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# Kratom, A Substance of Increasing Concern

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# Thomas Penders Disclosures

- Dr. Thomas Penders has no conflicts of interests or disclosures relevant to the content of this presentation.

*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

- Dr. Cornel Stanciu has no conflicts of interests or disclosures relevant to the content of this presentation.

*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.*

# Educational Objectives

- At the conclusion of this activity participants should be able to:
  - Recognize the salient aspects of Kratom's background, psychoactive effects and its pharmacological action
  - Review the state of knowledge about the impact of Kratom on mental health and its potentially dangerous adverse effects
  - Identify and manage Kratom withdrawal as well as provide maintenance treatment

# Introduction

- In September of this year, the Food and Drug Administration (FDA) commissioner statement indicating that we must remain vigilant and aggressive against trends that threaten to reverse our progress as we deal with the devastating crisis of opioid misuse and overdose plaguing our nation.
- He went on to address the dangers associated with rise in the use of Kratom, addressing marketers making claims for therapeutic effects for products containing the plant commonly known as Kratom, a botanical with potential for abuse.

# Introduction

- Our goal to to review the background relating to the origin, use, pharmacology, effects and adverse reactions including deaths of Kratom and Kratom products.
- We will be discussing current evidence that supports statements made by the FDA.
- Discuss the identification and management of individuals who present using Kratom.
- Discuss the current legal state of Kratom including the current stance of the DEA given the agencies previous statements indicating that Kratom is “an imminent hazard to public safety.”
- Discuss management of patients presenting with use of Kratom, including withdrawal (case-based).

# Leaves of *Mitragyna Speciosa*



# Historical Background

- 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



# 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 drunk 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 2018, 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

