ASAM REVIEW COURSE 2023

Cannabis Use Disorder: Science, Trends, and Clinical Implications

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Financial Disclosure

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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 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

- **13%** of users have Cannabis Use Disorder

Increased Risk for Use Disorder

- 9% of people who use marijuana may develop ‘pre-substance dependence.’
- 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

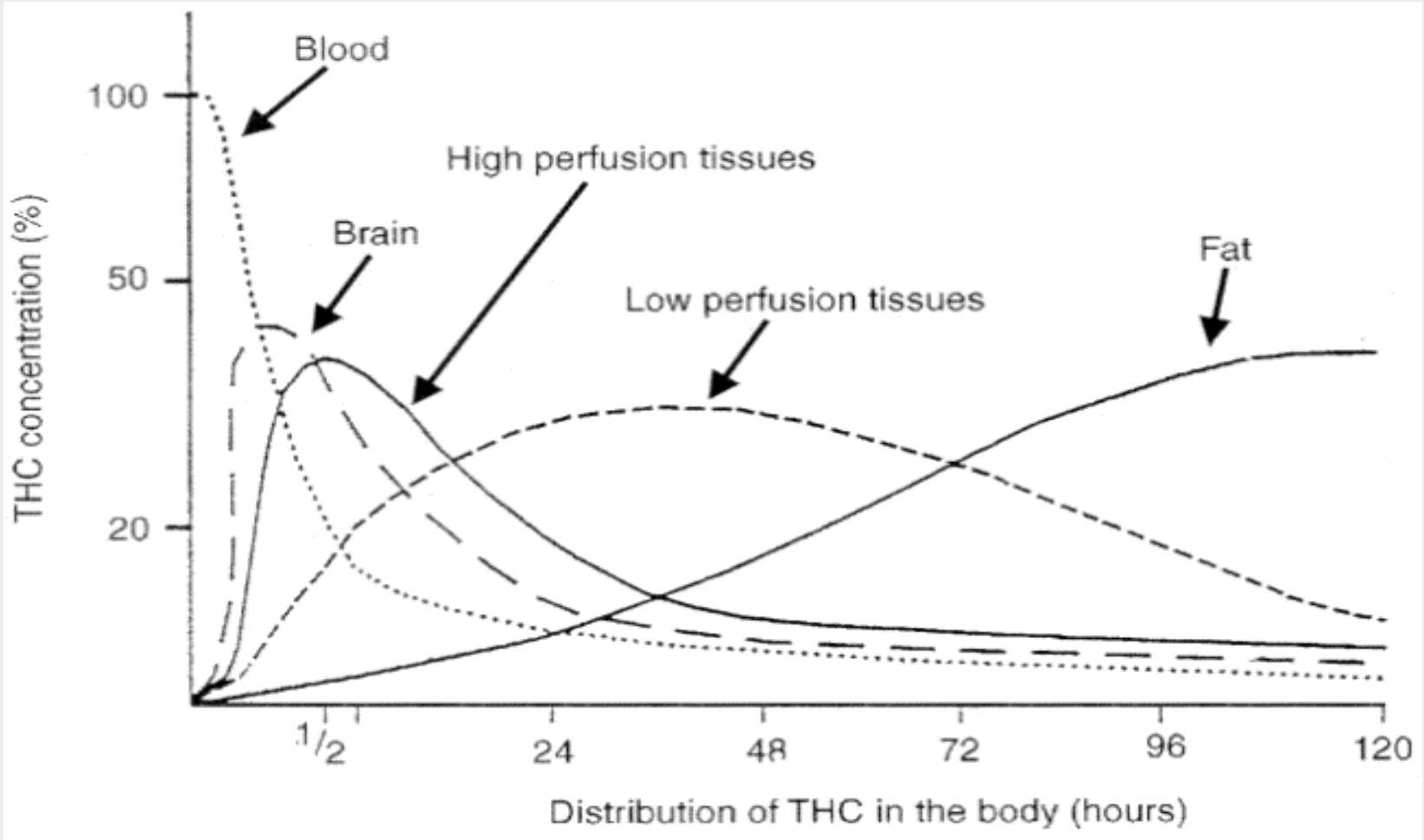
- Higher affinity for cannabinoid receptors than THC
- Have active metabolites that prolong their durations of action
- Increased potential for toxicity
- “Spice” or “K2”
- Not detected on standard UDS

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.

