ASAM REVIEW COURSE 2026

Cannabis Use Disorder: Science, Trends, and Clinical Implications

Mashal Khan, MD
Attending of Clinical Psychiatry
Associate Program Director, Addiction Psychiatry Fellowship
New York Presbyterian Hospital-
Weill Cornell Medicine
New York, NY

Financial Disclosure

Mashal Khan, MD

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Learning Objectives

- Increase knowledge about current epidemiological trends in cannabis use in the United States.
- Name the different formulations of cannabis that impact individuals today.
- Review medications that have an evidence base for treating cannabis withdrawal and cannabis use disorder.

Epidemiology

Cannabis Use/Misuse

- In 2024, an estimated 44.3 million Americans- **15.4%** of the population aged 12 years or older had used cannabis in the preceding month.

- In 2015, it was 22.2 million (**8.9%**) Americans aged 12 years and older.

- By the end of 2023, more than half of the U.S. population lived in a state that had legalized recreational (adult-use) cannabis – a major driver of rising use, CUD prevalence, and product potency.

Increased Risk for Use Disorder

- 9% of users develop Cannabis Use Disorder
- Cannabis use peaks in the late teens to early 20s, then declines
- The risk increases to 17% in people who start using in adolescence.
- The risk increases to 25 to 50% in people who are daily users (most of whom started using marijuana early in adolescence).

Cannabis Basics

- The cannabis plant has 104 cannabinoids; only 2 (THC and CBD) have been extensively studied for potential therapeutic applications.

- THC is the most psychoactive component – (*inhaled, ingested*)

- CBD is postulated to have other mechanisms of action (anti-inflammatory, analgesic, etc.).

Cannabis Plant

Natural, Plant - Derived Cannabinoids

- Cannabis
- Sativa, Indica, or Hybrid
- Genus Cannabis; “hemp” = low-THC (<0.3%) cultivars, “marijuana” = higher-THC cultivars

Natural, Plant - Derived Cannabinoids

Most common preparations:

*Marijuana

*Hashish

*Hash Oil

THC Concentrations vary—

For example, extraction of THC with butane (“dabs”) can contain up to 90% THC.

Synthetic Cannabinoids

- Higher affinity for cannabinoid receptors than THC
- Have active metabolites that prolong their durations of action
- Increased potential for toxicity
- “Spice” or “K2”
- Not detected on standard UDS

Synthetic Cannabinoids

Seely et al. Spice Drugs are More than Harmless Herbal Blends: A Review of the Pharmacology and Toxicology of Synthetic Cannabinoids. Prog Neuropsychopharmacol Biol Psychiatry. 2012;39(2):234-243.

Spice/K2, Synthetic Marijuana. dea.gov.

Semi-Synthetic “Hemp-Derived” Cannabinoids

- Delta-8-THC – isomer of Delta-9-THC, psychoactive but less potent; often chemically synthesized from CBD

- THC-O-acetate & HHC – semi-synthetic analogs, higher potency, unregulated production

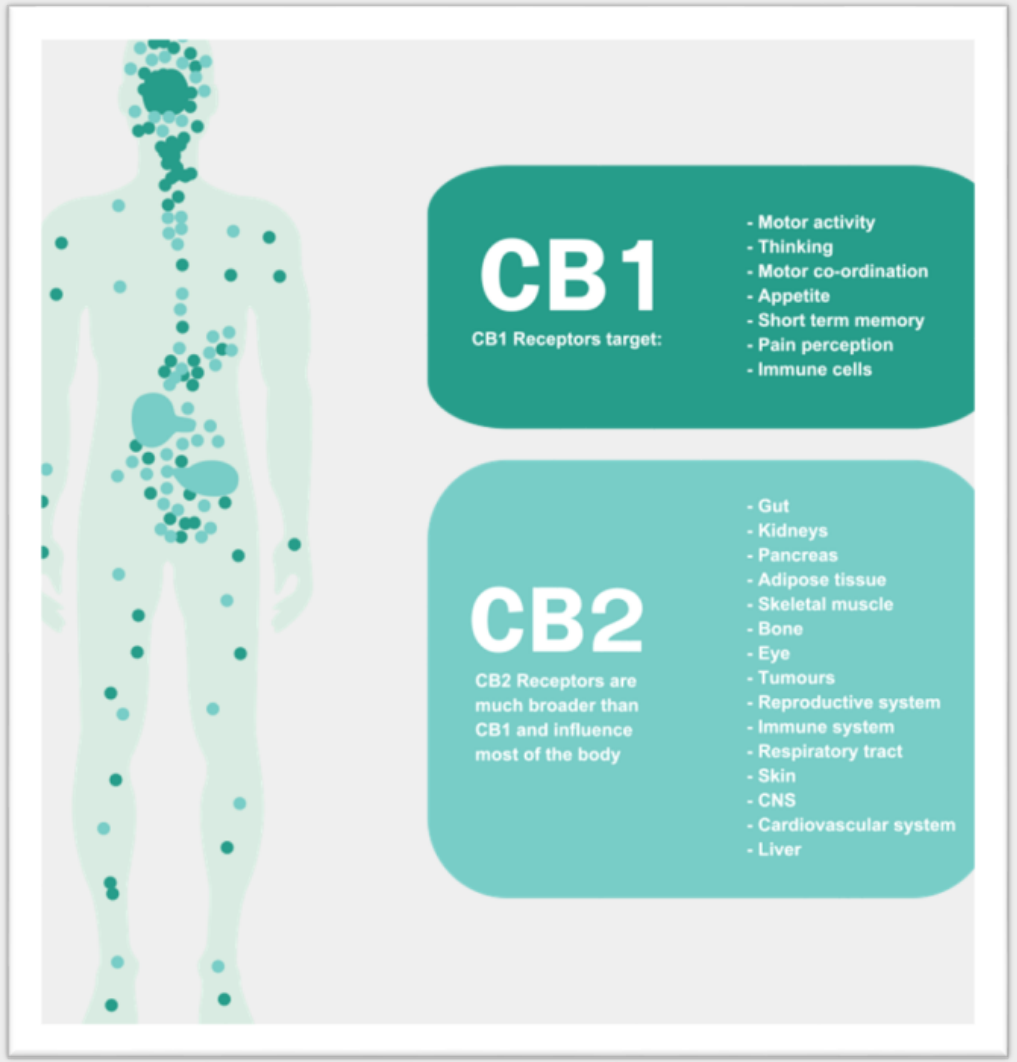
Cannabinoid Receptor Neurobiology

The Cannabinoid System

- THC activates the CB1 and CB2 cannabinoid receptors:
  - CB1 has high density in cerebellum, basal ganglia, hippocampus, cerebral cortex. *G protein mediated system*.
  - CB1 has low density in the brainstem, hence low risk of respiratory depression.
  - CB2 is found in spleen, hematopoietic cell lines, mast cells.