# 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

# 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?



# 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%)

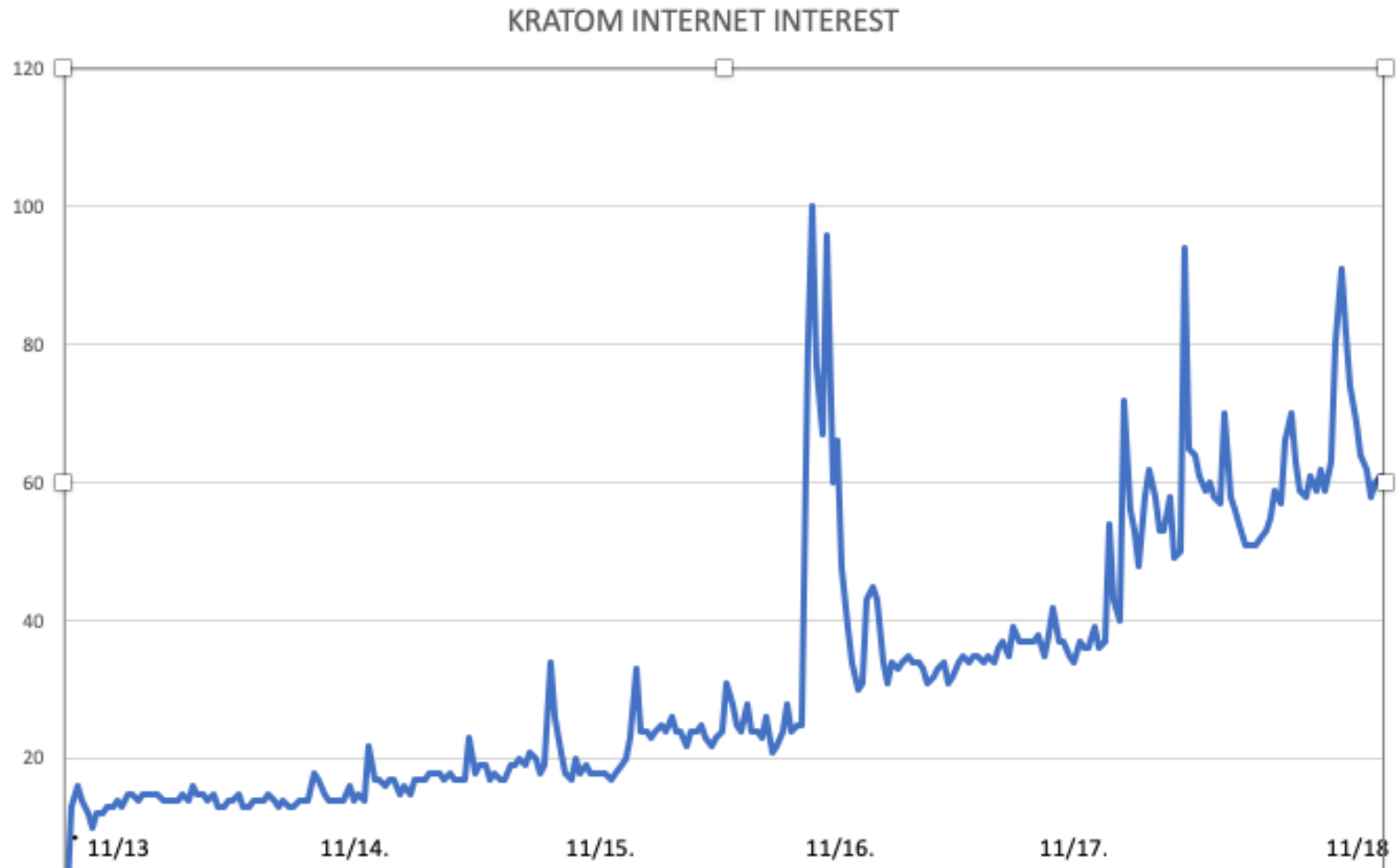
# Kratom Survey Method of Consumption

- How do you usually use Kratom?
  - Liquid Kratom 54%
  - Powdered Kratom consumed with food 2.2%
  - Self-prepared Kratom tea 13%
  - Powdered Kratom (pure or in pill form) 32.6%
  - Powdered Kratom consumed with beverage 48.6%

