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TREATMENT FOR NOVEL PSYCHOACTIVE SUBSTANCES

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CNRA

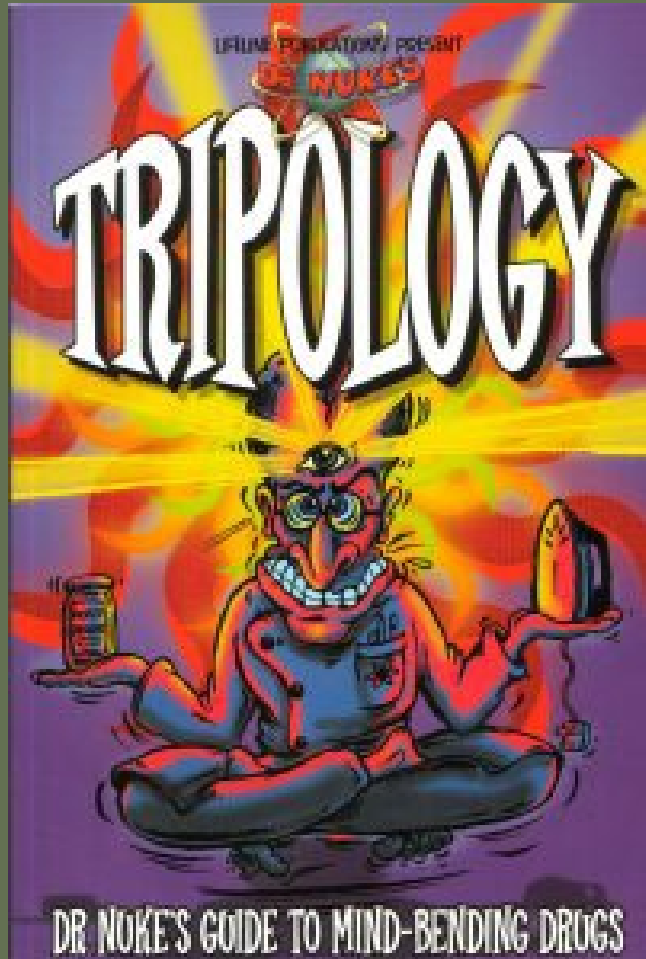
Center for
Neurobehavioral
Research on Addiction

 **UTHealth[®] Houston**
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LEARNING OBJECTIVES

- Identify emerging psychoactive substances, including
 - Kratom
 - Phenibut
 - Synthetic cannabinoids
 - Others
 - Tianeptine
 - Salvia
- Discuss treatment of medical and psychiatric complications resulting from use of emerging substances of abuse.

