



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

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Disclosures

- Consultant/Independent Contractor: AcetRx Pharmaceuticals, BioDelivery Sciences International, Firstox Laboratories, Salix Pharmaceuticals
- Speaker's Bureau: AcetRx Pharmaceuticals, Salix Pharmaceuticals
- Advisory Board: AcetRx 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

- 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?

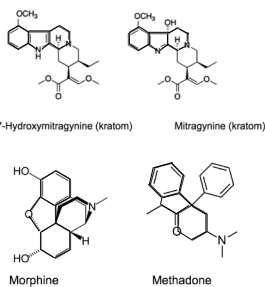
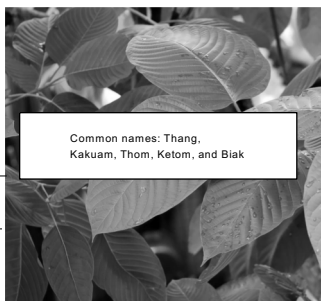
Quotes from Kratom Advocates

- "Kratom is a natural product, so how can it be harmful?"
- "Show me one article that proves kratom can be harmful."
- Dr. Fudin;
 - "...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."
 - "...either made this up off the top of his head, or someone told him this."
- "If kratom is an opiate, why doesn't it cause a positive urine screen for opiates?"
- "There is no use for using naloxone on a kratom overdose. If you "overdose" you get sick and puke."

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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Adkins, Jessica, Edward W Boyer, and Christopher R McCurdy. "Mitragynin speciosa, a psychoactive tree from Southeast Asia with opioid activity." Current topics in medicinal chemistry 11, no. 9 (2011): 1165-1175.



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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 Pharmacology

- 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 pharmacodynamic pathways

1. Suhaimi, Farah W., Nurul HM Yusoff, Rahimah Hassan, Sharif M. Mansor, Viveswaran Navaratnam, Christian P. Müller, and Zurina Hassan. "Neurobiology of Kratom and its main alkaloid mitragynine." *Brain research bulletin* 126 (2016): 29-40.
 2. Takayama, Fumihisa. "Chemistry and pharmacology of analgesic indole alkaloids from the rubiaceous plant, *Mitragyna speciosa*." *Chemical and Pharmaceutical Bulletin* 52, no. 8 (2004): 916-928.
 3. Taufik Hidayat, M., Evry Apriyam, B. M. Nabshah, M. A. A. Moklas, F. Shanda, and M. A. Farhan. "Determination of mitragynine bound opioid receptors." *Adv Med Dent Sci* 3 (2010): 65-70.



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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 activation²
 - Counteracts opioid withdrawal
 - 7-hydroxymitragynine > mitragynine: mu R agonists²
 - Mitragynine: alpha-2 adrenergic Rs agonist²

1. Suhaimi, Farah W., Nurul HM Yusoff, Rahimah Hassan, Sharif M. Mansor, Viveswaran Navaratnam, Christian P. Müller, and Zurina Hassan. "Neurobiology of Kratom and its main alkaloid mitragynine." *Brain research bulletin* 126 (2016): 29-40.
 2. Beyer, Eckhard W., Kavita M. Saba, Jessica E. Kufner, Christopher R. McCurdy, and John H. Halpern. "Self-treatment of opioid withdrawal using kratom (*Mitragyna speciosa* korth)." *Addiction* 103, no. 6 (2008): 1048-1050.



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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

1. Taufik Hidayat, M., Apriyam E., Nabshah B.M., Moklas M.A., Shanda F., Farhan M.A. Determination of mitragynine bound opioid receptors. *Adv Med Dent Sci* 2010;3(1):65-70 Beyer et al. 2007
 2. Shetty SK, Ghoshanagiri SA, Shenoi S, Prasad T, Ramani Mittal-Dave A. Systematic Review with Case Series. *Journal of Addiction Therapy* 2019; Jan 5:1-7
 3. Kambale DR, Sharma A, King TL, Laiti F, McCurdy CR, Arroy BA. Metabolic profiling and identification of enzymes responsible for the metabolism of mitragynine, the major alkaloid of *Mitragyna speciosa* korth. *Toxicol Lett* 2019; Dec 34:1-6
 4. Hughes RL. Fatal combination of mitragynine and quinine-a case report with discussion of a potential herb-drug interaction. *Forensic Science, Medicine and Pathology* 2019 Mar 14:1013-1018.



