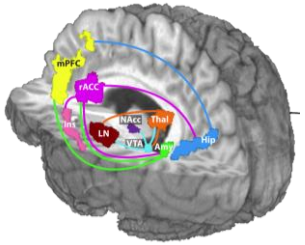

Cannabis Use & Related Disorders in Youth During the Age of Legalization

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Disclosures

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National Institutes of Health		X
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American Academy of Child & Adolescent Psychiatry		X
Johns Hopkins University School of Medicine		X
Doris Duke Charitable Foundation		X
National Network of Depression Centers		X
Substance Abuse and Mental Health Services Administration	X	X

AGENDA

- What is cannabis, How does it work, How has it changed?
- Developmental and long-term health effects of adolescent cannabis exposure
- Diagnosis and relevant prognostic features of cannabis use disorders in young people
- Effective evidence-based practices for treating youth with cannabis use disorders

What is Cannabis?

Cannabis Components

Delta-9-tetrahydrocannibinol (Δ^9-THC)

Major psychoactive component

Responsible for "high" from marijuana (MJ)

THC potency: ↑ in recent years

Cannabidiol (CBD)

Non-intoxicating; no craving

May ↓ undesirable THC effects

Medical benefits (less clear for youth)

100s of Other Components

Terpenes – in many plants (e.g., oranges)

Boosts MJ effects (e.g., ↓pain)

Cannabigerol (CBG) – non-intoxicating

↓ inflammation and ↑ appetite in animals

↓ intraocular pressure

Cannabichromene (CBC) – non-intoxicating

CBC+THC ↓ inflammation in animals

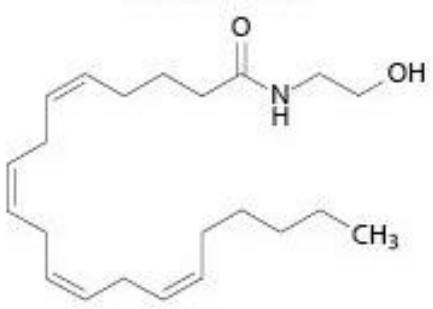
Blocks pain/inflammation (e.g., arthritis)

Phytocannabinoids Act on the Endogenous Cannabinoid (eCB) System to Produce Brain & Behavioral Effects

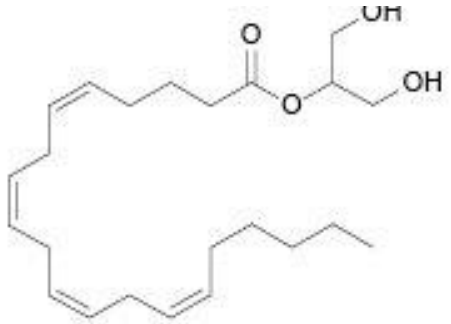
Homology between Endogenous and Exogenous Cannabinoids

Endogenous cannabinoids

Anandamide (ANA)

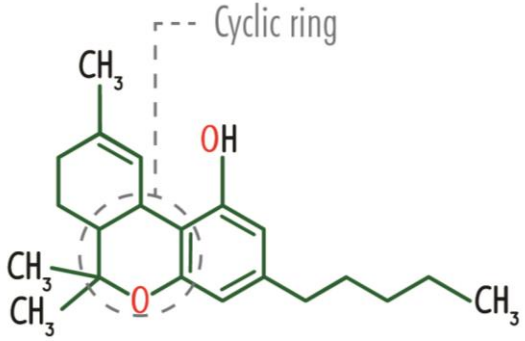


2-Arachidonyl glycerol (2-AG)

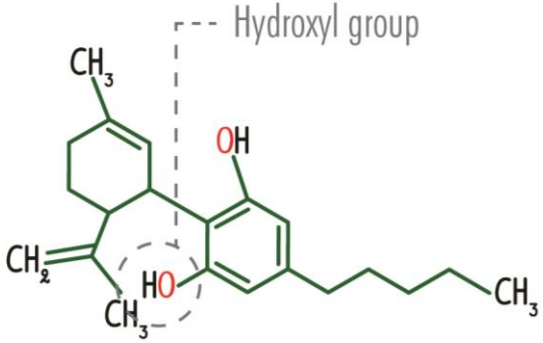


Exogenous cannabinoids

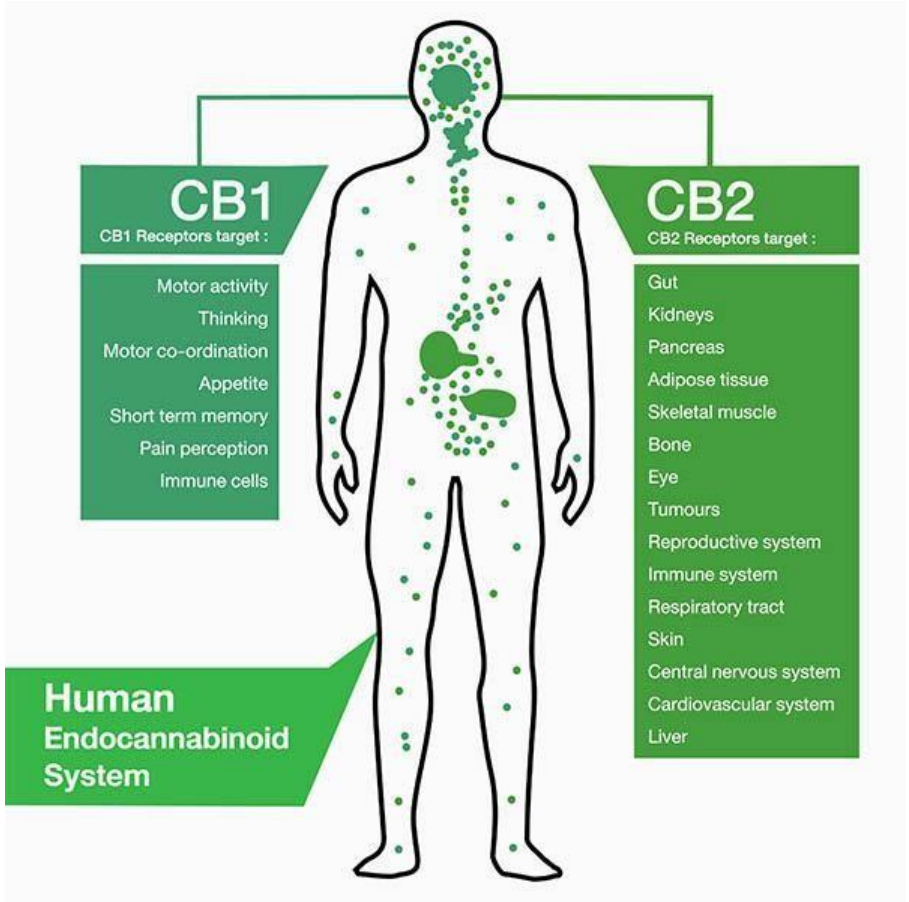
Tetrahydrocannabinol (THC)



Cannabidiol (CBD)

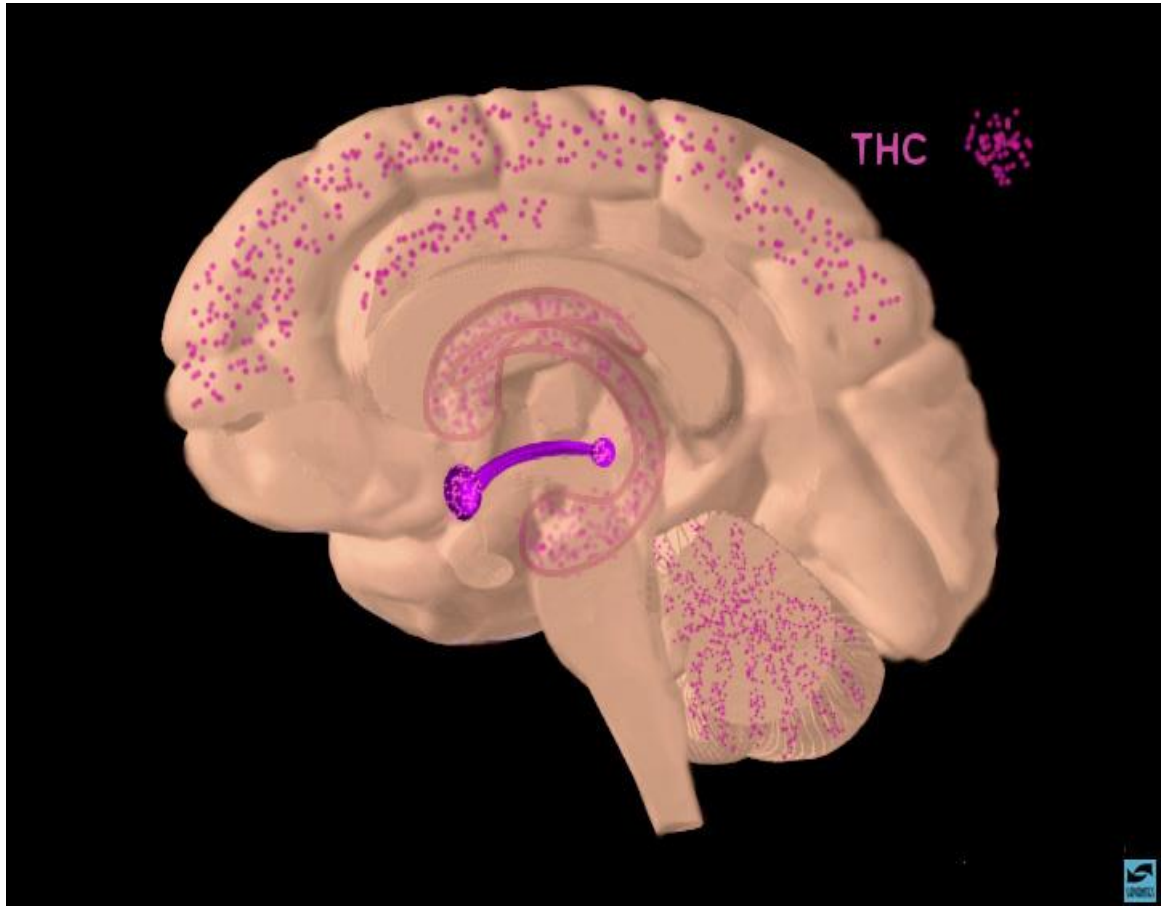


Human Endocannabinoid System (eCBs)

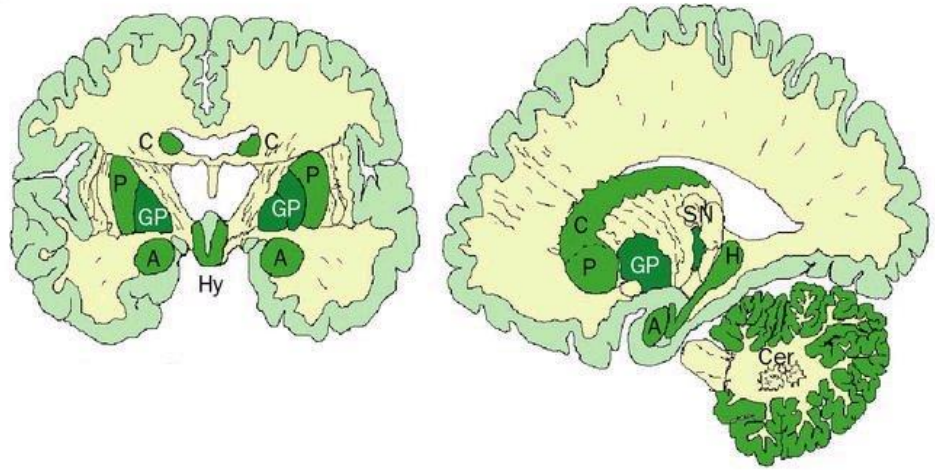


CB1 Receptors in the Brain:

CBR1 receptors in the Brain



CBR1 receptor densities



<u>Highest CB_1 receptor densities</u>: Striatum, Amygdala, Hippocampus, Hypothalamus, Cerebellum

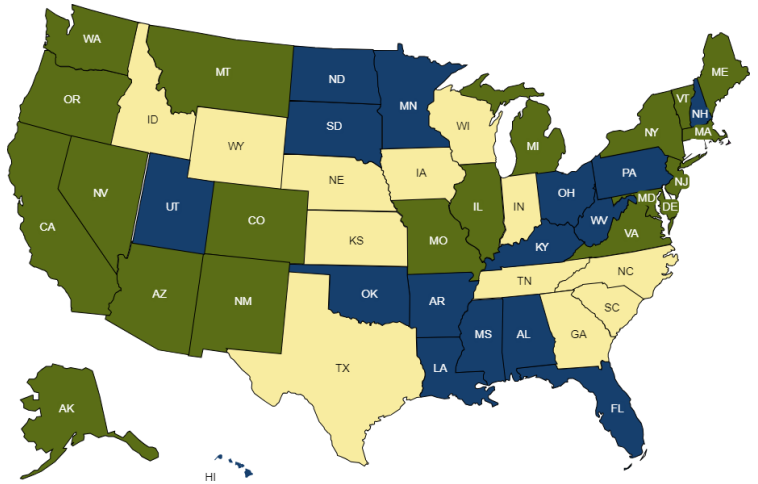
<u>CB_2 Receptors</u>: Expressed in Neuroglia and Peripherally

REFERENCES: Baker D et al. *Lancet Neurol*. 2003;2(5):291-298; Gogtay N et al. *Proc Natl Acad Sci U S A*. 2004;101(21):8174-8179.

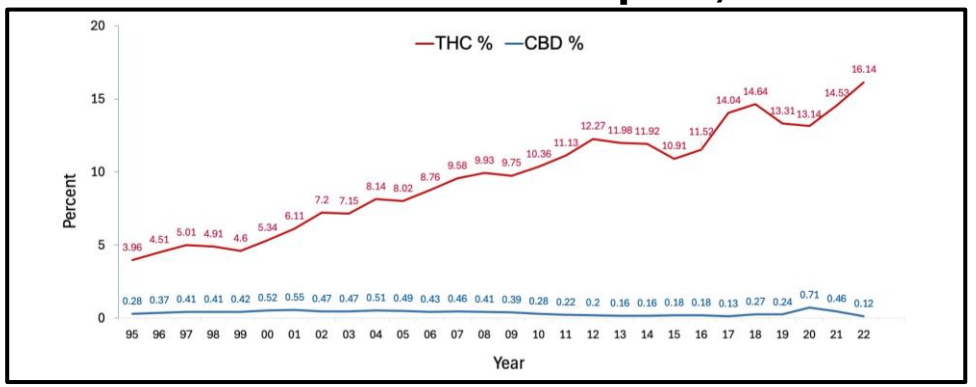
The cannabis landscape in America has changed dramatically in the past two decades

- Changing state cannabis laws (CL) & legal availability
- Commercialization (marketing & advertising)
- Changing products & potency
- Changing attitudes, beliefs, behaviors

U.S. States with Enacted Recreation CL (RCL), Medical CL (RCL), & No CL, 2024



Average Percentage of delta-9-THC and CBD in DEA Cannabis Samples, 1995-2022



SOURCE: Adapted from Hasin, 2024

Expansion of novel products, formulations and methods of administration of cannabinoids

Flower via Smoking (e.g., joints, blunts, spills, pipes, etc.)

15-20% THC

Liquid Concentrates via a vaporizer (e.g., oils, vape pen)

40-80% THC ★

Solid Concentrates via a Dab Rig (e.g., dabs, wax, budder, shatter)

40-80% THC ★

Edibles & beverages (e.g., gummies, brownies, infused drinks)
% THC & CBD varies widely ★

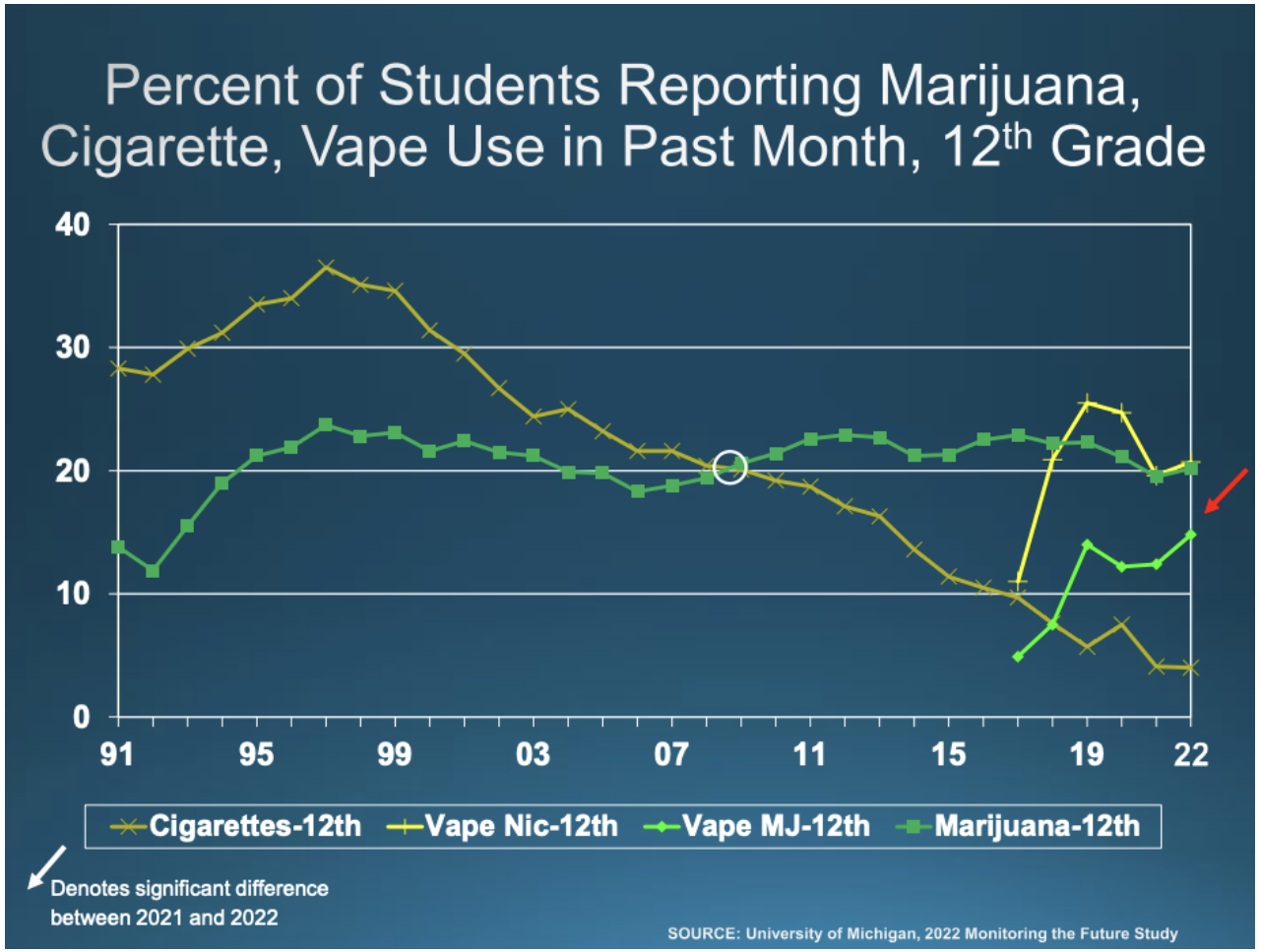
Cannabis beverage

Topicals via transdermal (e.g., salves, lotions, creams)
% THC & CBD varies widely

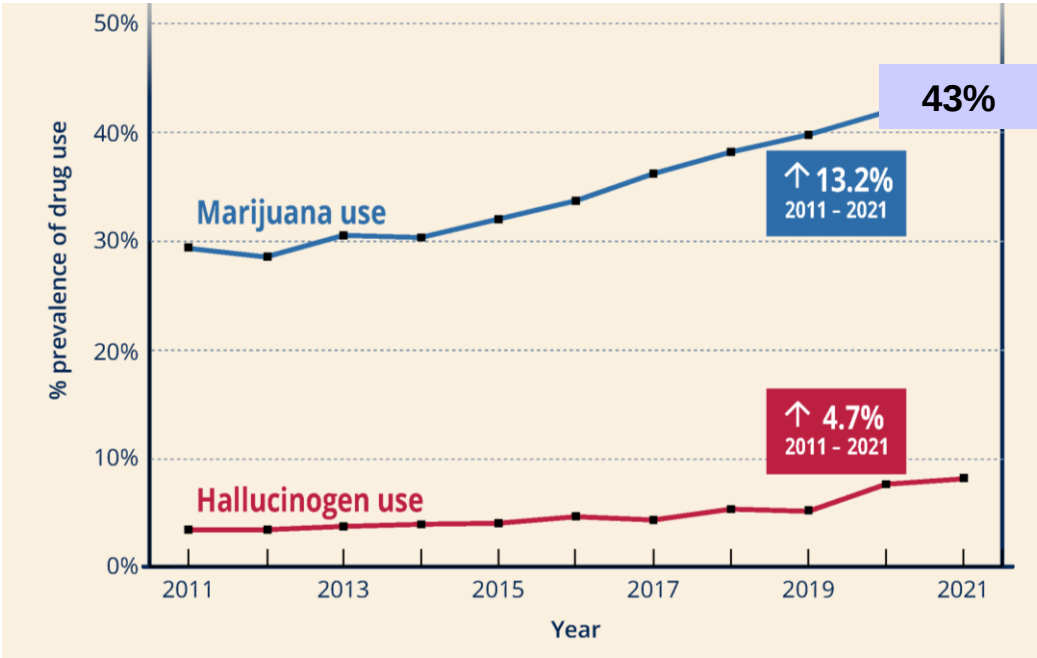
Sources: Spindler et al., 2019; Hammond et al. 2020; Sharma et al., 2023; Hasin, 2023

★ = ↑ prevalence in U.S. youth

Prevalence of Smoked and Vaped Cannabis & Tobacco Use Among U.S. High Schoolers, College Students, Young Adults 1990-2022



Past-year CANNABIS USE is at historic highs in young adults and college students



Regarding Cannabis Use Disorders:

- Cannabis use disorder (CUD) is the #1 substance-related disorder that U.S. teens present for SUD treatment (>75% admissions)
- 40% of U.S. CUD admissions are < 20 years old

DATA SOURCE: Data are from 2021 and 2022 Monitoring the Future Study data releases; https://monitoringthefuture.org/wp-content/uploads/2022/12/mtf2022.pdf

Medical Cannabis for child neuropsychiatric conditions

- Use of medical MJ in children is controversial

- Children and adolescents can obtain medical MJ with parent's written permission

- In states with MJ legislation, MJ is being prescribed and used for childhood mental health conditions with no scientific evidence to support this practice
  - **Depression + anxiety disorders**
  - **ADHD**
  - **Autism**
  - **Bipolar disorder**

The Charlotte's Web MJ Strain story

To date, the only childhood-onset medical conditions that cannabinoid-based medications have shown preliminary efficacy for are Lennox-Gastaut syndrome and Dravet syndrome, two rare childhood-onset seizure disorders (~ 0.0066% of U.S. pop)

Hammond CJ et al. *Interntl Review of Psychiatry*. 2020;32(3); 221-234.