NOVEL 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 1

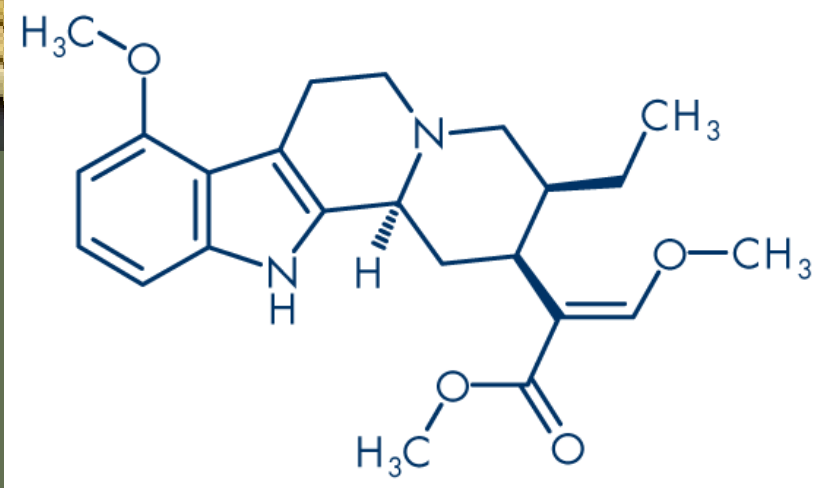
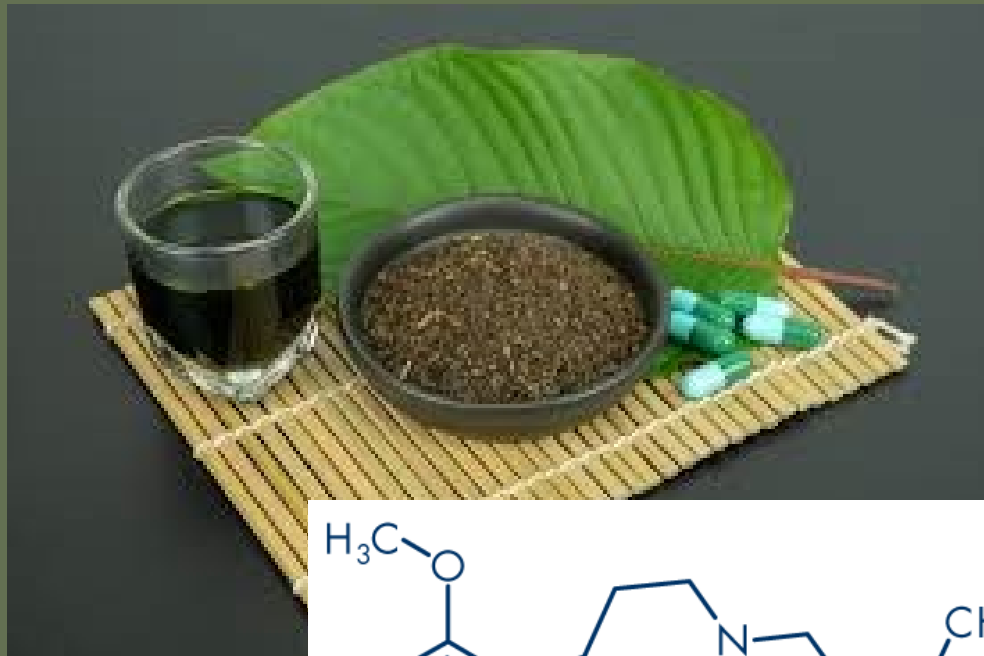
- 59 y/o man with past use of cannabis in 20s, heavy alcohol use in 40s, illegal methylphenidate use in 40s, and hydrocodone abuse until inpatient detox 4 years ago
- Past psychiatric hx of GAD for which he is on SSI Disability
- He takes kratom 500 mg capsules 64 TID (192 caps/d, or 96 grams/day) daily 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)



