

ECHO IDAHO



ECHO Idaho: Opioid Addiction and Treatment

Kratom: What Providers Need to Know

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Andrea Winterswyk, Pharm.D., BCPS, BCPP

Clinical Pharmacy Specialist, Mental Health and Substance Use Disorders

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Learning Objectives

- Describe the key mechanisms by which kratom exerts pharmacological action related to its intended uses
- Design a therapeutic treatment plan for management of patients requiring kratom detoxification and maintenance of kratom dependence
- Explain the role played by kratom in regard to substance use disorder-related morbidity and mortality

Kratom



Image: <https://www.sociedelic.com/kratom-weapon-drug-addiction-withdrawal-natural-remedies/>

Origins of Kratom

- Species: *Mitragyna speciosa*
 - Biologically active alkaloids:
 - Mitrygynine 66%
 - Paynantheine 9%
 - Speciogynine 7%
 - **7-hydroxymitragynine 2% ****
 - Speciophylline 1%
- Appearance leaf form: See right
 - Mitragynine isolated: white amorphous powder, soluble in ETOH, chloroform, acetic acid
- Origin: Tropical evergreen tree native to Indonesia, Thailand, and Myanmar
 - Tree reaches heights of 50 feet; spread of 15 feet
 - Member of the Rubiaceae family (Coffee!)
- Common names: Kratom, thang, kakuam, thom, ketum, biak



Am J Health-Syst Pharm. 2017; 74:e589-95
Swogger M, et al. *Drug & AlcDep.* 2016.
DEA Drug Fact Sheet: Kratom

Uses of Kratom

- Multiple varying rationales: analgesia, anxiolysis, attenuation of opioid withdrawal symptoms, weight loss, energy, sleep
- Routes:
 - Oral ingestion
 - Leaves are dried or powdered, crushed and then smoked, brewed with tea, or placed in gel capsules, tablets, extracts
 - Kratom leaf may be chewed
- Different colors of veins on leaves = differing potencies?

Green Vein	Red Vein	White Vein
		
 Effects: Gentle stimulation Better concentration Mood lifting	 Effects: Pain killing Sedating / Relaxing Insomnia	 Effects: High energy Better productivity Help with depression
 Onset: 20 to 40 minutes	 Onset: 20 to 40 minutes	 Onset: 20 to 40 minutes
 Duration: Up to 8 hours	 Duration: 5 hours	 Duration: 3 to 5 hours

Kratom Legal Debate

- Reports of use date back to mid-1800s
- Most clinicians had not heard of kratom prior to 2016
 - DEA announced plan for temporary Schedule I status in August 2016
 - Scheduling withdrawn in October 2016 due to public outcry

“[The American Kratom Association](#), the largest kratom advocacy group in the United States, helped spur an outpouring of public comments. In response, the DEA put a hold on its scheduling plans, and the Food and Drug Administration now is preparing an eight-factor analysis of kratom’s safety.”

