# Clinical Characterization of Kratom: Is it a Craze or Here to Stay?

Kirsten E. Smith, Ph.D., M.S.W.
Stephanie T. Weiss, M.D., Ph.D.
Translational Addiction Medicine Branch
National Institute on Drug Abuse Intramural Research Program


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## Disclosure Information

- Focus Session: Clinical Characterization of Kratom: Is it a Craze or Here to Stay? April 2, 2022
  - Presenter 1: Kirsten E. Smith, Ph.D., M.S.W.
    - Commercial Interests: No Disclosures
  - Presenter 2: Stephanie T. Weiss, M.D., Ph.D.
    - Commercial Interests: No Disclosures

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## Learning Objectives

- Describe historical & current uses of kratom, including recent epidemiological data on kratom use in US.
- List clinical characteristics of kratom use, intoxication, use disorder, and possible interventions for each.
- Identify clinically relevant pharmacodynamic effects and pharmacokinetic interactions of the kratom alkaloid, mitragynine.

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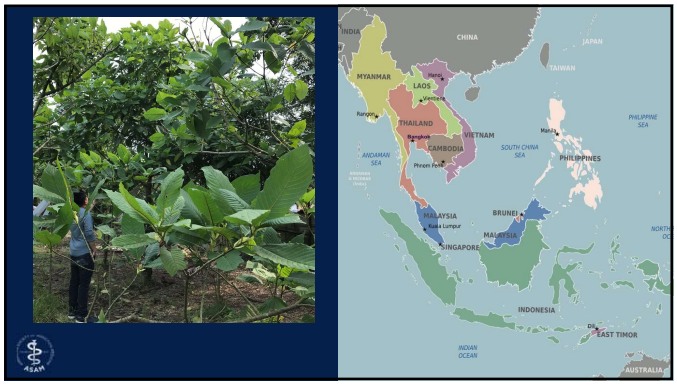
## What is Kratom?



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**Self-Treatment of Opioid Withdrawal with a Dietary Supplement, Kratom**

Edward W. Boyer, MD, PhD,[1] Kavita M. Babu, MD,[1] Grace E. Macalino, PhD,[2] Wilson Compton, MD, MPH[3]

[1]Division of Medical Toxicology, Department of Emergency Medicine, University of Massachusetts Medical School, Worcester, Massachusetts
[2]Tufts-New England Medical Center, Boston, Massachusetts
[3]National Institute on Drug Abuse, Rockville, Maryland

ADDICTION SSA SOCIETY FOR THE STUDY OF ADDICTION

**Self-treatment of opioid withdrawal using kratom (*Mitragynia speciosa korth*)**

Edward W. Boyer, Kavita M. Babu, Jessica E. Adkins, Christopher R. McCurdy, John H. Halpern

Routledge Taylor & Francis Group

**Experiences of Kratom Users: A Qualitative Analysis**

Marc T. Swogger, Ph.D.[a], Elaine Hart, M.S.[a], Pim Erowid, B.A.[a], Earth Erowid, B.A.[a], Nicole Trabold, Ph.D.[a], Kaila Yee, B.A.[a], Kimberly A. Parkhurst, B.A.[a], Brittany M. Priddy, B.S.[a] & Zach Walsh, Ph.D.[a]

Contents lists available at ScienceDirect
Drug and Alcohol Dependence
journal homepage: www.elsevier.com/locate/drugalcdep
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Full length article
Patterns of Kratom use and health impact in the US—Results from an online survey
Oliver Grundmann*

Contents lists available at ScienceDirect
Drug and Alcohol Dependence
journal homepage: www.elsevier.com/locate/drugalcdep
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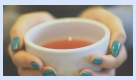
Full length article
Prevalence and motivations for kratom use in a sample of substance users enrolled in a residential treatment program
Kirsten Elin Smith*, Thomas Lawson

