PCSS Medications for Opioid Use Disorders

Providers Clinical Support System

Understanding Kratom: Consumption Patterns and Treatment Strategies for Kratom Addiction

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- The overarching goal of PCSS-MOUD is to increase healthcare professionals' knowledge, skills, and confidence in providing evidence-based practices in the prevention, treatment, recovery, and harm reduction of OUD.

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Educational Objectives

- At the conclusion of this activity participants should be able to:
  - Understand Kratom's literature, covering its uses, risks (overdose, addiction), and product toxicities.
  - Evaluate Kratom's role in harm reduction, distinguishing between evidence-based practices and misconceptions.
  - Implement evidence-based treatments for Kratom addiction, facilitating informed discussions and effective interventions with patients.

INTRODUCTION

The Plant - *Mytragyna Speciosa* Korth

- Tropical evergreen tree/shrub related to the coffee plant.
- Native to Southeast Asia
- Indigenous to Thailand, Indonesia, Malaysia and Papua New Guinea.
- First formally described in 1839 by Dutch colonial botanist Pieter Korthals.

Traditional Use

- Used for centuries by the indigenous population to enhance stamina and combat physical ailments from hard labor.
- Not regarded as “drug use”, but rather as a way of life, embedded in traditions and customs.
- Therapeutically also used for self-managing pain, cough and diarrhea.
- Leaves are chewed, brewed as tea, or to a lesser degree smoked, producing a complex stimulant and opioid-like effect.

Use in Southeast Asia

- In time it has also gained popularity as an opioid substitute.
- Its potential for tolerance and dependence has long been apparent.
- Reports of significant adverse effects or mortality in Asia are not extensively documented.
- A recent trend in the region is its use in urban settings by young individuals as part of polydrug concoctions for euphoric effects.

Use in the West

- Dry or crushed leaves; concentrated extracts, powders, capsules; tablets, liquids, and gum/resin.
- Readily available at smoke shops or through online vendors with no quality control.
- Dramatic increase in importation since 2016.

Use in the West

- Kratom is increasingly used by people who advocate for it as a plant-based remedy to self-manage pain, mental health symptoms, and opioid withdrawal.
- Growth of Kratom use in the Western world also parallels increasing concerns over adverse effects, abuse, and addictive potential.
- Adverse effects associated with Kratom products span multiple organ systems including hepatic, renal, cardiac, endocrine, and neurological.
- Fatalities involving kratom are increasingly documented, however involve co-ingestions, or polydrug combinations.

Epidemiology

Study	Study sponsor / recruitment	Sample	Prevalence
Palamar, 2021 (NSDUH 2019 data reported in 2020)	US Federal survey by SAMHSA (N=67,625) Nationally-representative sample, face-to-face interviews	General US population aged 12+	Lifetime: 1.5% Past year: 0.7% Past month: 0.3%
Schimmel, 2020	US survey by RADARS System panel of paid responders (N=59,714) Non-probability sample with online self-administration	General US population aged 18+	Lifetime: 1.3% Past year: 0.8%
Covvey, 2020	US survey via Qualtrics Panels (N=1,842) Non-probability sample with online self-administration	General US population aged 18–59	Lifetime: 6.1% Past year: 4.1% Past month: 3.5%
AKA	Estimate of number of US kratom consumers based on Southeast Asian kratom export volume in consultation with kratom venders and retailers	Average monthly volume of Kratom exported to the US / average monthly volume of kratom use by the US kratom consumer = approximate number of US kratom consumer	15,600,244 estimated US kratom consumers
Botanical Education Alliance and AKA	US surveys of kratom venders and retailers 2014-2016	Kratom venders and retailers	3–5 million kratom consumers
Stanciu (this study)	Addiction Services embeded within a state psychiatric hospital (N = 578) Addiction psychiatry evaluations via self report	SMI patients referred to the addiction services for substance use interventions	Lifetime: 2.2% Past year: 1.9% Past month: 1.7%

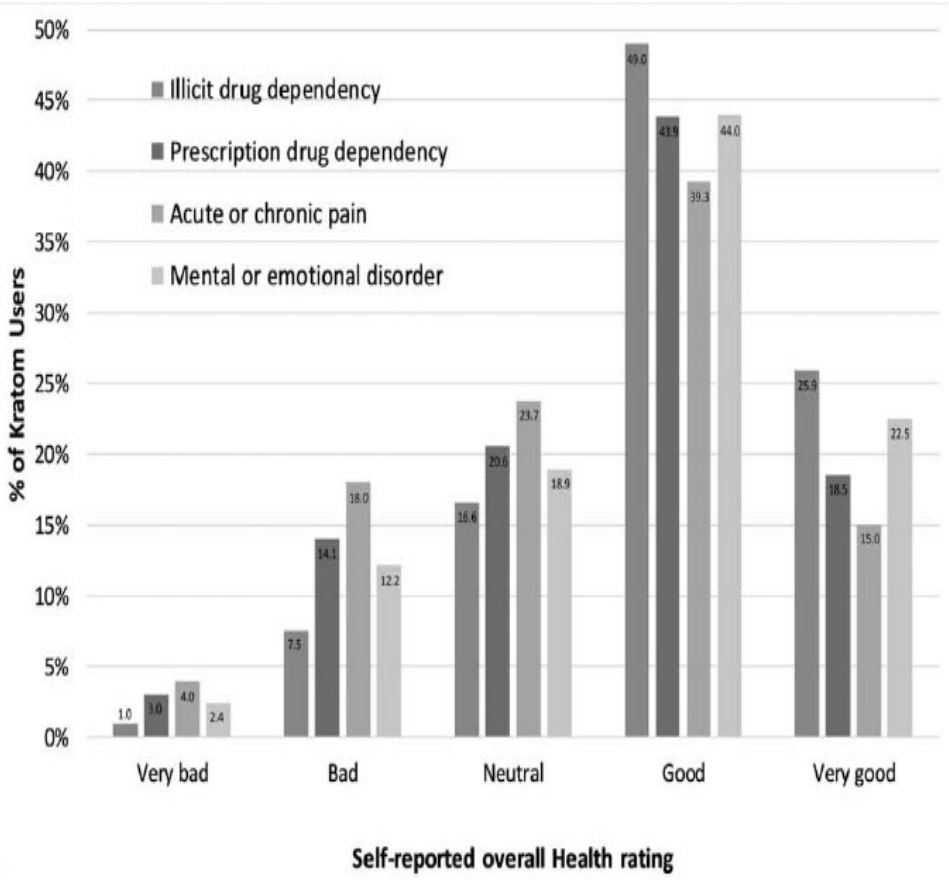
- The prevalence of Kratom use in the United States is not well defined, with lifetime estimates ranging from 0.9 to 6.1%
  - versus 2.9 to 12% in Thailand.

