

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

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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**



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.

What is Kratom?











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

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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



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Routledge
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Experiences of Kratom Users: A Qualitative Analysis

Marc T. Swogger, Ph.D.^a; Elaine Hart, M.S.^b; Fire Erowid, B.A.^c; Earth Erowid, B.A.^c; Nicole Trabold, Ph.D.^d; Kaila Yee, B.A.^b; Kimberly A. Parkhurst, B.A.^b; Brittany M. Priddy, B.S.^b & Zach Walsh, Ph.D.^e



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Full length article

Patterns of Kratom use and health impact in the US—Results from an online survey



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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



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How many people are using kratom in the US?

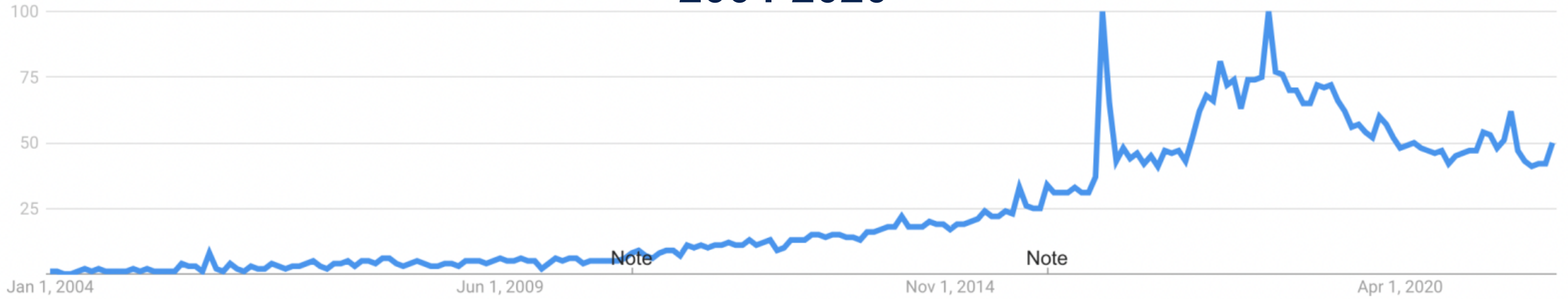


Prevalence estimates vary widely

- 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



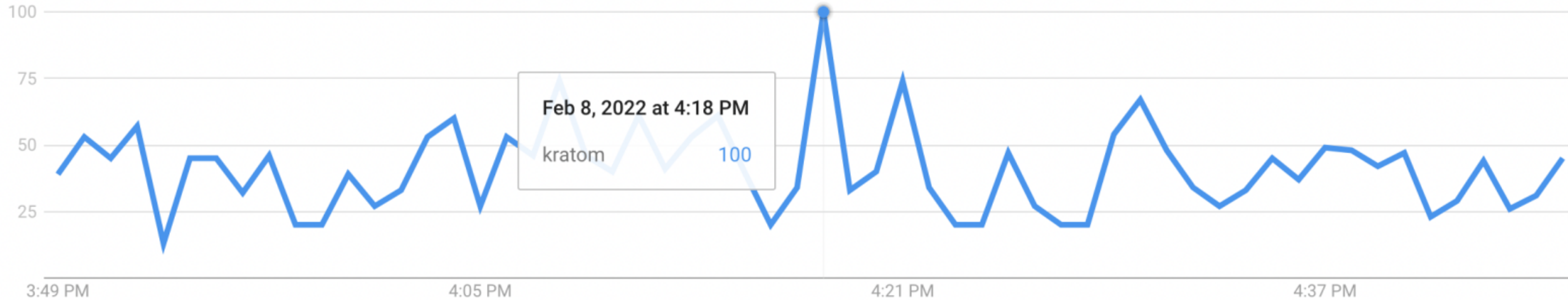
2004-2020



Past 5 years






Past *hour*, as of February 8, 2022





Non-Prescribed Buprenorphine Use Mediates the Relationship between Heroin Use and Kratom Use among a Sample of Polysubstance Users

Kirsten E. Smith ^{a,b}, Amanda M. Bunting^{*c}, Robert Walker^{b,d}, Martin T. Hall ^a, Oliver Grundmann ^e, and Olivia Castillo^f



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Kratom as a substitute for opioids: Results from an online survey

Marion A. Coe^{a,*}, Janine L. Pillitteri^b, Mark A. Sembower^b, Karen K. Gerlach^b, Jack E. Henningfield^{a,c}



