Emerging Drugs of Abuse

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Disclosures

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  • I have no financial conflicts of interest
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  • I have no financial conflicts of interest
Objectives

• At the end of the lecture, participants should be able to
  • Name substances which have been increasing in use over the past several years
  • Discuss the mechanism of action of these substances
  • Discuss the intoxication and withdrawal syndromes of these substances
  • Describe how to treat intoxication or withdrawal from these substances
Mitragyna speciosa, from coffee plant family
Psychoactive herb from Southeast Asia with opioid and/or stimulant activity, depending on amount used
Raw plant contains higher concentrations of mitragynine than 7-hydroxymitragynine (7-HMG)
Traditionally used to
  - Boost energy
  - Reduce cough
  - Reduce depression
  - Alleviate pain
Also used as a substitute for opium
Kratom Bliss is an invigorating organic leaf ground to a fine powder. This amazing miracle leaf is derived from Southeast Asia. It's great for mind, body, and soul. A truly unique experience that's as relaxing as it is uplifting.
Background

• In the US, kratom is
  • Unregulated herbal remedy
    • In 2016, DEA announced plan to move to Schedule 1, huge outcry and DEA withdrew notice of intent
    • Several stories of how it was a harmless, good alternative for some as opioid substitute
    • DEA put it on "Drugs and Chemicals of Concern" list
Advocates in September 2016 held a march in Washington, D.C., to protest a proposal to classify kratom as having a high potential for abuse. The Drug Enforcement Administration later withdrew its proposal.

Courtesy of the American Kratom Association
Background: Kratom

- Sold as dietary supplement
- Sold in smoke shops, online
- Available in capsules, whole leaves, liquid, powder
  - Can be consumed as a tea
- Not detectable by standard urine drug testing
Psychopharmacology

• Partial agonists for the mu-opiate receptor (and possibly kappa receptors)
• Bind as partial agonists or antagonists to the delta-opioid receptors
• May affect other neurotransmitters adrenergic system as well
• 7-HMG has a higher affinity for the opioid receptors, possibly better bioavailability and CNS penetration than mitragynine
Pharmacology

• Dosing
  • 1-5 g stimulating effect
  • 5-15 g mu-opioid effect
• Effects begin within 5 mins of using
• Half-life for experienced users 23 hours
• Effects reversed with naloxone
Adverse Effects

- Tachycardia
- Agitation
- Drowsiness
- Nausea
- Dizziness
- Hypotension and hypertension
- Constipation
- Tremor
- Decreased appetite
- Seizures
- Psychosis
Consequences of Use

- Physiologic dependence, may develop more slowly than other opioids
  - Animal studies (conditioned place preference, tolerance to antinociceptive effects similar to that seen with morphine, cross-tolerance developed with morphine)
  - Humans who chew leaves: 1-3 leaves initially, then increase up to 10-30 leaves per day; using 3-10 times per day
- Withdrawal syndrome similar to opioids
- Case studies of babies born to women using kratom, needed treatment for NAS
- Seizures, DILI
- 24 deaths as of October 2017
- DEA has noted 44 deaths since 2009 either in the scientific literature or in autopsy and medical examiner reports, many since 2014
As of May 24, 2018, 199 people infected with the outbreak strains of *Salmonella* were reported from 41 states. 74% consumed kratom.
People infected with the outbreak strains of *Salmonella* L 4, [5],12:b:-, Javiana, Okatie, Heidelberg, Weltevreden and Thompson, by state of residence, as of May 24, 2018 (n=199)

https://www.cdc.gov/salmonella/kratom-02-18/index.html
**Kratom Exposures**

- From January 2010 to December 2015, there were 660 calls to U.S. poison centers related to kratom exposure.
- There was a 10-fold increase in calls from 2010 to 2015 (26 to 263 calls).
  - 65% were isolated exposure to kratom.
  - When used with another substance, substances tended to be alcohol, opioids, benzodiazepines, acetaminophen, other herbal products.
- When sex of exposed person was known, 71.7% were male.
- When age of exposed person was known, 28 years was mean age (range 2 months to 69 years).
- Outcome of poison center calls: 24.5% minimal symptoms; 41.7% moderate symptoms (required tx); 7.4% major symptoms (life-threatening, residual disability); 1 death.
Calls to Poison Control

