

Psychoactive Substances Update: Kratom, Cannabinoids, Fentanyl & More

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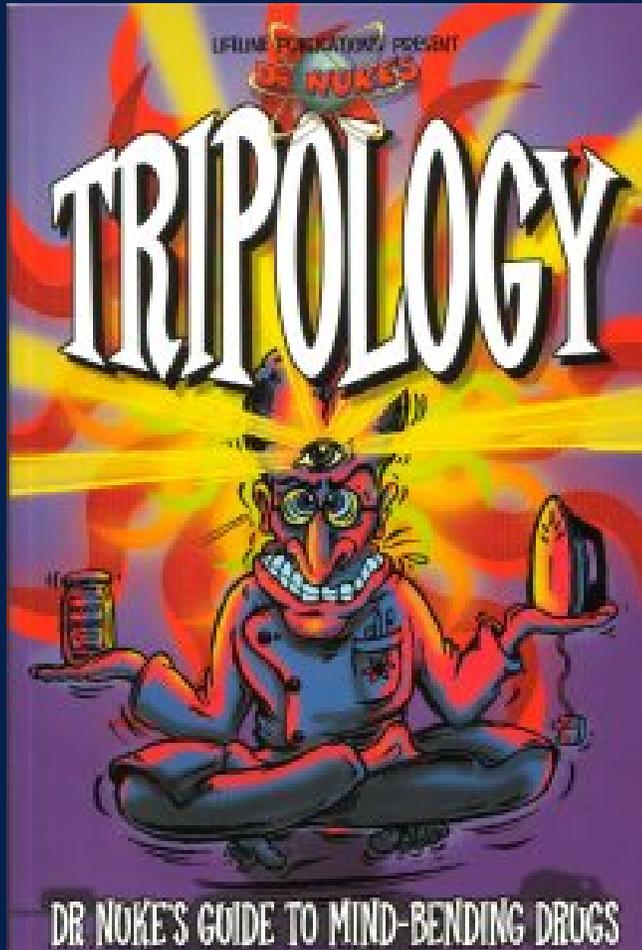
Disclosure Information (Required)

- ◆ Michael Weaver, MD, DFASAM
 - ◆ No Disclosures
- ◆ John Hopper, MD, DFASAM
 - ◆ No Disclosures

Learning Objectives

- ◆ Identify emerging psychoactive substances, including kratom, synthetic cannabinoids, nonpharmaceutical fentanyls, gabapentin, and others.
- ◆ Recognize clinical clues to intoxication with emerging natural and synthetic substances, and ways to differentiate from other drug use.
- ◆ Discuss treatment of medical and psychiatric complications resulting from use of emerging substances of abuse.

New Psychoactive Substances



- ◆ Variety of compounds that change with time to avoid detection and legal authorities
- ◆ Not detected on current drug screens
- ◆ Many different 'brand' names
- ◆ Contents and concentration vary widely

Case

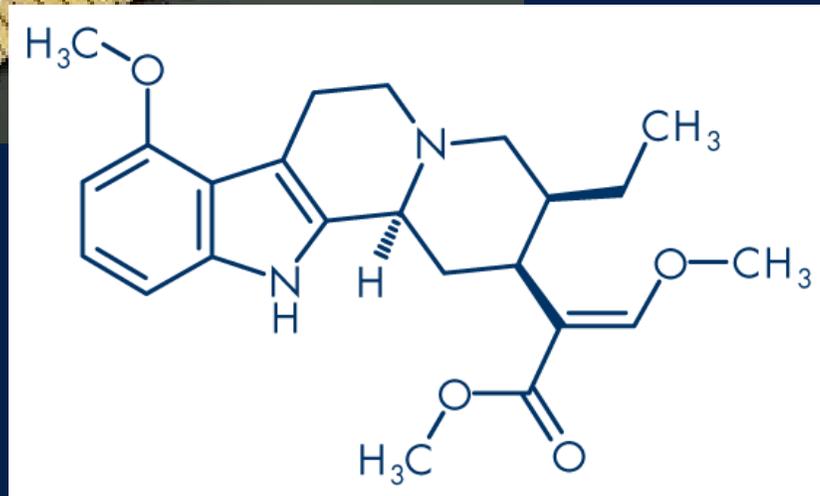
- ◆ 59 y/o man with past use of cannabis in 20s, heavy alcohol use in 40s, illegal methylphenidate use in 40s, and hydrocodone abuse until inpatient detox 4 years ago
- ◆ Past psychiatric hx of GAD for which he is on SSI Disability
- ◆ He takes kratom 500 mg capsules 64 TID (192 caps/d, or 96 grams/day) daily for several months since his mother died
- ◆ When he stops, he has significant worsening of depression with occasional suicidal thoughts, lethargy, and mild diarrhea; the depression is bad enough for him to resume kratom use
- ◆ He presents for treatment of problems from kratom use

What is kratom?