Prevalence and characteristics of self-reported kratom use in a representative US general population sample

Jordan R. Covvey, PharmD, PhD, BCPS^a , Samantha M. Vogel, PharmD, BCPP^{b,c}, Alyssa M. Peckham, PharmD, BCPP^{d,e} and Kirk E. Evoy, PharmD, BCACP, BC-ADM, CTTs^{b,f,g} 

ORIGINAL RESEARCH

Self-reported Health Diagnoses and Demographic Correlates With Kratom Use: Results from an Online Survey

Rhiannon Bath, Tanner Bucholz, Amy F. Buros, PhD, Darshan Singh, PhD, Kirsten E. Smith, MS, Charles A. Veltri, PhD, and Oliver Grundmann, PhD



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Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Kratom (*Mitragyna speciosa*): User demographics, use patterns, and implications for the opioid epidemic

Albert Garcia-Romeu^{a,*}, David J. Cox^a, Kirsten E. Smith^b, Kelly E. Dunn^a, Roland R. Griffiths^{a,c}



Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Therapeutic benefit with caveats?: Analyzing social media data to understand the complexities of kratom use

Kirsten E. Smith^{a,*}, Jeffrey M. Rogers^a, Destiny Schriefer^a, Oliver Grundmann^b

 frontiers
in Pharmacology

ORIGINAL RESEARCH
published: 20 December 2021
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Kratom Use in the US: Both a Regional Phenomenon and a White Middle-Class Phenomenon? Evidence From NSDUH 2019 and an Online Convenience Sample

Jeffrey M. Rogers^{1,*}, Kirsten E. Smith¹, Justin C. Strickland² and David H. Epstein¹



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Experimental and Clinical Psychopharmacology

<https://doi.org/10.1037/pha0000518>

Social, Psychological, and Substance Use Characteristics of U.S. Adults Who Use Kratom: Initial Findings From an Online, Crowdsourced Study

Kirsten E. Smith¹, Kelly E. Dunn², Oliver Grundmann³, Albert Garcia-Romeu², Jeffrey M. Rogers¹, Marc T. Swogger⁴, and David H. Epstein¹

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



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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.

