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BEST PRACTICES IN MANAGING PATIENTS WITH KRATOM ADDICTION

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Thomas Penders Disclosures

- Thomas Penders, MD, has disclosed that he does not have a relevant financial relationship with an ACCME defined commercial interest.

The content of this activity may include discussion of off label or investigative drug uses. The faculty is aware that is their responsibility to disclose this information.

Cornel Stanciu Disclosures

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Target Audience

- The overarching goal of PCSS is to train healthcare professionals in evidence-based practices for the prevention and treatment of opioid use disorders, particularly in prescribing medications, as well for the prevention and treatment of substance use disorders.

Educational Objectives

- **At the conclusion of this activity participants should be able to:**
  - **Review the current state of knowledge surrounding Kratom and its impact on patients with addictive disorders**
  - **Present the clinical evidence from literature and our survey of national addiction experts in managing Kratom use**
  - **Discuss challenges and approaches to best manage this comorbidity**

INTRODUCTION

Kratom description of plant

- Kratom derives from a tropical evergreen tree or shrub related to the coffee plant.
- Native to Southeast Asia, Thailand, Malaysia, and Papua New Guinea.
- Used by indigenous population historically as a stimulant to enhance stamina and reduce fatigue.
- Also used in traditional medicine for a variety of conditions including pain.

Leaves of Mitragyna Speciosa

Uses in Southeast Asia

- In South East Asia, Kratom is used as an antidiarrheal, a cough suppressant, an antidiabetic, an intestinal deworming agent.
- Used as a wound poultice.
- Aid in treatment of heroin addiction.
- Outside Asia, anecdotal use of Kratom preparations for the self-treatment of chronic pain and opioid withdrawal symptoms and as a replacement for opioid analgesics have been reported.

Modes of Use

- Fresh or dried Kratom leaves are chewed or drank as a tea.
- Lemon juice is often added to facilitate the extraction of the active ingredient.
- Traditionally, before drinking, sugar or honey is added to mask the bitter taste of the brew.
- Less commonly, the leaves can be dried and smoked.
- Prepared as cold cocktail containing leaves, a caffeinated soft drink with codeine-containing cough syrup.
- Users in Southeast Asian countries remove the stems from the leaves before eating.
- Salt is added to prevent constipation. The chewed material is swallowed, chased with warm water, coffee or sugar syrup.
- Kratom users chew one to 3 fresh leaves at a time.

Kratom Products

- Leaves, dried or crushed.
- Extracts, powders, capsules.
- Tablets, liquids, and gum/resin.
- Readily available at shops or online.
- Dramatic increase in importation in 2016.
- Amounts accounted for millions of doses for recreational use.
- Often declared and falsely labeled similar to other newer drugs of abuse.