FIGURE. Number of reported exposure calls to poison centers related to kratom use, by year — National Poison Data System, United States and Puerto Rico, January 2010–December 2015.
Treatment

- Withdrawal using clonidine
- Buprenorphine
- Naltrexone-XR
OCT 17 2017

The Honorable Robert W. Patterson
Acting Administrator
Drug Enforcement Administration
U.S. Department of Justice
8701 Morrissette Drive
Springfield, VA 22152

Dear Mr. Patterson:

Pursuant to the Controlled Substances Act (CSA), 21 U.S.C. § 811 (b), (c), and (f), the Department of Health and Human Services (HHS) is recommending that the substances mitragynine and 7-OH-mitragynine be permanently controlled in Schedule I of the CSA. Mitragynine and 7-OH-mitragynine are mu opioid receptor agonists that represent two of the principle psychoactive constituents of the plant *Mitragyna speciosa* (*M. speciosa*), commonly referred to as *kratom*. In assessing the relative abuse potential of mitragynine and 7-OH-mitragynine, FDA reviewed and evaluated all of the available data on the abuse potential of mitragynine and 7-OH-mitragynine. In order to conduct a full evaluation of mitragynine and 7-OH-mitragynine, it was necessary to review information on the use of *M. speciosa*, the only natural source of mitragynine and 7-OH-mitragynine. Identification of *M. speciosa* cannot be accomplished solely through chemical analysis of mitragynine and 7-OH-mitragynine content alone. This is because adulteration of botanical material from any plant with mitragynine and 7-OH-mitragynine would make its chemical analysis indistinguishable from that of mitragynine and 7-OH-mitragynine from *M. speciosa*. Thus, our scheduling recommendation does not include a recommendation for scheduling *M. speciosa* due to the difficulty in identifying the plant.
- Green: Kratom is legal and no restrictions
- Light Green: Legislation in these state has failed or has been amended
- Orange: There is pending legislation on Kratom in these states
- Red: banned states schedule I for Kratom
- Purple: Study involving Kratom
- Red Dot: banned city for Kratom

http://speciosa.org/home/kratom-legality-map/
CASE DISCUSSIONS
Tianeptine
Tianeptine

• Atypical opioid agonist
• Atypical antidepressant (5-HT)
• Atypical anxiolytic
• TCA
Background

- Marketed as Stablon 12.5 mg
- Sold in France. Outlawed in Russia.
- Street dose 500 mg to 3,000 mg (3 grams)
  - Tianeptine sodium is injected
  - Tianeptine free base is orally ingested
  - Co-ingestions include heroin, phenibut, alcohol, benzodiazepines
- Tianeptine sold on internet
- New Mind in Chicago is distributor
- Sold as a “work supplement”
- “Not intended for human consumption”
WARNING: Strictly for research / laboratory purposes.
H302: Harmful if swallowed. H332: Harmful if inhaled.
H313: May be harmful in contact with skin.
P280: Wear protective gloves / clothing / eye protection.
Store securely in a cool, dry and dark environment.
Toxicological properties have not been fully investigated.
This product has not been approved for human consumption.
Psychopharmacology

• Tianeptine has antidepressant and anxiolytic effects with a relative lack of sedative, anticholinergic, and cardiovascular side effects.
• It has been found to act as an atypical agonist of the \( \mu \)-opioid receptor with clinically negligible effects on the \( \delta \)- and \( \kappa \)-opioid receptors.
• \( \mu \)-Opioid receptor agonists typically induce euphoria, and in accordance, tianeptine does so at high doses well above the normal therapeutic range.
Tianeptine Opioid Actions

- In 2014, tianeptine was found to be a μ-opioid receptor (MOR) full agonist using human proteins.

