CANNABIS

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The ASAM Board Exam Study Course in Addiction Medicine
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Learning Objectives

At the end of the course, you will be able to:

- Describe basic epidemiology of cannabis use disorders, as well as changes in harm perception and use.
- Use basic information about routes of administration, pharmacodynamics, and toxicology to understand physiologic effects and monitoring.

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Learning Objectives

At the end of the course, you will be able to:

- Characterize effects of use of marijuana.
- Differentiate between cannabis use and a cannabis use disorder.
- Understand the underlying neurobiology and how this impacts physiologic effects and drug design.
- Compare various treatment modalities and targets to understand current and potential treatments.

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Marijuana

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Marijuana

Cannabis

Sativa or ***Indica***

- Subspecies of hemp plant
- Common throughout world

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Synthetic Cannabinoids

- 3 grams of synthetic cannabinoids sprayed on vegetable matter, herbal incense or meditation potpourris
- Labeled "not for human consumption"
- No age restriction
- Sold in stores or on the Internet as "legal high"

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Synthetic Drug Abuse Prevention Act of 2012

- Cannabimimetic Agents are Schedule I.
- "Unless specifically exempted or unless listed in another schedule, any material, compound, mixture, or preparation which contains any quantity of cannabimimetic agents, or which contains their salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible within the specific chemical designation."

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Epidemiology

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Past vs. Present

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Cannabis Use Disorders are Common

- 22 million users in past month
- 13% users have CUD
- 305,000 sought Rx for CUD

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Increasing Addiction Risk

- 9% of people who use marijuana will become addicted.
- The risk increases to 17% in people who start using in their teens.
- The risk increases to 25 to 50% in people who are daily users (most of whom started using marijuana early in adolescence).

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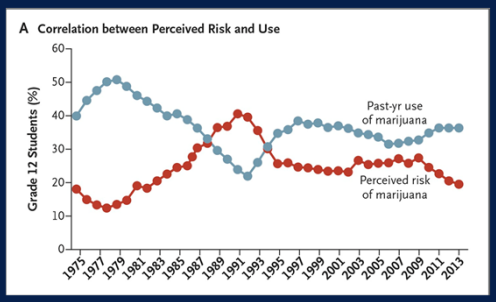
Increased Use and Decreased Perceived Risk



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Decreased Harm Perception

- 36% of teens think MJ harmless
- 43% favor legalization
  - 80s: 15%
  - 90s-00s: 30%
- Harm perception lowest in 40yrs
  - Often precedes ↑ prevalence

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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

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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.

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The Basics

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Desirable Effects

- Mild euphoria and relaxation
- The giggles
- Increased sensitivity to external stimuli:
  - Colors seem brighter
  - Smells are more pungent
- Distortion of time perception

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Average THC % Increase Over Time

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↑ Potencies

- In 1960s-70s potency ~1-2% THC
- Today, up to 20-25% THC

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Routes of Administration

- Smoked marijuana:
- Reaches the brain in minutes.
- Effects last 1 - 3 hours.
- Delivers a lot of THC into the bloodstream.

- Eating or drinking marijuana:
- Takes ½ - 1 hour to have an effect.
- Effects last up to 4 hours.
- Delivers significantly less 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

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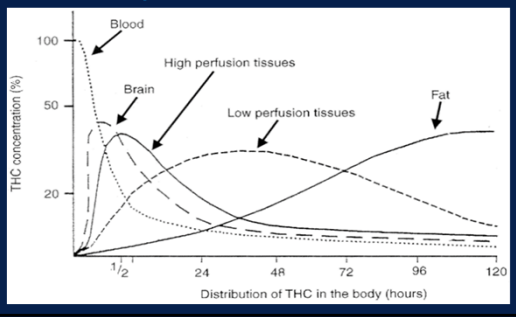
Biphasic Distribution



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Toxicology Testing

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

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Effects of Use

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Physiological Effects

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

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Neurocognitive Effects

- Short-term memory impairment
- Judgment impairment
  - …leading to risky sexual behaviors
- Motor coordination impairment
  - …interfering with driving skills

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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

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Driving Under the Influence

- THC primarily impairs automatic driving functions
  - Can be compensated with behavioral strategies
- Alcohol impairs complex tasks requiring conscious control
- Combining THC with alcohol
  - Eliminates the compensatory strategies that help with THC
  - Results in impairment even at doses that would be insignificant for either drug alone

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A Motivational Syndrome

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

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Impaired Cognition

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

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Physical Health

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

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Pregnancy

- Endocannabinoid system plays a role in the control of brain maturation, particularly emotional responses
- Babies exposed to THC:
  - Neurological development effects
- Children exposed to THC:
  - Problem-solving skills, memory, attention
- THC-specific vs. associated environmental factors hard to sort out