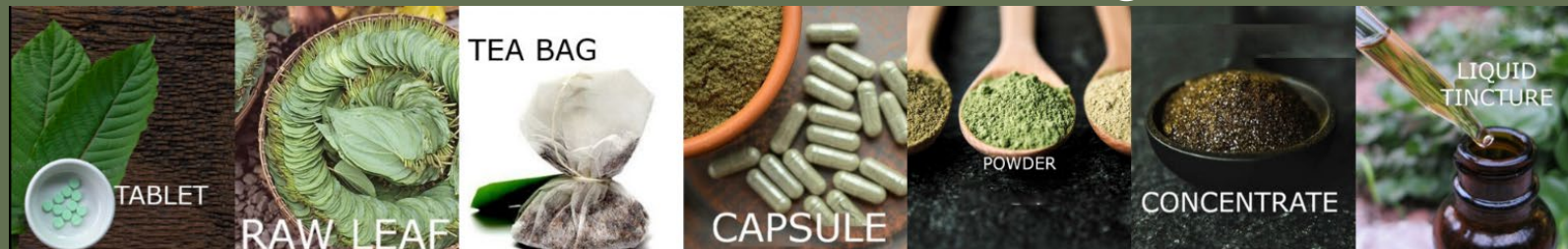
KRATOM PHARMACOLOGY



- 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



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



KRATOM INTOXICATION

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



KRATOM WITHDRAWAL

- 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

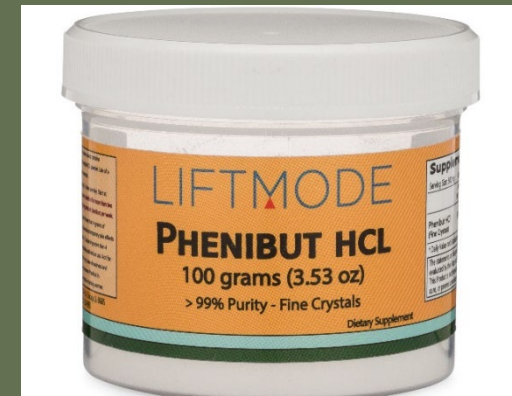
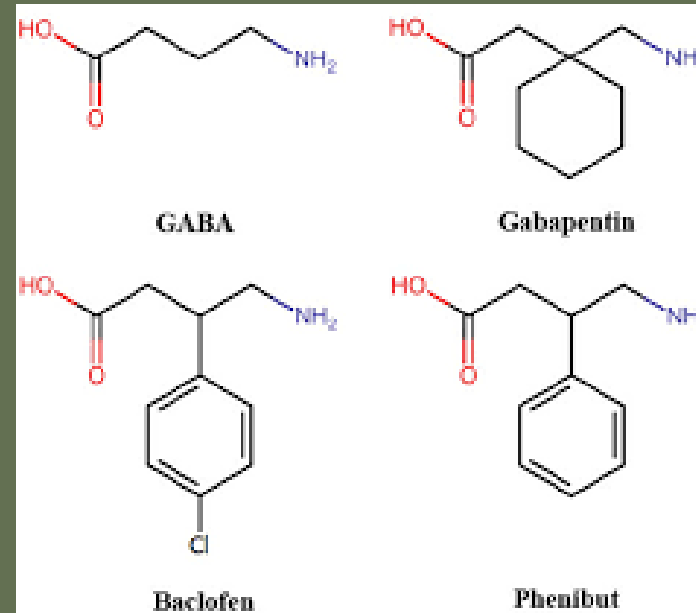
CASE 2

- 15-year-old male
- Drowsy but talkative and somewhat rambling
- Parents found jar of white powder in his room
- He was told it could boost his brain power to study in school by relaxing him
- Bought online with credit card (without parental consent)
- Took by oral ingestion, effects resolved in <24 hours

WHAT IS PHENIBUT?

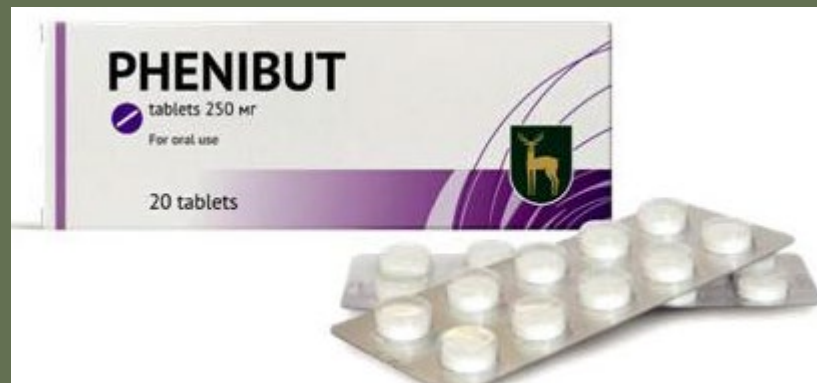
- GABA_B agonist
 - Chemically similar to baclofen and gabapentin
 - CNS depressant
 - Similar effects to GHB
- Oral administration
 - Snorting is painful
- Available as powder or capsules
 - Cost \$1/gram
- Onset 2-4 hours, peak in 4-6 hours, lasts 15-24 hours

- Desired effects
 - Euphoria
 - Reduction of anxiety
 - Social confidence
 - Sleep (hypnotic effects)



PHENIBUT USE

- Available in Russia as treatment for anxiety and insomnia
 - Not available in U.S. or Europe
 - Typical dose is 0.25-0.5 mg TID
- Obtained through the Internet
 - Dietary supplement
 - “Noofen”
 - Can be legally purchased in U.S.
- Recreational doses of 10 mg/day
 - Highest dose reported was 35 mg/day
- Effects of low doses
 - Stimulation
 - Wakefulness, productivity
 - Euphoria
- Effects of higher doses
 - Sedation
 - Anxiolytic effects
 - Muscle relaxation
 - Cognitive slowing