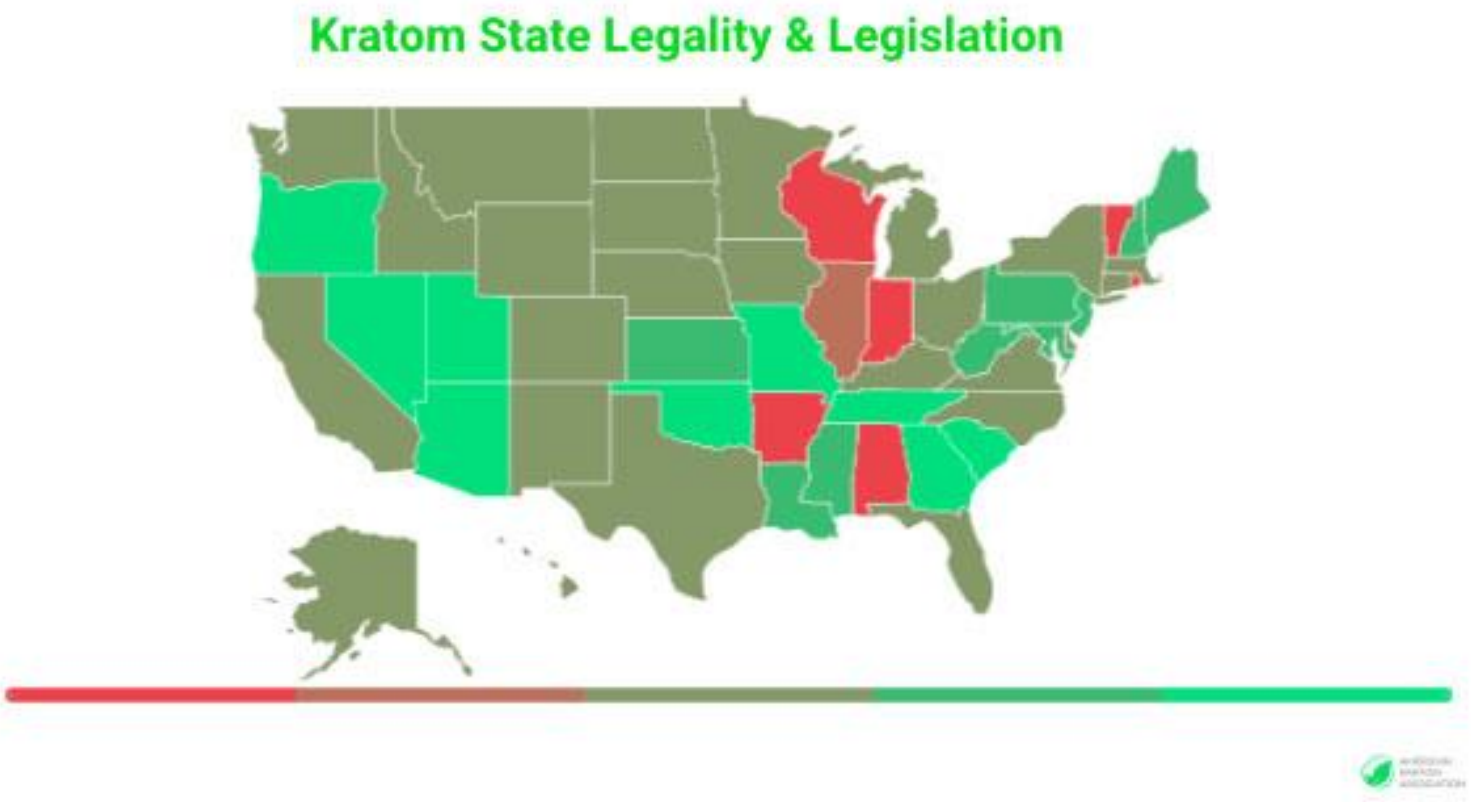
Legal Status

- Kratom was legal to grow and purchase in all 50 states until 2015.
- DEA identified Kratom as a substance of concern.
- As of June 2019, Kratom is illegal to buy, sell, and use in the states of Wisconsin, Rhode Island, Vermont, Indiana, Arkansas, Alabama and Ohio.
- Illegal counties of Sarasota, Florida; San Diego, California; Washington, DC and Denver, Colorado.
- The status in Canada is somewhat ambiguous. Use and sale of Kratom in Thailand is illegal.
- Banned in Australia, Poland, Denmark, Sweden, Malaysia and Vietnam.
- In many other jurisdictions there is no regulation of its use or sale.

Legal Status

- Currently uncontrolled under federal regulation.
- In August 2016, DEA submitted a notice of intent to temporarily schedule the opioids mitragynine and 7-hydroxymitragynine, as schedule I substances under the CSA.
- American Kratom Association self-described non-profit consumer advocacy organization claims to represent 5 million Kratom users in the US successfully campaigned for withdrawal of planned scheduling.
- DEA withdrew scheduling request in October 2016.

US Legislation



Epidemiology

- Little formal survey data available on prevalence of use in the US population.
- Not included in Monitoring the Future or National Survey on Drug Use and Health.
- CDC report on calls to Poison Control Centers from 2010 - reveals 666 calls with 10-fold increase over the period of the survey.
- Online survey of users identified through the American Kratom Association and through social media mentions.

Epidemiology in SE Asia

- Use of Kratom as a recreational drug amongst a younger demographic in both SE Asia and the West.
- 55% of regular users of Kratom become dependent.
- Lack of reports of toxicity in surveys of users in Thailand.
- Emerging throughout the world as substance helpful in self-management of opioid withdrawal.

Singh D et al, 2014

Survey of Kratom Users

- 10,000 Kratom users were surveyed with goal of determining:
  - Who is consuming Kratom and for what purpose? What perceived beneficial and detrimental effects are reported by users?
  - What do Kratom users report as a commonly used dose and frequency of consumption?
  - Does Kratom represent a potential for abuse and withdrawal?
  - Symptoms?

Grundman O. et al. 2017

Kratom Survey Demographics

- Kratom users are primarily middle aged (31-50, 55.9%).
- Male (56.9%); Married or partnered (54.3%).
- White non-Hispanic (89.4%).
- Employed (56.8%).
- Insured (61.1%).
- Some college (82.3%).
- Income > $35,000 (63.2%).
- Duration of use: > 1 year but < 5 years (56.6%).

Kratom Survey Reasons for Use

- 41% had disclosed their use to healthcare provider
- Self-treatment of chronic pain 68%
- Self-treatment of anxiety/depression 65%
- Self-treatment related to opioid misuse (including opioid withdrawal:
  - Use of illicit drugs 7.7%
  - Use of Prescription opioids 26.0%

PHARMACOLOGY

Behavioral Pharmacology

The effects in humans are dose-dependent:

- Small doses (1-5g)
  - Stimulatory effects (~ cocaine or amphetamines).
- Larger dosages (>5g)
  - Sedative-narcotic, analgesic effects (~ opioids).

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%	

Hassan Z et al 2012

- Leaf analysis:
  - 40 structurally related alkaloids, flavonoids, terpenoid saponins, polyphenols, and various glycosides.
- >25 indole alkaloids
  - Mitragynine **(MG)**
  - 7-hydroxymitragynine **(7OHMG)**

Potency

Competitive Binding Studies

- MG's affinity:

  1. Opioid Receptors (Kappa, Mu, Delta)
  - Mu partial agonist (~Buprenorphine (**Bup**))
    - **7OHMG > MG > morphine**
  - Kappa antagonism more potent than Bup, morphine

  2. Other Rs (serotonergic, noradrenergic and dopaminergic)
  - Alpha-2 adrenergic R agonist
  - 5-HT2A R antagonist
  - D1 R agonist *
  - ?5-HT2C, 5-HT7, also D2 and A2A adenosine Rs

Taufik H et al. 2010; Matsumoto et al. 2004; Babu et al 2008
Boyer et al. 2007; Boyer et al. 2008; Stolt et al. 2014.