- ◆ Derivative of *Mitragyna speciosa* (kratom) tropical tree
 - ◆ Native to Indonesia, Malaysia, and Thailand
- ◆ Leaves used medicinally in Southeast Asia
 - ◆ Stimulatory effects (similar to caffeine) at low doses (1-5 grams)
 - ◆ Analgesic and sedative effects at higher doses (6-15 grams)



Pharmacology



- ◆ Main psychoactive compound: **mitragynine**
- ◆ 40 structurally similar alkaloids, including 7-Hydroxymitragynine (7-OHM)
- ◆ Agonists at multiple opioid receptors: mu, kappa, delta
- ◆ 26% lower intensity than morphine (partial agonist)
 - ◆ Not as strong a euphoric high compared to most opioids
 - ◆ Much less likely to cause fatal respiratory depression

Kratom Availability

- ◆ Widely available in US
 - ◆ Regulated as a dietary supplement by the FDA
 - ◆ Not considered a controlled substance by the DEA
 - ◆ Federally listed as a “drug of concern”
 - ◆ Several states have listed as a controlled substance
- ◆ First reports of importation into US in 1980s
- ◆ Marketed as “natural high” or opioid substitute
- ◆ Sold on the Internet
 - ◆ >600 vendors sell to US
 - ◆ Price of 99 cents per gram
 - ◆ Easy access to wide variety of unregulated and untested products
 - ◆ Patchwork of state and local bans ineffective at restricting access
 - ◆ Vendors do not abide by bans



Kratom Use

- ◆ Consumed as
 - ◆ Chew leaves
 - ◆ Tea (brewed from leaves)
 - ◆ Powder made of dried leaves
 - ◆ Powder in capsules
 - ◆ Mix into food
 - ◆ Gum or extract
 - ◆ Smoke leaves
- ◆ Lifetime prevalence of 6% in nationally representative sample of US adults in 2020
- ◆ Mostly male, age 25-44
- ◆ Kratom users twice as likely to also use nicotine and cannabis
 - ◆ Higher use of illicit drugs
- ◆ 43% use to bypass drug test
 - ◆ Previous incarceration
 - ◆ Previous SUD treatment



Adverse effects

- ◆ Agitation
- ◆ CNS depression
- ◆ Altered mental status
- ◆ Tachycardia
- ◆ Seizures
- ◆ Death
 - ◆ May also be from other compounds combined with kratom
- ◆ Tolerance
- ◆ Withdrawal syndrome



Kratom withdrawal

- ◆ Withdrawal syndrome
 - ◆ Similar to opioid withdrawal
 - ◆ Mostly subjective symptoms
 - ◆ Chills
 - ◆ Nausea/vomiting/diarrhea
 - ◆ Myalgia
 - ◆ Rhinorrhea
 - ◆ Anxiety and restlessness
 - ◆ May persist longer than typical opioid withdrawal (up to 3 months)
- ◆ Treatment
 - ◆ Buprenorphine/naloxone used most often
 - ◆ Mitragynine is partial mu opioid agonist like buprenorphine
 - ◆ Abstain from kratom for 24 hours prior to induction
 - ◆ Monitor with COWS
 - ◆ Maintenance doses of 16-24 mg daily in divided doses (BID-QID)
 - ◆ Similar to dosing for other opioids

35 year old woman with ADHD

- ◆ Arrives to the ED with palpitations, breathing fast, insomnia.
- ◆ Using fentanyl for about 3 months.
- ◆ Usually snorts $\frac{1}{4}$ gram; last use 36 hours ago.
- ◆ Took 2 buprenorphine/naloxone 8 mg strips when she felt “drug sick”, over 30 hours after last fentanyl.
- ◆ About 20 minutes after taking the “Subs” she felt terrible and presented to ED about 40 minutes later.
- ◆ She reports being prescribed dextroamphetamine for 4 years and started trading it for Subs when she can’t get “fetty”



35 year old woman with ADHD, cont.