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Toxicity and Adverse Effects

- 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 products⁴

1. Saingam D, Assanangkornchai S, Geater AF, Balhup O. Pattern and consequences of kratom (Mitragyna speciosa Korth.) use among male villagers in southern Thailand: a qualitative study. *International Journal of Drug Policy*. 2013 Jul 1;24(4):351-8. Gershman et al., 2018
 2. Kronstrand R, Thelander G, Lindstedt D, Roman M, Kugelberg FC. Fatal intoxications associated with the designer opioid AH-7921. *Journal of analytical toxicology*. 2014 Oct 1;38(9):599-604.
 3. Palanisamudram Shekar S, Rojas EE, D'Angelo CC, Gillenwater SR, Martinez Galvis NP. Legally Lethal Kratom: A Herbal Supplement with Overdose Potential. *Journal of psychoactive drugs*. 2019 Jan 1;51(1):28-30.
 4. Tang MH, Chong CY, Ching DC, Mak TW. Clinical testing for ketamine. *Ketamine: Use and Abuse*. 2015 Mar 16:341.



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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?

1. Suhaimi FW, Yusoff NH, Hassan R, Mansor SM, Navaratnam V, Müller CP, Hassan Z. Neurobiology of Kratom and its main alkaloid mitragynine. *Brain research bulletin*. 2019 Sep 1;126:29-40.
 2. Kruegel AC, Grunbaum O. The medicinal chemistry and neuropharmacology of kratom: A preliminary discussion of a promising medicinal plant and analysis of its potential for abuse. *Neuropharmacology*. 2018 May 15;134:100-20.
 3. Sandoz CN, Grossenroggen SA, Ammend S, Penders T. Kratom Withdrawal: A Systematic Review with Case Series. *Journal of psychoactive drugs*. 2019 Jan 5;1-7.
 4. Smid MC, Charles JE, Gordon AJ, Wright TE. Use of Kratom, an opioid-like traditional herb, in pregnancy. *Obstetrics & Gynecology*. 2018 Oct 1;132(4):926-8.



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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. Hillstrand J, Olaszewski D, Sedefov R. Legal highs on the Internet. *Substance use & misuse*. 2010 Feb 1;45(3):330-40.
 2. Bergen-Cico D, MacCaughey K. Kratom (Mitragyna speciosa) use, addiction potential, and legal status. In: *Neuropharmacology of Drug Addictions and Substance Misuse* 2016 Jan 1 (pp. 903-911). Academic Press.
 3. Prusalek WC, Jovan AK, Anandkar SV. Pharmacology of kratom: an emerging botanical agent with stimulant, analgesic and opioid like effects. *The Journal of the American Osteopathic Association*. 2012 Dec 1;112(12):790-9.
 4. 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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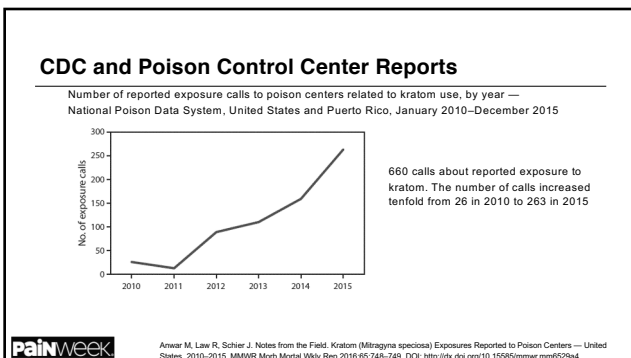
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Regulation (continued)

- 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

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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Epidemiology of Kratom Use

- 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.



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?



Grundman 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%)



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

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User Characteristics

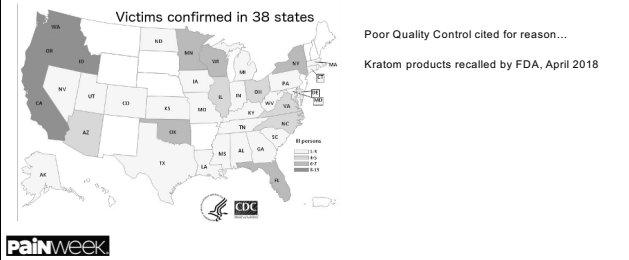
- 41% disclosed use to healthcare provider
 - Self-treatment of chronic pain 68%
 - Self-treatment of anxiety/depression 65%
 - Self-treatment related to opioid misuse (including opioid withdrawal)
- 7.7% had previous or current history of illicit drugs use
 - Including prescribed or illicit RX opioids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



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

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Adding Insult to Injury



Urine Screen

- 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. Benchikh E, McConnell I, Lowry P, Fitzgerald P, inventors; Randox Laboratories Ltd, assignee. Immunoassay for detecting kratom, its constituents and their use. United States patent US 9,952,206. 2018 Apr 24.

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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)?
- Crated
 - 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

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Post Test Question #3

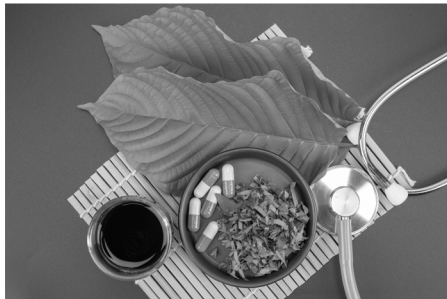
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Questions?



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