ECHO Idaho: Opioid Addiction and Treatment

Kratom: What Providers Need to Know
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The speaker has no relevant financial relationship(s) to disclose.
The speaker has no actual or potential conflicts of interest in relation to this presentation

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Learning Objectives

- Describe the key mechanisms by which kratom exerts pharmacological action related to its intended uses.

- Design a therapeutic treatment plan for management of patients requiring kratom detoxification and maintenance of kratom dependence.

- Explain the role played by kratom in regard to substance use disorder-related morbidity and mortality.
Kratom

Origins of Kratom

• Species: *Mitragyna speciosa*
  – Biologically active alkaloids:
    • Mitrygynine 66%
    • Paynantheine 9%
    • Speciogynine 7%
    • 7-hydroxymitragynine 2% **
    • Speciophylline 1%

• Appearance leaf form: See right
  – Mitragynine isolated: white amorphous powder, soluble in ETOH, chloroform, acetic acid

• Origin: Tropical evergreen tree native to Indonesia, Thailand, and Myanmar
  – Tree reaches heights of 50 feet; spread of 15 feet
  – Member of the Rubiaceae family (Coffee!)

• Common names: Kratom, thang, kakuam, thom, ketum, biak
Uses of Kratom

- Multiple varying rationales: analgesia, anxiolysis, attenuation of opioid withdrawal symptoms, weight loss, energy, sleep

- Routes:
  - Oral ingestion
  - Leaves are dried or powdered, crushed and then smoked, brewed with tea, or placed in gel capsules, tablets, extracts
  - Kratom leaf may be chewed

- Different colors of veins on leaves = differing potencies?

DEA Drug Fact Sheet: Kratom
Image: vietrealm.com
Kratom Legal Debate

- Reports of use date back to mid-1800s
- Most clinicians had not heard of kratom prior to 2016
  - DEA announced plan for temporary Schedule I status in August 2016
  - Scheduling withdrawn in October 2016 due to public outcry

“The American Kratom Association, the largest kratom advocacy group in the United States, helped spur an outpouring of public comments. In response, the DEA put a hold on its scheduling plans, and the Food and Drug Administration now is preparing an eight-factor analysis of kratom’s safety.”

American Society for Biochemistry and Molecular Biology
Kratom Current Legal State

• FDA has not approved Kratom for any medical use
• DEA delayed ruling on scheduling of kratom and listed as “Drug and Chemical of Concern”
  ▪ Risk of abuse, contaminated product, seizures upon withdrawal, neonate dependence issues, drug interactions?, liver injury, etc.
• Not controlled under Federal Controlled Substances Act
  ▪ Some states regulate sales
  ▪ Illegal to possess in some states: (2017 information)
    ▪ Alabama, Arkansas, Indiana, Tennessee, Vermont, Wisconsin
• Purchased over internet and in smoke shops, gas stations, tea shops, bars, other boutique shops
  – Chopped leaves, capsules, compressed tablets, concentrated extracts

Am J Health-Syst Pharm. 2017; 74:e589-95
DEA Drug Fact Sheet: Kratom
Trakulsrichai et al, Drug Design, Develp, & Ther. 2015
Wow! People really seem to like kratom... I need to learn more about how this stuff REALLY works!
Pharmacologic Action

Kratom alkaloids (>40 types)

Non-Opioid Activity
- α-2 adrenergic agonism
- Potential 5HT2a-related action

Opioid Pharmacology
- MG and 7-OH-MG bind to OR
- MOR > DOR & KOR

COX-2 mRNA inhibition

White. Am J Health-Syst Pharm. 2017; 74:e589-95
DEA Drug Fact Sheet: Kratom
Pharmacologic Effects

• Onset: within 5-10 minutes
• Duration: 2 to 5 hours
• Dose-dependent effects:
  - Low doses → stimulant-like (1-5 grams)
    • Stimulant effects, increased alertness, physical energy, talkativeness
  - High doses → opioid-like (>5 grams)
    • Sedation; Euphoria
    • 630g dose = drug-liking of 5mg IV morphine

• Adverse Effects
  - Nausea, itching, sweating, dry mouth, constipation, increased urination, tachycardia, vomiting, drowsiness
  - Anorexia, insomnia, hepatotoxicity, hallucinations
Do you think the health store can help recommend the best dose for my paw pain?
Pharmacokinetics

