



**Northwestern Medicine**


## Kratom: An Herbal Supplement of Atomic Concern?

Taylor Conklin, PharmD  
PGY1 Pharmacy Resident  
Northwestern Memorial Hospital  
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Advisor: Robert Pecho, PharmD  
Clinical Pharmacist  
PGY1 Pharmacy Practice Coordinator  
Northwestern Memorial Hospital


### Pharmacy Technician Learning Objectives

- Review the history, mechanism of action, off-label uses, and common side effects of kratom
- Distinguish between state and federal laws for kratom and why this is relevant to patient's use
- Identify possible treatments for kratom overdose




## Disclosures

Taylor Conklin and Robert Pecho do not have any conflicts of interest to disclose regarding the subject matter




## Background on Kratom



### Pharmacist Learning Objectives

- Review the history, pharmacology, off-label indications, and side effect profile of kratom
- Distinguish current federal and state legislation regarding kratom and question how it relates to current use
- Discuss historical strategies for management of kratom intoxication and outline plans to treat patients



### Kratom in the Media




**INSIDE** By Mark Hey | Dec 19, 2018 | 10:00am

## Inside Kratom, the Gas Station Drug That Could End the Opioid Crisis

The green powder from Southeast Asia could help fight addiction—but is that the whole story?

<https://www.youtube.com/watch?v=P9SliuHaiXA>



Image from Joe Rogan Experience (Podcast) <http://vodcasts.joerogan.net/>, Accessed December 23, 2018  
Mark Hey "Inside Kratom, the Gas Station Drug That Could End the Opioid Crisis." <https://www.vice.com/en-us/article/inside-kratom-the-gas-station-drug-that-could-end-the-opioid-crisis>, Accessed December 23, 2018.  
Joe Rogan Podcast <https://www.youtube.com/watch?v=P9SliuHaiXA>, Accessed December 23, 2018.



### Patient Case #1

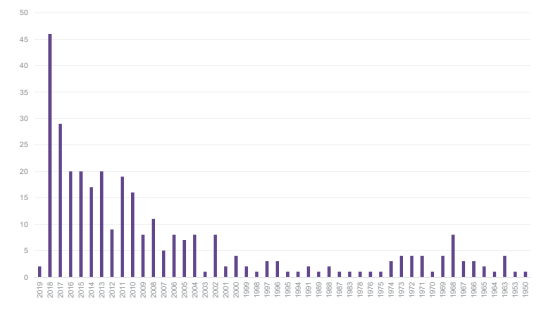
Sally Sassafras

- EMS responds to a call of an unresponsive woman on the boardwalk of Navy Pier.
  - Down ~15 minutes
- She does not respond to sternal rubs and has minimal respiratory drive
- A bystander hands you a brownish-green powder from a baggie
- What are your next steps?





### Growth to Western Civilization

PubMed - Articles on Kratom



J Am Osteopath Assoc. 2012 Dec;112(12):792-9.




### Patient Case #2

P.B.

- CC: "I wanna stay clean. You 'gon help me Mr. Pharmacist?"
- HPI: 18-year old homeless male presents to ED with complaints of withdrawal symptoms
  - Subjective: Irritability, agitation, anxiety
  - Objective: Sweating, diarrhea
- Past Medical History: heroin use disorder (Jan 2016-Jan 2018)
- Medications:
  - Tylenol 500 mg PO q4-6h prn
  - Kratom 2 grams PO TID
- Urine toxicology screening

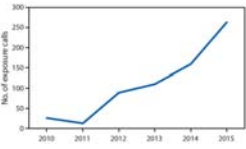
Drug	Detection
Cannabis	Negative
Cocaine	Negative
Opioids	Negative
Benzodiazepines	Negative




### Exposures Reported to Poison Centers

Morbidity and Mortality Weekly Report, U.S. 2010-2015

- 24.5% Minor**
  - Minimal signs or symptoms, resolved rapidly
- 41.7% Moderate**
  - Non-life threatening, but requiring treatment
- 7.4% Major**
  - Life-threatening signs of symptoms, residual disability
- 26.2% Unknown**
  - No effects were reported