Biphasic distribution



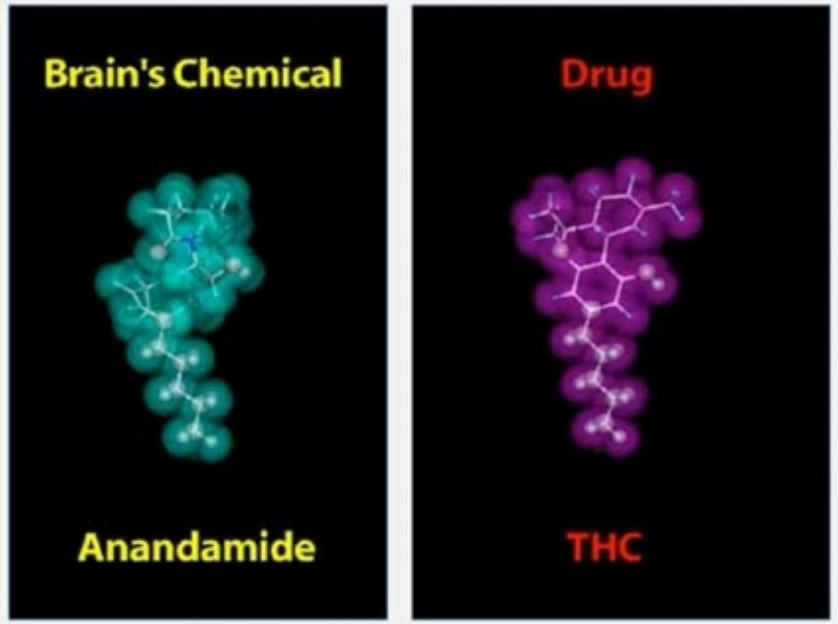
2019 National Drug Threat Assessment. US Department of Justice Drug Enforcement Administration. December 2019.

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.

9-tetrahydrocannabinol (THC)

