

Complexities & Controversies in Assessing, Diagnosing, & Managing Kratom Use

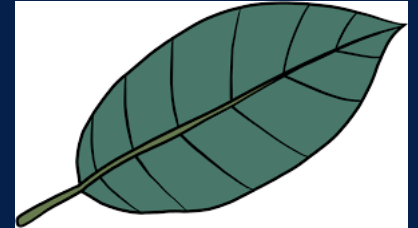
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American Society of Addiction Medicine 56th Annual Conference



Disclosure Information

- ◆ Presenter 1: Robert Levy, M.D.
No Disclosures
- ◆ Presenter 2: Stephanie T. Weiss, M.D., Ph.D.
No Disclosures
- ◆ Presenter 3: Ian Latham, M.D.
No Disclosures
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International Plant and Herbal Alliance, paid scientific consultant; serves as expert witness in legal cases involving kratom



Learning Objectives

- ◆1: Define the different types of kratom products in the US and describe how product, formulation, and dose are relevant in the understanding of kratom use.
- ◆2: Identify differences between kratom-related physical dependence symptoms (e.g., tolerance, withdrawal) and kratom use disorder, and explain their relevance in assessment and treatment.
- ◆3: Develop clinical skills to conduct assessments of kratom use and kratom use disorder, including appropriate use of laboratory testing, and evaluate treatment options in light of confounding factors.
- ◆ 4: Describe the benefits and controversies of current treatment methods for KUD, including opioid agonist therapy, for both isolated KUD and KUD with comorbid SUDs.

What is kratom?



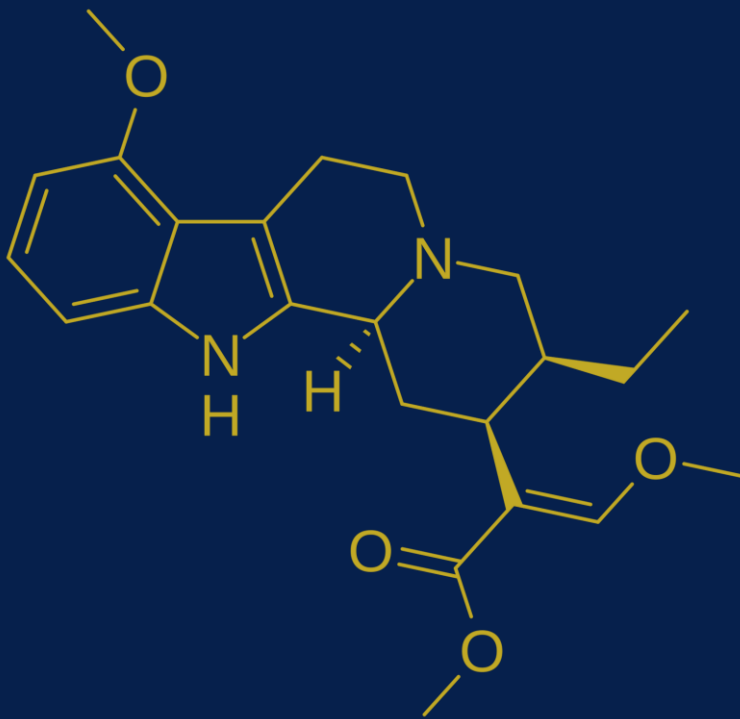
Mitragynine (MG)

(~34-50% alkaloid content)

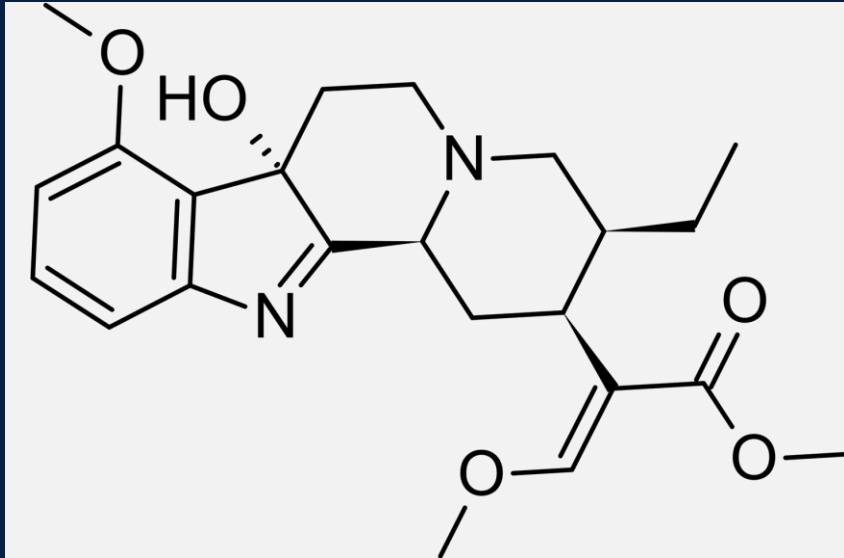
Weakly binding partial MOR agonist.

Agonist at α_{1A} and α_{1D} adrenergic receptors.

Some serotonergic, dopaminergic, and adenosinergic pharmacology activity.



7-hydroxymitragynine (7-OH)