- ◆ Past peak symptoms at the time of ED assessment
- ◆ Received 2 mg/0.5 mg sublingual buprenorphine/naloxone at recommendation of addiction medicine consult
- ◆ Felt better after about 30 minutes
- ◆ Subsequently received additional 8 mg/2 mg buprenorphine/naloxone
- ◆ Patient had appointment for IOP the next day, was offered follow-up with addiction medicine but declined



Non-Pharmaceutical Fentanyl (NPF)

- ◆ 1979 – Overdose deaths in Orange County CA attributed to alpha-methyl-fentanyl (China White – synthetic fentanyl)
- ◆ Various NPF analogs available, some scheduled by DEA
- ◆ Users may seek out “branded” products: “Apache”, “China Girl”, “Dance Fever”, “Goodfella”, “Jackpot”, “Murder 8”, “TNT”, “Tango and Cash”, “Drop Dead”, “Lethal Injection”, “Get High or Die Trying”
- ◆ NPF in counterfeit opioid pills; ingestion may result in death.
- ◆ Lipophilicity may account for precipitated withdrawal from buprenorphine

32 year old man with hx. OUD

- ◆ History of work-related back injury initially prescribed opioids
- ◆ Started using heroin (nasal) from friends at work
- ◆ Spent 8 months in jail for drug and weapons charges
- ◆ Abstinent from opioids for 3 years after incarceration
- ◆ Found in alley by police, suspected overdose.
 - ◆ Nasal naloxone X 2 with no change in response
 - ◆ Unable to cooperate with field sobriety test
 - ◆ Sleepy, difficult to arouse, unable to stand without assistance

32 year old man w OUD, cont.

- ◆ Brought to ED
- ◆ Patient seems sedated, speech slurred
- ◆ Breathalyzer negative
- ◆ Urine immunoassay negative
- ◆ Supportive care, patient gradually becomes more alert...
- ◆ What class of drugs is the patient most likely using?
 - ◆ [If you live in Michigan, you'll find it on the PDMP]



Gabapentinoids

Gabapentin

- ◆ Indications: partial seizures; post-herpetic neuralgia (PHN)
- ◆ Not DEA Scheduled
- ◆ Tracked by PDMP in about 10 states

Pregabalin

- ◆ Indications: Diabetic peripheral neuropathy; PHN; fibromyalgia; partial seizures; neuropathic pain with spinal cord injury
- ◆ DEA Schedule V

Gabapentinoids

- ◆ In a study of recreational users (N=15) of sedative/hypnotic drugs, including alcohol, LYRICA (450 mg, single dose) received subjective ratings of "good drug effect," "high" and "liking" to a degree that was similar to diazepam (30 mg, single dose).

Gabapentinoids

- ◆ Increasing reports of misuse among patients with;
 - ◆ History of incarceration
 - ◆ History of opioid use disorders
 - ◆ History of psychiatric disorders
- ◆ Misuse typically involves doses above therapeutic levels
 - ◆ > 600 mg Pregabalin
 - ◆ >3600 mg Gabapentin
 - ◆ Tolerance and withdrawal syndromes reported (sedative)
- ◆ Common SE: drowsiness, somnolence, dizziness, ataxia, and fatigue

24 year old woman with hx. of OUD

- ◆ Polysubstance use starting at age 19
- ◆ Progressed to heroin injection by age 22
- ◆ Started court mandated treatment
- ◆ Now on IM naltrexone for 6 months
- ◆ Presents after a seizure, BAL 0.0 in ED
- ◆ Family reports that over the last few weeks she lost her job and has been using family car to “look for work”
 - ◆ Often comes home with slurred speech and seems “drugged out”

