ASAM REVIEW COURSE 2024

# 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

- No relevant disclosures

# 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 2021, an estimated 65.2 million Americans- **27.1%** 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.
- Cannabis use peaks in the late teens to early 20s, then declines

# Increased Risk for Use Disorder

- **9%** of users develop Cannabis Use Disorder
- 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
- Subspecies of the hemp plant

# 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.*

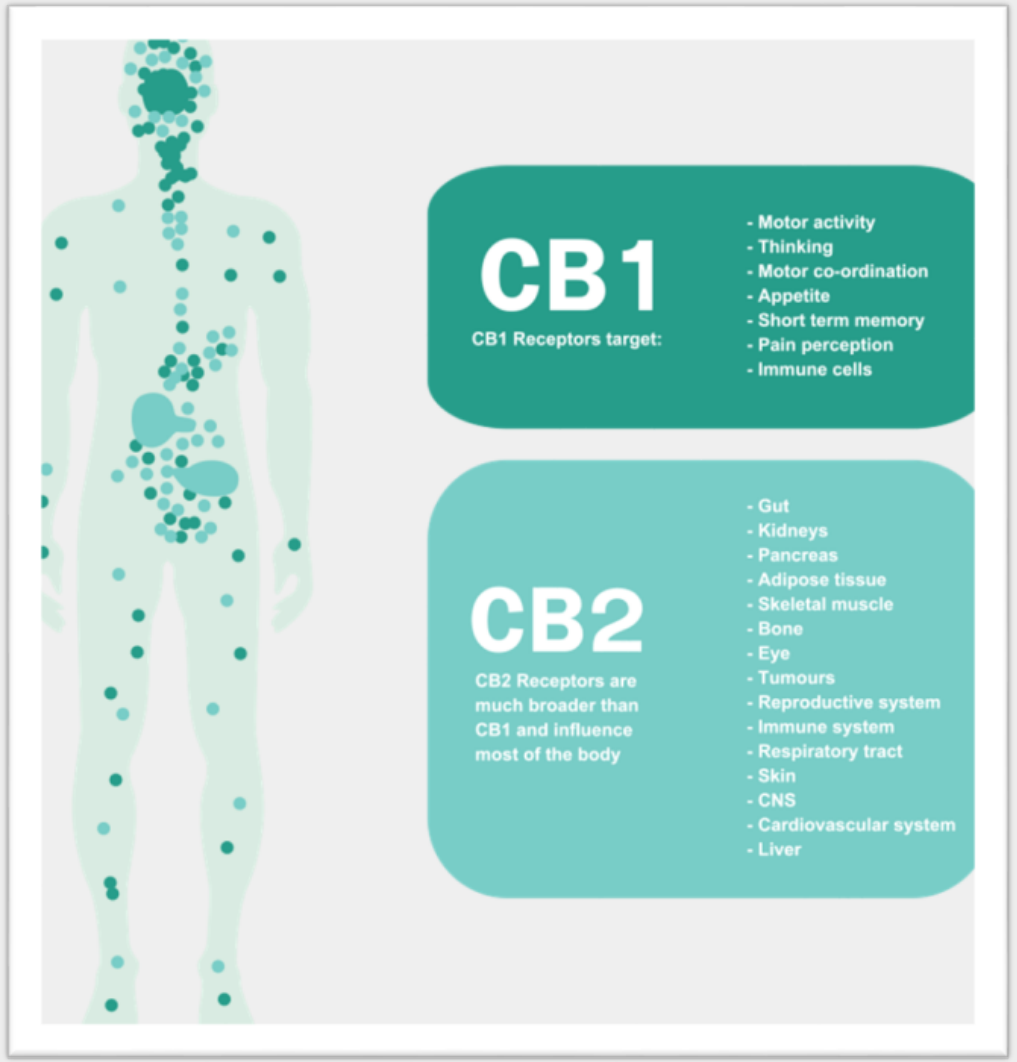