Annie M. Law R, Sohier J. Notes from the Field: Kratom (*Mitragyna speciosa*) Exposures Reported to Poison Centers — United States, 2010–2015. MMWR Morb Mortal Wkly Rep 2016;65:746–749. DOI: <https://doi.org/10.1093/mmwr.mm6512a1>



### Kratom

*Mitragyna speciosa*

**Background**

- Tree native to Southeast Asia
- Rubiaceae family
- Street names: "Biak-biak," "Ketum" "Kahuam" "Ithang" "Thom"


**Consumption**

- Ingestion of raw leaves
- Crushed leaves
  - Smoked
  - Brewed with tea
  - Powder for capsules

**Use in Southeast Asia**

- Enhance mood and well-being
- Increase work efficiency and tolerate heat
- Heroin addiction

Image courtesy of USADA. <https://www.usda.gov/webteam/vegetables-profile-images/>. Accessed December 21, 2016. Ruffa RB (ed) Kratom and other mitragynins: the chemistry and pharmacology of opioids from a non-opium source. CRC Press, Boca Raton, FL, pp 309–330




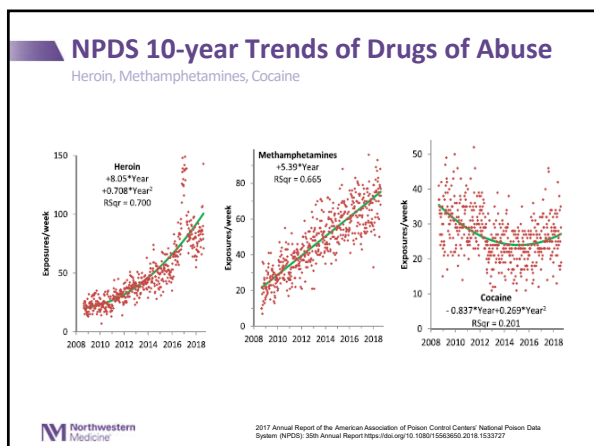
### 2017 Human Exposures to Drugs of Abuse

American Association of Poison Centers' National Poison Data System (NPDS)

Drug of Abuse	Increase (%/year)	Exposures (last 52 weeks)	Increase (Exposures/year)	95% CI
Synthetic Opioids	242%	25	1.17	[0.509, 1.82]*
Kratom	63.3%	529	6.44	[2.91, 9.98]*
Heroin	20.9%	4186	16.8	[4.05, 29.57]*
Methamphetamines	13.1%	3766	9.49	[-12.6, 31.5]
Cocaine	0.817%	1371	0.215	[-5.60, 6.03]

2017 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 35th Annual Report <https://doi.org/10.1080/15563660.2018.1533727>





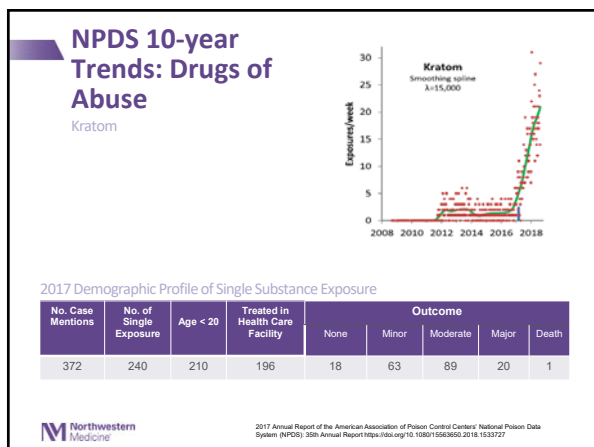
### Pharmacology

Kratom

**Mitragynine**

- Kratom leaves contain over 25 alkaloids
  - Mitragynine (66%)
  - 7-OH mitragynine (2%)
  - Speciociliatine (7%)
  - Paynantheine (9%)
  - Speciogynine (1%)
- Mitragynine
  - Structurally similar to yohimbine