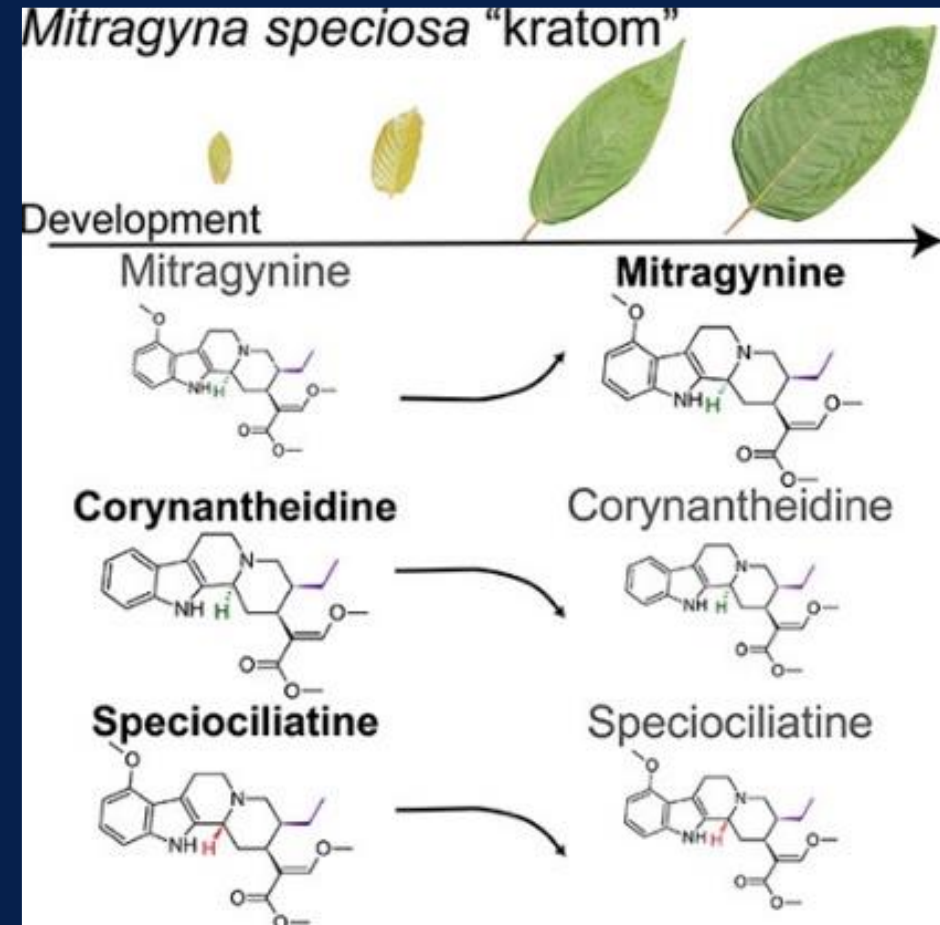
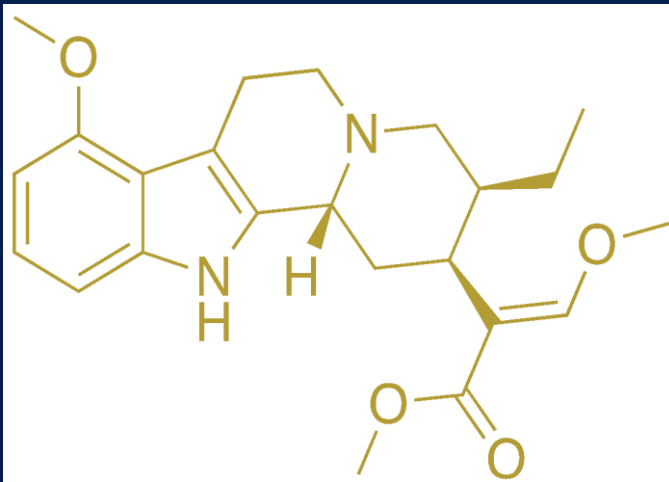
Mitragynine is metabolized in liver & intestines *into* 7-OH.

In dried leaf 7-OH can be found in trace amounts from oxidization

Highly selective MOR agonist with binding affinity 14-22 times that of morphine.

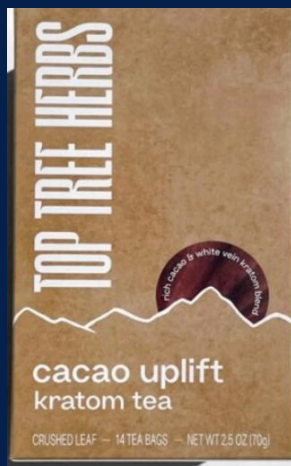
Metabolized relatively quickly.

Speciociliatine: partial MOR agonist with 3-fold higher binding affinity than MG. Metabolized quickly via CYP3A4.



Not all kratom is equal: The important distinction between native leaf and extract products

Oliver Grundmann✉, Albert Garcia-Romeu, Christopher R. McCurdy, Abhisheak Sharma, Kirsten E. Smith, Marc T. Swogger, Stephanie T. Weiss



- Whole-leaf product samples (N=341) were similar in alkaloid composition, matching the genetic fingerprint expected for *Mitragyna speciosa*. No evidence of drug adulteration.
- Mitragynine *intake per use*: mean **31.3 mg** (range 2.0-205.9 mg).
- Estimated mean *daily intake* of mitragynine: **134.6 mg**.
- 7-hydroxymitragynine ranged from BLLOQ-0.20% (w/w or w/v; median of 0.01%), indicating 7-OH is not a major or natural component of kratom or kratom products.

LETTER TO THE EDITOR |  Free Access

The rise of novel, semi-synthetic 7-hydroxymitragnine products

Kirsten E. Smith , Edward W. Boyer, Oliver Grundmann, Christopher R. McCurdy, Abhisheak Sharma

First published: 03 December 2024 | <https://doi.org/10.1111/add.16728>

“7OH” products are:

- Quickly metabolized
- Some circumvent first-pass metabolism
- Cannot be tested for currently
- Chemical unknowns
- Residual MG (huge clinical & forensic tox implications).
- National Poison Data System





Contents lists available at [ScienceDirect](#)

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}

ORIGINAL RESEARCH

Prevalence of Kratom Use Disorder among Kratom Consumers

Katherine Hill, MPH, Oliver Grundmann, PhD, Kirsten E. Smith, PhD, and Corneliu N. Stanciu, MD



Original Investigation | Substance Use and Addiction

Ecological Momentary Assessment of Self-Reported Kratom Use, Effects, and Motivations Among US Adults

Kirsten E. Smith, PhD; Leigh V. Panlilio, PhD; Jeffrey D. Feldman, BA; Oliver Grundmann, PhD; Kelly E. Dunn, PhD, MBA; Christopher R. McCurdy, PhD; Albert Garcia-Romeu, PhD; David H. Epstein, PhD

Assessment of Kratom Use Disorder and Withdrawal Among an Online Convenience Sample of US Adults

Kirsten E. Smith, PhD, Kelly E. Dunn, PhD, MBA, Jeffrey M. Rogers, BA, Albert Garcia-Romeu, PhD, Justin C. Strickland, PhD, and David H. Epstein, PhD



Contents lists available at [ScienceDirect](#)

Drug and Alcohol Dependence Reports

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

Commentaries

Kratom withdrawal: Discussions and conclusions of a scientific expert forum[☆]

Jack E. Henningfield^{a,b,*}, Marek C. Chawarski^c, Albert Garcia-Romeu^b, Oliver Grundmann^d, Norsyifa Harun^e, Zurina Hassan^e, Christopher R. McCurdy^{d,f,g}, Lance R. McMahon^h, Abhishek Sharma^{f,g}, Mohammed Shoaibⁱ, Darshan Singh^e, Kirsten E. Smith^j, Marc T. Swogger^k, Balasingam Vicknasingam^e, Zachary Walsh^l, Daniel W. Wang^a, Marilyn A. Huestis^{a,m}



Contents lists available at [ScienceDirect](#)

Drug and Alcohol Dependence

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


Kratom addiction per DSM-5 SUD criteria, and kratom physical dependence: Insights from dosing amount versus frequency

Jeffrey M. Rogers^a, Stephanie T. Weiss^b, David H. Epstein^c, Oliver Grundmann^d, Katherine Hill^e, Kirsten E. Smith^{f,*}

Physical dependence & addiction

Current Addiction Reports
<https://doi.org/10.1007/s40429-023-00474-7>

Diagnostic Ambiguities and Underuse of Clinical Assessment Tools: A Systematic Review of Case Reports on Kratom Addiction and Physical Dependence

Kirsten E. Smith¹  · Jeffrey D. Feldman¹ · Destiny Schriefer² · Stephanie T. Weiss³ · Oliver Grundmann⁴ · Kelly E. Dunn⁵ · Darshan Singh⁶ · Christopher R. McCurdy⁴ · Gisela Butera⁷ · David H. Epstein¹

- ◆ No reliable prevalence estimates for KUD.
- ◆ Published case report literature on kratom-related physical addiction, withdrawal, dependence, “misuse/abuse” in the dozens, and often confounded.
- ◆ Problematic assessment & diagnostic methods.

