

Kratom Use Complicating Treatment of Substance Use Disorder (SUD)

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NO CONFLICTS OF INTEREST



Massachusetts Consultation Service

MCSTAP

for Treatment of Addiction and Pain

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What is MCSTAP?

- Real-time, phone consultation to clinicians on safe prescribing &

MISSION: *To support primary care teams in increasing their capacity for & comfort in using evidence-based practices in screening for, diagnosing, treating, & managing the care of all patients with chronic pain &/or SUD*



Outline: Kratom Use Complicating Treatment of Substance Use Disorder

- MCSTAP Overview
- Learning Objectives
- Case Reviews: Presentation & Key historical data
- Literature review
 - Use(s)
 - Adverse effects
 - Management / Treatment of Disordered Use
- Final Case Review: Treatment options by case
- Q&A



Learning Objectives

- Increase ability to assess individual patients that are using Kratom with or without other prescribed or illicit substances.
- Increase ability to diagnose & assess the severity of Kratom UD
- Increase ability to assess, address (mitigate), & monitor identified risks
- Increase interest in the Harm Reduction approach to managing & treating patients with both OUD & Kratom
- Understand how MCSTAP helps support clinicians at the Point of Care



Case Reviews:

Presentation & Key historical data



CASE 1. SUD, OUD-Kratom, AUD, no MOUD & MDD

31 y.o. F, administrative assistant

A. Major depressive Disorder; B. 1° OUD (No MOUD); C. 2° AUD (No MAUD)

Substance Use History:

- **Opioids**
 - Used oxycodone p.o./i.n, for 2 yrs. | Successful self-detox during pregnancy.
- **Kratom**
 - Daily kratom started post-partum (5 years; ? amount)
 - Several **unsuccessful attempts to taper Kratom** use over the past 1.5 years.
- **Alcohol**
 - Wine: 1 bottle daily

Patient's Request

- Wants to stop kratom use completely, tried “bup-nal” from ‘friends’ many years ago when she couldn’t get oxycodone, never took it regularly
- Never treated with Methadone (IM/PO), Naltrexone, or Acamprosate
- Never medically detoxed
- Contemplative re: Treatment for AUD including MAUD



CASE 2. OUD-Kratom, Amphetamines

27 y.o. M w/ ADHD on stimulants; Now mis-using Kratom

- Recent ED visit for seizures from apparent misuse of amphetamines
- Uses Kratom heavily, daily (? Amount)
- Reports opioid withdrawal symptoms upon abstinence
- Caller is a buprenorphine prescriber
- Clinician Questions:
 - Is buprenorphine therapy is effective & appropriate in this situation?
 - MCSTAP & Clinician discussed:
 - Opioid effects of Kratom
 - Potential benefit of treatment with Buprenorphine
 - Caution to avoid precipitated withdrawal discussed



CASE 3. Depression, Anxiety, ADHD Ritalin, OUD-Kratom

A 27 y.o. M w/ hx of Depression/Anxiety/ADHD was prescribed Methylphenidate (Ritalin) by a prior prescriber

- Established care 4-6 months ago with the current clinician (caller); the patient's PCP
- Past treatment: Bupropion (Wellbutrin); Didn't tolerate; Atomoxetine not helpful
- Currently using Kratom - 27 teaspoons/day; Recently instructed to taper 2 teaspoons of Kratom/day

Current medications: Methylphenidate (Ritalin); Trial of naltrexone unsuccessful

Recent UDT: Methadone (unexpected), Buprenorphine (unexpected), Methylphenidate (expected)

Clinician Questions:

- PCP knows little about Kratom; Other MAT providers advised against buprenorphine
- PCP goal: Taper off kratom (*Is this the patient's goal as well?*)

Clinician & MCSTAP Consultant Discussed:

- Kratom: a dose-dependent mix of stimulant & opioid effects; Can treat with MOUD
- Often contaminated/adulterated with:
 - Fentanyl, heroin, methadone (less common)
 - Ensure patient had Narcan, safety planning, etc.
- Maintain treatment engagement
- If taper unsuccessful, consider induction to Buprenorphine for maintenance MOUD
- Maintain a low barrier to retention
- But, OK to set boundaries (e.g. "Drug screen must be negative for fentanyl to keep prescribing Ritalin.")



CASE 4. Kratom, Anxiety, Chronic Pain

40 y.o. male using Kratom Daily

- Clinician caller who is not waivered to prescribe Buprenorphine

Clinician

- Requesting help Diagnosing & managing probable Kratom Use Disorder (KUD)

MCSTAP Consultant & Clinician Caller

- Discussed Kratom characteristics & associated dangers
- Reviewed diagnostic criteria for OUD
- Discussed possible referral to addiction treatment providers in the area
- Discussed providing OD prevention by prescribing a Naloxone Rescue Kit
- Discuss approach to address co-occurring pain & anxiety



CASE 5. Kratom & Cannabis, OUD, Weight loss

Patient using Kratom for > 5 yrs.

- Has Long-term Dependence (~3 grams used 3 x daily)
- Motivated to discontinue Kratom permanently
- Ongoing weight loss reported (X 1 month)
- Anxiety & depression (X 6 months)

Past substance Use

- h/o OUD in remission X 2 yrs.
- In past, smoked marijuana daily, d/c'd several months ago

Clinician

- Seeking general guidance



5 MCSTAP Calls Involving Kratom (2019-2021)

Case	Age, Gender, Employed	Formal Other OUD Dx?, In Tx?	Presumed OUD (Kratom)	Amphetamine Use	Cannabis Use	ADHD Dx	AUD Dx?	Stimulants Rx 'd	Oxy-codone	Anxiety, Depression, Chronic Pain	UTS
1	31, F, Yes	Yes, ?	X	-	-	Yes	Yes	Yes	Yes	-	-
2	27, M, ?	Yes, ?	X	X	-	-	-	-	-	-	-
3	27, M, ?	?, ?	X (Tx w/ Naltrexone, No response)	-	-	-	-	Ritalin & Strattera (in past) no response	-	-	Methadone, Bupe., Ritalin
4	40, M, ?	?, ?	?	-	-	-	-	-	-	Anxiety, Chronic Pain	-
5	?, ?, ?	Yes, ?	Yes	-	Yes, Abstinent	-	-	-	-	Yes	-



