Clinical Presentations of Substance Intoxication and Withdrawal

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Learning Goals/Objectives

- Discuss the initial assessment of the intoxicated patient or patient in withdrawal
- Learn the different types of drug testing available, as well as how to interpret these tests
- Recognize the common presenting signs of intoxication and withdrawal from common addictive substances
- Describe treatment of intoxication and withdrawal, including any FDA-approved medications

Importance of Learning About Addiction

- 1 out of 7 individuals will have a serious substance use problem (13.5% lifetime prevalence)
- 1 out of 3 Americans are directly affected by addiction
- Up to 50% of ER admissions are related to substance use
- Care for patients with sequelae of addiction: hepatitis, skin infections, during pregnancy, children of affected parents, trauma/surgery, etc.
- Addiction is a common problem among physicians and other health care providers

Patient Assessment

- Patients who are presenting with substance intoxication or withdrawal may have presenting symptoms which mimic other conditions, including psychosis, mania, and stupor/coma
- Even if patient intoxication is suspected, they should still receive regular vital signs, complete history, physical exam, and laboratory tests as needed, to rule out other conditions that can mimic intoxication
  - Hypo/hyperglycemia, electrolyte disturbances, hepatic encephalopathy, stroke, meningitis/sepsis, etc.
- Consider checking PDMP (OARRS in Ohio)

Toxicology Screening

- Every patient presenting with suspected intoxication or withdrawal should undergo toxicology testing
- Multiple matrices can be used for toxicology testing, including:
  - Urine
  - Blood
  - Oral fluid
  - Hair
- Urine is most commonly used, given the ease of collection, non-invasive nature, and longer detection window (compared to blood)

Types of Toxicology Testing

- For initial screening for substances of misuse, most hospitals and laboratories have a screening panel of ~10 common substances
- Screening tests are typically done via immunoassay; these tests have high cross-reactivity and can have a high rate of false positives
  - List of known cross-reactive substances available from the lab or test manufacturer/product insert
  - If more definitive testing is needed, GC-MS or LC-MS may be available for confirmatory testing

Screening Substance Panels

- Become familiar with your lab and what substances show as "positive"
- For example, the standard opiate screen at most hospitals tests for compounds that are morphine- or codeine-based
  - This will detect heroin (diacetylmorphine), but will NOT detect fentanyl, oxycodone, methadone, or buprenorphine very well

Presenting Signs of Alcohol Intoxication

- Signs of alcohol intoxication include:
  - Slurred speech
  - Incoordination
  - Unsteady gait
  - Nystagmus
  - Impairment in attention or memory
  - Stupor or coma
- May smell of alcohol or report recent alcohol use
- Testing should include BAC/BAL; can obtain by blood or breathalyzer

Clinical Effects of Alcohol

BAL (mg%)	Clinical Manifestations
20-99	Loss of coordination; changes in mood, personality, behavior
100-199	Neurologic impairment with increased reaction time, ataxia, incoordination, and mental impairment
200-299	Very obvious intoxication unless marked tolerance; nausea, vomiting, marked ataxia
300-399	Hypothermia, severe dysarthria, amnesia, stage I anesthesia
400-599	Onset of alcoholic coma; progressive obtundation, decreased respirations, BP, and temperature; decreased or absent reflexes
600-800	Often fatal because of loss of airway-protective reflexes, pulmonary aspiration, or from respiratory arrest

The ASAM Principles of Addiction Medicine, 2019.