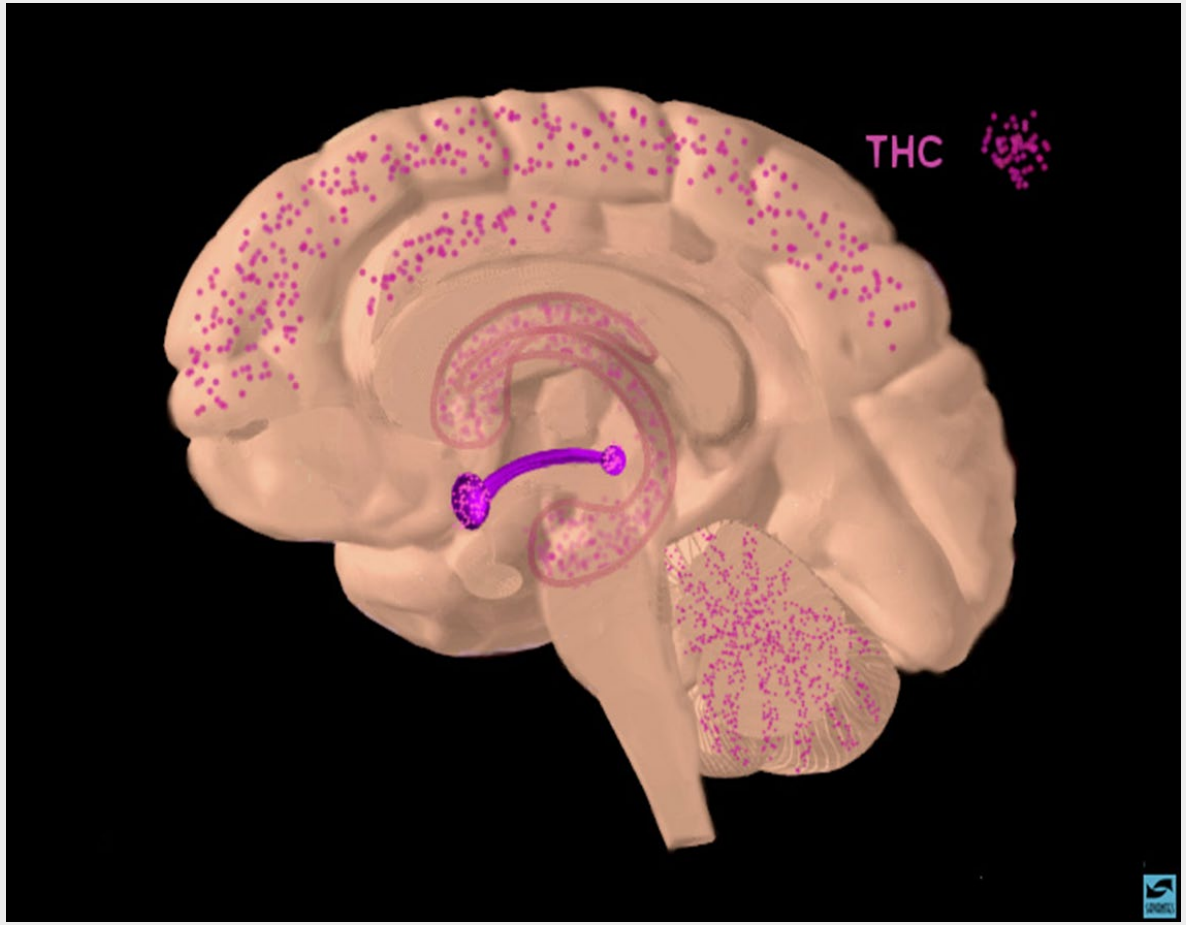


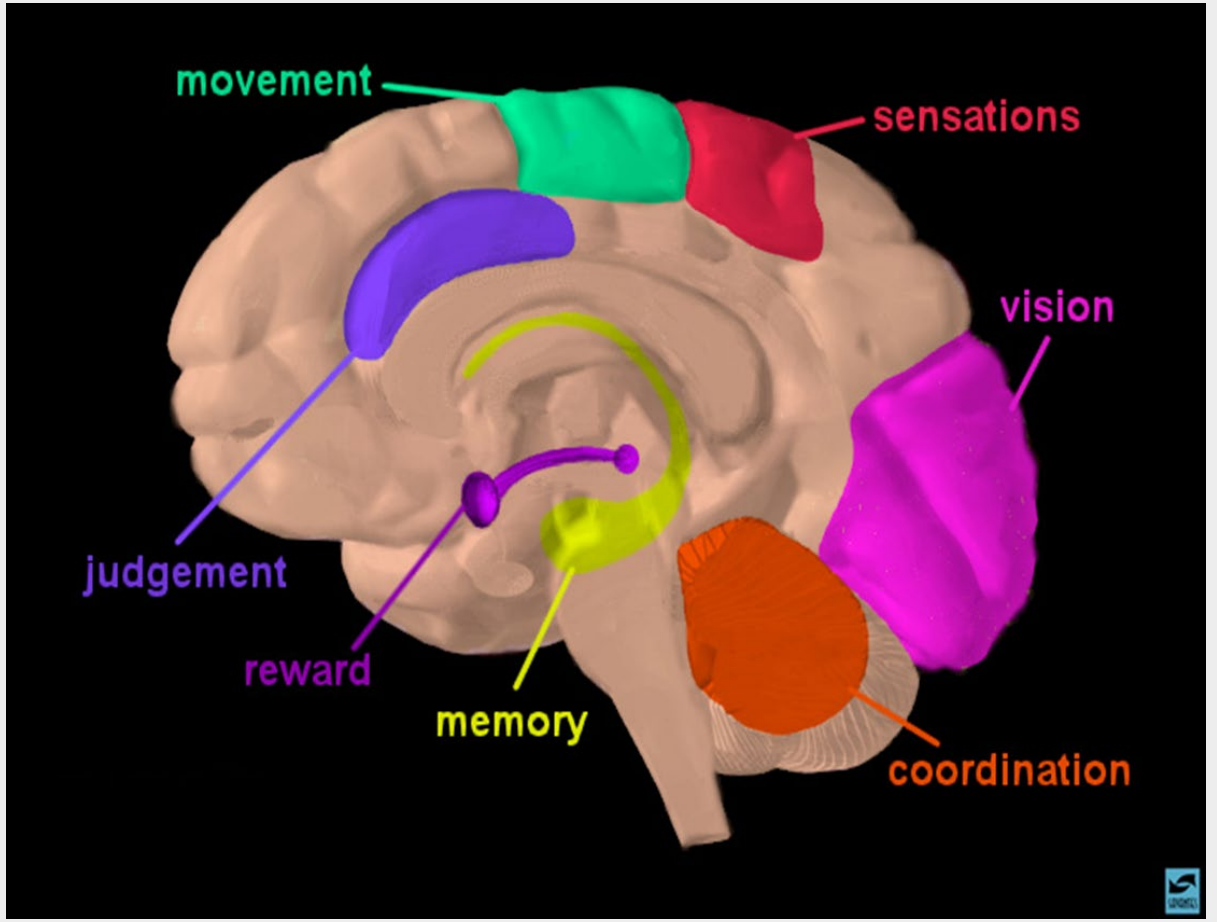
- Primary psychoactive constituent
- Endocannabinoid system
  - Brain development
- Mimics anandamide
  - Dial down neuron activity