Cannabinoid Receptors

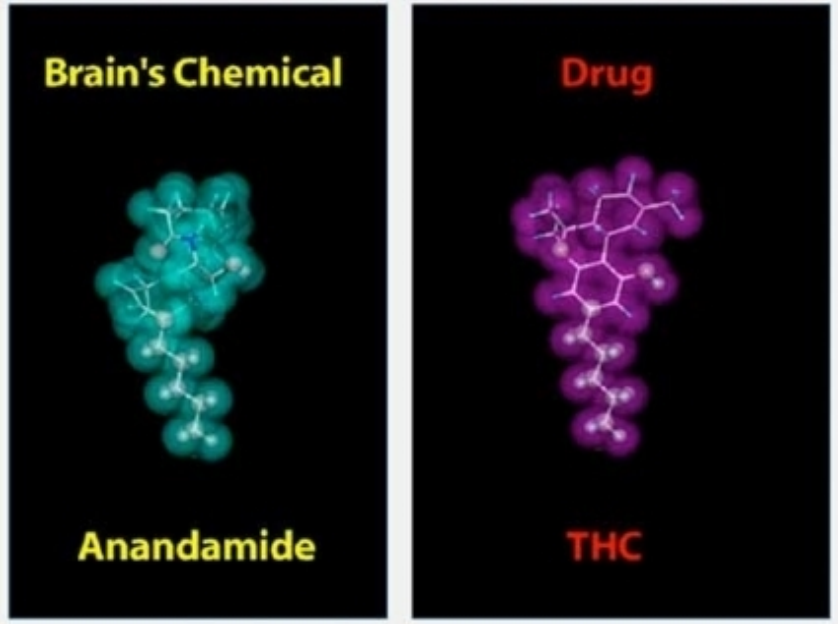
- CB1 – CNS site of CB binding
  - Memory, learning, problem solving, coordination
  - Activated by anandamide, other CBs
  - Modulates neurotransmitters
- CB2 – immune cells outside CNS
  - Anti-inflammatory effects



Cannabinoids (CBs)

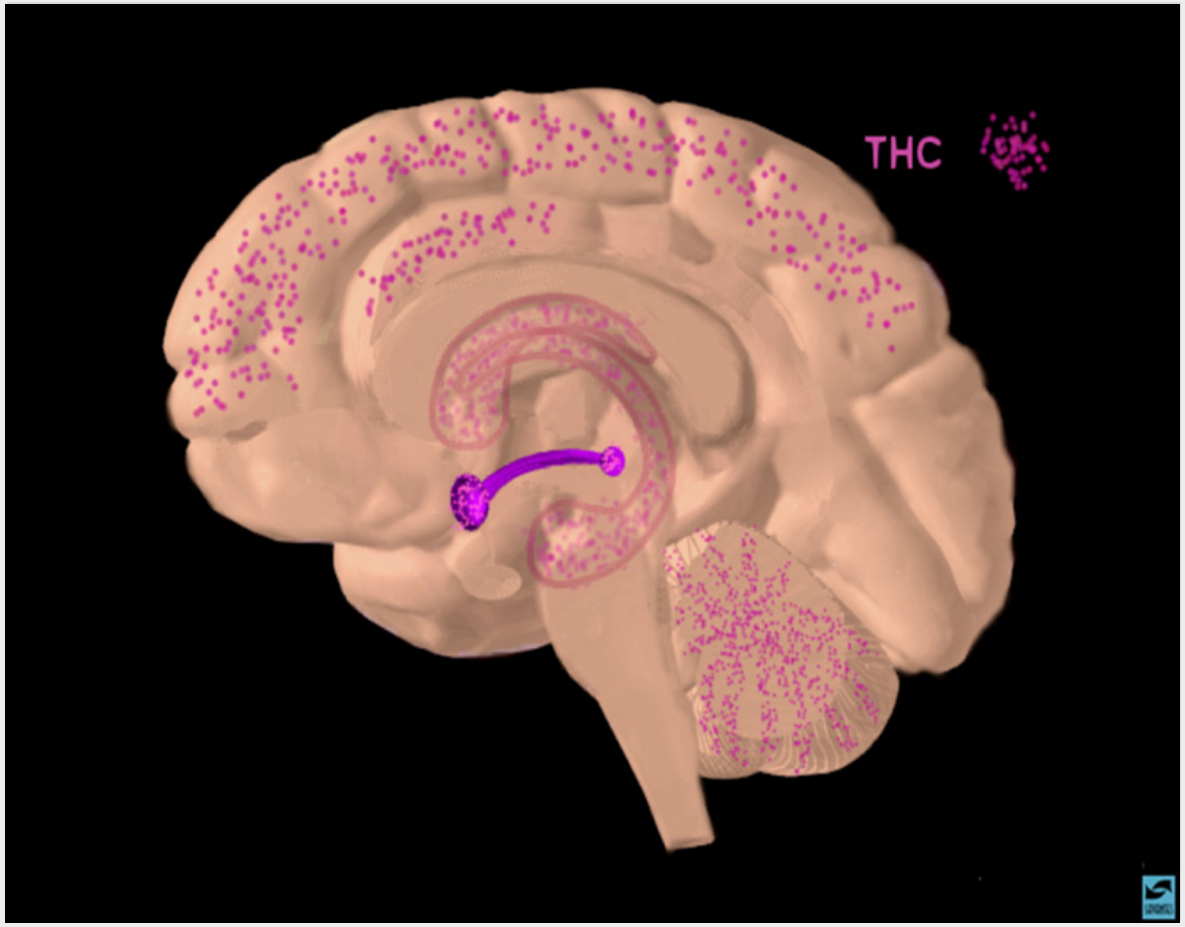
- > 400 chemicals, ↓ neurotransmitter release
- Natural CBs
  - **Endogenous** – Anandamide, 2-Arachidonoylglycerol (AEA, 2-AG)
  - **Exogenous** – Sativa or Indica plant (marijuana)
    - Tetrahydrocannabinol (THC) – psychoactive
    - Cannabidiol (CBD) – non-intoxicating; centrally active (e.g., anticonvulsant)

