

Kratom or Bait'em: History, Pharmacology, PK, and Regulation Revisited

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Disclosures

- Consultant/Independent Contractor: AcelRx Pharmaceuticals, BioDelivery Sciences International, Firstox Laboratories, Salix Pharmaceuticals
 Speaker's Bureau: AcelRx Pharmaceuticals, Salix Pharmaceuticals
- Advisory Board: AcelRx Pharmaceuticals, BioDelivery Sciences International, Salix Pharmaceuticals
- Other: Abbott Laboratories (non-speaker's bureau), BioDelivery Sciences International (Collaborative publications), GlaxoSmithKline (GSK) (Collaborative non-paid poster presentations), Scilex Pharmaceuticals (Collaborative non-paid publications)

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Learning Objectives	
Ecarring Objectives	
■ Describe the history and background of Kratom	
 Match various pharmacologic and pharmacokinetic mechanisms of kratom to currently available prescription medications 	
List the issues surrounding kratom dosage forms	
■ Review clinical utility, epidemiology, and kratom usage among advocates	
Outline drug interactions associated with kratom	
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Pretest Question #1	
Which of the following is/are true regarding kratom's	
mechanism of action?	
A. Blocks reuptake of dopamine B. Has opioid antagonist properties	
C. Is an opiate by definition	
D. All of the above	
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Pretest Question #2	
According to the FDA and DEA respectively, kratom	
A. is an unsafe natural substance and classified as Schedule I	
B. is legal in some states and illegal in others	
C. potentially dangerous, but not Scheduled by Federal Regulation	
D. c and c above	
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Pretest Question #3

Kratom is a...

- A. CNS psychostimulant
- B. CNS sedative hypnotic
- C. Antidepressant
- D. All of the above

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What Inspired this Lecture?

Quotes from Kratom Advocates

- "Kratom is a natural product, so how can it be harmful?"
- "Show me one article that proves kratom can be harmful."
- The Fulfin;

 "...implies kratom is an opioid. It's not. You can simply Google it, and then look up the definition of opioid."

 "...incorrectly stated that kratom can interact with other drugs and cause agitation, heart attack and stroke.

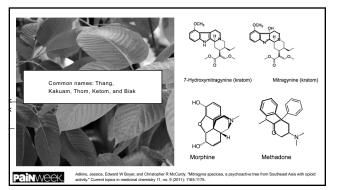
 "...ether made this up off the top of his head, or someone told him this."

- "There is no use for using naloxone on a kratom overdose. If you "overdose" you get sick and puke."

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Fudin J. Kratom, Save 'em, Bait 'em, or Crate 'em. February 5, 2018. http://paindr.com/kratom-save-em-bait-em-or-crate-em/

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Historical Perspective

- Source
- -Tropical evergreen shrub or tree related to the cocoa plant
- Location
- -Native to Southeast Asia, Thailand, Malaysia, and Papua New Guinea
- Historical Usage
- -Used by local populations in each of these counties as a stimulant, generally by farm workers to enhance wakefulness and long work days
- -Pain, depressed mood, anxiety
- Southeast Asia Uses
- -Diarrheal, antitussive, diabetes, anthelmintic, heroin addiction
- Outside Asia
- -Chronic pain, opioid withdrawal

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Routes of Ingestion

- Raw leaves or dried leaves are chewed or prepared in tea
- Preparation
- -Citric juice added to enhance flavor and accelerate active ingredient
- -Bitter Taste
 - •Masked with sweeteners (sugar, honey)
- ■Smoked
- -Pipe, rolled into cigarettes, vaped
- Chewing
- -1 to 3 fresh leaves at a time



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Kratom Trends



Dried or crushed
Extracts, powders
Available at Head Shops
Capsules, tablets, liquids, and gum/resin
Significant increase in imports (Regulation + CDC)
Millions of doses for recreational are used throughout US
Natural Food supplement, and therefore, claims, purity / quality not regulated



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Kratom	Pharmacol	oav

- •Over 25 chemically similar alkaloids with variable / mixed properties1
- Pharmacologically active components
- -7-hydroxymitragynine
- -Mitragynine
- ■Opioid (R- enantiomer) agonists²

 - -Kappa > mu > delta³
 -Other mixed mechanisms of action and various pharmcodynamic pathways

 - Suharin, Fareh W., Naud HM Yuaofi, Rahimah Hassan, Sharif M. Mansor, Visweewaran Navarahram, Christian P Moller, and Zurina Hassan. Neurobiology of Kratina and Its main shalosine of trilingymen. 'Etisia' research bulletin 156 (2016), 24-40.

