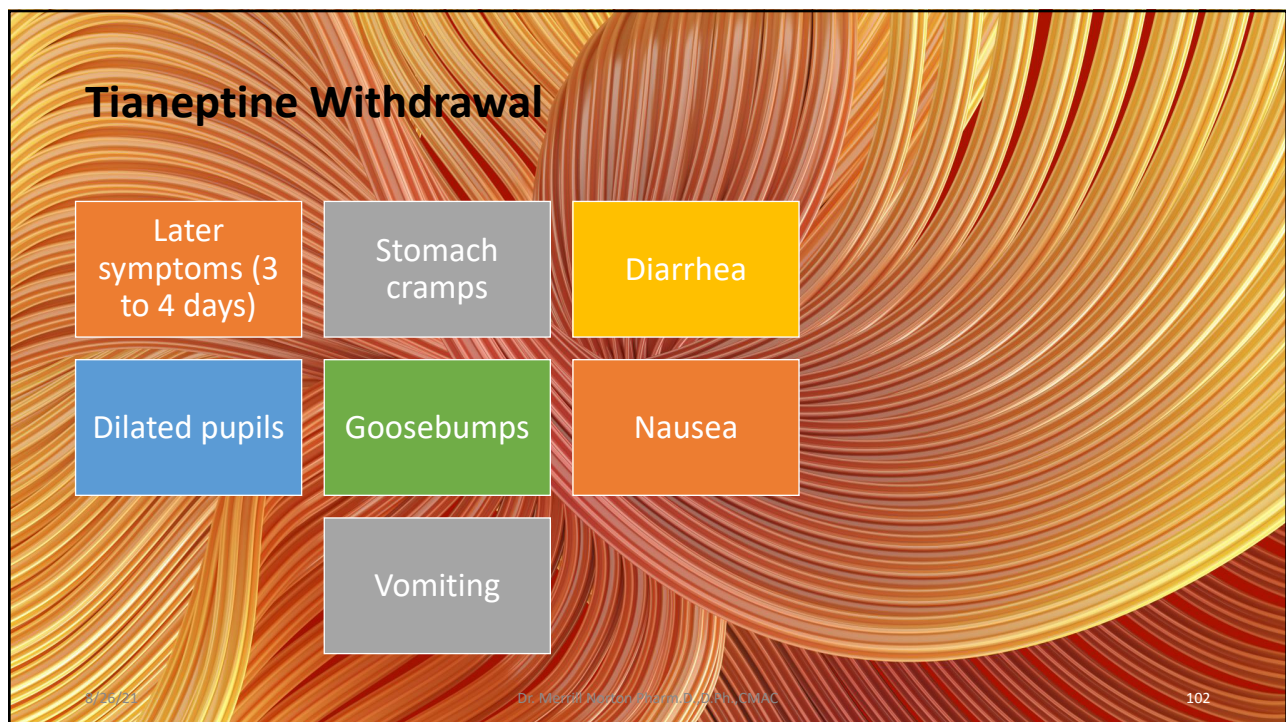
Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

100

100



101



102

## Tianeptine Detoxification

Many doctors will not give opioid medications for withdrawal from tianeptine due to being unfamiliar with the drug and possible drug interactions.

Patients may be treated with only clonidine and Atarax, and either weaned off tianeptine or forced to quit cold turkey.

This will be frightening and painful, but it should be over in about a week.

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

103

103

## Tianeptine Detoxification

Buprenorphine is an opioid medication, primarily given as a treatment for heroin addiction.

Initial treatment will begin with buprenorphine alone which is called Subutex.

It will be given gradually to avoid rapid opioid withdrawal. You will then be stabilized on a dose then weaned off.

Or, the patient will be given continued treatment with a combination of buprenorphine and naloxone.

Naloxone is an opioid antagonist that is used to prevent people from injecting the buprenorphine to get high.