- The MOR is required for the acute and chronic antidepressant-like behavioral effects of tianeptine in mice and that its primary metabolite had similar activity as a MOR agonist but with a much longer elimination half-life.

- In addition to its therapeutic effects, activation of the MOR is likely to also be responsible for the abuse potential of tianeptine at high doses that are well above the normal therapeutic range.
Tianeptine Opioid Actions

• Tianeptine produced opioid-like behavioral effects such as analgesia and reward. Tianeptine may be acting as a biased agonist of the MOR and that this may be responsible for its atypical profile as a MOR agonist.

• Recreational, non-medical tianeptine users suggest that significant withdrawal effects resembling those of other typical opioid drugs (including but not limited to depression, insomnia, cold/flu-like symptoms) manifest following prolonged high dose usage.
Senate Bill 801 (as introduced 1-31-18)
Sponsor: Senator Rick Jones
Committee: Judiciary
Date Completed: 2-6-18

CONTENT

The bill would amend the Public Health Code to classify tianeptine sodium as a Schedule 2 controlled substance.

Article 7 of the Code governs the manufacture, distribution, and possession of controlled substances, and prescribes a range of criminal penalties, depending on whether a person violates controlled substance. Article 7 identifies specific drugs as controlled substances. The Michigan Board of Pharmacy to add controlled substances to the list of controlled substances in a particular schedule depends on whether a substance is scheduled for medical use in the United States. Such classification may lead to physical or psychological dependence.

Section 7214 designates certain substances as Schedule 2. A substance is a controlled substance if it has currently accepted medical use in treatment, has a potential for abuse, and the possibility of addiction by medical use with severe restrictions; and the addiction to the substance could lead to physical dependence. The bill would amend the Public Health Code to classify tianeptine sodium as a Schedule 2 controlled substance.
Tianeptine overdose reversed by naloxone (Narcan). Tianeptine NAS withdrawal symptoms resolved by morphine.
CASE DISCUSSIONS
Phenibut
Background

- 4-amino-3-phenyl-butyric acid
- Analogue of GABA
  - Similar to baclofen and gabapentin
- Used in Russia (since 1960s) and Latvia for
  - Alcohol withdrawal
  - Anxiety
  - Insomnia
  - PTSD
  - Stuttering
  - Vestibular disorders
- Recommended dose = 250-500 mg
- When misused, doses exceed 1.5 grams
Background

- Not approved for use in US, EU, Australia
- Available to purchase online
- Sold as a nootropic supplement
  - Substance that may improve cognitive function, particularly executive functions, memory, creativity, or motivation, in healthy individuals
- Study found 48 internet suppliers selling phenibut ranging from 5 g to 1000 kg
- Price as low as $0.23 per gram
- Used to self-medicate anxiety, insomnia, cravings for alcohol
- Taken orally, usually in doses >1g
  - Case reports of using 30 g
- Usually younger population uses
- Have history of using substances
Psychopharmacology

- Believed to act primarily on GABA$_B$ receptors and GABA$_A$ receptors, but to a lesser extent
- May also act on dopamine receptors
- Antagonizes beta-phenethylamine (PEA), an endogenous anxiogenic
- Preclinical data indicate that most of the pharmacologic activity is through the R-enantiomer
GABA activity

- Rapidly develop tolerance and withdrawal
- Withdrawal symptoms similar to alcohol or benzodiazepine withdrawal
  - Psychomotor agitation
  - Light and sound sensitivity
  - Muscle pain and twitches
  - Tachycardia
  - Nausea
  - Tremor
  - Insomnia
  - Derealization
  - Depersonalization
  - Hallucinations
Consequences of Use

• Case reports of people arriving to ED with
  • Intoxication
  • Altered mental status
  • Agitation requiring, may require sedation and intubation
  • Withdrawal
Treatment

• For withdrawal, there are published case reports of using:
  • Baclofen
  • Phenobarbital
CASE DISCUSSIONS
Other substances

• Benzodiazepine-like substances
  • Etizolam
  • Clonazolam
• Dextromethorphan
References