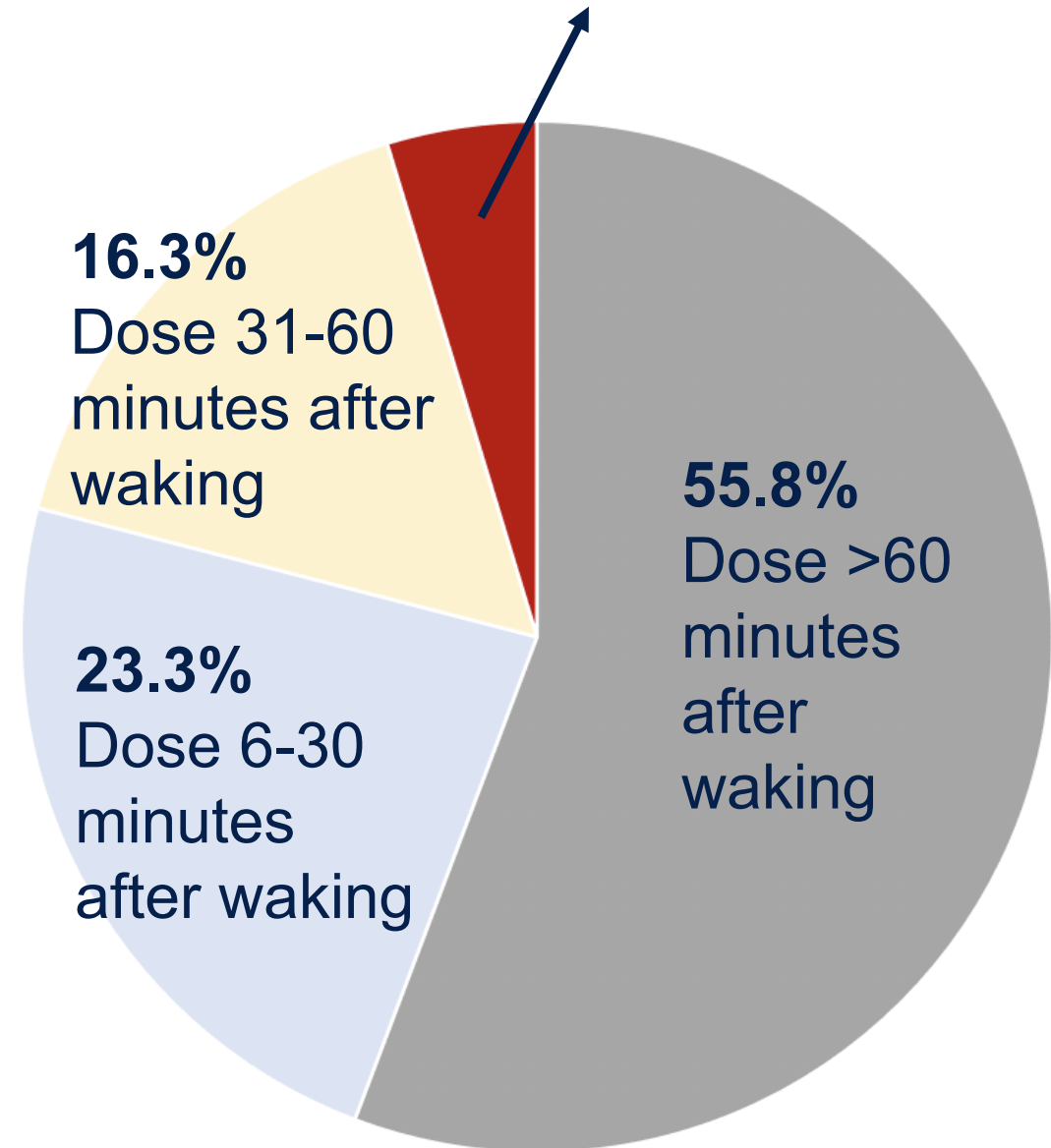
Typical regular kratom dose

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)

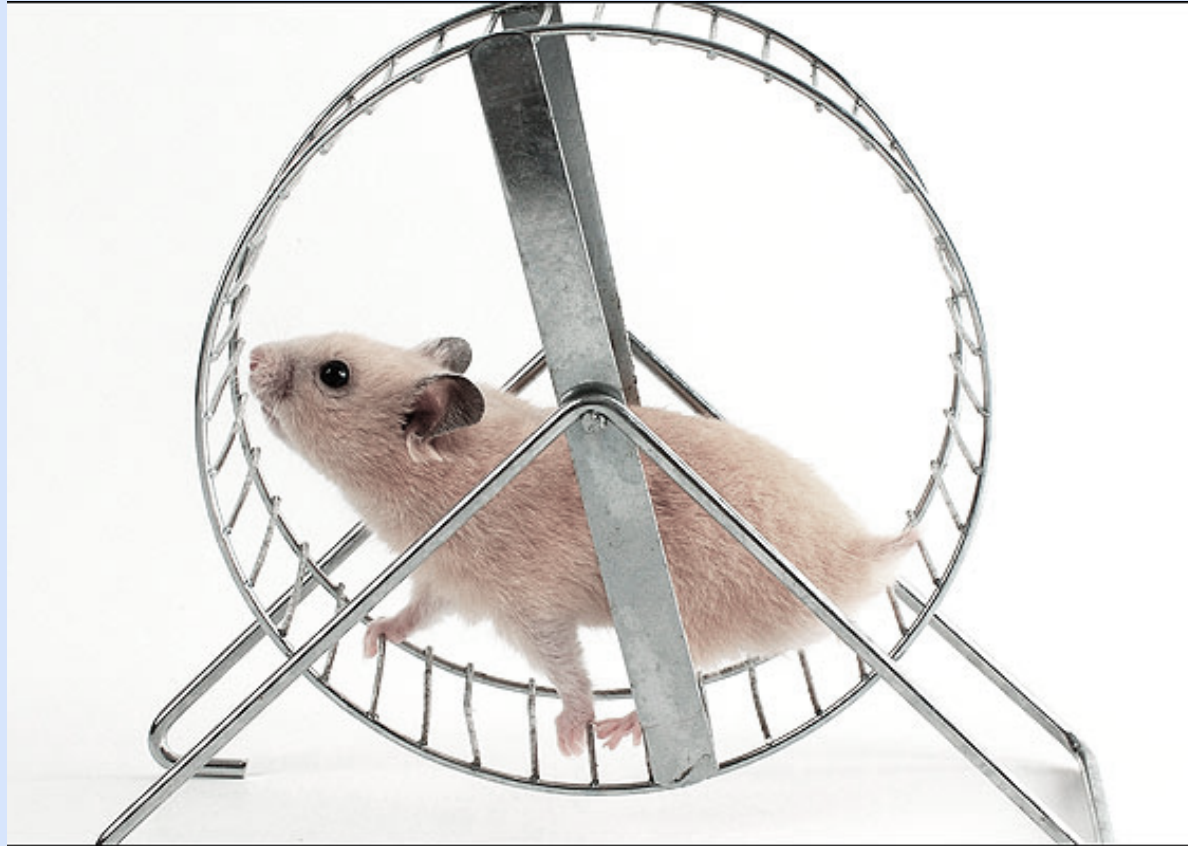
41.1% typically use *more* during the first waking hour

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

4.7% Dose <5 minutes after waking



Kratom Use Motivations



The list of motivations keeps growing...