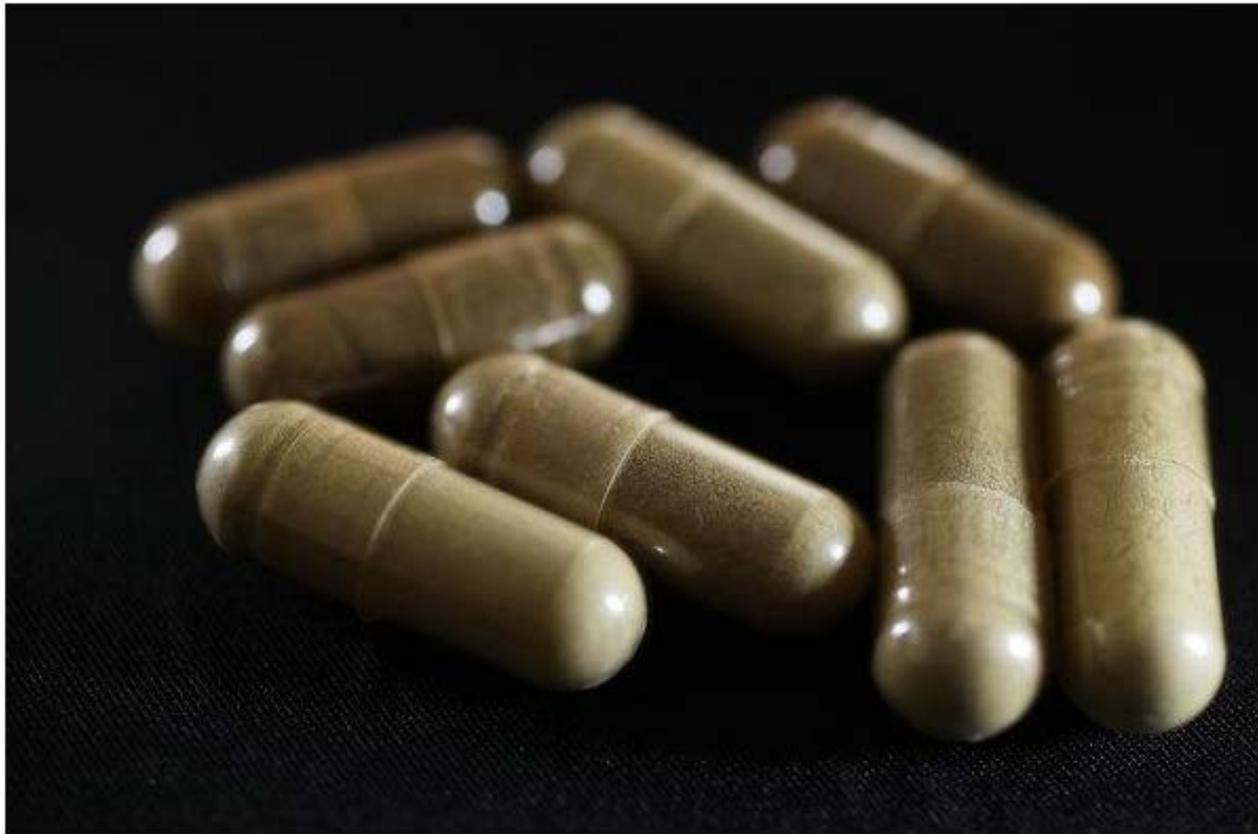
American Society for Biochemistry and Molecular Biology



Kratom Current Legal State

- FDA has not approved Kratom for any medical use
- DEA delayed ruling on scheduling of kratom and listed as “Drug and Chemical of Concern”
 - Risk of abuse, contaminated product, seizures upon withdrawal, neonate dependence issues, drug interactions?, liver injury, etc.
- Not controlled under Federal Controlled Substances Act
 - Some states regulate sales
 - Illegal to possess in some states: (2017 information)
 - Alabama, Arkansas, Indiana, Tennessee, Vermont, Wisconsin
- Purchased over internet and in smoke shops, gas stations, tea shops, bars, other boutique shops
 - Chopped leaves, capsules, compressed tablets, concentrated extracts

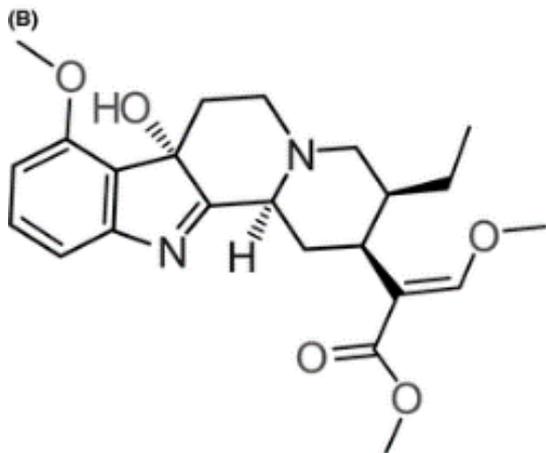
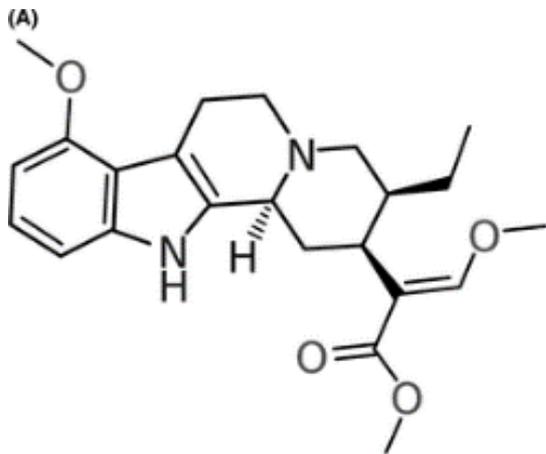
Opioid Users Call Kratom a Godsend. The F.D.A. Says It's a Menace.