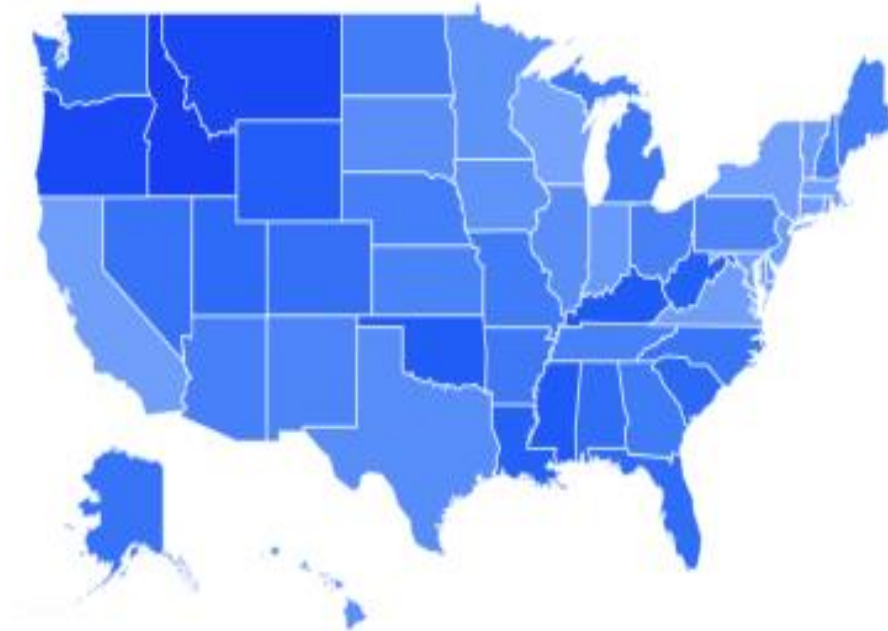
# Kratom Survey Reasons for Use

- 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%

# Kratom Internet Searches



# Kratom Searches by State



1 Idaho

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2 Oregon

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3 Montana

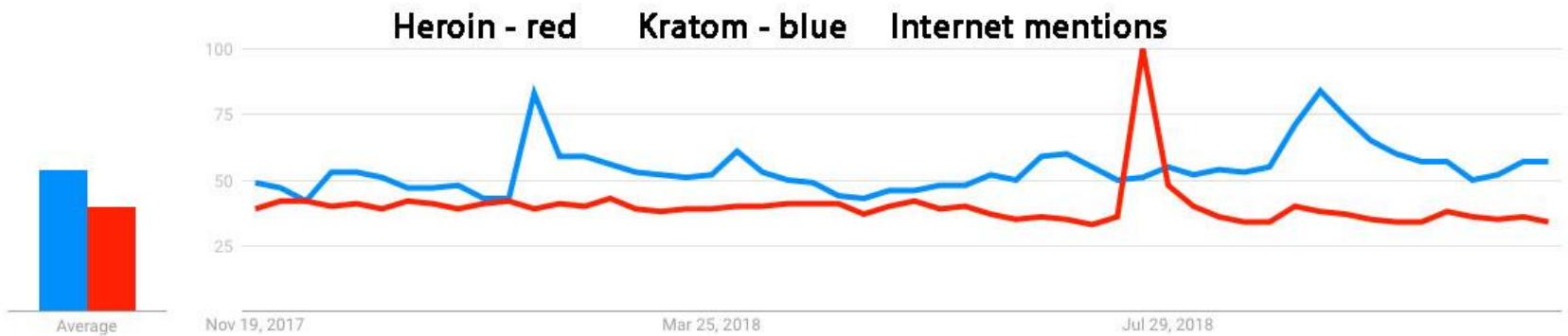
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4 Kentucky

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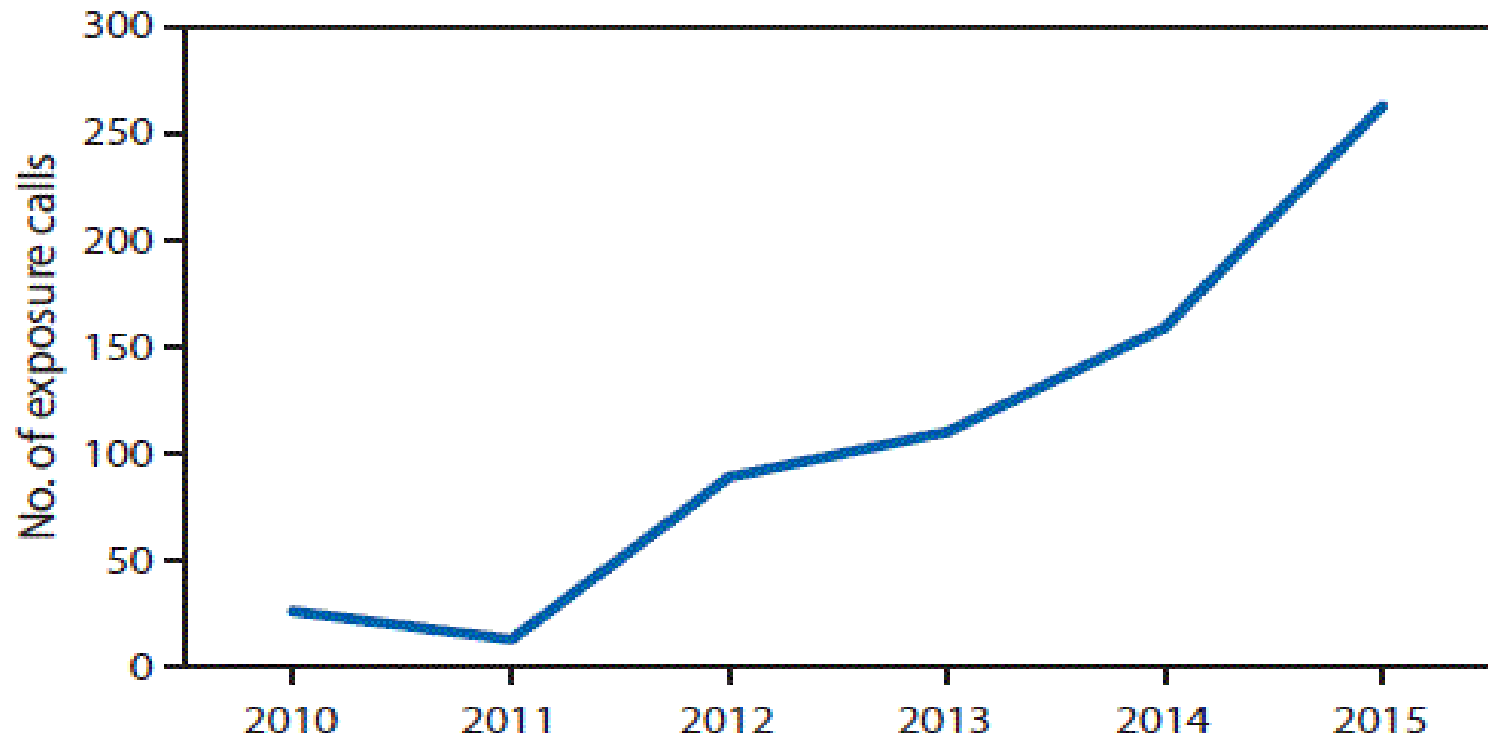
5 Mississippi