Treatment of Alcohol Intoxication

- Alcohol poisoning/overdose can be life-threatening; need to monitor respiratory and cardiovascular status
- In most cases, supportive care is all that is needed
- Ensure that thiamine is given prior to glucose
- In extreme cases, hemodialysis efficiently removes alcohol
- Beware of non-beverage alcohol (methanol, isopropyl alcohol, ethylene glycol)

Rate of Alcohol Metabolism

- Metabolism:
  - For a person with an average rate of alcohol metabolism, the blood alcohol level would drop by 0.010-0.020 g/dL per hour.
- A patient with alcohol use disorder may begin to show alcohol withdrawal with a blood alcohol content (BAC) well above the "legal limit" (0.080 g/dL in those over age 21)
  - Example: A patient admitted to the hospital with BAC 0.400 may begin to have withdrawal symptoms 10 hours after arrival
  - BAC ~0.200 when withdrawal begins

Presenting Signs of Alcohol Withdrawal

- Signs of alcohol withdrawal include:
  - Autonomic hyperactivity (e.g., sweating or pulse rate greater than 100 bpm)
  - Increased hand tremor
  - Insomnia
  - Nausea or vomiting
  - Transient visual, tactile, or auditory hallucinations or illusions
  - Psychomotor agitation.
  - Anxiety.
  - Generalized tonic-clonic seizures

Pathophysiology of Alcohol Withdrawal

- Alcohol produces CNS depression via GABAergic neurotransmission
- GABA = inhibitory
  Glutamate = excitatory
- Cessation of alcohol = removal of GABA activity = removal of inhibition= results in excitatory state
- Thus, the withdrawal symptoms exhibited are a result of this excitatory state

Timeline of Alcohol Withdrawal Symptoms

Stage	Onset (hours since last drink)
Withdrawal symptoms	6-36 hours
Hallucinosis	12-48 hours
Alcohol-withdrawal seizures	8-48 hours
Alcohol Withdrawal Delirium/ Delirium tremens	48-96 hours

- Do not need to experience one step to progress to the next
- Alcohol withdrawal can be life-threatening and often needs to be monitored in an inpatient setting
- Gold standard for treatment of alcohol withdrawal = benzodiazepines

Medications for Alcohol Use Disorder

Medication	Brand Name	Dose	Mechanism	Other Facts
Disulfiram	Antabuse	250 mg daily	Aversive symptoms if alcohol ingested	Risk of death if alcohol ingested; less use now with newer options
Naltrexone (oral)	Revia	50 mg daily	Opioid antagonist	Decreases reinforcing effects of alcohol; monitor hepatic function
Acamprosate	Campral	666 mg TID	GABA agonist & NMDA modulator	Most robust effect is to maintain abstinence; renal excretion
Naltrexone (IM)	Vivitrol	380 mg IM monthly	Opioid antagonist	May help improve adherence; like oral form, reduces risk of heavy drinking

Benzodiazepine Intoxication and Withdrawal

- Benzodiazepines have a very similar mechanism of action to alcohol- both work to enhance GABAergic neurotransmission
- Because of this similar mechanism, benzodiazepine intoxication and withdrawal have very similar presenting symptoms as alcohol
  - Treatment is also similar- usually substitute a longer-acting benzodiazepine and taper
- Similar to alcohol, benzodiazepine withdrawal can be life-threatening

Differences Between Alcohol and Benzodiazepine Withdrawal

- However, depending on the specific benzodiazepine used, time course can vary, as most benzos have longer half-lives than alcohol, and symptoms of withdrawal may not present very several days prior to cessation of use
- Also, risk of seizures in withdrawal is higher with benzodiazepine use (20-30% compared to 3%)
- There are no FDA-approved medications for benzodiazepine use disorder

Signs of Opioid Intoxication

- Pupillary constriction
  - Can get pupillary dilation due to anoxia from severe overdose
- Drowsiness or coma
- Slurred speech
- Impairment in attention or memory
- Opioids act on endogenous opioid receptors (namely mu, but also kappa and delta), which results in increased release of dopamine
- Opioid intoxication can be life-threatening
  - Respiratory depression - usual cause of death
  - Also non-cardiogenic pulmonary edema
  - Antidote for heroin overdose- naloxone, given IM or IN