PHENIBUT INTOXICATION

- No antidote for phenibut poisoning
- Case reports of users found unresponsive
- Movement disorder may help differentiate
 - Seen in over 25% of cases
 - Tremor, myoclonus, rigidity
 - Dystonia, stereotypies, catatonia
- Agitated delirium requiring intubation
 - Nearly half of 39 cases
 - Often requires multiple meds for sedation from hyper-agitation
- Tonic-clonic seizures
- Average hospitalization of 5 days
- 1 case of death reported

PHENIBUT WITHDRAWAL

- Tolerance
 - Occurs within days of consecutive dosing
 - Develops with using 1 mg/day
- Withdrawal syndrome
 - Anxiety, insomnia, dizziness, nausea, impaired coordination
 - Visual/auditory hallucinations
- Movement disorder in 54%
 - Tremors, myoclonus, rigidity
- Seizures in 5% of reported cases
- Treatment of withdrawal
 - Benzodiazepines
 - Baclofen
 - Gabapentin
- No standardized protocols for withdrawal treatment
 - Research is case reports and case series



CASE 3

- 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

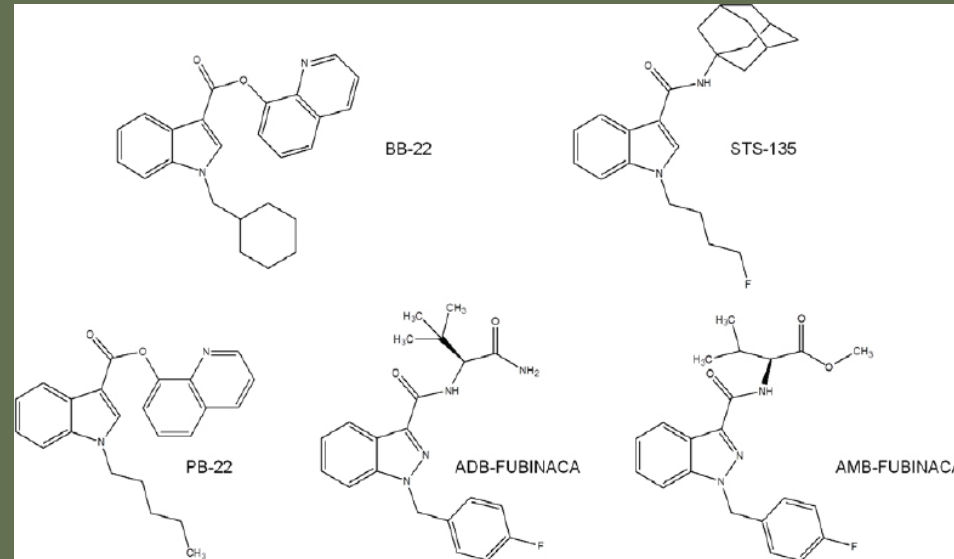
WHAT ARE SYNTHETIC CANNABINOIDS?



- Synthetic derivatives of tetrahydrocannabinol (THC)
 - 10-200x greater potency than THC
 - Work on CB receptors throughout human body as full agonists
- More severe medical and psychiatric effects than Cannabis
- Street 'brand' names
 - K2, Spice, Kush
 - Also known as Fake weed, Legal high
- Originally synthesized for research purposes in different university laboratories
- Largest and most structurally diverse category of NPS
 - 280 compounds identified to date