# Internet Mentions vs. Heroin



# CDC Reports to Poison Control Centers

National Poison Data System – United States and Puerto Rico  
January 2010 - December 2015

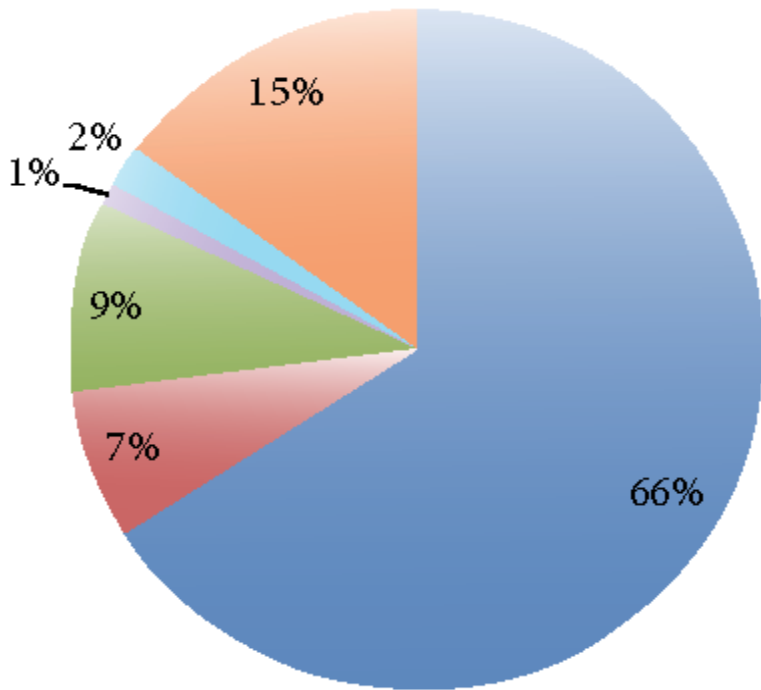


Anwar M, Law R, Schier J. Notes from the Field. Kratom (*Mitragyna speciosa*)  
Exposures Reported to Poison Centers — United States, 2010–2015. MMWR  
Morb Mortal Wkly Rep 2016;65:748–749. DOI:  
<http://dx.doi.org/10.15585/mmwr.mm6529a4>

# Pharmacology



# Complex Composition



- Mitragynine ( $C_{23}H_{30}N_2O_4$ )
- Paynantheine ( $C_{23}H_{28}N_2O_4$ )
- Hydroxymitragynine ( $C_{23}H_{30}N_2O_5$ )
- Speciogynine ( $C_{23}H_{30}N_2O_4$ )
- Speciociliatine ( $C_{23}H_{30}N_2O_4$ )
- Other

- Leaf analysis: An estimate of Thai Kratom extract composition. The phytochemicals isolated from various parts of the tree include overall 40 structurally related alkaloids as well as several flavonoids, terpenoid saponins, polyphenols, and various glycosides.