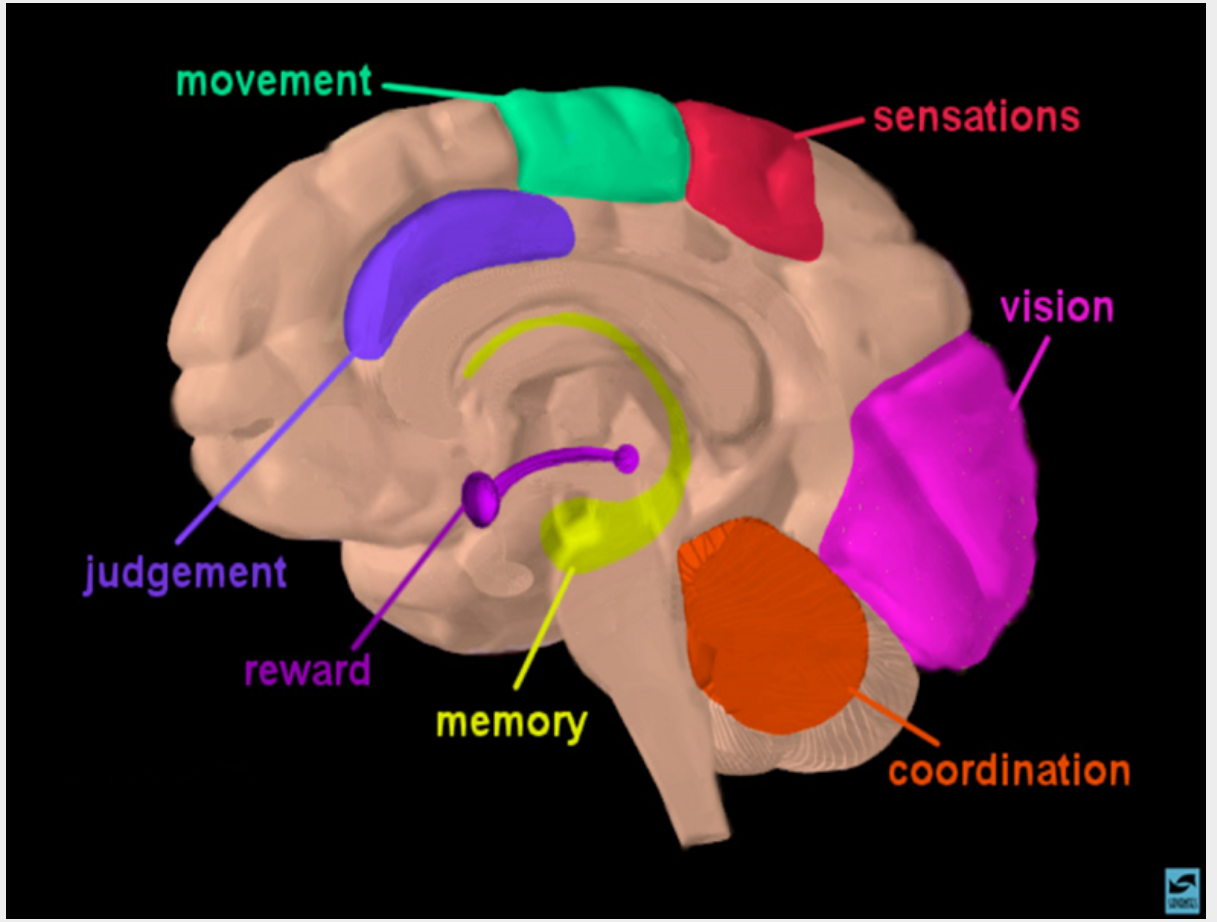
9-tetrahydrocannabinol (THC)



- Primary psychoactive constituent
- Endocannabinoid system
  - Brain development
- Mimics anandamide
  - Dial down neuron activity

CB1 Receptor Locations in the Brain





Neurotransmitter modulation

- Dopamine – euphoria, reward, pleasure
- GABA- muscle relaxation and sleepiness
- ↓ Glutamate- relaxation, ↓ memory

Cannabis Intoxication

- *Desired effects*: relaxation, euphoria, slowed time perception, altered sensory perception, increased appetite.

- *Undesired effects*: impaired concentration, anterograde amnesia, anxiety, panic attacks, paranoia, derealization/depersonalization, acute psychosis (may include hallucinations, which are more commonly visual but can also be auditory).

Synthetic Cannabinoid Toxicity

Central Nervous System	Seizures	*Cardiovascular*	Tachycardia
	Agitation		Hypertension
	Irritation		Chest pain
	Loss of consciousness		Cardiac Ischemia
	Anxiety		
	Confusion	*Gastrointestinal*	Nausea
	Paranoia		Vomiting
Metabolic	Hypokalemia	*Autonomic*	Fever
	Hyperglycemia		Mydriasis
		Other	Conjunctivitis

Seely et al. Marijuana-based Drugs: Innovative Therapeutics or Designer Drugs of Abuse? Mol Interv. 2011;11(1):36-51.

Routes of Administration

- Smoked:
  - Reaches the brain in minutes
  - Effects last 1 - 3 hours
  - Delivers significant amount of THC into the bloodstream