# Cannabinoid Receptor Neurobiology

# 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

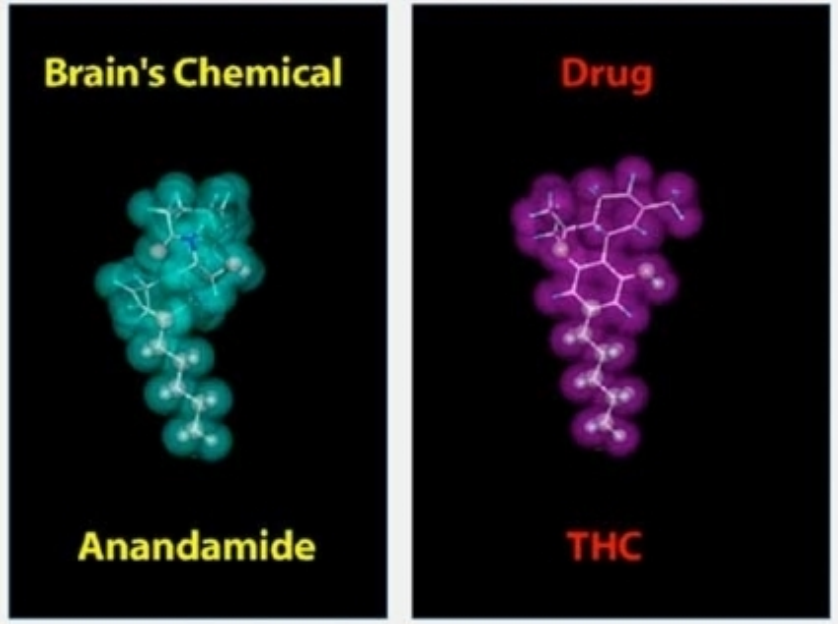
- CB1 – CNS site of CB binding
  - Memory, learning, problem solving, coordination
  - Activated by anandamide, other CBs
  - Modulates neurotransmitters
- CB2 – immune cells outside CNS
  - Anti-inflammatory effects



# Cannabinoids (CBs)

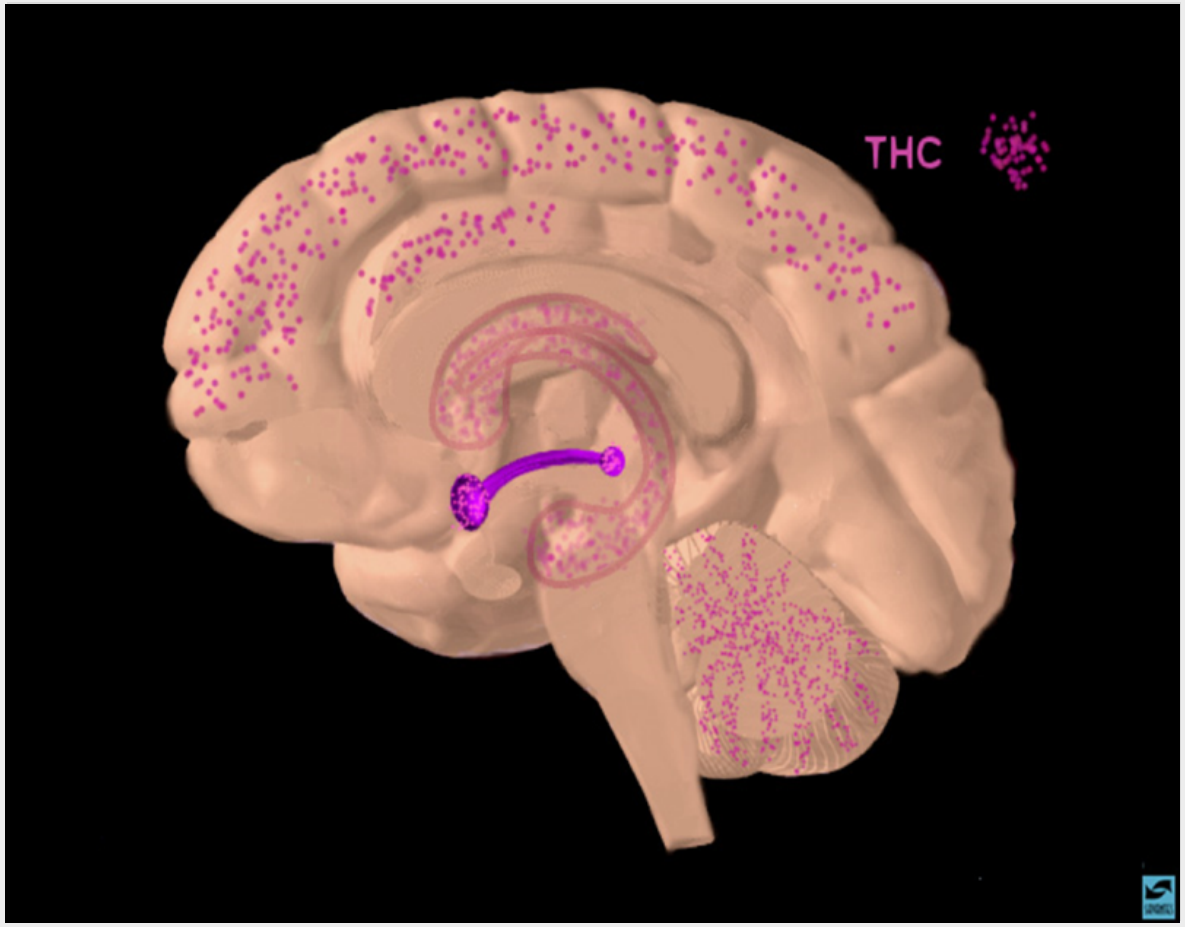
- > 400 chemicals, ↓ neurotransmitter release
- **Natural CBs**
  - **Endogenous** – Anandamide, 2-Arachidonoylglycerol (AEA, 2-AG)
  - **Exogenous** – Sativa or Indica plant (marijuana)
    - Tetrahydrocannabinol (THC) – psychoactive
    - Cannabidiol (CBD) – no effect in brain