**Source:** Cinosi E.; Martinotti; et all. Following “the Roots” of Kratom (*Mitragyna speciosa*): The Evolution of an Enhancer from a Traditional Use to Increase Work and Productivity in Southeast Asia to a Recreational Psychoactive Drug in Western Countries; Biomed Res Int. 2015; 2015: 968786

# Complex Composition Continued

- > 25 indole alkaloids with anti-nociceptive, anti-inflammatory, anti-depressant and muscle relaxant properties
- Active constituents:
  - Mitragynine
  - 7-Hydroxymitragynine
    - Opioid R-agonists in-vivo and in-vitro
    - In vivo studies: tolerance, cross-tolerance to morphine, and a precipitated withdrawal when naloxone is administered
    - Animal studies suggest potency might exceed that of morphine

# Complex Composition Continued

- Competitive binding study
  - Mitragynine's highest affinity at kappa receptors (13x more potent than morphine) followed by mu and delta
  - Mu-R partial agonism (~Buprenorphine)
  - Kappa-R antagonism (greater affinity than Buprenorphine)
- Animal studies
  - Mitragynine may be involved in noradrenergic and serotonergic pathways, stimulating post-synaptic alpha-2 adrenergic receptors, and inhibit 5-H2A receptors

# Effects

The effects of kratom in humans are dose-dependent:

- Small doses (1-5g): stimulatory effects resembling cocaine or amphetamines.
- Larger dosages(>5g): sedative-narcotic, pain reducing effects that resemble opioids.



Photo by Psychonaught

# High Dose

- 7-hydroxymitragynine is the more potent opioid receptor agonist
- Mitragynine has the agonistic activity at the alpha-2 adrenergic receptors
- Kratom used as a way to counteract opioid withdrawal

# Pharmacokinetics

- Mitragynine  $t_{1/2}$  is relatively short
- Individuals typically dose every 6-12 hours
- Withdrawal symptoms begin ~12 hours after last use in most of the case reports
- The duration of withdrawal is relatively short – less than 4 days in all case reports.

# Herb-Drug Interactions

- Mitragynine has been reported to inhibit CYP P450:
  - 2C9
  - 2D6
  - 3A4
  - ~Mild 1A2