Cannabinoids (CBs)

- > 400 chemicals, ↓ neurotransmitter release
- Natural CBs
  - Endogenous – Anandamide (“bliss”)
  - Exogenous – Sativa plant (marijuana)
    - Tetrahydrocannabinol (THC) – psychoactive
    - Cannabidiol (CBD) – no effect in brain

CB1 Receptor Locations in the Brain



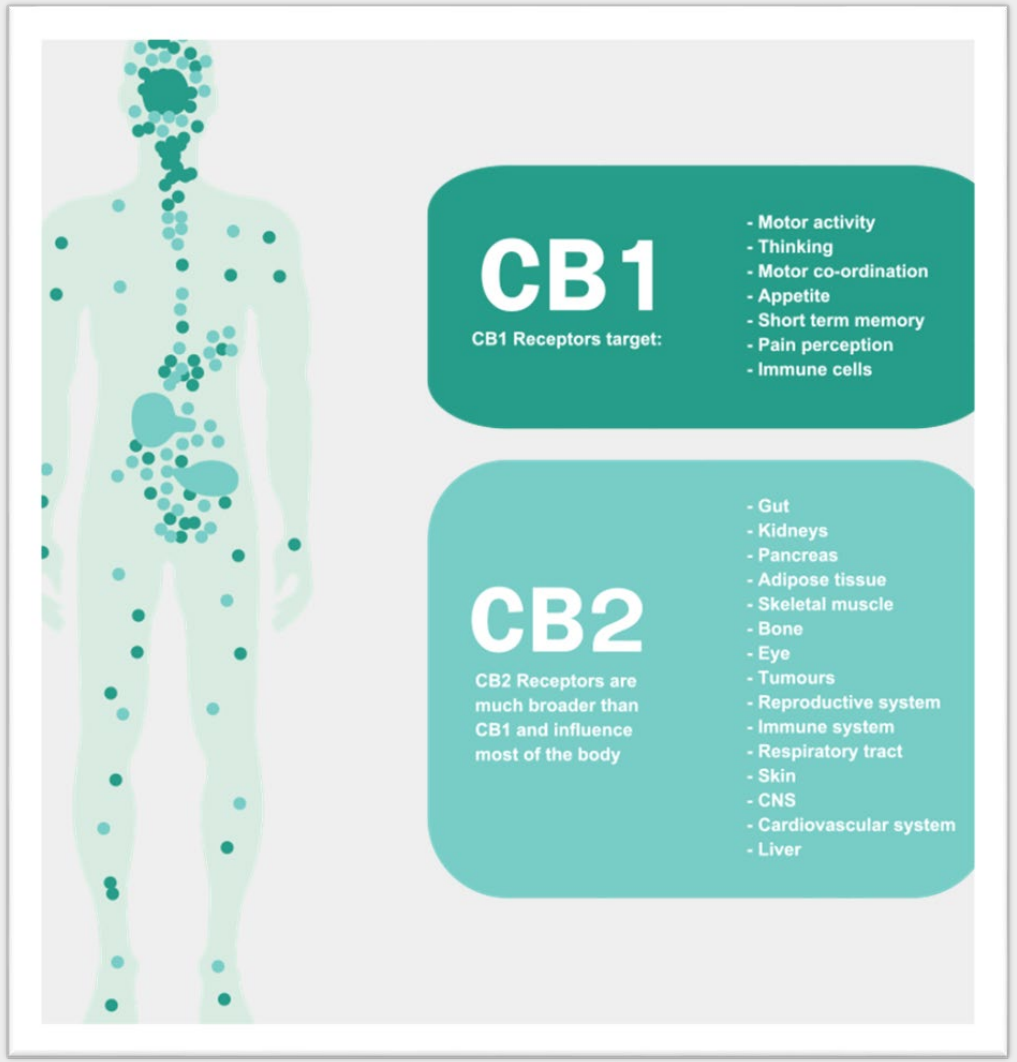


The Endocannabinoid System

- Endocannabinoids (AEA, 2-AG) are naturally produced by the body.
- They bind to cannabinoid receptors.
- Endocannabinoids bind both CB 1 and CB 2.
- Endocannabinoids function as “retrograde messengers.”