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

104

104



# Tianeptine Overdose

- Tianeptine overdose fatalities are associated with serum concentrations ranging from 4,000 to 18,000 ng/mL.
- Tianeptine dependence and a withdrawal syndrome of anxiety, sweating, myalgias, chills, and depression have been described.
- Mixing opioids and tianeptine can cause extreme confusion, difficulty maintaining consciousness, slowed breathing, and oxygen deprivation.
- Because tianeptine is similar to opioids in the way it affects the brain, it could potentially potentiate the effects of alcohol. If the two drugs are taken together, they could suppress your nervous system to a dangerous degree.
- Alcohol doesn't act on opioid receptors, but it does work on a chemical in the brain that's designed to control excitability in the nervous system called gamma-Aminobutyric acid (GABA). This slows the CNS down.

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

105

105

# Tianeptine Overdose Symptoms

- The experience concerning cases of acute tianeptine intoxication (maximum quantity: 2250 mg, ingested in a single dose) primarily reveals alertness disorders which can lead to coma, especially in case of multiple intoxications.
- Tianeptine has no known specific antidote. In case of acute intoxication, a symptomatic treatment and routine monitoring must be started. Medical monitoring in a specialized setting is recommended.

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

106

106

# Tianeptine Overdose

- Treatment  
In all cases stop treatment and monitor the patient closely.
- - Gastric lavage
- - Cardiac-respiratory, metabolic and renal monitoring
  - Symptomatic treatment of any clinical manifestations, especially assisted
- ventilation and correction of metabolic and renal disorders

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

107

107

# Tianeptine Treatment

**Tianeptine withdrawal produces effects at the same organ systems and may mimic opioid withdrawal.**

**Common symptoms include agitation, hypertension, tachycardia, diaphoresis and tremors.**

**Tianeptine withdrawal is treated supportively with intravenous benzodiazepines and fluids.**

**More recently, buprenorphine/naloxone has been used as an adjunctive therapy in this setting.**

- Trowbridge, Paul, MD, MPH, Walley, Alexander, MD, MSc. Use of Buprenorphine-Naloxone in the Treatment of Tianeptine Use Disorder. J Addict Med. 2019;13(4):331-333.  
doi:10.1097/ADM.0000000000000490.

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

108

108

## Other Gas Station Drugs

<b>Imodium (Loperamide):</b> Overdose deaths reported.	<b>Dextromethorphan (DMX):</b> DXM abuse is responsible for some 6,000 emergency room visits each year, almost half of which are among patients between the ages of 12 and 25.
<b>Caffeine Pills:</b> one tablespoon of caffeine power, or 10,000 milligrams, can be fatal for an adult. Even in lower doses it can cause dehydration, panic attacks, and heart irregularities.	<b>Herbal Diet Pills:</b> substance use disorders common.
<b>Laxatives:</b> eating disorders used to control weight.	<b>Benadryl (diphenhydramine):</b> can put people in a lucid, dreamy state when taken in high doses.

8/26/21 Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC 109

109

## Imodium (loperamide)

- What is it? - Over the counter anti-diarrheal medication (peripherally acting mu-opioid agonist; synthetic opiate)
- Typical daily dose: 8-16 mg per day
- At 70+ mg, users experience saturation of the P-glycoproteins that usually keep the drug from breaching the blood brain barrier, and opioid-like effects occur
- Side effects: QRS widening, QTc prolongation, syncope, sudden death, and ventricular dysrhythmias
- 91% increase in poison control center calls from 2010-2016

8/26/21 Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC 110

110

## Dextromethorphan

- What is it? – An active ingredient in many over the counter cough and cold medications
- At high doses (over 1500 mg/day) DXM blocks NMDA receptors and can induce psychological symptoms similar to PCP or ketamine such as delusions, hallucinations, and paranoia
- Side effects: hypertension and diaphoresis from inhibition of catecholamine uptake
- According to the Ontario Student Drug Use and Health Survey, 9.7% of students in grades 7 to 12 reported using dextromethorphan recreationally in 2013, compared with 6.9% in 2011
- While some states have begun to limit the quantity of DXM sold or restrict sales to individuals over 18-years of age, there is currently no federal ban or restriction on DXM

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

111

111

## Caffeine Pills

- 85% of the US population consumes at least 1 cup of coffee a day
- Caffeine pills available in gas stations typically have 100-200 mg of caffeine per serving
- Safe daily amount (non-pregnant): up to 400 mg
- However, caffeine tolerance and metabolism are highly individualized
- Side effects: energy crash 3-4 hours later, jitters, irritability, acid reflux, insomnia, dehydration, migraines, anxiety, heart palpitations, dependence, withdrawal