Epidemiology

- Association data supports a greater burden of mental health and substance use disorders, especially opioids, among users.
- Lifetime nonmedical opioid use is also associated with a greater likelihood of Kratom use.
- In SE Asia:
  - Tolerance occurs within 3 months, and some escalate use 4-10x within the first few weeks.
  - 55% of regular users become dependent, with some reports suggesting a relapse rate of 78-83% at 3 months.

Survey of consumers

- Demographics:
  - Middle-aged (31-50 years of age), white male.
  - Married, employed, and insured.
  - Some college education with an income of over $35,000 / year.
  - Duration of use >1 year but < 5 years.
- Reasons for use
  - Self-manage chronic pain (68%), anxiety, or depression (65%) and as an opioid replacement.
  - 40% of users endorse the use of Kratom to reduce/stop opioid use, with 74% claiming >6mo success in abstinence.
  - 41% disclosed use to healthcare providers.
- Ratings of improvements show a majority of consumers rate overall health as “good”.



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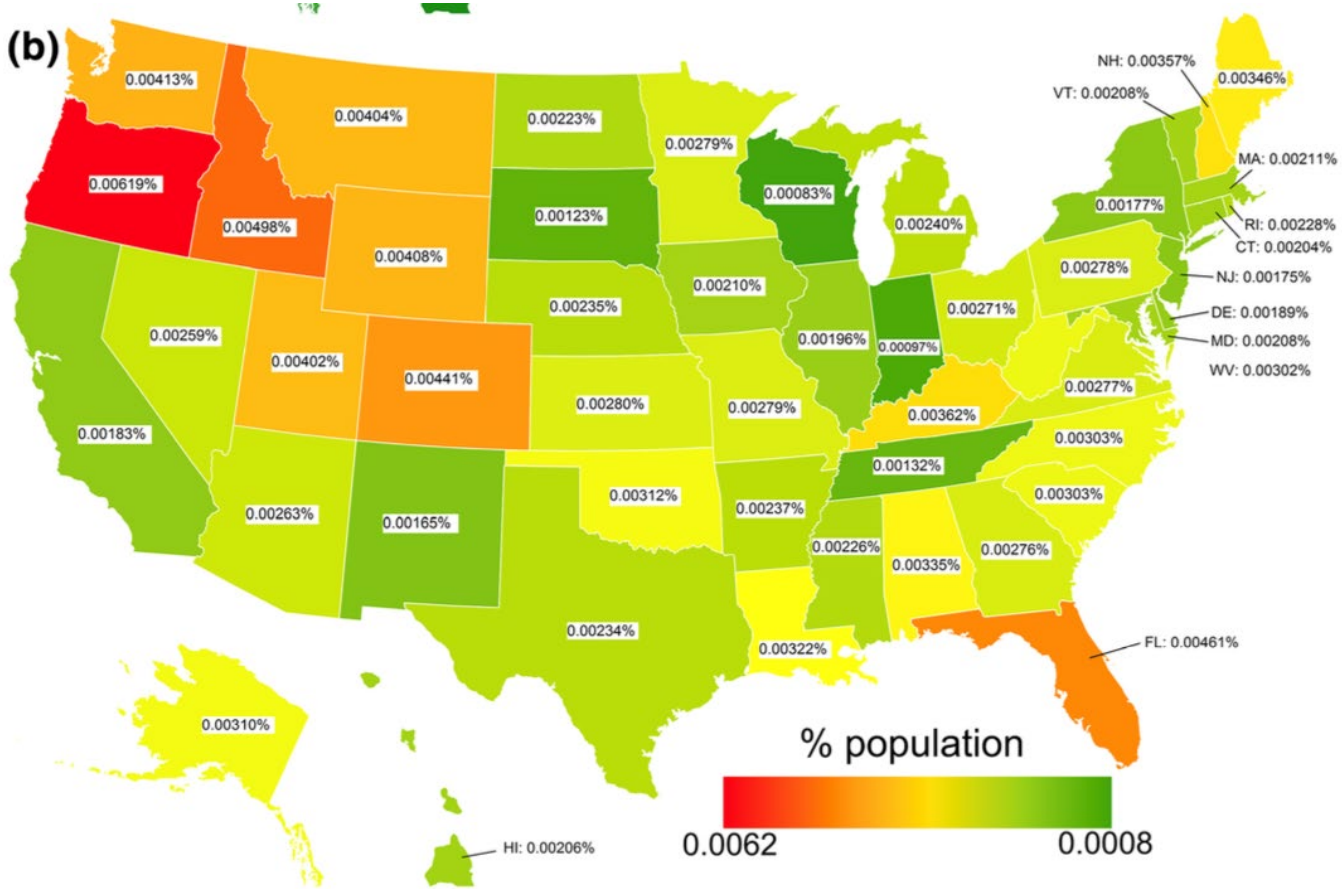
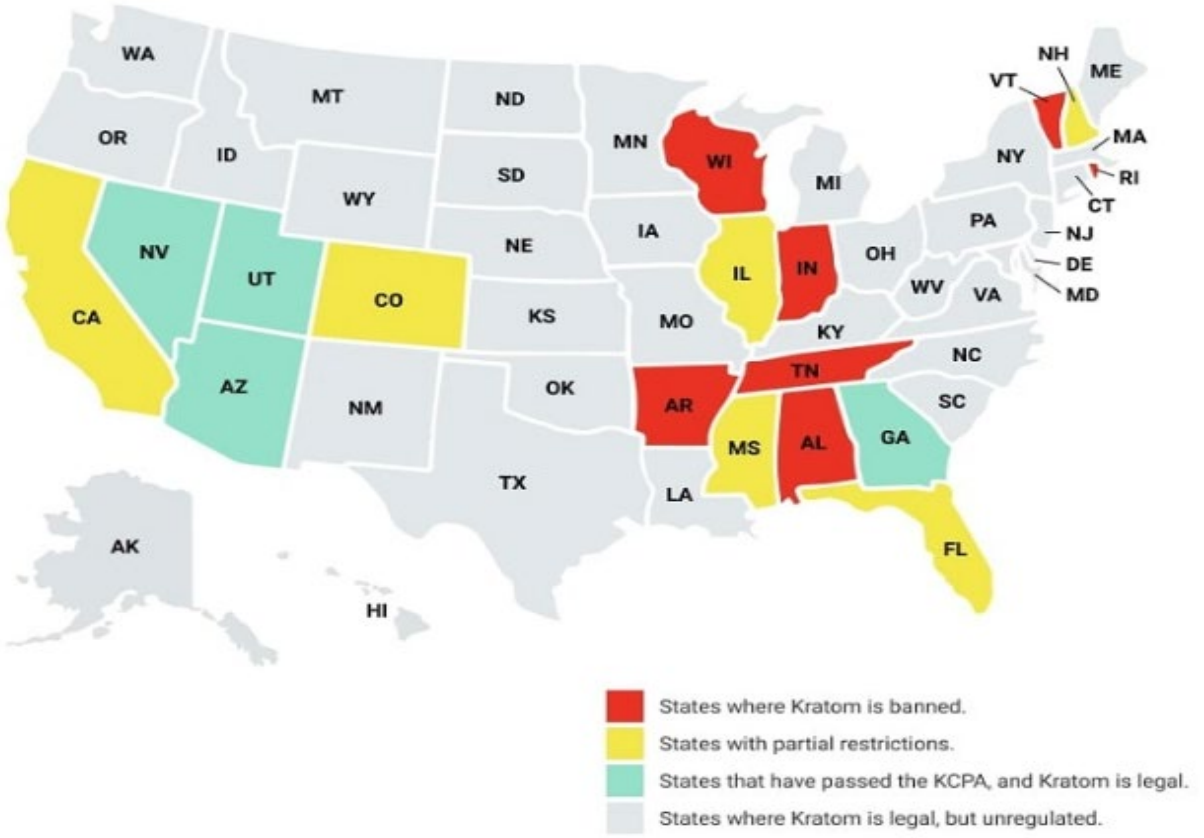
Distribution of Consumers