U.S. Kratom Use Increasing

3 -5 million People in U.S. use **Kratom**, a herbal supplement, recreationally or to self-manage medical conditions (e.g. pain, insomnia) despite little evidence of its safety & efficacy

- Used recreationally: For pleasure or to enhance outward experiences (e.g. use at a music festival)
- Purchased in smoke/tobacco shops; online; & smaller local stores in locations that permit its use.
- Serious safety concerns (Kratom-related calls to U.S. poison control)
 - 2011: 13 calls; 2017: 682 calls;
 - 2011-2017: Dozens of overdose deaths s involving kratom.
 - Not FDA approved for use as a medical treatment.
 - Advertised as a herbal supplement for use as a **medical treatment**; Several companies fined heavily for this
- Legal food supplement (Federal, 1/20); Unlawful in 6 U.S. states; Banned in some cities & counties
- Anecdotal reports use for:

• Muscle pain	• PTSD	• Reduce opioid craving	• Appetite suppression
• Panic attacks	• Diarrhea	• Menstrual cramps	• Tapering opioids/alcohol



BU School of Medicine



What is Kratom? (KRAY-tem)

- A leaf from *Mitragyna speciosa* tree
 - A common Southeast Asian tree (Malaysia, Thailand & Indonesia)
 - Low dose: Stimulates CNS; Subjectively ↑'s energy levels
 - High dose: opioid-like effects
- *M. speciosa* leaves can be:
 - Chewed whole
 - Converted into a liquid extract, powder, capsules/tablets.
 - Brewed as a tea using Kratom / Kratom gum.
 - As known as: Biak, Kakuam, Ketum, Thang (Ithang) & Thom.

Main active ingredients:

- Mitragynine
- 7-Hydroxymitragynine (stimulates Brain mu-opioid receptors)
- Effective up to 5 hours after oral ingestion



Pharmacokinetics of Mitragynine

- Administration: Oral, poor oral bioavailability.
- Pharmacodynamics:
 - Weak base rapidly & passively transported across the intestinal wall & blood-brain barrier b/o high lipid solubility & permeability.
 - Plasma-protein bound (85–95%)
 - Rats & humans: rapid absorption /p PO administration ($T_{max} \sim 1.5$ h, $C_{max} \sim 0.3\text{--}1.8 \mu\text{M}$).
 - Half-life $t_{1/2}$ was 3–9 hrs.
- Metabolism:
 - Extensive metabolization by Liver CYP450 isozymes, primarily by CYP3A4.
 - Impact on CYP enzymes unlikely impacts drug metabolism at typical concentrations
 - Mostly excreted as metabolites in urine
- Bioavailability/Absorption:
 - Bioavailability: $\sim 21\%$



Pharmacokinetics of Mitragynine, a major analgesic alkaloid in kratom, (*Mitragyna speciosa*): A systematic review, Yaa K, ET.AL. Asian Journal of Psychiatry, Vol. 43, June 2019, Pages 73-82.



How is Kratom Used & Detected?

Administration

- Kratom leaves: chewed, smoked, or a powder for tea (Hassan et al., 2013).
- Beneficial effects: ↑ Relaxation, Pain relief, Energy, ↓ Depression (Swogger et al. 2015; Grundmann 2017)

Intoxication

Opioid Effects (Main kratom alkaloids > opioid agonist effects (Hassan et al., 2013):

- Opioid agonist effects at higher doses (DEA, 2013; Rech et al., 2015).
- Main active ingredients (Mitragynine & 7-hydroxymitragynine)

Stimulant effects: At low doses

Withdrawal: Aggression, lacrimation, muscle & bone aches, & jerky limb movements (DEA, 2013)).

Death: a/w coincident kratom & polysubstance use (Neerman et al., 2013; McIntyre et al., 2015)

Identification / Detection

- Not detected by routine toxicology or conventional confirmatory drug screening tests
- HPLC or Mass spectrometry required for detection & identification (Cinosi et al., 2015)



Reasons for Kratom Use

Reasons for kratom use.

	Number; % of respondents			
	<i>All reasons^a for use among those endorsing...</i>		<i>Main reason for use among those endorsing...</i>	
	Current kratom use (N = 2,867)	Past kratom use (N = 157)	Current kratom use (N = 2,867)	Past kratom use (N = 157)
To relieve pain	2,344; 81.8%	109; 69.4%	1,388; 48.4%	63; 40.1%
Anxiety or depression	1,903; 66.4%	82; 52.2%	579; 20.2%	23; 14.6%
To increase focus or energy	1,569; 54.7%	55; 35.0%	292; 10.2%	8; 5.1%
Cut down or quit using prescription pain medication	1,054; 36.8%	49; 31.2%	160; 5.6%	14; 8.9%
Insomnia	808; 28.2%	29; 18.5%	28; 1.0%	3; 1.9%
To cut down or quit using OTC pain medicine	792; 27.6%	20; 12.7%	16; 0.6%	1; 0.6%
To cut down or quit using alcohol	517; 18.0%	18; 11.5%	64; 2.2%	0; 0.0%
Recreational use (e.g., to get high)	475; 16.6%	33; 21.0%	70; 2.4%	11; 7.0%
To relieve withdrawal symptoms	416; 14.5%	43; 27.4% ^b	62; 2.2%	21; 13.4%
PTSD	442; 15.4%	13; 8.3%	48; 1.7%	1; 0.6%
To cut down or quit using illicit or illegal drugs	346; 12.1%	15; 9.5%	55; 1.9%	3; 1.9%
To cut down or quit using tobacco	154; 5.4%	4; 2.6%	2; 0.1%	0; 0.0%
Control blood sugar	129; 4.5%	1; 0.6%	6; 0.2%	0; 0.0%
Curiosity	80; 2.8%	18; 11.5% ^b	3; 0.1%	6; 3.8%
Other	179; 6.2%	3; 1.9%	94; 3.3%	3; 1.9%

^a Percentages sum to over 100 because respondents were able to select multiple options.

^b Indicates a significant difference between those reporting current and past kratom use, $\chi^2, p < .0001$.