	<i>N</i>	<i>%</i>	<i>M</i> <i>effectiveness</i>	<i>(SD)</i> <i>effectiveness</i>
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)

	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)

	<i>N</i>	<i>%</i>	<i>M</i> <i>effectiveness</i>	<i>(SD)</i> <i>effectiveness</i>
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	.	.

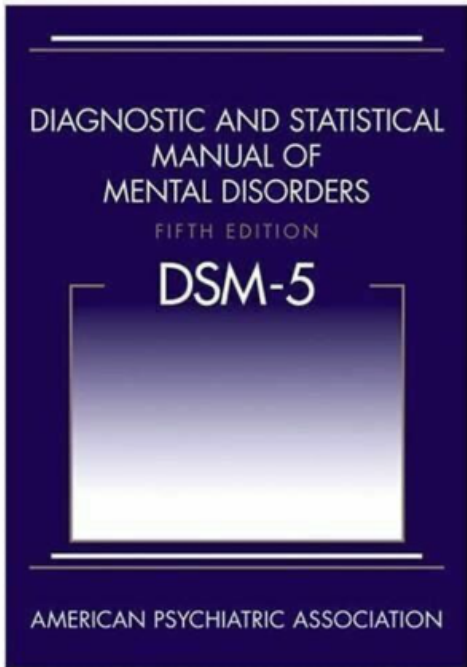
Kratom Withdrawal



	Total (N=129)		Current KUD (N=38)		Remitted KUD (N=23)		Never KUD (N=68)	
		<i>M</i>		<i>M</i>		<i>M</i>		<i>M</i>
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?