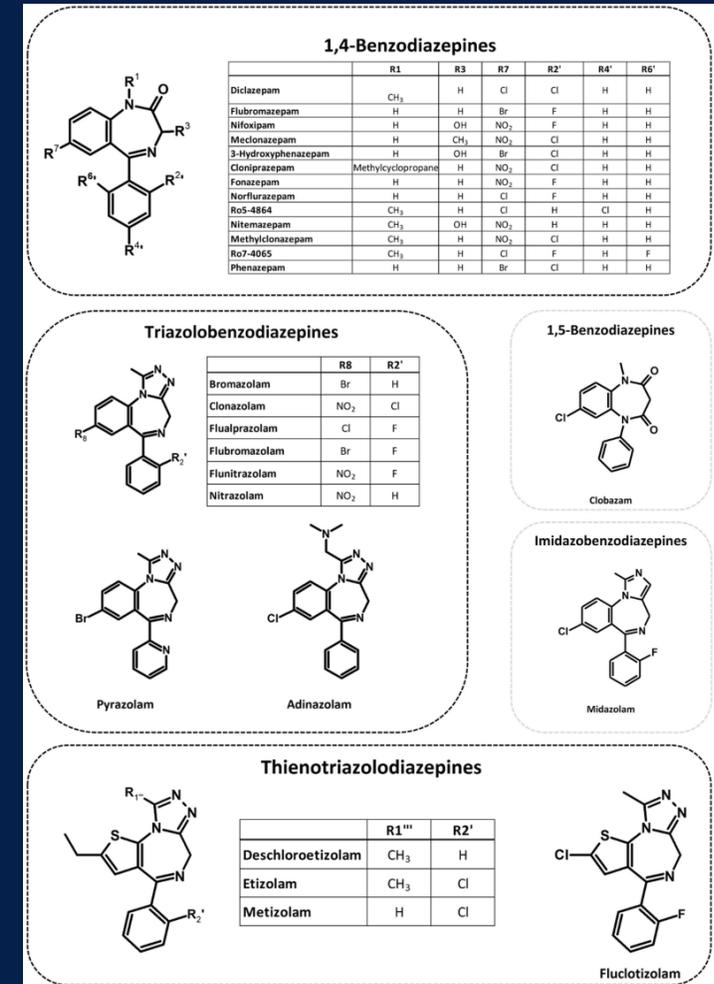
24 year old woman, continued

- ◆ What might present as a sedative-hypnotic toxidrome resulting in withdrawal seizures?
 - ◆ Family does not believe she is using alcohol
 - ◆ Urine immunoassay in ED inconclusive for benzodiazepines...
- ◆ In post-ictal state patient reports taking 10-15 “pressed” Xanax bars a day...



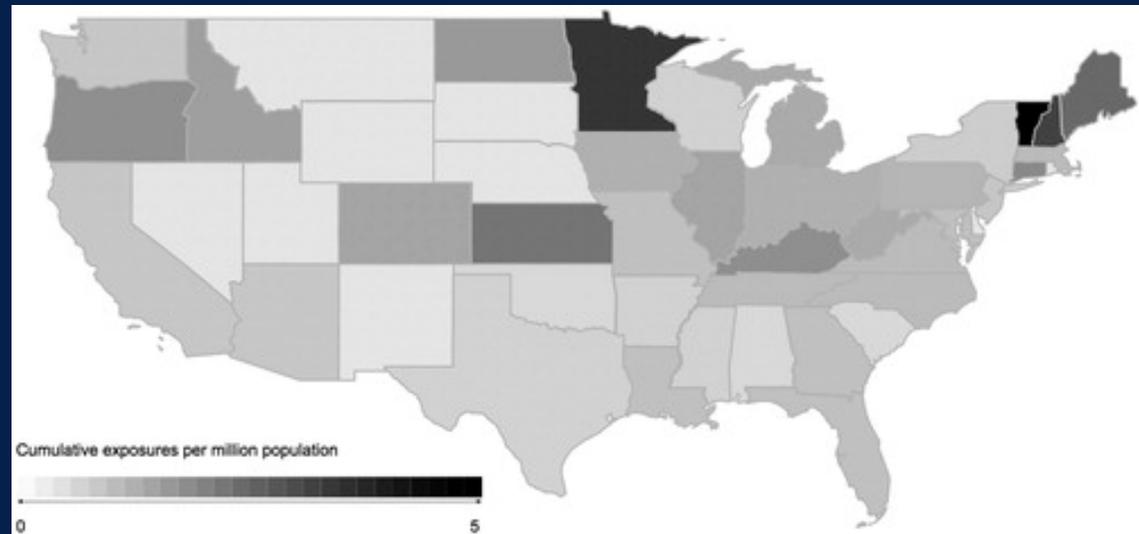
Designer Benzodiazepines

- ◆ Structural variants of 1,4 benzodiazepines and triazolobenzodiazepine
 - ◆ “Designed” to circumvent legal prohibitions
- ◆ Sold on internet
- ◆ May contain non-benzo drugs (e.g., fentanyl, cocaine) in “pressed” form
 - ◆ Compound is pressed into a pill mold