Wow! People really seem to like kratom... I need to learn more about how this stuff REALLY works!



Pharmacologic Action



Kratom
alkaloids
(>40
types)

Non-Opioid
Activity

- α -2 adrenergic agonism
- Potential 5HT_{2a}-related action

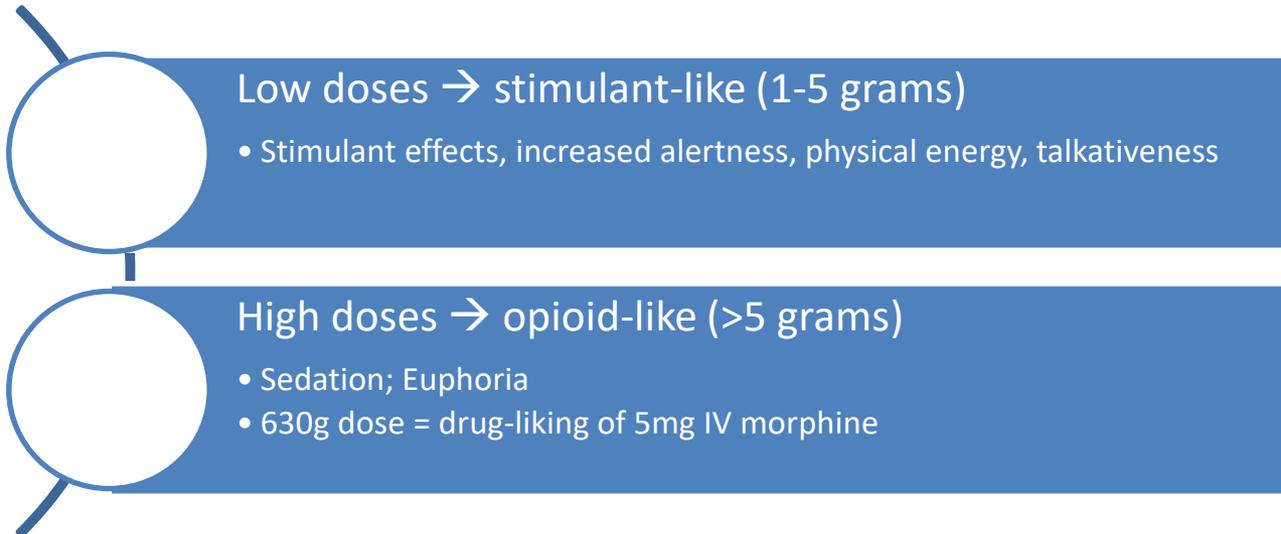
Opioid
Pharmacology

- MG and 7-OH-MG bind to OR
- MOR > DOR & KOR

COX-2 mRNA
inhibition

Pharmacologic Effects

- Onset: within 5-10 minutes
- Duration: 2 to 5 hours
- Dose-dependent effects:



- Adverse Effects
 - Nausea, itching, sweating, dry mouth, constipation, increased urination, tachycardia, vomiting, drowsiness
 - Anorexia, insomnia, hepatotoxicity, hallucinations

KRATOM

DOSE GUIDE

1 The begining

The stimulating and mode boosting effects are subtle but noticaeble

Mild 2

You can definitely feel the moodboosting and stimulating effects

3 Moderate

In this level there is a balance between stimulation, euphoria, sedation and pain killing effects

Strong 4

The effects are sedative, euphoric and very analgesic.