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Mental Health

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

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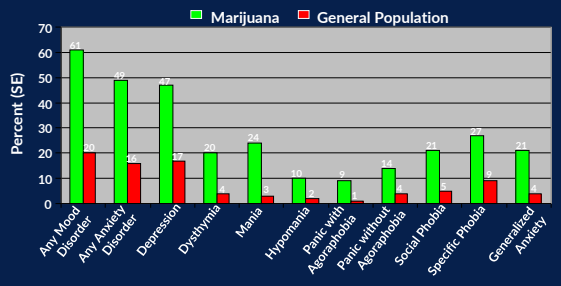
Psychiatric Co-Morbidity



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

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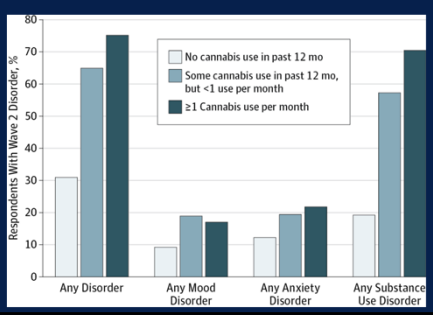
Psychiatric Co-Morbidity



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Ongoing Debates…

- Cancer
  - Cannabis has up to 70% more carcinogens than tobacco
  - Meta-analysis from 2020
    - ≥1 joint/day x 1 yr+ → ↑ testicular cancer
      - Lung cancer findings mixed; no clear evidence for other cancers
- Bronchitis and chronic cough
- Warning for Coronary Artery Disease
- Amotivational syndrome debate

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Diagnosis

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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

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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

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Which of the following is a criterion for cannabis use disorder according to the DSM V?

A. Smoking more than 1 gram of marijuana per day.
B. Feeling high from marijuana.
C. Being arrested for a cannabis related crime.
D. Problems with your role at work due to cannabis use.

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Basic Science

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Cannabinoids (CBs)

- > 400 chemicals, ↓ neurotransmitter release
- Natural CBs
  - Endogenous – Anandamide ("bliss")
  - Exogenous – Sativa plant (marijuana)
    - Tetrahydrocannabinol (THC) – psychoactive
    - Cannabidiol (CBD) – no effects

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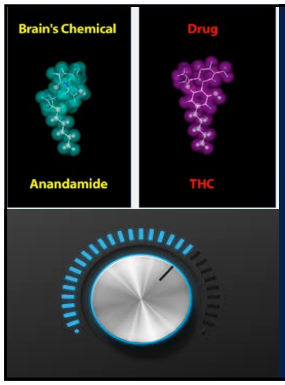

Δ9-tetrahydrocannabinol (THC)

- Primary psychoactive constituent
- Endocannabinoid system
  - Brain development
- Mimics anandamide
  - Dial down neuron activity
  - THC longer and stronger

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The Cannabinoid System

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

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Screening Tools

Alcohol Screening is an Effective Prevention Strategy

The CAGE Questionnaire

- Cut Down
- Annoyed
- Guilty
- Eye-Opener

2 or more positive responses are strongly associated with alcohol dependence.

National Institute on Alcohol Abuse and Alcoholism (NIAAA): "Helping Patients Who Drink Too Much"

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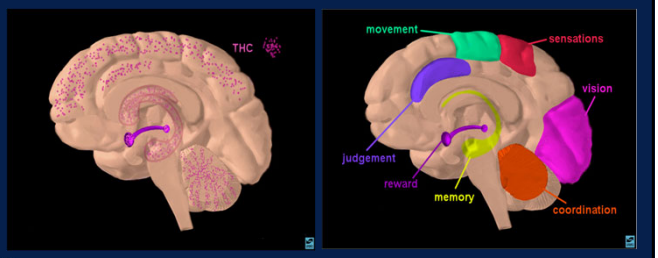
CB1 Receptor Locations in the Brain



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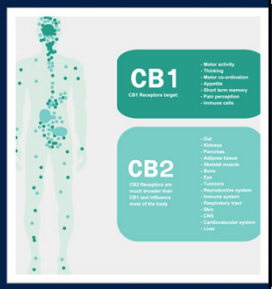
Cannabinoid Receptors

- 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



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Neurotransmitter Modulation

- Dopamine (DA) - euphoria, reward, pleasure
- GABA - muscle relaxation, sleepiness
- ↓ Glutamate - relaxation, ↓ memory

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Cognitive Effects

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Residual Cognitive Effects of MJ

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

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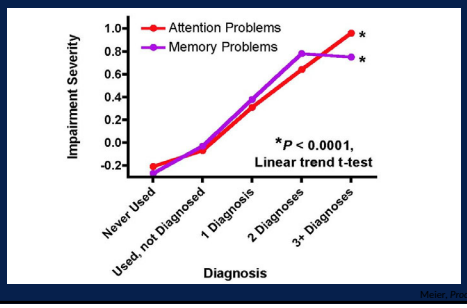
Attention and Memory



Meier, *Proc. Natl. Acad. Sci.*, 2012.