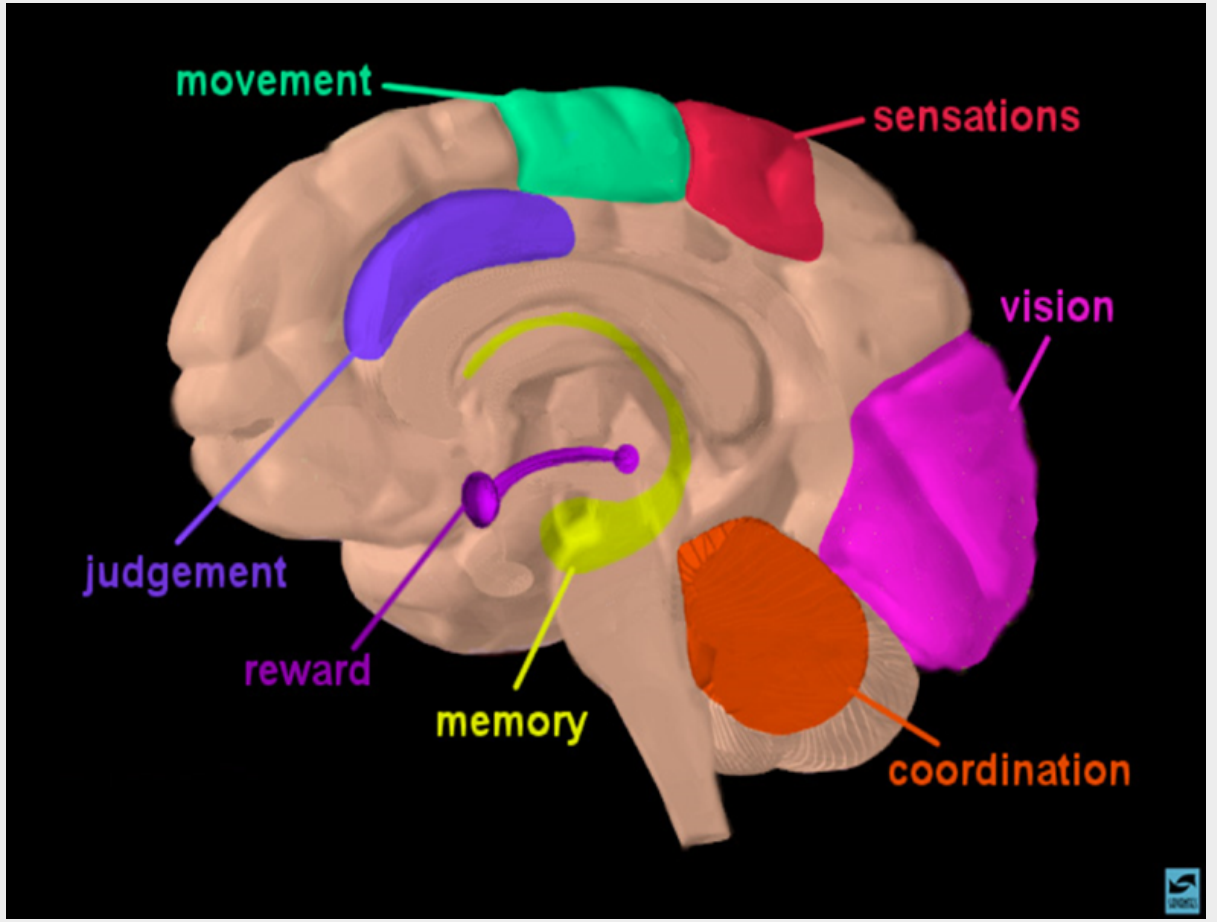
# 9-tetrahydrocannabinol (THC)




- 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, psychosis (visual – not auditory hallucinations).

