Not for Human Consumption: New Drugs of Abuse and Their Detection

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Disclosures

- Consultant: Axial Healthcare
- The views and opinions expressed in this presentation are those of the author and do not necessarily reflect the official policy or position of any agency of the United States government, including the Department of Veterans Affairs.

Learning Objectives

- Explain the pharmacology and toxicology of new drugs of abuse
- Describe the desired and undesired effects of new drugs of abuse
- Select and interpret urine drug tests for new drugs of abuse

PAINWEEK

Current Situation

- Opioid overdose epidemic
  - Rising overdoses related to illicitly manufactured fentanyl
  - Use of other substances for opioid-like effects or treat opioid withdrawal
- Multiple new drugs of abuse are emerging
  - Rapidly changing molecule
  - Some legal, others attempt to skirt the law
  - Difficult to detect with standard UDM
  - Can lead to significant adverse events

PAINWEEK

Introduction

Fentanyl and derivatives	Krokodil: desomorphine	Salvia	Kratom
Loperamide	Synthetic cathinones: bath salts and flakka	Synthetic cannabinoids: spice	

PAINWEEK

Fentanyl and Fentanyl Derivatives

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Tom Petty and Prince

- Prince 4/21/16
  - Cause of death: accidental overdose
  - Toxicology tests confirmed fentanyl but further details not released
- Tom Petty 10/3/17
  - Cause of death: accidental overdose
  - Toxicology
    - Fentanyl
    - Oxycodone
    - Temazepam
    - Alprazolam
    - Citalopram
    - **Acetyl fentanyl**
    - **Despropionyl fentanyl**

https://www.buzzfeed.com/claudiarosenbaum/tom-petty-died-of-accidental overdose?utm_term=.vh8qZLEbVj#.vh8qZLEbVj
https://www.practicalpainmanagement.com/resources/news-and-research/prince-died-fentanyl-overdose

PAINWEEK

Fentanyl

- Synthetic opioid
- Schedule II controlled substance
- 50-100 times as potent as morphine
- Indicated for the treatment of acute or chronic severe pain
- Available pharmaceutically patches, buccal, IV
- Prescribing rates were stable during this time frame

https://www.cdc.gov/drugoverdose/opioids/fentanyl.html
https://www.cdc.gov/drugoverdose/pdf/pbss/PBSS-Report-072017.pdf
https://www.whitehouse.gov/sites/whitehouse.gov/files/images/Final%20STANDARD%20size%20of%20Fentanyl%20Safety%20Recommendations%20for%20First%20Respond....pdf
https://www.dea.gov/druginfo/Fentanyl_BriefingGuideforFirstResponders_June2017.pdf

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Illicit Forms of Fentanyl or Synthetic Opioids

- 4-fluoroisobutyryl fentanyl
- Furanyl-fentanyl
- Acryl-fentanyl
- Acetyl-fentanyl
- Carfentanil
  - Schedule II
  - 10,0000x as potent as morphine``
- 3-methylfentanyl
- U-47700

- Illicit fentanyl analogues will be subject to criminal prosecution in the same manner as for fentanyl and other controlled substances

PaiNweek

https://www.dea.gov/divisions/hq/2017/hq110917.shtm
https://www.dea.gov/druginfo/Fentanyl_BriefingGuideforFirstResponders_June2017.pdfhttps://www.dea.gov/pr/multimedia-library/image-gallery/images_fentanyl.shtml

Illicitly Manufactured Fentanyl

- Illicit sources the main culprit of overdoses
- Mixed with heroin and/or cocaine – user may be unaware
- Available in multiple forms: powder, tablets, capsules, liquid, rocks, spiked on blotter papers
- Routes: oral, intranasal, IV, buccal
- Street names: Apache, China Girl, China White, Dance Fever, Friend, Goodfella, Jackpot, Murder 8, TNT, Tang, Cash
- Sources: China, Mexico

https://www.cdc.gov/drugoverdose/opioids/fentanyl.html
https://www.cdc.gov/drugoverdose/pdf/pbss/PBSS-Report-072017.pdf
https://www.whitehouse.gov/sites/whitehouse.gov/files/images/Final%20STANDARD%20size%20of%20Fentanyl%20Safety%20Recommendations%20for%20First%20Respond....pdf
https://www.drugabuse.gov/drugs-abuse/fentanyl
https://www.dea.gov/druginfo/Fentanyl_BriefingGuideforFirstResponders_June2017.pdf

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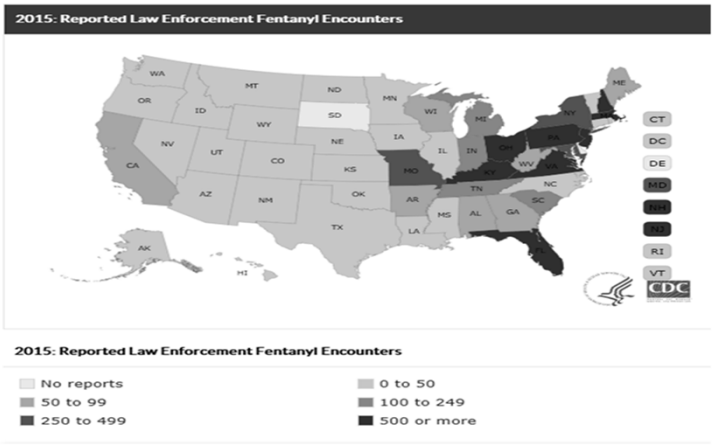
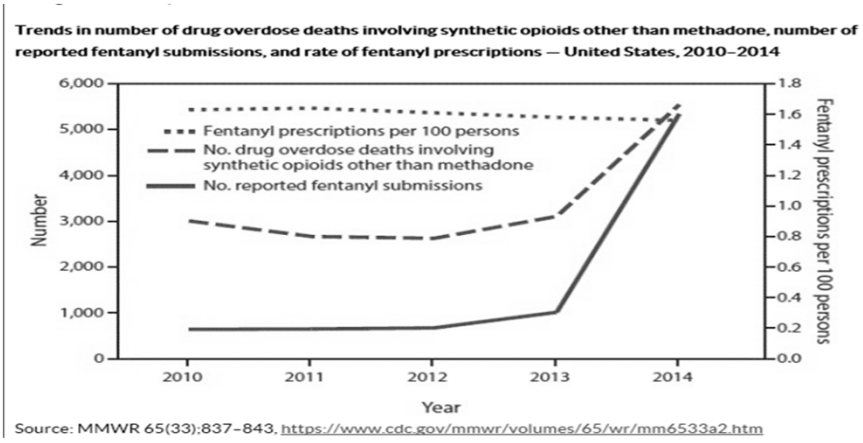
Law Enforcement Encounters by State 2015



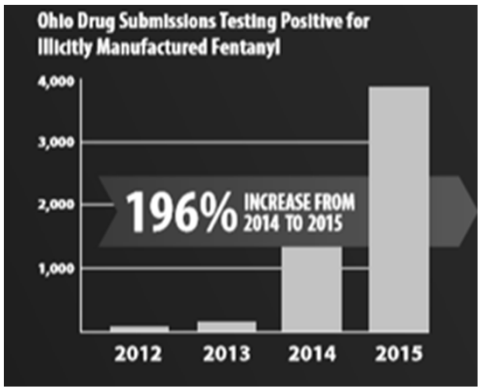
https://www.cdc.gov/drugoverdose/data/fentanyl-le-reports.html
https://www.cdc.gov/drugoverdose/pdf/pbss/PBSS-Report-072017.pdf