Signs of Opioid Withdrawal

- Dysphoric mood
- Anxiety
- Nausea or vomiting
- Stomach cramps
- Muscle aches
- Lacrimation or rhinorrhea
- Pupillary dilation, piloerection, or sweating
- Diarrhea
- Yawning
- Insomnia

- Opioid withdrawal IS NOT life threatening, but is exceedingly uncomfortable
- Time course of withdrawal depends on half-life of opioids being used
  - Can be 6-12 hours for short-acting opioids, or 36-72 hours for longer-acting opioids like methadone
- Medications with longer half-lives generally have less severe spontaneous withdrawal syndrome-but longer duration of withdrawal syndrome

Treatment of Opioid Withdrawal

- For those with OUD, typically involves medically supervised withdrawal or induction on opioid-agonist therapy (methadone or buprenorphine)
- Can also use alpha-2 agonists like clonidine or lofexidine
- Symptomatic treatment for symptoms- dicyclomine, hydroxyzine, ibuprofen, loperamide, ondansetron

FDA-Approved Medications for OUD

- Methadone
  - Long acting mu agonist
  - Can only be done in OTP setting
- Buprenorphine/naloxone (Suboxone)
  - Mu partial agonist/antagonist; kappa antagonist
  - Naloxone is not absorbed in the GI tract
  - Approved for OBOT; must have DATA 2000 waiver
- Long acting injectable naltrexone (Vivitrol)
  - Used monthly
  - Must be completely detoxed from opioids to begin

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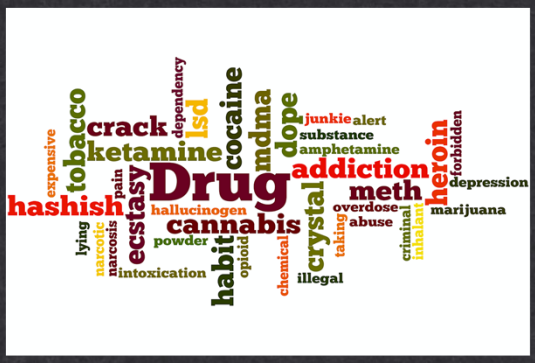
All the rest….



- Stimulants
  - Cocaine
  - Methamphetamine
  - MDMA
- Synthetic Cathinones
- Marijuana
- Hallucinogens
  - Classic (LSD)
  - Dissociative (PCP, Ketamine)
- Inhalants

Stimulants: Cocaine[1,2]

- Origin: Coca plant South America >100 years ago
- Schedule II drug
- Street Names
  - Blow, coke, crack, rock, snow
- Snort, PO, smoke or inject
- Signs and Symptoms
  - Blocks reuptake of dopamine
  - Sympathetic effects (catecholamines)
    - Tachycardia,
    - tachypnea,
    - hypertension,
    - mydriasis
    - Vasoconstriction
    - bruxism

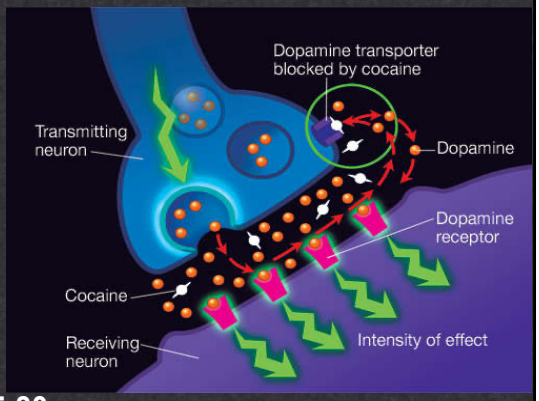
Dopamine Surge

Mesolimbic Dopamine System
- Midbrain: ventral tegmental area to the nucleus accumbens
- Reward pathway
- Regulates emotion and motivation

Reward Behaviors
- Euphoria
- Energy
- Lose inhibitions
- Less appetite

Duration:
- Smoke: immediate onset, lasting 5-10 mins
- Snort: slower, but lasts 15-30 mins