Cannabidiol (CBD) for Child Neuropsychiatric Conditions

- CBD may have benefits for some psychiatric conditions in the future
- At the present, limited safety and efficacy data in pediatric populations and no guidelines for administration, dosing, monitoring, etc.
- CBD or Hemp Products that are available on the market are not what is being tested in clinical trials and are often mislabeled

CBD tinctures

CBD capsules + gummies

CBD vape oil, e-juice, vape pens

CBD topicals

CBD infused food and drinks

Hammond CJ et al. *Interntl Review of Psychiatry*. 2020;32(3); 221-234.

Changes in Cannabis Use among U.S. Youth during the Age of Cannabis Legalization

- ↑ MJ use, regular use, MJ use disorders in U.S. adults (parents of teens)
- ↑ Availability/accessibility of MJ products reported by U.S. teens
- Δ in types of products, source (dispensaries), methods of administration, & ↑ poly-cannabis use by US youth
- ↑ Vaping of cannabis (Δ9-THC), cannabidiol (CBD), & THC analogues (Δ8-THC, Δ10-THC) and ↑ Use of cannabis 'concentrates' among US youth
- ↑ Rates of past-year and regular cannabis use among US young adults, reaching highest levels since 1970s
- ↓ Perception that MJ is harmful, which is at all-time low across age groups
- ↑ Cannabis-related emergency department visits, hospital admissions, & MVCs

Sources: Hammond et al., Int Review of Psych (2020 Hammond CJ et al. *Adolesc Psychi* 2023; Dai et al., JAMA Network 2023.

Recreational and medical cannabis laws & past-month cannabis use in U.S. Adolescents & Young Adults

Aditya Pawar, MBBS

Systematic Review and Meta-analysis: Medical and Recreational Cannabis Legalization and Past-month Cannabis Use Among U.S. youth (30 studies in quantitative analysis)

Fig 1: Meta-analysis of MCL-only effects

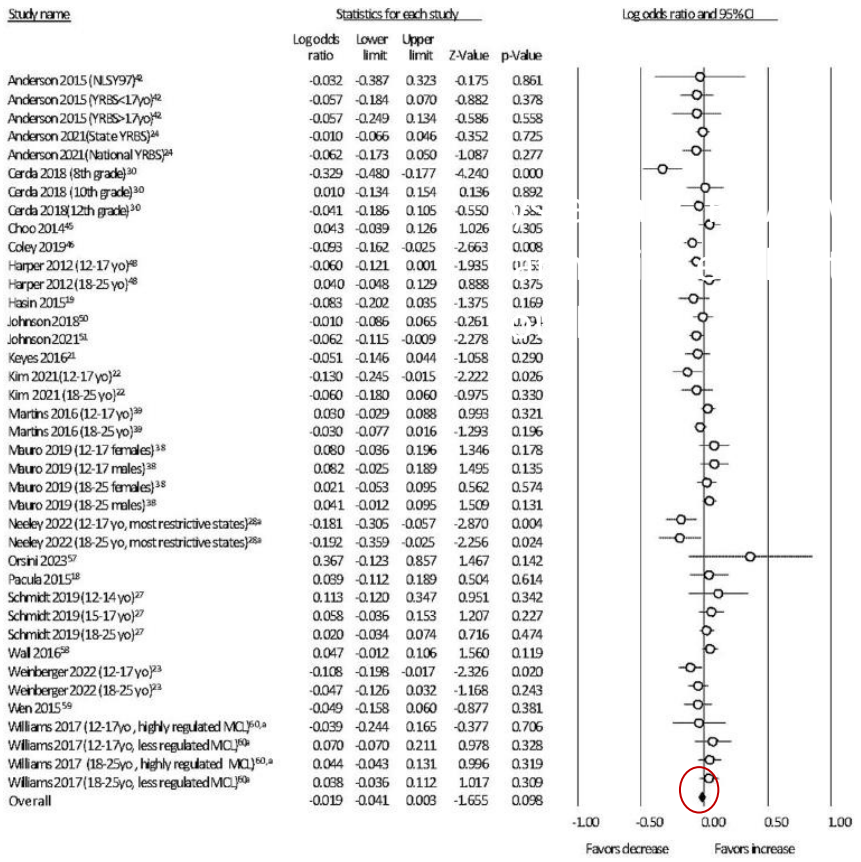
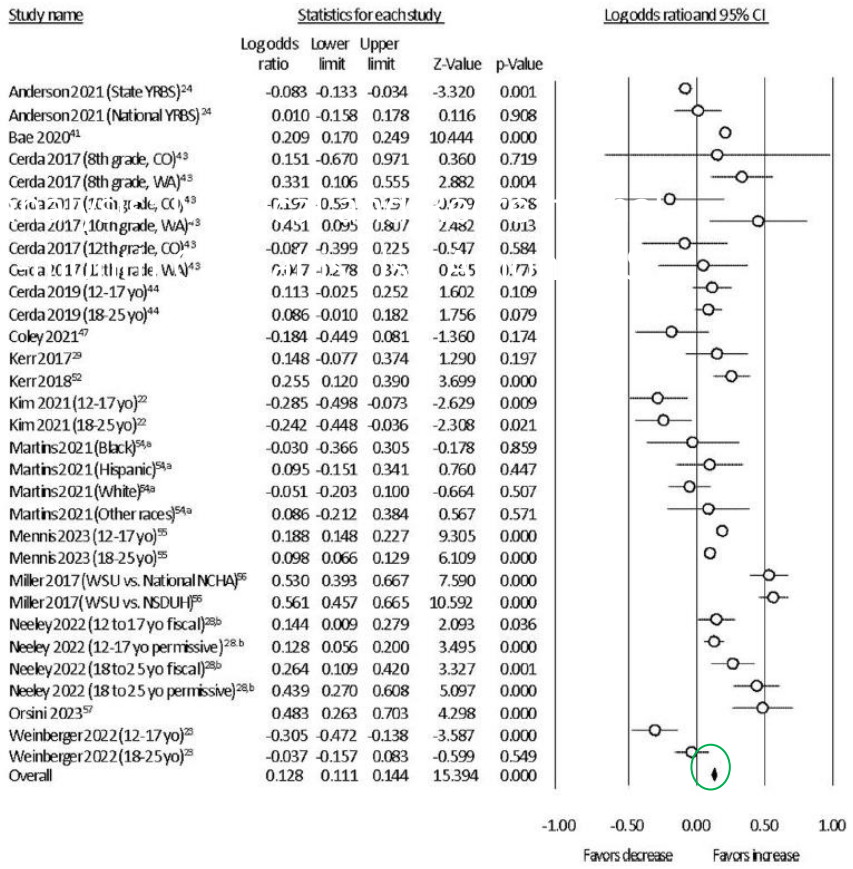


Fig 2: Meta-analysis of RCL effects



No sig. association between MCL and use (OR = .98)

Association between RCL and ↑ past-month use (OR=1.13)

Source: Pawar AKS, Firmin ES, Wilens TE, **Hammond CJ**. *J Am Acad Child Adolesc Psychiatr. 2024 March 27. doi: 10.1016/j.jaac.2024.02.016*

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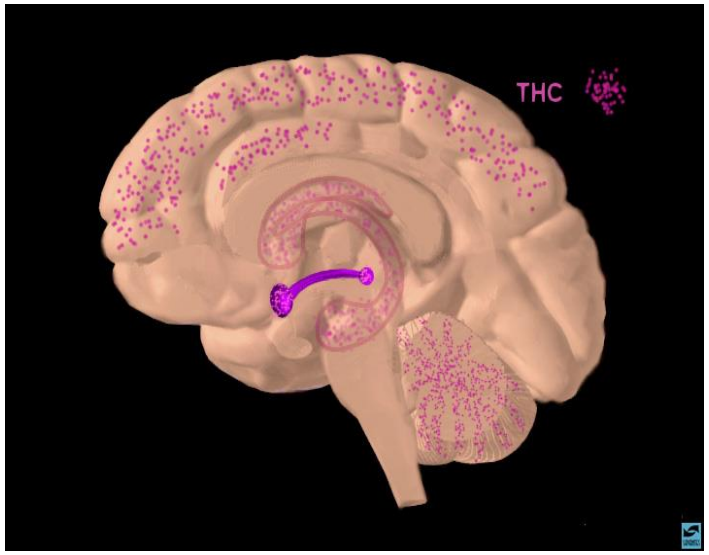
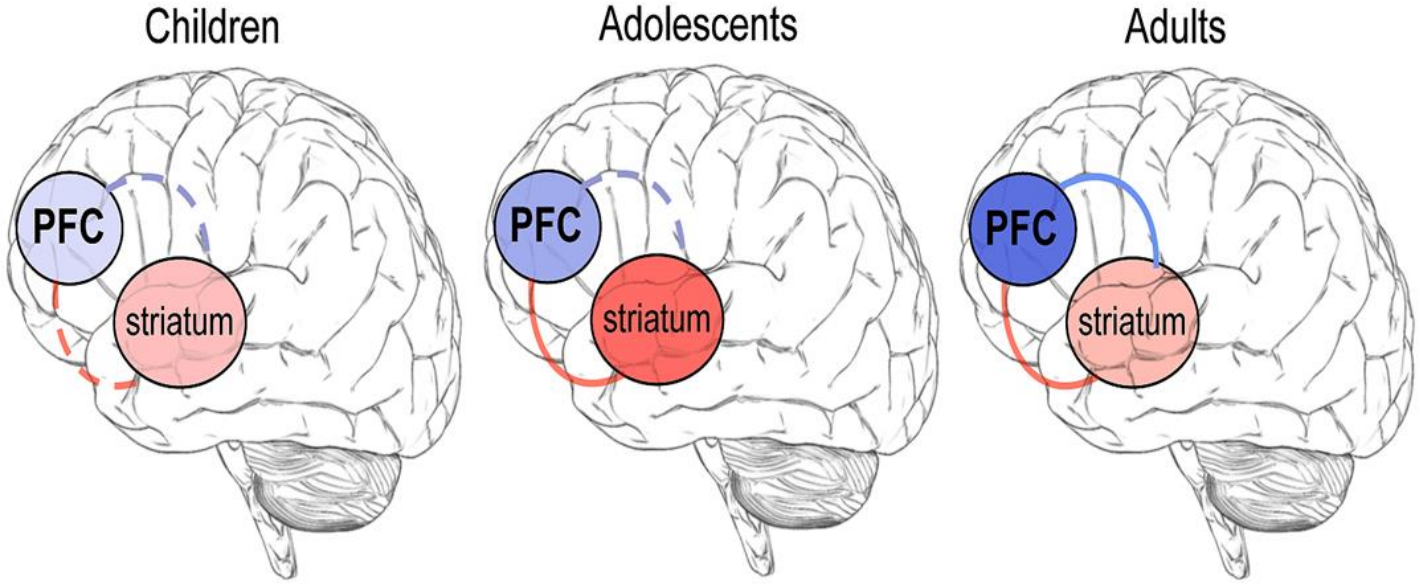
Adolescent's Brains Are Still Developing Making Them More Vulnerable to Cannabis Exposure