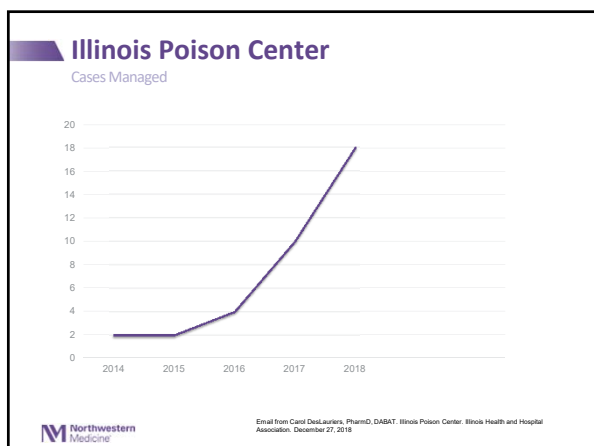
Northwestern Medicine  
<http://ajphaphis.org>; 2016 Jan;130(1):127-38. doi: 10.1007/00014-015-1279-y. Epub 2015 Oct 28. Accessed December 23, 2018



### Pharmacology of Kratom Compounds

Alkaloids	Mechanism of Action
Mitragynine	Activity on $\mu$ , $\delta$ , and $\kappa$ receptor Stimulates postsynaptic $\alpha 2$ -adrenergic receptors 5-HT <sub>2A</sub> receptor antagonist
7-OH Mitragynine	13- and 46-fold higher potency than morphine and mitragynine, respectively
Speciociliatine	ACh receptor antagonist
Paynantheine	Inhibits muscarinic receptors on ileal smooth muscle
Speciogynine	Inhibits muscarinic receptors on ileal smooth muscle

Northwestern Medicine  
<http://ajphaphis.org>; 2012 Dec;112(12):792-9. Accessed December 23, 2018.



### Brainstorming

What drugs or drug classes does kratom resemble?

Northwestern Medicine  
 Image courtesy of Glynn; <https://doi.org/10.1001/5563650.2018.1533727> Accessed December 23, 2018.

## Pharmacokinetics

Parameters	Mean ± SD
Tmax (h)	0.83 ± 0.35
Terminal T <sub>1/2</sub> (h)	23.24 ± 16.07
Vd/F (L/kg)	38.04 ± 24.32
CL/F (L/hr kg)	98.1 ± 51.34

- Large volume of distribution
  - Mainly distributed out of circulation
- Linear (first order) pharmacokinetics
- Metabolism:
  - Likely hepatic
  - Strong CYP2D6 inhibitor
  - Urine excretion: 0.14%, unchanged drug

Northwestern Medicine | [Pharmacokinetics](#), 2013 Oct 5(4):241-6. doi: 10.4103/0974-8490.118806. [Drug News Brief](#), 2015 Apr 29;9:2421-9. doi: 10.2147/DDBT.S79658. eCollection 2015.

## Kratom Withdrawal Symptoms

Singh et al.

Category	Symptoms
Physical	Lethargy, irritability, frequent yawning, runny nose, muscular pain, cramps, joint pain, diarrhea, sweating
Psychological	Restlessness, anxiety, depression, aggression, sadness, nervousness, delusions, hallucinations, intense craving

Northwestern Medicine | [Drug News Brief](#), 2014 Jun 1;139:132-7. doi: 10.1016/j.drugadotep.2014.03.017. Epub 2014 Mar 22.