Coea MA, et.al. Kratom as a substitute for opioids:
Results from an online survey, Drug and Alcohol
Dependence, Vol 202, 1 September 2019, Pages 24-32



Problems with Kratom

“Comes from a plant - Believe must be safe to use.”

- No medical efficacy/effectiveness studies
- FDA dietary supplement; Not regulated like med
- Multiple Adverse Drug Effects (ADE) including:

Overdose

- 2016 - 2017: 91 overdose fatalities (CDC).
- Other drugs: usually fentanyl - involved in most deaths (some OD's a/w kratom alone)

Addiction

- Possible, despite use as a detox aid, concerns about dependence.
- No standard protocols for use as a treatment

Risk of contamination

- Report: ~200 people sick: salmonella-tainted kratom (2018)
- Amount of active ingredients can differ from the label
- Dangerous substances may also contaminate Kratom
- Analysis of 30 kratom products: ↑ nickel & lead levels (2019)

Dizziness	Loss of appetite and weight loss	Reports of withdrawal symptoms in infants.
Drowsiness, CNS depression (Cumpston, et.al. 2018), Mild sedation (Swogger et al., 2015)	Appears to pass from mother to child through the placenta/breast milk.	Toxic levels unknown; Differs by person, formulation, ingested dose, duration of use & amount of active ingredient.
Itching	Tachycardia	Severe breathing issues
Irritability, agitation a/o aggression	Constipation a/o urination issues	Liver damage
Altered mental status, Confusion	Elevated BP, Hypertension, (Anwar et al., 2016).	Kidney failure
Sweating and/or chills	Anxiety or depression	Seizures (25% in 12 pts from Poison Control (Cumpston, et.al. 2018)
Dry mouth	Interaction with medications	Coma & death.
Nausea a/o vomiting; Dyspepsia	Muscle pain	

Kratom: Online Survey of Current U.S. Users

Online survey of people who use kratom in the United States (Grundmann, 2017)

- Mostly white, male, age 21-50, employed, & some college education
- Many reported use of kratom for self-treatment of pain
- **Motivations for use included:**
 - Analgesia
 - Opioid holidays, economic alternative to opioids, opioid replacement therapy (Boyer et al., 2007)
 - Other (Self-treatment of anxiety, depression, & PTSD (Grundmann, 2017))
- **Other Uses**
 - Antidepressant effects d/to kappa-opioid antagonism (Lalanne, 2014; Kruegel & Grundmann, 2017).
 - NB: Depressive symptoms reportedly improve with buprenorphine (mu-agonist/kappa antagonist)
 - In persons in SUD treatment, Kratom has been used to replace heroin & prescription opioid use
 - Kratom is rarely the persons' drug of choice (Smith and Lawson, 2017)



Kratom Use & Mental Health

- Systematic review (Kratom use & Mental health (1960-2017))
- Findings:
 - Potential harm reduction tool (opioid replacement in addicted persons)
 - In Many users: Kratom appears to enhance mood & relieve anxiety
 - In some users:
 - Negative mental health effects (primarily withdrawal symptoms):
 - Apparently mild compared to those of other opioids
 - Kratom withdrawal can be highly uncomfortable
 - Maintaining abstinence difficult may be for various reasons including:
 - Legal to purchase & possess
 - Easy to procure
 - General low ADE profile → Perception of being low risk



Kratom use and mental health: A systematic review, [Swogger MT, Walsh Z](#),
[PMID: 29248691, Drug Alcohol Depend, 2018 Feb 1;183:134-140. Epub 2017 Dec 7.](#)



Is Kratom Being Used for Self-medication by Substance Users?

- Survey of Kratom use & Motivations (2017):
 - 12-Step-oriented residential program. N=500 clients
 - Non-evidence-based use for chronic pain, mitigating drug dependence, & withdrawal symptoms
- Findings:
 - Lifetime kratom use (20.8%); Past-12-month use (10.2%)
 - Users younger (32.1 y.o. vs. 35.9 y.o., $p < 0.001$)
 - Use Reasons
 - **Harm Reduction:** 68.9% (to reduce/abstain from non-prescription opioids (NPO) a/o heroin)
 - **Drug substitution:** 64.1% to replace NPO/heroin (Dependence/withdrawal from other substances)
 - **For Pain:** 18.4% use b/o disability or chronic pain.
 - **Satisfaction:** 33% & “would try it again”
 - Not preferred/less appeal than heroin, amphetamines, & Suboxone.



Prevalence and motivations for kratom use in a sample of substance users enrolled in a residential treatment program, [Smith KE, Lawson T, PMID: 28950240, Drug Alcohol Depend. 2017 Nov 1;180:340-348. doi: 10.1016/j.drugalcdep.2017.08.034. Epub 2017 Sep 20.](#)



Kratom user demographics & use patterns

Design: Cross-sectional, anonymous online survey (Jan-Dec 2017),

Sample:

- N=2,798 kratom U.S. users (97 %), mean age 40 (SD = 12); predominantly White (90 %), female (61 %),

Findings:

- 56 individuals (2 %) met DSM-5 criteria (past-year moderate/severe kratom-related use disorder (KUD)
 - Primarily taken orally; Doses of 1-3 g (49 %); Daily use (59 %) most common.
- Patient's indication for use: Pain (91 %), Anxiety (67 %), Depression (65 %)
- Kratom used to d/c or ↓ Rx or illicit opioid use (citing ↓ opioid W/D & Craving a/w kratom use (41%) N=1,144
 - 36% (n=411) reporting >1-year continuous abstinence from opioids attributed to kratom use.
 - ~ 1/3 reported ADE from kratom: (mostly mild in severity) lasting ≤ 24 hours
 - 17 participants (0.6 %) sought treatment for ADEs
- Overall Satisfaction with Kratom
 - High ratings of effectiveness
 - Little trouble reported w/ use of kratom (Mean trouble rating = 3.2 (SD=9.8; Scale range: 0 – 100).