The endocannabinoid (eCB) System: CB1 Receptors in the Brain



The eCB System Serves as a Key Modulator of Adolescent Developmental Processes

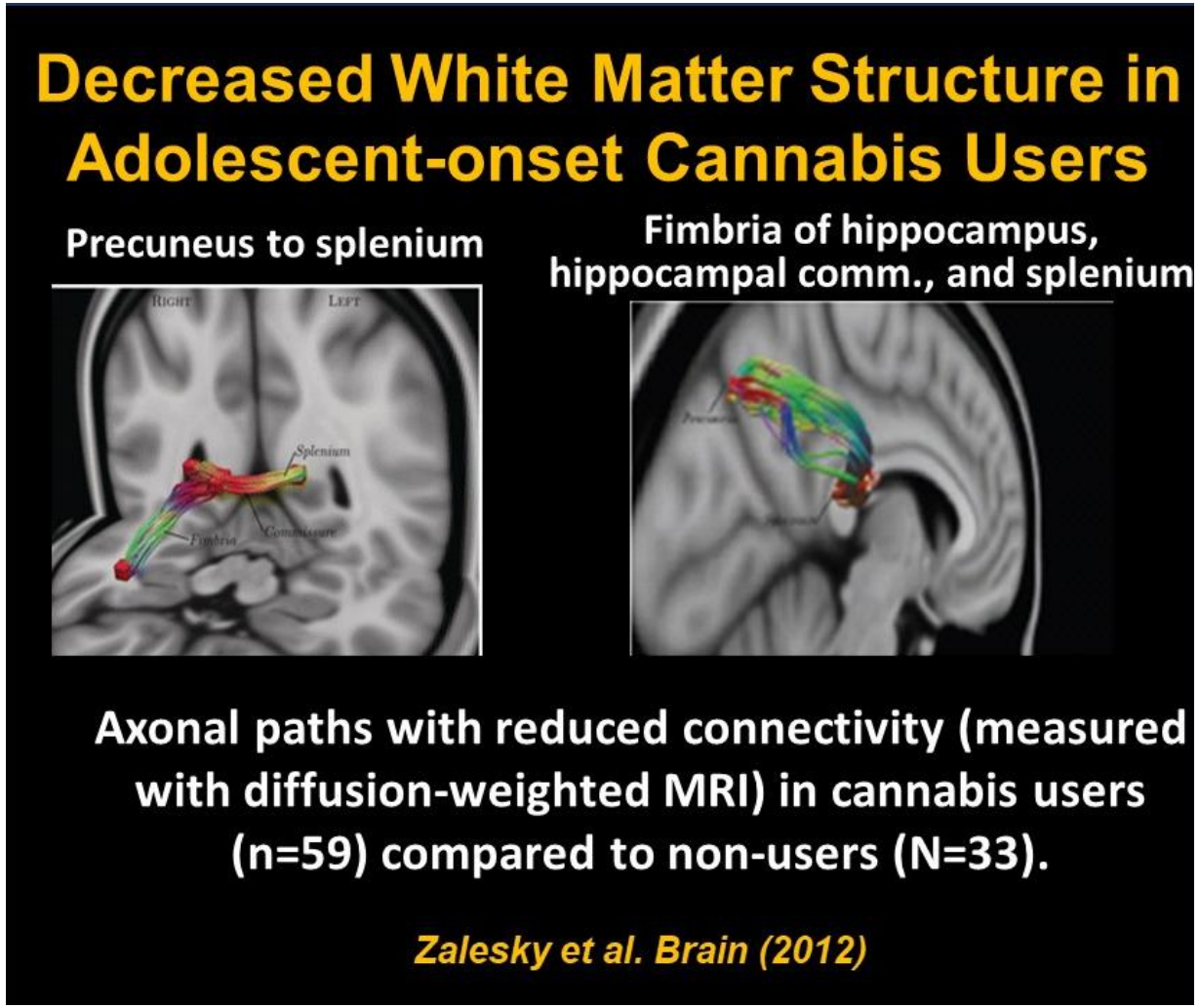
Imbalance in Cognitive Control and Reward and Emotion Processing Brain System



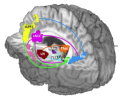
Gogtay N et al. *Proc Natl Acad Sci USA*. 2004;101(21):8174-8179.**;** Baker ST et al. *J Neurosci.* 2015;35(24):9078-9087; Dosenbach NU et al. *Science*. 2010;329(5997):1358-1361**;** Casey BJ et al. *Dev Rev*. 2008;28(1):62-77.

Adolescent Cannabis Use and Short- and Long-term Effects on Brain Function and Structure

- Mixed evidence of effects on brain volume, thickness (increase, decrease, no diff)
- Altered white matter structure ('insulation') with heavy use
- Altered brain waves (EEG) related to attention, reward, emotional process
- ↓ brain blood flow
- ↑ brain response while learning
- Effects are Larger and More consistent with earlier age of onset and chronic use during adolescence



Modified from Tapert, AMSP



Mechanisms

Adolescents with cannabis use disorders have altered brain activity during executive control, emotion processing, and reward processing

brain sciences

A Meta-analysis of fMRI Studies of Youth Cannabis Use: Alterations in Executive Control, Social Cognition/Emotion Processing, and Reward Processing in Cannabis Using Youth

Christopher J. Hammond MD PhD; Aliyah Allick MHS; Grace Park MPH; Bushra Rizwan MD; Kwon Kim; Rachael Lebo MLS; Julie Nanavati PhD; Muhammad A. Parvaz PhD; Iliyan Ivanov MD

Fig. 1. Brain Activity differences between adolescents with CUD and non-using TD controls

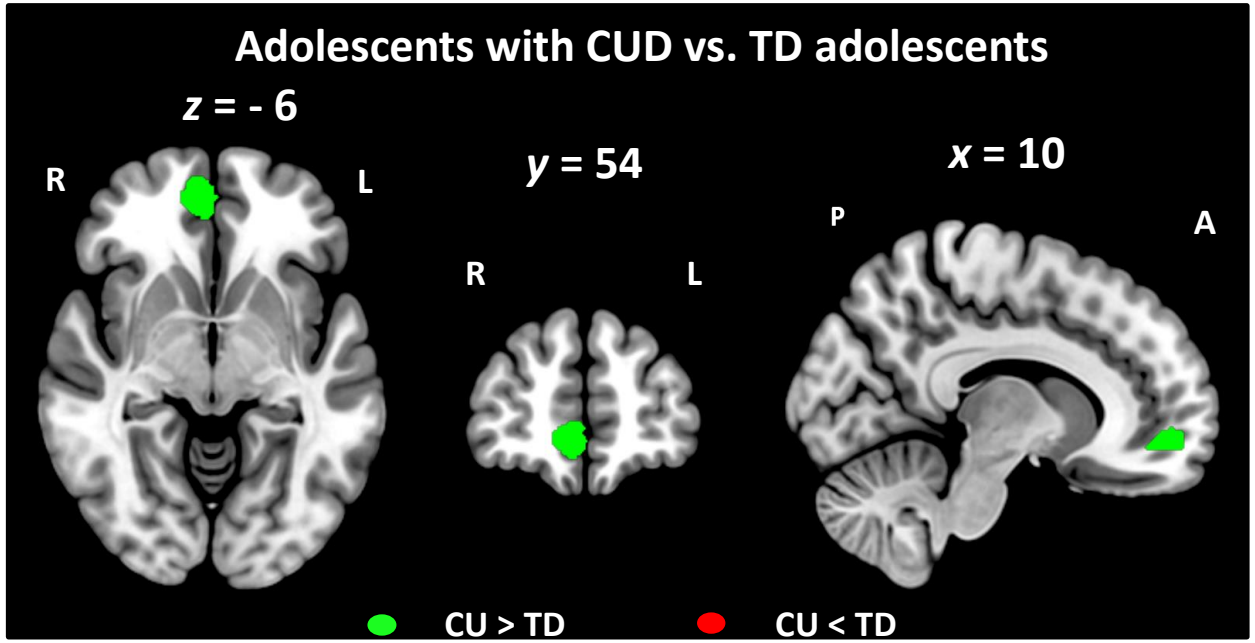
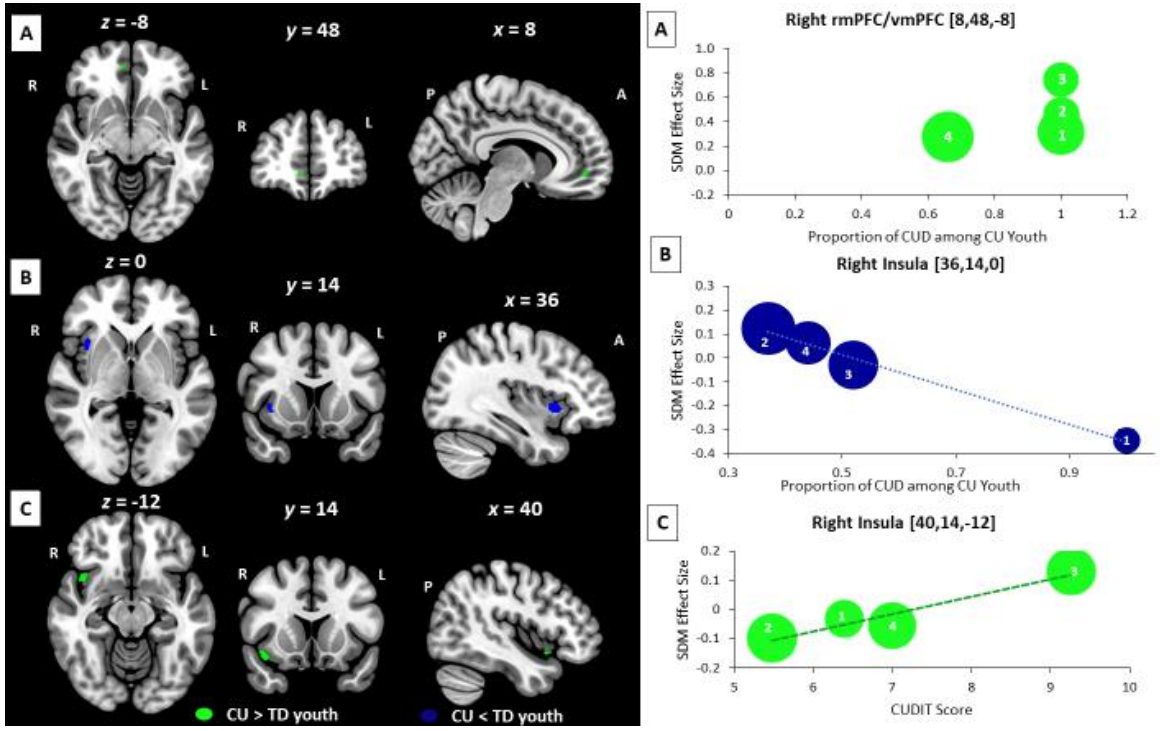


Fig. 2. Associations Between Cannabis Problem Severity and Brain Activity in MJ users during executive control (A), reward (B), and emotion processing (C).