# Adverse Effects

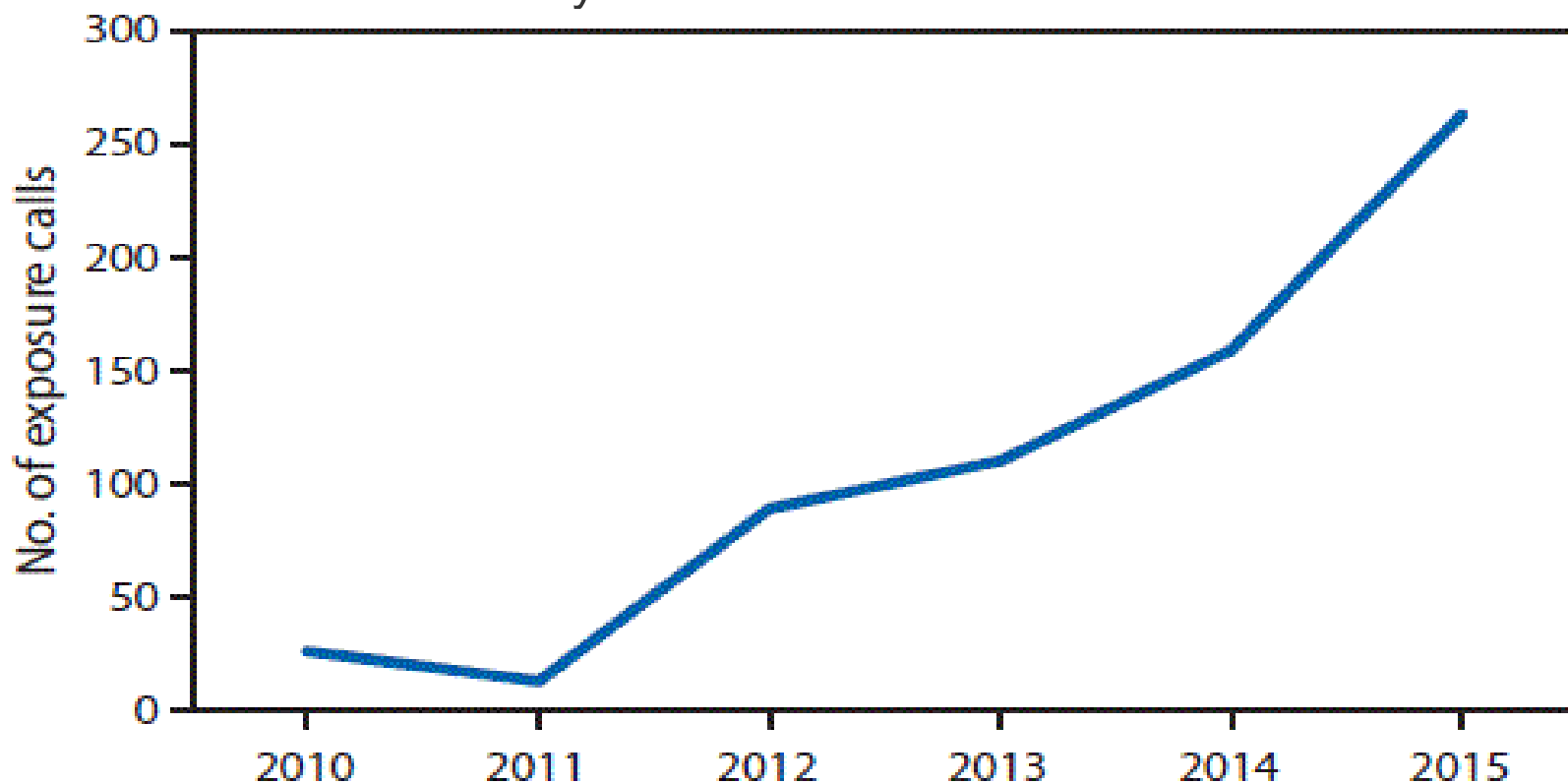


# Reported Side Effects

- After > 1 year of regular use
  - Weight loss
  - Insomnia
  - Constipation
  - Skin hyperpigmentation
  - Extreme fatigue
- Delusions, hallucinations, seizures, respiratory depression, hepatotoxicity, coma, and death also reported

# Kratom-Related Reported Exposure Calls

National Poison Data System - United States and Puerto Rico  
January 2010 - December 2015



# Fatal Overdoses Involving Kratom

From July 2016 to June 2017, 25 fatal overdoses involving Kratom across 8 CDC SUDORS states were identified