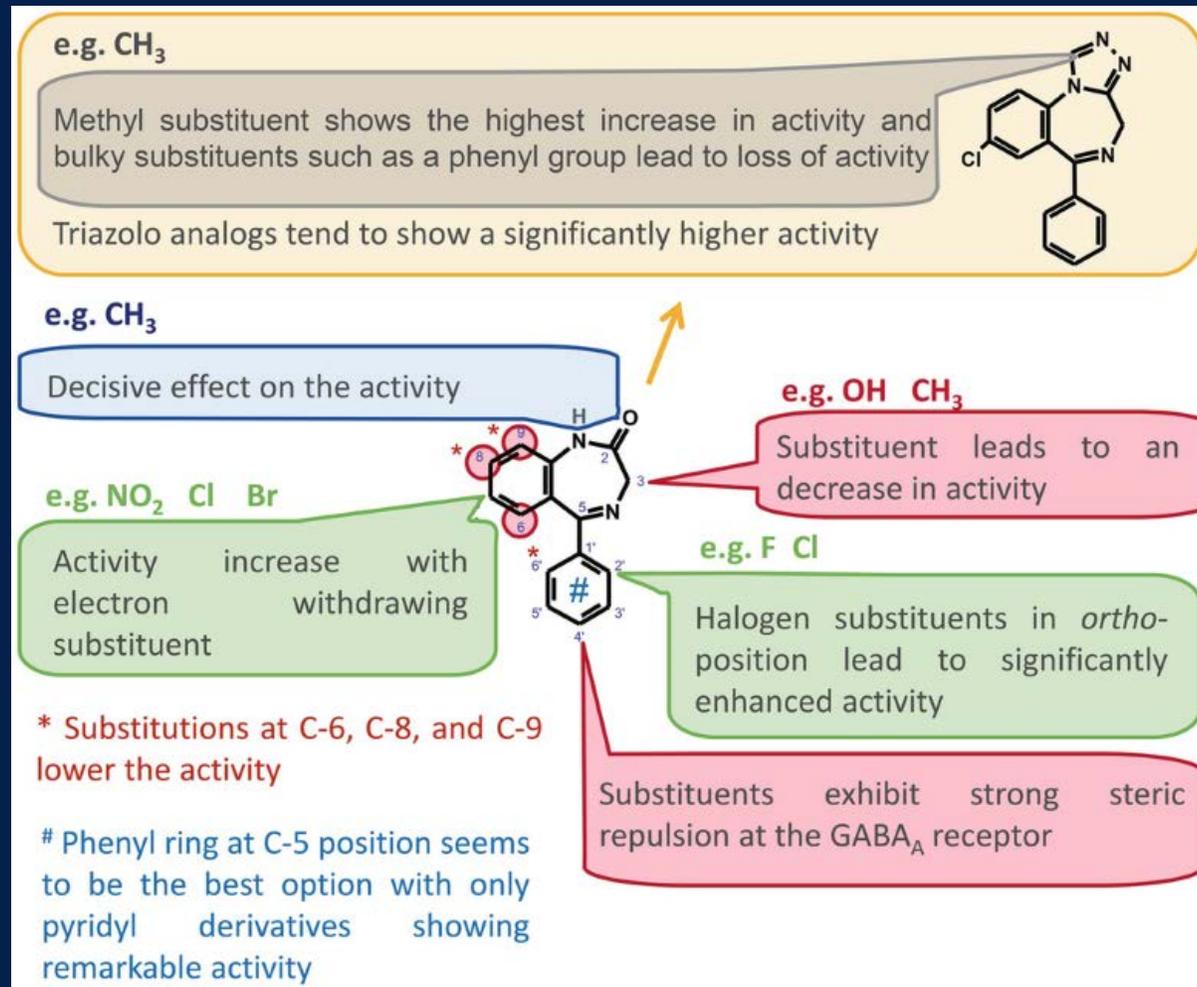
Designer Benzodiazepines

- ◆ Exposures reported to National Poison Data System increased every year from 2014 to 2017.
 - ◆ 234 single agent exposures in 40 states
- ◆ Most common drugs were etizolam and clonazepam.
- ◆ Hospital admission
 - ◆ 36% of cases



Carpenter JE, et al.. Designer benzodiazepines: a report of exposures recorded in the National Poison Data System, 2014-2017. Clin Toxicol (Phila). 2019

Designer Benzodiazepines



Case

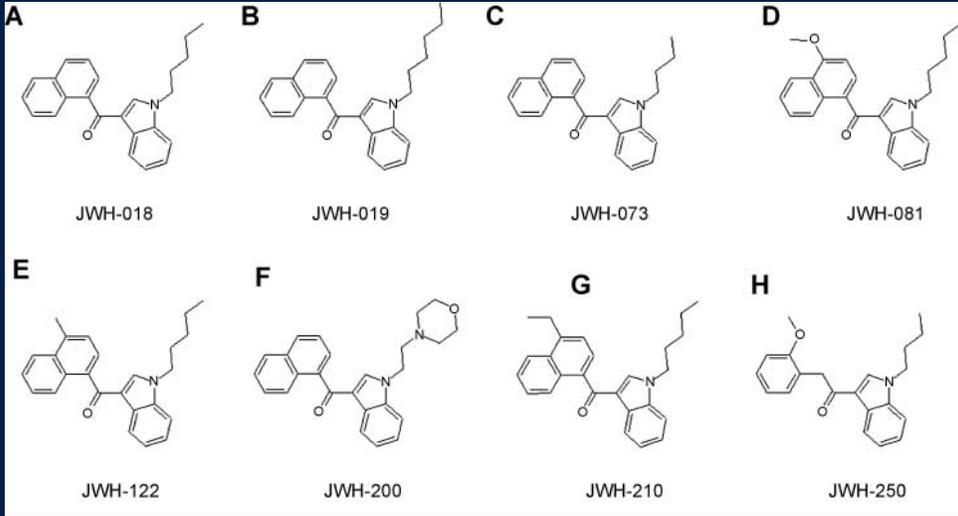
- ◆ 17 y/o male bought a joint from a homeless man
- ◆ Drove to a nearby town and wandered into a salon speaking incoherently, so taken to jail for public intoxication
- ◆ Police took to ED and found to have CK of 1300, BP of 190/110, creatinine of 2.5, and urine drug screen was negative
- ◆ Became combative and required sedation with intubation
- ◆ Diagnosed with psychosis, hypertensive urgency, and rhabdomyolysis with acute renal failure

What are Synthetic Cannabinoids?