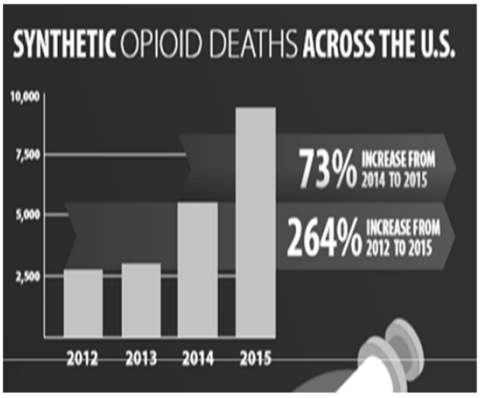
Overdose Deaths Involving Synthetic Opioids (Excluding Methadone)



https://www.cdc.gov/niosh/topics/fentanyl/illegaluse.html

Fentanyl Submissions and Synthetic Opioid Deaths





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https://www.cdc.gov/drugoverdose/pdf/pbss/PBSS-Report-072017.pdf

Safety Recommendations for First Responders

Preventing exposure

- Wear gloves when suspect fentanyl is present
- Avoid anything that can make fentanyl airborne
- Wear a NIOSH-approved respirator, eye protection, reduce skin contact when small amount visible

Exposure

- Notify others
- Do not touch eyes, mouth, skin
- Wash skin with cool water and soap
- Do NOT use hand sanitizers
- Wash your hands after incident and before eating/drinking/using restroom
- Follow decontamination procedures

Overdose suspected

- Move away and call EMS
- Give naloxone
- Provide rescue breathing and/or CPR

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https://www.whitehouse.gov/sites/whitehouse.gov/files/images/Final%20STANDARD%20size%20of%20Fentanyl%20Safety%20Recommendations%20for%20First%20Respond....pdf

Prevention

- Increase amount of naloxone first responders carry
- Recognize and treat overdoses
- Multiple doses may be needed
- Expand access of naloxone to people at risk and family
- Give take-home naloxone

PAINWEEK https://www.cdc.gov/drugoverdose/pdf/pbss/PBSS-Report-072017.pdf

Detection

- Synthetic opioid not detected via opiate immunoassay
- Fentanyl screen
- LCMS/GCMS testing

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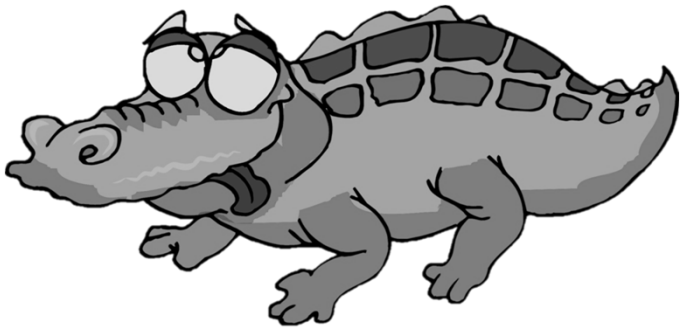

"Krokodil:" Desomorphine

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"Krokodil:" Introduction

- Active substance is desomorphine
- Street names: krokodil, crocodile, zombie drug
- Synthetic mu-opioid agonist similar to heroin
- Schedule I controlled substance in Controlled Substances Act (CSA)
- Available from illicit sources

Gahr M et al. "Krokodil" – revival of an old drug with new problems. Substance Use and Misuse. 2012;47(7):861-863
Rech MA et al. New drugs of abuse. Pharmacother. 2015;35(2):189-197
Desomorphine. Drug Enforcement Administration. Office of Diversion Conrol. Drug & Chemical Evaluation Section http://www.deadiversion.usdoj.gov/drug_chem_info/desomorphine.pdf. Accessed 17 April 2016

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Desomorphine: History

- First synthesized in the USA in 1932 as an alternative to morphine
- Used commercially in Switzerland
- Less expensive alternative to heroin in Russia and European countries
- Reports of use in the U.S. in Missouri, Arizona, Utah, and Illinois but unconfirmed
  by Drug Enforcement Agency (DEA)

Gahr M et al. "Krokodil" – revival of an old drug with new problems. Substance Use and Misuse. 2012;47(7):861-863
Rech MA et al. New drugs of abuse. Pharmacother. 2015;35(2):189-197

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Desomorphine: Kitchen Chemistry

- Made in at-home laboratories with a process similar to methamphetamines
- Uses chemicals that are cheap, readily available, and highly toxic
- Requires minimal laboratory equipment
- Doses can be made in under an hour
- Made into a suspension that is injected intravenously usually without a filter

Gahr M et al. "Krokodil" – revival of an old drug with new problems. Substance Use and Misuse. 2012;47(7):861-863
Rech MA et al. New drugs of abuse. Pharmacother. 2015;35(2):189-197,

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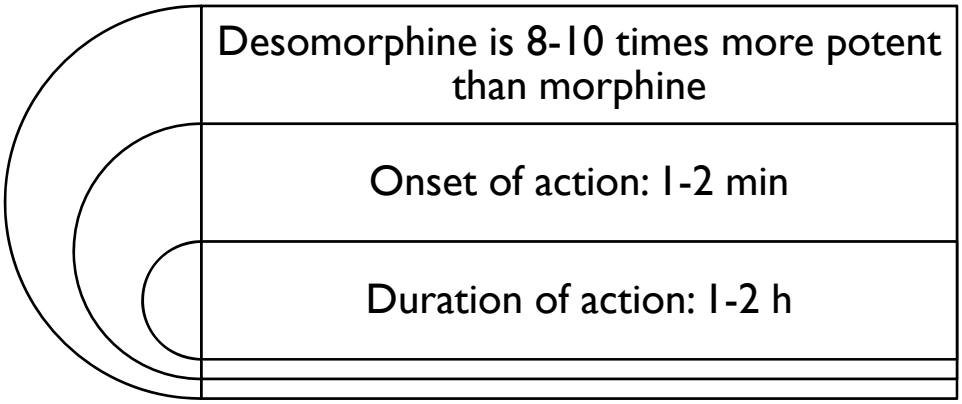
Desomorphine: Pharmacology and Kinetics



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Rech MA et al. New drugs of abuse. Pharmacother. 2015;35(2):189-197

Desomorphine: Adverse Effects

- Adverse effects typical of opioids
- Immediate damage to blood vessels, muscles, and bones
- At injection site, tissue necrosis and gangrene
- Systemic adverse effects may include: bacteremia, osteomyelitis, meningitis, speech/motor skill impairments, liver and kidney damage, venous ulcers, and skin eschars
- Average survival from first use is estimated at 2 years

Gahr M et al. "Krokodil" – revival of an old drug with new problems. Substance Use and Misuse. 2012;47(7):861-863
Rech MA et al. New drugs of abuse. Pharmacother. 2015;35(2):189-197

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Desomorphine: Treatment

- Supportive care
- Naloxone administration
- Precautions for opioid withdrawal
- No evidence for mixed opioid agonists/antagonists but may be considered
- Screen for infectious diseases
- Patients may also need intensive psychiatric care, nutrition evaluations, and both physical and psychiatric rehabilitation

Rech MA et al. New drugs of abuse. Pharmacother. 2015;35(2):189-197

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Desomorphine: Detection

- Synthetic opioid
- Not typically detected by opiate immunoassay
- Cross-reactivity with opiate and oxycodone immunoassays variable
- Detected from gas chromatography-mass spectroscopy (GCMS)
- Remnants of codeine may be detected by immunoassay

Kateslou M et al. A krokodil emerges from the murky waters of addiction. Abuse trend of an old drug. Life Sci. 2014;103:81-87
Winborn J et al. Desomorphine screening using commercialky available enzyme-linked immunosorbent assays. J Analytical Toxicology. 2017;41:455-460.