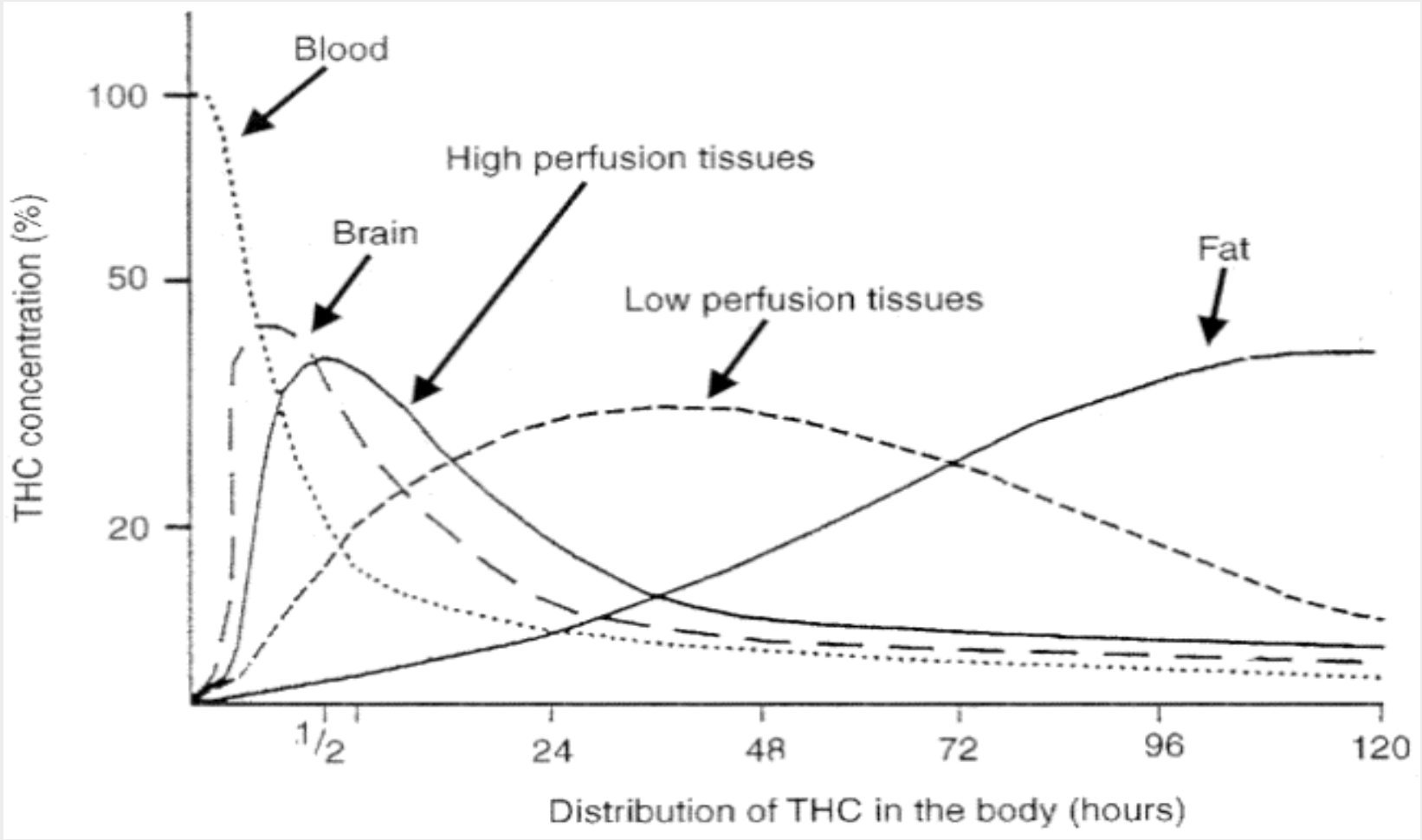
Smoked	*Vaporized*	*Eaten/Drunk*
Smoked in a pipe, bowl, cigarette	Inhaled through machine that converts active compounds into inhalable form	Consumed as ingredient in baked goods, candies, sodas
Rapid effects	Rapid effects	Takes time to reach brain, so effects are delayed

Routes of Administration

- Eating or drinking marijuana:
  - Takes ½ - 1 hour to have an effect
  - Effects last up to 4 hours
  - THC is metabolized by the liver into 11-hydroxy-THC
  - 11-Hydroxy-THC is more lipophilic, potent and has a longer half-life.

Smoked	*Vaporized*	*Eaten/Drunk*
Smoked in a pipe, bowl, cigarette	Inhaled through machine that converts active compounds into inhalable form	Consumed as ingredient in baked goods, candies, sodas
Rapid effects	Rapid effects	Takes time to reach brain, so effects are delayed

Biphasic distribution



2019 National Drug Threat Assessment. US Department of Justice Drug Enforcement Administration. December 2019.

Toxicology Testing

- Casual use:
  - Up to 10 days in urine
  - 50% positive in hair samples
- Heavy use:
  - Up to 30 days in urine
  - 85% positive in hair samples

- Measures THC
- Weight loss gives serial UTox spike
- Dronabinol gives positive test
- Passive inhalation gives negative test

Cannabis Withdrawal

- Reported by up to 1/3 of persons who use cannabis frequently.
- Cannabis withdrawal is recognized by the DSM 5.
- Clinical trials – show reduction of withdrawal symptoms with synthetic THC (dronabinol), nabilone, nabiximol, and gabapentin.

Cannabis Withdrawal

Causing distress & ≥ 3 of the following:

- Irritability
- Anxiety
- Sleep problems
- ↓ Appetite/weight loss
- Depressed Mood
- Restlessness

AND ≥ 1 of the following:

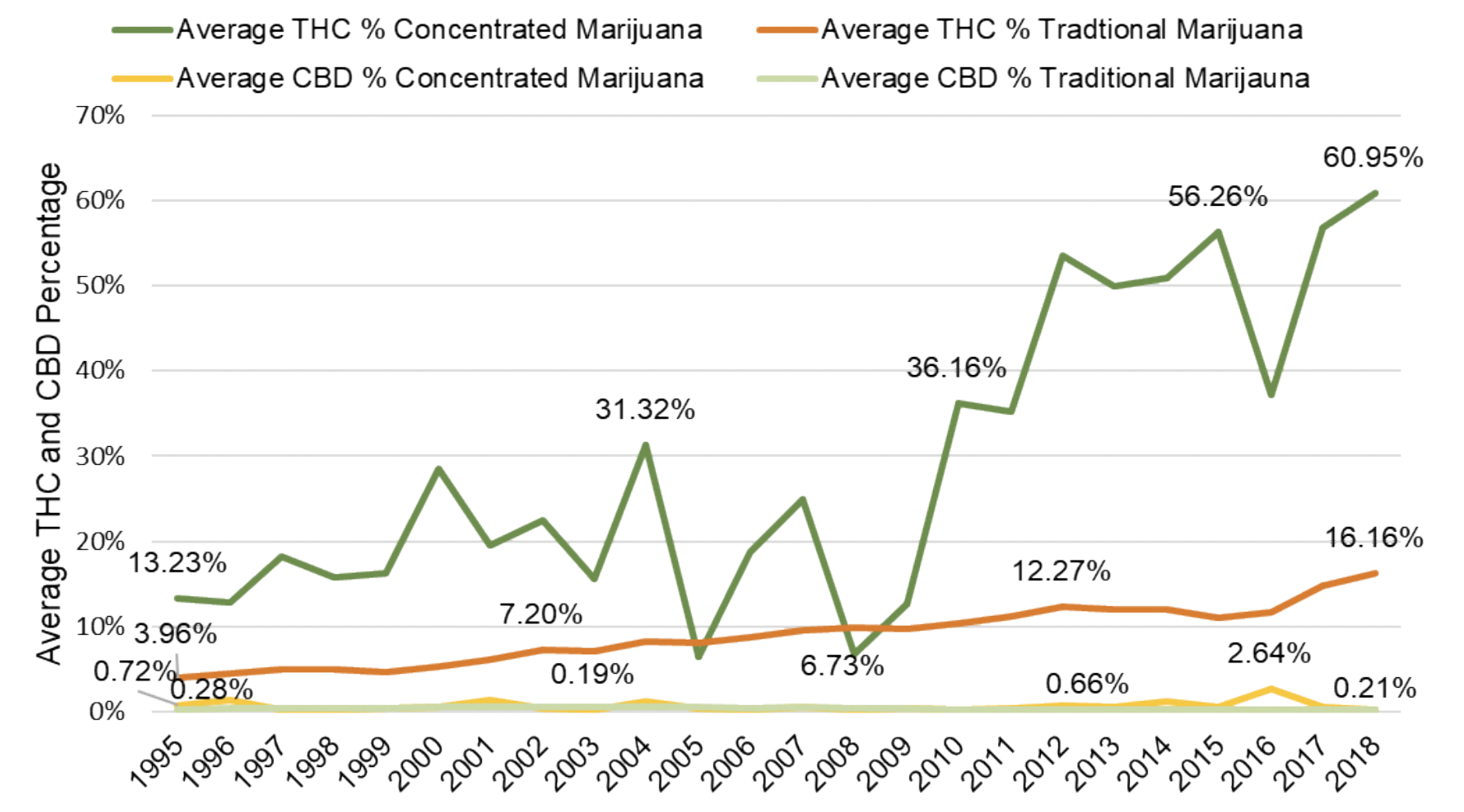
- Abdominal pain
- Sweating
- Shakiness/tremors
- Fever/chills
- Headache

THC Potency is Increasing

- Average flower potency has climbed well past 31% in many legal markets; concentrate products (dabs, wax, shatter, live resin) now routinely exceed 70–90% THC

- Widespread availability of THC edibles (food and beverage products) and butane-extracted hash oil products (“dabs”, “budder”, “shatter”, “wax”)

THC Percent is Increasing



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Special Populations and Cannabis

- Adolescents
- Pregnant persons

Decreased Harm Perception: Adolescents

- 36% of teens think cannabis is harmless
  - 43% favor legalization
  - 80s: 15%
  - 90s-00s: 30%

- Harm perception lowest in 40 yrs
  - Often precedes ↑ prevalence

Rates ↑ Across Adolescence

- Ever tried
  - ~17% 8th graders
  - ~50%12th graders
- Past year use
  - 12% 8th graders
  - 35% 12th graders
- Current use (past month)
  - 7% 8th graders
  - 21% 12th graders
  - Surpasses current alcohol and tobacco use

Special Populations: Young Children

- Accidental Pediatric Edible Ingestion
  - Rising ED visits and poison control calls among young children, driven by THC edibles resembling candy, cookies, or gummies
  - Presentation: lethargy, ataxia, somnolence, occasionally respiratory depression in young children (proportionally larger dose per kg)
  - Management is largely supportive; consider child safety/home environment counseling and safe storage

Adolescent Brain

- May be vulnerable to the addictive nature of cannabis and neurotoxic effects, including development of psychiatric disorders.
- One study showed decline in IQ among cannabis users before the age of 18, with much less recovery of neuro-psych functioning.
- NSDUH data: risk for cannabis dependence is higher if use begins before age 16 (17% versus 9%)
- Most and latest change in areas of:
  - Reward and motivation
  - Cognition

Pregnancy

- Endocannabinoid system plays a role in the control of brain maturation, particularly emotional responses

- THC crosses the placenta (also note effect of smoking)

Pregnancy

- Babies exposed to THC:
  - Neurological development effects
  - Reduction in fetal growth, also other negative effects on the infant

Pregnancy

- Children exposed to THC:
  - Problem-solving skills, memory, attention deficit

- THC-specific vs. associated environmental factors hard to sort out; ongoing debate and research.

Effects of Use

Physiological Effects

- Adrenergic look-alike:
  - Tachycardia
  - Hypertension (but orthostatic hypotension)
  - Tachypnea
  - Dry mouth
- Conjunctival injection
- Appetite increase

Impaired Cognition

- ↓ Ability to learn
- ↓ Attention, concentration
- ↓ Abstract reasoning and decision-making
- ↓ Memory

Neurocognitive Effects

- Short-term memory impairment
- Judgment impairment
- Motor coordination impairment (increased risk of MVA)

Impaired Driving

- Acute THC
  - → ↓ Peripheral vision
  - → ↓ Motor coordination
    - → ↑ reaction time
    - → ↓ time/distance judgment
- #1 reported illicit drug in accidents/fatalities
  - 2x accident risk
  - 3-7x risk of causing accident

Physical Health

- Respiratory
  - ↓ Function
  - ↑ Infections
- ↑ Stroke/Temporary brain blood constriction

Cannabinoid Hyperemesis Syndrome (CHS)

- Seen in long-term, frequent (often daily) cannabis users
- Classic features:
  - Cyclic, severe nausea and vomiting
  - Compulsive hot showers/baths for symptom relief
  - Diffuse abdominal pain
  - Resolves with sustained cannabis cessation (key distinguishing feature from cyclic vomiting syndrome)
- **Treatment:** IV fluids, capsaicin cream to the abdomen, haloperidol/droperidol (more effective than typical antiemetics like ondansetron), benzodiazepines as adjuncts, and cessation counseling

Cardiovascular Risk with Cannabis Use

- Acute use: tachycardia and increased myocardial oxygen demand can trigger angina/MI in susceptible patients
- Regular/heavy use: associated with increased risk of MI and stroke, independent of tobacco use
- Cannabis arteritis – rare peripheral arteritis resembling Buerger's disease, seen in young, otherwise healthy heavy cannabis users
- Reversible Cerebral Vasoconstriction Syndrome (RCVS) – thunderclap headache, vasospasm, can cause ischemic/hemorrhagic stroke