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

112

112

Coffee and Tea Drinks (Coffee Shops)	Serving Size	Caffeine (mg)	Over-the-Counter Pills and Supplements	Serving Size	Caffeine (mg)
Starbucks Coffee, Pike Place Roast	venti, 20 oz.	410	Hydroxycut Hardcore	2 capsules	270
Starbucks Coffee, Blonde Roast	grande, 16 oz.	360	Hydroxycut Platinum	2 capsules	200
Starbucks Coffee, Pike Place Roast	grande, 16 oz.	310	Jet-Alert Double Strength	1 caplet	200
Dunkin' Coffee	large, 20 oz.	270	NoDoz	1 caplet	200
Starbucks Coffee, Dark Roast	grande, 16 oz.	260	Vivarin	1 tablet	200
Starbucks Caffè Americano	grande, 16 oz.	225	Zantrex Red	2 capsules	200
Dunkin' Coffee	medium, 14 oz.	210	Excedrin Migraine	2 caplets or geltabs	130
Starbucks Caffè Mocha—hot or iced	grande, 16 oz.	175	Excedrin Tension Headache	2 caplets	130
Dunkin'—Latte or Cappuccino	medium, 14 oz.	166	Pamprin Max Pain + Energy	2 caplets	130
Starbucks Espresso	doppio, 1.5 oz.	150	Blowfish for Hangovers	2 tablets	120
Starbucks—Caffè Latte or Cappuccino	grande, 16 oz.	150	Midol Complete	2 caplets	120
Starbucks Chai Latte—hot or iced	grande, 16 oz.	95	Jet-Alert Regular Strength	1 tablet	100
Starbucks Coffee Frappuccino	grande, 16 oz.	95	Bayer Back & Body Extra Strength	2 caplets	65
Starbucks Matcha Green Tea Latte—hot or iced	grande, 16 oz.	80			
Starbucks Decaf Coffee, Pike Place Roast	grande, 16 oz.	25			

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

113

113

11  
4

8/26/21

# Herbal Diet Pills

- **Natural does not mean safe**
- **Companies often make exaggerated claims such as “lose 30 pounds in 30 days”**
- **Companies that make supplements are responsible for the safety of their products. They must ensure that their products are free of contaminants and that they're accurately labeled.**
- **Dietary supplements don't require approval by the U.S. Food and Drug Administration (FDA). But if a supplement is found to be unsafe, the FDA can issue warnings or ask that it be withdrawn from the market**
- **Side effects can occur from added ingredients not included in the label. These might include: anxiety, increased heart rate or blood pressure, addiction, long-term metabolism problems**

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

114

11  
5

8/26/21

## Herbal Diet Pills

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

- **Example: Belviq**
- When the FDA first approved Belviq in 2012, the results looked promising. The bar for the FDA to approve weight-loss drugs is high, and this one seemed to meet all the requirements.
- People did, in fact, lose weight using this drug, which targeted serotonin receptors in the brain that made a person feel full after eating. This sounded like a win, and it may be tempting for people to try it even today.
- However, this drug must be avoided. Side effects include dizziness, lack of energy, nausea, constipation, and dry mouth. Its effects on people with diabetes are especially adverse.
- Things started looking really bad for Belviq when it was suspected of causing tumor growth in animals. Over the years, it became linked to an increased risk of cancer, especially lung, pancreatic, and colorectal.
- The drug was voluntarily recalled in 2020. It may be tempting to try because there are some results, but this dangerous tablet is not worth the risk. There are better options out there.

115

## Laxatives

- **What are they?** - medications in this category are used to counteract difficulties in having bowel movements
- **Largest group of people that abuses laxative:** people with eating disorders such as anorexia or bulimia nervosa
- **Another group that abuses laxatives:** athletes that compete in sports that require certain weight limits (i.e. wrestling)
- Abuse can lead to electrolyte and acid/base imbalances
- The renin-aldosterone system becomes activated due to the loss of fluid, which leads to edema and acute weight gain when the laxative is discontinued. This can result in reinforcing further laxative abuse when a patient feels bloated and has gained weight.