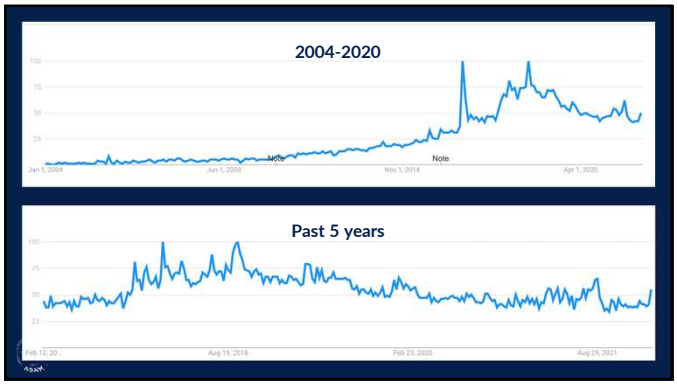
## How many people are using kratom in the US?



**Prevalence estimates vary widely**

- National Survey on Drug Use and Health (2018-2019)
  - past-month rate: 0.3%
  - past-year rate: 0.8% (2.6 million)
- Covvey *et al*. (2020): 6.1% had ever tried kratom
- American Kratom Association: ~15 million






## Past *hour*, as of February 8, 2022


## Survey (& Social Media) Self-Report: *Who is using kratom?*

- Sex/Gender split.
- Mostly Non-Hispanic White
- Late 30s-early 40s *(though this is changing)*
- Most high-school educated, many college-educated.
- Income distribution
- Most using 1-5 years
- Many use regularly, but some report having quit or used intermittently.
- Doses 2-5 times per day on average.
- Preference for kratom over other substances varies.



## Survey (& Social Media) Self-Report: *Who is using kratom?*

- Use initiation Early or Late 30s
- Other drug use history or current substance use.
- Poorer psychosocial and health indicators.

**...and we're starting to see shifts already**

## Dosing Routines & Effects



**59.7%** Used kratom>100 times

**80.6%** Used kratom >4 times per week (regular use)

**61.9** average weeks of regular use

**41.9%** Considers themselves *current* regular kratom user

**2.7** average kratom doses per day

**65.0** Weeks spent using on typical dosing regimen

**Acute effects:**

**79.8%** Felt effect every (or almost every) time kratom was dosed.

**Onset of effects (time for typical kratom dose effects to *begin*):**

**0.0%** Seconds **82.9%** Minutes **11.6%** Hours

**Duration of effects (time to *stop* feeling typical dose effects):**

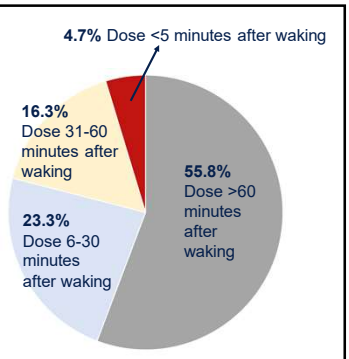
**1.6%** Minutes **91.5%** Hours

**7.0%** Unsure because I would dose before effects wore off.

| Typical regular kratom dose | |
|---|---|
| Capsules | 5.38 (±4.8) |
| Grams | 4.57 (±3.6) |
| Spoonfuls | 2.52 (±2.7) |
| Tablespoons | 2.09 (±1.0) |
| Cups of Teas | 1.62 (±1.1) |

**41.1%** typically use *more* during the first waking hour

**54.3%** would hate to give up their first kratom dose of the day compared to other times of day.




## Kratom Use Motivations

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## The list of motivations keeps growing…

| | N | % | M effectiveness | (SD) effectiveness |
|---|---|---|---|---|
| Just to feel less crappy in general and improve quality of life. | 86 | 66.7 | 74.2 | (±21.9) |
| Self-treat anxiety symptoms. | 69 | 53.5 | 69.4 | (±22.9) |
| Address occasional feelings of sleepiness or low energy. | 65 | 50.4 | 78.0 | (±21.2) |
| Relieve short-term pain (acute pain management) | 64 | 49.6 | 71.9 | (±22.1) |
| For recreation, fun, or to relax. | 63 | 48.8 | 72.4 | (±24.6) |
| Boost energy, stamina and/or endurance (for work, exercise). | 62 | 48.1 | 77.1 | (±21.8) |
| Reduce social anxiety. | 60 | 46.5 | 75.8 | (±17.4) |
| Self-treat depression symptoms. | 54 | 41.8 | 66.6 | (±22.7) |
| Self-treat long-term pain issues and symptoms (chronic pain management) | 46 | 35.7 | 72.1 | (±21.6) |
| Kratom is safer than other substances. | 43 | 33.3 | 90.4 | (±11.2) |
| To achieve a euphoric high. | 39 | 30.2 | 70.9 | (±22.3) |
| As a short-term substitute/replacement for opioids (rx opioids, heroin). | 32 | 24.8 | 66.7 | (±27.1) |
| Couldn't get a hold of other, more preferred drugs. | 31 | 24.0 | 75.4 | (±24.4) |
| Self-treat headaches/migraines. | 31 | 24.0 | 65.3 | (±22.9) |