Physical dependence & addiction

Current Psychiatry Reports (2024) 26:487–496
<https://doi.org/10.1007/s11920-024-01524-1>

REVIEW



Controversies in Assessment, Diagnosis, and Treatment of Kratom Use Disorder

Kirsten E. Smith¹ · David H. Epstein² · Stephanie T. Weiss²

Accepted: 17 July 2024 / Published online: 13 August 2024

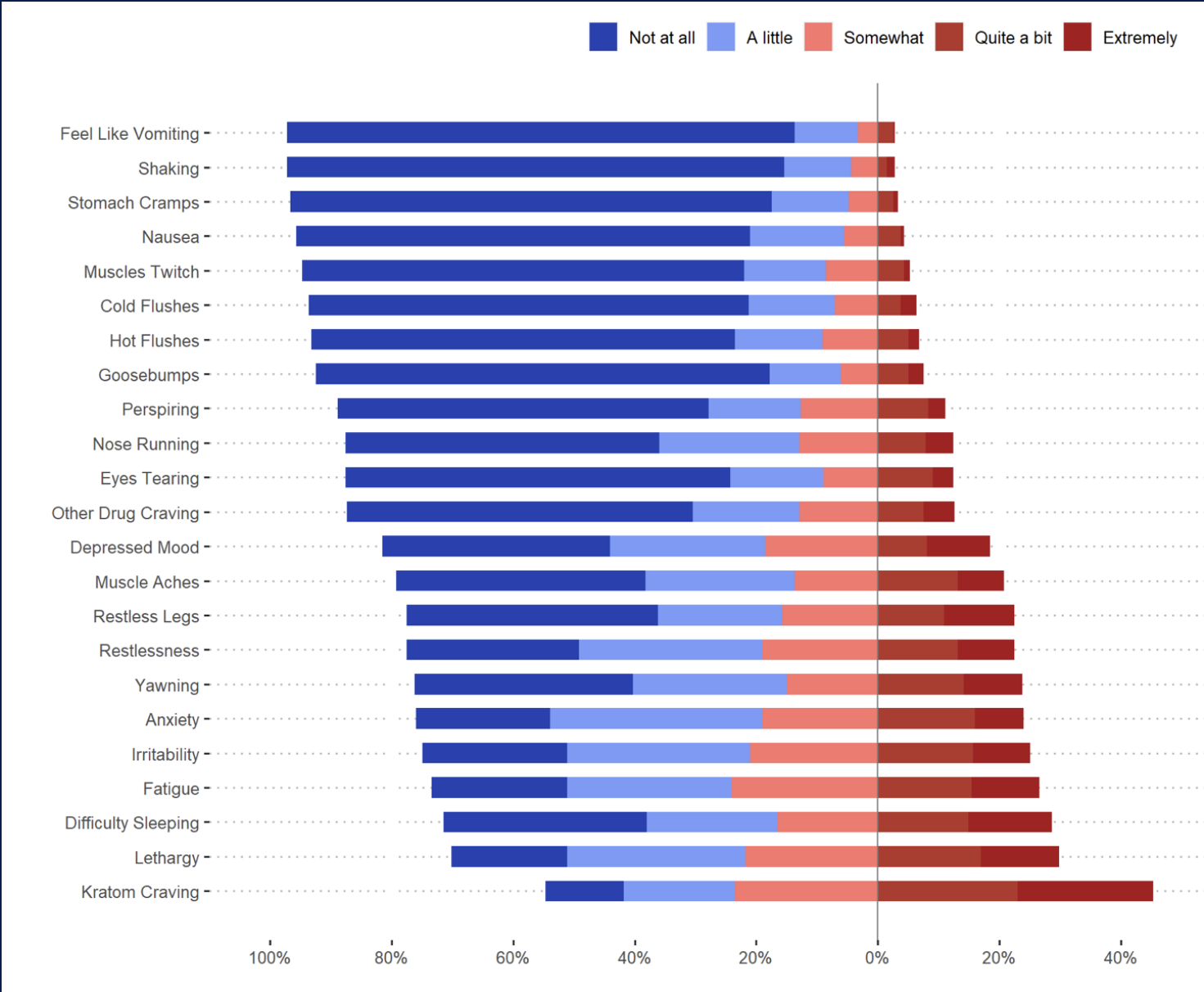
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- ◆ **Research:** DSM-5-derived SUD for kratom (KUD) most samples <50% meet diagnostic criteria.
- ◆ KUD severity: majority mild-moderate.
- ◆ Many meeting criteria based on symptoms of withdrawal, tolerance, & craving.
- ◆ **Withdrawal self-reported globally to be mild-moderate.**



See also: A Garcia-Romeu et al., 2021; J Henningfield et al. 2024; J Henningfield et al., 2023; K Hill et al., 2023; K Smith et al., 2023; K Smith., 2022;

Kratom withdrawal after stopping use ≥ 1 day

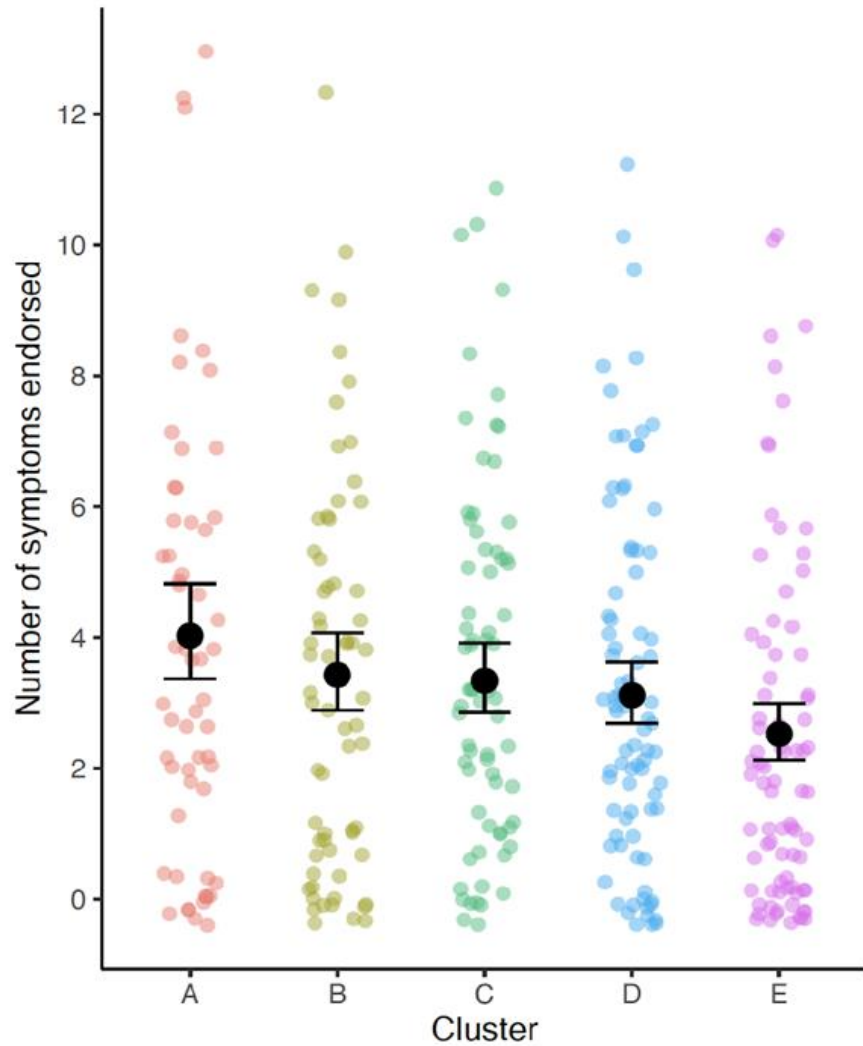


Controlling for demographics, standardized typical ***dose amounts*** were related to 9 of 23 WD symptoms.