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

116

116

## Laxatives

- Overall, the lifetime occurrence of laxative abuse has been reported to be 4.18% in the general population.[19] However, the authors reported that the rates are substantially higher in people who suffer from an eating disorder.
- The lifetime occurrence among individuals with bulimia nervosa was 14.94%, greater than a 3-fold increase over the prevalence in the general population.
- Other studies have reported that laxative abuse among patients with bulimia nervosa range from 18% to 75%.[20–22]
- In a consecutive series of 100 patients with bulimia nervosa, Mitchell et al.[23] reported finding that 36% had abused laxatives for weight control purposes during the month prior to evaluation.
- More recently, Steffen et al.[24] reported that laxatives had been used at some point to control weight or “get rid of food” by 67% of 39 eating disorder patients surveyed. Of these, 31% reported abuse of laxatives during the month prior to evaluation.

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

117

117

## Benadryl (diphenhydramine )

- What is it? – Benadryl is an over-the-counter antihistamine allergy medication
- At high doses, this medication can cause serious heart problems, seizures, coma, or death
- The “Benadryl Challenge” surfaced on the popular video platform TikTok last year – young people were encouraged to take excessive amounts of Benadryl to induce hallucinations
- The FDA released a statement in September 2020 warning parents about the trend

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

118

118

## Poppers

- What are they? – Alkyl nitrites, most common being amyl nitrite
  - They used to be sold in glass vials and made a popping sound when crushed
- When inhaled, they cause vasodilation and a slight euphoric effect
- Commonly used in the homosexual community and in the club scene
- Users typically use poppers before sex to relax them and prepare them for sex
- Because of their fruity aroma, they're often sold as air fresheners, but they're also sold as leather cleaner, headphone cleaner, or nail polish remover
- Often used in combination with other drugs
- Side effects: rapid blood pressure lowering resulting in syncope, tachycardia, skin irritation around nose and mouth, headaches

8/26/21 119

119

## References

1. Duman RS, Malberg J, Thome J. Neural plasticity to stress and antidepressant treatment. *Biol Psychiatry*. 1999;46:1181–1191. [[PubMed](#)] [[Google Scholar](#)]
2. Manji HK, Duman RS. Impairments of neuroplasticity and cellular resilience in severe mood disorders: implications for the development of novel therapeutics. *Psychopharmacol Bull*. 2001;35:5–49. [[PubMed](#)] [[Google Scholar](#)]
3. Pittenger C, Duman RS. Stress, depression, and neuroplasticity: a convergence of mechanisms. *Neuropsychopharmacology*. 2008;33:88–109. [[PubMed](#)] [[Google Scholar](#)]
4. Duman RS, Monteggia LM. A neurotrophic model for stress-related mood disorders. *Biol Psychiatry*. 2006;59:1116–1127. [[PubMed](#)] [[Google Scholar](#)]
5. Manji HK, Gottesman II, Gould TD. Signal transduction and genes-to-behaviors pathways in psychiatric diseases. *Sci STKE*. 2003;2003:e49. [[PubMed](#)] [[Google Scholar](#)]
6. Sheline YI. Neuroimaging studies of mood disorder effects on the brain. *Biol Psychiatry*. 2003;54:338–352. [[PubMed](#)] [[Google Scholar](#)]
7. Kasper S, McEwen BS. Neurobiological and clinical effects of the antidepressant tianeptine. *CNS Drugs*. 2008;22:15–26. [[PubMed](#)] [[Google Scholar](#)]
8. Svenningsson P, Bateup H, Qi H, Takamiya K, Huganir RL, Spedding M, Roth BL, McEwen BS, Greengard P. Involvement of AMPA receptor phosphorylation in antidepressant actions with special reference to tianeptine. *Eur J Neurosci*. 2007;26:3509–3517. [[PubMed](#)] [[Google Scholar](#)]