# 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

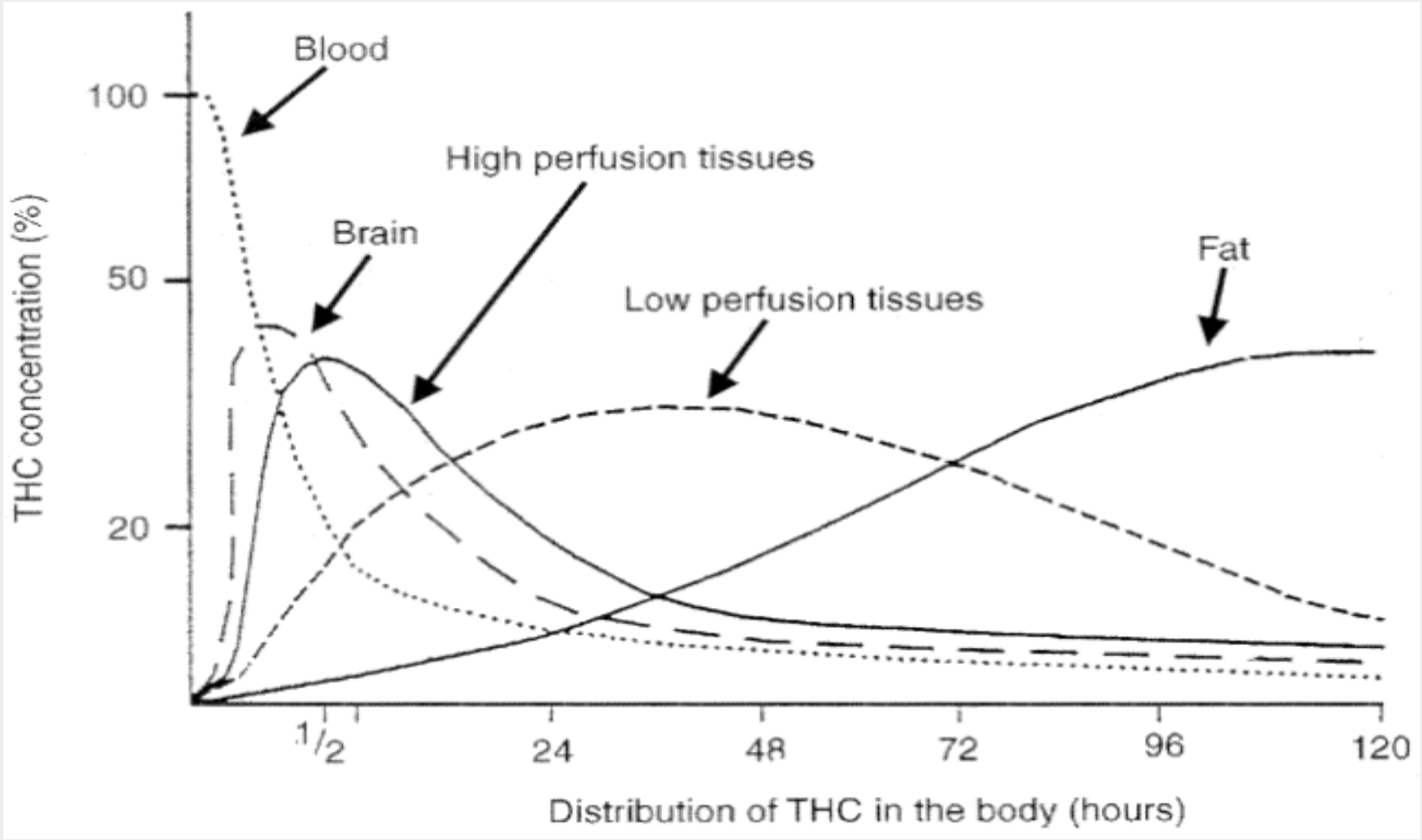
| *Smoked* | *Vaporized* | *Eaten/Drunk* |
|---|---|---|
| Smoked in a pipe, bowl, cigarette | Inhaled through machine that converts active compounds into inhalable form | Consumed as ingredient in baked goods, candies, sodas |
| Rapid effects | Rapid effects | Takes time to reach brain, so effects are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