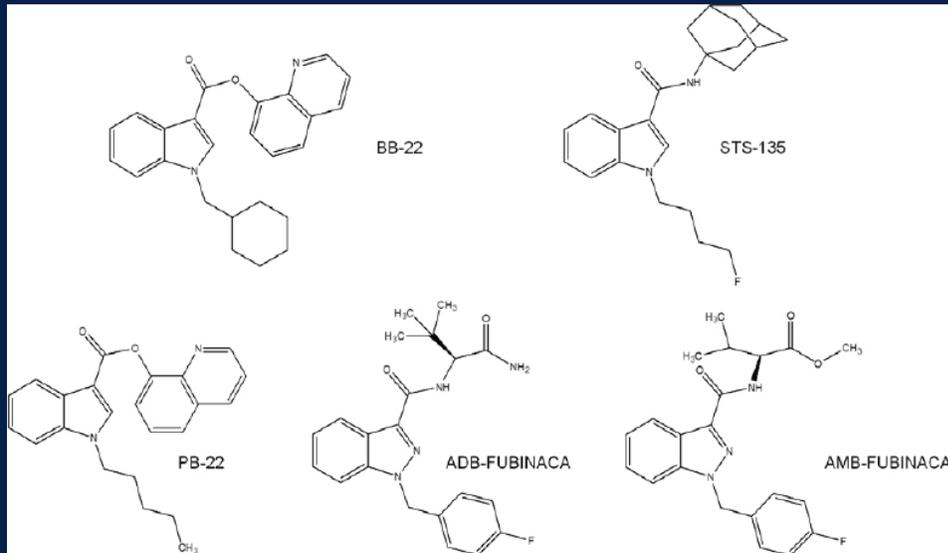
- ◆ Street 'brand' names
 - ◆ K2, Spice, Kush
- ◆ Similar to Marijuana
 - ◆ More severe medical and psychiatric effects than Marijuana
- ◆ Also known as
 - ◆ Fake weed
 - ◆ Legal high
- ◆ Often sold as "potpourri"



Pharmacology



- ◆ Synthetic derivatives of tetrahydrocannabinol (THC)
 - ◆ 10-200x greater potency than THC
 - ◆ Work on CB receptors throughout human body as full agonists
- ◆ Originally synthesized for research purposes in different university laboratories
- ◆ Largest and most structurally diverse category of NPS
 - ◆ 280 compounds identified to date



Synthetic Cannabinoid use

- ◆ Initial use among young adults, especially those who use marijuana
- ◆ Still primarily male, but now more non-White users
- ◆ Rapid growth in use by adults with unstable housing
 - ◆ Homeless
 - ◆ Residing in shelters
 - ◆ Prisoners
- ◆ Most are smoked
 - ◆ Joint, bowl, waterpipe
 - ◆ Can be used orally or intranasally



Acute clinical effects

- ◆ Growing prevalence of adverse effects
- ◆ 30x more likely to go to ED than cannabis users
- ◆ 1st generation: cannabis-like unwanted effects
- ◆ 2nd generation: cardiovascular stimulant-like toxicity
- ◆ 3rd generation: neurological toxicity
 - ◆ Seizures
 - ◆ Psychosis



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Psychiatric effects

- ◆ Tolerance
- ◆ Withdrawal
 - ◆ Depression, anxiety
 - ◆ Irritability, mood swings
 - ◆ Cravings
- ◆ Anxiety, agitation
- ◆ Psychosis
 - ◆ Paranoia, delusions
 - ◆ Hallucinations
 - ◆ Can persist for months
 - ◆ Worsens existing psychiatric disorders
 - ◆ Those with family history of psychiatric disorders are more vulnerable