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Desomorphine: US Case Report – 2014

- 30 yo male presenting to St. Louis, MO hospital with pain, swelling, and ulceration of left thigh
- Injecting heroin daily into arms and thighs for 7-8 years ($300/day)
- Injecting krokodil into thigh for last 6-7 months because it was cheaper
- Initially had blisters at injection sites that turned black
- After 1 month, necrotic areas peeled off leaving a necrotic ulcer
- 2 months before admission noticed increased swelling of left little finger which progressed to blisters that later turned black and auto-amputated
- While inpatient, treated with intravenous antibiotics and wound care
- Patient left against medical advice and was lost to follow-up

PAINWEEK

Thekkemuriyi DV et al. Krokodil – a designer drug from across the Atlantic, with serious consequences. Am J Med. 2014;127(3):e1-e2

Desomorphine: US Case Report – 2016

- 23 yo female w/ hx of IVDA presented to ED with pain and swelling in hands, forearms because of ulcers
- Ulcers been there x 12 months and started after starting to use krokodil
- Burning sensation during injection
- Purulent drainage from injection site with pain and swelling
- Necrosis developed after several months
- During physical exam, ulceration extended into deep fascia but mostly hypertrophic scarring
- CT showed extensive soft tissue thickening and stranding in forearms

PAINWEEK

Haskin A, et al. A new drug with a nasty bite: a case of krokodil-induced skin necrosis in an intravenous drug user. JAAD Case Rep. 2016;2(2):174-176.

Salvia

PAINWEEK

https://www.dea.gov/pr/multimedia-library/publications/drug_of_abuse.pdf

Salvia: History

- Hallucinogen from the plant *Salvia divinorum*, a sage plant of the mint family
- Salvinorin A is the psychoactive molecule
- Endemic to Sierra Mazatec region in Mexico
- Utilized by Mazatec Indians for hallucinogenic properties
- Traditional remedy for rheumatism, diarrhea, and migraine
- Not listed in the CSA, DEA drug of concern
- Regulatory controls in several states
- Kappa opioid receptor agonist and modulates endocannabinoid system

Mahendran R et al. Salvia divinorum: an overview of the usage, misuse, and addiction processes. Asia-Pacific Psychiatry. 2015;8:23-31
Salvia divinorum and salvinorum A. Drug Enforcement Administration. Office of Diversion Control. Drug & Chemical Evaluation Section. http://www.deadiversion.usdoj.gov/drug_chem_info/salvia_d.pdf. Accessed 17 April 2016
Rech MA et al. New drugs of abuse. Pharmacother. 2015;35(2):189-197
https://www.dea.gov/pr/multimedia-library/publications/drug_of_abuse.pdf

PAINWEEK

Salvia: Street Names

- Magic Mint
- Sally D
- Diviner's Sage
- Lady Sally
- Puff
- Incense Special

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Mahendran R et al. Salvia divinorum: an overview of the usage, misuse, and addiction processes Asia-Pacific Psychiatry. 2015;8:23-31

Salvia: Prevalence and Availability

- 1.3% among U.S. adults
- Most commonly used by young adults aged 18-25 years
- Common among recent users of lysergic acid diethylamide (LSD), ecstasy, heroin, phencyclidine (PCP), and cocaine
- Users often self-report anxiety and depression
- Grown domestically and imported
- Available online and in local shops

PAINWEEK

Mahendran R et al. Salvia divinorum: an overview of the usage, misuse, and addiction processes. Asia-Pacific Psychiatry. 2015;8:23-31
Salvia divinorum and salvinorum A. Drug Enforcement Administration. Office of Diversion Control. Drug & Chemical Evaluation Section http://www.deadiversion.usdoj.gov/drug_chem_info/salvia_d.pdf. Accessed 17 April 2016
Rech MA et al. New drugs of abuse. Pharmacother. 2015;35(2):189-197

Salvia: Reasons for Use

- Curiosity, relaxation, getting "high," dream-like states
- < 22 years used for fun or boredom
- > 22 years for spiritual effects

Mahendran R et al. Salvia divinorum: an overview of the usage, misuse, and addiction processes Asia-Pacific Psychiatry. 2015;8:23-31

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Salvia: Patterns of Use

- Tea
  - –Method used by Mazatec Indians for spiritual experience
- Chew leaves
  - –Absorption via buccal cavity with rapid onset of effect
- Vaporization/smoking
  - –Most intense psychoactive effects
  - –Similar effects to ketamine and tetrahydrocannabinol (THC)

Mahendran R et al. Salvia divinorum: an overview of the usage, misuse, and addiction processes Asia-Pacific Psychiatry. 2015;8:23-31

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Salvia: Pharmacokinetics

- Absorption
  - Buccal
  - Lungs
- Metabolism
  - First pass limits oral use
  - CYP2D6, CYP1A1, CYP2C18, and CYP2E1
  - UGT2B7
- Excretion
  - Bile
  - Urine
- Onset
  - Smoked and buccal : seconds-minutes
- Duration
  - Smoked: 30 minutes
  - Buccal: 1 hour
- Half-life
  - Dose related
  - 75 minutes

Mahendran R et al. Salvia divinorum: an overview of the usage, misuse, and addiction processes
Asia-Pacific Psychiatry. 2015;8:23-31
Rech MA et al. New drugs of abuse. Pharmacother. 2015;35(2):189-197
Thornton MD et al. Bath salts and other emerging toxins. Pediatr Emer Care. 2014;30:47-55

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Salvia: Effects

Positive/Desired Effects
• Relaxation and improved mood • Calmness • Psychedelic-like effects • Altered state of consciousness • Vivid visual hallucinations • Auditory hallucinations • Increased instrusive thoughts • Feelings of dissociation, depersonalization, and derealization • Increase in sensual and aesthetic appreciation • Floating feeling • Increased self-confidence • Increased insight • Spritual experiences

Negative/Undesired Effects
• Loss of control • Difficulty integrating experiences • Racing thoughts • Tiredness, physical exhaustion • Dizziness and drowsiness • Irritability, anxiety, fear, panic • Psychomotor agitation • Amnesia • Dysphoria • Lack of motor coordination • Profound sweating • Chills • Nausea, vomiting, abdominal pain

PAINWEEK

Zawilska JB et al. Salvia divinorum: from Mazatec medicinal and hallucinogenic plant to emerging recreational drug
Hum Psychopharmacol Clin Exp. 2013;28:403-412

Salvia: Treatment

- Patients rarely present for treatment
- No known antidote
- Theoretical use of naloxone
  - Likely require 5-10 times the typical naloxone dose
- Supportive care
  - Benzodiazepines for agitation

Thornton MD et al. Bath salts and other emerging toxins. Pediatr Emer Care. 2014;30:47-55
Vandrey R, et al. Novel drugs of abuse: a snapshot of an evolving marketplace. Adoles Psychiatry. 2013;3(2)

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Salvia: Detection

- Detected via GCMS or liquid chromatography mass spectroscopy (LCMS)
- Subject to adulteration

Mahendran R et al. Salvia divinorum: an overview of the usage, misuse, and addiction processes Asia-Pacific Psychiatry. 2015;8:23-31
Thornton MD et al. Bath salts and other emerging toxins. Pediatr Emer Care. 2014;30:47-55:123-134

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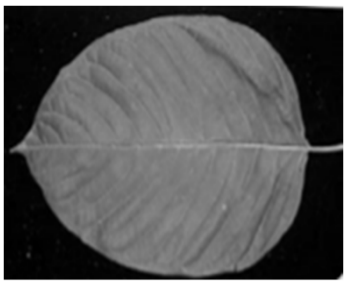

Kratom

https://www.dea.gov/pr/multimedia-library/publications/drug_of_abuse.pdf

PAINWEEK

Kratom: History

- Active compound is mitragynine, an alkaloid, found in a tropical tree native to Southeast Asia
- Opioid-like properties
- Nonprescription herbal available on the Internet and in head shops
- Typically sold as leaves, powder, extract, capsule, pellet, or gum
- Kratom can be smoked, chewed, or drank as a tea
- 10 fold increase in U.S. poison center calls from 2010-2015