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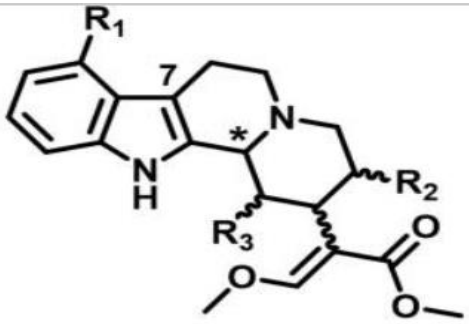
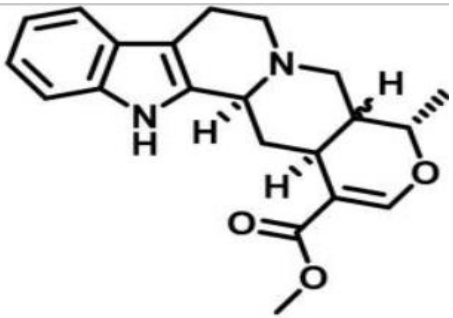
PHASE Model



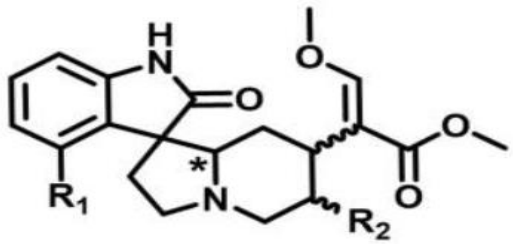
mitragynine congeners (MC)

1 - 10



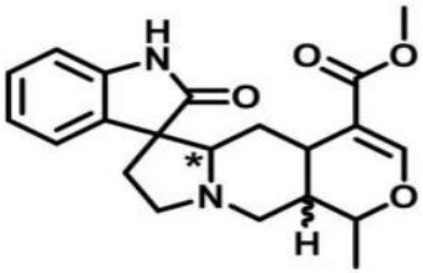
pyran-fused MC

11 - 12



oxindole congeners (OC)

13 - 21



pyran-fused OC

22 - 25

Morphine

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Ellis CR et al. 2020

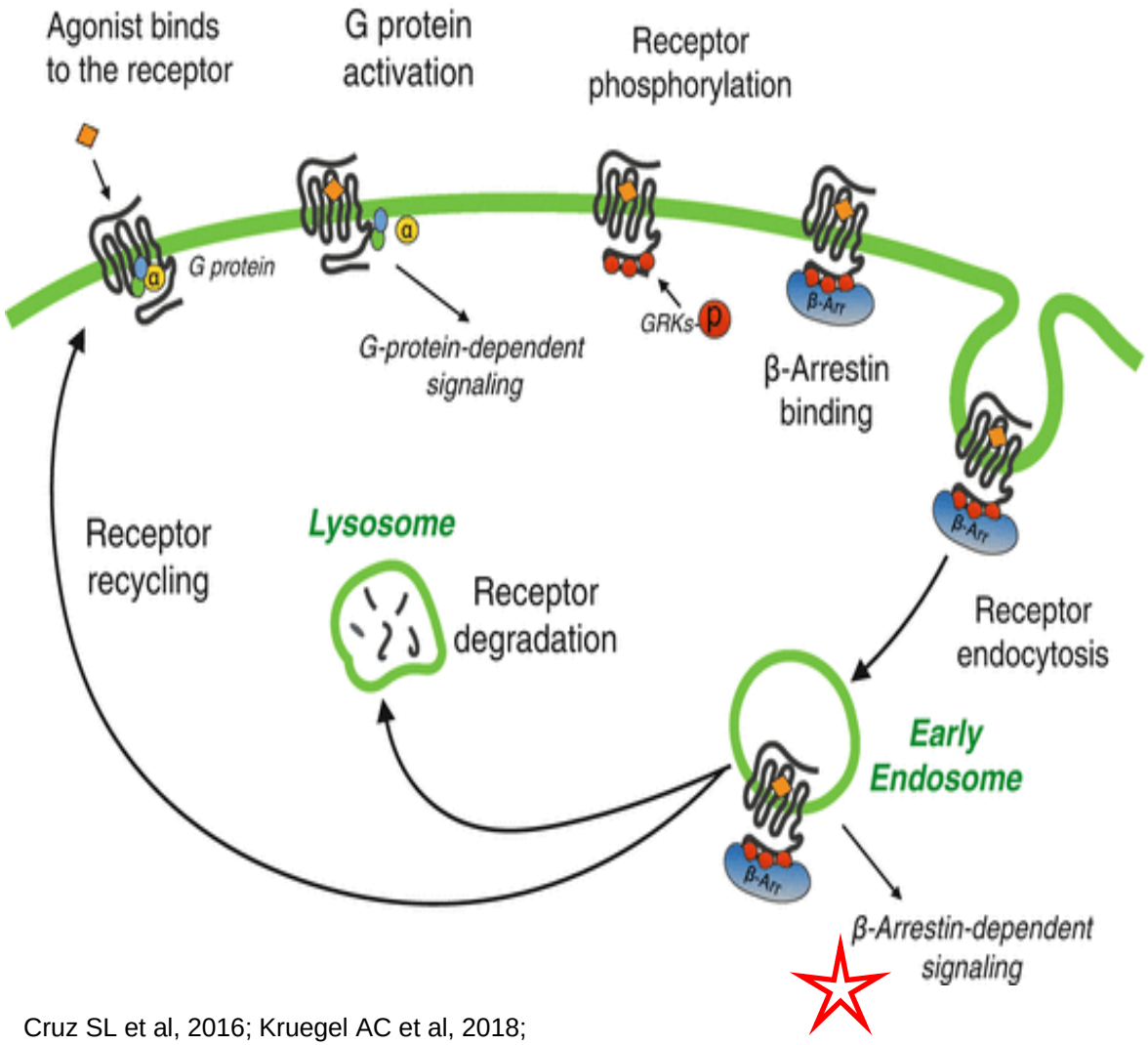
Opioid Receptors

		Mu		Kappa		Delta	
ID	Name	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	+ -