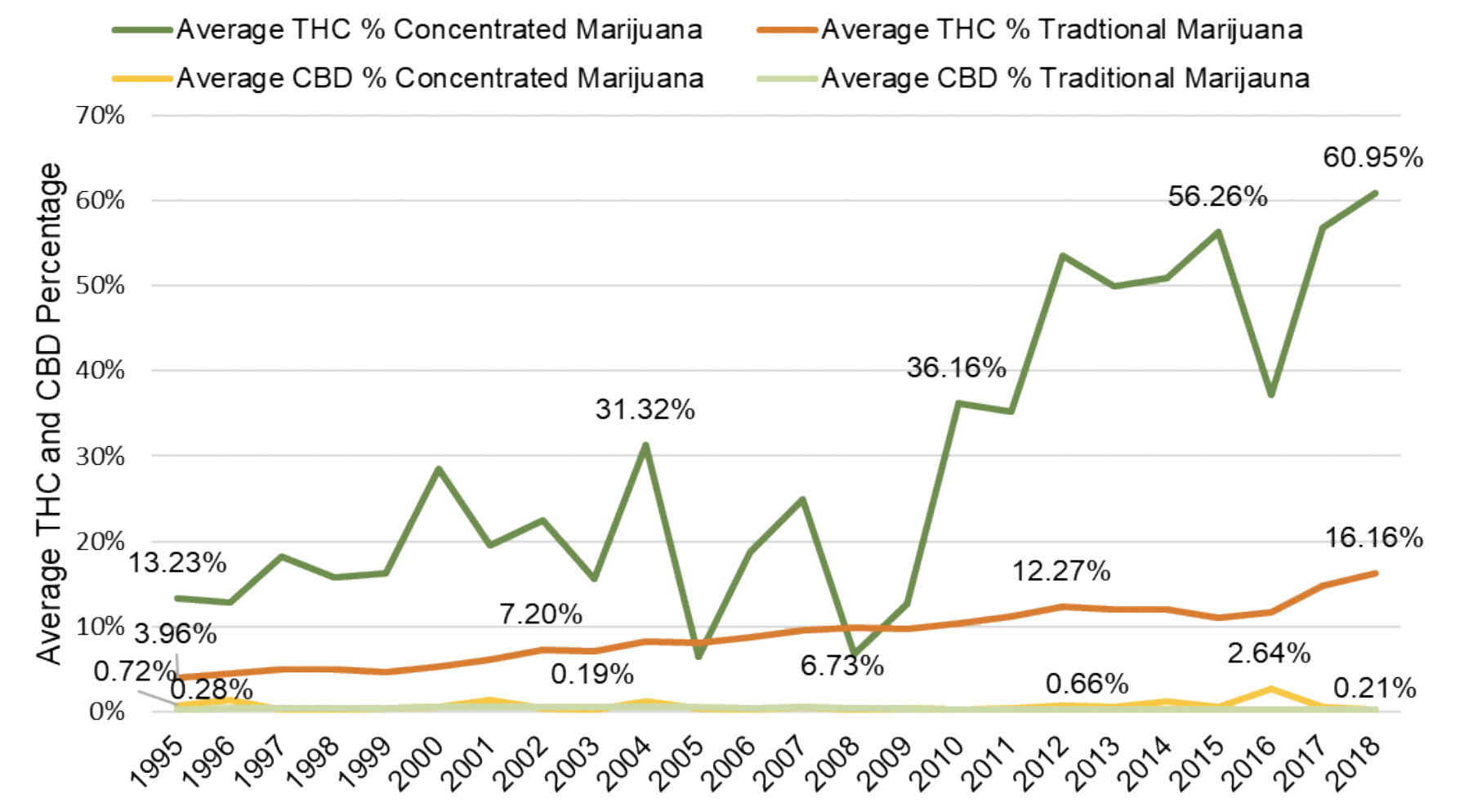
**AND ≥ 1 of the following:**

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

# THC Potency is Increasing

- Up to 31 % in products
- Widespread availability of THC edibles (food and beverage products) and butane-extracted hash oil products (“dabs”, “budder”, “shatter”, “wax”)
- Rate of ED visits per 100,000 for cannabis-related adverse reactions has dramatically risen: **96.2 to 146.2** (2004 in 2011).