Rech MA et al. New drugs of abuse. Pharmacother. 2015;35(2):189-197
Cinosi E et al. Following "the roots" of kratom: the evolution of an enhancer from a traditional use to increase work and productivity in Southeast Asia to a recreational drug in western countries. Biomed Res Internat. 2015;1-11
https://www.dea.gov/pr/multimedia-library/publications/drug_of_abuse.pdf

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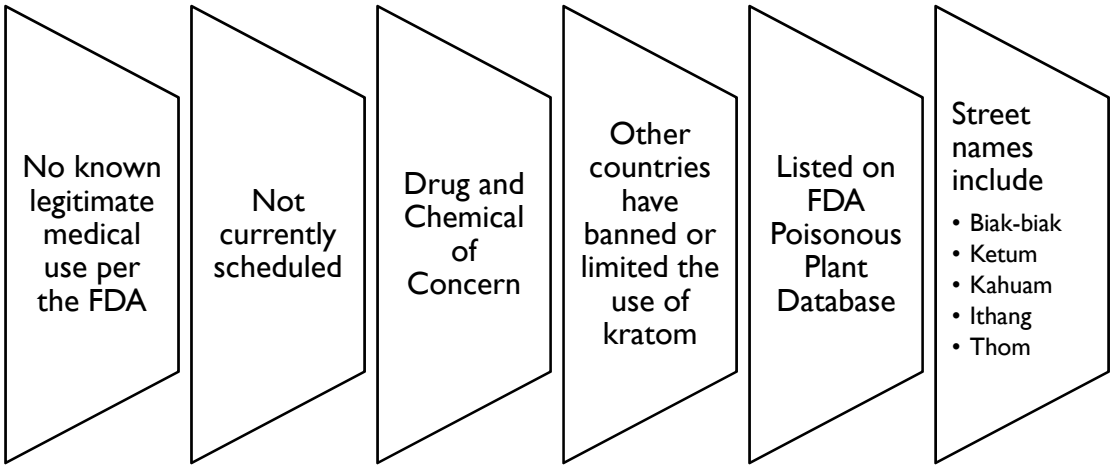
Kratom: Legality



Rech MA et al. New drugs of abuse. Pharmacother. 2015;35(2):189-197
Ulbrich C et al. An evidence-based systematic review of kratom (Mitragyna speciosa). J Dietary Suppl. 2013;10(2):152-170
partment of Justice. Drug Enforcement Agency. Federal Register. https://s3.amazonaws.com/public-inspection.federalregister.gov/2016-20803.pdf. (Accessed 2016 Aug 30)
https://www.dea.gov/pr/multimedia-library/publications/drug_of_abuse.pdf

Statement from FDA Commissioner 11/14/17

- "Concerned about harmful unapproved products"
- "similar effects to narcotics like opioids, and carries similar risks of abuse, addiction and in some cases, death"
- U.S. poison control center calls increased 10-fold from 2010 to 2015
- 36 deaths reported
- Must go through regulatory process before marketing therapeutic uses
- Prevent shipments of kratom from entering U.S.

https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm584970.htm

Statement from FDA Commissioner 2/6/18

- PHASE (Public Health Assessment via Structural Evaluation) model
  - 22/25 compounds in kratom bind to mu-opioid receptors
  - Strength of bond similar to controlled opioids
  - Affect body like opioids
- 44 reported deaths
- Used in combination with illicit drugs, prescription opioids, benzodiazepines, loperamide
- "Kratom should no be used to treat medication conditions, nor should it be used as an alterative to prescription opioids"
- "No evidence to indicate that kratom is safe and effective for any medical use"

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https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm595622.htm

Kratom: Uses

- Reduce musculoskeletal pain and to increase energy, appetite, and sexual desire
- Used for the treatment of hypertension, diarrhea, and cough
- In Western countries, increasing use for self-treatment of pain and for opioid withdrawal
- Substitute for heroin

Rech MA et al. New drugs of abuse. Pharmacother. 2015;35(2):189-197

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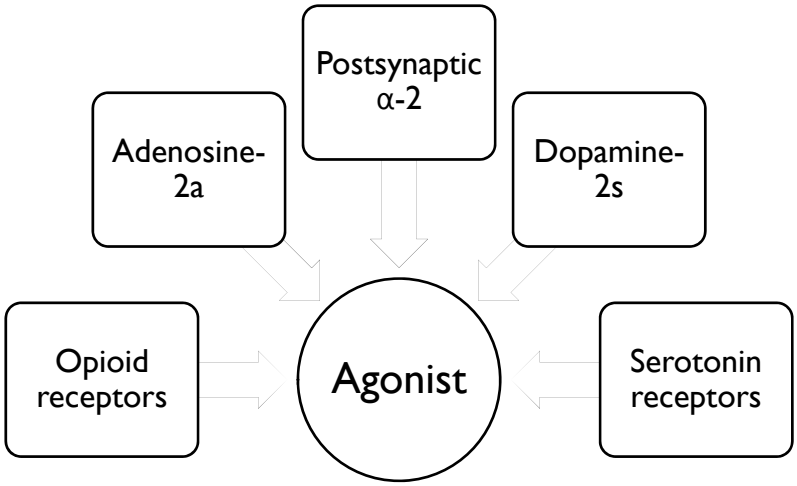
Kratom: Pharmacology



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Rech MA et al. New drugs of abuse. Pharmacother. 2015;35(2):189-197

Kratom: Pharmacokinetics

- Onset: 5-10 minutes
- Duration: 2-5 hours
- Dosing
  - 1-5 g: mild stimulant effects
  - 5-15 g: opioid-like effects
- Inhibits CYP3A4, CYP2D6, CYP1A2

Rech MA et al. New drugs of abuse. Pharmacother. 2015;35(2):189-197
Ulbrich C et al. An evidence-based systematic review of kratom (Mitragyna speciosa). J Dietary Suppl. 2013;10(2):152-170

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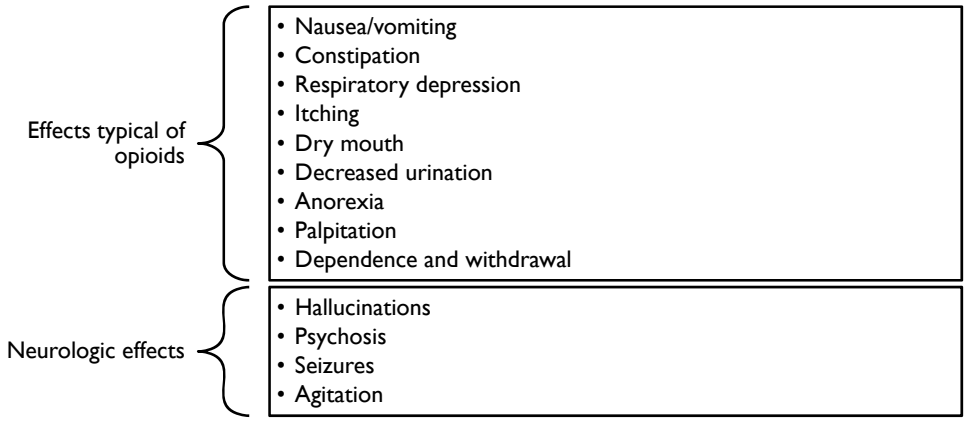
Kratom: Adverse Effects



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Rech MA et al. New drugs of abuse. Pharmacother. 2015;35(2):189-197
Singh D et al. Kratom (mitragyna speciose) dependence, withdrawal symptoms, and craving in regular users. Drug Alcoohol Dependence. 2014;139:132-137