Kratom (*Mitragyna speciosa*): User demographics, use patterns, and implications for the opioid epidemic, [Garcia-Romeu A, et.al. Drug Alcohol Depend. 2020 Mar 1;208:107849, PMID: 32029298, PMCID: PMC7423016, doi: 10.1016/j.drugalcdep.2020.107849. Epub 2020 Feb 3.](#)



Kratom Use in the Non-Medical Use of Prescription Drugs Program

Design:

- Validated non-probability cross-sectional survey of U.S. Non-Medical Use of Prescription Drugs Program,
- 2018 3rd QTR; 2019 1st QTR; N=59,714 individuals
- Aged ≥ 18 yrs. old, weighted to represent the adult US population (n = 252,063,800)

Findings:

- Current Prevalence (Past-year adult Kratom use): **0.8%** [95% CI] = 0.7% - 0.9%, N=2,031,803 adults
- Life-time prevalence: **1.3%** (95% CI = 1.2-1.4), N=3,353,624 adults; Users are younger (mean 35 years, P < 0.001)
- Kratom users, when compared with non-users, have **higher proportions** of:
 - **Males** (61.0 vs. 48.6%, P < 0.001); **Students** (14.1 vs. 7.5%, P < 0.001)
 - **Health-care professionals** (9.7 vs. 4.5%, P < 0.001)
 - **Fewer bachelor's/advanced degree graduates** (33.4 vs. 42.6%, P < 0.001) compared with non-users.
 - No significant differences in Kratom use by Race, Household income, or Employment status.
- Individuals with past-year kratom use:
 - 37% (95% CI = 32-41) non-medically used prescription opioids
 - 22% (95% CI = 18-26) used illicit opioids
 - 54% (95% CI = 50-59) used another illicit drug
 - 67% (95% CI = 63-72) used cannabis
 - DAST-10 results more substantial/severe in kratom users (21% versus 1%, P < 0.001) vs. non-users.
 - Kratom users: reported more serious substance abuse profiles vs. non-users or users of cannabis, alcohol, or cigarettes.



Prevalence and description of kratom (*Mitragyna speciosa*) use in the United States: a cross-sectional study, [Schimmel J, et.al.; 2021 Jan;116\(1\):176-181. PMID: 32285981, DOI: 10.1111/add.15082, Epub 2020 Apr 28.](#)



Kratom Use Patterns & US Health impact: Online survey

- **Design:**

Anonymous, cross-sectional online survey (October 2016) of current US Kratom users. The sample was obtained through social media & online resources from the **American Kratom Association** (N=8049 respondents completed the survey)

- Kratom is primarily used by:

- Middle-aged (31-50 years); Income \geq \$35,000

- Reported purpose: Self-treatment of Pain (68%), Emotional/mental conditions (66%)

- ADE

- Dose-dependent negative effects
- Primarily GI ((nausea & constipation)
- Present mostly in individuals on high doses (\geq 5g/dose) or taking \geq 22 doses/week)

- Desired effects

- Dose-dependent opioid-like effect
- Provides perceived beneficial effects in relieving pain & mood disorders, and withdrawal symptoms associated with prescription opioid use



Patterns of Kratom use and health impact in the US-Results from an online survey, [Oliver Grundmann, Drug Alcohol Depend, 2017 Jul 1;176:63-70, PMID: 28521200, doi: 10.1016/j.drugalcdep.2017.03.007. Epub 2017 May 10.](#)



Self-reported Health Diagnoses & Demographic Correlates with Kratom Use

Aim: Does Kratom demographics & use patterns correlate w/ existing health conditions?

Design: Anonymous, online, cross-sectional survey. N= 8049 Kratom users (10/2016)

Findings:

- When comparing explanations for Kratom use, individuals using Kratom to mitigate illicit drug dependence reported less pain & better overall health vs. those using Kratom solely for acute/chronic pain
- Self-reported mental health (ADHD/ADD, anxiety, bipolar disorder, post-traumatic stress disorder, & depression) improved **more than** somatic complaints (back pain, rheumatoid arthritis, acute pain, chronic pain, fibromyalgia)
- Likelihood of ↑ Kratom use in women & older patients
- Clinicians should Engage Patients:
 - To address safety concerns
 - To address limitations of Kratom use in clinical practice



Self-reported Health Diagnoses and Demographic Correlates With Kratom Use: Results From an Online Survey, [Bath R, et.al. J Addict Med. May/June 2020;14\(3\):244-252. PMID: PMC7446542](#)



Use of Kratom In Substance Using Populations

Background

- In Asia, *Mitragyna speciosa* (e.g., “kratom”) has been used to mitigate alcohol and drug dependence.
- Some Observers Suggest that Kratom may have the potential for use as harm-reduction, e.g. as an opioid substitute or to treat or mitigate opioid withdrawal symptoms

Study Aim/Design:

- Anonymous survey (April 2017) to determine correlates of past-year kratom use in a sample of polysubstance using patients enrolled in residential recovery programs in Kentucky

Findings:

- Past-year kratom use reported (10.4%; N=478)
- Past-year heroin use (not past-year prescription opioid use was found to be significantly a/w Kratom use
- People w/ past-year heroin use were **2.5 X more likely to also report past-year kratom use**
- Non-prescribed buprenorphine use partially explained the relationship between buprenorphine & kratom use
- Amphetamines were preferred; however Past-year Amphetamine use negatively a/w past-year kratom use
- The rate of past-year kratom use was less than (<) rates of alcohol & illicit drug use.
- Kratom not preferred over heroin or prescription opioids.



Smith KE, et.al. J of Psychoactive Drugs, Volume 51, 2019 - Issue 4, Pages 311-322, ePub 08 Apr 2019



Kratom as a Substitute for Opioids

- Kratom is used to make tea-like brews or swallowed in powdered form for various health & well-being reasons including to relieve pain & opioid withdrawal.
- An anonymous online survey of kratom users (2867 current users and 157 former users) was conducted in September 2017 through the American Kratom Association and associated social media sites.
- Kratom was used primarily to:
 - relieve pain (endorsed by 48% of respondents),
 - for anxiety, PTSD, or depression (22%),
 - to increase energy or focus (10%)
 - and to help cut down on opioid use and/or relieve withdrawal (10%).
- > 90% used it in place of opioids indicated that it was helpful to relieve pain, reduce opioid use, and relieve withdrawal.
- Incidence of ADEs: 13%; Reactions overwhelmingly mild & self-managed
- Kratom use noted in conditions that often require opioids (e.g. pain & reduction of opioid use)