Chronic Use:
- Dopamine receptors downregulated



https://www.drugabuse.gov/publications/research-reports/cocaine/how-does-cocaine-produce-its-effects

Complications of cocaine use and treatment

- **Complications**
  - CVA
  - MI
  - dissection
  - Seizures
  - Dehydration/rhabdomyolysis
  - Excited delirium
  - Overdose
  - Epistaxis, septal perforation
  - Respiratory complications "talc lung"
  - HIV/Hep B/C/STIs
- **Treatment**
  - Supportive, can include IV benzos
  - Agitation: ketamine, Haldol
  - BP control

Cocaine Use Disorder

Patterns of use leading to dopamine down regulation

Withdrawal symptoms

Depression	Fatigue	Increased appetite	Insomnia	Slowed thinking

Treatment

Motivational incentives/contingency management	Cognitive-behavioral therapy	Pharmacologic: no FDA approved (studies ongoing)

Methamphetamine[3,4]

- Origin: early 20th century used as a nasal decongestant
- Pseudoephedrine
- Most of the supply from Mexico- but small labs throughout US
- Combat Methamphetamine Epidemic Act 2005
- Street Names: meth, blue, ice, crystal
- Inhaled, Smoked, Injected or Swallowed
- Schedule II Stimulant

How does methamphetamine differ from cocaine?

Much longer duration
- Increases dopamine release and blocks dopamine reuptake
- 50% of the drug is eliminated in 12 hours, versus 1 hour for cocaine

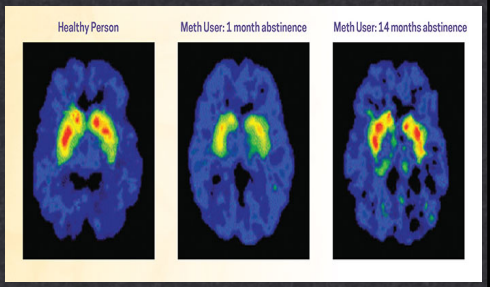
Acute intoxication and complications similar to cocaine

Chronic Use/stimulant use disorder
- Psychosis (paranoia, hallucinations, repetitive motor activity)
- Brain remodeling-lack of focus, cognitive delay
- Memory loss
- Unstable mood (can lead to violent or aggressive behavior)
- Weight loss
- Dental decay
- Skin changes

https://www.drugabuse.gov/publications/drugfacts/methamphetamine

Methamphetamine Use Disorder

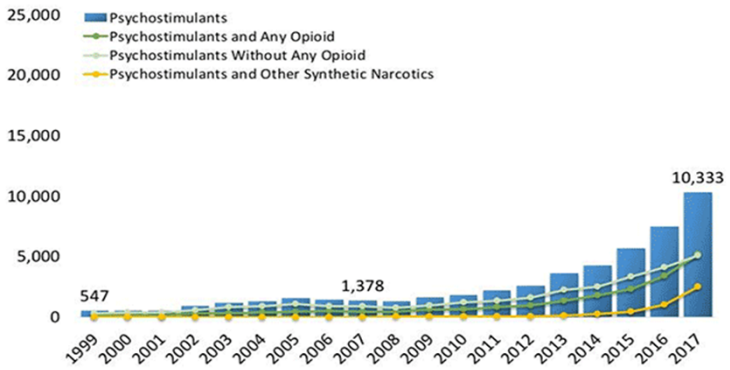
- Withdrawal
  - Depression
  - Anxiety
  - fatigue
- Treatment
  - Behavioral (similar to cocaine)
  - No FDA pharmacological treatments (studies ongoing)
  - Other:
    - Transcranial Magnetic Stimulation
    - Biofeedback
    - Vaccines (block drug with antibody)



https://www.drugabuse.gov/publications/research-reports/methamphetamine/what-are-long-term-effects-methamphetamine-misuse