# THC Percent is Increasing




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

# 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

# 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

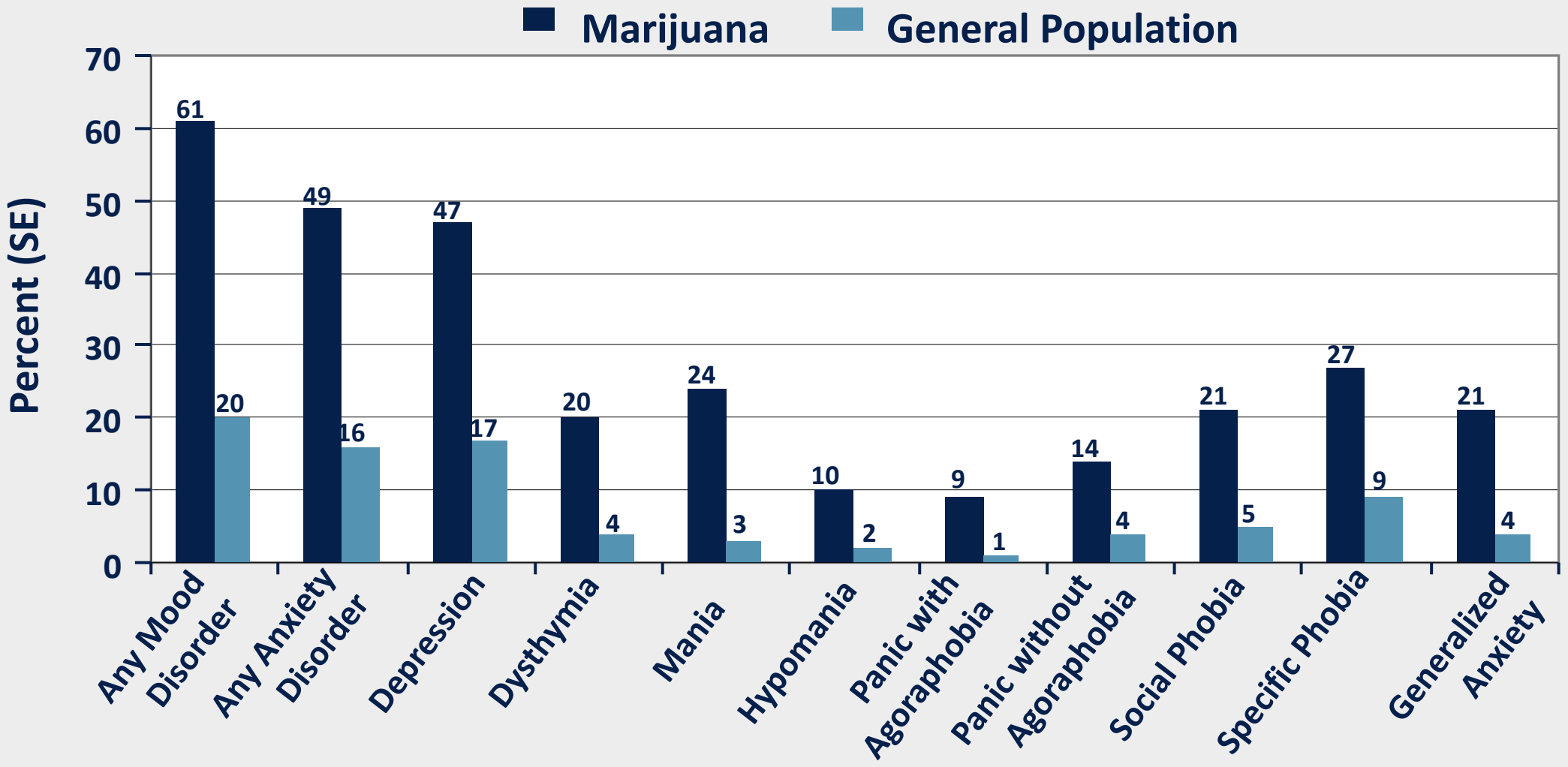
# Psychiatric

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

# Amotivational Syndrome

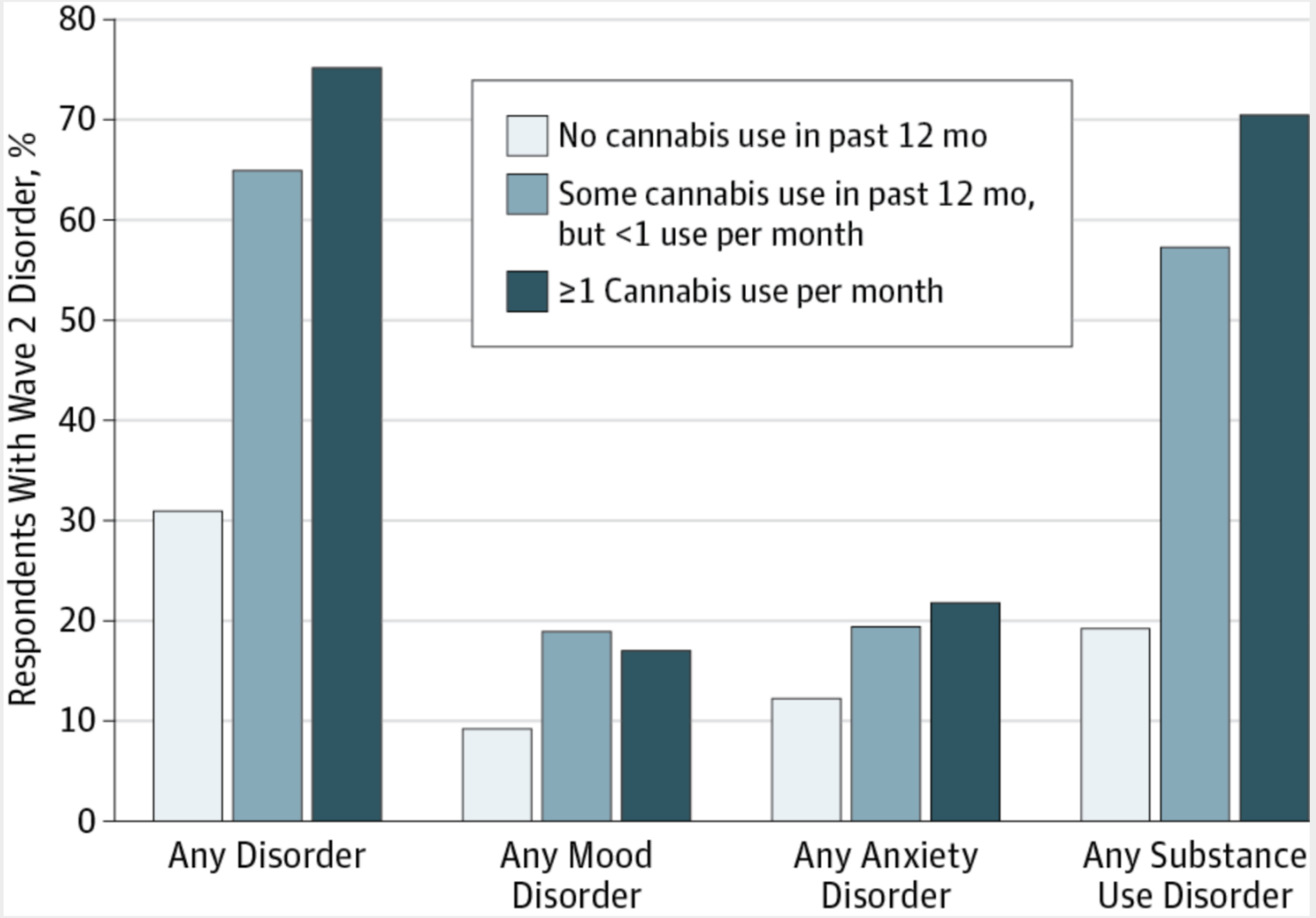
- Mental slowing
- ↓ Planning ability
- ↓ Judgment, concentration, memory
- Apathy, ↓ pursuit of goals

# 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

# 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<br>• 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**<br>• Contains THC | -- |
| Gabapentin | GABA modulation | • **Decrease self-reported cannabis use**<br>• **Reduced withdrawal symptoms** | -- |
| N-acetylcysteine | Correct glutamate dysregulation | • Decreased use in adolescents<br>• Did not show same benefit in adults | • Gray et al., 2012[9] |
| Naltrexone | Mu-opioid receptor antagonist | • Enhanced subjective effects of cannabis<br>• 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<br>• Drowsiness/insomnia<br>• Vivid reams<br>• *Anaphylactoid reactions seen with IV admin, not PO* |
| **Pharmacokinetics** | • Bioavailability for oral: 9%<br>• Metabolized to cysteine and glutathione<br>• 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<br>Mason (2012) [10]: 50 cannabis-dependent adults (18-65 years old)<br>• Gabapentin 1200mg vs placebo for 12 weeks<br>  • Titrated up to 300mg / 300mg / 600mg over the course of 4 days |
| **Clinical benefit** | • Increase in negative UDS<br>• Decrease self-reported cannabis use<br>• Reduction in withdrawal symptoms (mood disturbance, craving, and sleep disturbances) |