Multiple Other Receptors

		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	- -

Atypical Opioid Properties



- Similarities to opioids:
  - Binding to opioid Rs initiates G-protein-coupled receptor (GPCR) signaling.
- Differences from opioids:
  - GPCR activation does not initiate the β-arrestin pathway
    - "biased agonism"

Cruz SL et al, 2016; Kruegel AC et al, 2018; Varadi A et al, 2016.

Additional Atypical Opioid Properties

- In mediating opioid-like analgesic effects, MG also blocks pain signaling through other mechanisms as well.
  - Activates α-2 adrenergic postsynaptic Rs present in modulatory “descending” pain pathways.
  - Impairs neuronal pain transmission by blocking Ca^{2+} channels.
  - Anti-inflammatory effects, secondary to the inhibition of COX-2 and prostaglandin E_2 mRNA expression.

Matsumoto K. et al, 1996; Matsumoto et al., 2005; Shaik MW et al., 2009; Utlar Z. et al., 2011

ADVERSE EFFECTS

Animal Studies

- Chronic alkaloid ingestion associated with addictive behavior (enhanced punishment tolerance; reward-seeking behavior) and cognitive impairment. [1]
  - 7OHMG >> MG

- Ascending doses of kratom alkaloids result in an increase in: [2]
  - Blood pressure
  - Liver function tests
  - Creatinine

- Drug : drug interactions. [3]
  - MG inhibits: - CYP 2C9, 2D6, 3A4
    - Glucuronidation (UDP-glucuronosyltransferases)

1. Ilmie MU et al, 2015; Hemby SE et al, 2019; Ismail NIW et al, 2017 Hassan Z et al, 2019; Sabetghadam A et al, 2013;
2. Smith LC et al, 2019
3. Kong WM et al, 2011; Meireles V et al, 2019; Azizi J et al, 2013. Azizi J 2010; Anwar R et al, 2012; Lim EL et al, 2013.

Human Case Reports

- With chronic (> 1 year) 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]

Eastlack SC et al, 2020

Poison Data Bank / Medical Reports

- 2019 retrospective review of cases reported to the National Poison Data System and New York City Office of the Chief Medical Examiner:
  - Agitation (18.6%), tachycardia (16.9%), drowsiness (13.6%), confusion.
  - Serious neurological sequelae: seizures (6.1%), hallucinations (4.8%), coma (2.3%).
  - Toxicity occurred in a dose-dependent manner.

Eggleston W et al. 2019

Kratom-related Deaths

- Swiss Webster mice: LD50 identical between IV administered 7OHMG, MG, heroin.

- Co-ingestions and other active use disorders predispose patients to death
  - 87% of samples submitted to forensic laboratory also contain opioids.

- Knowledge of deaths attributed to Kratom alone is difficult to accurately quantify.

Smith LC et al 2019; Eggleston W et al. 2019; Corkery JM et al, 2019; Papsun DM et al 2019.

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MANAGEMENT AND CLINICAL CASES

Toxicity and Overdose

- Toxicity
  - Supportive management in most.
  - 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 -- some reports of mixed results with reversal agents (naloxone) and such have not been evaluated in clinical trials.
  - Co-ingestions are common.

Overbeek DL et al 2018; Mousa MS et al, 2018

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Withdrawal

- Mimics opioid withdrawal:
  - Starts ~12-24 hours from last use, can last up to 4 days.
    - Symptomatic management of a hyperadrenergic state and/or use of opioid receptor agonists (Methadone) or partial agonists (Buprenorphine).
  - Cravings.
  - High risk of relapse to use on cessation (~78-89% at 3 months).

- Withdrawal intensity positivity correlated to:
  - Daily amount consumed
  - Duration and frequency of use

Stanciu CN et al, 2019; Singh D et al, 2014;
Khazaeli A et al, 2018; Galbis-Reig D et al, 2019.