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



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).

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.

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

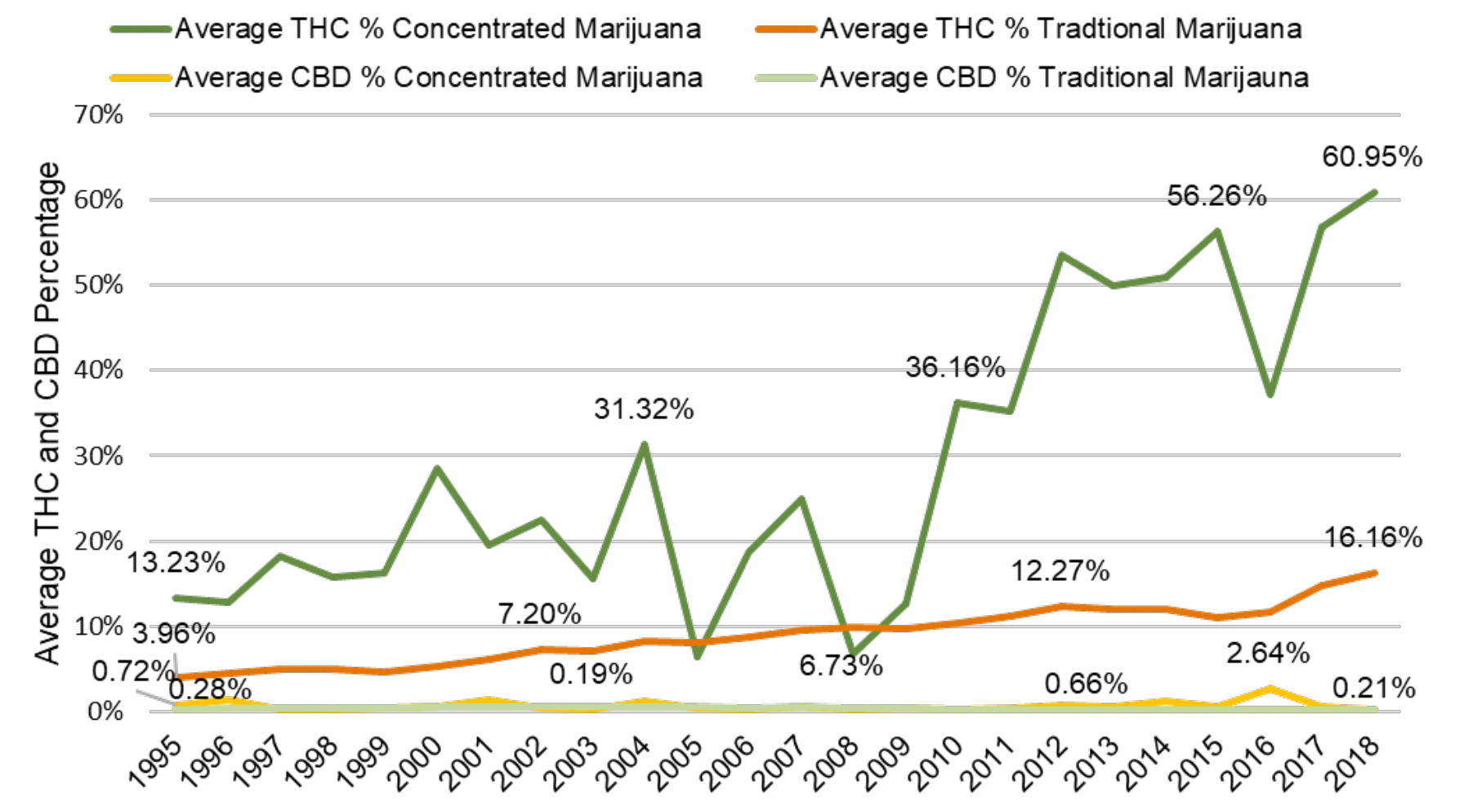
Causing distress & ≥ 3 of the following:

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

AND ≥ 1 of the following:

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

THC Percent is Increasing



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

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).