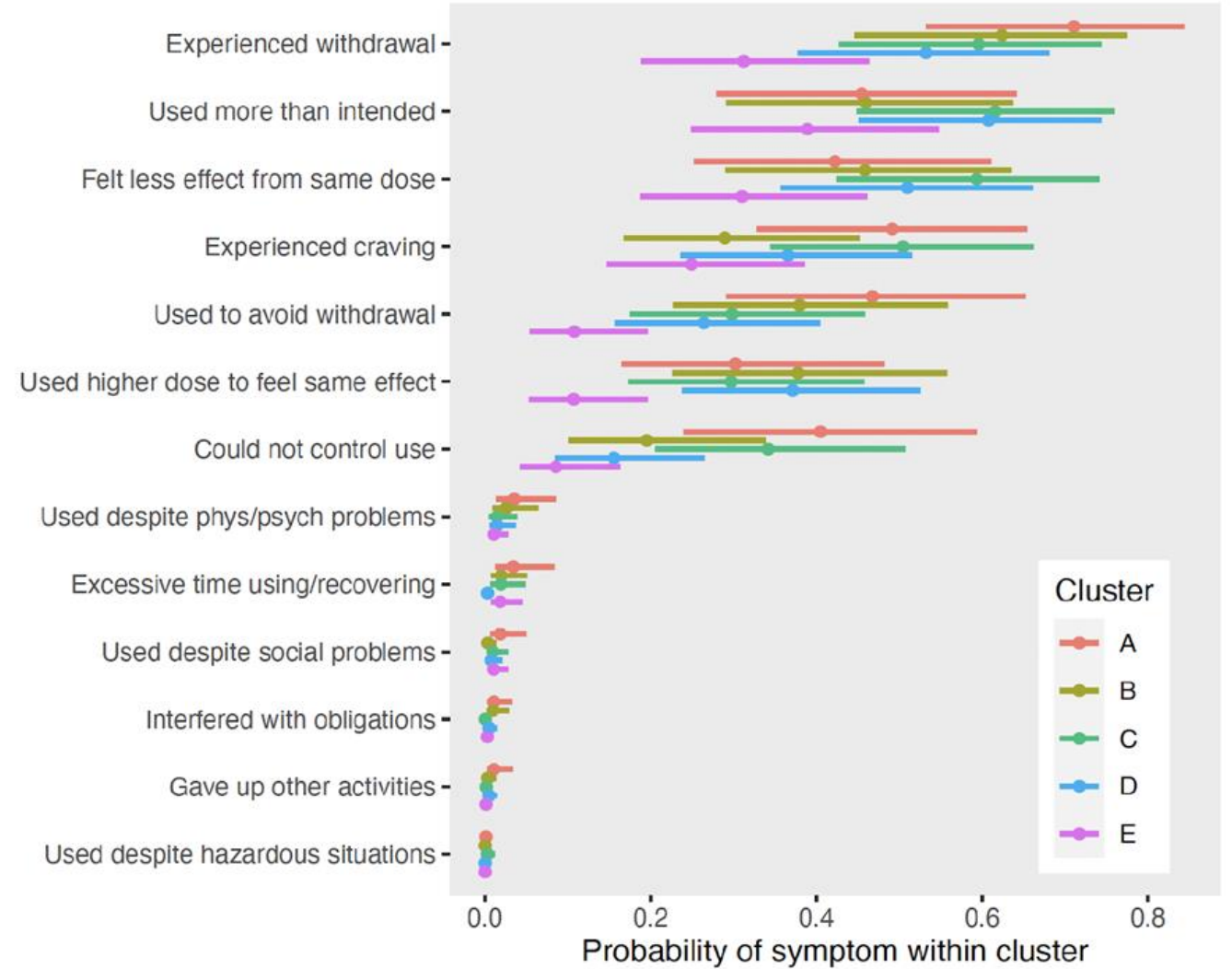
Higher ***frequency/day*** was associated with higher odds of experiencing **19 of 23** WD symptoms.



A: Number of DSM symptoms endorsed



B: Prevalence of specific symptoms



Considerations of DSM-5 SUD

- ◆ No single criterion is necessary or sufficient for SUD diagnosis.
- ◆ Criteria do not reflect use frequency.
- ◆ SUD criteria characterize addiction in terms of consequences.
- ◆ *Criteria do not currently reflect use motivations (except withdrawal avoidance).*
 - ◆ **Many use kratom instrumentally with seeming net benefit result.**
- ◆ **Heterogeneity:** Identical SUD diagnosis can be given to patients with none of the same symptoms.

Evaluation of use & KUD complicated by:

- Product formulation diversity.
- Patient history, comorbidity, and co-use of other substances.
- Clinician's inability to test for all kratom alkaloids
 - Mitragynine is current marker for kratom use.
 - No way to currently test for 7-OH.
- Novel formulations confused as “kratom”:
 - 7OH should be treated as OUD**
 - Blended products (kava + kratom) cannot be evaluated as kratom—addiction assessment will may be product-specific.**



**“Kratom” is an increasingly
meaningless term.**

You must define “it.”

*Ultimately, KUD may be more akin to
multiple SUDs due to complex pharmacology
at the level of the plant, its constituent
alkaloids, and the products.*

Meet Jeff, Our Case Study Patient

Case adapted from:

CASE REPORTS

Isolated Kratom Use Disorder Treated With Extended-Release Buprenorphine Taper

Swart, Benjamin B. MD; Reznikoff, Charles MD; Steen, Katie MD

[Author Information](#) ☺

Journal of Addiction Medicine 18(5):p 602-604, 9/10 2024. | DOI: 10.1097/ADM.0000000000001328

Case 1 (Jeff) -- Introduction

- ◆ Jeff, a 36-year-old male
- ◆ Referred by primary care physician for “kratom addiction”
- ◆ Electronic Medical Record Review:
 - ◆ No relevant past medical history
 - ◆ No current medications
 - ◆ PDMP with no controlled substances for the past year

What are the first questions you want to ask this patient?

Screening

- ◆ Who needs to be screened for KUD?
- ◆ Individuals report use of kratom for:
 - ◆ Management of chronic pain
 - ◆ Opioid withdrawal management
 - ◆ Opioid and other substance addiction
 - ◆ Euphoria
 - ◆ Symptoms of anxiety/depression/fatigue
- ◆ Universal screening among SUD patients?