FDA MedWatch Report

- 25 yo male began using kratom and "developed skin rashes, losing hair, vomiting, loss of appetite, and irritability."
- He passed away during his sleep Feb 1st. There was vomit next to him in bed.
- "Under the impression from false marketing and internet messages that it was a safe alternative supplement. He has never been a hard drug user so he was not using Kratom as an alternative drug like many Kratom advocates."
- "We strongly believe warning labels of the side effects and suggested dosage regulation should be provided to consumers at the very least."
- "As we are currently seeing Kratom sold next to candy at the gas station, at bars, restaurants, coffeeshops etc. I would like to do as much as I can to increase risk awareness and truth behind this rapidly growing and very trendy drug"

PAINWEEK

https://www.fda.gov/downloads/aboutfda/centersoffices/officeoffoods/cfsan/cfsanfoiaelectronicreadingroom/ucm588952.pdf

Kratom: Serious Toxicities and Fatalities

Serious toxicity is rare
- Higher doses (>15 g)
- Coingestants typically involved

Chronic, high doses (14-21 g/day x 14 days)
- Jaundice
- Pruritis
- Severe hypothyroidism

Fatalities
- "krypton" – kratom + O-desmethyltramadol
- Pulmonary edema found on autopsies suggesting respiratory depression

Rech MA et al. New drugs of abuse. Pharmacother. 2015;35(2):189-197
Ulbrich C et al. An evidence-based systematic review of kratom (Mitragyna speciosa). J Dietary Suppl. 2013;10(2):152-170
[illegible]nd R et al. Unintentional fatal intoxication with mitragynine and O-desmethyltramadol from the herbal blend krypton. J Analytical Toxicol. 2011;35:242-247
Anwar M, Law R, Schier J. Kratom (Mitragyna species) exposures reported to poison centers – United States, 2010-2015. MMWR. 2016;65(29):748-749

Kratom: Detection

- Not detected by opiate immunoassay
- Detected via LCMS

Neerman MF et al. A drug fatality involving kratom
J Forensic Sci. 2013; 58(S1):S278-S278

PAINWEEK

Kratom: Treatment

Addiction	Overdose		
May respond to opioid replacement therapy	Similar to treatment of an opioid overdose	Mixed data on the use of naloxone in animal studies	Consider use of naloxone

PAINWEEK

Rech MA et al. New drugs of abuse. Pharmacother. 2015;35(2):189-197

Loperamide: Poor Man's Methadone

PAINWEEK

Loperamide: Background

Available over-the-counter (OTC)

Prior to 1988 listed as Schedule V in CSA

Inhibits intestinal peristalsis

- Mu-opioid receptor agonist
- Calcium channel inhibitor
- Calmodulin inhibition
- Paracellular permeability reduction

Thought to have limited abuse potential

- Poor systemic bioavailability (0.3%)
- CNS penetration
- P-glycoprotein (p-gp) efflux

PAINWEEK

Eggleston W et al. Loperamide abuse associated with cardiac dysrhythmia and death. Ann Emerg Med. 2016; 1-4
Dierksen J et al. Poor man's methadone: a case report of loperamide toxicity: Am J Forensic Med Pathol. 2015;36:268-270

Dosing

- Therapeutic doses:
  - Adults and children 12 years and over
    - Caplets: 2 caplets after the first loose stool; 1 caplet after each subsequent loose stool; but no more than 4 caplets in 24 hours
    - Liquid: 30 mL (6 tsp) after the first loose stool; 15 mL (3 tsp) after each subsequent loose stool; but no more than 60 mL (12 tsp) in 24 hours
- Abuse:
  - Supratherapeutic doses 30-200 mg higher
  - Concomitant use of p-gp inhibitor

Imodium® A-D Diarrhea Caplets and Liquid Treatment product website. Available at: http://www.imodium.com/products-imodium-a-d. Accessed June 9, 2016
Eggleston W et al. Loperamide abuse associated with cardiac dysrhythmia and death. Ann Emerg Med. 2016; 1-4
Dierksen J et al. Poor man's methadone: a case report of loperamide toxicity: Am J Forensic Med Pathol. 2015;36:268-270
Spinner HL et al. Ventricular tachycardia associated with high-dose chronic loperamide use. Pharmacother. 2015;35(2):234-238

PAINWEEK

Loperamide: Abuse

- Increasing reports of abuse
- 71% increase in reports of intentional loperamide exposures from 2011-2014
- Potential for abuse
  - Accessible
  - Low cost
  - OTC
  - Lack of social stigma
  - Increasing legislation and regulations with opioids
- Reasons for abuse
  - Prevent opioid withdrawal
  - Euphoria

Eggleston W et al. Loperamide abuse associated with cardiac dysrhythmia and death. Ann Emerg Med. 2016; 1-4

PAINWEEK

FDA MedWatch: Loperamide (Imodium) Drug Safety Communication: Serious Heart Problems With High Doses From Abuse and Misuse

- RECOMMENDATION: Health care professionals should be aware that use of higher than recommended doses of loperamide can result in serious cardiac adverse events
  - Possible cause of unexplained cardiac events including QT interval prolongation, Torsades de Pointes or other ventricular arrhythmias, syncope, and cardiac arrest
- In cases of abuse, individuals often use other drugs together with loperamide in attempts to increase its absorption and penetration across the blood-brain barrier, inhibit loperamide metabolism, and enhance its euphoric effects
- In the 39 years from when loperamide was first approved in 1976 through 2015, FDA received reports (through FDA Adverse Event Reporting System) of 48 cases of serious heart problems associated with use of loperamide
  - Thirty-one of these cases resulted in hospitalizations, and 10 patients died. More than half of the 48 cases were reported after 2010

FDA Safety Communication: FDA warns about serious heart problems with high doses of the antidiarrheal medicine loperamide (Imodium), including from abuse and misuse.
Available at: http://www.fda.gov/Drugs/DrugSafety/ucm504617.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery. Last accessed June 9, 2016

PAINWEEK

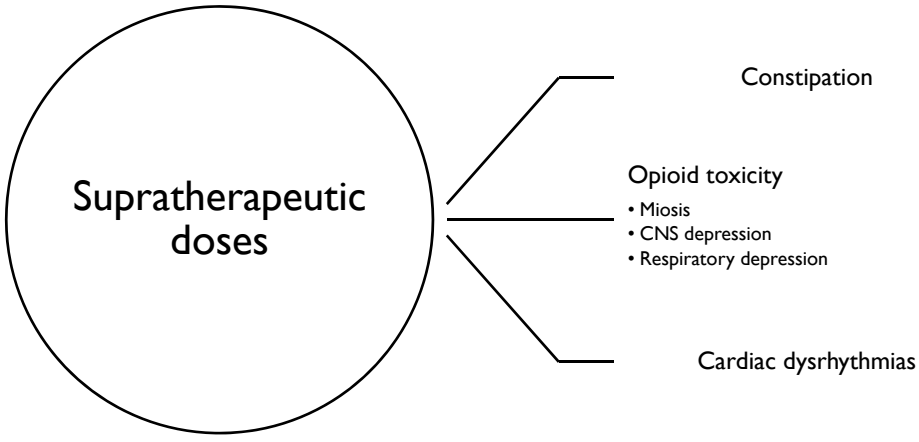
Loperamide: ADE

- Therapeutic doses
  - Usually mild
    - Nausea
    - Constipation
    - Drowsiness
    - Headache
  - Does not lead to withdrawal with administration of naloxone
  - Serious
    - Toxic megacolon
    - Pancreatitis
    - Gastroenteritis

PAINWEEK

Eggleston W et al. Loperamide abuse associated with cardiac dysrhythmia and death. Ann Emerg Med. 2016; 1-4

Loperamide: ADE (cont'd)