• In vitro, kratom extract was found to inhibit the following CYP P-450 isoenzymes:
  - 2C9
  - 2D6*
  - 1A2
  - 3A4
  *most potent inhibition

• Using CYP system to boost effects via the “4 x 100” cocktail (common in adolescent population in Thailand):
  - Kratom leaves are boiled and mixed w/caffeine soda, dextromethorphan, codeine
  - + diphenhydramine (CYP2D6 inhibitor)

Am J Health-Syst Pharm. 2017; 74:e589-95
**Pharmacokinetics**

<table>
<thead>
<tr>
<th>Rat Data:</th>
<th>Available Human Data: <em>(small studies)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tmax: 1.2 – 1.8 h</td>
<td>Tmax: 0.83 ± 0.35 h</td>
</tr>
<tr>
<td>T ½: 3.9 – 9.4 h</td>
<td>T ½: 23.24 ± 16.07 h</td>
</tr>
<tr>
<td>Vd: 37.9 – 89.5 L/kg</td>
<td>Vd: 38.04 ± 24.32 L/kg</td>
</tr>
</tbody>
</table>

**Reminder: Rule of Five**

5x the t ½ = the time at which the drug is “completely” (97%) eliminated from the body

1 x ½ life = 50% original drug removed
2 x ½ life = 75%
3 x ½ life = 87.5%
4 x ½ life = 93.75%
5 x ½ life = 98.875%

DEA Drug Fact Sheet: Kratom
Image: [https://images.app.goo.gl/kv5HpYrjoke4Y2TX6](https://images.app.goo.gl/kv5HpYrjoke4Y2TX6)
Laboratory Detection

PROVIDER INSTRUCTIONS:
1. If positive, this panel test will quantify the following:
   - 7-HYDROXYMITRAGYNINE
   - MITRAGYNINE

   *A cost of $78.50 will incur if either of the above is performed.

2. This test request 30 mLs (NLT 20) of urine.

Test Code: 791750
TAT: 6 - 11 Days

PROCESSING INSTRUCTIONS:
1. This test requires 30 mLs (NLT 20) REFRIG, Random Urine.
   Please make two aliquots, one to send using the LabCorp Aliquot Tube and one backup aliquot (reserve the Primary cup if possible) and store in the walk-in.
Urine Drug Level Examples?

- **161.0 ng/mL**
  - 3/15
  - Last reported use 3/14 (~5g total)

- **8.1 ng/mL**
  - 3/24
  - 9 days after first value

- **2.3 ng/mL**
  - 4/4
  - 11 days after 2nd value
  - 20 days after 1st value
# Kratom Withdrawal

- Withdrawal can be difficult to manage and serious

**Hostility, Aggression, Emotional Lability**

**Physical Opioid Withdrawal Symptoms**

**Seizures and Death (case reports)**

<table>
<thead>
<tr>
<th>Adjunctive medications for management of uncomplicated kratom withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Withdrawal Symptoms:</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Anxiety, dysphoria, lacrimation, rhinorrhea:</td>
</tr>
<tr>
<td>Myalgias:</td>
</tr>
<tr>
<td>Sleep disturbance:</td>
</tr>
<tr>
<td>Nausea:</td>
</tr>
<tr>
<td>Diarrhea:</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>GI Cramping:</td>
</tr>
</tbody>
</table>
Kratom Withdrawal Management

Table 1. Pharmacologic Effects of Kratom From Human Trials

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Therapy for Adverse Events</th>
<th>Withdrawal Effects</th>
<th>Therapy for Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachycardia and hypertension</td>
<td>Benzodiazepines, negative chronotropic drugs</td>
<td>Agitation and anxiety</td>
<td>Benzodiazepines, α-2 agonists</td>
</tr>
<tr>
<td>Nausea and constipation</td>
<td>Antiemetics, laxative plus stool softener</td>
<td>Abdominal pain and diarrhea</td>
<td>Nonopioid antidiarrheals</td>
</tr>
<tr>
<td>Confusion and hallucinations</td>
<td>Benzodiazepines, naloxone</td>
<td>Limb muscle spasms</td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>Seizures</td>
<td>Benzodiazepines, naloxone, anticonvulsants</td>
<td>Joint and muscle pain</td>
<td>Nonopioid pain relievers</td>
</tr>
<tr>
<td>Sedation</td>
<td>Naloxone</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Treatments for adverse events and withdrawal are general treatment suggestions and were not studied in any clinical trials of kratom.