5 Very strong

Most people cant handle this stage. The sedative effects are substantial and the euphoria can cause hallucinations



Do you think the health store can help recommend the best dose for my paw pain?

Pharmacokinetics

- In vitro, kratom extract was found to inhibit the following CYP P-450 isoenzymes:



- Using CYP system to boost effects via the “4 x 100” cocktail (common in adolescent population in Thailand):
 - Kratom leaves are boiled and mixed w/caffeine soda, dextromethorphan, codeine
 - + diphenhydramine (CYP2D6 inhibitor)



Pharmacokinetics

Rat Data:

T_{max}: 1.2 – 1.8 h

T_½: 3.9 – 9.4 h

V_d: 37.9 – 89.5 L/kg

Available Human Data: (small studies)

T_{max}: 0.83 ± 0.35 h

T_½: 23.24 ± 16.07 h

V_d: 38.04 ± 24.32 L/kg

Reminder: Rule of Five

5x the t_½ = the time at which the drug is “completely” (97%) eliminated from the body

1 x ½ life = 50% original drug removed

2x ½ life = 75%

3x ½ life = 87.5%

4x ½ life = 93.75%

5x ½ life = 98.875%



And I thought I'd never have to do math again after college!

Laboratory Detection

 Order a Lab Test

Available Lab Tests

- 7-HYDROXYMITRAGYNINE <KF
- 7-HYDROXYMITRAGYNINE**
- 72 HR FECAL FAT <FECAL FA
- A HEPATITIS IGG <HEPATIT
- A HEPATITIS IGM <HEPATIT
- A1C <HEMOGLOBIN A1c
- A2 RECEPTOR ANTIBODY <
- A2M <ALPHA-2 MACROG
- ABG <BLOOD GASES - E

KRATOM URINE CONFIRM PANEL

Collect Sample: URINE

Specimen: URINE

Urgency: ROUTINE

Collection Type: Send Patient to Lab

Collection Date/Time: NOW

How Often?: ONE TIME

How Long?:

KRATOM URINE CONFIRM PANEL URINE SP

Accept Order

Quit

PROVIDER INSTRUCTIONS:

1. If positive, this panel test will quantify the following:
**7-HYDROXYMITRAGYNINE
MITRAGYNINE**
***A cost of \$78.50 will incur if either of the above is performed.**
2. This test request 30 mLs (NLT 20) of urine.