At Risk Populations

- ◆ National Survey on Drug Use and Health data suggest highest prevalence of use among “white, middle-class, suburban” persons (Rogers et. al 2021)
 - ◆ Continued assessment needed, particularly with new products
- ◆ Associations noted with people who use e-cigarettes, people who use stimulants, historical use of other substances
- ◆ International data also suggest association in youth with worse academic performance, conventional cigarette smoking, close friend substance use
 - ◆ Not yet seen in US data, relatively low youth rates of use

Polysubstance use

- ◆ National data suggest nearly one-third of people who use kratom have at least one co-occurring SUD
 - ◆ Significantly higher rates of OUD and StUD vs never-users
- ◆ Significantly higher prevalence of lifetime cannabis use among those who use kratom (~92% vs 49% in general population)
- ◆ National and international data also suggest higher use of other opioids, higher rates of stimulant misuse

Risks of Polysubstance Use

- ◆ Co-use of other opioids with kratom increases risk of drug-related death
- ◆ Coroner data for kratom-related fatalities suggest high rates of co-ingestion
- ◆ Internet community analysis suggests poor experiences with kratom use for opioid withdrawal and other SUD management
- ◆ Safety of active kratom use alongside MOUD (buprenorphine, methadone) not well studied or understood

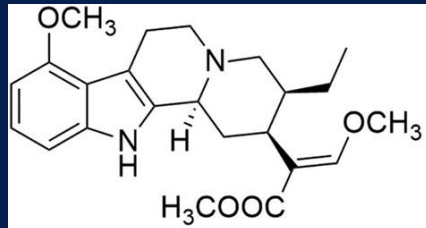
Screening Tools

- ◆ No validated kratom-specific screening tools available
- ◆ Consider use of other validated substance use screening tools such as Drug Abuse Screening Test (DAST), CAGE-AID, Opioid Risk Tool
 - ◆ Consider explicitly identifying kratom as a substance of use for all patients
- ◆ No data to suggest effectiveness of SBIRT model in kratom use

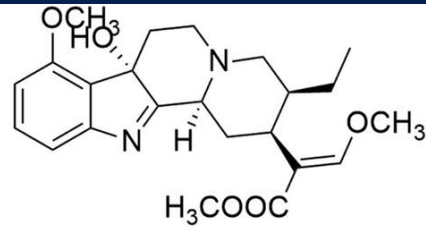
Challenges in Diagnosis

- ◆ Kratom Use Disorder not explicitly defined by DSM 5-TR, though can use same 11 criteria applies to other SUD
- ◆ When viewed as an “other specified” SUD, diagnosis of KUD is within DSM standards
- ◆ Patients may be more likely to identify perceived benefits and disregard adverse effects or negative impact on life
- ◆ Similar to cannabis, legal status may impact patient perception on appropriateness of use

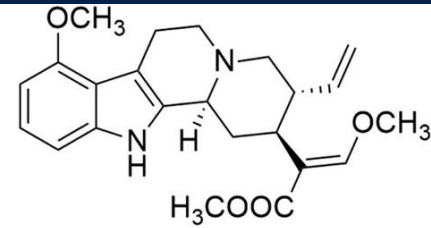
Testing



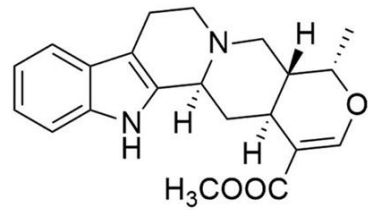
Mitragynine



7-Hydroxymitragynine



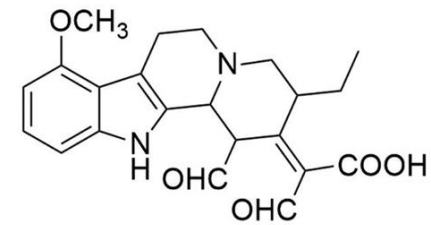
Paynantheine



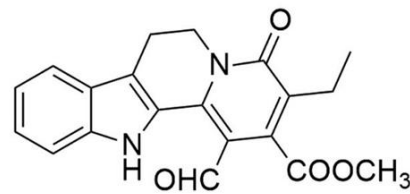
Ajmalicine



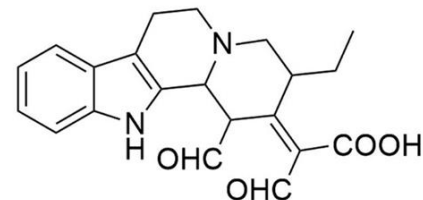
Mitragynaline



Mitragynalinic acid



Corynantheidaline



Corynantheidalinic acid

Testing

- ◆ Mitragynine is most common testing target, not included in most common drug screens
 - ◆ Generally requires referral to toxicology lab
- ◆ Cross-reactivity between 7-OH-MG and mitragynine variable across assays
- ◆ 7-OH-MG fairly challenging to test, avidly forms adducts which limit sensitivity and reproducibility of chromatography
- ◆ 7-OH-MG also generally unstable in biological specimens, limiting extractability and testing

Testing

- ◆ Rapid testing not available, though in development
 - ◆ On one ELISA product, cross-reactivity for 7-OH-MG only 20%
- ◆ Mitragynine may be detectable in nail specimens, 7-OH-MG not detected (though would be expected)

Screening and Diagnosis complicated by...

- ◆ Limited prevalence data to easily identify at-risk populations
- ◆ Rapidly changing product base and target populations
- ◆ Lack of kratom-specific screening tools
- ◆ Variable patient perception of benefits/risk of use
- ◆ Association with polysubstance use
- ◆ Increased risk of mortality among patients with co-occurring OUD
- ◆ Limited availability of testing for mitragynine
- ◆ 7-OH-mitragynine is technically challenging to test, currently no commercial tests available

Case 1 (Jeff) – Patient Interview

- ◆ First use of kratom about 2 years ago
- ◆ Works as software developer, saw online kratom advertisement for “increased productivity”
- ◆ Initially using 0.5-1 tablespoon of dry powder dissolved water daily, felt “calm and thoughtful”
- ◆ Use escalated over 1 year
- ◆ One year ago noticed withdrawal syndrome with discontinuation
- ◆ Now swallowing 1 tablespoon (~7g) of dry powder every three hours

What else do you want to know?

Case 1 (Jeff) – Additional Information

- ◆ Withdrawal symptoms: anxiety, restlessness, dysphoria, irritability, and difficulty concentrating
 - ◆ Onset within 4 hours of last use
- ◆ Denies history of psychiatric illness, chronic pain, or previous substance use disorders
- ◆ No family history of substance use disorders
- ◆ Has made previous attempts to quit multiple times
 - ◆ Went as long as 2 weeks before returning to use, limited by cravings and withdrawal symptoms
 - ◆ Has never received medications for withdrawal management

Ok, what else?