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Dose Dependent Pharmacological Activity

- ■Low (1-5g)
- -Stimulatory due to neuroamines
- Antidepressant-like effect associated with MAO, serotonin, noradrenaline and dopamine¹
- High (>5g)
- -Sedative and analgesic properties due to opiate receptor activiation²
- -Counteracts opioid withdrawal
 - •7-hydroxymitragynine > mitragynine: mu R agonists²
 - •Mitragynine: alpha-2 adrenergic Rs agonist²
 - Subalini, Farsh W., Nauri HM Yusof, Hamishol Hassani, Surar Int. Ministrot, Yesterson on International, Lettocher F. International Conference on International Conference

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Kratom Pharmacokinetics

- Mitragynine half-life¹
- -7-24 hours depending on alkaloid
- Dosing occurs every 6-12 hours
- Withdrawal symptoms begin ~12 hours after last use²
 - Note, WD may be from serotonin or opioid, or both
- Metabolism
- Phase I, Cytochrome P450 (CYP450), 3A4, 2D6, 2C93
- Drug Interactions
- -Substrate interactions from above -Mitragynine inhibits CYP P450 2C9, 2D6, 3A4, 1A2⁴

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Taulis Hidayot M, Apryuni E, Nabishah BM, Moklas MA, Shanda F, Farban Stancia CN, Granssegarma SA, Ahmes S, Penders T, Kralser Wibbrassal Karabia SH, Sasarma A, King T, Lee FT, McCarel CP, Avary SM, Melabolis Haghes RL. Falal combination of mitragynine and quellapina—a case report;15(1):110-2.

Toxicity and Adverse Effects -Weight loss; insomnia; constipation; skin hyperpigmentation; extreme fatigue¹ According to CDC and other sources, increased... -Kratom-related exposure calls to poison control centers^{2,3} -Fatal overdoses involving kratom · Co-ingestions² Adulterated and combination products^{3,4} Sängam D, Assanangkomchai S, Geater AF, Balthip D, Pattern and consequences of krathom (Miragyna speciosa Korth.) use among male villagers in s Thalland: a qualitative study, international Journal of Drug Policy, 2013 Jil 1244(JSS1-8. Genthman et al., 2018 C. Kronstrand R. Histoder G. Lindstein D. Roman M, Kugeber DF. Fall intoxicolar associated with the designer opioid AH-7921. Journal of analytical lossociogy, 2014 Oct 1,38(§):958-904. Patasamudiam Dehardar S, Rigota EE, D Angelo CC, Gilensader SR, Martinez Galvie NP. Legally Lethal Kratom: A Herbal Supplement with Overdose Poter Journal of psychosories and pp. 2019 Jan. 1551 (1):24-30. Tang MR, Chong CF, Ching DC, Mart V, Wilcrail esting for letamine: Use and Abuse. 2015 Mar 18:341. Painweek. 16

Treating Kratom Withdrawal

- Opioid Withdrawal 1,2,3
- -Replacement therapy with buprenorphine, methadone, or other and taper
- -Neonatal Abstinence Syndrome⁴
- · Opioid replacement
- Serotonin Withdrawal
 - -Options?
- Suhaimi FW, Yusoff NH, Hassan R, Mannor SM, Navanánam V, Müller CP, Hassan Z, Neurobiology of Kratom and its main alkaloid mitragynine. Brain research
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 Sancio LO, Cineaseagaem SA, Le Codora Al, Waller TE. Use of Kratom, and psojid dishe traditional left. in pregnancy Obstetrics & Gymecology. 2010 Ct 1:12(2):2526.

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Regulatory Considerations¹⁻⁴

- Up until 2015, Kratom was legal to grow and purchase in all 50 states
- •2011 to 2016, CDC & DEA identified Kratom as a substance of concern
- ■Illegal in several states as of 2018
 - -Alabama, Arkansas, Indiana, Ohio, Rhode Island, Vermont, Wisconsin
- Illegal in certain counties / cities
- -Denver CO; San Diego CA; Sarasota FL, Washington DC
- Illegal in Certain Countries
- -Australia, Denmark, Malaysia, Poland, Sweden, Thailand, and Vietnam

 - 1. Hilleword, J. Chromoth D. Sockfor, P. Logal highe on the Hermit Subdiscro used, missous 2010 Feb 14:5(3):330-40.

 Bergen Co. D. Michright, Y. Chem Billingura perspices) says, additions potential, and legal status. In Neuropsathology of Drug Addictions and Substance Misses 2016 Jan 1 (pp. 838-911). Academic Peass.

 P. Prosidasie M.W., Drum J.K., Andruster S. Pharmacology of Interna on emerging behavioral agent with simulant, analysis: and opioid-like effects. The Journal of the American Obstopation Association. 2012 Dec 1:11(12):3762-0.

 Celliffor O.W. Web M.E. The scheduling of Victorium and selective use of data. Journal of psychoactive drugs. 2018 Mar 15:50(2):114-20.