# Gabapentin

| | |
|---|---|
| **Risks** | Well tolerated ☺ Headache, nausea, insomnia and depression |
| **Pharmacokinetics** | • Bioavailability: inversely proportional due to saturable absorption<br>  • Immediate release<br>  • 900mg/day: 60%<br>  • 1200mg/day: 47%<br>  • 3600mg/day: 33%<br>  • 4800mg/day: 27%<br>  • Extended release: increased with higher fat content<br>• Half-life:<br>  • ≤ 12 years old: 5hr<br>  • > 12 years: 5-7hr<br>  • **Longer in patients with decreased renal function** |

# CB1 Receptor Agonists

Cannabidiol (CBD)

Epidiolex ®


Dronabinol (THC)

Marinol®

Syndros®

Nabilone (THC)

Cesamet®


Nabixmols (THC + CBD)

Stavivex® *not FDA approved*

# 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

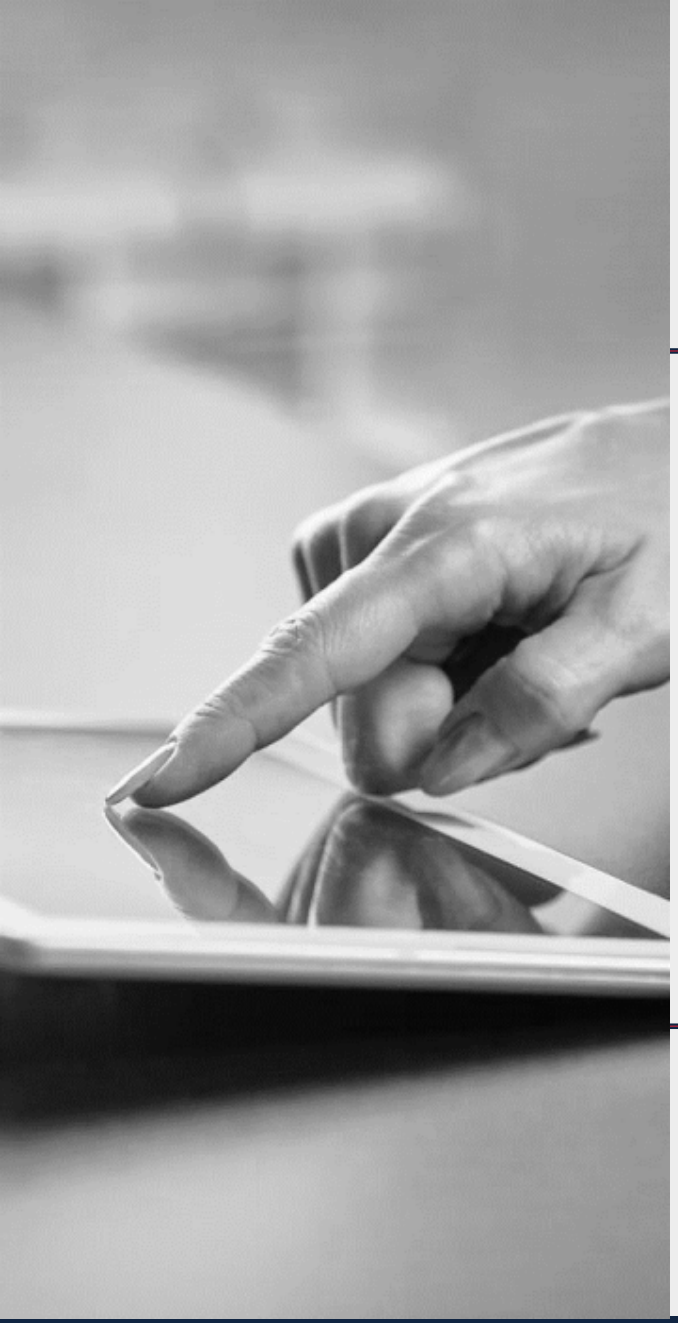
B. Baclofen

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 easily passes into breast milk and crosses membranes and is transferred to the developing fetus, and therefore impacts pregnancy success in females only.
B. While THC does not pass into breast milk, studies show that it does easily crosses membranes and is transferred to the developing fetus.
C. While human studies on the effect of prenatal THC exposure on the developing brain are preliminary, they correlate with studies carried out in animals and show that THC easily passes into breast milk and crosses membranes and is transferred to the developing fetus.
D. While no human studies have been done on the effect of prenatal THC exposure, animal studies show that it does easily pass into breast milk, crosses membranes, and is transferred to the developing fetus.



# Get in Touch


301.656.3920

education@asam.org

www.asam.org