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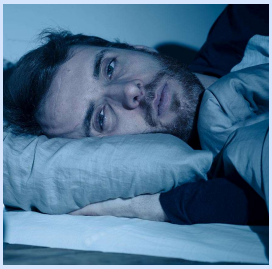
| | N | % | M effectiveness | (SD) effectiveness |
|---|---|---|---|---|
| Relieve withdrawal symptoms from nonprescribed opioids or heroin | 25 | 19.4 | 72.2 | (±25.1) |
| Self-treat chronic fatigue syndrome. | 25 | 19.4 | 72.7 | (±24.4) |
| As a short-term substitute/replacement for alcohol. | 24 | 18.6 | 66.3 | (±21.9) |
| Doctors won't prescribe you the drugs you need. | 24 | 18.6 | 82.3 | (±19.8) |
| Self-treat ADD/ADHD symptoms. | 24 | 18.6 | 61.6 | (±24.4) |
| Self-treat post-traumatic stress symptoms. | 23 | 17.8 | 61.9 | (±28.3) |
| As a long-term substitute/replacement for opioids (rx opioids, heroin). | 21 | 16.3 | 74.6 | (±24.9) |
| Relieve withdrawal symptoms from medically prescribed opioids | 20 | 15.5 | 74.2 | (±22.8) |
| Take as part of a self-designed "stack" of drugs that help you feel good. | 18 | 14.0 | 69.4 | (±21.6) |
| Because you prefer the kratom "high" to "highs" you get from other drugs. | 16 | 12.4 | 78.0 | (±21.7) |
| To believe withdrawal symptoms from a variety of different drugs. | 14 | 10.9 | 71.9 | (±25.7) |
| As a short-term substitute/replacement for stimulants (meth, cocaine) | 13 | 10.1 | 72.4 | (±28.9) |
| Self-treat irritable bowel syndrome. | 13 | 10.1 | 77.1 | (±18.6) |
| As a long-term substitute/replacement for alcohol. | 10 | 7.8 | 75.8 | (±24.7) |
| Self-treat bipolar symptoms. | 10 | 7.8 | 66.6 | (±26.1) |
| Relieve alcohol withdrawal symptoms | 8 | 6.2 | 72.1 | (±29.7) |



| | N | % | M effectiveness | (SD) effectiveness |
|---|---|---|---|---|
| Relieve withdrawal symptoms for nonprescribed buprenorphine | 7 | 5.4 | 90.4 | (±15.3) |
| As a long-term substitute/replacement for buprenorphine | 5 | 3.9 | 70.9 | (±16.0) |
| As a long-term substitute/replacement for stimulants | 4 | 3.1 | 66.7 | (±6.9) |
| Relieve withdrawal from "nootropics" or cognitive-enhancing supplements. | 4 | 3.1 | 75.4 | (±13.7) |
| Relieve withdrawal symptoms from nonprescribed methadone | 4 | 3.1 | 65.3 | (±4.7) |
| Relieve withdrawal symptoms from prescribed buprenorphine | 4 | 3.1 | 72.2 | (±3.1) |
| As a short-term substitute/replacement for buprenorphine | 3 | 2.3 | 72.7 | (±14.0) |
| As a short-term substitute/replacement for methadone. | 3 | 2.3 | 66.3 | (±13.1) |
| As a long-term substitute/replacement for methadone. | 3 | 2.3 | 82.3 | (±4.5) |
| Difficulties obtaining buprenorphine or methadone. | 3 | 2.3 | 61.6 | (±8.5) |
| Relieve withdrawal symptoms from prescribed methadone | 2 | 1.6 | 61.9 | (±7.8) |
| None of these. | 1 | 0.8 | . | . |