Case 1 (Jeff) – Additional Information

- ◆ He endorsed using more kratom than intended, spending excessive time and money on obtaining, using, and recovering from kratom use
- ◆ Also reported significant negative mood symptoms related to his kratom use and its effect on his life
- ◆ He voices concern about continued kratom use despite mounting problems at work and home.
 - ◆ Specifically notes decreased productivity at work, withdrawing from friends, arguments with family leading to avoidance of gatherings

Is this “kratom use disorder”? If so, what severity?

Audience Show of Hands

Does Jeff meet criteria for diagnosing KUD?

1. Yes
2. No
3. I don't know

DSM-5 Criteria for SUD

- **Pharmacologic**
 - Tolerance
 - Withdrawal

- **Impaired control**
 - Using more than intended
 - Unable to cut back
 - Spends excessive time
 - Craving

- **Social impairment**
 - Failure to meet obligations
 - Interpersonal difficulties
 - Decreased social activities
- **Risky use**
 - Physically hazardous
 - Continued use despite knowing it's problematic

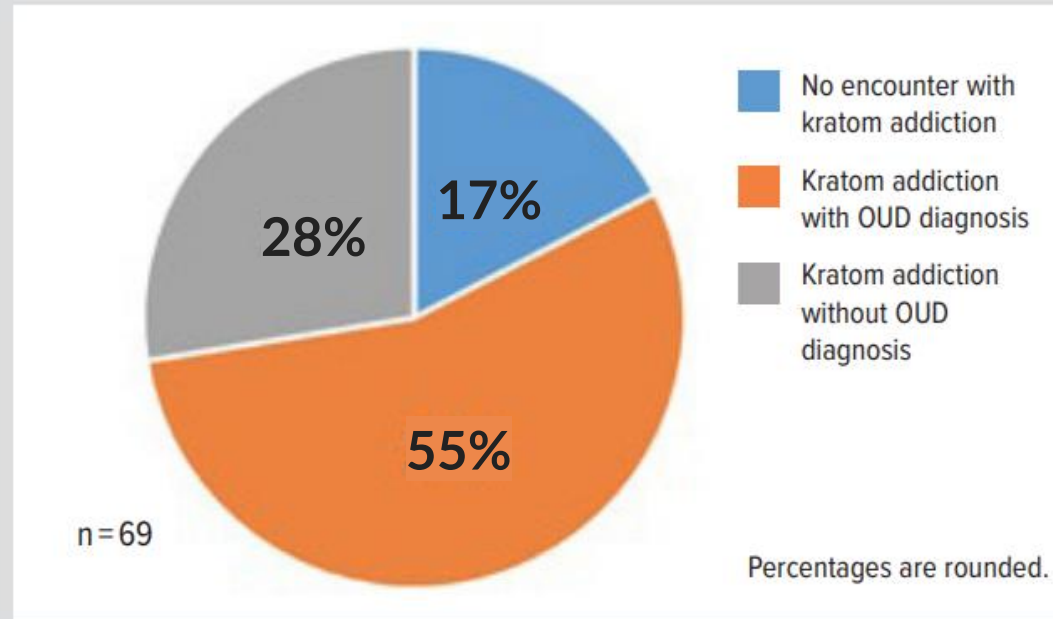
You diagnose Jeff with severe KUD....

What do you want to do next? (Raise hand)

1. Recommend non-pharmacological therapy of some kind (such as individual counseling, 12-step, group therapy, etc.)
2. Offer to start Jeff on a non-opioid Medication for Opioid Use Disorder (MOUD) like naltrexone.
3. Offer to start Jeff on an Opioid Agonist Therapy (OAT) like buprenorphine or methadone.
4. You have no idea what to do, so let's start with some lit searching and maybe consult someone who can help us.

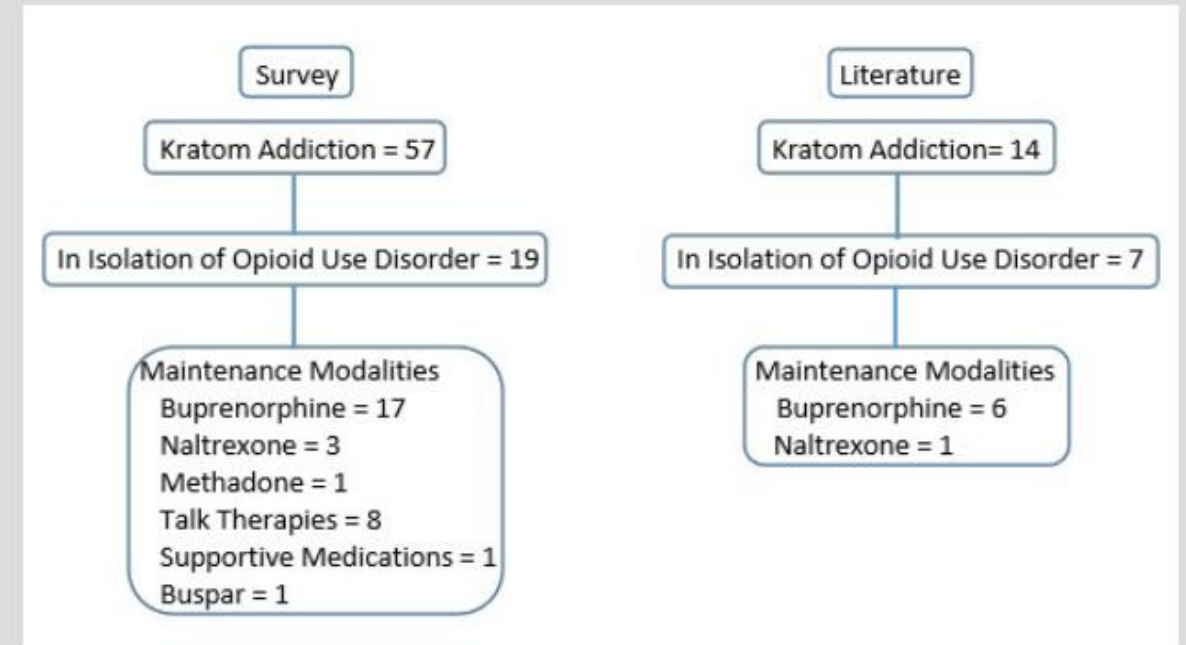
Buprenorphine Wins the Popularity Contest....

Figure 2. Percentage of Survey Participants Who Have Encountered Any Kratom Addiction



Abbreviation: OUD, opioid use disorder

Figure 3. Pharmacological Modalities for Managing Kratom Use Disorder When Found in Isolation of Opioid Use Disorder



but the evidence is entirely limited to case reports and expert opinion

Nonpharmacologic Approaches to Treating KUD

- Limited published literature on this topic
 - A 2-patient case series proposes that contingency management may be a useful adjunct in treating comorbid KUD/OUN
 - No published cases using behavioral therapy to treat isolated KUD, although one survey respondent reported doing so (and seven others reported using it together with OAT)
- Despite the lack of studies to provide evidence for efficacy of nonpharmacological therapies in KUD patients, they are low risk and unlikely to cause harm.