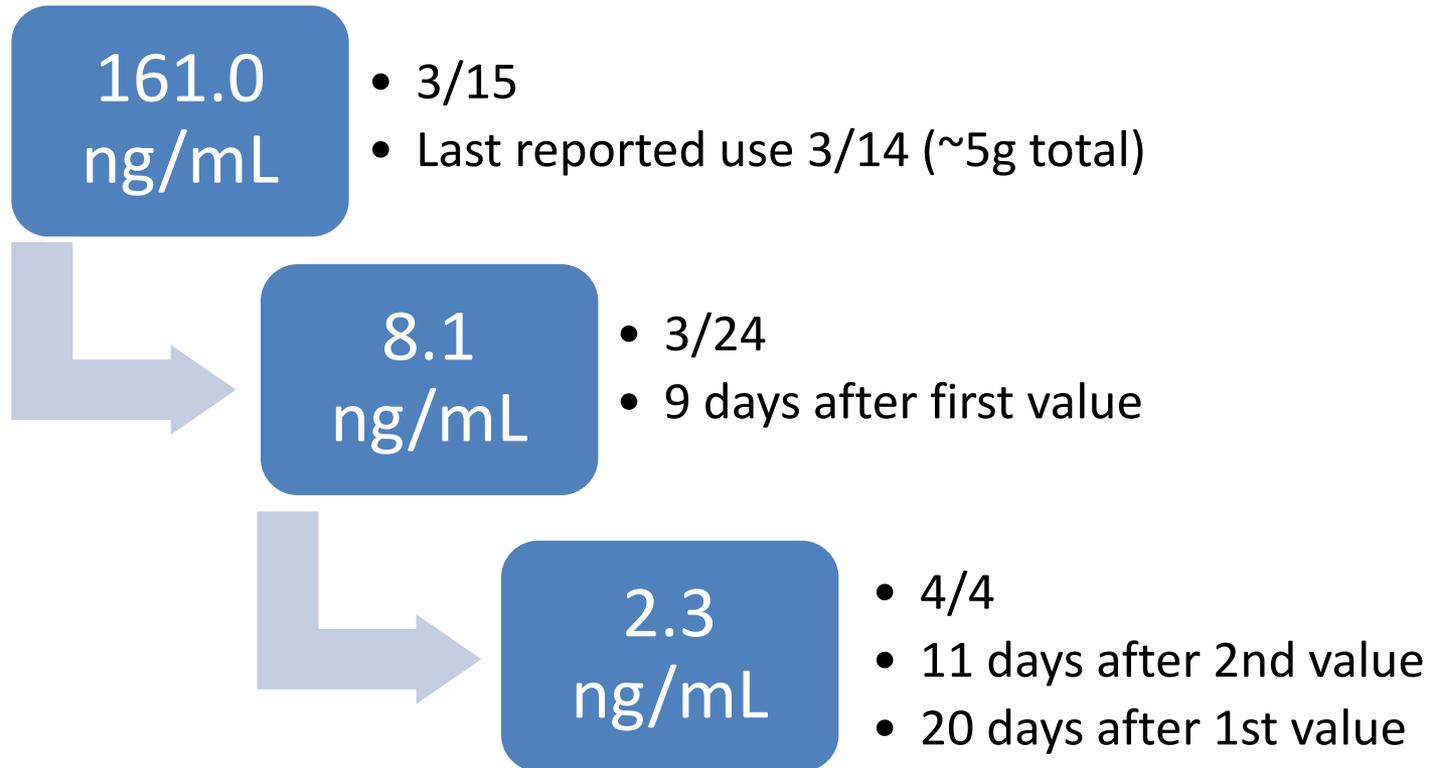
Test Code: 791750

TAT: 6 - 11 Days

PROCESSING INSTRUCTIONS:

1. This test requires 30 mLs (NLT 20) REFRIG, Random Urine. Please make two aliquots, one to send using the LabCorp Aliquot Tube and one backup aliquot (reserve the Primary cup if possible) and store in the walk-in.

Urine Drug Level Examples?



Kratom Withdrawal

- Withdrawal can be difficult to manage and serious

Hostility,
Aggression,
Emotional Lability

Physical Opioid
Withdrawal
Symptoms

Seizures and Death
(case reports)

Adjunctive medications for management of uncomplicated kratom withdrawal

Withdrawal Symptoms:	Clonidine 0.1mg q6h PRN 0.1MG PO Q2H PRN FOR KRATOM/OPIOID WITHDRAWAL - COWS >8 0.2MG PO Q2H PRN FOR KRATOM/OPIOID WITHDRAWAL - COWS >12 (Hold for SPB <90 or Pulse <56: MAX DOSE=0.6mg/24hours)
Anxiety, dysphoria, lacrimation, rhinorrhea:	Hydroxyzine 25-50mg TID PRN
Myalgias:	NSAIDS, APAP, methocarbamol 500-1500mg TID PRN
Sleep disturbance:	Trazodone 50-100mg or gabapentin 300-1800mg PRN
Nausea:	Promethazine, ondansetron, prochlorperazine
Diarrhea:	Loperamide 4mg then 2mg after each loose stool; max 16mg/day Bismuth subsalicylate 524mg q30min-1hr; max 4192/day
GI Cramping:	Dicyclomine 10-20mg q6-8hrs PRN

Kratom Withdrawal Management

Table 1. Pharmacologic Effects of Kratom From Human Trials^{2,6,9,13,20,21,24-34,a}

Adverse Events	Therapy for Adverse Events	Withdrawal Effects	Therapy for Withdrawal
Tachycardia and hypertension	Benzodiazepines, negative chronotropic drugs	Agitation and anxiety	Benzodiazepines, α -2 agonists
Nausea and constipation	Antiemetics, laxative plus stool softener	Abdominal pain and diarrhea	Nonopioid antidiarrheals
Confusion and hallucinations	Benzodiazepines, naloxone	Limb muscle spasms	Benzodiazepines
Seizures	Benzodiazepines, naloxone, anticonvulsants	Joint and muscle pain	Nonopioid pain relievers
Sedation	Naloxone

^aTreatments for adverse events and withdrawal are general treatment suggestions and were not studied in any clinical trials of kratom.