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

Mild **21.7%**

Moderate **0.5%**

Severe **0.5%**

Past-year Severity

Mild **14.0%**

Moderate **7.0%**

Severe **8.5%**

...but something important we noticed

Individual Symptoms for kratom DSM-5 SUD diagnosis

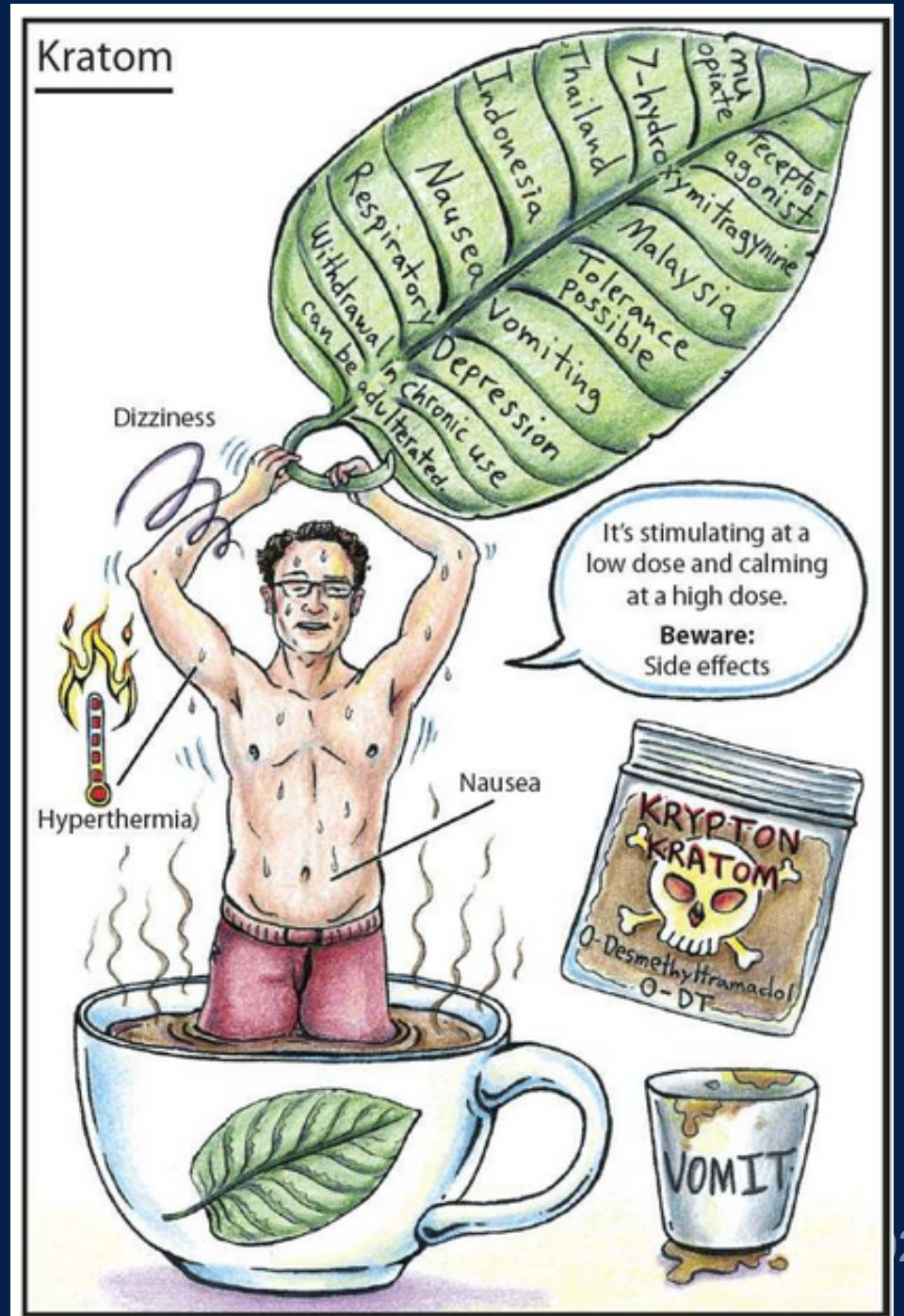
I used kratom in larger amounts and/or over a longer period than I had intended to.	45.7%
I kept using the same amount of kratom, but didn't feel it as much.	38.8%
I needed to use larger amounts of kratom just to feel the same effect.	33.3%
I had physical or psychological withdrawal symptoms during times 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 α_2 (and α_1 ?) receptors
 - ✱ Agonism of 5-HT_{2A} (and 5-HT_{1A}?) receptors
 - ✱ Serotonin and norepinephrine reuptake inhibition

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

Common Effects Uncommon

	Number of cases (%)	Effects	Number of cases (%)	Number of cases (%)
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)