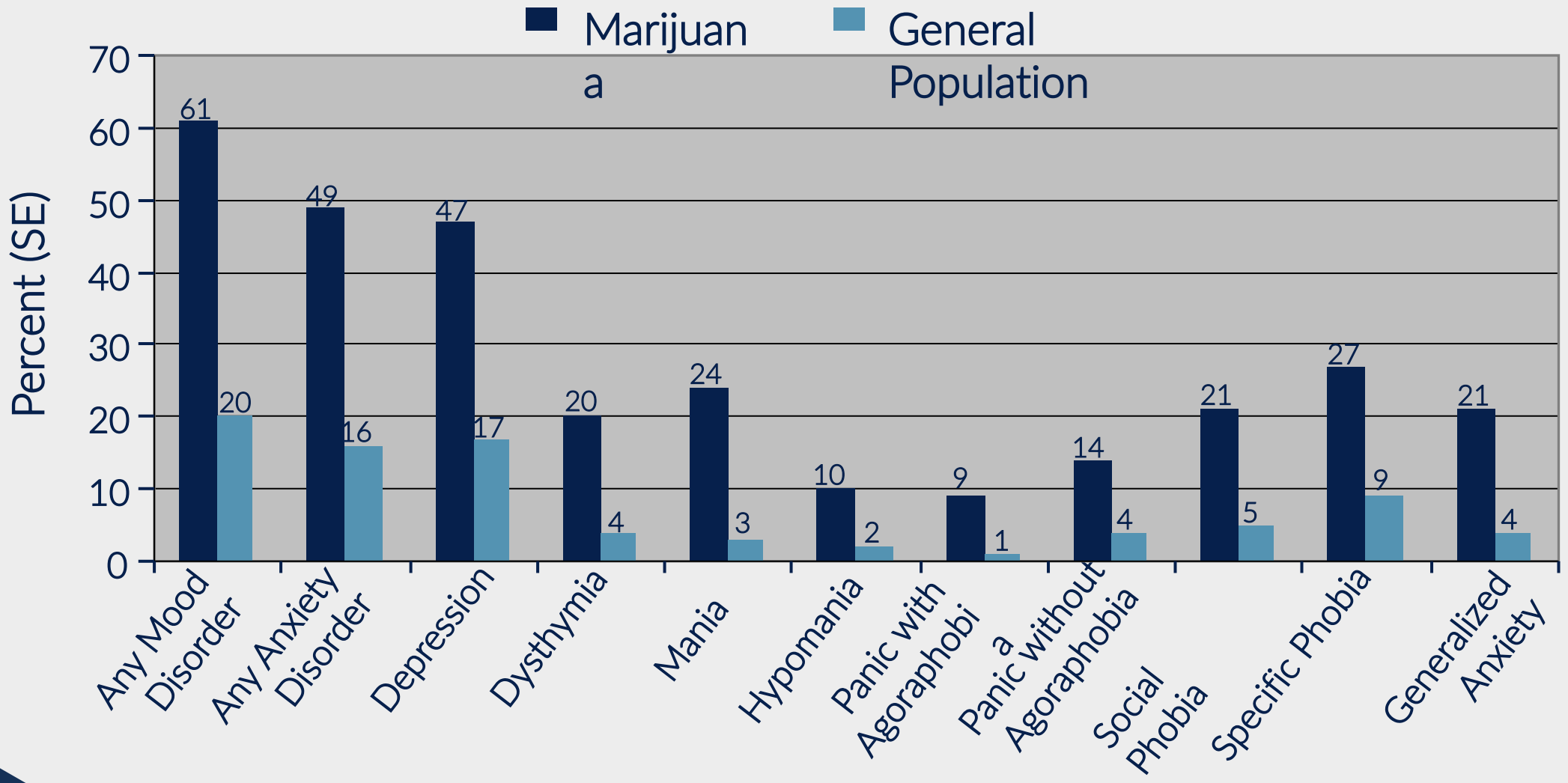
Psychiatric

- Anxiety
  - Acute THC → ↓ anxiety
  - Long-term THC → ↑ anxiety
- ↑ Depression
- ↑ Psychosis

Amotivational Syndrome

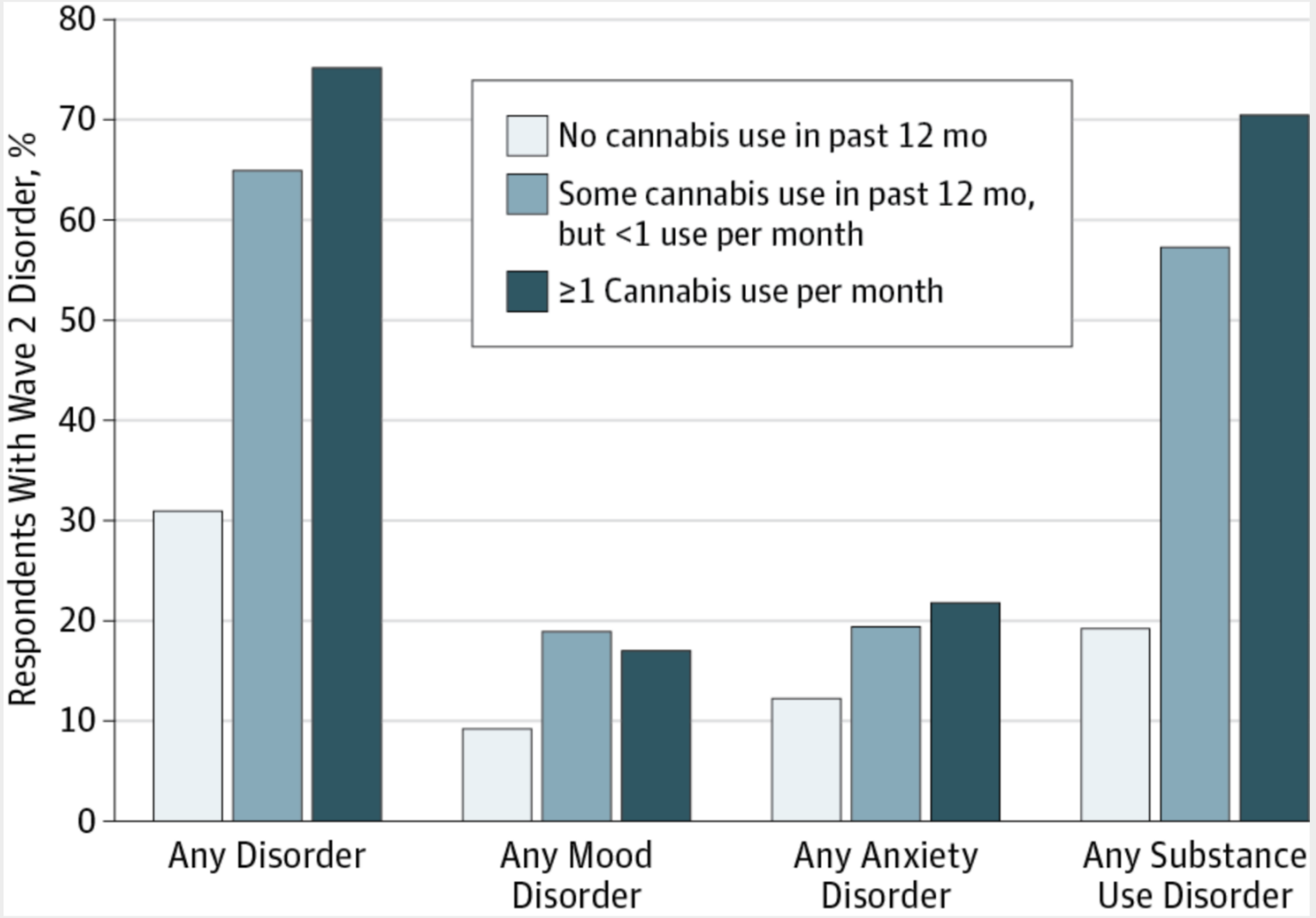
- Mental slowing
- ↓ Planning ability
- ↓ Judgment, concentration, memory
- Apathy, ↓ pursuit of goals