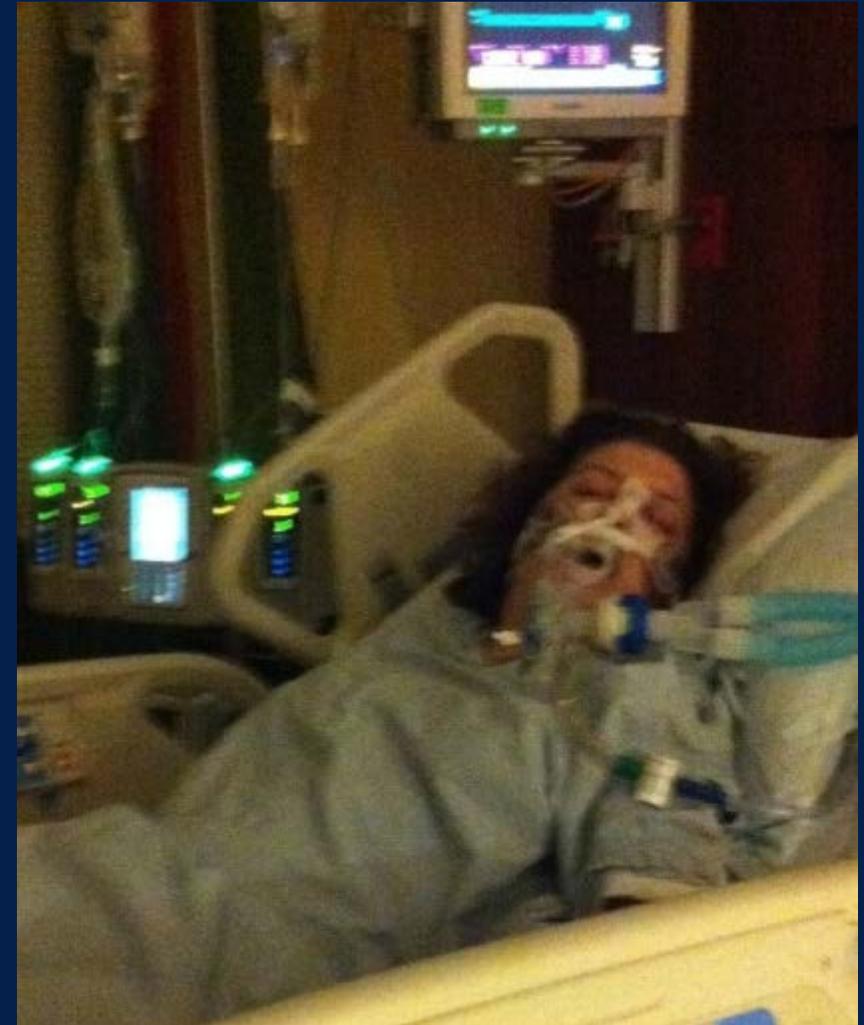


Severe Adverse Events

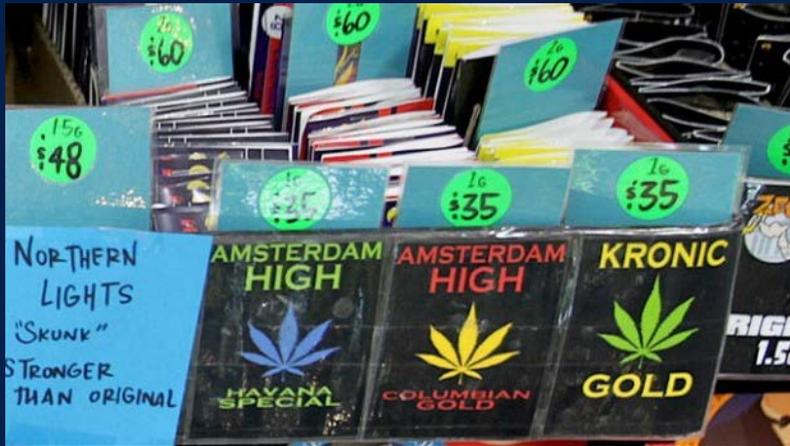
- ◆ Rates of exposures are not uniform across the US
- ◆ 33 individuals in “zombielike” state in New York City in 2016
 - ◆ Exposure to AB-FUBINACA
- ◆ 320 individuals with severe bleeding (coagulopathy) in Midwest and Northeast in 2018
- ◆ 1663 overdoses hospitalized in Washington, DC in 2018
- ◆ Slight overall average decrease in SC-related ED visits from Jan 2016 to Sept 2019
 - ◆ <1 SC exposure out of every 10,000 ED visits
- ◆ Even nearly fatal cases (unresponsive with no response to naloxone) appear to have the potential of reversibility
 - ◆ AMB-FUBINACA (AK-47 24k Gold) or ADB-PINACA (Kronic)

Treatment of intoxication

- ◆ Verbal reassurance
- ◆ Benzodiazepines for agitation, anxiety
- ◆ Try to avoid antipsychotics
 - ◆ Lower seizure threshold
- ◆ Most nonpsychiatric symptoms resolve in 1-3 days
 - ◆ Supportive care
- ◆ Cardiac monitoring
 - ◆ Arrhythmias
 - ◆ Hypertension
- ◆ IV fluids



Is this patient using “Fake Weed”?