## Kratom Withdrawal



| | Total (N=129) | | Current KUD (N=38) | | Remitted KUD (N=23) | | Never KUD (N=68) | |
|---|---|---|---|---|---|---|---|---|
| | | *M* | | *M* | | *M* | | *M* |
| Anxiety | 32.6% | 63.2 | 50.0% | 73.1 | 43.5% | 70.9 | 19.1% | 42.8 |
| Irritability | 32.6% | 63.5 | 55.3% | 74.1 | 34.8% | 76.6 | 19.1% | 38.4 |
| Desire to use another substance | 28.7% | 67.1 | 52.6% | 75.3 | 26.1% | 73.0 | 16.2% | 48.8 |
| Low energy | 28.7% | 68.9 | 50.0% | 82.6 | 26.1% | 71.0 | 17.6% | 46.0 |
| Difficulty Sleeping | 22.5% | 74.3 | 42.1% | 71.8 | 26.1% | 82.5 | 10.3% | 73.1 |
| Restlessness | 22.5% | 56.2 | 44.7% | 58.8 | 21.7% | 65.1 | 10.3% | 43.9 |
| Nausea | 21.7% | 47.0 | 36.8% | 52.5 | 34.8% | 48.1 | 8.8% | 32.8 |
| Body aches | 21.7% | 63.1 | 44.7% | 68.4 | 21.7% | 51.2 | 8.8% | 57.8 |
| No energy | 20.9% | 75.5 | 36.8% | 88.4 | 26.1% | 69.3 | 10.3% | 55.0 |
| Upset stomach | 20.2% | 52.0 | 36.8% | 58.9 | 21.7% | 56.8 | 10.3% | 34.9 |
| Depressed mood | 20.2% | 66.1 | 39.5% | 75.5 | 17.4% | 69.0 | 10.3% | 44.4 |
| Mild-moderate kratom craving | 19.4% | 67.8 | 36.8% | 69.0 | 17.4% | 81.8 | 10.3% | 57.6 |
| Daytime sleepiness | 18.6% | 68.7 | 23.7% | 84.0 | 21.7% | 81.0 | 14.7% | 48.8 |
| Hot flashes | 15.5% | 54.0 | 36.8% | 51.4 | 8.7% | 81.5 | 5.9% | 49.8 |
| Runny nose | 14.7% | 55.9 | 34.2% | 68.4 | 17.4% | 24.3 | 2.9% | 38.0 |
| Restless legs | 13.2% | 65.5 | 21.1% | 82.6 | 21.7% | 57.8 | 5.9% | 40.8 |
| Craving for another drug | 13.2% | 77.0 | 36.8% | 76.6 | 8.7% | 68.0 | 1.5% | 100.0 |
| Cold flashes | 7.8% | 62.0 | 18.4% | 63.4 | 4.3% | 68.0 | 2.9% | 54.2 |
| Watery eyes | 7.0% | 64.2 | 18.4% | 73.1 | 8.7% | 33.0 | 0.0% | 0.0 |
| Vomiting/emesis | 6.2% | 22.4 | 10.5% | 35.3 | 4.3% | 36.0 | 4.4% | 0.7 |
| Intense kratom craving | 5.4% | 89.9 | 15.8% | 94.2 | 4.3% | 64.1 | 0.0% | 0.0 |

## Kratom Use Disorder?

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*Yes*
*Yes, but not in the past year*
*No*

**29.5%** Current (past-year) KUD (n=38)
**17.8%** Remitted KUD (n=23)
**52.7%** Never KUD (n=68)

| Lifetime Severity | Past-year Severity |
|---|---|
| Mild 21.7% | Mild 14.0% |
| Moderate 0.5% | Moderate 7.0% |
| Severe 0.5% | Severe 8.5% |