## Off-Label\* Indications and Side Effects

Indications	Dose	Side Effects
-Stimulant	1-5 grams	Mild stimulant effect ▶ Increased alertness and physical energy Pleasant euphoria ▶ Loss of muscle coordination Anxiety and internal agitation
-Chronic pain management -Acute opioid withdrawal -"Legal high"	5-15 grams	Analgesia Constipation Euphoria Sedation
Acute or chronic toxic ingestion	> 15 grams	Seizures Psychosis Intrahepatic cholestasis Thyroid dysfunction

**\*Quality randomized controlled trials do not exist to describe these subjective effects**

Northwestern Medicine | [Epub Drug Bull.](#), 2016 Sep;126(P1):141-46. doi: 10.1016/j.brainbullet.2016.05.004. Epub 2016 May 10.

## Strains\*



Red Vein	White Vein	Green Vein
<i>Pontianak Red Horn, Red Thai, Borneo Red, Red Vein Sumatra</i>	<i>Pontianak White Horn, White Vein Sumatra, Borneo White</i>	<i>Malaysian Green and Pontianak Green Horn</i>
Best selling	Known as stimulant and positive mood enhancer	Mild energy booster
Pleasant and calming effects	Coffee-mimetic	More subtle effects on pain
Prevent withdrawal symptoms of opioids	Commonly mixed with red strains	Relieves social fears

**\*Quality randomized controlled trials do not exist to describe these subjective effects**

Northwestern Medicine | <https://www.kratomgardens.com/kratom-strains>, Accessed December 23, 2018.

## Addictive Nature

Vicknasingam et al.

Concomitant Drug Use and Reason for Using Kratom	Short-term user	Chronic-user
Ever used heroin	55.6%	34.4%
Induces euphoria	5.6%	12.5%
Helps decrease addiction to other drugs	95.8%	82.8%
Reduces withdrawal symptoms	87.5%	79.7%
Perceived Benefit	Short-term user	Chronic-user
Helps me work harder	87.5%	76.6%
Makes me more active	86.1%	76.6%
Increases sex desire	84.7%	73.4%
Increases appetite	77.8%	57.8%
Reduces heroin withdrawal symptoms	62.5%	46.9%

Northwestern Medicine | [PLoS One](#), 2010 Jul 21(4):e2338. doi: 10.1016/j.drugs.2009.12.003. Epub 2010 Jan 25.

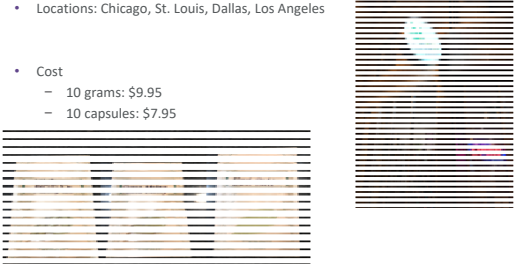
## Drug Screening and Analysis

- Undetectable on standard toxicology screening
- Methods of detection (urine and blood)
  - High-performance liquid chromatography
  - Linear ion trap mass spectrometry

Northwestern Medicine | [J Anal Toxicol.](#), 2012 Nov-Dec;36(9):616-25. doi: 10.1093/jat/bks073. Epub 2012 Sep 28.

### Accessibility and Cost

- Locations: Chicago, St. Louis, Dallas, Los Angeles
- Cost
  - 10 grams: \$9.95
  - 10 capsules: \$7.95



Photos taken by Taylor Conklin January 7, 2019  
<http://www.northwestern.edu/commission> Accessed December 23, 2016

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### Technician Assessment

For what off-label indication is P.B. using kratom?

- A. Social anxiety
- B. High blood pressure
- C. Heroin addiction
- D. Seizures

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### CBD/Kratom Supply



Photos taken by Taylor Conklin January 7, 2019

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### Technician Assessment

You are working as a pharmacy technician at CVS. A patient approaches the counter asking for an over-the-counter urine drug test kit. Which of the following drugs is NOT detectable?