It seems like kratom toxicity and withdrawal can present in quite the range of symptoms!



Risks of Kratom Use

- 2011-2017, National Poison Control Center received >1800 calls concerning exposure to kratom
- CDC analyzed data from the State Unintentional Drug Overdose Reporting System (SUDORS) to determine impact from July 2016-December 2017

July 2016-
June 2017

- Kratom listed as a cause of death in **11 states**

July 2017 –
December 2017

- Kratom listed as a cause of death in **27 states**

Risks of Kratom Use

State Unintentional Drug Overdose Reporting System (SUDORS) - Overdose Deaths July 2016-Dec 2017



Co-occurring substances listed as a cause of death	Kratom detected on toxicology (n = 152) No. (%)	Kratom determined to be a cause of death (n = 91) No. (%)
Any fentanyl	99 (65.1)	51 (56.0)
Heroin	50 (32.9)	23 (25.3)
Benzodiazepines	34 (22.4)	24 (26.4)
Prescription opioids	30 (19.7)	22 (24.2)
Cocaine	28 (18.4)	15 (16.5)
Alcohol	19 (12.5)	11 (12.1)
Methamphetamine	13 (8.6)	—

Clinical Case

KT is a 43-year-old male patient with alcohol use disorder, hypertension, and anxiety, presenting to you in the outpatient clinic for the first time. He has struggled with his alcohol use for many years, and is wondering about medication assisted treatment with naltrexone to help with his cravings. His current medications include lisinopril 20mg daily, albuterol inhaler as needed, and a daily multivitamin. His alcohol use pattern is reported as mostly in the evening after work to help him “wind down” and for sleep, about 5-6 drinks. He endorses using “a supplement from the health store” to help with his anxiety during work hours. When asked, he describes this supplement is kratom, and he is taking approximately 10-12 capsules daily (0.5g/capsule).



- Is patient appropriate for MAT with naltrexone?
- What additional information would you like to have prior to trial of naltrexone?

Some Recent Case Reports ...

- 64-year-old male found unconscious and seizing
- Regularly used kratom for chronic pain
- Urine concentration of mitragynine 167 ± 15 ng/mL detected

- 25-year-old man suspected kratom had induced his intrahepatic cholestasis
- Diagnosis confirmed by liver biopsy
- Mitragynine was detected in both urine and serum samples

- 44-year-old man admitted for kratom detoxification
- Consuming ~40g kratom divided into 4 doses over 24h
- Experienced withdrawal symptoms despite regular use
- Suggests short half-lives of active substances in kratom and a dependence syndrome primarily via agonist activity at the opioid receptors

- Term infant born to mother with daily kratom tea use to self-treat opioid dependence
- Term infant born to mother using kratom daily believing it a safe alternative for pain
- Both infants required treatment with opiates for neonatal abstinence syndrome (NAS)



Kratom - Key Points

Kratom is used for pain, anxiety, sleep, alertness, appetite suppression, and many others

Use of kratom has drastically increased in popularity in the United States

Kratom has been found to carry risk of abuse or dependence

FDA released multiple announcements regarding safety (inc. formal public health advisory)

Kratom and active alkaloids do NOT carry Schedule with the DEA

Pharmacologic effects are dose-dependent, ranging from stimulant- to opioid-like

Drug interactions are possible and sometimes used intentionally to amplify effects

Withdrawal can sometimes be serious and may require medical attention

Mitragynine and 7-hydroxymitragynine can be detected in special urine assays

One of the best things we can do to better care for our patients is to ask about kratom

Questions?

andrea.winterswyk@va.gov

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