Kratom as a substitute for opioids: Results from an online survey, Coe MA, et.al. Drug Alcohol Depend. 2019 Sep 1;202:24-32. PMID: 31284119, doi: 10.1016/j.drugalcdep.2019.05.005. Epub 2019 Jun 29



Treating Kratom Use Disorder with Buprenorphine

- Kratom contains > 40 structurally related alkaloids
 - Main component: Mitragynine is a weak mu-opioid agonist (Cinosi et al., 2015; Warner et al., 2016).
 - 2nd key component: 7-hydroxymitragynine (2% of kratom by weight) which is a potent opioid mu-agonist (13-X more potent than morphine; 46 X more potent than mitragynine - Cinosi et al., 2015)
- Both compounds act as:
 - Weak kappa- & delta-opioid receptors antagonists in vitro (Kruegel and Grundmann, 2017).
 - Broad receptor affinities: Serotonergic, Adrenergic, Dopaminergic, & GABAergic (Cinosi et al., 2015).
- Exhibits dose-dependent effects (Chang-Chien et al., 2017):
 - Acts as a mild stimulant at low doses (<5 g)
 - Opioid-like effects at moderate doses (5 to 15 g)
 - Sedation at high doses (>15 g) & Peak concentration at 50 min (0.83 hours); Half-life $t_{1/2}$ = 23 hrs.
- Any **addictive** potential of Kratom remains a matter of discussion, however, **dependence** is common in regular kratom users (Southeast Asia)
- These dependent persons maintain high-levels of social function (Singh et al., 2016).
- U.S. Kratom supply may have ↑'s level of toxicity b/o adulterants from distributors
- Higher doses tend to be used among Western Kratom users (Singh et al., 2016).



Treatment of Kratom Dependence With
Buprenorphine-Naloxone Maintenance, Megan
Buresh, MD, J Addict Med 2018;12: 481–483



Treatment of Kratom Dependence w/ Buprenorphine-Naloxone Maintenance

Population:

- N=4,302 surveyed, 2,826 (66%) met inclusion criteria/complete survey (28 excluded various issues), Final N=2,798 (Kratom users after other exclusions)
- Recruitment sources: American Kratom Association (53%), FB/Social media (44%)

Findings:

- Average age 40.2 years (s.d.=11.8); Female: 60.7%
- Married/Committed relationship: 66.5%
- Employed: 68.4%; Some college education: 83.9%
- Median annual household income: \$50,000- \$59,000
- Largest geographic residential concentration in U.S. South (41.0%).
- Past year substance use in addition to Kratom:
 - Alcohol (Past-year use: 47%, Tobacco: 42%, Cannabis: 37%, Opioids: 33%
 - Opioid w/d symptoms or difficulty controlling opioid use: 52.9%



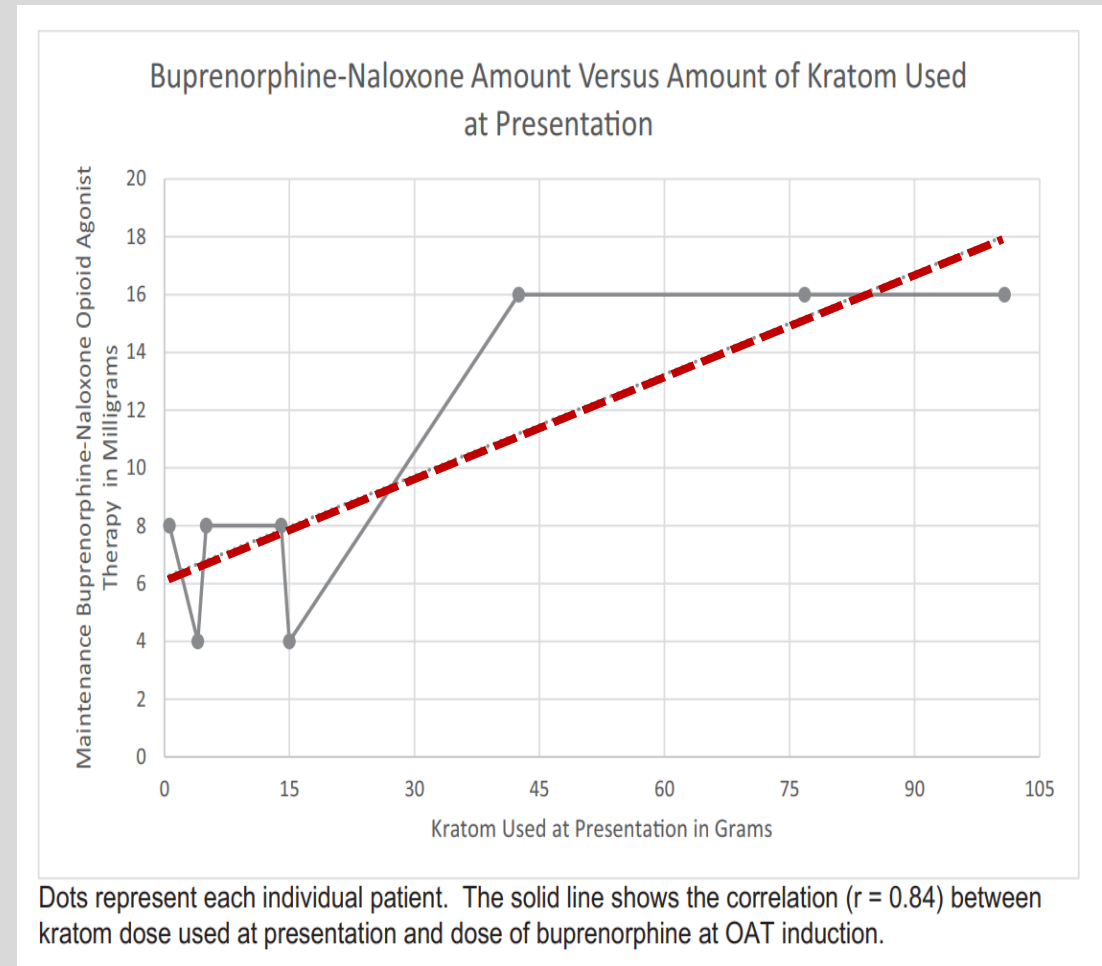
Treatment of Kratom Dependence With Buprenorphine-Naloxone Maintenance, Megan Buresh, MD, J Addict Med 2018;12: 481–483



Treatment of Kratom Dependence w/ Buprenorphine-Naloxone Maintenance

Treatment Recommendations:

- Recommendations for treatment of patients using:
 - <20 g Kratom/d: buprenorphine-naloxone MOUD (4/1 mg - 8/2 mg) q.d.
 - >40 g Kratom/d: buprenorphine-naloxone MOUD (12/3 mg - 16/4 mg) q.d.
- Some patients may require adjustment of their initiating OAT dose depending on their use of other drugs along with kratom
- Patients should be able to self-taper at their kratom use before starting buprenorphine MOUD.
- Final buprenorphine dose appears to be correlated with self-reported kratom dosing



Physical & Psychological health

Kratom using patients reporting chronic pain over the past 3 months n=1,924; (68.8%).