PAINWEEK

Eggleston W et al. Loperamide abuse associated with cardiac dysrhythmia and death. Ann Emerg Med. 2016; 1-4
Dierksen J et al. Poor man's methadone: a case report of loperamide toxicity: Am J Forensic Med Pathol. 2015;36:268-270

Loperamide: Detection

- Not detected via opiate immunoassay
- Able to be detected via GCMS/LCMS

Eggleston W et al. Loperamide abuse associated with cardiac dysrhythmia and death Ann Emerg Med. 2016; 1-4

Dierksen J et al. Poor man's methadone: a case report of loperamide toxicity: Am J Forensic Med Pathol. 2015;36:268-270

PAINWEEK

Loperamide: Treatment

- CPR and ACLS first-line for cardiopulmonary arrest
- Treatment of ventricular dysrhythmias
- Naloxone is reasonable from animal and human data
- Report to FDA MedWatch

Eggleston W et al. Loperamide abuse associated with cardiac dysrhythmia and death. Ann Emerg Med. 2016; 1-4

PAINWEEK

FDA Drug Safety Communication 1/30/18

- FDA working with manufacturers of loperamide
- Package loperamide in blister packs or other single dose packaging
- Limit number of doses per package

PAINWEEK ttps://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm594403.htm

"Oklahoma man wants over-the-counter drug that killed his son to be regulated" 12/121/17

- 29 yo male with 15 year hx of substance use died of an overdose
- Toxicology report: loperamide
- Cause of death: "acute loperamide toxicity"
- "Just slide it in with Sudafed and, the second they do that, it will save a life. That minute that the kid can't go in there and get a box full of Imodium, he's going to live that day." Joel Hild (father of decedent)
- Possible bill proposal from State representative Cyndi Munson

PAINWEEK http://kfor.com/2017/12/12/oklahoma-man-claims-that-over-the-counter-drug-killed-his-son/

Bath Salts: Synthetic Cathinones

https://www.dea.gov/pr/multimedia-library/publications/drug_of_abuse.pdf

PAINWEEK

In the News

- **"**Two Ocean County women charged with having bath salts, heroin" (New Jersey 1/26/18)
- "3 accused of selling bath salts in Madison Co" (New York 1/25/18)
- "Police, treatment professionals see 'resurgence' of meth, bath salts" (West Virginia 9/5/17)
- "Florida deputies discover bath salts disguised as candy" (Florida 10/27/17)

http://www.uticaod.com/news/20180125/3-accused-of-selling-bath-salts-in-madison-co
http://www.pressofatlanticcity.com/news/two-ocean-county-women-found-in-possession-of-bath-salts/article_838edfea-3e48-579d-aac2-70743a85d3f8.html
http://www.wdtv.com/content/news/Police-treatment-professionals-see-resurgence-of-meth-bath-
http://kfor.com/2017/10/27/florida-deputies-discover-bath-salts-disguised-as-candy/salts-442809223.html

PAINWEEK

Bath Salts: Background

- Novel synthetic stimulant
- Cathinone derivatives
- Odorless, white/tan/gray powder or fine crystals
- $25-75 per 0.5 g package
- Marketed as “legal” high
- Sold in head shops, Internet, gas stations
- Labeled not for human consumption or plant food

Jerry J et al. Synthetic legal intoxicating drugs: the emerging 'incense' and 'bath salt' phenomenon. Cleve Clin J Med. 2012;79(4):258-264
Zawilska JB, et al. Designer cathinones – an emerging class of novel recreational drugs. Forens Sci Internat. 2012;231:42-53
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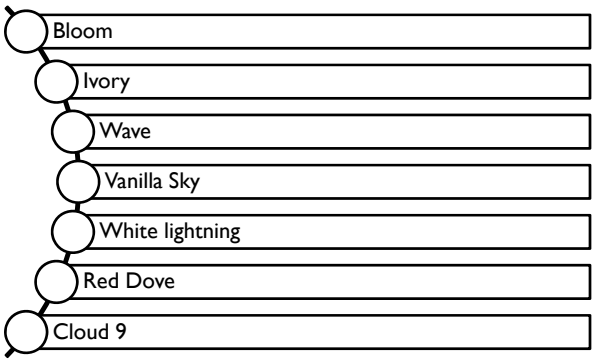
Miotto K et al. Clinical and pharmacological aspects of bath salt use: a review of the literature and case reports. Drug Alcohol Depend. 2013;132:1-12

Bath Salts: Street Names



Prosser JM et al. The toxicology of bath salts: a review of synthetic cathinones. J Med Toxicol. 2012;8:33-42
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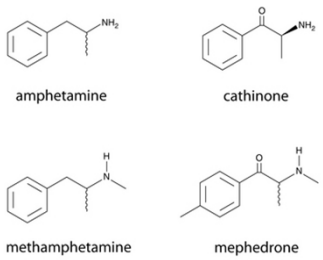
Cathinone

- Chemical name: (S)-2-amino-1-phenyl-1-propanone
- Schedule I
- Beta-keto analog of amphetamine
- CNS stimulant
- Found in leaves of *Catha edulis* (Khat) plant
  - Chewing of leaves for stimulant effects popular in Middle Eastern countries
  - Must chew fresh leaves



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Rech MA> New drusg of abuse. Pharmacother. 2015;35(2):189-197
Image:http://www.bing.com/images/search?q=cathinone+amphetamine+chemical+structure&FORM=HDRSC2#view=detail&id=6BA1892785464094749 6E954A35D1B354780EE73

PAINWEEK

Synthetic Cathinones

- Butylone
- Dimethylcathinone
- Ethcathinone
- Ethylone
- 3-Fluormethcathinone
- 4-Fluromethcathinone
- **Mephedrone**
- Methcathinone
- Methedrone
- **Methylenedioxy-pyrovalerone (MDPV)**
- **Methylone**
- Pyrovalerone

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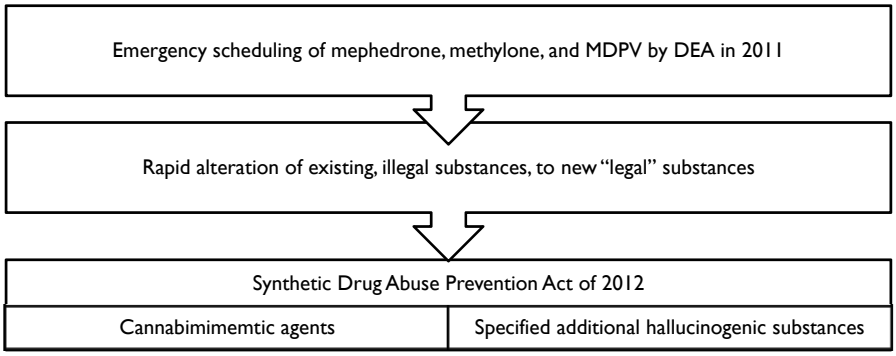
Jerry J et al. Synthetic legal intoxicating drugs: the emerging 'incense' and 'bath salt' phenomenon Cleve Clin J Med. 2012;79(4):258-264
Gunderson EW et al. Substituted cathinone products: a new trend in "bath salts" and other designer stimulant drug use. J Addict Med. 2013;7(3):153-162

PAINWEEK

Bath Salts: Legality



PAINWEEK

Thornton et al. Bath salts and other emerging toxins. Pediatr Emer Care. 2014;30:47-55

Bath Salts: Prevalence

- Primarily used in young men
  - Mean age mid to late 20s
  - Ranging from teens to 40s
- Exposures reported in children as young as 6
- First reports in 2010, increasing in 2011, and peaking in 2012
- 0.9% annual prevalence in grades 8, 10, and 12
- Most samples from DEA National Forensic Laboratory Information System
  - South 57%
  - Midwest 25%
  - Northeast 16%
  - West 2%