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,	Legal in most of US and

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

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

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**

Kratom Toxicity Workup

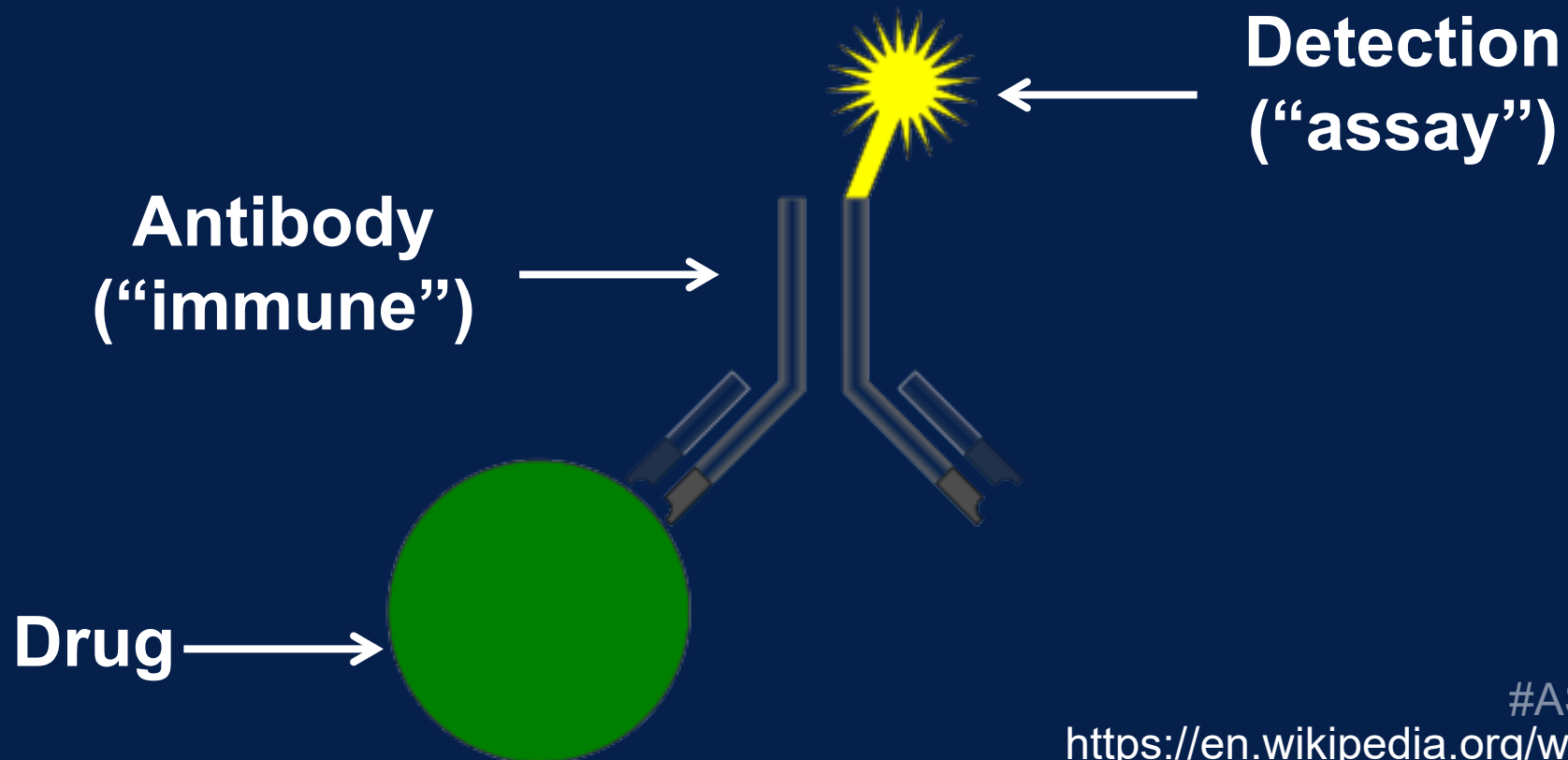
- ✱ **Primarily a clinical diagnosis**
 - ✱ Good history and physical exam
 - ✱ Consider withdrawal in regular users

- ✱ **Labs based upon clinical judgment**
 - ✱ CMP if liver toxicity suspected
 - ✱ UDS: unlikely to be helpful

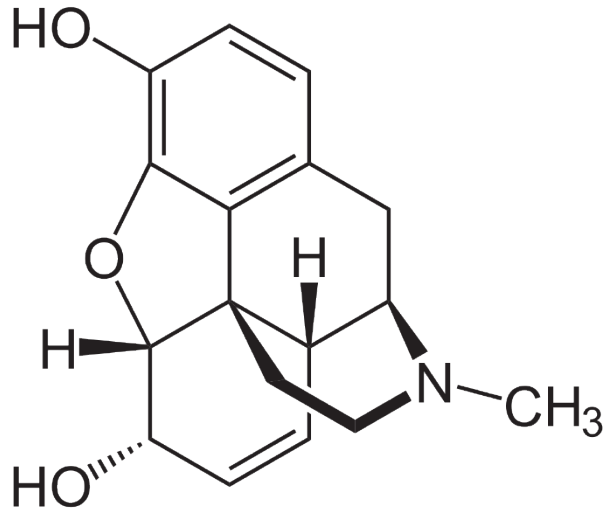


Kratom Will Not Show Up on a Urine Drug Screen

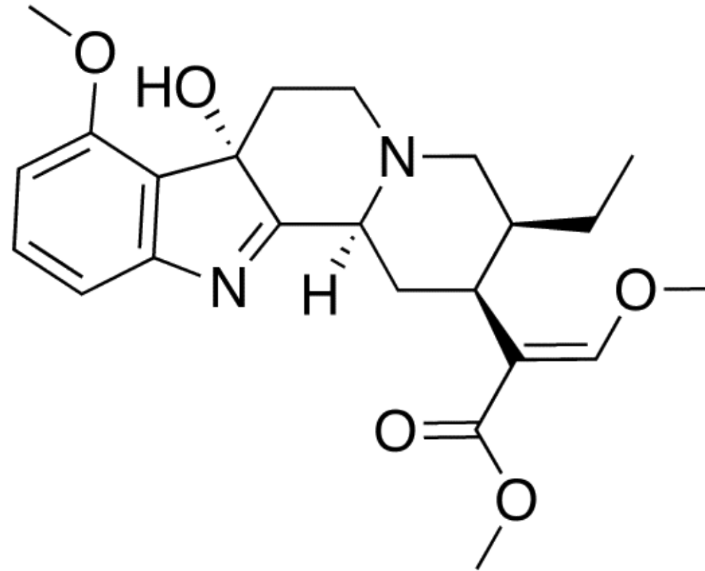
- ☀️ Immunoassay to detect common street drugs of abuse or their metabolites in urine