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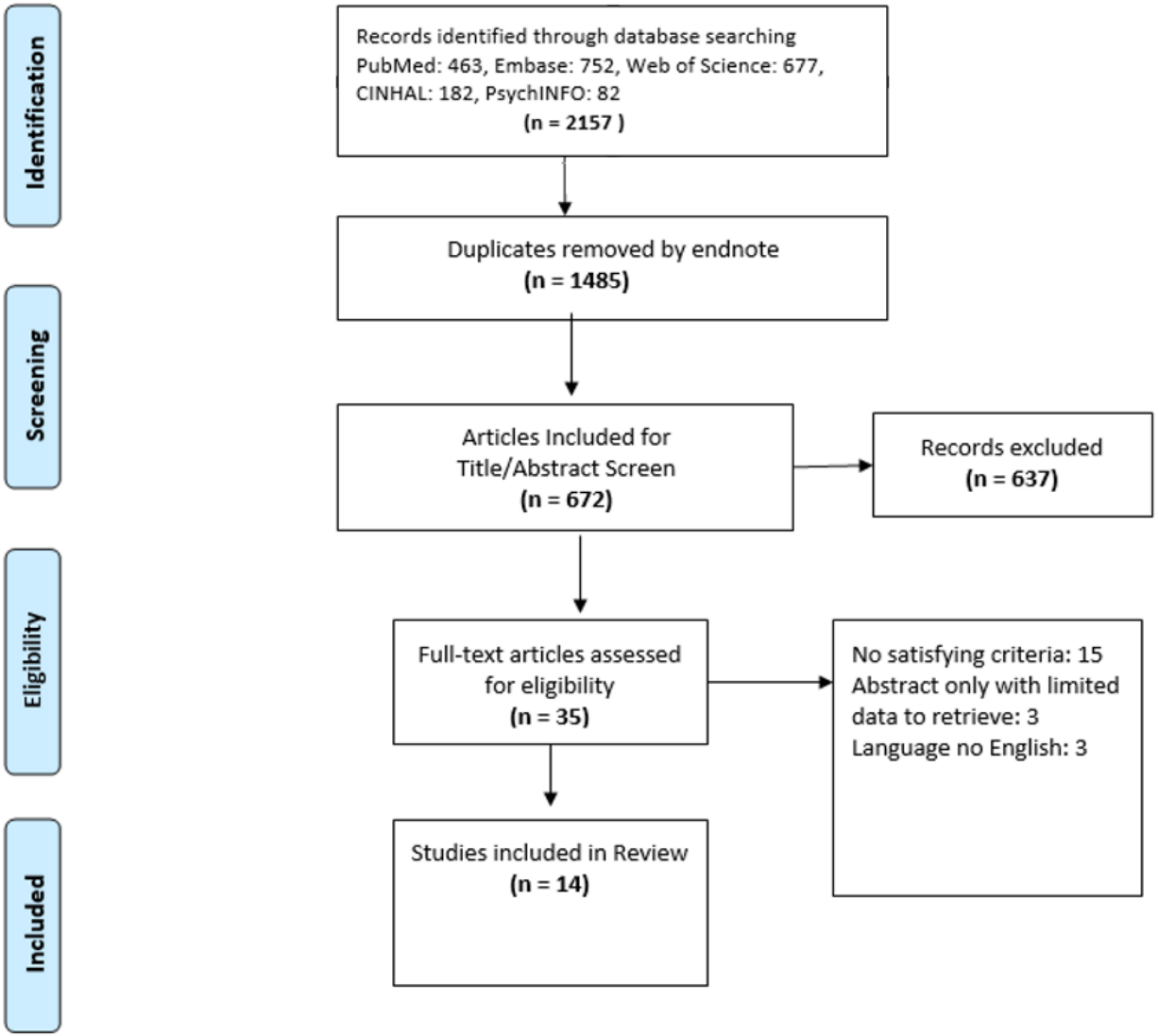
Treatment Guidelines

- To date, no guidelines exist to guide long-term management of kratom addiction.

- Efforts to establish a “standard of care”.
  - *Stanciu C., Ahmed S., Hybki B., Penders T., Galbis-Reig, D. Pharmacotherapy for Management of “Kratom Use Disorder”, A Literature Riverw with Survey of Experts. Wisconsin Medical Journal* – approved pending publication.

“KUD”

Literature Review



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KUD + OUD Cases

Author, year	Extent of use	Reason for use	Intervention	Maintenance regimen	Reported outcome
Khazareli, 2018	Nine months, one tablespoon of powder dry plant six times daily	Pain	Inpatient Bup-mediated withdrawal, however taper was difficult and maintenance was required.	Bup-nx 8-2mg twice daily	Sober at 18 months
Cheng, 2019	Eight months, one capsule of kratom product five to ten times daily.	Energy	Outpatient induction	Bup-nx 16-4mg once daily	Sober, no cravings at subsequent follow up visits
Smid 2018	Four months of smoked dry kratom, unknown amount and frequency	Opioid substitution	Inpatient induction in pregnancy, increased at 36 weeks	Bup-nx 16-4mg once daily (20-5mg at 36 weeks)	Sober at subsequent follow up visits
Buresh, 2018	One year use of kratom product, unknown details	Pain	Outpatient induction	Bup-nx 24-6mg once daily	Sober at 7 months
Boyer, 2008	Several years, episodic use during opioid withdrawal as tea.	Opioid substitution	Outpatient induction	Bup-nx 16-4mg once daily	Sober at subsequent follow up visits
Mandeep, 2019	Unknown details.	Opioid substitution	Outpatient induction	Bup-nx 8-2mg twice daily	Sober at 2 months
Hartwell, 2018	Various, this is a report of 9 veterans.	Pain and opioid substitution	Various	Bup-nx, naltrexone, methadone	Unknown