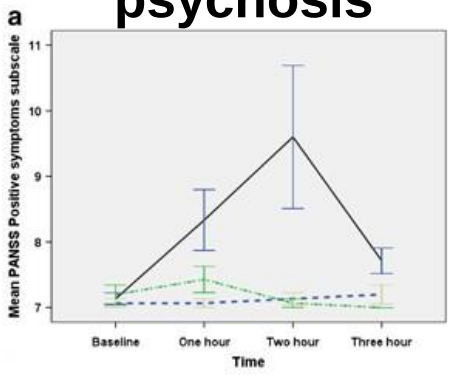
REFERENCE: Brain Sci. 2022, 12(10), 1281; https://doi.org/10.3390/brainsci12101281

Distinct Effects of THC and CBD and Potential Protective Effects of CBD Against THC-induced Dysfunction

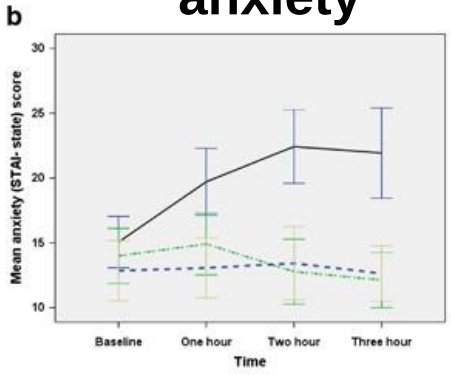
Distinct Neurobehavioral Effects of Δ9-THC and CBD in Adults

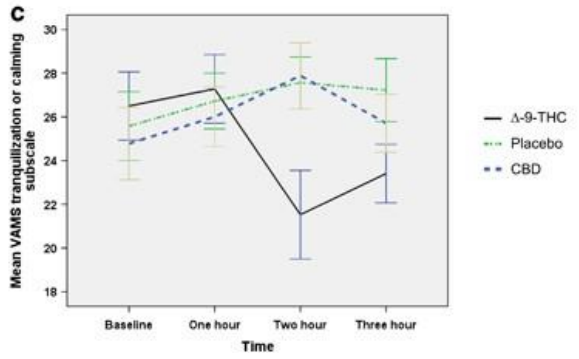
Psychiatric symptoms

psychosis



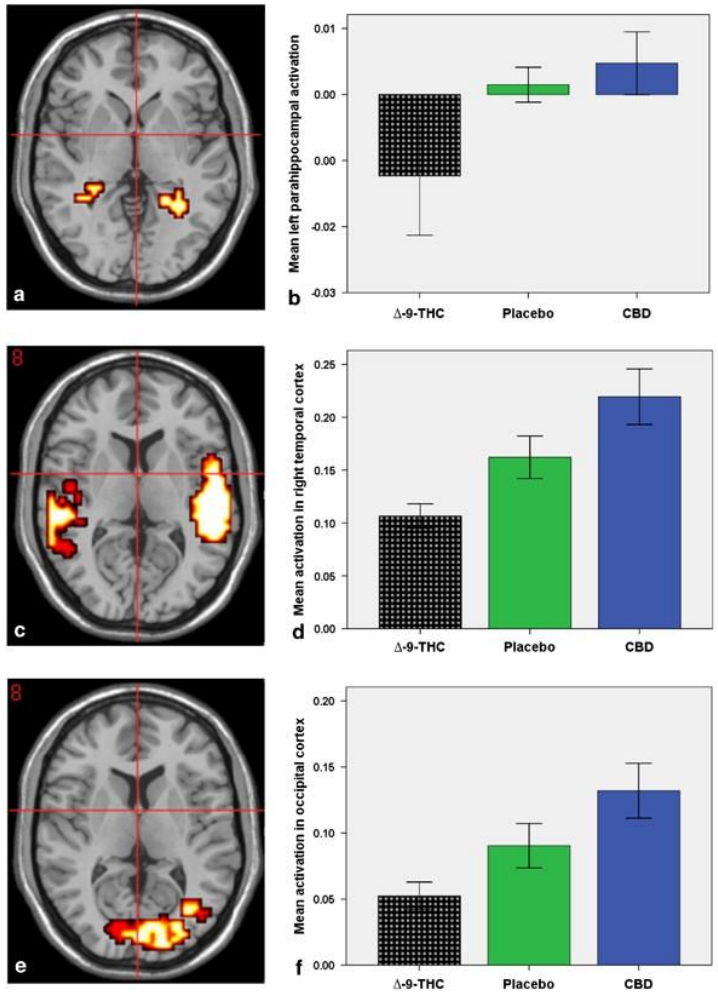
anxiety





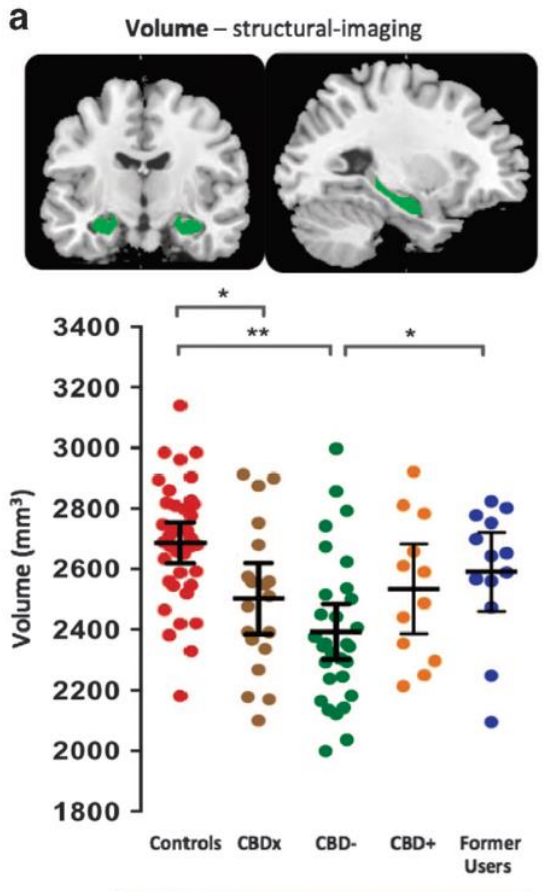
sedation

Response inhibition



Fusar-Poli P et al. *Arch Gen Psychiatry*. 2009;66(1):95-105; Bhattacharyya S et al. *Arch Gen Psychiatry*. 2012;69(1):27-36; Yücel M et al. *Transl Psychiatry.* 2016;6(1):e710.

CBD May Protect Against THC Related Hippocampal Atrophy in Chronic MJ using Adults



CBD is Not Risk Free

Human CBD studies

- Drug-to-drug interactions
- Hepatic abnormalities
- Diarrhea
- Fatigue
- Vomiting
- Somnolence

Animal CBD studies

- Developmental toxicities
- Embryo-fetal mortality
- CNS inhibition and neurotoxicity
- Hepatocellular injuries
- Male reproductive system alterations
- Hypotension

Huestis et al., 2019; Ahmed et al., Sci Reports 2018

Cannabis Use and Negative Health Outcomes

In a dose-dependent manner, adolescent cannabis use is associated with adverse **academic** (Pope et al., 2003; Fergusson et al., 2015), **occupational** (Fergusson et al., 2015), **cognitive** (Jager & Ramsey, 2008; Meier et al., 2012; Randolph et al., 2013; Camchong et al., 2016), **psychiatric** (Fergusson et al., 2002; Patton et al., 2002; Moore et al., 2007; Gobbi et al., 2019), and **substance use outcomes**(Volkow et al., 2014, 2016; Levine et al., 2017)

- Cannabis use in adolescence is associated with increased incidence and worsened course of **psychotic**, **mood**, and **anxiety disorders**, and **increased suicidality** (Hayatbakhsh et al., 2007; Moore et al., 2007; Gage et al., 2016; Gobbi et al., 2019)
- Adult-onset cannabis users may experience fewer adverse effects (Fergusson et al., 2015)

Age of Onset Matters for Adverse Effects

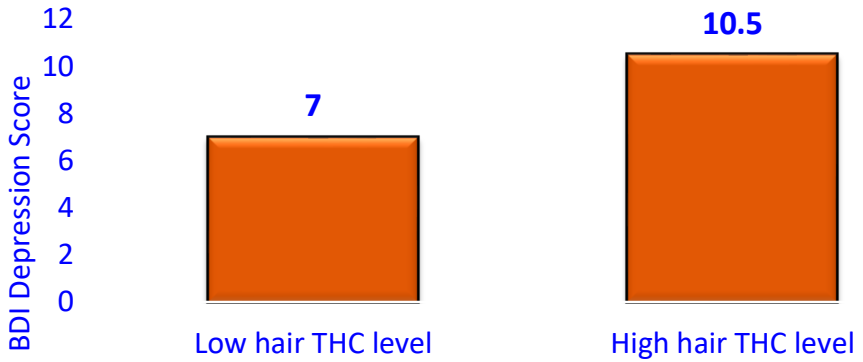
Early onset of cannabis use increases risk for later life:

- Major Depression
- Alcohol Use Disorders
- Other Substance Use Disorders
- Suicidality
- Anxiety Disorders
- Bipolar Disorder
- Psychosis
- Delinquent behaviors

1:6 teens vs. 1:10 adults who try cannabis > few times will develop cannabis use disorder

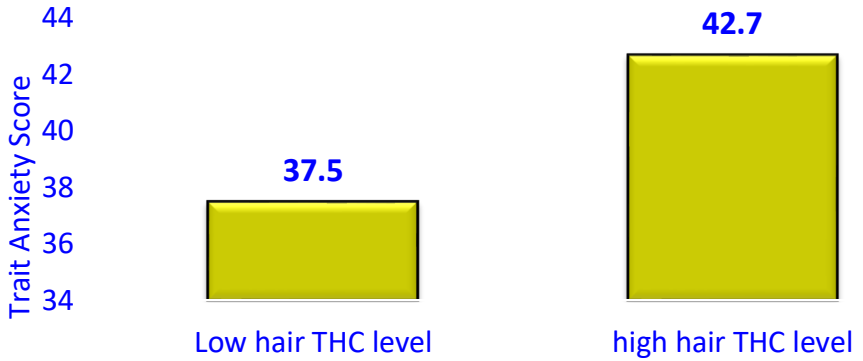
Cannabis Potency (% THC) Matters for Adverse Effects

Increased Depression severity



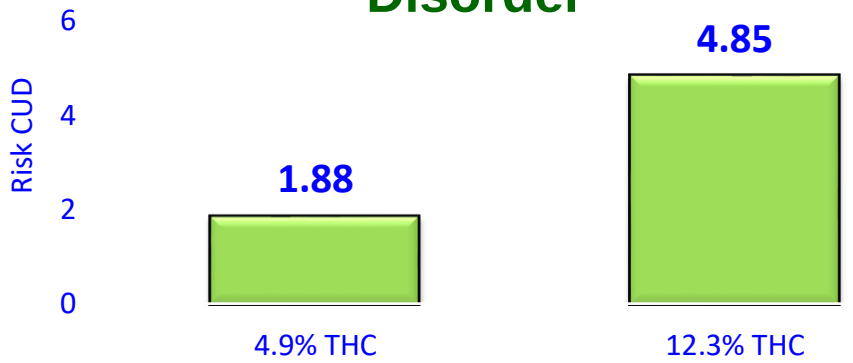
Morgan CJ,et al. *Psychol Med*. (2012)

Increased Anxiety Symptoms



Morgan et al. Psychological Medicine (2012)

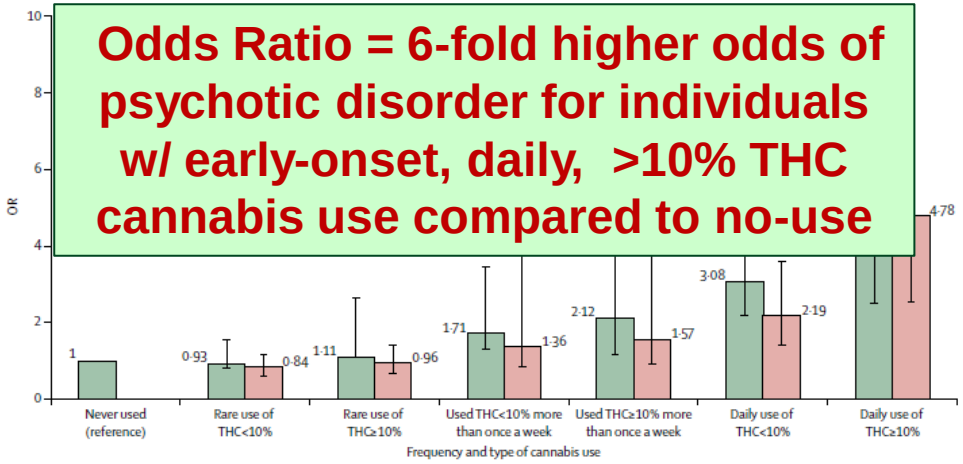
Increased Risk Cannabis Use Disorder



Arterberry, et al. Drug Alcohol Dependence (2019)

Increased Risk Psychotic Disorders

Odds Ratio = 6-fold higher odds of psychotic disorder for individuals w/ early-onset, daily, >10% THC cannabis use compared to no-use



DiForti, et al. Lancet Psychiatry (2019)

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What is SBIRT?