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

120

120



## References

- 9. Qi H, Mailliet F, Spedding M, Rocher C, Zhang X, Delagrèze P, McEwen B, Jay TM, Svenningsson P. Antidepressants reverse the attenuation of the neurotrophic MEK/MAPK cascade in frontal cortex by elevated platform stress; reversal of effects on LTP is associated with GluA1 phosphorylation. *Neuropharmacology*. 2008 [[PubMed](#)] [[Google Scholar](#)]
- 10. Bergink V, van Megen HJ, Westenberg HG. Glutamate and anxiety. *Eur Neuropsychopharmacol*. 2004;14:175–183. [[PubMed](#)] [[Google Scholar](#)]
- 11. Lowy MT, Wittenberg L, Yamamoto BK. Effect of acute stress on hippocampal glutamate levels and spectrin proteolysis in young and aged rats. *J Neurochem*. 1995;65:268–274. [[PubMed](#)] [[Google Scholar](#)]
- 12. Paul IA, Skolnick P. Glutamate and depression: clinical and preclinical studies. *Ann N Y Acad Sci*. 2003;1003:250–272. [[PubMed](#)] [[Google Scholar](#)]
- 13. Sanacora G, Rothman DL, Mason G, Krystal JH. Clinical studies implementing glutamate neurotransmission in mood disorders. *Ann N Y Acad Sci*. 2003;1003:292–308. [[PubMed](#)] [[Google Scholar](#)]
- 14. Skolnick P, Legutko B, Li X, Bymaster FP. Current perspectives on the development of non-biogenic amine-based antidepressants. *Pharmacol Res*. 2001;43:411–423. [[PubMed](#)] [[Google Scholar](#)]
- 15. Zarate CA, Jr, Du J, Quiroz J, Gray NA, Denicoff KD, Singh J, Charney DS, Manji HK. Regulation of cellular plasticity cascades in the pathophysiology and treatment of mood disorders: role of the glutamatergic system. *Ann N Y Acad Sci*. 2003;1003:273–291. [[PubMed](#)] [[Google Scholar](#)]
- 

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

121

121

## References

- 16. Curzon G, Kennett GA, Sarna GS, Whitton PS. The effects of tianeptine and other antidepressants on a rat model of depression. *Br J Psychiatry Suppl*. 1992;51–55. [[PubMed](#)] [[Google Scholar](#)]
- 17. Thiebot MH, Martin P, Puech AJ. Animal behavioural studies in the evaluation of antidepressant drugs. *Br J Psychiatry Suppl*. 1992;44–50. [[PubMed](#)] [[Google Scholar](#)]
- 18. Kelly JP, Leonard BE. The effect of tianeptine and sertraline in three animal models of depression. *Neuropharmacology*. 1994;33:1011–1016. [[PubMed](#)] [[Google Scholar](#)]
- 19. Wagstaff AJ, Ormrod D, Spencer CM. Tianeptine: a review of its use in depressive disorders. *CNS Drugs*. 2001;15:231–259. [[PubMed](#)] [[Google Scholar](#)]
- 20. McEwen BS, Olie JP. Neurobiology of mood, anxiety, and emotions as revealed by studies of a unique antidepressant: tianeptine. *Mol Psychiatry*. 2005;10:525–537. [[PubMed](#)] [[Google Scholar](#)]
- 21. McEwen BS, Magarinos AM, Reagan LP. Structural plasticity and tianeptine: cellular and molecular targets. *Eur Psychiatry*. 2002;17 (Suppl 3):318–330. [[PubMed](#)] [[Google Scholar](#)]
- 22. Costa e Silva JA, Ruschel SI, Caetano D, Rocha FL, da SL, Jr, Arruda S, Ozun M. Placebo-controlled study of tianeptine in major depressive episodes. *Neuropsychobiology*. 1997;35:24–29. [[PubMed](#)] [[Google Scholar](#)]
- 23. Loo H, Saiz-Ruiz J, Costa e Silva JACE, Ansseau M, Herrington R, Vaz-Serra A, Dilling H, De Risio S. Efficacy and safety of tianeptine in the treatment of depressive disorders in comparison with fluoxetine. *J Affect Disord*. 1999;56:109–118. [[PubMed](#)] [[Google Scholar](#)]
- 24. Lepine JP, Altamura C, Ansseau M, Gutierrez JL, Bitter I, Lader M, Waintraub L. Tianeptine and paroxetine in major depressive disorder, with a special focus on the anxious component in depression: an international, 6-week double-blind study dagger. *Hum Psychopharmacol*. 2001;16:219–227. [[PubMed](#)] [[Google Scholar](#)]