KUD-only Cases

Author, year	Extent of use	Reason for use	Intervention	Maintenance regimen	Reported outcome
Galbis-Reig, 2016	Two year history of using kratom extract	Pain	Inpatient supportive (clonidine mediated) detox after several outpatient attempts	Naltrexone PO 50mg daily	Unknown
Smuhl, 2019	Two year use of 30 grams daily of kratom crushed leaf, every 2 hours mixed with water	Anxiety, insomnia	Outpatient induction	Bup-nx 4-1mg once daily	Attempted taper at 3 months and relapsed to use, sobriety maintained upon restarting
Smid, 2018	Seven months, unknown details	Pain, anxiety	Outpatient initiation following kratom cessation due to cravings	Bup 2mg daily	Sober at subsequent follow up visits
Buresh, 2018	Unknown duration, 0.25 ounces every 4 hours	Pain	Outpatient induction	Bup-nx 4-1mg four times daily	Sober at 9 months
Agapoff, 2019	Three years use of 30g daily of kratom crushed leaf as smoothie	Focus, concentration	Outpatient induction	Bup-nx 8-2mg once daily	Sober at 16 months, tapered to 6-1.5mg
Diep, 2018	Unknown duration, overdosed on 600mg of kratom product	Unknown	Inpatient initiation while in rehabilitation due to cravings	Bup-nx 2-0.5mg three times daily	Able to taper after 45 days, unknown follow-up outcome
Sheleg, 2011	One year use, tincture every 4 hours, unknown details	Pain	Inpatient induction on Bup due to withdrawal	Methadone	Outpatient transition to Methadone

Survey of Addiction Experts

Are you a physician (MD / DO) or resident/fellow in training?

If NO – survey ends

If YES -- Have you encountered patients with an addiction to Kratom

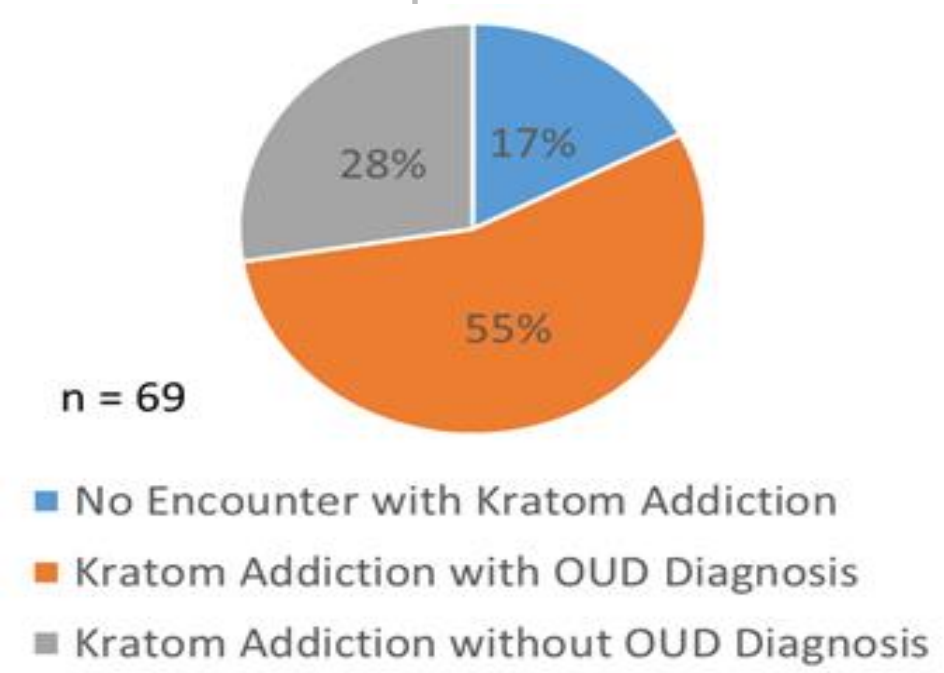
If NO – survey ends

If YES – Did all of these patients have a concurrent (or past) history of opioid use disorder?

If YES – survey ends

If NO -- How have you managed their abstinence from kratom?

- Nonpharmacologically (ie. talk therapies)
- Buprenorphine
- Methadone
- Naltrexone
- Other (please type in)