- Heavily concentrated in the South, followed by West and Midwest, and few in the Northeast



Legal Status and Regulation on Sales

- Malaysia, Vietnam – illegal.
- Thailand – illegal until 2021.
- In the US it was legal to grow and purchase in all states until 2015.
- Uncontrolled under federal regulation.
- In 2016 the DEA submitted an intent to schedule under the CSA, but later that year withdrew.
- The Kratom Consumer Protection Act exists in some states as legislation to ensure consumer access to Kratom with a framework for regulatory oversight.



PHARMACOLOGY

Behavioral Pharmacology

- The effects in humans have historically been described as dose-dependent:

- Small doses (1-5g)
  - Stimulatory, caffeine-like, effects.
- Larger dosages (>5g)
  - Sedative, analgesic effects.

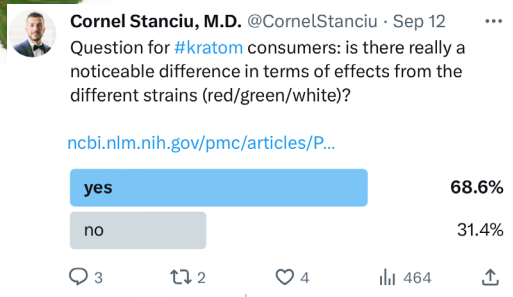
Complex Composition

Alkaloid	Percentage	Effect
Mitragynine	66%	Analgesic, antitussive, antidiarrheal, adrenergic, antimalarial
Paynantheine	9%	Smooth muscle relaxer
Speciogynine	7%	Smooth muscle relaxer
7-Hydroxymitragynine	2%	Analgesic, antitussive, antidiarrheal
Speciociliatine	1%	Weak opioid agonist
Mitraphylline	<1%	Vasodilator, antihypertensive, muscle relaxer, diuretic, antiamnesic, immunostimulant, anti-leukemic
Isomitraphylline	<1%	Immunostimulant, anti-leukemic
Speciophylline	<1%	Anti-leukemic
Rhynchophylline	<1%	Vasodilator, antihypertensive, calcium channel blocker, antiaggregant, anti-inflammatory, antipyretic, anti-arrhythmic, antithelmintic
Isorhynchophylline	<1%	Immunostimulant
Ajmalicine	<1%	Cerebrocirculant, antiaggregant, anti-adrenergic, sedative, anticonvulsant, smooth muscle relaxer
Corynantheidine	<1%	Opioid agonist
Corynoxine A	<1%	Calcium channel blocker, anti-locomotive
Corynoxine B	<1%	Anti-locomotive
Mitrafoline	<1%	
Isomitrafoline	<1%	
Oxindale A	<1%	
Oxindole B	<1%	
Speciofoline	<1%	Analgesic, antitussive
Isospeciofoline	<1%	
Ciliaphylline	<1%	Analgesic, antitussive
Mitraciliatine	<1%	
Mitragynaline	<1%	
Mitragynalinic acid	<1%	
Corynantheidalinic acid	<1%	

- Leaf analysis
  - 40 structurally related alkaloids, flavonoids, terpenoid saponins, polyphenols, and various glycosides.
- >25 indole alkaloids
  - 1-2% by weight
  - Mitragynine (MG)
    - ~60%
  - 7-hydroxymitragynine (7OHMG)
    - Extremely small representation of plants
    - Metabolic product of MG (CYP3A4)

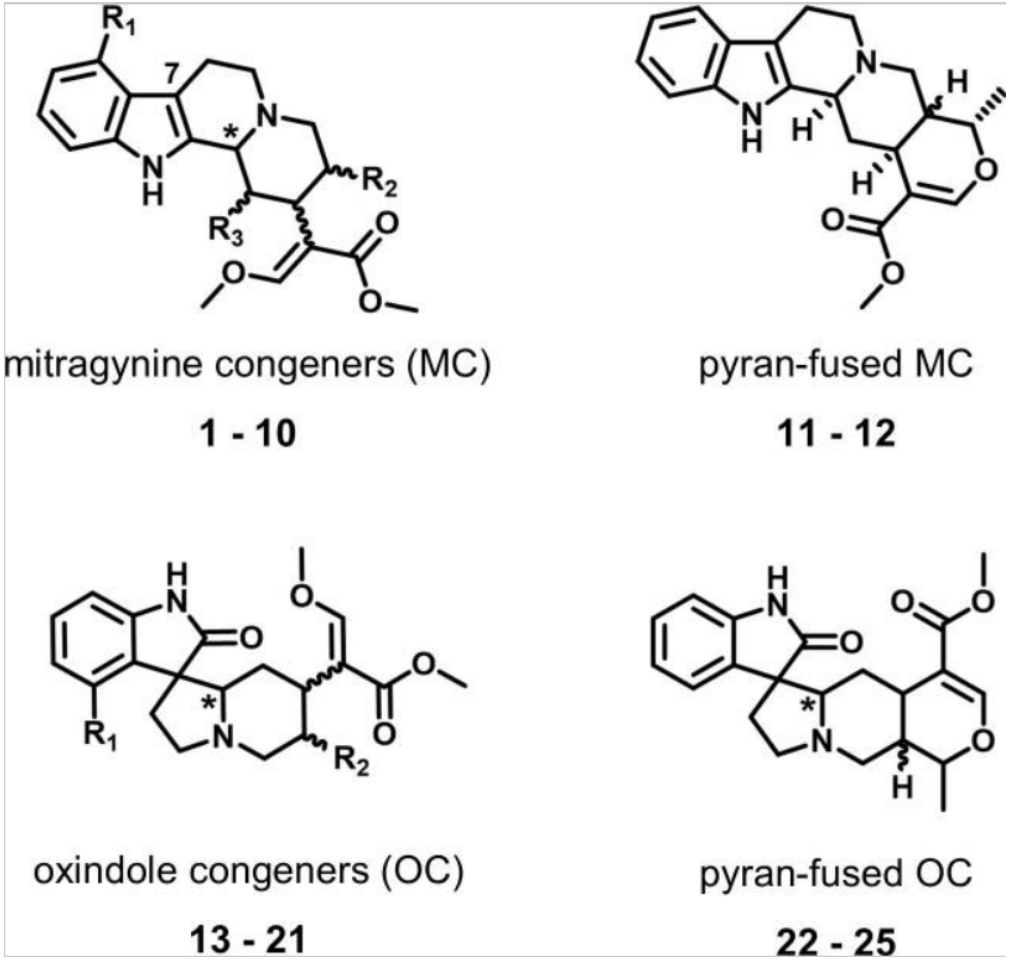
“Potency”

- White vein – stimulating, to help with concentration.
- Green vein – improves mood, and depression.
- Red vein – calming effects, to help relax/sleep.