ACUTE CLINICAL EFFECTS

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



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 SC INTOXICATION



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

TIANEPTINE

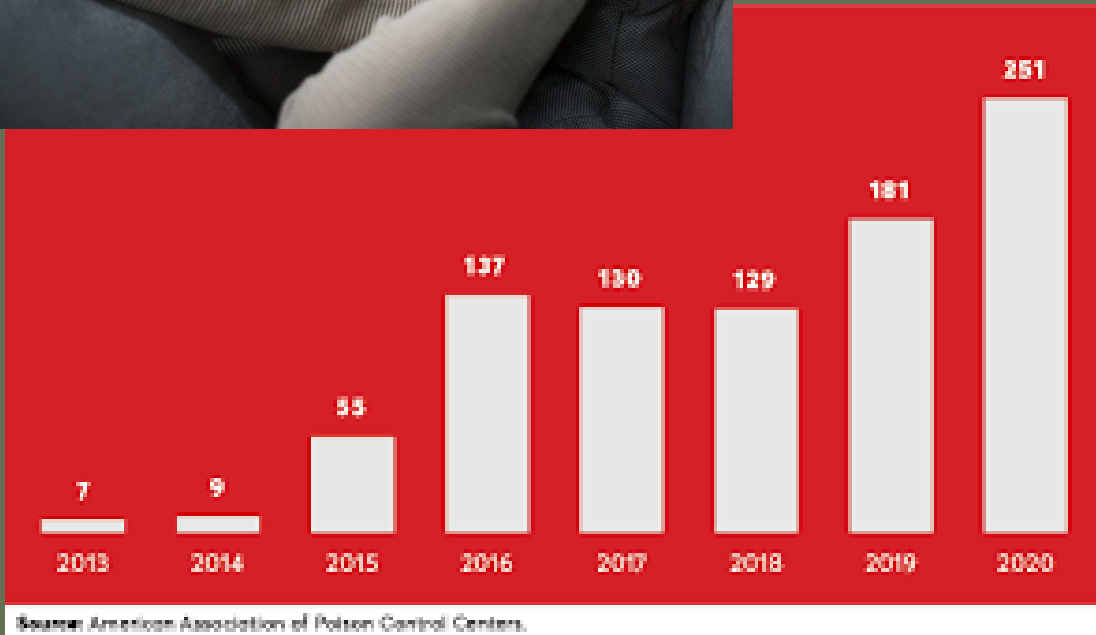
- Atypical tricyclic antidepressant
 - Increases serotonin reuptake
 - Mu opioid agonist activity
- Approved as antidepressant in some European and Latin American countries
 - Prescribed as 12.5 mg TID
 - Stablon, Coaxil
- Available in US as a dietary supplement
 - Readily available online
 - ZaZa, Tianna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



TIANEPTINE MISUSE



- 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 OF TIANEPTINE ADDICTION

- Intoxication

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

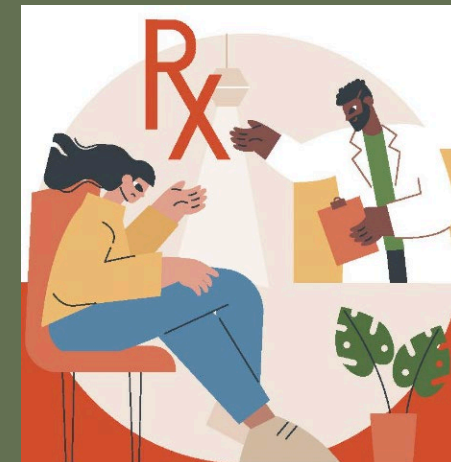


- Withdrawal

- 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



SALVIA

- *Salvia divinorum*
 - Mint family
 - Chew or smoke leaves
 - Magic Mint, Sally D, Diviner's Sage
- Salvinorin A
 - Kappa opioid agonist
 - Hallucinogen effects similar to ketamine
- 1.3% of U.S. adults have tried
 - Primarily White males
- Case reports of psychosis
- No reports of death
- Illegal in most of Europe
- Monitored by DEA in U.S.
- Different states have different regulations



IS THIS PATIENT USING A NPS?



- Ask about drug use
 - Know common street names
- Urine drug testing
 - Polysubstance use is the norm
 - Negative test doesn't rule out NPS use
- Sample of substance with patient
 - Powder, capsule, leaves, etc.
 - Packages, paraphernalia
 - Send to lab for identification



TREATMENT OF NPS ADDICTION

- Behavioral counseling
 - Individual
 - Facilitated groups
- Mutual-help groups
 - 12-Step (Narcotics Anonymous)
 - SMART Recovery
- Family therapy
 - Often adolescents and young adults who use NPS



SUMMARY

- Kratom has opioid-like effects, including a withdrawal syndrome
- Phenibut is a sedative with severe effects of intoxication and withdrawal
- 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
- Salvia is a plant with hallucinogen effects similar to ketamine

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QUESTIONS?