It seems like kratom toxicity and withdrawal can present in quite the range of symptoms!
Risks of Kratom Use

- 2011-2017, National Poison Control Center received >1800 calls concerning exposure to kratom
- CDC analyzed data from the State Unintentional Drug Overdose Reporting System (SUDORS) to determine impact from July 2016-December 2017

### July 2016- June 2017
- Kratom listed as a cause of death in **11 states**

### July 2017 – December 2017
- Kratom listed as a cause of death in **27 states**

## Risks of Kratom Use

State Unintentional Drug Overdose Reporting System (SUDORS) - Overdose Deaths July 2016-Dec 2017

- 27,338
- 152 kratom-positive (0.56%)
- 152 kratom-involved (59.9%)

<table>
<thead>
<tr>
<th>Co-occurring substances listed as a cause of death</th>
<th>Kratom detected on toxicology (n = 152) No. (%)</th>
<th>Kratom determined to be a cause of death (n = 91) No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any fentanyl</td>
<td>99 (65.1)</td>
<td>51 (56.0)</td>
</tr>
<tr>
<td>Heroin</td>
<td>50 (32.9)</td>
<td>23 (25.3)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>34 (22.4)</td>
<td>24 (26.4)</td>
</tr>
<tr>
<td>Prescription opioids</td>
<td>30 (19.7)</td>
<td>22 (24.2)</td>
</tr>
<tr>
<td>Cocaine</td>
<td>28 (18.4)</td>
<td>15 (16.5)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>19 (12.5)</td>
<td>11 (12.1)</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>13 (8.6)</td>
<td>—</td>
</tr>
</tbody>
</table>
KT is a 43-year-old male patient with alcohol use disorder, hypertension, and anxiety, presenting to you in the outpatient clinic for the first time. He has struggled with his alcohol use for many years, and is wondering about medication assisted treatment with naltrexone to help with his cravings. His current medications include lisinopril 20mg daily, albuterol inhaler as needed, and a daily multivitamin. His alcohol use pattern is reported as mostly in the evening after work to help him “wind down” and for sleep, about 5-6 drinks. He endorses using “a supplement from the health store” to help with his anxiety during work hours. When asked, he describes this supplement is kratom, and he is taking approximately 10-12 capsules daily (0.5g/capsule).

- Is patient appropriate for MAT with naltrexone?
- What additional information would you like to have prior to trial of naltrexone?
Some Recent Case Reports ...

- 64-year-old male found unconscious and seizing
  - Regularly used kratom for chronic pain
  - Urine concentration of mitragynine 167 ± 15 ng/mL detected

- 25-year-old man suspected kratom had induced his intrahepatic cholestasis
  - Diagnosis confirmed by liver biopsy
  - Mitragynine was detected in both urine and serum samples

- 44-year-old man admitted for kratom detoxification
  - Consuming ~40g kratom divided into 4 doses over 24h
  - Experienced withdrawal symptoms despite regular use
  - Suggests short half-lives of active substances in kratom and a dependence syndrome primarily via agonist activity at the opioid receptors

- Term infant born to mother with daily kratom tea use to self-treat opioid dependence
  - Term infant born to mother using kratom daily believing it a safe alternative for pain
  - Both infants required treatment with opiates for neonatal abstinence syndrome (NAS)
| Kratom is used for pain, anxiety, sleep, alertness, appetite suppression, and many others |
| Use of kratom has drastically increased in popularity in the United States |
| Kratom has been found to carry risk of abuse or dependence |
| FDA released multiple announcements regarding safety (inc. formal public health advisory) |
| Kratom and active alkaloids do NOT carry Schedule with the DEA |
| Pharmacologic effects are dose-dependent, ranging from stimulant- to opioid-like |
| Drug interactions are possible and sometimes used intentionally to amplify effects |
| Withdrawal can sometimes be serious and may require medical attention |
| Mitragynine and 7-hydroxymitragynine can be detected in special urine assays |
| One of the best things we can do to better care for our patients is to ask about kratom |
Questions?

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References


References


References


ECHO Idaho: Opioid Addiction and Treatment

Join us for our next session

For information, please visit uidaho.edu/echo