- Commercial products differ in composition.

Phase Model

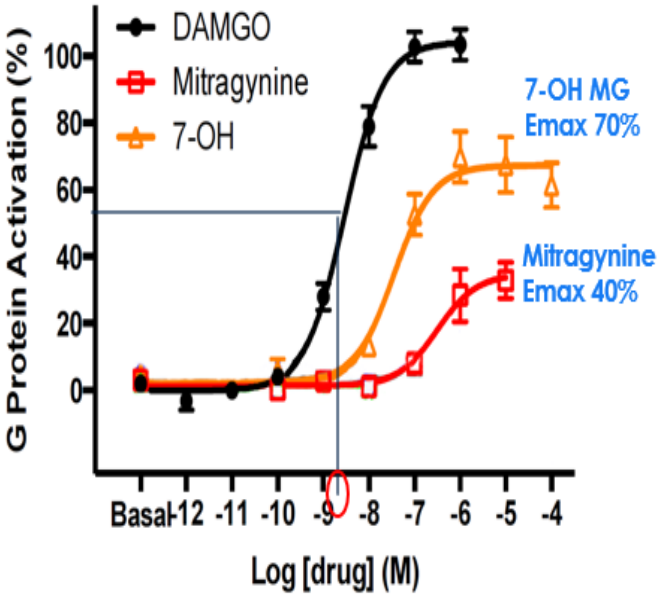

mitragynine congeners (MC)
1 - 10
pyran-fused MC
11 - 12
oxindole congeners (OC)
13 - 21
pyran-fused OC
22 - 25

Opioid Receptors

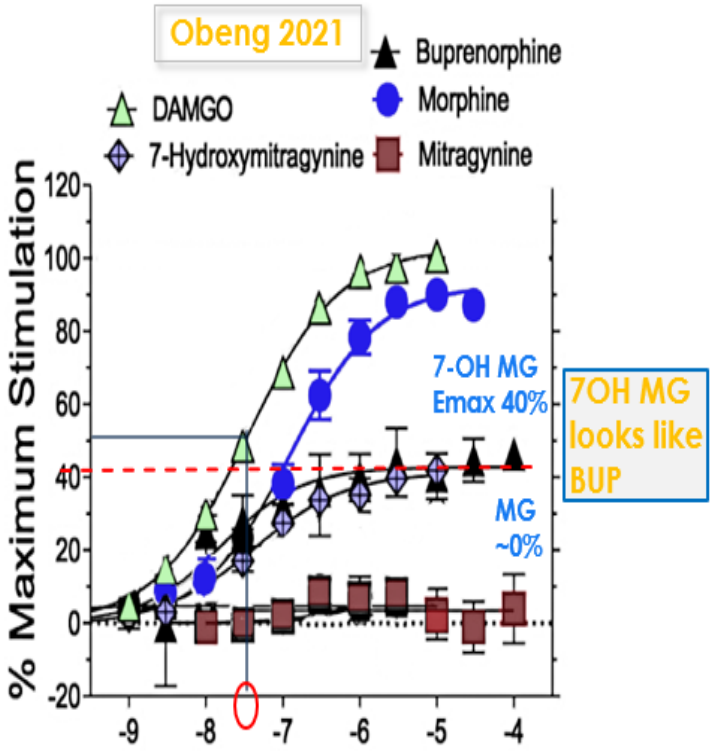
ID	Name	Mu		Kappa		Delta	
		K_i [μM]	Prediction (Clarity/SEA)	K_i	Prediction	K_i	Prediction
1	Mitragynine	0.74	T T	1.3	T T	6.5	T T
2	Speciogynine	1.0	T T	3.6	T T	>10	T T
7	7-hydroxymitragynine	0.070	T T	0.32	T T	0.47	T T
11	Ajmalicine	8.96	+ -	>10	- -	>10	- -
12	Tetrahydroalstonine	>10	+ -	>10	- -	>10	- -
14	Corynoxine B	1.6	- +	>10	- +	7.6	- -
16	Isorhynchophylline	0.54	- +	>10	- +	6.4	- -
20	Corynoxeine	>10	- +	>10	- -	>10	+ -
21	Isocorynoxeine	>10	- +	>10	- -	>10	+ -