**...but something important we noticed**

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## *Individual Symptoms for kratom DSM-5 SUD diagnosis*

| | |
|---|---|
| I used kratom in larger amounts and/or over a longer period than I had intended to. | 45.7% |
| I kept using the same amount of kratom, but didn't feel it as much. | 38.8% |
| I needed to use larger amounts of kratom just to feel the same effect. | 33.3% |
| I had physical or psychological withdrawal symptoms during times I stopped using kratom. | 33.3% |
| I made at least one unsuccessful attempt to cut down or control my kratom use. | 32.6% |
| I experienced cravings, strong desires, or urges for the kratom. | 31.8% |
| I kept using kratom in order to avoid withdrawal symptoms. | 28.7% |
| I kept using kratom despite knowing it was causing or worsening physical or psychological problems for me. | 15.5% |
| I spent a great deal of time on activities necessary to get kratom, use the kratom, or recover from kratom's effects. | 15.5% |
| I kept using kratom despite knowing it was causing or worsening social or interpersonal problems for me. | 14.0% |
| I gave up or reduced some important social, occupational, or recreational activities because of my kratom use. | 10.9% |
| My kratom use repeatedly interfered with my major role obligations (at work, school, or home). | 9.3% |
| I repeatedly used kratom in situations where it was physically hazardous. | 8.5% |

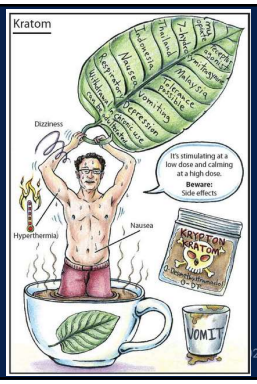


## *BACK TO DOSE....*

| **Among those who reported feeling effects from each dose (N=103)** | |
|---|---|
| Effects ***are*** compatible with ***and*** help me meet my daily obligations. | 54.40% |
| Effects ***are*** compatible with, but do ***not*** help me meet my daily obligations. | 29.10% |
| The kratom effects are ***not*** compatible with my daily obligations. | 3.90% |
| No, the effects are ***not*** compatible with my daily obligations, ***and*** they sometimes undermine my ability to meet daily obligations. | 2.90% |
| Don't use enough to know if effects are compatible or helpful daily. | 8.70% |
| None of those are quite true for me | 1.00% |



## A (Very) Brief Survey of Kratom Pharmacology, Toxicology, and Therapy




Kloss, B. T. (2014). McGraw Hill Education, NY.

## How Does Kratom Work?

- Proposed Mechanisms of Mitragynine Activity
  - Partial agonism of μ opioid receptors
  - Partial agonism (antagonism?) of κ and δ opioid receptors
  - Agonism of $\alpha_2$ (and $\alpha_1$?) receptors
  - Agonism of 5-$HT_{2A}$ (and 5-$HT_{1A}$?) receptors
  - Serotonin and norepinephrine reuptake inhibition

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Boyer, E. W. *et al.* (2008) Addiction; 103(6): 1048-1050.

## Acute Clinical Effects of Kratom Exposures Reported to US and Thai Poison Centers

Common Effects

Uncommon Effects

| | | | |
|---|---|---|---|
| Hallucinations/ delusions | 63 (8.3) | 5 (3.0) | 68 (7.3) |
| Coma | 56 (7.4) | 3 (1.8) | 59 (6.4) |
| Tremor | 53 (7.0) | 5 (3.0) | 58 (6.3) |
| Diaphoresis | 43 (5.7) | 12 (7.1) | 55 (5.9) |
| Respiratory depression | 51 (6.7) | 0 (0) | 51 (5.5) |
| Electrolyte abnormality | 26 (3.4) | 21 (12.5) | 47 (5.1) |
| Muscle rigidity | 7 (0.9) | 32 (19.1) | 39 (4.2) |
| Dystonia | 5 (0.7) | 16 (9.5) | 21 (2.3) |
| Nausea | 75 (9.9) | 14 (8.3) | 89 (9.6) |

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Davidson, C., *et al.* (2021) *The American journal of drug and alcohol abuse*, *47*(1): 74-83.