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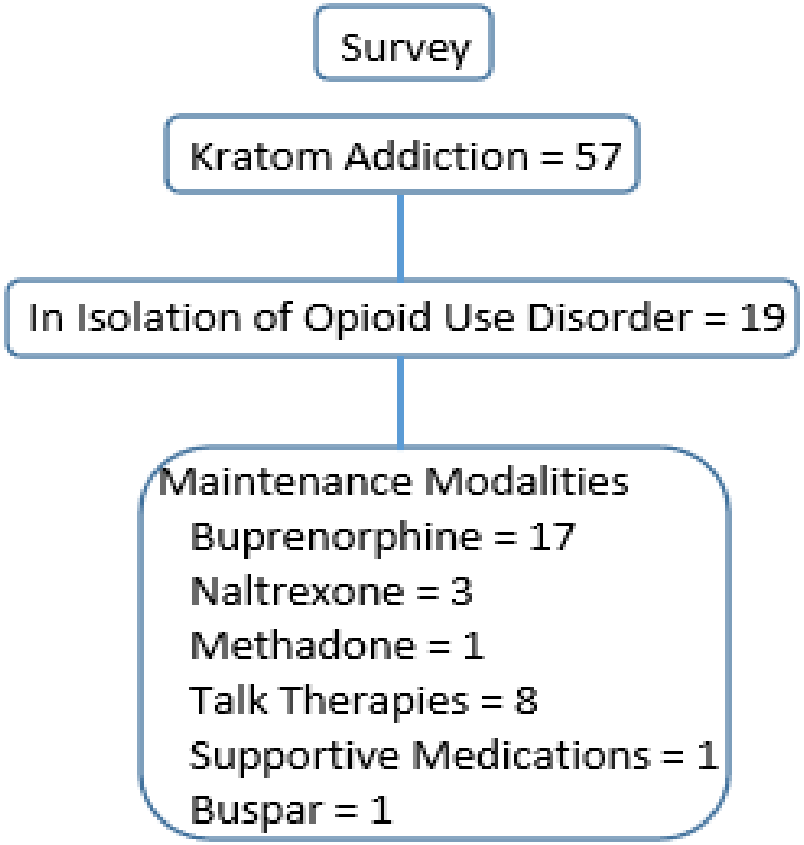
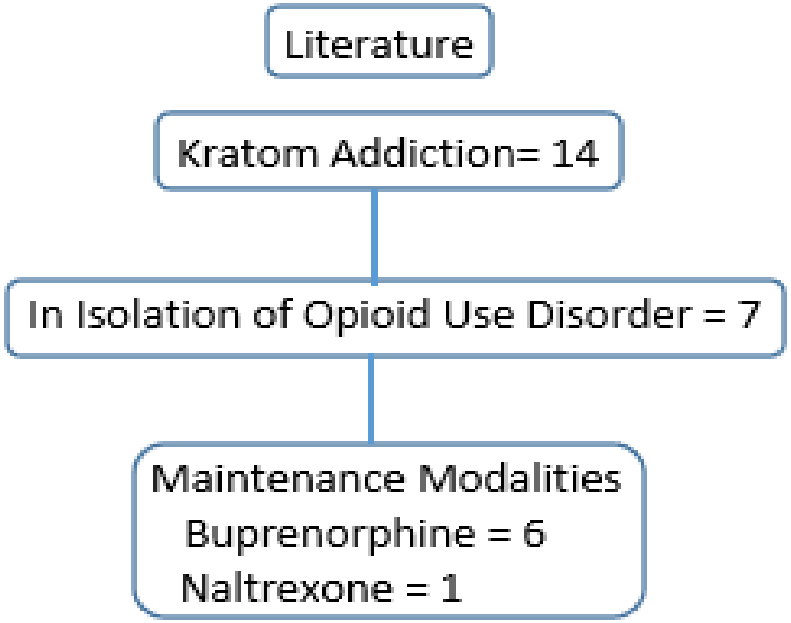
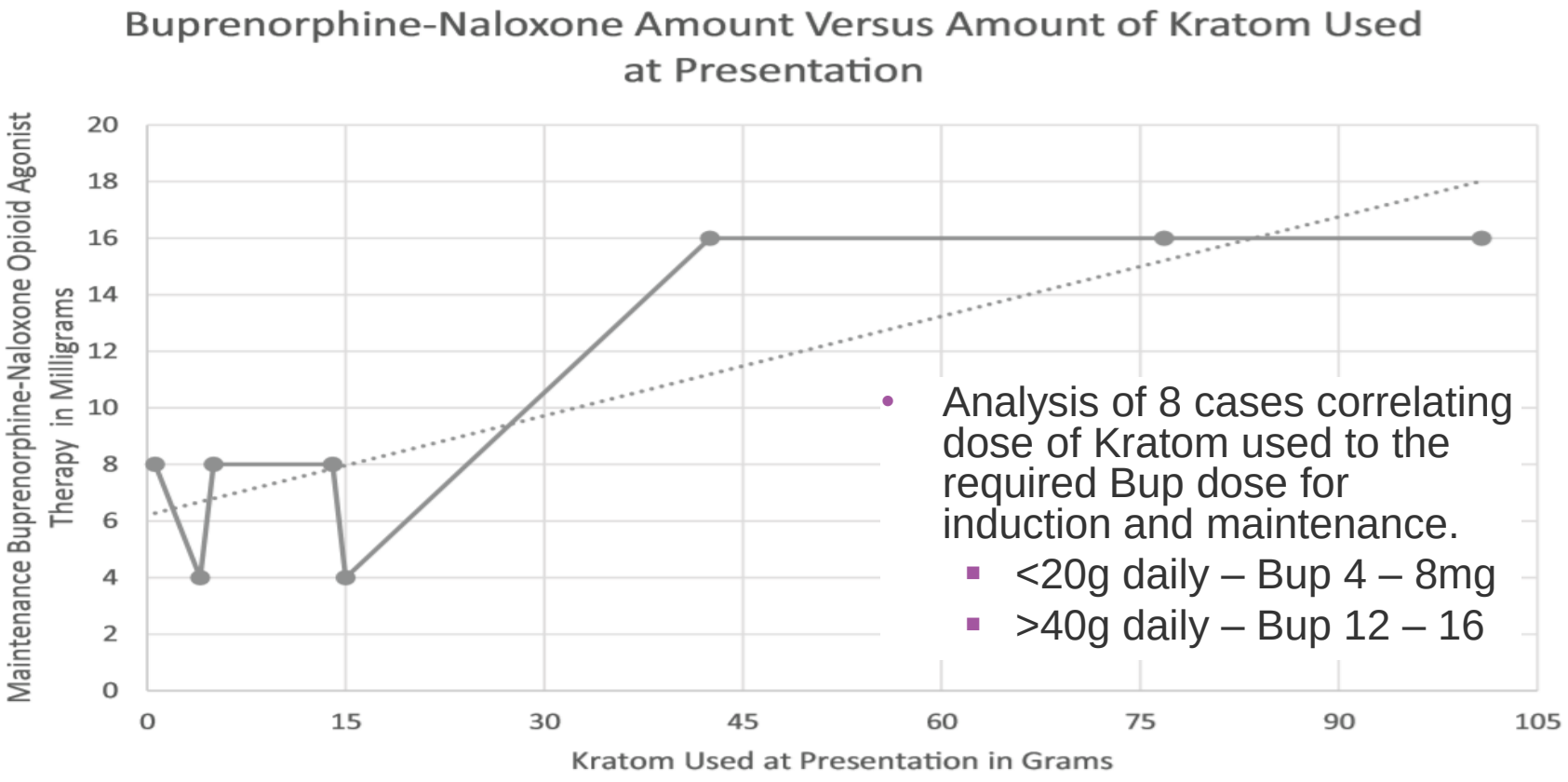
Survey of Addiction Experts