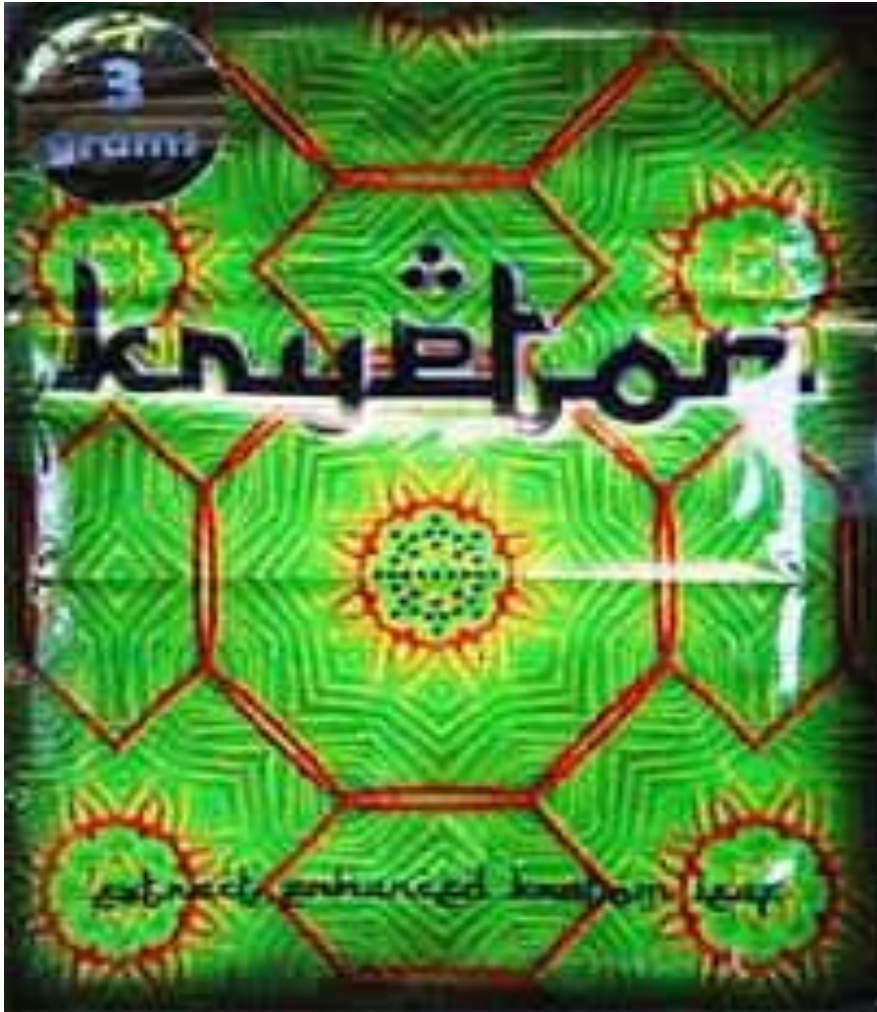
States	ME	NH	NM	OH	PA	RI	WV	WI	Total
Opioid overdose deaths	301	402	322	4,534	3,231	265	844	825	10,724
Deaths involving Kratom	4	2	1	3	8	1	5	1	25
Percent involving Kratom	1.3%	0.5%	0.3%	0.07%	0.25%	0.4%	0.6%	0.1%	0.23%

Caution: testing of Kratom is not uniform thus these numbers are underestimates

# Kratom-Related Deaths

- In 2017, the FDA began issuing a series of warnings about Kratom and now identifies at least 44 deaths related to its use.
- Most Kratom associated deaths appeared to have resulted from adulterated products or taking Kratom along with other potent substances.

# Adulterated Products



- “Krypton”  
(kratom+caffeine+O-desmethyltramadol)
- Multiple available combination products
- Several cases of deaths involving adulterated Kratom products

# More Kratom-Related Concerns

*The U.S. Food and Drug Administration along with the Centers for Disease Control and Prevention (CDC) and state and local officials are investigating a multistate outbreak of Salmonella infections linked to products reportedly containing kratom..*

## **June 29, 2018 Update:**

The FDA's outbreak investigational activities have concluded, but the FDA continues to address the issue of *Salmonella* in kratom. The FDA reminds consumers that raw products contaminated with *Salmonella* can make people sick if they consume them, and can also cross-contaminate surrounding surfaces and possibly expose others to *Salmonella*.

# Withdrawal

- In recent years, more and more presentations for symptoms secondary to abrupt discontinuation of long term use
  - First noted 12-24 hours from last use and can last up to 4 days
  - Symptoms mimic opioid withdrawal
  - Physiological: mydriasis, nausea, sweating and chills, muscle and body aches, tremors and twitches, diarrhea, rhinorrhea, and lacrimation
  - Psychological: insomnia, restlessness, irritability/hostility, fatigue, anxiety and mood disturbances and sometimes hallucinations.
  - Cravings also develop
- Withdrawal intensity has been positively correlated to the daily amount consumed as well as the duration and frequency of use

1. Stanciu C., Gnanasegaram, S., Penders M. et al.; Kratom Withdrawal – A Systematic Review with Case Series; J Psychoactive Drugs. 2018
2. Manda et al. 2014
3. Singh, Müller, Vicknasingam et al. 2014; Trakulsrichai et al. 2013
4. Saingam et al. 2016; Singh, Müller, Vicknasingam et al 2014

# Withdrawal Management

- No concrete guidelines on management
- Best approach follows that of opioid withdrawal with symptomatic management of a hyper-adrenergic state
- Duration is consistent with that of opioid withdrawal
- Very few reports of buprenorphine or methadone-assisted detoxification
  - FDA made the recommendation to the DEA for Kratom to be classified as an opioid



# Maintenance

- No evidence of how to handle long-term maintenance of sobriety.
- High tendency to relapse to Kratom use due to distressing withdrawal symptoms, particularly body aches.
- Cravings do exist.
- Whether the same protocol as for opioid with medication-assisted treatment, psychosocial interventions should occur remains to be explored.