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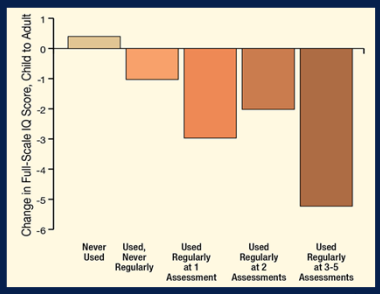
IQ Drop



Meier, *Proc. Natl. Acad. Sci.*, 2012.

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Likely Reversible with Abstinence

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

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Cognitive Deficit Resolution in Adults

- Apparent after a few days of abstinence
- Complete return-to-baseline by 30 days

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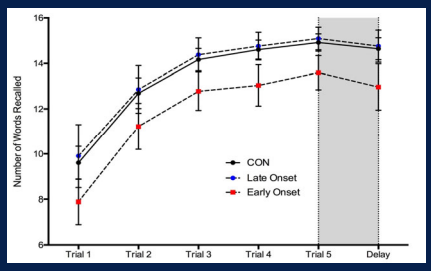
Learning Among Early and Late Onset MJ Users



Schuster et al., 2014

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Brain Differences with Early MJ

- Size, shape and function of brain regions
  - Important for:
  - Reward and motivation
  - Cognition
- Efficiency of inter-region connectivity

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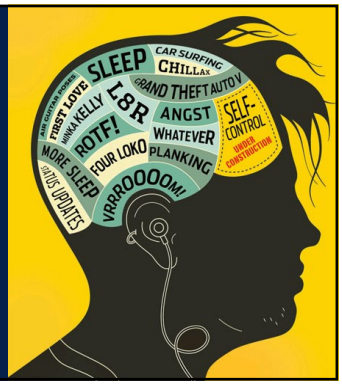
Adolescent Brain

- CB1 Receptors ↑↑↑ from infancy to age 30
- Most and latest change in areas of:
  - Reward and motivation
  - Cognition



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Similar Recovery in Adolescents?

- Contradictory and controversial findings
  - Some suggest no lasting deficits
  - Others find persistent deficits in 1+ domains
  - Most show at least partial recovery by 30d
- Recovery likely, though longer than adults

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Treatment

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Treatment for CUD is Challenging

- Few data-supported approaches
- ~ 50% achieve abstinence
- ~ 70% relapse
- No FDA-approved medications

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Psychosocial Treatments

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

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Psychosocial Tx for CUD

- Cognitive Behavioral Therapy (CBT)
  - Basic idea: thoughts = feelings and behaviors
  - Identify and correct problem thoughts and behaviors
  - Explore positive and negative CB consequences
  - Identify craving quickly to avoid CB use

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Psychosocial Tx for CUD

- Relapse Prevention Therapy (RPT)
  - Identify, avoid, cope
    - Effective coping skills
    - Pt's belief he/she can change
  - Keep CB use lapses "short"

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Negative Pharmacological Studies

Baclofen
Bupropion
Buspirone
Mirtazapine
Naltrexone
Nefazodone
Quetiapine
Valproate

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Medication for CUD

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

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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	• Decrease drug seeking behavior • Increase time of clean UDS	• Gray et al., 2012[9]
Naltrexone	Mu-opioid receptor antagonist	• Enhanced subjective effects of cannabis • No change in frequency of cannabis use	--

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N-acetylcysteine (NAC)

Mechanism of Action	• Prodrug of the amino acid cysteine • Correct glutamate dysregulation
Notes	Used in cocaine addiction, pathological gambling, skin picking and obsessive compulsive disorder
Doses	• 1200mg BID Gray (2012)[9]: 116 cannabis-dependent individuals (15-21 years old) • NAC 2400mg/day vs placebo • Urine drug screen (UDS) negative for THC • 2 weeks after treatment, abstinence 36.2 vs 20.7%, respectively
Clinical benefit	• Decrease drug seeking behavior • Increase time of clean UDS

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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

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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)

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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**

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CB1 Receptor Agonists

- Cannabidiol (CBD)
  - Epidiolex ®

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

- Nabiximols (THC + CBD)
  - Stavivex® *not FDA approved*

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Nabiximols

- Study in JAMA Internal Medicine July 2019 → 128 adults seeking treatment; 12 week trial; combo with six CBT sessions
- Each spray contained 2.7 mg THC: 2.5 mg CBD; up to 32 sprays/day
- Can reduce cannabis dependence when combined with behavioral therapy
- Used cannabis 33% fewer days; 54% cut use by 50% or more; no difference in #days abstinent; had a ~50% drop out rate
- THC via a safer route → harm reduction model

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

A. N-acetylcysteine
B. Baclofen
C. Quetiapine
D. Mirtazapine

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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

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Summary

- Cannabis includes marijuana plants and synthetic cannabinoids
- Cannabis use is common, risk of a use disorder increases with earlier onset of use
- Marijuana contains more THC now than in the past, which likely impacts risk for psychosis, anxiety, and negative consequences
- Marijuana effects cognition, but this is reversible in adults, impacts on adolescents less clear
- Most treatment is psychosocial, but several drug targets are being investigated

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Questions? Thoughts?

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