Opioid Receptor Efficacy

Kruegel 2016

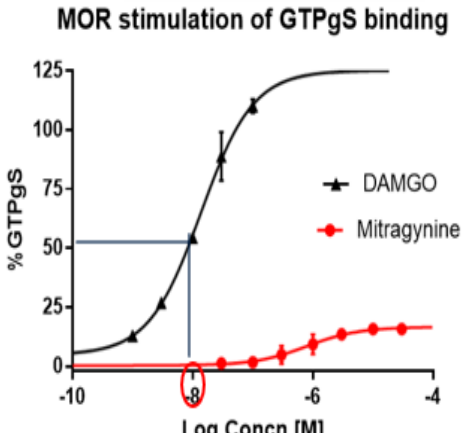


Obeng 2021



7OH MG looks like BUP

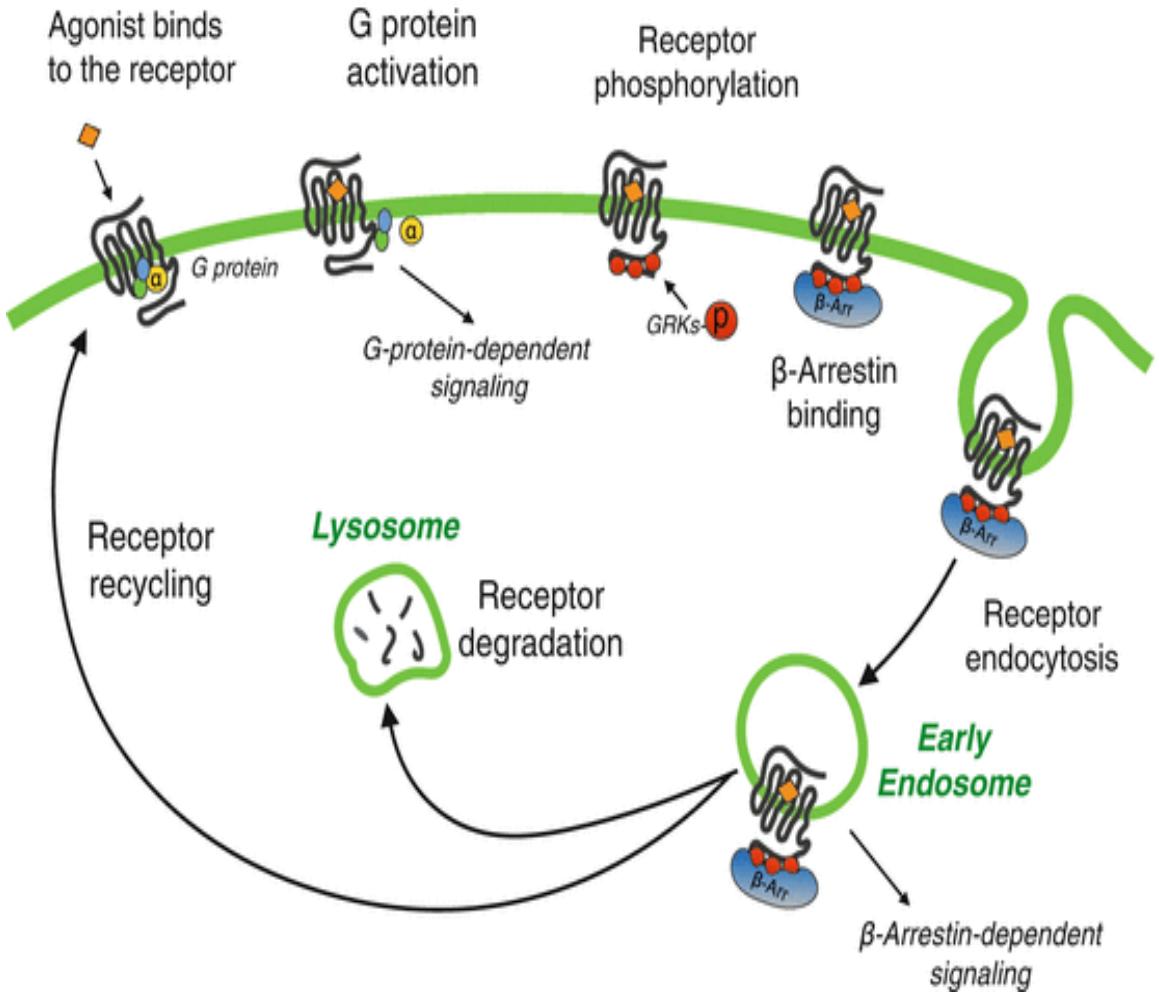
NIDA Contract study with Eurofins



	Mitragynine	DAMGO
EC50	7.907e-007	1.369e-008

	Mitragynine	DAMGO
Top	16.61	125.1

Atypical Interactions with Opioid Receptors



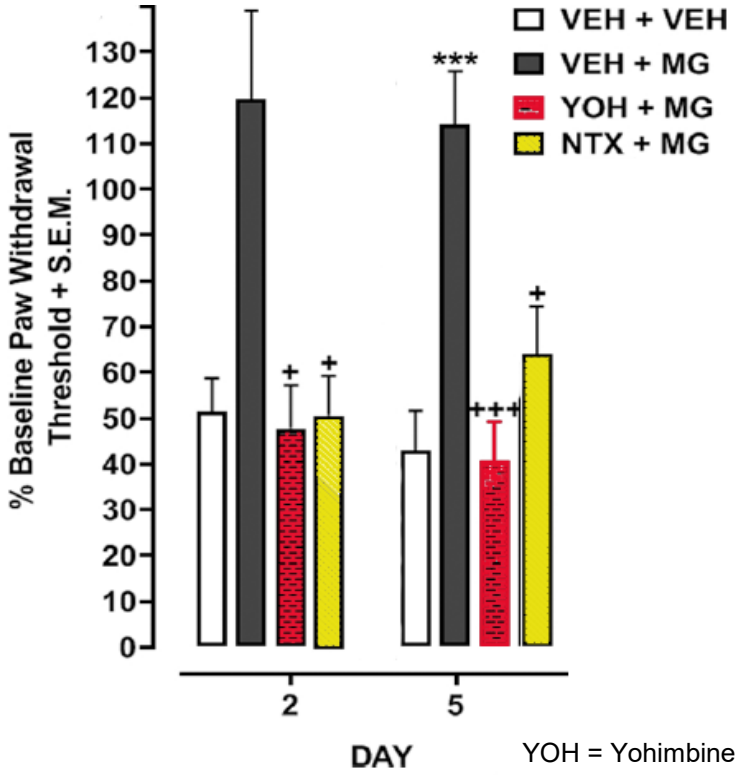
- Similarities to opioids:
  - Partial agonism at mu receptors
  - Binding to opioid Rs initiates G-protein-coupled receptor (GPCR) signaling.
- Differences from opioids:
  - GPCR activation by indole alkaloids does not initiate the β-arrestin pathway
    - "biased agonism"
- MG also exerts non-opioid receptor pain-relieving effects by stimulating alpha-2 and inhibiting cyclooxygenase-2 mRNA and protein expression.

Other Receptor Systems

			Adrenergic Receptors						Serotonin Receptors		
			Alpha-2A		Alpha-2B		Alpha-2C		5-HT1A		5-HT2A
ID	Name	K_i [μM]	Prediction (Clarity/SEA)	K_i	Prediction	K_i	Prediction	K_i	Prediction	K_i	Prediction
1	Mitragynine	2.3	+ +	4.9	+ +	3.5	- +	5.8	- -	7.3	+ -
2	Speciogynine	0.36	+ +	2.6	+ +	0.68	- +	0.54	- -	2.9	+ -
7	7-Hydroxy mitragynine	>10	+ -	>10	+ -	>10	+ -	>10	- -	>10	- -
11	Ajmalicine	0.045	T T	0.043	T T	0.065	- T	0.42	+ -	>10	- -
12	Tetrahydroalstonine	0.018	T T	0.040	T T	0.053	- T	0.38	+ -	2.6	- -
14	Corynoxine B	>10	- -	>10	- -	>10	- -	>10	- -	>10	- -
16	Isorhynchophylline	4.8	- -	>10	- -	>10	- -	>10	- -	>10	- -
20	Corynoxeine	>10	- -	8.4	- -	>10	- -	>10	- -	>10	- -
21	Isocorynoxeine	>10	- -	>10	- -	>10	- -	>10	- -	>10	- -

MG

- MG relieves neuropathic pain.
  - Relief blocked by both opioid and adrenergic blockers.