- A. Cannabis
- B. Cocaine
- C. Kratom
- D. Opioids

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### Pharmacist Assessment

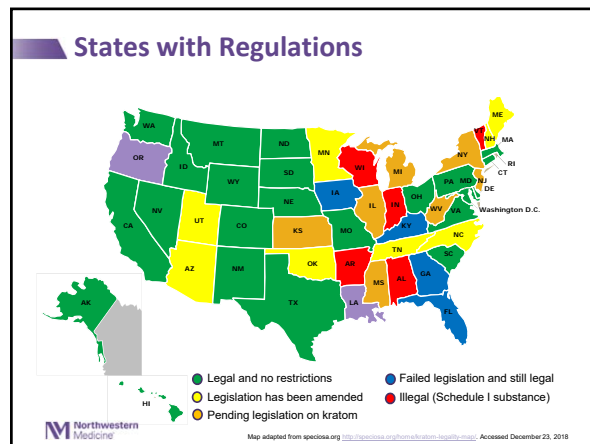
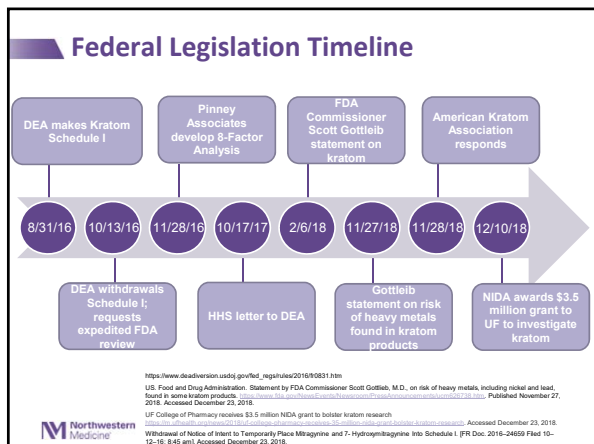
Which of the following is not a pharmacological action of mitragynine?

- A. 5-HT2A receptor antagonist
- B. ACh receptor antagonist
- C. Post-synaptic  $\alpha$ 2-adrenergic receptor agonist
- D. Activity on  $\mu$ ,  $\delta$ , and  $\kappa$  receptor

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# Legislation

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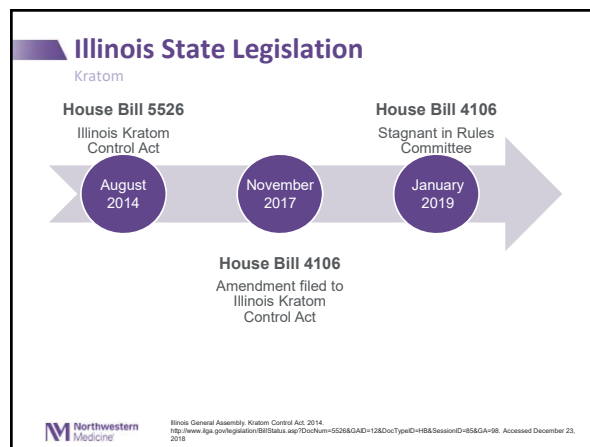


### Brainstorming

Discuss the DEA's decision to Schedule and withdraw kratom within 30 days.

- > Good decision?
- > Bad decision?

Image courtesy of iStock. <https://www.iStock.com/istockphoto>. Accessed December 23, 2018.



- ### 8-Factor Analysis: Kratom
1. Actual and relative potential for abuse
  2. Scientific evidence of its pharmacological effects, if known
  3. The state of current scientific knowledge regarding the drug
  4. Its history and current pattern of abuse
  5. The scope, duration, and significance of abuse
  6. What, if any, risk there is to public health
  7. Its psychic or psychological dependence liability
  8. Whether the substance is an immediate precursor of a substance already controlled
- HHS and FDA. Assessment of Abuse Potential of Drugs: Guidance for Industry. <https://www.fda.gov/oc/2017/01/2017-01-20-assessment-of-abuse-potential-of-drugs-guidance-for-industry>. January 2017. Accessed December 23, 2018.