Psychiatric Co-Morbidity



NESARC, 2005; slide courtesy of Dr. Frances Levin.

Psychiatric Co-Morbidity



Diagnosis

Substance Use Disorder

In Same Year, ≥2 of:

- Tolerance
- Withdrawal
- Use more/longer
- Unable to ↓ use
- Use despite problems
- Craving
- Failed roles
- Hazardous use
- Social problems
- ↓ Activities
- Lots time use

Screening-tools

- CUDIT-R (Cannabis Use Disorder Identification Test – Revised)
  - 8-item, validated self-report screening tool for problematic cannabis use
  - Useful for primary care and addiction settings to identify patients who warrant further diagnostic evaluation

Cognitive Effects

Residual Cognitive Effects

- Memory
  - Learning & retaining new information
- Attention and concentration
  - Response speed & variability
- Executive functioning
  - Working memory
  - Verbal fluency

Likely Reversible with Abstinence

- Biological markers normalize ~4wks
  - CB receptor density in brain
  - Cortical blood volumes
- Especially in cognitive areas

Treatment

Treatment for CUD is Challenging

- Few evidence-based supported approaches
- ~ 50% achieve remission
- ~ 70% return to use
- No FDA-approved medications

Psychosocial Treatments

- Motivational Enhancement Therapy
- Cognitive Behavior Therapy
- Contingency Management
- Family-Based Programs

Pharmacologic Treatment Options

Medication	Mechanism	Comments	Literature in Adolescents?
Atomoxetine	Norepinephrine reuptake inhibitor	• No change in cannabis use • Worsened irritability and GI side effects	• Thurstone et al., 2010[7]
Bupropion	Norepinephrine reuptake inhibitor	• Exacerbated withdrawal (irritability, insomnia)	• Riggs, et al., 2013[8]
Buspirone	Serotonin partial agonist	• Conflicting evidence on cravings and irritability	--
Dronabinol	CB1 receptor agonist	• **Reduced symptoms of withdrawal** • Contains THC	--
Gabapentin	GABA modulation	• **Decrease self-reported cannabis use** • **Reduced withdrawal symptoms**	--
N-acetylcysteine	Correct glutamate dysregulation	• Decreased use in adolescents • Did not show same benefit in adults	• Gray et al., 2012[9]
Naltrexone	Mu-opioid receptor antagonist	• Enhanced subjective effects of cannabis • No change in frequency of cannabis use	--

Medication for CUD

- N-acetylcysteine (NAC)
  - Amino acid derivative, OTC supplement
  - Restores normal glutamate activity
  - Pros: ↓ use in Non-Treatment Seeking adolescents, *not in adults*
  - Cons: did not ↓ craving

N-acetylcysteine (NAC)

Risks	• Nausea/vomiting • Drowsiness/insomnia • Vivid reams • *Anaphylactoid reactions seen with IV admin, not PO*
Pharmacokinetics	• Bioavailability for oral: 9% • Metabolized to cysteine and glutathione • Half-life: ~ 18 hours

Gabapentin

Mechanism of Action	• Blocks alpha-2d subunit of the voltage-gated calcium channel which modulates GABA in the amygdala
Notes	• FDA approved for multiple indications, including partial seizures in ages 3-12
Doses	• Goal of ~1200mg/day Mason (2012) [10]: 50 cannabis-dependent adults (18-65 years old) • Gabapentin 1200mg vs placebo for 12 weeks • Titrated up to 300mg / 300mg / 600mg over the course of 4 days
Clinical benefit	• Increase in negative UDS • Decrease self-reported cannabis use • Reduction in withdrawal symptoms (mood disturbance, craving, and sleep disturbances)

Gabapentin

Risks	Headache, nausea, insomnia and depression

Pharmacokinetics	• Bioavailability: inversely proportional due to saturable absorption
	  • Immediate release
	  • 900mg/day: 60%
	  • 1200mg/day: 47%
	  • 3600mg/day: 33%
	  • 4800mg/day: 27%
	  • Extended release: increased with higher fat content
	• Half-life:
	  • ≤ 12 years old: 5hr
	  • > 12 years: 5-7hr
	  • Longer in patients with decreased renal function

FDA-Approved & Investigational Cannabinoid Medications

Cannabidiol (CBD)
Epidiolex ®

Dronabinol (THC)
Marinol®
Syndros®
Nabilone (THC)
Cesamet®

Nabiximols (THC + CBD)
Sativex® *not FDA approved*

Note: CBD (Epidiolex) is not a CB1 agonist – its mechanism is distinct from THC-based agents (dronabinol, nabilone, nabiximols), which act at CB1.