- **Screening:** Identify youth patients with unhealthy substance use

- **Brief Intervention:** Conversation to motivate youth who screen positive to consider healthier decisions (e.g. cutting back, quitting, or seeking further assessment).

  In schools and PCP offices: BI for prevention and early intervention for all who are screened based upon risk level.

- **Referral to Treatment**: Providing linkages to specialty SUD treatment for youth with suspected or diagnosed SUD.

SBIRT Screening

- There are a number of effective tools available to healthcare providers and prevention professions for screening.

- Evidence-Based Screening Tools for Adolescent Populations:
  - AUDIT-C and AUDIT, GAIN-SS, **S2BI**, DAST, NIDA Modified ASSIST Levels 1 and 2, NIAAA Youth Guide Screen, and the **CRAFFT**.

Diagnosing Cannabis Use Disorders in Youth

DSM-5 Cannabis Use Disorder

2+ of 11 symptoms in same year

- Tolerance (defined by either)
  - ↑ Amount for same effect
  - ↓ Effect with same amount
- Withdrawal (defined by either)
  - Withdrawal syndrome
  - Use to ↓ withdrawal

- Larger amounts used
- Much time spent
- Attempts to cut down
- Neglecting major roles
- Important activities ↓
- Interpersonal problems
- Physical/psych problems
- Hazardous use
- Cravings

Cannabis Withdrawal in Adolescents

- Experienced by most heavy MJ using youth (50-75%)
- Clinically significant withdrawal in 42% of youth with CUD
- No major medical/psychiatric consequences
- More severe withdrawal = worse prognosis
- Withdrawal severity is greater in **frequent MJ users**, **women**, and youth with **psychiatric comorbidities**

Diagnosing Cannabis Withdrawal in Youth

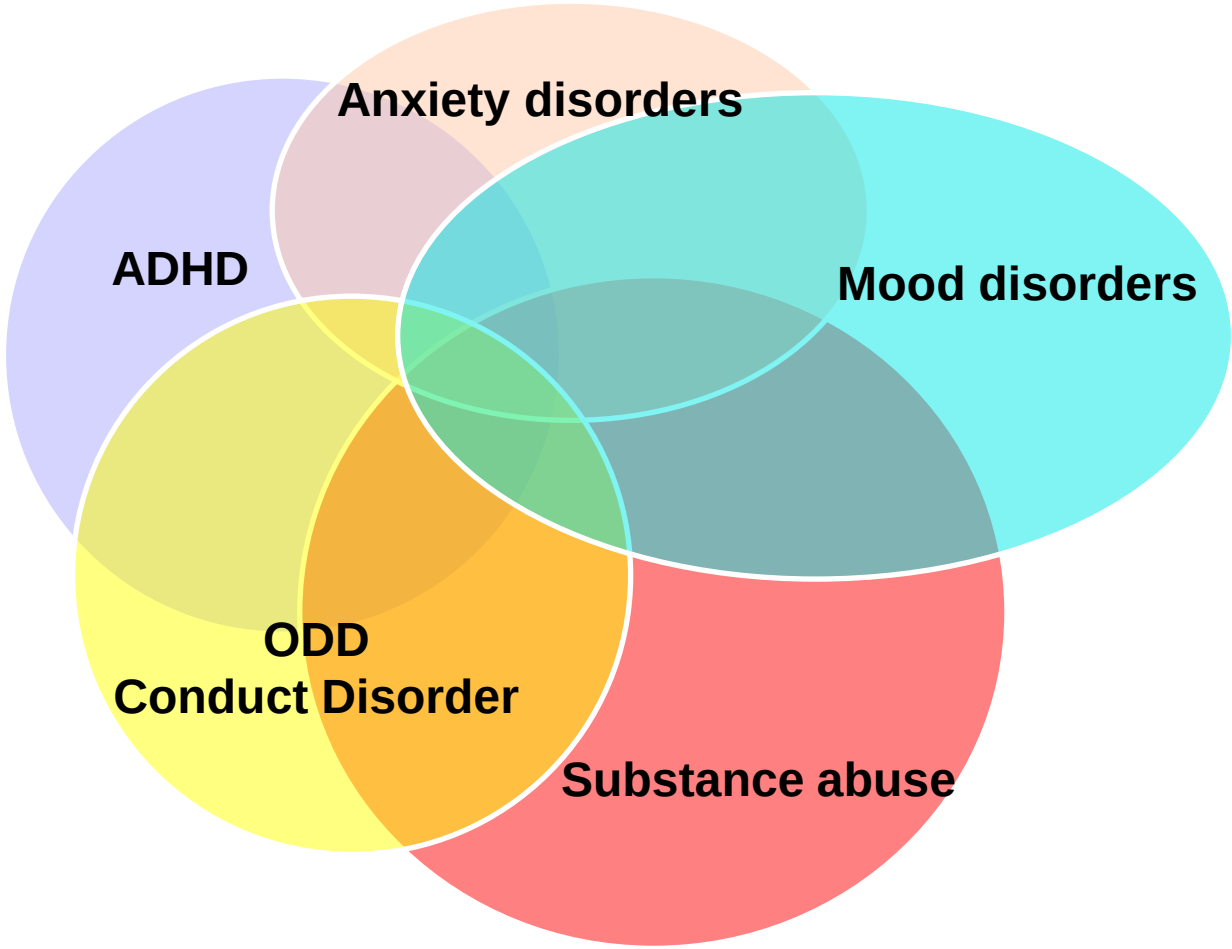
DSM-5 Cannabis Withdrawal Syndrome

3+ signs/symptoms that develop after cessation of prolonged use

- Irritability, anger, aggression
- Nervousness/anxiety
- Sleep difficulty
- Decreased appetite
- Depressed mood
- Restlessness
- Physical symptoms
  - Stomach pain, headaches
  - Fever, chills, sweating

Co-occurring Disorders are the "Norm" in Youth Who Regularly Use Cannabis and Meet Criteria For CUD

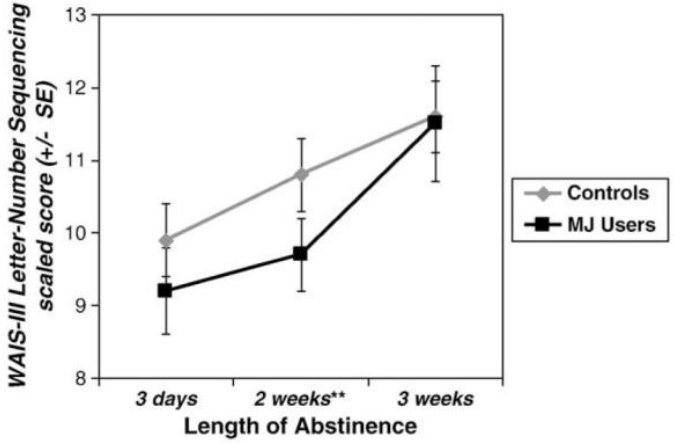
- Conduct disorder: 50-80%
- ADHD: 13-77%
- Major Depression: 20-50%
- Anxiety Disorders: 10-40%
- PTSD: 14-39%
- Bipolar Disorder: 15%
- Psychosis: 2-10%
  - Higher rates (3-6x) in early-onset, daily, and high THC potency users



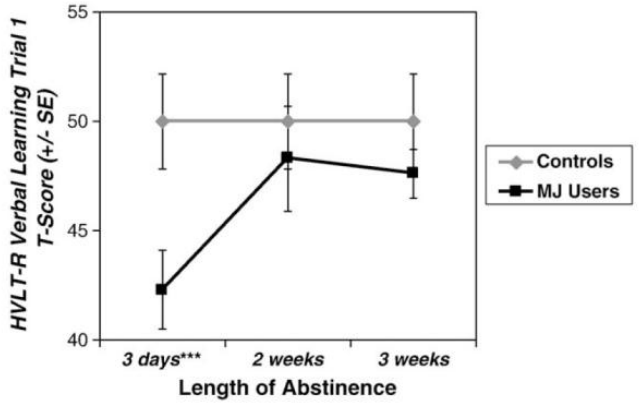
Godley et al., 2014; Hser et al. 2001; Buckstein and Horner, 2011; Singh, 2008; Kessler et al., 1995; Stein et al. 2000

Abstinence-related Improvements in Depression, Anxiety, and Cognition in Adolescent MJ Users During 21- and 28-day Abstinence

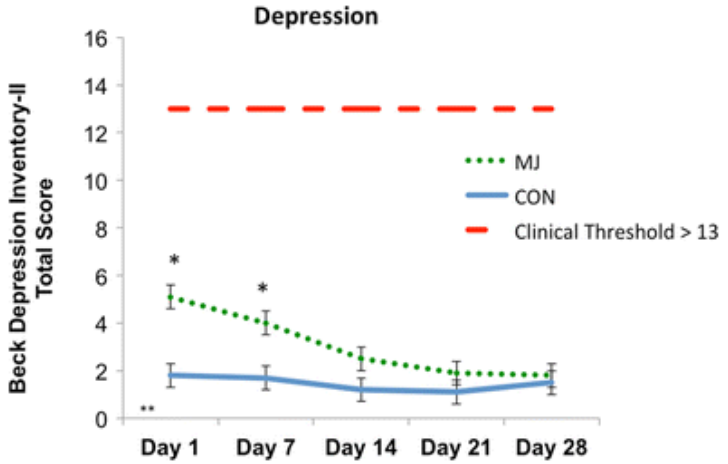
Working memory



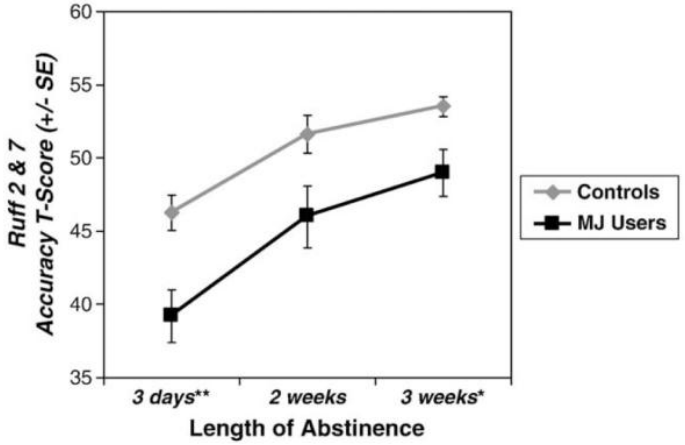
Verbal memory



Depressive symptoms

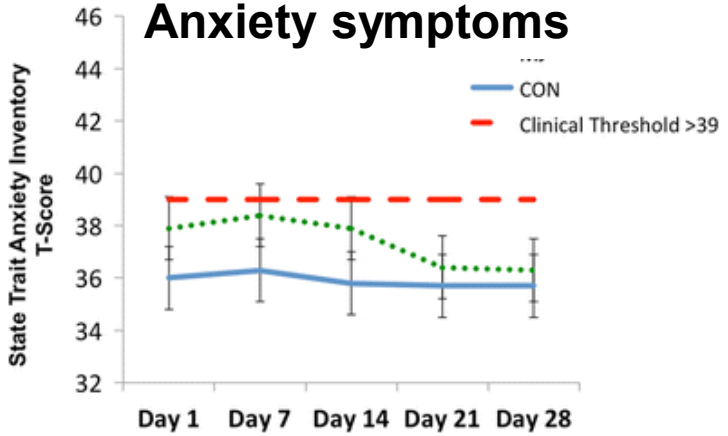


Attention



Changes in cognitive function and affective symptoms during the first 28-days of cannabis abstinence in adolescents