### In Your Opinion: Legal vs. Illegal


Spend two minutes discussing your stance on the legality of kratom with a partner

Image courtesy of iStock. <https://www.iStock.com/istockphoto>. Accessed December 23, 2018.

### Pharmacist Assessment


Which of the following statements is false regarding the federal timeline of kratom?

- A. The DEA has request that the FDA expedite its scientific and medical evaluation and scheduling recommendation for kratom
- B. The NIDA awarded a \$3.5 million grant to the University of Florida to investigate kratom's clinical use
- C. Kratom was temporarily placed as a Schedule II to avoid imminent hazard to public safety
- D. FDA commissioner Scott Gottlieb has made repeated statements warning the public of kratom's potential of abuse



### Fatal Intoxications with "Krypton"


- Krypton
  - Kratom
  - O-Desmethyltramadol
- 9 fatalities in Sweden from 2009-2011
- Both specimens detected in urine and blood

 [J Anal Toxicol. 2011 May;35\(4\):243-7.](#)

### Technician Assessment


Which of the following best describes the current legal status the Kratom Control Act in the state of Illinois

- A. Minors under 18 years of age cannot possess, buy, or distribute kratom
- B. Violation is a Class B misdemeanor
- C. Fines begin at \$500
- D. Legislation is currently pending to expand regulations against all persons (including adults)
- E. All of the above




### Management of Kratom Misuse

Adverse Event	Management	Outcome
Tachycardia and hypertension	Benzodiazepines, negative chronotropic drugs	Symptom resolution
Nausea/Constipation	Antiemetics, laxative + stool softener	Symptom resolution
Kratom Withdrawal/Addiction	Buprenorphine/Naloxone induction	Compliant with maintenance treatment
Seizures	Benzodiazepines (BZDs) Anti-Epileptic Drugs (AEDs)	Aborted seizure
Intrahepatic Cholestasis	Discontinue kratom	Symptom resolution
Hypothyroidism	Buprenorphine induction Levothyroxine	Improved thyroid function
Sedation Cardiorespiratory arrest	Naloxone Intralipids	Death

 [J Addict Med. 2018 Jul 4. doi: 10.1097/ADM.0000000000000435. \[Epub ahead of print\]](#)  
[J Addict Med. 2011 Dec;5\(4\):300-1. doi: 10.1097/ADM.0b013e318221765a.](#)  
[J Anal Toxicol. 2011 Sep;35\(7\):227-31. doi: 10.1097/JAT.0b013e3182141655.](#)

# Kratom Toxicity Management




### Case Presentation

P.B.

- HPI: 18-year old homeless male presents to ED with complaints of withdrawal symptoms
  - **Objective:**
  - B.P. 162/110 mmHg, 108 bpm
  - (+) diaphoresis
  - (+) sweating
  - (+) yellowing of skin, eyes, RUQ pain 7.5/10

LFTs	Value
AST	62
ALT	110
Alk Phos	389
TBili	30.8


- The patient admits to taking kratom 2 g PO TID for ~11 months to help prevent future heroin use. He recently lost his job selling CDs on Michigan Ave. and has not used kratom for 5 days.
- The medicine intern is unsure of how to treat this patient and asks the pharmacist for a recommendation.



### Pharmacist Assessment

Based upon P.B.'s clinical presentation, which regimen would you recommend

- A. Discontinue kratom, buprenorphine-naloxone induction
- B. Discontinue kratom, metoprolol tartrate 25 mg q6h, buprenorphine-naloxone induction
- C. Discontinue kratom via 7-14 day taper, clonidine 0.1 mg q6-8h, buprenorphine-naloxone induction
- D. Continue kratom, clonidine 0.1 mg q6-8h



### Technician Assessment

A patient comes into your hospital unconscious and not breathing. EMS found a bottle of kratom powder in the patients pocket on the way to the hospital. Which of the following medications would be best to administer to reverse symptoms of a kratom overdose?

- A. Lamotrigine
- B. Buprenorphine-Naloxone
- C. Naloxone
- D. Activated Charcoal