Alarming Trends

Figure 6. **National Drug Overdose Deaths Involving Psychostimulants With Abuse Potential (Including Methamphetamine), by Opioid Involvement**
Number Among All Ages, 1999-2017



Source: : Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2017 on CDC WONDER Online Database, released December, 2018

MDMA: 3,4-methylenedioxy-methamphetamine[5,6]

- Ecstasy, X, Molly (rarely pure)
- synthetic drug popular in '80's for raves
- stimulant and hallucinogen
- increases dopamine, norepinephrine, and serotonin
- Increased energy, distorted perception, bruxism, hyperthermia, decreased inhibitions
- lasts about 3-6 hours, often take 2nd dose
- Complications: dehydration, heat stroke, rhabdo
- Unclear if addiction potential, but withdrawal pattern includes fatigue, depression, anorexia

Synthetic Cathinones (Bath Salts)[7]

- New Psychoactive Substance
- Synthetic variant related to the khat plant (E Africa)
  - Bliss
  - Cloud Nine
  - Lunar Wave
  - Vanilla Sky
  - White Lightening
- Sold in gas stations "not for human consumption", "plant food", "screen cleaner"
- Cheap substitutes for other stimulants (often in Molly)
- Smoked, snorted, swallowed, or injected

Synthetic Cathinones

- Unknown mechanism, but similar to amphetamines, cocaine and MDMA
- Common metabolite, 3,4-methylenedioxypyrovalerone (MDPV) is 10x as potent as cocaine
- Profound paranoia, hallucinations, decreased inhibitions, panic, excited delirium (violent)
- Addiction potential and withdrawal symptoms include depression, anxiety, tremors, insomnia, paranoia
- Treatment: behavioral modalities, look for undiagnosed mental health

Marijuana[8,9]

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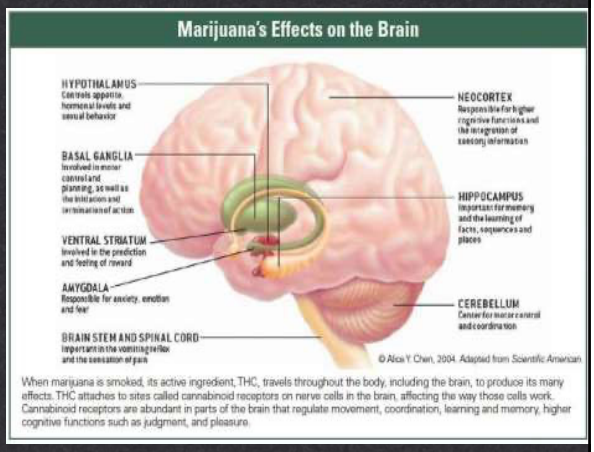
  - Dipped cigarettes
  - Extracts (dabbing)-potent THC resins.: 50-80% THC

Marijuana

- Anandamide = endogenous cannabinoid
- THC is able to bind to endogenous cannabinoid receptors (CB_1)
- onset depends on route of administration
  - If inhaled duration is typically 1-3 hours
  - <u>Acute intoxication</u>
    - Injected conjunctivae, miosis
    - Mild tachypnea, tachycardia, lowered BP
    - Lack of coordination, ataxia
    - Appetite stimulant
    - Urinary retention

Short term:

- Altered sensorium (brighter colors)
- Poor motor coordination and reaction(cerebellum and basal ganglia)
- Cognition delay
- Anterograde amnesia (hippocampus)
- Mood alteration-euphoria (dopamine), relaxation
- Hallucinations
- Delusions
- Potential for psychosis (can mimic)



https://www.drugabuse.gov/publications/research-reports/marijuana/how-does-marijuana-produce-its-effects

Marijuana: Long Term Effects and Complications

Long Term

- Cognition and memory: some mixed results
- Paranoia
- Worsens symptoms in patients with schizophrenia
- May predispose psychosis in patients with genetic traits toward mood disorders, previously undiagnosed
- seizure
- Chronic bronchitis