CB1 Antagonists/Inverse Agonists: Rimonabant

- Rimonabant: a CB1 receptor inverse agonist developed for weight loss and smoking cessation
- Approved in Europe (2006) but never approved in the U.S.; withdrawn from the European market (2008) due to:
  - Significantly increased risk of depression and suicidality
  - Anxiety and other psychiatric adverse effects

Medicinal Uses of Cannabis/Cannabinoids

- Dronabinol: FDA approved for treatment of anorexia associated with weight loss in patients with AIDS, chemotherapy-induced nausea/vomiting.
- Nabilone: FDA approved for treatment of chemotherapy-induced nausea/vomiting.
- Studies also ongoing re: effects on other disease states (epilepsy, MS).

Therapeutic Potential

- Pain (cancer, multiple sclerosis)
- Nausea (cancer)
- Loss of appetite and wasting (HIV/AIDS)
- Increased ocular pressure (glaucoma)
- Inflammation (rheumatoid arthritis, Crohn's disease, ulcerative colitis)
- Epilepsy

In Summary

Cannabis includes plants and synthetic cannabinoids.

Cannabis use is common, risk of a use disorder increases with earlier onset of use.

Cannabis contains more THC now than in the past.

Cannabis can affect cognition, but this is reversible in adults, impacts on adolescents less clear.

Most treatment is psychosocial, but several drug targets are being investigated.

Which of the following trends in youth from the Monitoring the Future study about marijuana use and perception of harm is true?

A. Since the early 1990's, the percentage with perceived risk of harm from marijuana has been higher than past year use of marijuana.
B. Since about 2009, there has been a growing gap between decreased perception of harm and increased past year use of cannabis.
C. The lowest past year cannabis use was in the late 1970's.
D. The perceived risk of harm for cannabis fell throughout the 1980's.

Which of the following medications has a trial supporting efficacy in cannabis use disorder in adolescents?

A. N-acetylcysteine

B. Baclofen

C. Quetiapine

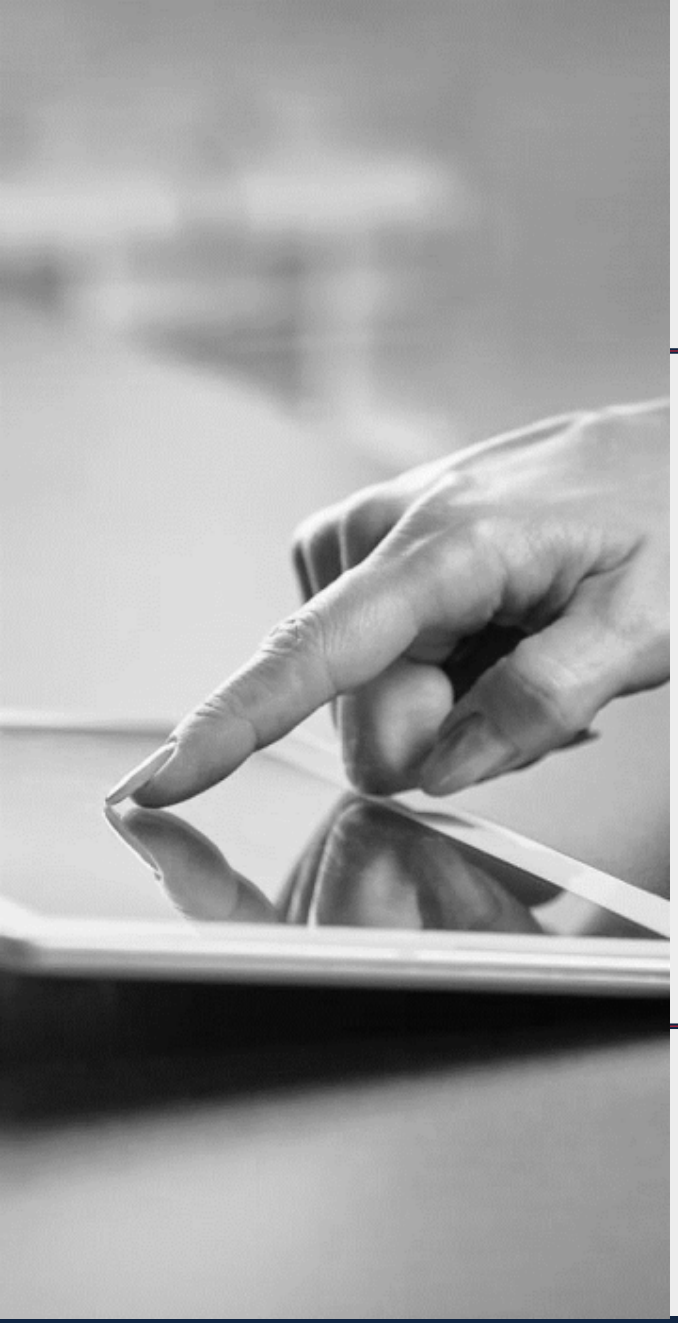
D. Mirtazapine

Cannabis use is reported in greater than 10% of pregnancies. Which correctly lists the reasons cannabis users who are planning to become pregnant should be cautioned against cannabis use:

A. THC does not cross the placenta or pass into breast milk, so the only risk to the fetus or infant is from secondhand smoke exposure after birth.
B. THC easily crosses the placenta and passes into breast milk, but because only the pregnant person is exposed, counseling about prenatal cannabis use is only relevant for female patients.
C. While human data on prenatal THC exposure are still limited, available evidence (consistent with animal studies) shows THC readily crosses the placenta and passes into breast milk, with potential effects on fetal growth and neurodevelopment.
D. Because no human studies have examined prenatal THC exposure, clinicians cannot give any guidance about cannabis use during pregnancy or lactation.

Board Question Answer Key & Rationale

- Q1 (MTF trends): Answer B
  - Since ~2009, a growing gap has emerged between declining perceived harm and sustained/rising past-year cannabis use; verify against the most recent MTF release, as post-pandemic data show shifting adolescent use trends
- Q2 (Medication with adolescent CUD trial): Answer A – N-acetylcysteine
  - Gray et al. (2012) showed NAC reduced cannabis use in non-treatment-seeking adolescents; baclofen, quetiapine, and mirtazapine lack supporting trials in adolescent CUD
- Q3 (Cannabis in pregnancy): Answer C
  - THC readily crosses the placenta and enters breast milk. Human neurodevelopmental data remain limited but are consistent with animal studies showing effects on fetal growth and brain development. Counseling applies to all patients who may become pregnant, not "females only" (A, B incorrect), and limited human data does not preclude clinical guidance (D incorrect)



Get in Touch

301.656.3920

education@asam.org

www.asam.org