- To manage abstinence:





More evidence for MOUD



- Analysis of 8 cases correlating dose of Kratom used to the required Bup dose for induction and maintenance.
  - <20g daily – Bup 4 – 8mg
  - >40g daily – Bup 12 – 16

Dots represent each individual patient. The solid line shows the correlation (r = 0.84) between kratom dose used at presentation and dose of buprenorphine at OAT induction.

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Weiss, ST et al, 2020

Conclusion

- In light of the detrimental risks associated with growing reports of KUD and lack of any randomized controlled trials to explore treatment as well as guidelines, there is evidence that the indication of MOUD should be extended to KUD as well.
  - This is especially true if one's use of Kratom is considered high risk, involves high doses, and meets DSM-5 diagnostic criteria for a moderate or severe use disorder.
  - Consideration should also be given to referral of patients for counseling or enrollment in 12-step addiction treatment programs.

Q & A

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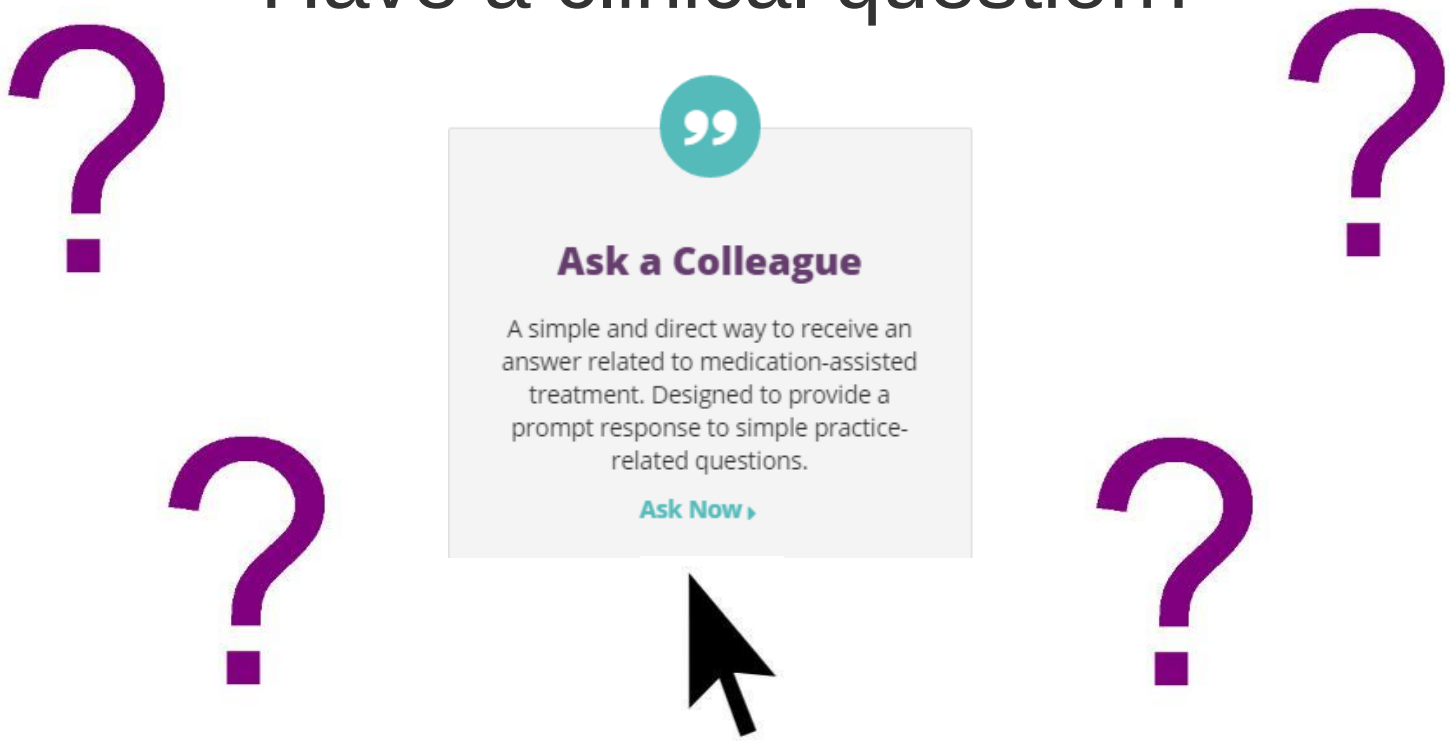

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