Complications

- Cannabinoid Hyperemesis Syndrome
- 9-30% develop THC use disorder, especially if use starts < 18 y/o
- Withdrawal syndrome (tobacco) and treatment is behavioral (some use of gabapentin)

Synthetic Cannabinoids: New Psychoactive Substances[10]

- Fake weed (K2, Spice, Kush, Black Mamba, Kronic, and Joker) buy in gas stations, head shops, or online
- Smoked vaped (herbal or liquid incense) or drink as tea
- Similar labeling to bath salts "natural", often not detectable in routine drug screens
- Bind to similar THC receptors with greater affinity and unpredictable duration
- Effect similar to THC, but more psychosis and can lead to violent behavior and death (suicide, tachycardia, violence)
- Addiction potential with no approved treatments
- Marinol (dronabinol): FDA approved for N/V with chemo and anorexia

Hallucinogens[12,13]

- Classic
  - LSD
  - Psilocybin
  - Peyote

Serotonin receptors: prefrontal cortex (mood, cognition, perception)

- Dissociative
  - PCP (phencyclidine): schedule II
  - Ketamine: schedule III
  - Dextromethorphan (DXM): OTC
  - Salvia

N-methyl-D-aspartate (NMDA) receptors (glutamate) cognition, emotion and pain perception

  - Minor dopamine (higher doses)

https://www.drugabuse.gov/publications/research-reports/hallucinogens-dissociative-drugs/what-are-dissociative-drugs

https://www.drugabuse.gov/publications/research-reports/hallucinogens-dissociative-drugs/what-are-hallucinogens

Classic: LSD (D-lysergic acid diethylamide)

https://www.drugabuse.gov/publications/drugfacts/hallucinogens

- Pill, liquid or blotting pieces
- Effects up to 12 hours with slow onset "trip"
- Short term
  - Altered sensorium (colors, shapes), and time perception
  - Tachycardia, elevated BP, raised temperature, diaphoresis
  - Nausea, vomiting
  - Decreased appetite
  - Insomnia
  - Paranoia, sometimes psychosis (rapid emotional shifts, impulsive)
- Long term
  - Persistent psychosis
  - Flashbacks or Hallucinogen Persisting Perception Disorder (underlying mental health)
  - Tolerance to same group, but not leading to dependence

Dissociative Hallucinogens

- Ketamine *vitamin K*
- Snorted as a powder or made as a pill
- Anesthetic, amnestic, immobility
- Hallucinations, detachment
- Tachycardia, elevated BP, tachypnea
- K-hole or emergence reaction
- Esketamine: nasal spray for depression
- Treatment for chronic pain

- Dextromethorphan *robo*
- OTC Cough suppressant (15 mg)
- Can be used for *sizzurp/purple drank*
- Complications can include seizures, respiratory distress, tachycardia, HTN crisis
- Dose dependent
  - 200-400mg: euphoria, hallucinations
  - 300-600mg: loss of motor coordination
  - 500-1500mg: dissociative sedation, depersonalization

Inhalants: huffing/sniffing/bagging[13]

- Volatile hydrocarbons (glue, fuel, spray paint, paint thinners, aerosol)
- More common in younger kids in the mid 90's
- Initial euphoria "rush" followed by dizziness, excitability, altered perception
- Higher doses: motor incoordination, slurred speech then drowsiness and headache
- Lasts several minutes
- Can lead to neurotoxicity (white matter), renal, cardiac injury and sudden death (cardiac arrest or asphyxiation)
- Possible withdrawal syndrome

Summary

- Initial assessment of the impaired patient should include a complete history, physical, and toxicology screening
- Learn the toxicology testing available in your lab and how to interpret these tests
- Presentations can have overlap, so lab testing and history are important
- Keep in mind most novel substances will not show up on toxicology testing
- For many intoxication and withdrawal syndromes, treatment is supportive
- Alcohol use disorder and opioid use disorder have FDA-approved medications for treatment

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