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

122

122

## References

- 25. Novotny V, Faltus F. Tianeptine and fluoxetine in major depression: a 6-week randomised double-blind study. *Hum Psychopharmacol.* 2002;17:299–303. [\[PubMed\]](#) [\[Google Scholar\]](#)
- 26. Szadoczky E, Furedi J. Efficacy and acceptability of tianeptine and sertraline in the acute treatment phase of depression. *Encephale.* 2002;28:343–349. [\[PubMed\]](#) [\[Google Scholar\]](#)
- 27. Waintraub L, Septien L, Azoulay P. Efficacy and safety of tianeptine in major depression: evidence from a 3-month controlled clinical trial versus paroxetine. *CNS Drugs.* 2002;16:65–75. [\[PubMed\]](#) [\[Google Scholar\]](#)
- 28. Nickel T, Sonntag A, Schill J, Zobel AW, Ackl N, Brunner A, Murck H, Ising M, Yassouridis A, Steiger A, Zihl J, Holsboer F. Clinical and neurobiological effects of tianeptine and paroxetine in major depression. *J Clin Psychopharmacol.* 2003;23:155–168. [\[PubMed\]](#) [\[Google Scholar\]](#)
- 29. Olie JP, Bayle F, Kasper S. A meta-analysis of randomized controlled trials of tianeptine versus SSRI in the short-term treatment of depression. *Encephale.* 2003;29:322–328. [\[PubMed\]](#) [\[Google Scholar\]](#)
- 30. Kasper S, Olie JP. A meta-analysis of randomized controlled trials of tianeptine versus SSRI in the short-term treatment of depression. *Eur Psychiatry.* 2002;17 (Suppl 3):331–340. [\[PubMed\]](#) [\[Google Scholar\]](#)
- 31. Novotny V, Faltus F. First signs of improvement with tianeptine in the treatment of depression: an analysis of a double-blind study versus fluoxetine. *Eur Neuropsychopharmacol.* 2003;13(suppl 4):S230. Ref Type: Abstract. [\[Google Scholar\]](#)
- 32. Loo H, Deniker P. Position of tianeptine among antidepressive chemotherapies. *Clin Neuropharmacol.* 1988;11 (Suppl 2):S97–102. [\[PubMed\]](#) [\[Google Scholar\]](#)

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

123

123

## References

- 33. Gueffi JD, Pichot P, Dreyfus JF. Efficacy of tianeptine in anxious-depressed patients: results of a controlled multicenter trial versus amitriptyline. *Neuropsychobiology.* 1989;22:41–48. [\[PubMed\]](#) [\[Google Scholar\]](#)
- 34. Invernizzi G, Aguglia E, Bertolino A, Casacchia M, Ciani N, Marchesi GF, Nardini M, Rapisarda V. The efficacy and safety of tianeptine in the treatment of depressive disorder: results of a controlled double-blind multicentre study vs. amitriptyline. *Neuropsychobiology.* 1994;30:85–93. [\[PubMed\]](#) [\[Google Scholar\]](#)
- 35. Brion S, Audrain S, De Bodinat C. Major depressive episodes in patients over 70 years of age. Evaluation of the efficiency and acceptability of tianeptine and mianserin. *Presse Med.* 1996;25:461–468. [\[PubMed\]](#) [\[Google Scholar\]](#)
- 36. Ridout F, Hindmarch I. Effects of tianeptine and mianserin on car driving skills. *Psychopharmacology (Berl)* 2001;154:356–361. [\[PubMed\]](#) [\[Google Scholar\]](#)
- 37. Wilde MI, Benfield P. Tianeptine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depression and coexisting anxiety and depression. *Drugs.* 1995;49:411–439. [\[PubMed\]](#) [\[Google Scholar\]](#)
- 38. Atmaca M, Kuloglu M, Tezcan E, Buyukbayram A. Switching to tianeptine in patients with antidepressant-induced sexual dysfunction. *Hum Psychopharmacol.* 2003;18:277–280. [\[PubMed\]](#) [\[Google Scholar\]](#)
- 39. Bonierbale M, Lancon C, Tignol J. The ELIXIR study: evaluation of sexual dysfunction in 4557 depressed patients in France. *Curr Med Res Opin.* 2003;19:114–124. [\[PubMed\]](#) [\[Google Scholar\]](#)

8/26/21

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

124

124

## Questions

---



125