- ◆ Ask about drug use
 - ◆ Know common street names
- ◆ Urine drug testing
 - ◆ Polysubstance use is the norm
 - ◆ Negative test doesn't rule out designer drug use
- Packages, paraphernalia
 - ◆ Send substance to lab

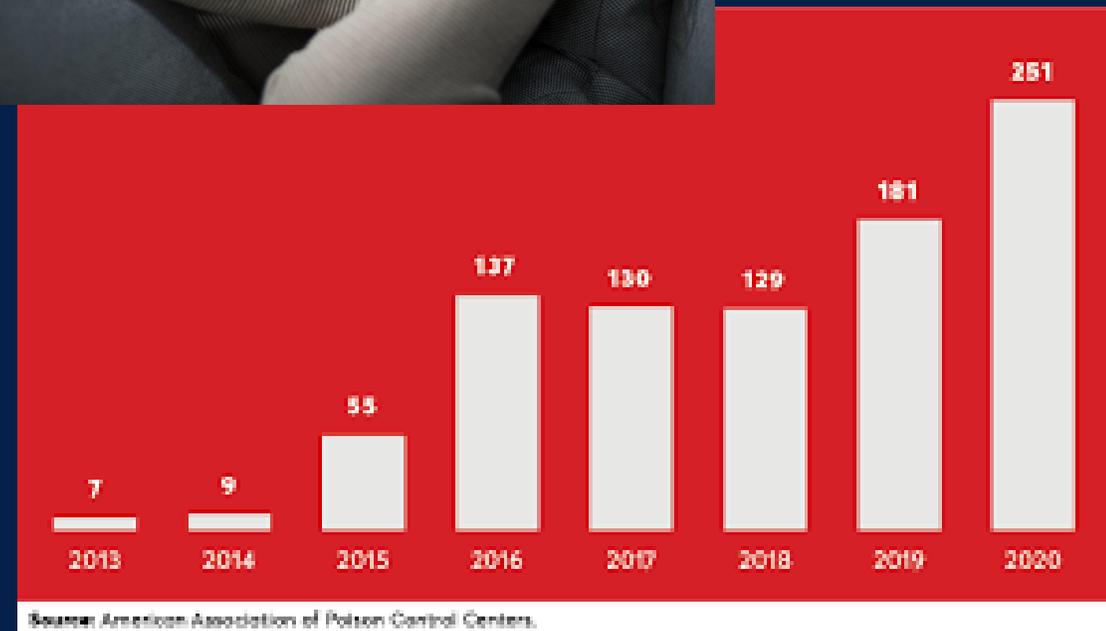
Tianeptine

- ◆ Atypical tricyclic antidepressant
 - ◆ Increases serotonin reuptake
 - ◆ Mu opioid agonist activity
- ◆ Approved as antidepressant in some European and Latin American countries
 - ◆ Prescribed as 12.5 mg TID
 - ◆ Stablon, Coaxil
- ◆ Available in US as a dietary supplement
 - ◆ Readily available online
 - ◆ ZaZa, Tianna Red



Tianeptine Abuse

- ◆ Abused sporadically in US since 2000
- ◆ Short half-life leads to repeated dosing, up to every 2 hours
- ◆ Doses up to 4000 mg/day
- ◆ Can be abused intravenously
- ◆ Sought and diverted at similar level to diazepam
- ◆ Significant increase in poison center reportings, especially since 2017



Treatment

◆ Intoxication

- ◆ Lethargy
- ◆ Agitation
- ◆ Naloxone can be given to prevent fatal overdose

◆ Withdrawal

- ◆ Characterized as consistent with opioid withdrawal
 - ◆ GI distress
 - ◆ Myalgias
- ◆ High levels of anxiety and depression, agitation
- ◆ Can give opioid agonists
- ◆ Benzodiazepines also used

◆ Long-term treatment

- ◆ Reasonable to use FDA-approved meds for OUD
 - ◆ Buprenorphine
 - ◆ Methadone
 - ◆ Naltrexone

Treatment of Addiction



- ◆ Behavioral counseling
 - ◆ Individual
 - ◆ Facilitated groups
- ◆ Mutual-help groups
 - ◆ 12-Step (Narcotics Anonymous)
 - ◆ SMART Recovery
- ◆ Family therapy



Summary

- ◆ Kratom has opioid-like effects, including a withdrawal syndrome
- ◆ Non-pharmaceutical fentanyls have contributed to opioid overdose deaths in the U.S.
- ◆ Gabapentinoids can be abused for euphoric effects at high doses
- ◆ Designer benzodiazepines are becoming more popular and may contain substances other than benzodiazepines
- ◆ Synthetic cannabinoids continue to be developed, with severe medical and psychiatric effects
- ◆ Tianeptine is a TCA-like dietary supplement with an opioid-like withdrawal syndrome

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