Kratom Legality Map ✓ Green Kratom is legal and on restrictions © Light Creen. Legalitation in these states have failed or has been anneated ® Orange. There is pending legislation on Kratom in these states © Other hamest answeledged for Kratom ✓ Player floody involving Kratom © Blike These states have edgeed the Kratom Consumer Protection And but These states have edgeed the Kratom Consumer Protection And but These states have edgeed the Kratom Consumer Protection And the Consumer Protection American Kratom Association, Last accessed 7/15/2020, https://speciosa.org/home/Kratom-legality-map/

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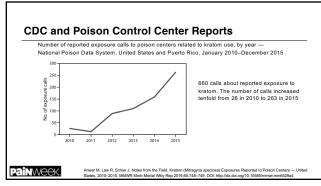
Regulation (continued)

- •FDA is watching, but still legal by Federal Regulation
- ■DEA Notice of Intent, 2016
- -Implement Schedule I status for mitragynine and 7- hydroxymitragynine
- ■American Kratom Association (millions)
- -Non-profit consumer advocacy organization successfully campaigned for withdrawal of planned scheduling
- •Blog, Social media newsfeed experience
- ■DEA withdrew scheduling request in October 2016

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Griffin OH, Webb ME. The scheduling of kratom and selective use of data. Journal of psychoactive drugs. 2018 Mar 15;50(2):114-20.

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		Kraton	

- •US, prevalence widespread but not established
- -CDC Poison Control Center calls (from 2010)
- -American Kratom Association (survey, social media mentions)
- Southeast Asia
 - -55% of regular users of Kratom become dependent
 - -Emerging worldwide as substance used in self-management of opioid withdrawal.

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Griffin OH, Webb ME. The scheduling of kratom and selective use of data. Journal of psychoactive drugs. 2018 Mar 15;50(2):114-20.

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Patterns of Kratom Use and Health Impact

- ■10,000 Kratom users surveyed
- -Who is consuming Kratom and for what purpose?
- What perceived beneficial and detrimental effects are reported by users?
- –What do Kratom users report as a commonly used dose and frequency of consumption?
- -Does Kratom represent a potential for abuse and withdrawal?
- -Symptoms/side effects?

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rundman O. Patterns of Kratom Use and Health Impact in the US. Drug and Alcohol Dependence. 2017:176:63-70.

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Survey Demographics

- Kratom users are primarily middle aged (31-50, 55.9%)
- •Male (56.9%); Married or partnered (54.3%)
- -White non-Hispanic (89.4%)
- -Employed (56.8%) -Insured (61.1%)
- -Some college (82.3%)
- -Income > \$35,000 (63.2%)

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Grundman O. Patterns of Kratom Use and Health Impact in the US. Drug and Alcohol Dependence. 2017:176:63-70.

User Characteristics

- ■41% disclosed use to healthcare provider
 - -Self-treatment of chronic pain 68%
 - -Self-treatment of anxiety/depression 65%
- -Self-treatment related to opioid misuse (including opioid withdrawal)
- *7.7% had previous or current history of illicit drugs use
- -Including prescribed or illicit RX opioids 26.0%

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Soundman O. Patterns of Kratom Lise and Health Impact in the LIS. Drug and Alcohol Dependence. 2017;176:63-7

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"Kratom Conspiracy Theory"

Outbreaks > FDA Investigated Multistate Outbreak of Salmonella ... https://www.tsa.gov/icootirecalsoutbreaks-emergence/outbreaks-unc0972926 htm > These profacts have been initiated to arrutations domained southeak of salemonistic hom ... Mitogene spociosa, commoily tensor has brained in a practition outbreak or salemonistic hom ... Mitogene spociosa, commoily tensor has trained in a practite of the pool proface in a product. — Fifty of these people have been hospitated and no details have been required and no details have been required.

People also search for kratom recall list kratom seized by fda kratom salmonella fake news eclipse kratom website kratom animonella reddit animonella kratom website

Kratom linked to dozens of illnesses from salmonella, health officials ... https://www.chsmics.com/resev/attom-astmonells-do-covering)* ~ Feb 20, 2019. Kratom grows naturally in the Southesst Asian countries of Thalland. ... so fat; 1 people have been hospitated with salmonella liness linked to their. "Out of 11 people interviewe eight (73 percent) reported consuming kratom, Ill people in this outbreak report consuming kratom pills, powder or tex. Salmonella outbreak linked to kratom supplements - New York Post https://wypost.com/2018/00/19/salmonella-outbreak-inked-to-kratom-supplements/ • Mair 19, 2018 - Salmonella outbreak linked to kratom supplements. By Miles Wehner, BGR ... with a

Multistate Outbreak of Salmonella 14.[5],12:b: Infections Linked to ... https://www.cdc.gov/salmonella/salxon/02-016/sock zhru https://www.cdc.gov/salmonella/salxon/02-016/sock zhru https://www.cdc.gov/salmonella/salxon/02-016/sock zhru products. ... Tahry-eight percent of it program was hespitalized, and no durbs were reported. ... 122 program with variable information, 50 (20%) were hospitalized ... As delificious distains of Salmonella was defined in lation.