YOH = Yohimbine

ADVERSE EFFECTS

Animal Studies

- Ascending doses of Kratom alkaloids result in an increase in:
  - Blood pressure
  - Liver function tests
  - Creatinine
  - Death preceded by convulsions, not respiratory depression

- Herb: drug interactions:
  - MG inhibits CYP 2C9, 2D6, 3A4 as well as glucuronidation by UDP-glucuronosyltransferases.

- Labilities:
  - MG less reinforcing than morphine and may be tolerance-sparing when co-administered.
  - 7OHMG substitutes for morphine, re-institutes conditioned place preference (CPP, measure of rewarding effects in animal models).

Human Case Reports

- After > 1 year of regular use:
  - Weight loss; Insomnia; Constipation; Skin hyperpigmentation; Extreme fatigue.

Organ system	Presentation signs and conditions	References
Hepatic	Acute liver failure, hepatitis, transaminitis, intrahepatic cholestasis, hepatomegaly	[23, 108–116, 131]
Endocrine	Hypothyroidism, hypogonadism	[26, 100]
Renal	Acute kidney injury	[67]
Cardiac	Cardiotoxicity, arrhythmia	[98, 99]
Pulmonary	Acute lung injury, ARDS	[101, 102]
Obstetric	Neonatal abstinence syndrome	[103–107]
Neurological	Acute brain injury, seizure, coma, cognitive impairment	[21, 81, 117, 118]

Poison Control Centers

- Kratom overdoses resemble adrenergic toxicity more so than opioids:
  - Nausea and tachycardia predominate.
  - Respiratory depression is rare.

Clinical effects	Total n (%[a])	Clinical effects	Total n (%[a])
Single-substance exposure total	1174		
Neurological		**Gastrointestinal**	
Agitated/irritable	269 (22.9)	Nausea	171 (14.6)
Drowsiness/lethargy	168 (14.3)	Vomiting	155 (13.2)
Confusion	125 (10.6)	Abdominal pain	76 (6.5)
Seizures (single/multiple)	113 (9.6)	**Respiratory**	
Tremor	79 (6.7)	Respiratory depression	42 (3.6)
Dizziness/vertigo	62 (5.3)	**Hematologic/hepatic**	
Hallucinations/delusions	61 (5.2)	AST, ALT > 100	59 (5.0)
Cardiovascular			
Tachycardia	251 (21.4)		
Hypertension	119 (10.1)		

Kratom-Related Deaths

- Co-ingestions and other active use disorders predispose patients to death (found in 87% of cases).
- It is challenging to identify which deaths are attributed to kratom alone.

Table 1: Details of Kratom-Attributed Overdoses in New England

State	Year	Gender	Age	Medical and psychiatric comorbidities	Prescribed medications	SUD	Kratom use	Last known responsive	Found unresponsive	Toxicology Findings	Autopsy findings	Other facts / comments
NH	2018	M	31	mostly unknown except new onset seizures, ~ months	unknown	Past illicit use, including heroin and fentanyl	Tea (per family), recent months considering it "safer than heroin or fentanyl"	5/10/18 ~00:00 EST	5/10/18 09:44 EST	5/11/2018 femoral blood: caffeine; cotinine; 11-OH-delta9-THC 2.1 ng/mL; delta9-carboxy-THC 11 ng/mL; delta9-THC 8.9 ng/mL; MG 890ng/mL.	Unremarkable	
ME	2020	M	25	unknown	none	Known polysubstance abuse history	unknown	same day	22:41 EST	Ethanol 338 mg/dL; cotinine; MG 23 ng/dL	Unremarkable	Hypodermic needle found at site
CT	none											
RI	cannot be disclosed	cannot be disclosed	cannot be disclosed	cannot be disclosed	cannot be disclosed	cannot be disclosed	cannot be disclosed	cannot be disclosed	cannot be disclosed	cannot be disclosed	cannot be disclosed	
MA	2022	F	36	atherosclerotic cardiovascular disease	cannot be disclosed	cannot be disclosed	cannot be disclosed	cannot be disclosed	cannot be disclosed	cannot be disclosed	cannot be disclosed	
VT	none											

Stanciu, C.N., et al. (2023). "Kratom Overdose Risk: A Review." Curr Addict Rep, 10(1), 9–28. DOI: 10.1007/s40429-022-00464-1

MANAGEMENT

Detection

- ~41% of Kratom consumers disclose consumption to healthcare providers.
  - In assessments, use non-judgmental, non-stigmatizing, questions
    - "Do you use any herbal medicines, like valerian root or kratom?"

- Not detected by routine toxicology or conventional confirmatory drug screening tests.
- HPLC or Mass spectrometry is required for detection & identification.

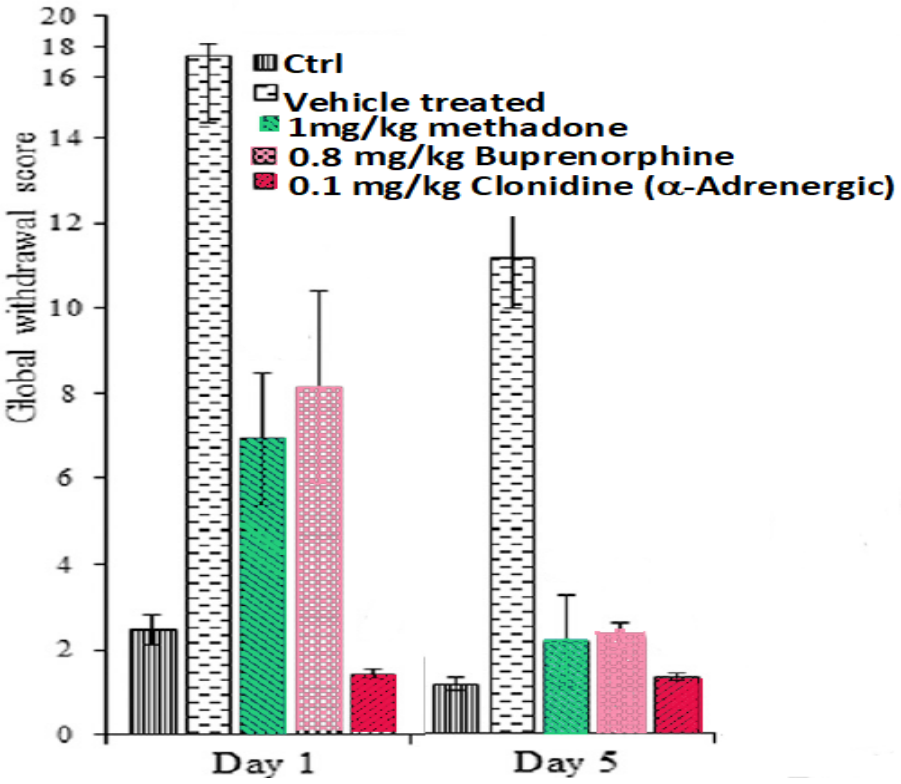
Toxicity

- Toxicity -- supportive management in most cases.
  - Acute hepatitis -- *N*-acetylcysteine (as in any other drug-induced hepatitis).
  - Seizures or neurological symptoms -- anti-epileptics.
  - Kidney injury, cardiovascular events, or other emergency presentations addressed with appropriate measures.