Findings:

- The mean Brief Pain Inventory (BPI) Pain severity score: 4.1 (SD=1.8),
- Mean pain interference score: 4.9 (SD=2.9) Range 0 – 10
 - ↑ scores a/w ↑ pain a/o pain interference in daily activities
- Study participants reported currently being:
 - prescribed pain medications (39.4%) or
 - using kratom for pain (87.6%)
- The Patient-Reported Outcomes Measurement Information System Global Health (PROMIS-GH) was used to assess two health subscales:
 - Physical health subscale: Mean = 13.7 (SD=3.2)
 - Mental health subscale: : Mean = 12.8 (SD= 3.5)
- Both converted to PROMIS-GH T-scores of about 45 which is slightly less than the U.S. general population (PROMIS-GH T-score Mean = 50)

Most Commonly Reported Lifetime Medical Diagnosis	
Back pain (72.5%) Lower back: 53.8% Upper back: 34.6%	Joint pain (54.5%) Shoulders: 33.1% Knees: 31.3%
Depression (65.0%)	Panic attacks (48.1%)
Muscle pain (62.9%)	Arthritis (43.8%)
Neck pain (55.0%)	



Hays, Bjorner, Revicki, Spritzer, & Cella, 2009



Kratom Use to Self-Manage Opioid Use

- N= 1,144 (40.9%) persons using Kratom to reduce/stop opioid use (Rx opioid meds & Illicit opioids)
- Report Kratom effective for managing opioid use in persons who reported past-year use of:

No opioid use (past year): 35.9%; n=411	Suboxone use (past year): 10.7%; n=122
Percocet: 33.2%; n=380	Methadone use (past year): 7.8%; n=89
Vicodin; 32.3%; n=369	Heroin: 5.8%; n=66

- Participants reported: ≥6 months opioid abstinence d/t Kratom use (74.2%; n=849)
 - Would recommend Kratom for opioid withdrawal treatment (99.2%; n=1,135)
- Kratom use for opioid use reduction was significantly a/w:

Increase

- Age at 1st Kratom use (use start ≤ age 65); (aOR > 8.9; 95% CI: 0.00, 12.9)
- ↑ number of opioids used in the past 12-months ($\chi^2=645$, $p < .001$)
- Past 12-month opioid use (aOR = 5.89; 95% CI: 3.35, 10.39)
- Frequency of current kratom use ($\chi^2=11$, $p = .03$)

Decrease

- Lifetime Kratom use (<100 occasions) (aOR = 0.26 95% CI: 0.13, 0.52)
- Never having experienced opioid W/D (aOR < 0.01; 95% CI: 0.00, <0.01)



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Garcia-Romeu A, et.al. Kratom (*Mitragyna speciosa*): User demographics, use patterns, and implications for the opioid epidemic, Drug Alcohol Depend. 2020 March 01; 208: 107849



Kratom Use to Self-Manage Opioid Use

- Kratom users compared by motivation type for between-groups comparisons of individuals using kratom to reduce opioid use (n=1,144), & those reporting kratom use for other reasons (e.g. pain or depression; n=1,654)
 - Groups similar in age, sex, relationship status, & geographic location
 - Groups differed significantly in education & employment status

- Persons using Kratom for opioid use reduction:

- ↓ Rates of college attendance
- ↓ Advanced degrees
- ↓ Current students
- ↑ Unemployment

Persons using Kratom to reduce opioid use were also:	
<p>Less likely to have a h/o UD a/w:</p> <ul style="list-style-type: none"> • Alcohol (p<.001) • Antidepressants (p=.028) • Hallucinogens (p=.014) 	<p>More likely to have used (past-yr) a/w:</p> <ul style="list-style-type: none"> • Tobacco (p<.001) • Opioids (p<.001) • Benzodiazepines (p<.001) • Cocaine (p=.002)



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Kratom Use to Self-Manage Opioid Use

Individuals using kratom to manage OUD reported significant:

- ↑ lifetime prevalence of the following medical diagnoses:
 - Back pain, Depression, Panic attacks
 - Menopause (Only Dx that is more common in persons **NOT** using Kratom for opioid use-reduction)

Individuals using Kratom to manage opioid use demonstrated:

- Significantly ↑ rates of kratom use for anxiety, depression, PTSD, bipolar mood, & pain.
- Exhibited ↑ likelihood of having used kratom w/in the last 24 hours
- ↑ doses were used/occasion; ↑ doses used/day; ↑ frequency of use
- ↑ prevalence of kratom-related withdrawal symptoms

Kratom User Reported Outcomes

- A. Greater drug liking (significant); B. Good effects; C. Alertness; D. Desire for Kratom; & E. Less sleepiness (significantly more likely)
- To meet DSM-5 criteria for a mild or moderate Kratom-related UD in the past year. (slightly more likely)



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Kratom Adverse Drug Effects & Withdrawal

Adverse Drug Effects (ADE)

- 19% of participants reported adverse effects from Kratom use
- 12.8% reporting possible kratom-related adverse effects.

Withdrawal

- 9.5% reported definite Kratom Withdrawal Symptoms
- 17.5% reported **possible** kratom-related withdrawal symptoms.
- Among those reporting definite or possible ADEs
 - 1% (n=9) reported serious to extreme severity
 - 1.9% (n=17) reported seeking medical treatment for adverse effects.
 - Most adverse effects were rated mild in severity (63.2%) and lasted ≤ 1 day (86.1%).