Mitragynine Structure Comparison



morphine

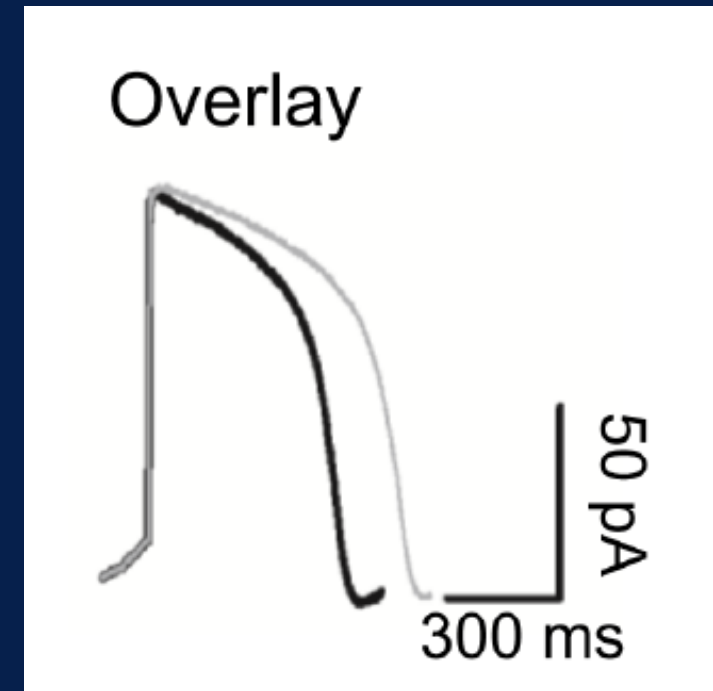
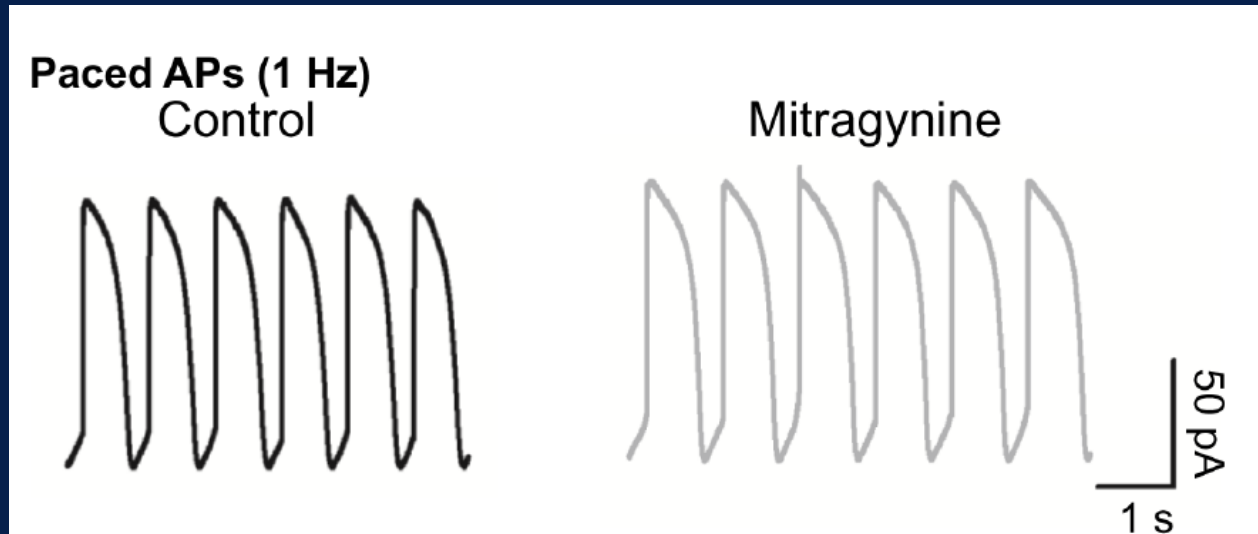


mitragynine

yohimbine

Kratom Toxicity Workup

☀️ **EKG: look for possible QTc prolongation**



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

Will naloxone work?