# Neonatal Abstinence Syndrome

- Report of baby delivered to user of 18-20g / day for 2 years requiring NICU admission on postpartum day 2 (feeding intolerance, jitteriness, irritability and vomiting) with morphine taper over 5 days
- Another report of a term neonate born to a chronic Kratom user and required treatment with opiates for neonatal drug withdrawal.
- Should opioid replacement be initiated during pregnancy?

# Screening

- Standard urine drug screens do not detect Kratom.
- Special confirmatory testing is needed:
  - Gas chromatography coupled with mass spectroscopy (GC-MS)
  - Liquid chromatography with linear ion-trap mass spectroscopy
  - Electrospray tandem mass spectroscopy

# Clinical Cases

# Clinical Cases



- Case 1: Kratom initiation to manage anxiety and mood with long term use leading to withdrawal (supportive opioid-like management)
- Case 2: Kratom transition from other opioids with difficulty in tapering off requiring induction on to agonist for maintenance

# Case 1



- 26 yo CF no h/o mental health / SUD.
- ED: restlessness, generalized body aches, overwhelming anxiety and thoughts of suicide.
- Vital signs: BP158/100 HR102 T107F SPO2 wnl.
- Skin was clammy.
- EKG; UA; Utox; CBC; CMP; TSH done.
- Lorazepam 0.5mg PO x2 with no resolution of anxiety symptoms.

# Case 1



- Two-year history of Kratom use q12hr abruptly stopped the previous day.
- “Natural” energy supplement
- Initially: ½ - 1 capsule daily
- Later: additional 2-3 capsules in the evening
- Inpatient admission
- DSM-5 diagnosis of Other Substance Use Disorder, in Withdrawal
- Clinical Opioid Withdrawal Scale (COWS) = 16

# Case 1



- Symptom triggered clonidine\* 0.1mg q2hr prn
- Scheduled gabapentin\* 300mg TID
- Day 1: clonidine\* x4; poor sleep, excessive sweating
- Day 2: COWS = 8; clonidine\* x1; irritability
- Day 3: COWS = 1; bright, upbeat and in good spirits. No clonidine\*.
- Day 4: discharge

\*The use of these supportive management agents is "off-label" for opioid withdrawal symptomatology.



# Case 2



- 32yo CM no h/o mental health, h/o OUD
- ED: “uncomfortable feeling”, sweats, diarrhea
- Vital signs: BP160/98 HR105 T102F SPO2 wnl.
- Skin was clammy.
- EKG; UA; Utox; CBC; CMP; TSH done.

# Case 2



- H/o heroin use since teens
- Several detoxifications
- Methadone maintenance
- 3 years ago begun Kratom use to taper
- ~20 grams, no cravings
- Failed attempts to come off
- Last use 24-30hr
- COWS = 15

# Case 2



- Buprenorphine 4mg x1 with drastic improvement
- Buprenorphine 4mg x1 complete resolution of symptoms
- Observation ~4hr and referral to next day outpatient  
Buprenorphine maintenance
- Stable on 16mg TDD

# Conclusions

- Kratom is a botanical with unique properties and of increasing prevalence in the western world, particularly in the United States where it has accelerated since 2016.
- Most users aim to gain control of subjective psychological problems, pain, and to manage opioid withdrawal.
- Legislation controlling its availability, distribution and use are ambiguous.
- Little is known about its side effects however very concerning reports are emerging especially related to Kratom-combination products.
- Dependence, tolerance, and withdrawal are common and management should likely align to that of opioids.
- Further studies are needed to elucidate potential therapeutic benefit as well as adverse effects.

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- PCSS Mentor Program is designed to offer general information to clinicians about evidence-based clinical practices in prescribing medications for opioid addiction.
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