Anxiety symptoms



Jacobus J et al. *Psychopharmacology.2017;* 234:3431–3442; Moitra E et al. *Depress Anxiety.* 2016;33(4):332-338; Hanson KL et al. *Addict Behav.* 2010;35(11):970-976; Arias, Hammond et al. 2020, Journal of Substance Abuse Treatment

AGENDA

- What is cannabis, How does it work, How has it changed?
- Developmental and long-term health effects of adolescent cannabis exposure
- Diagnosis and relevant prognostic features of cannabis use disorders in young people
- Effective evidence-based practices for treating youth with cannabis use disorders

Cannabis Prevention in the Age of Legalization:

The Importance of Parents (along w/ Providers) Having the "Marijuana Talk" with Pre-adolescents (9-12-year-olds)

INTERVENTION GAP: Most prevention interventions known to be effective for preventing cannabis use were developed and tested ≥15 years-ago (before RCL/MCL) and may not be as effective for Contemporary US Youth

Marijuana Talk Kit

Preventing Marijuana Use Among Youth

(SAMHSA Evidence-Based Resource Guide
Pub#: PEP21-06-01-001; date: 2021)

The SUPPER Project

Substance **U**se **P**revention **P**romoted
by **E**ating family meals **R**egularly

Sources: Marijuana Talk Kit: https://drugfree.org/wp-content/uploads/2017/02/Marijuana_Talk_Kit.pdf; The SUPPER Project: https://sites.tufts.edu/margieskeerlab/supper/ Skeer *et al.* PLoS One. 2022 Feb 2;17(2):e0263016; Cannabidiol (CBD) Information for Parents (developed by Miller/Hammond & NNDC CAMDG in 2023): https://nndc.org/wp-content/uploads/2023/03/NNDC-CAMD-Task-Group-CBD-Information-for-Parents-8.5x11-FINAL.pdf Stanford Cannabis Awareness & Prevention Toolkit (For Middle/High School Teachers): https://med.stanford.edu/cannabispreventiontoolkit.html **Citations**: Ryan SA, Ammerman SD, & COMMITTEE ON SUBSTANCE USE AND PREVENTION. Counseling Parents and Teens About Marijuana Use in the Era of Legalization of Marijuana. Pediatrics (2017). 139(3): e20164069 ; Matson et al., Am J Prev (2021); **Hammond CJ** et al., Int J Psych. (2020); Sharma P & **Hammond CJ** (2023). *Old Dog New Tricks: Cannabis Vaping in US Youth; SAMHSA Evidence-Based Resources.Preventing Marijuana Use Among Youth SAMHSA Publication No. PEP21-06-01-001. Rockville, MD. SAMHSA. 2021*

Evidence-based Psychosocial Treatments for Adolescent Cannabis Use Disorder

Psychosocial interventions are the <u>first line treatment</u> for cannabis use disorder in adolescents

- **<u>Mechanisms of Behavioral Change</u>**
  - ↑Adaptive Coping skills
  - ↓Family conflict
  - ↑Parent-teen relationships
  - Shift from risky to prosocial activities
  - Shift in environmental reinforcers

<u>Source:</u> Hammond & Sharma. (2017). Treatment Strategies for Substance Use Disorders in Adolescents. Psychiatric Times. <u>Other References</u>: Hogue, Henderson, Ozechowski, & Robbins, J Clin Child Adolesc Psychology (2014); Waldron & Turner, J Clin Child Adolesc Psychology (2008)

TABLE 2. Evidence-based behavioral interventions for adolescent substance use disorders

MI/MET	MI uses a directive, non-judgmental approach designed to increase motivation to change behavior
CBT	CBT uses skill training targeted at enhancing motivation, coping with cravings, and dealing with high-risk situations
FBT	FBT focuses on enhancing family communication skills and parent-teen relationships, reducing conflict and negative interactions, and improving parental monitoring and limit setting
A-CRA	A-CRA is a community-based approach that focuses on shifting environmental reinforcers (social, recreational, and vocational reinforcers) to reduce substance use behaviors
MST	MST is an intensive home-based intervention that addresses the multiple systemic factors that contribute to adolescent substance use disorders
CM	CM is an adjunctive approach that uses positive reinforcement in the form of rewards for abstinence, treatment engagement, and involvement in prosocial activities

MI, motivational interviewing; MET, motivational enhancement treatment; CBT, cognitive behavioral therapy; FBT, family-based therapy; A-CRA, adolescent-community reinforcement; MST, multisystemic therapy; CM, contingency management.

Can Treatment Matching Improve Outcomes for Youth Cannabis Use Disorder?

Moderating Effects of Age and Psychiatric Comorbidity on Abstinence Outcomes Following CBT vs. Family-based Therapies for Adolescent CUD

- 109 adolescents ages 13-18 with DSM-IV Cannabis Use Disorder randomly assigned to 6 months of MET/CBT12 or Multidimensional FT (MDFT) with 12 month follow up and examination of mediators of treatment response

- MDFT and MET/CBT were equally effective in reducing marijuana use
  - Older (17–18-year-olds) benefited more from MET/CBT and younger (13–16-year-olds) benefited more from MDFT
  - Adolescents with co-occurring psychiatric symptoms benefited more from MDFT while adolescents without comorbidity benefited more from MET/CBT

Hendriks, van der Shee, and Blanken, *Drug and Alcohol Dependence* (2012)

Adding Adjunctive Contingency Management (CM) Can improve outcomes for Youth CUD

Adjunctive voucher-based CM improves abstinence following psychosocial treatment for Adolescent CUD

- An effective modality for improving abstinence in adult SUDs
- Versatile and compatible with a broad number of other interventions
- Evidence for CM in Youth CUD:
  - 69 adolescents ages 14-18 randomly assigned to 14 weeks of MET/CBT +/- CM /voucher incentives with 3, 6, and 9 mo. follow up (f/u)
  - At 30-day post-treatment f/u visit: CM/voucher incentives + MET/CBT 53% achieved >10 weeks abstinence vs. 18% in MET/CBT alone
  - At 9-month f/u visit: No difference between groups

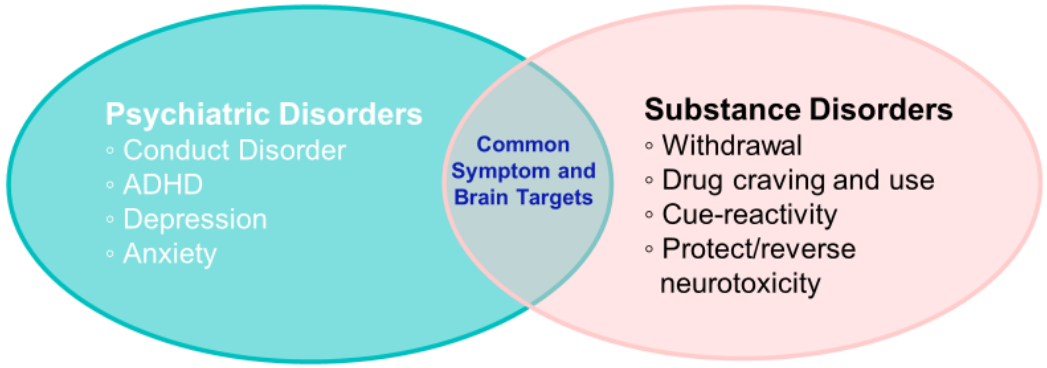
Stanger C, Budney AJ, Kamon JL; Thostensen J *Drug Alcohol Dependence* 2009

Treatment

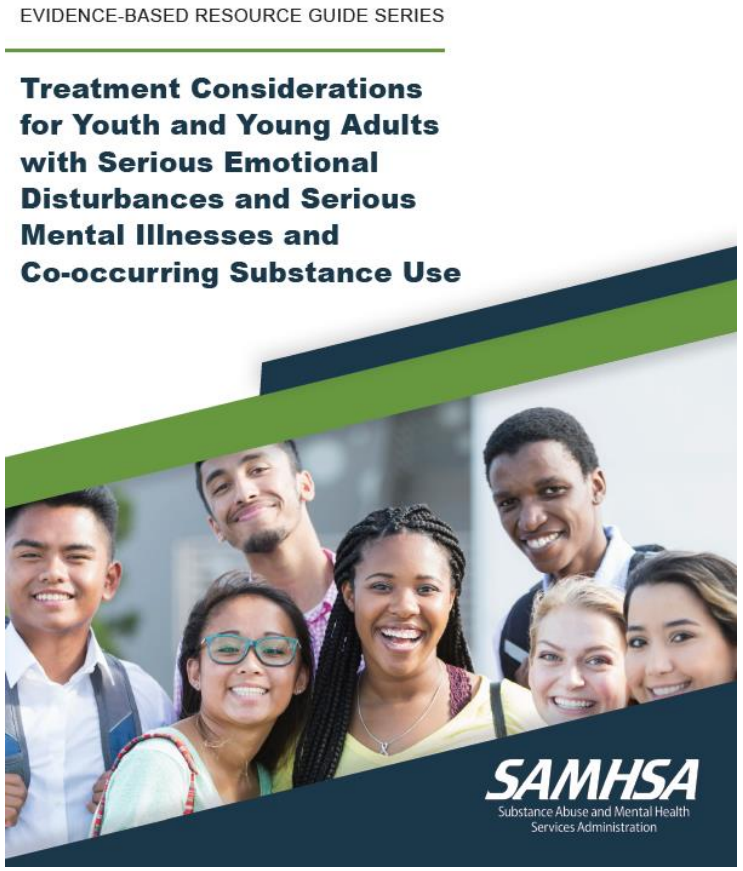
Treating Comorbid/Co-occurring Psychiatric Disorders Can Improve Outcomes For Youth CUD

INTEGRATED & CONCURRENT SUBSTANCE USE & MENTAL HEALTH TREATMENT IS ASSOCIATED WITH BETTER OUTCOMES

Fig 1: Common symptom cluster and brain targets



Source: Substance Abuse and Mental Health Services Administration (SAMHSA): Treatment Considerations for Youth and Young Adults with Serious Emotional Disturbances/Serious Mental Illnesses and Co-occurring Substance Use. Publication No. PEP20-06-02-001. Rockville, MD: National Mental Health and Substance Use Policy Laboratory, Substance Abuse and Mental Health Services Administration, 2021.
Link: https://store.samhsa.gov/sites/default/files/SAMHSA_Digital_Download/pep20-06-02-001.pdf



Is There a Role for Medication in Youth Cannabis Use Disorder Treatment?