- Overdose
  - Kratom-only overdoses resemble stimulant overdoses (cardiovascular, seizure).
    - Poison Control Center reports show low levels of meiosis, sedation, and respiratory depression.
  - Co-ingestions are common
    - Reports describe mixed outcomes with reversal agents (naloxone); no clinical trials exist.

Withdrawal

- Mimics opioid withdrawal, but milder:
  - Withdrawal intensity positivity correlated to:
    - Daily amount consumed.
    - Duration and frequency of use.
  - Starts ~12-24 hours from last use, can last up to 4 days
    - Symptomatic management of a hyperadrenergic state (i.e.. Clonidine).
    - Good response to opioid receptor agonists (Methadone), or partial agonists (Buprenorphine).
  - Cravings and relapse risk is high.



“Kratom Use Disorder”

- ~25.5% of consumers, however mild-mod severity (tolerance, withdrawal) and no functional impact.
- Vulnerability factors: male, young, consuming Kratom frequently, and having psychiatric and substance use disorders.

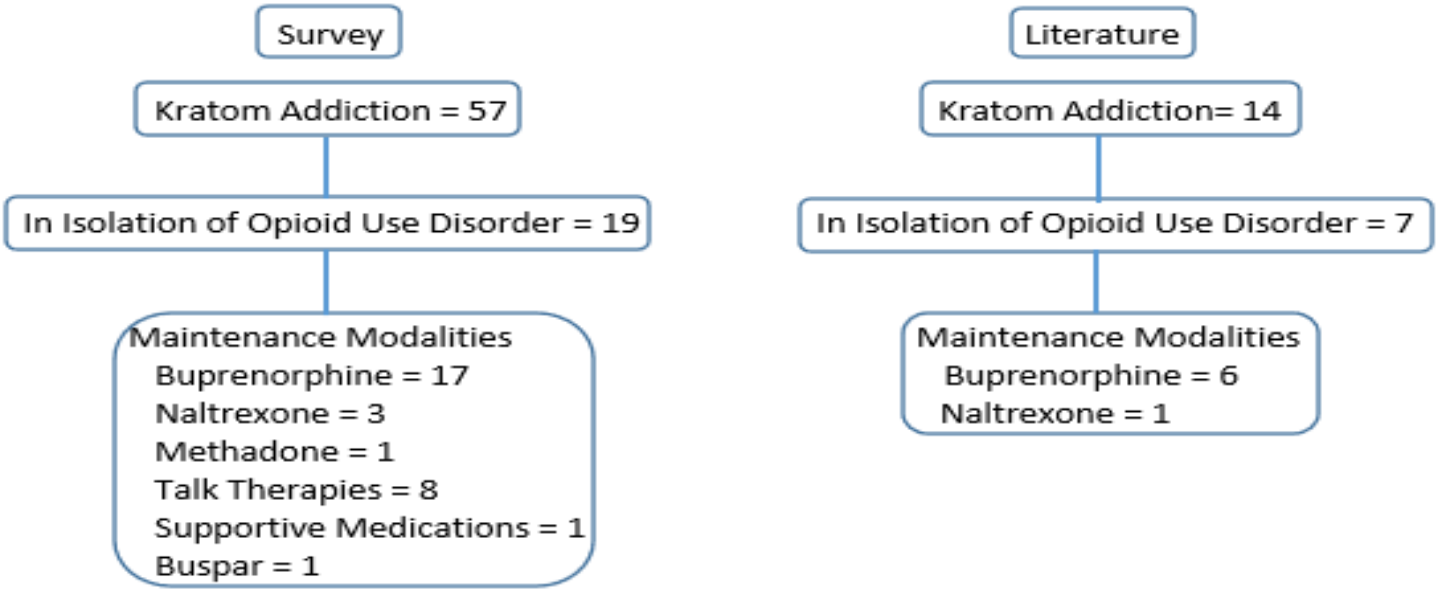
Table 2. KUD Symptoms Reported by Survey Participants, Stratified by Qualifying for a Potential KUD

Sample Characteristics	Full Sample (N = 2,061)		KUD (n = 525)		No KUD (n = 1,536)		p value*
	Frequency	%	Frequency	%	Frequency	%	
Kratom Use Disorder Symptoms							
Ever noticed a diminished effect with continuous use of the same amount of Kratom, or a need to increase the amount of Kratom to achieve the desired effect	648	31.4	427	81.3	221	14.4	<0.0001
Experienced withdrawal symptoms when abruptly stopping and continued use to avoid withdrawal or to manage these symptoms	447	21.7	357	68.0	90	5.9	<0.0001
Experience craving, or a strong desire or urge to use Kratom	340	16.5	298	56.8	42	2.7	<0.0001
Find self-using Kratom in larger amounts, or over a longer period, than initially intended	305	14.8	281	53.5	24	1.6	<0.0001
Find self-wanting to cut down or being unsuccessful at controlling Kratom use	183	8.9	179	34.1	4	0.3	<0.0001
Continue to use Kratom despite knowing that one has a physical or psychological problem caused or exacerbated by Kratom	106	5.1	104	19.8	2	0.1	<0.0001
Continue to use Kratom despite social or interpersonal problems related or exacerbated by the effects of Kratom	83	4.0	75	14.3	8	0.5	<0.0001
Spend a great deal of time in activities needed to obtain, use, or recover from the effects of Kratom	58	2.8	55	10.5	3	0.2	<0.0001
Often give up or reduced important occupational or social activities because of Kratom use or its effects	49	2.4	49	9.3	0	0	<0.0001
Find yourself using Kratom in situations where it can be physically hazardous	44	2.1	42	8.0	2	0.1	<0.0001
Often fail to fulfil work, home, or school obligations due to Kratom use or its effects	34	1.7	33	6.3	1	0.1	<0.0001
Severity							
Mild	-	-	347	66.1	-	-	
Moderate	-	-	105	20.0	-	-	
Severe	-	-	73	13.9	-	-	

* p value is for Chi-Square Test, comparing KUD to no KUD

Maintenance Treatment

- Our team's efforts to establish a "standard of care".



- Since 2021 several reports emerged.
  - Mixed evidence of amount used, and Buprenorphine dose needed.
- Those requiring MOUD for maintenance could represent a small group.