## Kratom-Associated Toxicity and Deaths

| | Southeast Asia | West (US and Europe) |
|---|---|---|
| Side Effects | Weight loss, dehydration, constipation, skin hyperpigmentation | N/V, stomach pain, chills and sweats, dizziness, unsteadiness, visual sx |
| Toxicity | Few literature reports of serious toxicity or death | Seizures, hepatotoxicity, coma, multiple deaths |
| Where Obtained | Locally | Internet, head shops |
| How Used | Often used alone (but not always) | Often combined with other drugs (illicit and meds) |
| Legal Status | Illegal in Thailand, Malaysia | Legal in most of US and some parts of Europe |

Singh, D. *et al.* (2016) Brain Research Bulletin; 126: 41-46.

## Proposed Kratom Toxicity Mechanisms

- Behavioral Factors
  - Buying kratom products online/in stores vs locally
  - Mixing it with other substances vs. using it alone
- Pharmacological Factors
  - Respiratory: Opioid respiratory depression potentiation
  - Stimulatory: seizures, alpha stimulation
  - Cardiotoxicity: QTc prolongation w/ torsades/sudden cardiac death
  - Hepatotoxicity: different CYP2D6 isoforms


Kerrigan, S. and Basiliere, S., 2022. *Wiley Interdisciplinary Reviews: Forensic Science*, 4(1), p.e1420.

## Are there any kratom-only deaths?

- None with totally convincing evidence
  - Routine testing does not detect mitragynine
  - Most cases lack comprehensive toxicological testing
- Review of UK cases (2019)
  - 156 kratom-associated deaths
  - 129 cases with post-mortem tox data reported
  - 27 cases with mitragynine as the "sole drug" implicated
  - 6 cases reported only finding mitragynine on analysis


Corkery, J.M., *et al.*, (2019) *Journal of psychopharmacology*, *33*(9): 1102-1123.

## Are there any kratom-only deaths?

- CO, USA (2019): retested blood samples from four "kratom-only" deaths using HPLC-MS
  - Three of the four cases actually contained multiple drugs
  - Fourth case could not be tested due to insufficient sample
- Takeaways:
  - Many coingestants are being missed by standard clinical and forensic testing regimens
  - Most kratom-associated deaths are polysubstance ingestions


Gershman, K. *et al.* (2019) NEJM; 380: 1-2.

## Kratom Toxicity Workup

- Primarily a clinical diagnosis
  - Good history and physical exam
  - Consider withdrawal in regular users
- Labs based upon clinical judgment
  - CMP if liver toxicity suspected
  - UDS: unlikely to be helpful

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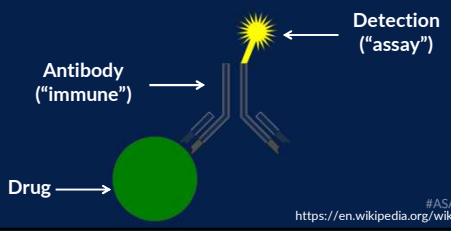
Schimmel, J. and Dart, R.C., 2020. *Drugs*, *80*(3), pp.263-283.

## Kratom Will Not Show Up on a Urine Drug Screen

- Immunoassay to detect common street drugs of abuse or their metabolites in urine

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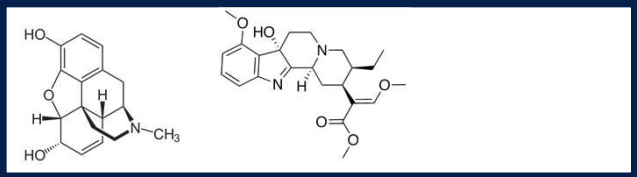
https://en.wikipedia.org/wiki/Immunoassay

## Mitragynine Structure Comparison




morphine mitragynine yohimbine

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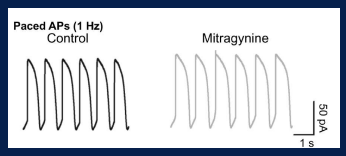
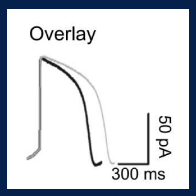
Obeng, S., *et al.* (2019) *Journal of medicinal chemistry* 63(1): 433-439.