Google search term: "saimonella outbreak traced to kratom grows by 50 percent" https://www.google.com/search/floource/spiGe**/ TAX:AHGGGGSG/Ge**/ Gersalm cella-outbreak etwaced-bi-ratioming-resub-y-00-fercentification-Saimonella-outbreak etwaced-bi-ratioming-resub-y-00-fercentification-grows-by-60-fercentification-groys-at-y-60-fercentific

FDA Investigated Multistate Outbreak of Salmonella Infections Linked to Products Reported to Contain Kratom. US Food and Drug Administration. June 29, 2018 Update. https://www.fda.gov/food/recallsoutbreaksemergencies/outbreaks/ucm597265.htm Last Accessed April 8, 2019

Answers to Quotes from Kratom Advocates

- "Kratom is a natural product, so how can it be harmful?"
 Vincristine and vinblastine from the perivinide plant
 Digitals from foxplowe used to treat supraventricular heart arrhythmias or to strengthen heart rhythm
 Altopine alfaciloids from belladonna (also known as deadly nightshade), the ingredient from berries used by Romeo and Julief to cause death.

- Autoprate assistances from betladonna (also known as deadly nightshade), the ingredient from berries used by Romeo and Juliet for cause death.

 "Show me one article that proves kratom can be harmful."

 See 1-7 not slide

 Dr. Fullin;

 "...implies kratom is an opioid. It's not. You can simply Google it, and then look up the definition of opioid."

 The original definition of an "spash" is a dup derived from the poppy givent or opium, that continue with one or more place in exceptions in the body. Opiumis

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- More to come...
 "There is no use for using naloxone on a kratom overdose. If you "overdose" you get sick and puke."
 Two emergencies; 1) noradrenergic overstimulation which can be treated with combined benzodiazepine (alprazolam, diazepam, etc.) In reduce adjation plus beta blockers (prograngloi and others) to slow the heart rate and reduce blood pressure; and 2 yound overdose which can be treated with relaction to block the option dreeplors.

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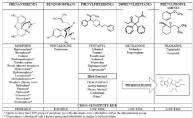
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- 1;130(1):127-38.
 Kapp FG, Maurer HH, Auwärter V, Winkelmann M, Hermanns-Clausen M. Intrahepaticcholestasis following abuse of powdered kratom (Mitragyna speciosa). Journal of Medical Toxicology, 2011 Sep 1;7(3):227-31.
 Galbis-Reig D. A case report of kratom addiction and withdrawal. WMJ. 2016 Feb;115(1):49-52.

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"If kratom is an opiate, why doesn't it cause a positive urine screen for opiates?"



Kratom is not detected in standard IA urine screens Special add-on testing for suspected kratom use, abuse, misuse - Unexplained increased heart rate - Consider kratom and cathinone add-ons Confirmatory testing¹ - Gas chromatography/mass spectroscopy (GC-MS) - Liquid chromatography with linear ion-trap mass spectroscopy - Electrospray tandem mass spectroscopy³ 1. Benchils E. McConell I. Lizery P. Falgeridd P. Inventors. Randos Laboratories Ltd., assignee. Immunoassay for det kratom, its constituents and their use. United States patient US 9:582-208, 2018 Agr 24.	ld-on testing for suspected kratom use, abuse, misuse ned increased heart rate
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-Electrospray tandem mass spectroscopy ³ 1. Benchihi E, McCornell I, Lowry P, Fitzgerald P, Inventors: Randox Laboratories Ltd., assignee. Immunoassay for det	
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Regarding Patient Use of Kratom

Should anyone have access to kratom (save 'em)?

Will your patient be...
• "Bated"

- -lured by political and advocacy rhetoric without having all the facts (bait 'em)?
- - -end up a statistic because a drug-drug interaction or drug-disease CI was missed (crate 'em)?

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Post Test Question #1

Which of the following is/are true regarding kratom's mechanism of action?

- A. Blocks reuptake of dopamine
- B. Has opioid antagonist properties
- C. Is an opiate by definition
- D. All of the above

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According to the FDA and DEA respectively, kratom...

- A. is an unsafe natural substance and classified as Schedule I B. is legal in some states and illegal in others
- C. potentially dangerous, but not Scheduled by Federal Regulation
- D. c and c above

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Post Test Question #3

Kratom is a...

- A. CNS psychostimulant
- B. CNS sedative hypnotic
- C. Antidepressant
- D. All of the above

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