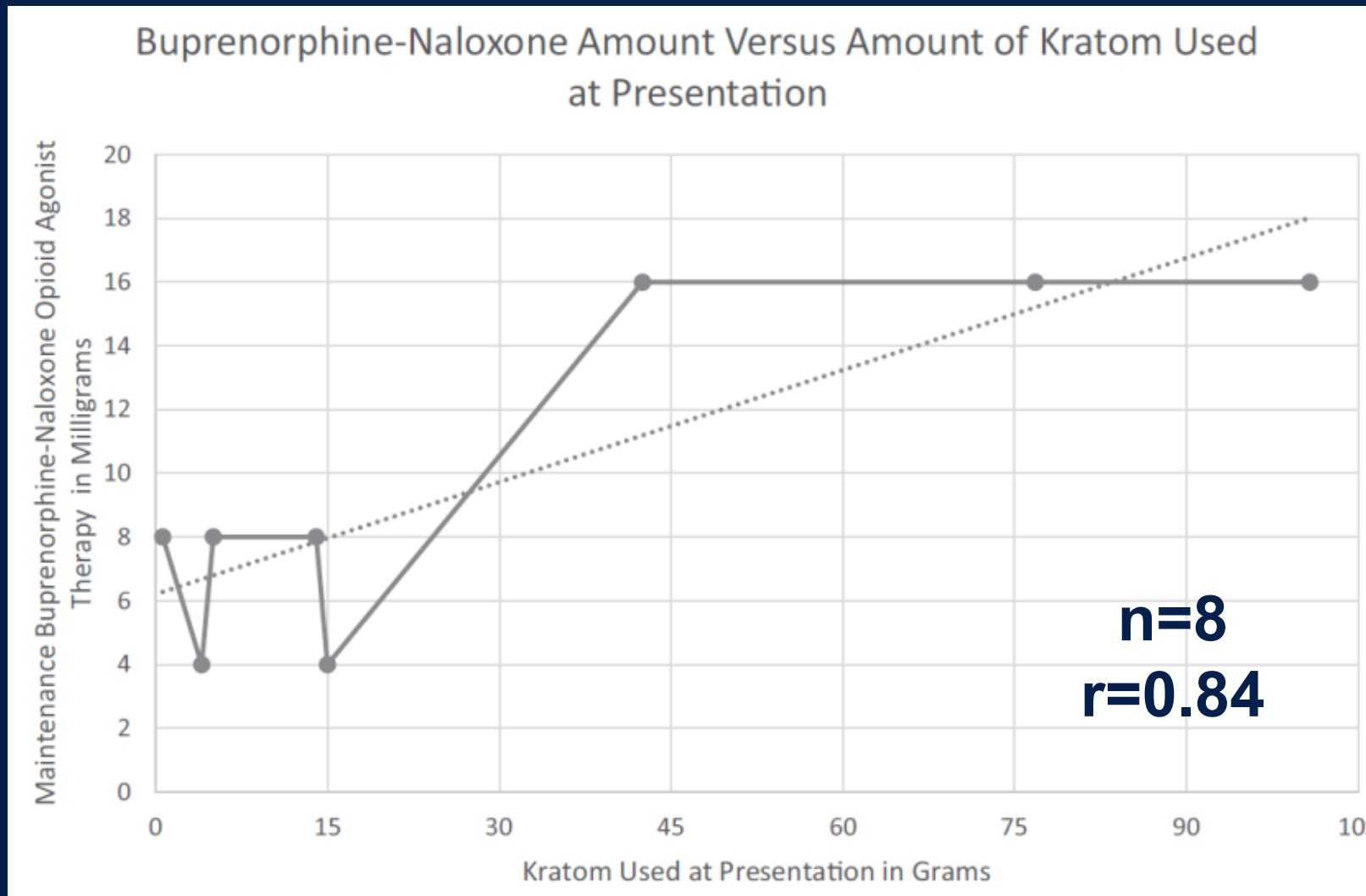
- ☀ ***In vivo*: One case report detailing successful resuscitation of an opioid toxidrome attributed to sole kratom use**
 - ☀ Use of other opioids was r/o by GC/MS
 - ☀ Doesn't specify which opioids were tested for

- ☀ **If the pt presents with an opioid toxidrome, give naloxone**
 - ☀ But use it to treat respiratory depression

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?



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

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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