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Kratom Withdrawal Syndrome

Study Findings

- Kratom withdrawal symptoms reported (9.5%)
- Possible Kratom-related withdrawal (17.5%)
- **ADE from Kratom was significantly a/w:**
- **Increased risk**
 - Male sex (female **aOR = 0.75**; 95% CI: 0.59, 0.95)
 - # of opioids used in the past 12-months (**aOR > 2.45** for people using 8+ different types of opioids; 95% CI: 0.00, 1.44)
 - Kratom-related withdrawal (**SOWS total**; aOR < 0.01 for **SOWS total <50**; 95% CI: 0.00, 1.21x1010),
- **Decreased risk**
 - past 12-month alcohol use (aOR = 0.61 for no alcohol in past 12 months; 95% CI: 0.48, 0.76)
 - past 12-month opioid use (aOR = 0.59 for no opioid use in past 12 months; 95% CI: 0.45, 0.76)
- **Self-reported Symptoms:**
 - Depression (aOR = 0.68 for no depression; 95% CI: 0.54, 0.87)
 - Pain severity ($\chi^2 = 9240.28$, $p < .001$),
 - Kratom-related DSM-5 SUD symptoms ($\chi^2 = 149.93$, $p < .001$)
 - All related to kratom adverse effects.
- **Symptoms of withdrawal following kratom abstinence**
 - Mean (SD) SOWS score = 8.8 (SD 8.4), indicating mild opiate withdrawal symptoms (i.e., SOWS score <11)
 - Most respondents (87.7%) did not meet diagnostic criteria for a past-year kratom-related SUD (DSM-5)
 - > 3% met diagnostic criteria for moderate and severe kratom-related SUD.
 - Troubled/bothered by Kratom use 3.2% (9.8) (0 - 100)



Garcia-Romeu A, et.al. Kratom (*Mitragyna speciosa*): User demographics, use patterns, and implications for the opioid epidemic, *Drug Alcohol Depend.* 2020 March 01; 208: 107849

SOW: Symptoms
of Withdrawal



Kratom Withdrawal Syndrome

The most highly rated subjective effects of kratom on a 0 to 100 VAS included:

- 'Good effects' (M=86.4; SD=23.0)
- 'Drug liking' (M=85.7; SD=23.7),
- 'Alert' (M=49.8; SD=30.9)
- 'Stimulated' (M=41.3; SD=28.6),

Lower ratings of:

- 'Euphoric' (mean=25.1; SD=27.1)
- 'High' (mean =12.0; SD=20.1)

Logistic regression analyses

- Kratom withdrawal predicted by:
 - # of kratom-related DSM-5 SUD symptoms ($\chi^2 = 3301.90$, $p < .001$)
 - Sex (female aOR = 0.21; 95% CI: 0.09, 0.47)
 - Total SOWS score ($\chi^2 = 77.25$, $p < .001$),
 - h/o experiencing opioid withdrawal (aOR = 0.14 for never experiencing opioid withdrawal; 95% CI: 0.05, 0.36).
- Seeking treatment for kratom use predicted by:
 - # of kratom-related DSM-5 SUD symptoms (all aOR < 0.01 for <9 DSM-5 SUD symptoms; 95% CI: 0.00, <0.01)
 - SOWS total (all aOR < 0.01 for SOWS total <50; 95% CI: 0.00, <0.01).



Garcia-Romeu A, et.al. Kratom (*Mitragyna speciosa*): User demographics, use patterns, and implications for the opioid epidemic, *Drug Alcohol Depend.* 2020 March 01; 208: 107849



Patterns/Reasons for Kratom Use Among Current & Former Opioid Poly-drug Users

Anecdotal evidence: Kratom is used to attain opioid abstinence, reduce opioid dependence, & mitigate withdrawal symptoms in poly-drug users and in current/former opioid users

Study Aim: Determine patterns/reasons for kratom use in current/former opioid poly-drug users in Malaysia.

Study Population:

- Cross-sectional study, N=204 opioid poly-drug users (142 current users vs. 62 former users) currently using Kratom
- Validated UPLC-MS/MS method was used to evaluate the alkaloid content of a kratom street sample.
- Demographic characteristics:
 - All factors in current vs. former opioid poly-drug users: **non-significant**, except
 - Marital status (Current users had ↑ odds of being single (OR: 2.2; 95%CI: 1.21–4.11; $p < 0.009$))
- All opioid poly-drug users regularly used kratom (3 glasses/~900 mL daily; ~170.19 mg mitragynine) to overcome opioid poly-drug use problems
- UPLC-MS/MS Analysis of street samples (~300 mL brewed kratom): Mitragynine, Paynantheine, Speciociliatine, Speciogynine, 7-Hydroxymitragynine
- **No significant differences: Current vs. Former opioid poly-drug users** for the following factors:
 - Duration of use: (OR: 1.1: 0.62–2.03; $p = ns$)
 - Daily quantity used: (OR: 1.5: 0.85–2.82; $p = ns$)
 - Frequency of use: (OR: 1.1: 0.62–2.06; $p = ns$)
- **Significant differences: Current vs. Former opioid poly-drug users:**
 - Current opioid users more likely to use kratom to ameliorate opioid W/D (**OR: 5.4**, 95% CI: 2.81–10.18; $p < 0.0001$)
 - Former opioid users more likely to use kratom euphoric (mood-elevating) effects (**OR: 1.9**, 95% CI: 1.04–3.50; $p < 0.035$)



Patterns and reasons for kratom (*Mitragyna speciosa*) use among current and former opioid poly-drug users, Singha D, et.al.
Journal of Ethnopharmacology Vol 249, 1 March 2020, 112462



Prescriber's Goals

- Setting expectations
- Maintain engagement
- Make a diagnosis
- Plan for Kratom Use Disorder including:
 - Indications for treatment of KUD with buprenorphine
 - Engage the patient in the treatment of this new use disorder



