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

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Target Audience

• The overarching goal of PCSS is to train a diverse range of healthcare professionals in the safe and effective prescribing of opioid medications for the treatment of pain, as well as the treatment of substance use disorders, particularly opioid use disorders, with medication-assisted treatments.
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 is 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 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 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%)
• 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
2. Oregon
3. Montana
4. Kentucky
5. Mississippi
Internet Mentions vs. Heroin

![Graph showing mentions of Heroin and Kratom over time]

- **Heroin - red**
- **Kratom - blue**
- **Internet mentions**

Average mentions are represented on the left side of the graph. Peaks are noted on Nov 15, 2017, Mar 25, 2018, and Jul 29, 2018.
Pharmacology
Complex Composition

- 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
• > 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

3. Takayama et al. 2002; Takayama et al. 2004
• 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

Taufik Hidayat et al. 2010
Matsumoto et al. 2004; Babu et al 2008
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.

Matsumoto et al. 2004
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

Matsumoto et al. 2004
Boyer et al. 2007; Boyer et al. 2008
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.

1. Taufik Hidayat M et al. 2010
2. Boyer et al. 2007
3. Boyer et al. 2008; Manda et al. 2014; McWhirter and Morris 2010; Galbis-Reig 2016
Herb-Drug Interactions

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

Hanapi et al., 2013.
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

Vicknasingam et al., 2010; Saingam et al., 2012
Kratom-Related Reported Exposure Calls

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

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

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

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-desmometamethyltramadol)
- 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 positivity 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
Withdrewal 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

McWhirter and Morris, 2010; Galbis-Reig, 2016; Stanciu et al 2018
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?

1. Mackay, Lindsay, and Abrahams 2010
2. Davidson et al. 2018
3. Smid et al 2018
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

1. Kaewklum et al. 2005
2. Philipp et al., 2009, 2010a, 2010b; Arndt et al., 2011
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
- 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.
• Adkins, Jessica, Edward W Boyer, and Christopher R McCurdy. "Mitragyna speciosa, a psychoactive tree from Southeast Asia with opioid activity." Current topics in medicinal chemistry 11, no. 9 (2011): 1165-1175. DOI:10.2174/156802611795371305


• Azizi J., Ismail S., Mansor S. M. Mitragyna speciosa Korth leaves extracts induced the CYP450 catalyzed aminopyrine-N-demethylase (APND) and UDP-glucuronosyl transferase (UGT) activities in male Sprague-Dawley rat livers. Drug Metabolism and Drug Interactions. 2013;28(2):95–105. doi:10.1515/dmdi-2012-0039

• Babu, Kavita M., Christopher R. McCurdy, and Edward W. Boyer. "Opioid receptors and legal highs: Salvia divinorum and Kratom." Clinical Toxicology 46, no. 2 (2008): 146-152. DOI: 10.1080/15563650701241795


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• US Food and Drug Administration. Statement from FDA Commissioner, Scott Gottlieb MD, on new warning letters FDA is issuing to companies marketing kratom with unproven medical claims; and the agencies ongoing concerns about kratom. Press Release, September 11, 2018. online: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm620106.htm
PCSS Mentoring Program

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

- PCSS Mentors are a national network of providers with expertise in addictions, pain, evidence-based treatment including medication-assisted treatment.

- 3-tiered approach allows every mentor/mentee relationship to be unique and catered to the specific needs of the mentee.

- No cost.

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https://pcssNOW.org/mentoring/
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