PAINWEEK

Gunderson EW et al. Substituted cathinone products: a new trend in "bath salts" and other designer stimulant drug use. J Addict Med. 2013;7(3):153-162
Thornton et al. Bath salts and other emerging toxins. Pediatr Emer Care. 2014;30:47-55

Bath Salts: Patterns of Use

- Frequency: daily to episodic
- Routes
  - Most often snorted or ingested orally
  - "Bombing"
  - "Keying"
  - Others
  - Users may combine or switch routes during binge
- Often used in combination with other drugs

PaiNweek

Prosser JM et al.The toxicology of bath salts: a review of synthetic cathinones. J Med Toxicol. 2012;8:33-42
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Miotto K, Striebel J, Cho AK, Wang C. Clinical and pharmacological aspects of bath salt use: a review of the literature and case reports. Drug Alcohol Depend. 2013;132:1-12

Bath Salts: Dosing

- No data on purity
- Generally 1 mg-1g
- Redosing during a session is common
- MDPV
  - 5-30 mg per ingestion
  - > 200 mg in a session
- Mephedrone
  - Snorted: 25-75 mg
  - PO: 150-250 mg
- Commonly used with other substances to increase desired effects and decrease undesired effects

PaiNweek

Coppola M et al. Synthetic cathinones: chemistry, pharmacology, and toxicology of a new class of designer drugs of abuse markets as 'bath salts" or "plant food."Toxicol Letters. 2012;211:144-149
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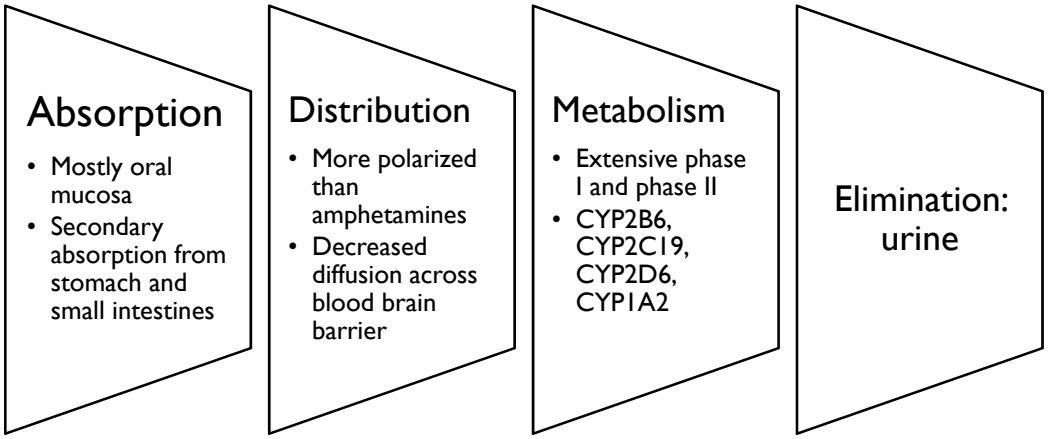
Bath Salts: Pharmacokinetics



PaiNweek

Capriola M. Synthetic cathinone abuse. Clin Pharmacol Adv Applic. 2013;5:109-115
Zawilska JB et al. Designer cathinones – an emerging class of novel recreational drugs. Forens Sci Internat. 2012;231:42-53

Bath Salts: Pharmacokinetics (cont'd)

- **Mephedrone**
  - Snorting
    - Onset: 10-20 min
    - Duration: 1-2h
  - PO
    - Onset: 15-45 min
    - Duration: 2-4h
  - IV
    - Onset: 10-15 min
    - Duration: 30 min
- MDPV
  - Onset: 60-90 min
  - Duration: 6-8h

PaiNweek

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Bath Salts: Desired Effects

- Sociability
- Energy
- Libido/sexual performance
- Capacity of work
- Euphoria
- Empathy

Coppola M et al Synthetic cathinones: chemistry, pharmacology, and toxicology of a new class of designer drugs of abuse markets as 'bath salts" or "plant food."Toxicol Letters. 2012;211:144-149

PaiNweek

Bath Salts: Common Presenting Symptoms

Physical

- Diaphoresis
- Hyperreflexia
- Hypertension
- Hyperthermia
- Jaw tension
- Mydriasis
- Myocardial infarction
- Nausea/vomiting
- Palpitations
- Respiratory distress
- Seizures
- Tachycardia
- Hyponatremia

Neuropsychiatric

- Aggression
- Agitation
- Anxiety
- Combative behavior
- Dysphoria
- Hallucinations
- Insomnia
- Paranoia
- Psychosis
- Suicidal thoughts

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PaiNweek

Bath Salts: Objective Findings During Intoxication

- Decreased renal function
- Acidosis
- Elevated creatinine kinase or troponins
- ECG changes
- Leukocytosis
- Increased LFTs
- Electrolyte abnormalities

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PAINWEEK

Bath Salts: Detection

- Routine toxicology tests ineffective
- May lead to false positive on methamphetamine screen
- MDPV may lead to false positive on PCP
- Samples
  - Blood, urine, stomach contents
  - Hair analysis
- Techniques
  - Gas chromatography-mass spectrometry
  - Liquid chromatography-mass spectrometry

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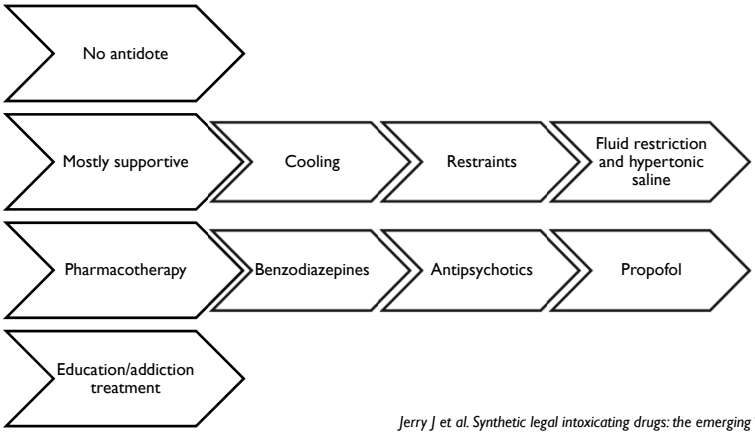
PAINWEEK

Bath Salts: Treatment of Intoxication



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PAINWEEK

Bath Salts: Dependence and Withdrawal

- Tolerance may occur following repeated dosing
- Dependence less likely than amphetamines or cocaine
- Dependence may occur with chronic high doses
- Withdrawal syndrome
  - –Depression
  - –Anhedonia
  - –Anxiety
  - –Sleep disorders
  - –Craving

Coppola M et al. Synthetic cathinones: chemistry, pharmacology, and toxicology of a new class of designer drugs of abuse markets as 'bath salts" or "plant food."Toxicol Letters. 2012;211:144-149
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PAINWEEK

Flakka

- α-pyrrolidinovalerophenone (α-PVP) or gravel
- Temporarily listed as Schedule I
- Similar in structure to cathinone
- Effects
  - Excitation, delirium, hyperstimulation, paranoia, hallucination
  - Kidney damage and failure
  - Aggression, self-injury, suicidal tendencies, and heart attacks also common

Wood MR et al. The dangerous new synthetic drug α-PVP as the hydrated chloride salt of α-pyrrolidinopentiophenone hydrochloride 0.786-hydrate. Acta Chrst. 2016;C72:48-51

Drug Enforcement Administration, Department of Justice. Schedules of controlled substances: extension of temporary placement of 20 synthetic cathinones I n Schedule I of the Controlled Substances Act. Final order. Fed Reigis.2016;81(43):11429-11411