CASES

Case 1 - Andrew

- 33yo Caucasian male h/o anxiety, depression (on Escitalopram 20mg and Propranolol 10mg BID), OUD in sustained remission x 12 y
- Started 2.5y ago, initially 2 caps per dose, progressively increased to 8 caps within a few weeks to manage various mood states.
- Distinct effects from kratom vs. Percocet: increased energy, uplifted mood, and motivation.
- Diminishing effects over time, he continued to consume 12-15 caps daily, transitioning to powdered kratom washed with water 1.5 y ago.
- Significant lifestyle disruptions in the last year, including marital strain, work interference, and financial burden.
- Struggled with increasing intervals between doses, experiencing withdrawal symptoms (cold sweats, "brain zaps", and cravings after 6-7 hr. abstinence).
- Detox and eventually transitioning to naltrexone using SOWS alongside clonidine, loperamide and gabapentin failed - could not abstain for >12 hr.
- Successfully transitioned to buprenorphine - 2mg daily with an additional 2mg dose as needed in the evening for craving management.

Case 2 - Fred

- 37yo Caucasian male h/o OUD in sustained remission admitted to inpatient psych due to depression, SI.
- General workup was unremarkable (EKG, labs, vs); Urine tox + THC.
- Disclosed a 6-mo h/o Kratom use, escalating to 11 capsules daily (3 in AM, 3 mid-day, 5 in PM), supplemented with an unknown quantity powder in water.
- Introduced to it as an antidepressant and had initially started with 1 cap in the morning however within days he increased his dosage to 3 caps to combat decreased effectiveness and maintain energy levels.
- Constipation is the only side effect, recent attempts to quit after learning about reports on the Internet of various adverse effects were hindered by cravings and "rebound depression."
- Last use 24hr prior to admission and he experienced progressively worsening nausea and flu-like symptoms which were first noticed 6 hours ago.
- COWS = 11, Methadone 5mg x1 administered, COWS = 2.
- Next day COWS remained 2, Clonidine 0.1mg x1 for anxiety, (HR 87 and BP 142/95).
- Aripiprazole 5mg (past response), fifth day he underwent a naltrexone challenge and received a monthly long-acting injectable.

Case 3 - Mark

- 43yo Caucasian male h/o anxiety, chronic pain, ADHD
- Anxiety is generalized with occasional panic attacks, has a therapist
- Past injuries, and back pain necessitating spinal fusion.
- Self-medicating for pain with kratom (~5 g of powder daily) for >5 years.
- Improves pain allowing him to be mobile without the use of any pharmacotherapies – which his orthopedic surgeon has discussed in the past.
- In addition to the pain benefit he also has noticed that kratom ingestion also tends to "bring the temperature down" on his anxiety.
- No adverse effects and his dose and frequency have remained the same as when he initiated.
- Has had stretches of up to 1wk of no kratom and never experienced withdrawal, or cravings despite pain exacerbation.
- Trintellix 20mg and Vyvanse 30mg
- Organic evaluation unremarkable (CMP, CBC, TSH), MG level 133 ng/mL was quantified.

***psychoeducation, motivational enhancement ongoing**

Summary

- The exact prevalence of kratom use is unknown, however clinicians are encountering more and more consumers.
- Despite consumers claiming benefits/harm reduction, it is possible for some to meet DSM criteria for a “use disorder” diagnosis.
- Kratom is a complex botanical, and its alkaloids interact with many receptor systems - including opioids.
- There is a spectrum of adrenergic and opiodendric involvement impacting each user, and withdrawal, and maintenance treatment requires individualized treatment.

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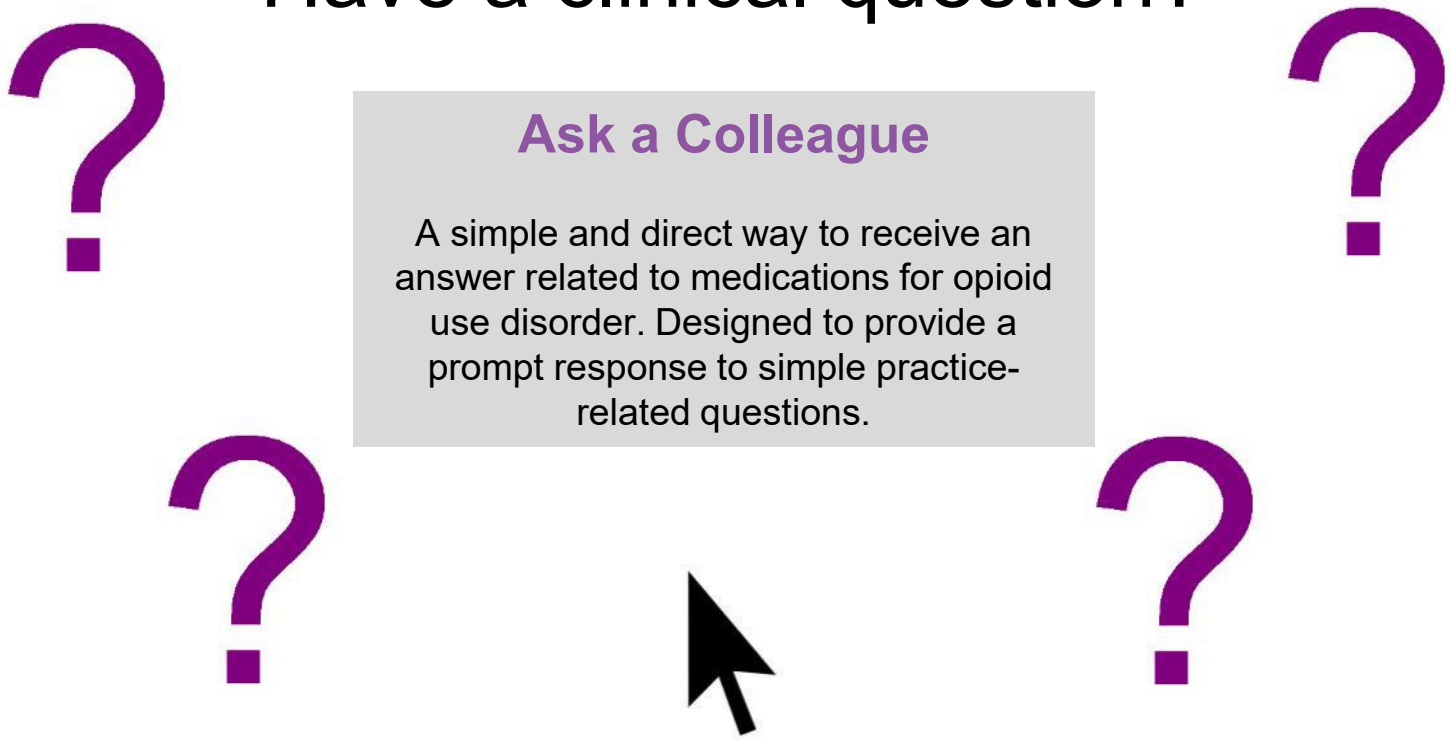

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