5 MCSTAP Calls Involving Kratom (2019-2021)

Case	Age, Gender	Formal Other OUD Dx?, In Tx?	Presumed OUD (Kratom)	Amphetamine Use	ADHD Dx	AUD Dx?	Stimulants Rx 'd	Oxy-codone	Anxiety, Depression, Chronic Pain	Treatment Plan
1	31, F	Yes, ?	Yes	-	Yes	Yes	Yes	Yes	-	<ul style="list-style-type: none"> Dx, Treat w/ Buprenorphine Address other comorbid U.D.s & MH conditions Regular UDTs / monitoring
2	27, M	Yes, ?	Yes	Yes	-	-	-	-	-	<ul style="list-style-type: none"> Dx, Treat w/ Buprenorphine r/o Stimulant U.D. Regular UDTs / monitoring
3	27, M	Probable, ?	<ul style="list-style-type: none"> Yes Tx'd w/ NTX in past No response 	-	-	-	<ul style="list-style-type: none"> Past Tx'd w/ Methylphenidate / Atomoxetine No response 	-	-	<ul style="list-style-type: none"> Dx, Treat w/ Buprenorphine Address other comorbid conditions Regular UDTs / monitoring
4	40, M	?, ?	?	-	-	-	-	-	Anxiety, Chronic Pain	<ul style="list-style-type: none"> Insufficient data
5	Adult, ?	Yes, ?	Yes	-	-	-	-	-	Yes	<ul style="list-style-type: none"> Insufficient data

Should Kratom be Scheduled as a Class I Controlled Substance?

Unclear if Kratom should be a Scheduled Class I Controlled Substance.

- Centuries of use to manage pain & other disorders
- Mid-twentieth century: used to manage opioid withdrawal
- **Some opioid effects**
 1. Low respiratory depression
 2. Low abuse potential compared to opioids of abuse.
- **Risk Assessment**
 - No documented threat to public health → emergency Schedule I designation
 - Although some pharmacological properties support controlled substance scheduling because of ready availability & large numbers of users, banning at this point risks creating new public health problems
 - Appropriate regulation by FDA is needed to ensure appropriate & safe use



The abuse potential of kratom according the 8 factors of the controlled substances act: implications for regulation and research, [Henningfield JE, et.al. PMID: 29273821 PMCID: PMC5813050.](#)



Maintaining Engagement / Continue MOUD

- Critical to maintain engagement in patients being treated with MOUD now challenged by another new or recurrent SUD.
- Engagement is considered Harm Reduction / Risk Mitigation because the patient is less likely to overdose/progress MOUD is continued along with active engagement/treatment addressing their Stimulant Misuse/Use Disorder.
- Until the OUD is adequately addressed/treated first, unstable patients are be expected to achieve success on their other co-morbid medical or mental health/behavioral conditions.



Thank You



Reasons For Kratom Use & Use Patterns

- Most respondents endorsed using kratom for:
 - *pain relief (91.3%),*
 - *and/or to treat mood-related issues: anxiety (67.2%) or depression (64.5%).*
- Among these, the majority said they would recommend kratom for:
 - *pain relief (98.7%)*
 - *mood-related issues (96.7%).*
- Mean (SD) efficacy ratings of kratom on a scale from 0 (not at all) to 100 (extremely) were:
 - *Treating pain: 83.3 (18.5);*
 - *Anxiety were 76.7 (24.3);*
 - *Depression were 76.5 (25.4).*
- Subgroups also reported using kratom for:
 - *post-traumatic stress (29.6%) mean (SD) efficacy ratings of 60.2 (38.2),*
 - *bipolar mood (24.6%), and 51.4 (39.9), respectively.*
- Mean (SD) age for kratom use initiation was 38 (12.2) years
- Majority of respondents reported using:
 - *kratom ≥ 100 times in their lifetime (76.2%),*
 - *used kratom in the 24 hours before completing the survey (80.7%).*



on was 1-3 grams (49.0%), followed by 4-6 grams (33.4%).

Daily use was reported by the majority of respondents (59.1%), mean (SD) of 2.7 (1.3) doses used per day.

- Ingesting kratom orally in powder form was the most common method of administration (43.6%) followed by drinking as a prepared beverage (e.g., tea, smoothie;

Diagnosis of Substance Use Disorders



Make a Formal Diagnosis

- If a new or recurrent SUD is being considered, at earliest time possible, make sure to **establish a specific diagnosis & perform a severity assessment** using the DSM-5 Criteria for Diagnosis of Substance Use Disorders
- Once establishing the diagnosis of OUD calculate the numeric score of the 11 criteria to assess its severity
- Discuss the diagnosis with the patient.
 - Are they receiving this diagnosis for the first time?
 - What does it mean for them?
 - How do they perceive it will affect them in the future?
 - Other open-ended questions?



Defining Addiction:

- A 1°, chronic disease of brain reward, motivation, memory & related circuitry
- Circuitry dysfunction → specific biological, psychological, social & spiritual symptoms
- Pathological pursuit of reward a/o relief via substance use & related behaviors
- Inability to consistently abstain
- Impairment in behavioral control
- Craving/Increased “hunger” for drugs/rewarding experiences
- ↓ recognition of major problems w/ one’s behaviors & interpersonal relationships
- Dysfunctional emotional response
- Cycles of relapse & remission common (Similar to chronic diseases)
- Progressive & can result in disability or premature death w/o treatment or engagement in recovery activities

Diagnosis:

- **New** or recurrent OUD:

First make a specific diagnosis if possible, then assess its severity

- Use DSM-5 Criteria for diagnosis of substance Use Disorders (UD)
- Assess each substance that the patient currently endorses for use
- Confirm a UD diagnosis for each substance used; Add a 1 for each DSM-5 criteria met; The sum reflects each UD's severity
- Diagnosis & severity assessment is critical to engaging & determining the severity of OUD in patients being treated for chronic pain with full-agonist opioids



DSM-5 defines a substance use disorder (SUD) as:

Presence of 1 or more of 11 criteria (Clustered in 4 groups)

A. Impaired control:

1. taking more or for longer than intended,
2. unsuccessful efforts to stop or cut down use,
3. spending a great deal of time obtaining, using, or recovering from use,
4. craving for substance

B. Social impairment:

5. failure to fulfill major obligations due to use,
6. continued use despite problems caused or exacerbated by use,
7. important activities given up or reduced because of substance use

C. Risky use:

8. recurrent use in hazardous situations,
9. continued use despite physical or psychological problems that are caused or exacerbated by substance use

D. Pharmacologic dependence:

10. tolerance to effects of the substance,
11. withdrawal symptoms when not using or using less