Kalin, S. et. al, (2020) *J. Opioid Management*, 16(5): 391-394; Stanciu, C. et. al, (2021), *Wisconsin Medical Journal*, 120(1): 54-61.
Smith, K.E.; Epstein, D.H.; Weiss, S.T. (2024) *Current Psychiatry Reports*, 26(9): 487-496.

Nonopioid MOUD Approach to Treating KUD

- Limited published literature on the use of naltrexone suggests that it may be effective in some but not all cases.
 - An individual case report of repeated attempted naltrexone maintenance of a patient with isolated KUD was unsuccessful, but the patient was eventually successfully maintained on buprenorphine.
 - A case of attempted induction on naltrexone of a patient with comorbid OUD/KUD from a small case series was also not successful - this patient was also subsequently successfully inducted on buprenorphine.
 - A second case from this same case series did successfully induct the patient onto long-acting injectable naltrexone.
- Despite the lack of studies to provide evidence for efficacy of naltrexone in KUD patients, it is worth considering as an option in appropriate patients with or without comorbid OUD.

Swart, B.B. *et al.* (2024) *JAM*, 18(5): 602-604; Gnanasegaram, S.A. *et. al.* (2024) *J. Psychoactive Drugs*, Nov. 4: 1-4.

Smith, K.E.; Epstein, D.H.; Weiss, S.T. (2024) *Current Psychiatry Reports*, 26(9): 487-496.

OAT MOUD Approaches to Treating KUD

In the United States, you basically have two OAT options, so which do you want to try? (raise hand)

1. Buprenorphine (plus/minus naloxone)

- a. Sublingual
- b. Long-acting injectable (LAI)

2. Methadone

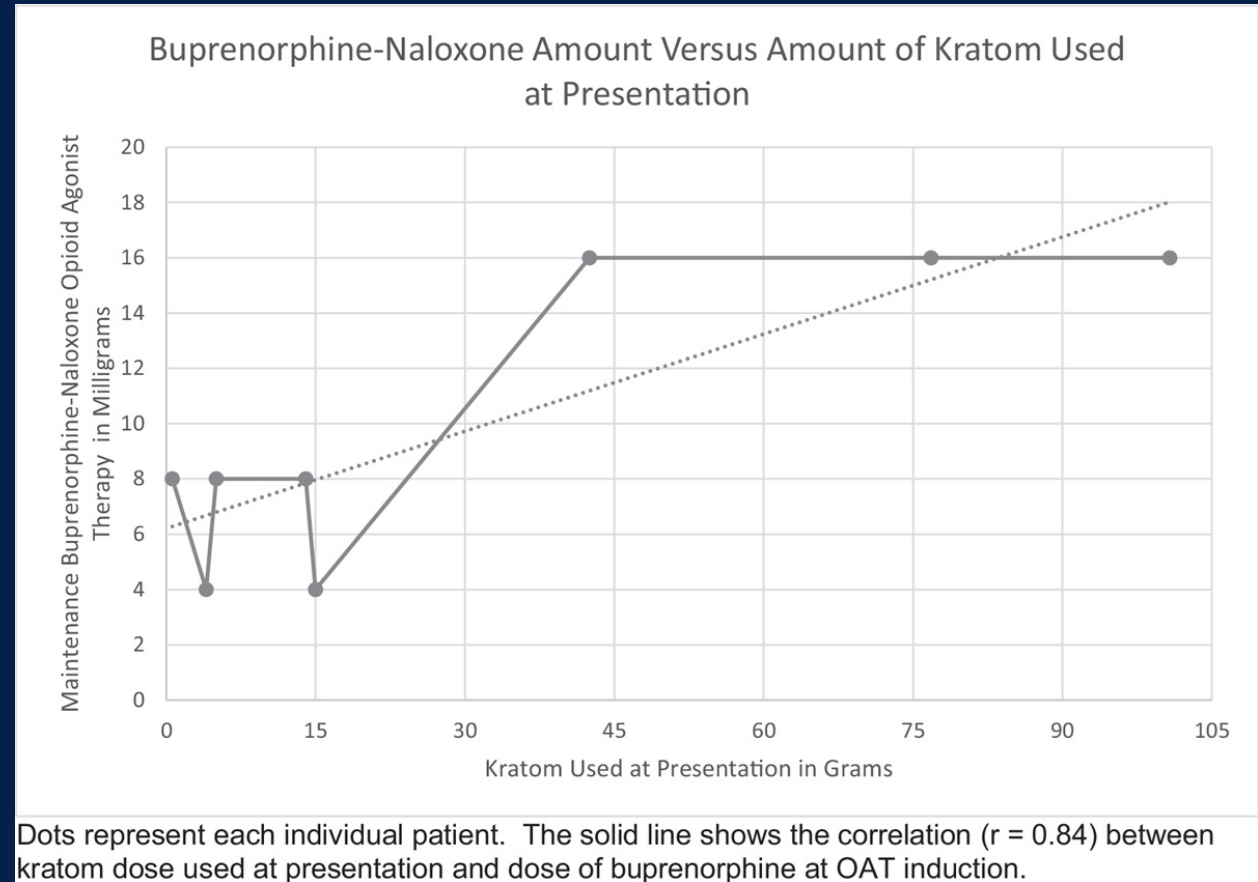
Methadone MOUD Approach to Treating KUD

- Limited published literature on the use of methadone suggests that it may be effective in at least some cases of KUD.
 - One small case series of three adolescent KUD patients from Malaysia successfully used low dose methadone (20-25 mg/day) for 5-18 months to treat isolated KUD
 - No US published cases using methadone to treat isolated KUD, although one survey respondent reported doing so.
- While methadone could be reasonable for treating some patients with a comorbid OUD, it should not be a first-line therapy for most isolated KUD patients, due to understandable concern about exposing opioid-naïve patients to the risks of a full opioid agonist.

Kamaludin, N.N., et. al (2021), *Bangladesh J. of Medical Science*, 20(3): 673-677; Stanciu, C. et. al, (2021), *Wisconsin Medical Journal*, 120(1): 54-61; Smith, K.E.; Epstein, D.H.; Weiss, S.T. (2024) *Current Psychiatry Reports*, 26(9): 487-496.

Buprenorphine for Treating KUD

- Three-patient case series of comorbid OUD/KUD + lit review (total 8 pts)
- Proposed initiating:
 - OUD/KUD patients taking <20 g kratom/day on 4/1-8/2 mg buprenorphine/naloxone
 - OUD/KUD patients taking >40 g kratom/day on 12/3-16/4 mg of buprenorphine/naloxone



Weiss, S. T. and Douglas, H.E. (2021), *JAM*: 15(2): 167-172.

Buprenorphine for Treating KUD

- 28-patient case series of patients with KUD treated w/ buprenorphine/naloxone
- Unclear how many pts had comorbid OUD
- Did not confirm the prior kratom dose/buprenorphine dose correlation

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

Algorithm for Diagnosis/Treatment of Comorbid KUD/OD

Diagnosis: Comorbid KUD/OD

- Discussion with patient about therapeutic options
- Initiate MOUD with buprenorphine, naltrexone, or methadone for KUD/OD
- Consider initiation of adjunctive non-MOUD therapy
- Follow-up and monitoring of patient clinical course

Assessment and Diagnosis of KUD

- History and physical exam, including assessment for opioid and stimulant withdrawal
- DSM-5-based instrument to assess for KUD and other SUDs
- Confirmatory testing for kratom alkaloids (mitragynine)

But...Jeff doesn't have OUD!

