Kratom, A Substance of Increasing Concern

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

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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 and an 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.
• Kratom users chew one to three 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
• Emerging throughout the world as substance used 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?

Grundman O. Patterns of Kratom Use and Health Impact in the US. Drug and Alcohol Dependence. 2017:176:63-70
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%)
• 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%
Internet Mentions vs. Heroin
Pharmacology
Pharmacodynamics

- Over 25 structurally related alkaloids with various properties\(^1\)

- Active constituents:
  - 7-hydroxymitragynine
  - Mitragynine
    - Opioid R-agonists\(^2\)
      - Kappa > mu > delta\(^3\)
    - Other receptor and pathway involvement

\(^1\)Suhaimi et al. 2016
\(^2\)Takayama et al. 2002; Takayama et al. 2004
\(^3\)Taufik Hidayat et al. 2010
Effects

• Dose dependent:
  - Low (1-5g): stimulatory
  - High (>5g): sedative, analgesic
  - Counteracts opioid withdrawal
    • 7-hydroxymitragynine > mitragynine: mu R agonists
    • Mitragynine: alpha-2 adrenergic Rs agonist

1,2Matsumoto et al. 2004
3Boyer et al. 2007; Boyer et al. 2008
Pharmacokinetics

- Mitragynine has a short half life\(^1\)
  - Dosing occurs every 6-12 hours\(^2\)
  - Withdrawal symptoms begin ~12 hours after last use\(^3\)

- Metabolism: CYP 3A4 (also 2D6, 2C9)\(^4\)

- Mitragynine inhibits CYP P450 (2C9, 2D6, 3A4, 1A2)\(^5\)

\(^1\) Taufik Hidayat M et al. 2010
\(^2\) Boyer et al. 2007
\(^3\) Stanciu et al. 2018
\(^4\) Kamble et al., 2018
\(^5\) Hanapi et al., 2013; Hughes et al., 2018
Adverse Effects
Reported Side Effects

• With > 1 year of regular use: weight loss; insomnia; constipation; skin hyperpigmentation; extreme fatigue\(^1\)

• Hepatotoxicity\(^2\)

• Increasing numbers of:
  ▪ Kratom-related exposure calls to poison control centers
  ▪ Fatal overdoses involving Kratom
    - Co-ingestions\(^3\)
    - Adulterated and combination products\(^4\)

\(^1\)Vicknasingam et al., 2010; Saingam et al., 2012
\(^2\)Shekar et al., 2018
\(^3\)Gershman et al., 2018
\(^4\)Kronstrand et al. 2011; Shekar et al., 2018
Withdrawal

• Mimic opioid withdrawal
  ▪ Starts 12-24 hours from last use, lasts up to 4 days
  ▪ Cravings
  ▪ NAS
    – Opioid replacement during pregnancy?

• Responds to similar interventions as for opioid withdrawal
  ▪ Buprenorphine or methadone-assisted detoxification

SOURCES:
Stanciu C., Gnanasegaram, S., Penders M. et al.; Kratom Withdrawal – A Systematic Review with Case Series; J Psychoactive Drugs. 2018

1 Singh, Müller, Vicknasingam et al. 2014; Trakulsrichai et al. 2013
2 Manda et al. 2014
3 Singh, Müller, Vicknasingam et al. 2014; Trakulsrichai et al. 2013
4 Mackay, Lindsay, and Abrahams 2010; Davidson et al (2018)
5 Smid et al 2018
6 McWhirter and Morris, 2010; Galbis-Reig, 2016; Stanciu et al 2018
Maintenance and MAT Considerations

• Guidelines lacking
  ▪ High relapse risk, cravings\(^1\)
  ▪ ?Same protocol as for opioid use disorder\(^2\)

• Buprenorphine, Methadone and Naltrexone
  ▪ A lot of unanswered questions…

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\(^1\) Singh et al. 2014; Singh et al. 2015
\(^2\) Khazareli et al., 2018; Buresh, 2018
Screening

- Not detected in standard urine drug screens
  - High index of suspicion
  - Special confirmatory testing
    - Gas chromatography coupled with mass spectroscopy (GC-MS)\(^1\)
    - Liquid chromatography with linear ion-trap mass spectroscopy\(^2\)
    - Electrospray tandem mass spectroscopy\(^3\)

\(^1\) Kaewklum et al. 2005
\(^2\) Philipp et al., 2009, 2010a, 2010b; Arndt et al., 2011
\(^3\) Lu et al. 2009; Lu et al. 2014
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 and adulterated 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.
Questions / Concerns from November 28, 18 Webinar

- Hyperpyrexia described in case presentation (T 107F)
- Implications on harm reduction / impact on opioid use and relapse risk
- Overdose (discussed)
- MAT considerations (discussed)
- Detection considerations (discussed)
Additional Questions?
References

• 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: 10.1080/156802611795371305


References

• 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
• Grundmann, Oliver. "Patterns of Kratom use and health impact in the US—Results from an online survey." Drug & Alcohol Dependence 176 (2017): 63-70. doi: 10.1016/j.drugalcdep.2017.03.007
References


References

References


• Stanciu C., Gnanasegaram, S., Penders M. et al.; Kratom Withdrawal – A Systematic Review with Case Series; J Psychoactive Drugs. 2018


• Takayama, Hiromitsu. "Chemistry and pharmacology of analgesic indole alkaloids from the rubiaceous plant, Mitragyna speciosa." Chemical and Pharmaceutical Bulletin 52, no. 8 (2004): 916-928. doi.org/10.1248/cpb.52.916


• 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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