PAINWEEK

Synthetic Cannabinoids: Spice

PAINWEEK

https://www.dea.gov/pr/multimedia-library/publications/drug_of_abuse.pdf

In the News

- "Traffic stop leads to arrest of 5 Madison County residents on drug charges" (Indiana 1/24/18)
  - Meth, heroin, pot, spice
- "Synthetic marijuana linked to multiple drug overdoses in CT" (Connecticutt 1/26/18)
- "Thomasville man arrested on 'spice' drug charges" (Georgia 12/22/17)

http://www.kfvs12.com/story/37357699/synthetic-drugs-linked-to-multiple-drug-overdoses-in-ct
http://www.heraldbulletin.com/news/local_news/traffic-stop-leads-to-arrest-of-madison-county-residents-on/article_e45269e6-8a2c-5ff9-830a-9460671548c3.html
http://www.timesenterprise.com/news/local_news/thomasville-man-arrested-on-spice-drug-charge/article_8fbb5d8b-9014-54c2-b4fc-b0fe7fccafcd.html

PAINWEEK

Spice: Background

- Known as fragrance, potpourri, herbal incense, K2, Spice
- Many listed as Schedule I controlled substances
- Synthesized in lab and dissolved in solvent
- Sprayed onto plant material and allow for solvent to evaporate
- Packaged as loose leaves or rolled
- Labeled "not for human consumption"
- Available in head shops, convenience stores, Internet
- Manufactured in Asia and smuggled into U.S.
- 3 g bag of K2 $30-$50

PAINWEEK

Kerston BP et al. Toxicology and management of novel psychoactive drugs. J Pharmacy Practice. 2015;28(1):50-65
Rosenbaum CD et al. Here today, gone tomorrow…and back again? J Med Toxicol.2012;8:15-32
Musselman ME. "Not for human consumption;" a review of emerging designer drugs. Pharmacother. 2014;34(7):745-757
https://www.dea.gov/pr/multimedia-library/publications/drug_of_abuse.pdf

Spice: Use

- Smoked via various methods
- Primarily used by white males in teens and 20s
- 80% of K2 users have also used marijuana at least once

Kerston BP et al.Toxicology and management of novel psychoactive drugs. J Pharmacy Practice. 2015;28(1):50-65

PAINWEEK

Spice: Pharmacology

- Full agonists of
  - Cannabinoid 1 (CB1) receptors located in brain
  - Cannabinoid 2 (CB2) receptors located on immune cells
- Activity at presynaptic CB1 receptors causes the release of inhibitory and excitatory neurotransmitters
- Leads to CNS effects

Kerston BP et al.Toxicology and management of novel psychoactive drugs. J Pharmacy Practice. 2015;28(1):50-65
Musselman ME."Not for human consumption;" a review of emerging designer drugs. Pharmacother. 2014;34(7):745-757

PAINWEEK

Spice: Pharmacokinetics

- Onset
  - Minutes to hours
  - Varies on product, amount, and route
- Duration about 1-3 h
- Metabolized by CYP2C9 and/or CYP1A2
- Excreted in the urine

Kerston BP et al. Toxicology and management of novel psychoactive drugs. J Pharmacy Practice. 2015;28(1):50-65

PAINWEEK

Spice: Desired Effects

- Increased energy
- Focus and creativity
- Euphoria
- Dream-like state
- Relaxation and anxiolysis
- Sensory, perception, and motor alterations
- Appetite stimulation

PAINWEEK

Kerston BP et al. Toxicology and management of novel psychoactive drugs. J Pharmacy Practice. 2015;28(1):50-65

Spice: Undesired Effects

Common	Severe
• Anxiety • Agitation • Irritability • Tachycardia • Hallucinations • Nausea/vomiting • Hypertension • Confusion • Xerostomia • Acute ischemic stroke • Tachycardia	• Psychosis • Seizures • Acute kidney injury • Palpitations • Hyperthermia • Rhabdomyolysis • Death • Suicidal ideation

Kerston BP et al. Toxicology and management of novel psychoactive drugs. J Pharmacy Practice. 2015;28(1):50-65
Musselman ME. "Not for human consumption;" a review of emerging designer drugs. Pharmacother. 2014;34(7):745-757
Thornton et al. Bath salts and other emerging toxins. Pediatr Emer Care. 2014;30:47-55

PAINWEEK

Spice: Withdrawal Syndrome

- May last a few days
- Symptoms
  - Headaches
  - Insomnia
  - Anxiety
  - Restlessness
  - Irritability
  - Somatic pain
  - Coughing, shortness of breath
  - Nausea

PAINWEEK

Kerston BP et al. Toxicology and management of novel psychoactive drugs. J Pharmacy Practice. 2015;28(1):50-65

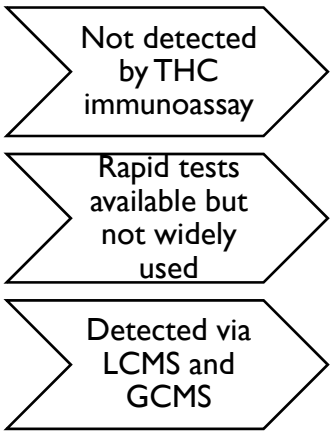
Spice: Treatment

- No antidote
- Supportive care and monitoring
  - IV fluids
  - Benzodiazepines for agitation, catatonia, and severe anxiety
  - Antipsychotics for psychosis and hallucinations
  - Anti-emetics
  - Rarely is intubation needed
- Consider coingestants

PaiNweek

Kerston BP et al.Toxicology and management of novel psychoactive drugs. J Pharmacy Practice. 2015;28(1):50-65
Musselman ME."Not for human consumption;" a review of emerging designer drugs. Pharmacother. 2014;34(7):745-757
Thornton et al. Bath salts and other emerging toxins. Pediatr Emer Care. 2014;30:47-55

Spice: Detection



PaiNweek

Kerston BP et al.Toxicology and management of novel psychoactive drugs. J Pharmacy Practice. 2015;28(1):50-65
Musselman ME."Not for human consumption;" a review of emerging designer drugs. Pharmacother. 2014;34(7):745-757

Question #1

BT is a 55 yo male who presents to the emergency room with signs of opioid withdrawal and necrotic lesions on his left arm. A UDS is obtained with the following results. After providing the sample, he admits to using "krokodil." What would you expect his UDS results to be assuming this is the only substance he is using?

A. (-) for all substances
B. (+) Opiates
C. (+) Amphetamines
D. (+) Oxycodone

PAINWEEK

Question #2

DK is a 61 yo male on tramadol 50 mg PO TID prn for chronic low back pain which provides analgesic and functional benefit. The patient states that he recently started drinking kratom tea. What would you expect an immunoassay drugs of abuse UDS panel to show?

A. (+) Opiates
B. (-) negative for all substances
C. (+) Oxycodone
D. (+) PCP

PAINWEEK

Question #3

- NB is a 36 yo male presenting to the ED with an opioid overdose reversed by paramedics with 6 doses of naloxone. A UDM is obtained. What substance most likely explains the results?

A. Heroin
B. Morphine
C. Hydrocodone
D. Fentanyl

Substance	Result
Opiates	Negative
Oxycodone	Negative
Methadone	Negative
Barbiturates	Negative
Benzodiazepines	Negative
PCP	Negative
THC	Negative
Cocaine	Negative
Amphetamines	Negative

PAINWEEK

Conclusion

- Rapidly changing molecules to avoid the law
- New use of substances due to reduced availability of prescription opioids
- Difficult to detect with standard urine drug testing
- Substances not necessarily “safe” and may cause severe reactions
- Patients may seek treatment which is typically supportive care

PAINWEEK

3 Things for Monday

- Give patients at risk for overdose naloxone and education
- Realize that UDM has limitations for detecting certain substances
- Refer patients for treatment of substance use disorders

PainWeek

PainWeek®

Not for Human Consumption: New Drugs of Abuse and Their Detection

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