Diagnosis: Comorbid KUD/OUD

- Discussion with patient about therapeutic options
- Initiate MOUD with buprenorphine, naltrexone, or methadone for KUD/OUD
- Consider initiation of adjunctive non-MOUD therapy
- Follow-up and monitoring of patient clinical course

Assessment and Diagnosis of KUD

- History and physical exam, including assessment for opioid and stimulant withdrawal
- DSM-5-based instrument to assess for KUD and other SUDs
- Confirmatory testing for kratom alkaloids (mitragynine)

Diagnosis: Isolated KUD

- Discussion with patient about therapeutic options
- Consider initiation of non-MOUD therapy for KUD
- Consider initiation of MOUD in appropriate patients after careful risk/benefit consideration
- Follow-up and monitoring of patient clinical course

Summary: KUD Diagnosis and Treatment

Recent Findings Literature reports of “kratom addiction” or KUD rarely specify the criteria by which patients were diagnosed. Individuals meeting DSM-5 KUD criteria typically do so via tolerance and withdrawal, using more than intended, and craving, not functional or psychosocial disruption, which occur rarely. Most clinicians who use medication to treat patients with isolated KUD select buprenorphine formulations, although there are no controlled studies showing that buprenorphine is safe or efficacious in this patient population.

Case 1 (Jeff) – Initial Management

- ◆ Jeff lives about 3 hours from the medical center and does not want to come on a regular basis
- ◆ He is hesitant about taking “another medication he can withdraw from” and “just wants help quitting”
- ◆ He is open to using medications for withdrawal management
- ◆ When asked about behavioral approaches to addiction treatment, he says “what do you mean, like AA?”

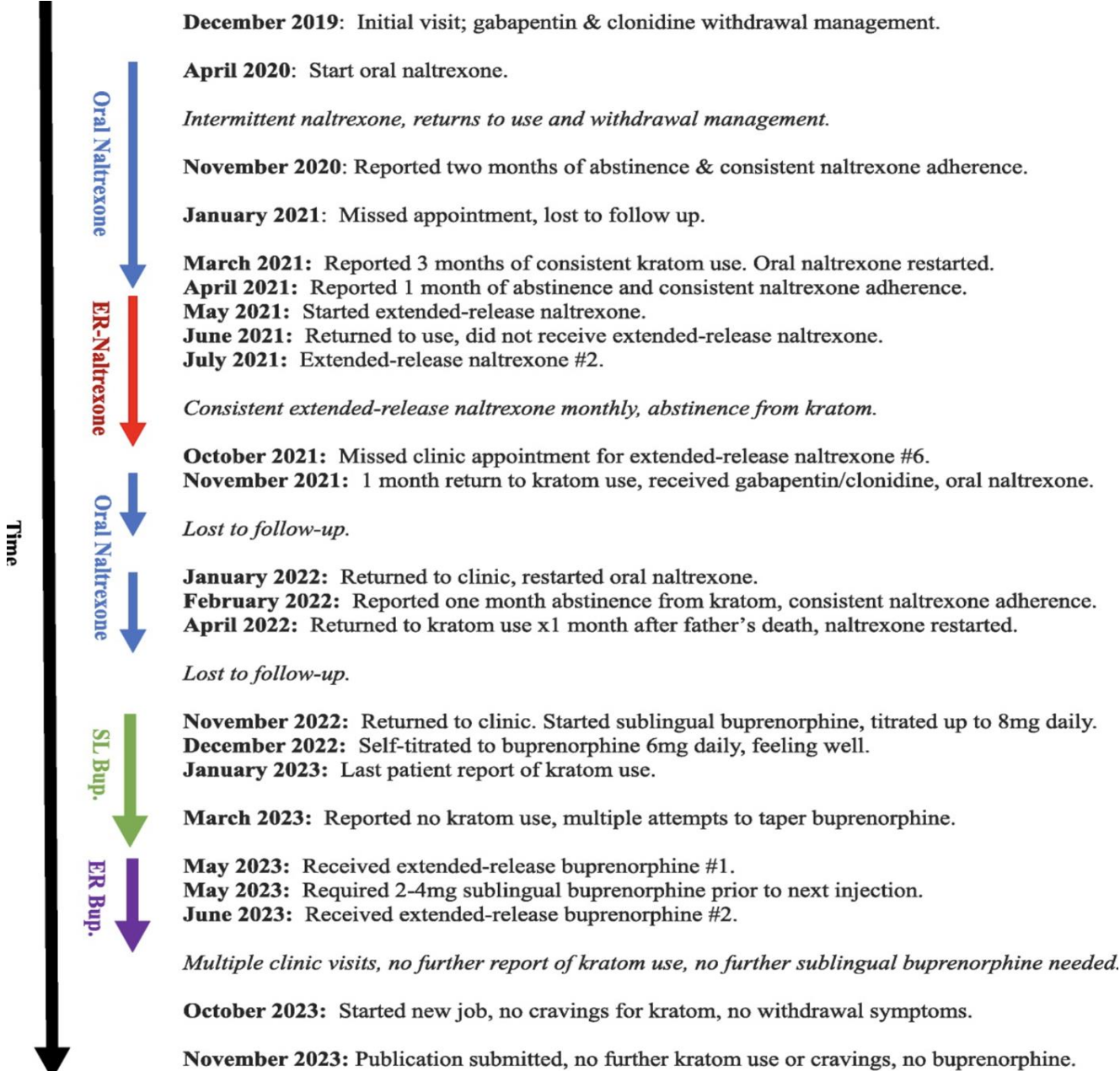
What is your treatment recommendation for Jeff?

Case 1 (Jeff) - Resolution

- Jeff was initially prescribed clonidine and gabapentin for home withdrawal management
- After returning to use 4 months later, he started PO naltrexone after another medically managed withdrawal
- Over the next two years, he had multiple cycles of return to use, withdrawal, and trials of PO and LAI naltrexone
- Eventually he was started on SL buprenorphine
- Later tapered from SL buprenorphine with monthly LAI buprenorphine x2, denying use or cravings at 6 months since last injection

Is this case the rule or the exception?

Case 1 (Jeff) - Resolution



Takeaways

- Clinicians *should not* focus on OUD features to the exclusion of others.
- Consider screening for KUD among patients with other SUDs, which may require asking specifically about kratom and other herbal product use
- Do not rely on testing to identify all cases of kratom use, particularly for patients using newer 7-hydroxymitragynine products

Takeaways

- Patients with comorbid OUD/KUD can and should be treated for their OUD just as you would treat any other patient with OUD.
- However, because kratom is not “just an opioid,” consideration must still be given to also treating the non-opioid effects of kratom even in patients with comorbid OUD/KUD.
- Patients who have KUD without a comorbid OUD require a nuanced, thoughtful approach that involves careful consideration of the risks and benefits along with shared decision-making.