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
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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

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 4%)
- 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.

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

Effects of Use

Physiological Effects

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

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

Impaired Cognition

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

Physical Health

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

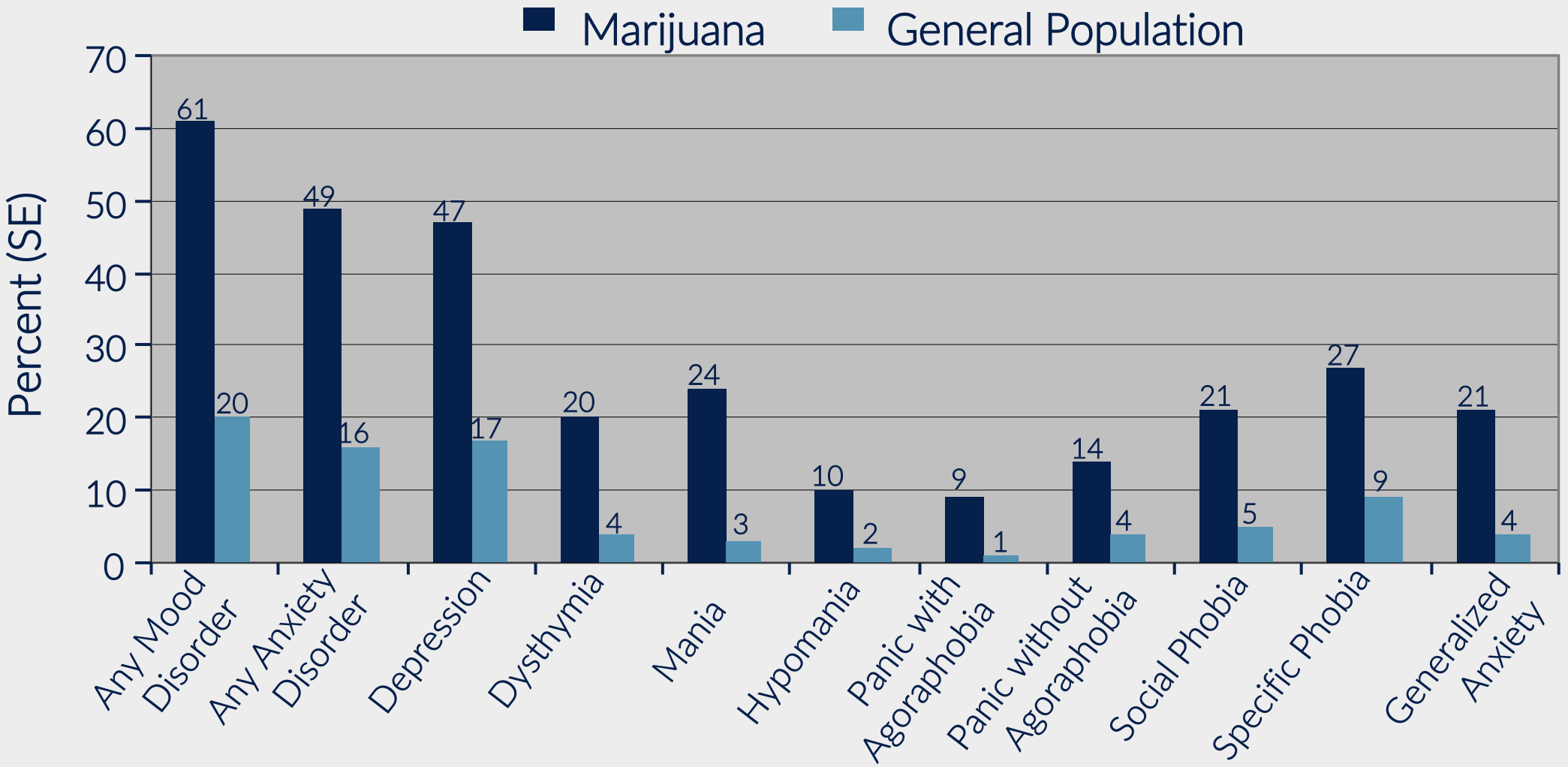
Psychiatric

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

Amotivational Syndrome

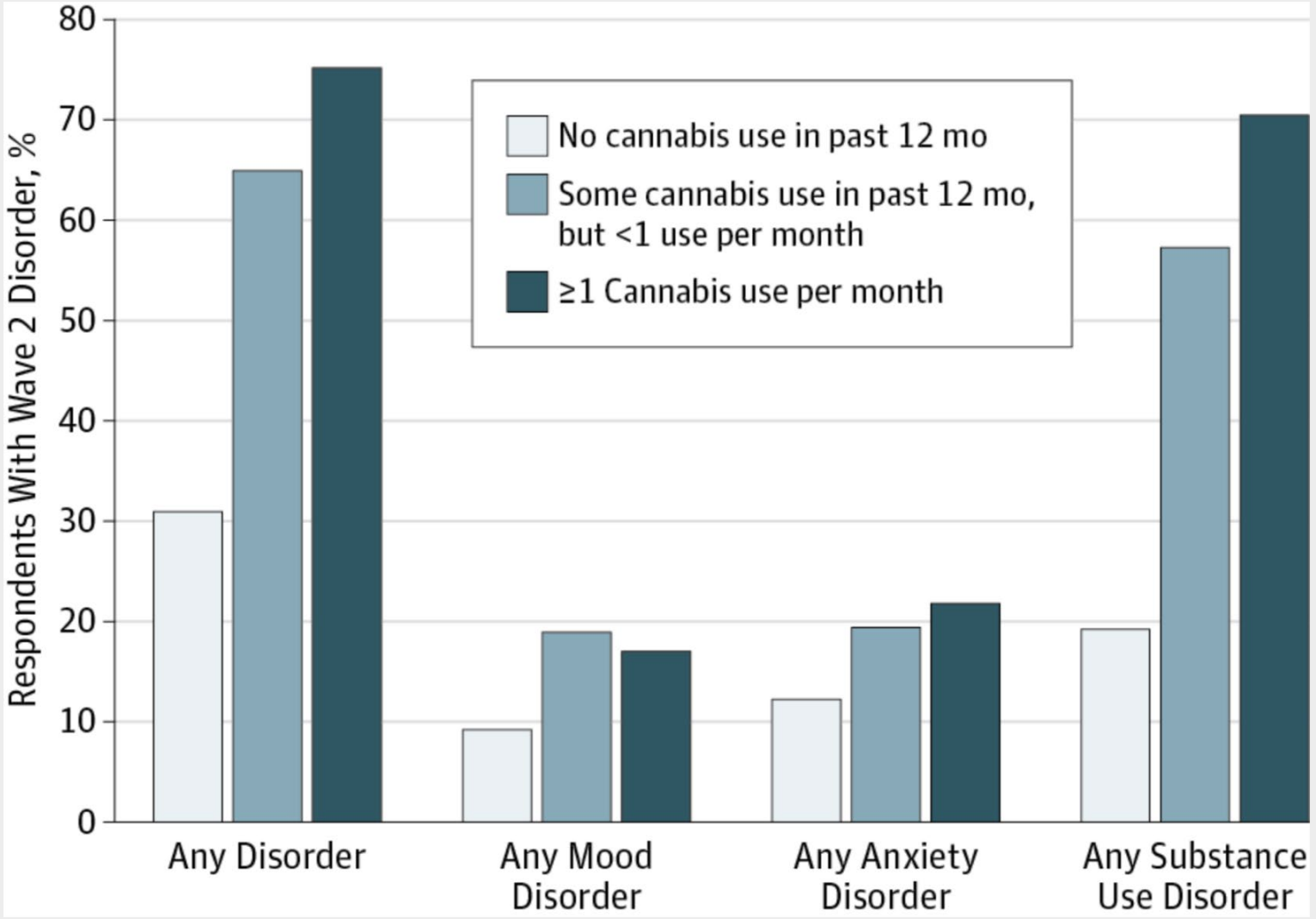
- Mental slowing
- ↓ Planning ability
- ↓ Judgment, concentration, memory
- Apathy, ↓ pursuit of goals

Psychiatric Co-Morbidity



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

Psychiatric Co-Morbidity



Diagnosis

Substance Use Disorder

In Same Year, ≥2 of:

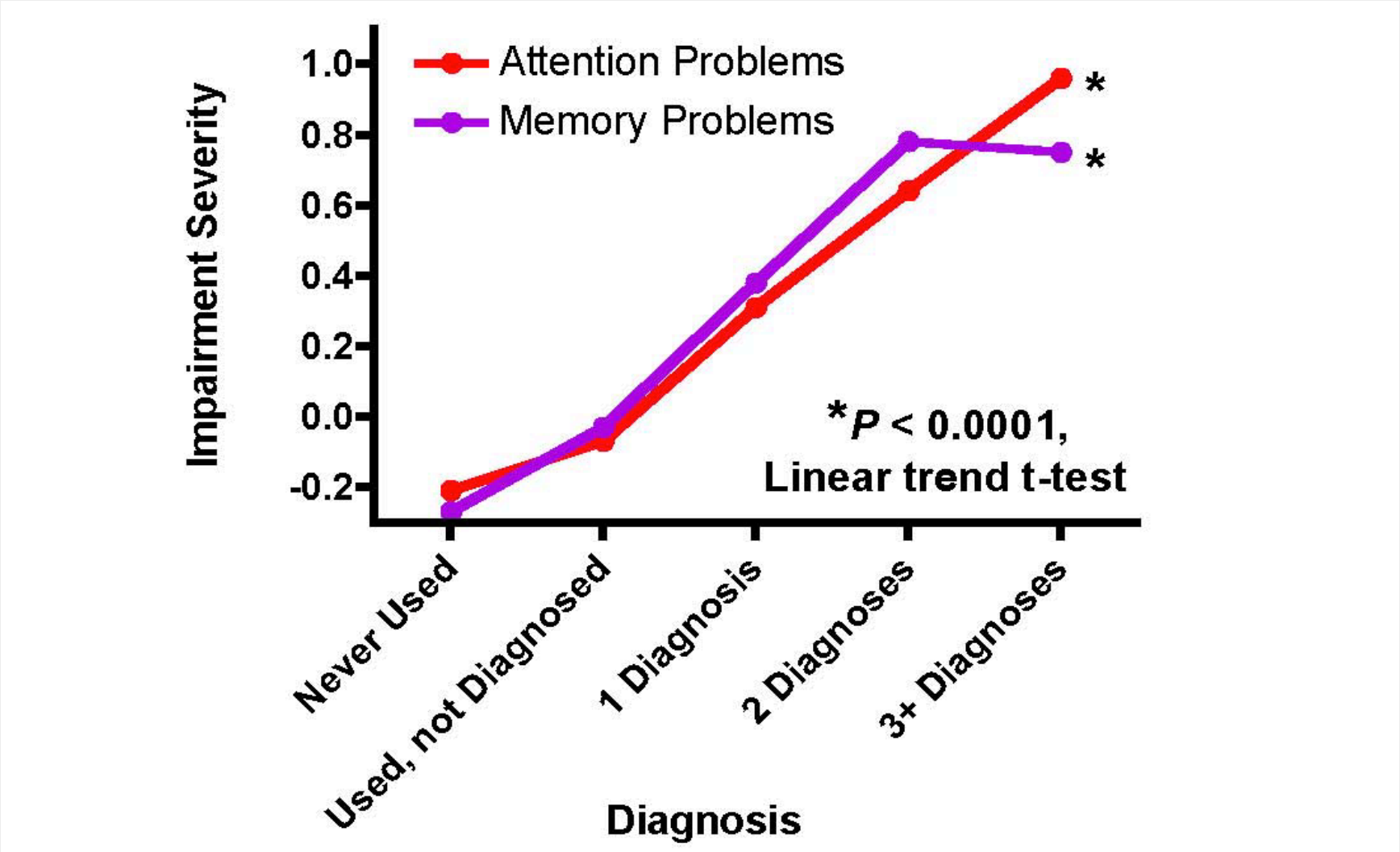
- Tolerance
- Withdrawal
- Use more/longer
- Unable to ↓ use
- Use despite problems
- Craving
- Failed roles
- Hazardous use
- Social problems
- ↓ Activities
- Lots time use

Cognitive Effects

Residual Cognitive Effects

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

Attention and Memory



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

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

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	--

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	Well tolerated ☺ 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

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

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