## Kratom Toxicity Workup

- EKG: look for possible QTc prolongation

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Lu, J. *et al.* (2014) PLOS ONE; 9(12): 1-18.

## Kratom Toxicity Treatment

- Primarily supportive
- Will naloxone work?
  - A definite maybe
  - *In vitro*: effect of mitragynine alkaloids was reversed by naloxone in guinea pig ileum

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Horie, S. *et al.* (2005) Planta Med.; 71: 231-236.

## Will naloxone work?

- *In vivo:* One case report detailing successful resuscitation of an opioid toxidrome attributed to sole kratom use
  - Use of other opioids was r/o by GC/MS
  - Doesn't specify which opioids were tested for
- If the pt presents with an opioid toxidrome, give naloxone
  - But use it to treat respiratory depression

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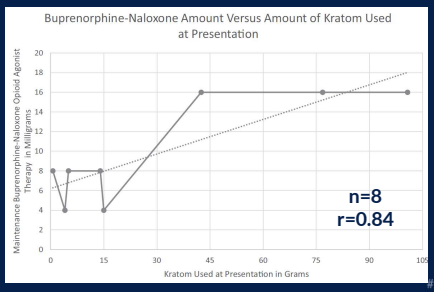
Overbeek DL *et al.* (2019) Clin. Pract. Cases Emerg. Med.; 3(1):24-26.

## Treatment of Kratom Withdrawal/KUD

| Reference | Withdrawal Treatment | KUD/Pain Treatment |
|---|---|---|
| Agapoff (2019) | Buprenorphine/naloxone | Buprenorphine/naloxone |
| Bowe (2020) | Buprenorphine/naloxone | Buprenorphine/naloxone |
| Buresh (2018) | N/A | Buprenorphine/naloxone |
| Diep (2018) | Intubation, sedation | Buprenorphine/naloxone |
| Galbis-Reig (2016) | Clonidine, Hydroxyzine | Naltrexone 50 mg PO |
| Kamaludin (2021) | Methadone | Methadone 20-25 mg PO |
| Khazaeli (2018) | Buprenorphine/naloxone | Buprenorphine/naloxone |
| Mackay (2018) | Morphine | N/A |
| McWhirter (2010) | Dihydrocodeine, Lofexidine | N/A |
| Sheleg (2011) | Buprenorphine | Methadone, Oxycodone |
| Stanciu (2019) | Clonidine, Gabapentin | N/A |
| Vento (2022) | Pregabalin, Bupropion, Trazodone | Tramadol, Clomipramine |

## Do Doses Correlate?




n=8
r=0.84

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Weiss, S.T. & Douglas, H.E. (2021) *J Add. Med*, *15*(2): 167-172.

## Treatment of KUD

**Table 2.** Previous Daily Kratom Use and Daily Stabilizing Buprenorphine Dose Comparisons.

| Past kratom use (g/d) | No. of patients | Stabilizing buprenorphine dose |
|---|---|---|
| 0–10 | 3 | 10 mg |
| 11–20 | 4 | 12 mg |
| 21–30 | 2 | 8 mg |
| 31–40 | 1 | 16 mg |
| 41–50 | 1 | 10 mg |
| 51–60 | 7 | 15 mg |
| 61–70 | – | – |
| 71–80 | 2 | 16 mg |
| 81–90 | – | – |
| 91–100 | 1 | 12 mg |
| 101–110 | – | – |
| 111–120 | 2 | 16 mg |
| >121 | 4 | 12 mg |

n=28
r=0.12

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## Summary

- Kratom has been used in the West for over a decade but has been used in Southeast Asia for centuries.
- Kratom alkaloids have multiple pharmacological effects that are thought to cause its stimulatory and opioid properties
- Kratom intoxication, withdrawal, and dependence is primarily a clinical diagnosis and treatment is supportive, but opioid agonist therapy appears to be useful

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## Questions

## Contact Info


**Email:**
kirsten.smith@nih.gov

**Twitter:**
@kirstenelins

**Email:**
stephanie.weiss@nih.gov