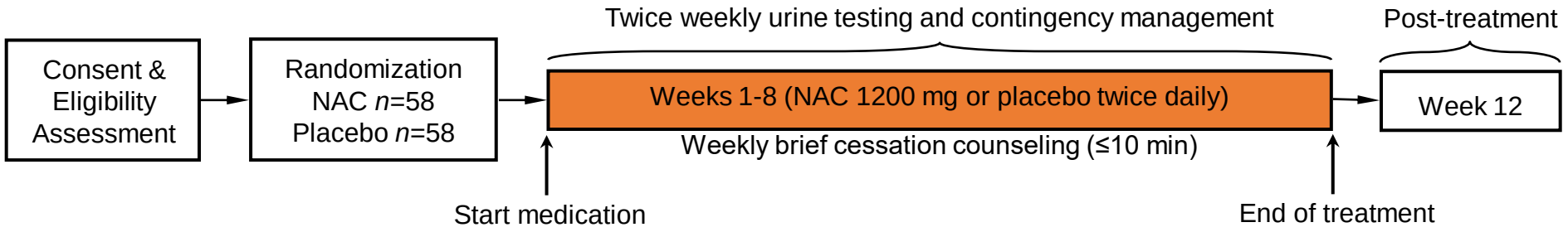
- Pharmacotherapies are used to augment psychosocial interventions for tobacco, alcohol, and opioid use disorders
- There are no FDA-approved mediations for the treatment of CUD
- Strategies for off-label use of medications in adult CUD pharmacotherapy have targeted:
  1. Withdrawal
  2. Relapse Prevention**
  3. Co-occurring psychiatric conditions**

**Focus of Adolescent CUD Pharmacologic Trials

Hammond and Gray, 2016; Breezing and Levin, 2020

NAC Trial for Adolescent CUD (Gray et al., 2012)

- Participants: N=116 cannabis dependent adolescents (ages 15-21 years)
- Design: 8-week, double-blind, placebo-controlled study of NAC for CUD

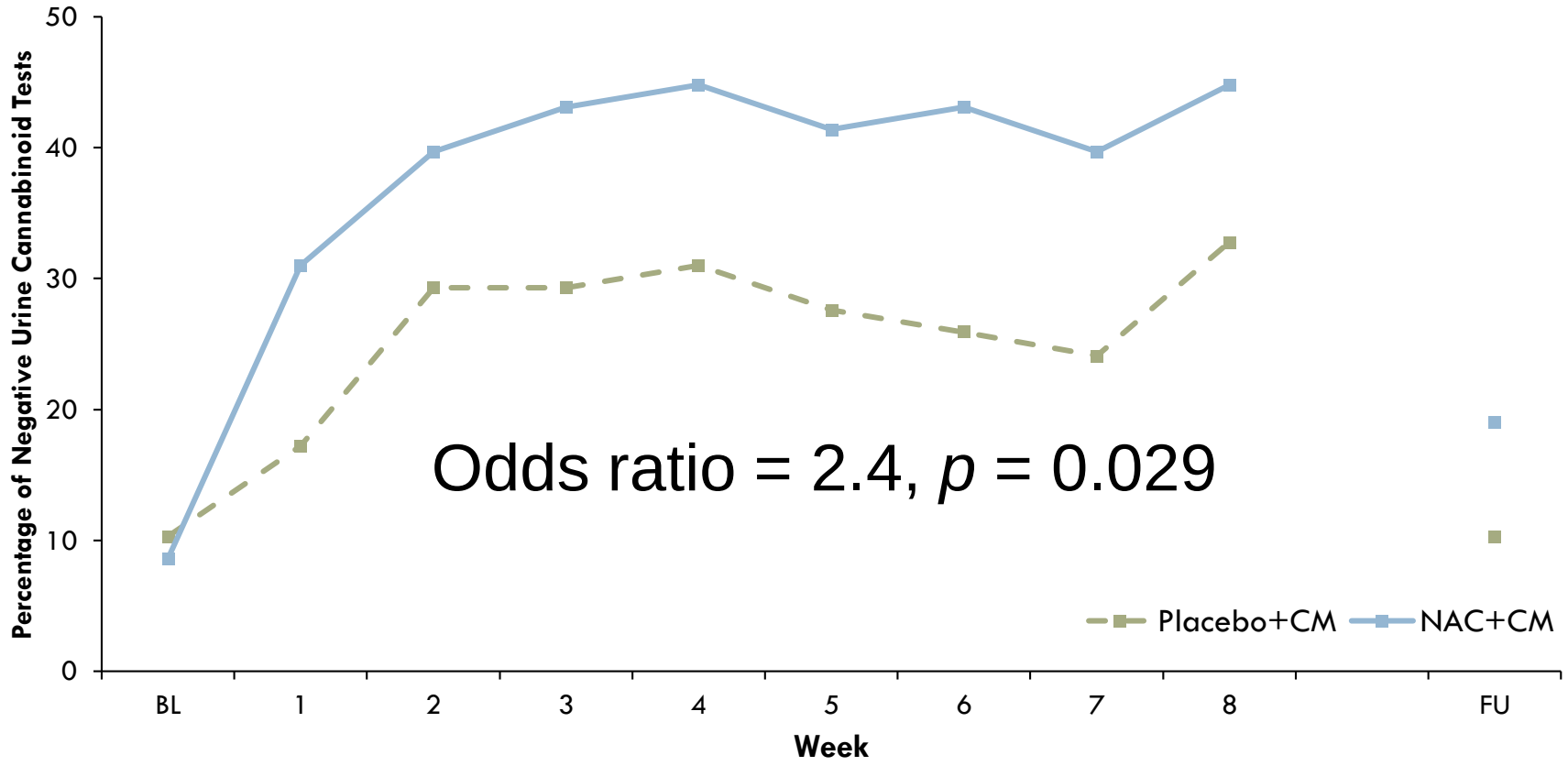


- Medication: 1200 mg BID of N-acetyl-cysteine (NAC) or placebo
- BT platform: weekly brief cessation counseling and twice-weekly CM
- Outcomes: **1º**: Efficacy: Odds of negative urine cannabis test (UCT) during treatment; safety/tolerability; adherence; **2º**: self-reported cannabis use (via TLFB)

NAC Trial for Adolescent CUD (Gray et al., 2012)

Primary Efficacy Outcomes

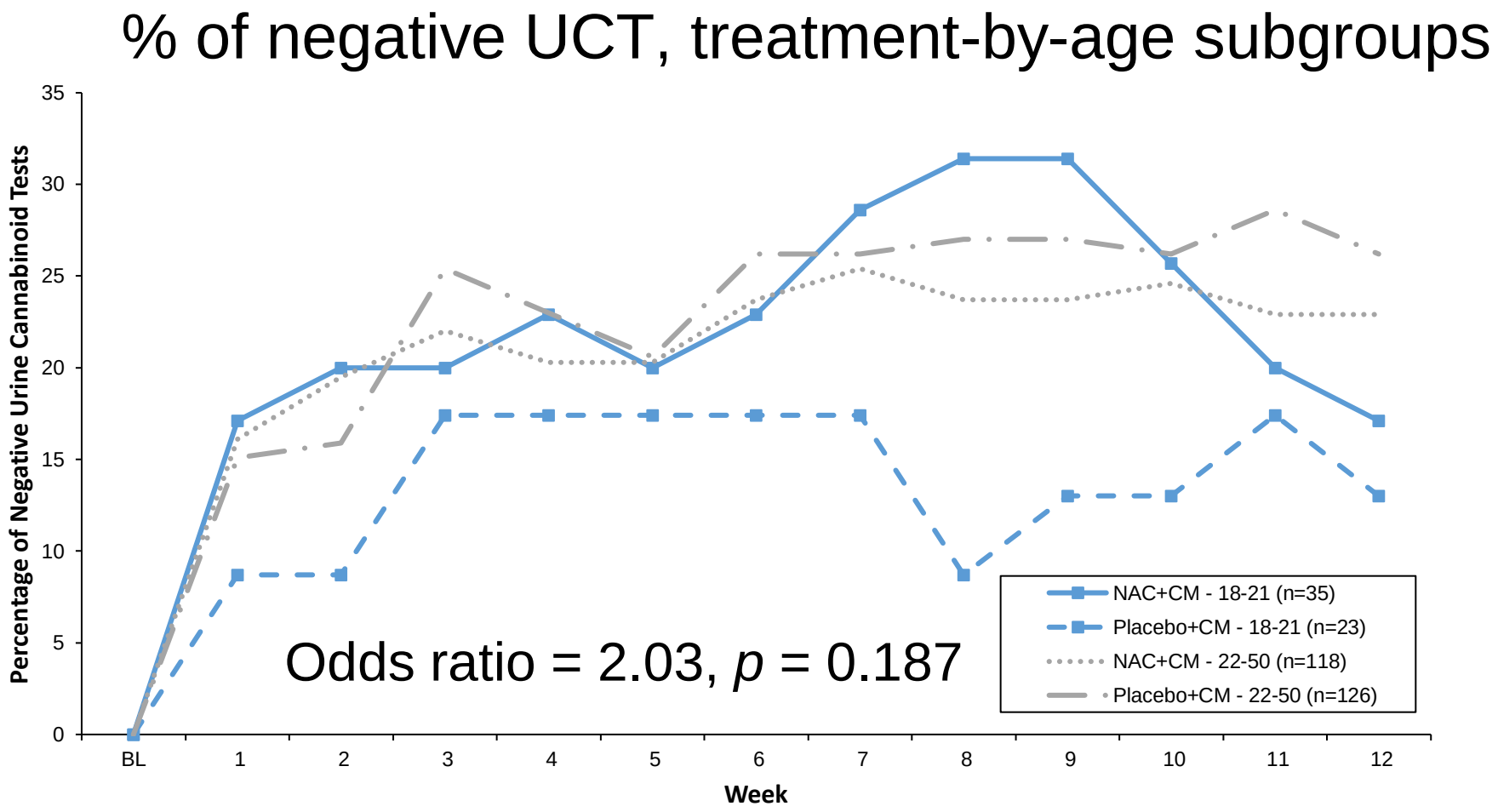
% of negative UCT, by treatment group



Intent-to-treat (all randomized participants) with participants assumed to be non-abstinent at any missed visit

NIDA CTN 0053 Trial of NAC for Adult CUD (Gray et al., 2017)

Age 18-21 yrs. vs. Age 22-50 yrs. Post-hoc Comparison



Intent-to-treat (all randomized participants) with participants assumed to be non-abstinent at any missed visit

What is Current Thinking Regarding NAC for Adolescent CUD?

Summary: In sum, NAC is the only pharmacotherapy with positive published ITT clinical trial abstinence findings for youth CUD

- NAC may improve MJ abstinence by targeting compulsive drug-seeking
- Anecdotally, pharmacologic effects are subtle and emerge gradually
- NAC may be an efficacious adjunct for youth who do not respond adequately to psychosocial treatments
  - Strategic use: Adjunctive medication combined with psychosocial treatment
  - Dosage: 1200 mg BID is dose used/tolerated in CUD trials
  - Duration of treatment: Variable, generally ≥ 2 months is recommended

Gray KM, 2020

Conclusions

1. Adolescent cannabis use disorder (CUD) is an important public health problem and patterns of cannabis use are changing in US youth during this age of cannabis legalization.

2. Early exposure to cannabis, in particular high THC cannabis, during adolescence is associated with adverse health outcomes.

3. More research is needed to clarify the role of CBD and other non-THC cannabinoids for treating pediatric psychiatric conditions or mitigating THC-induced adverse health outcomes before we can recommend these products for pediatric patients.

Conclusions

4. Psychosocial treatments (e.g., MI/MET, CBT, FBT) are the first line interventions for cannabis use disorders in adolescents.

5. Emerging evidence suggests that abstinence outcomes following psychosocial treatment for youth CUD may be improved by adding adjunctive contingency mgt, aggressively treating comorbid psychiatric disorders, and through targeted medication treatment, for relapse prevention (with N-acetylcysteine) or for comorbid ADHD or MDD (in youth whose ADHD or depressive symptoms have not improved with psychosocial treatment alone).

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Synopsis of CUD Pharmacotherapy Literature

CUD Medication Trials with Positive Primary Outcome Results		
Fully Powered Controlled Trials		
N-Acetyl-Cysteine (NAC) (ages 13-21 years)		
Pilot Controlled Trials		
Buspirone	Gabapentin	Oxytocin
Nabiximols	FAAH Inhibitor (PF-03357845)	Cannabidiol
Topiramate		
Human Laboratory Controlled Studies		
Nabiximols		
FAAH Inhibitor (PF-03357845)		

CUD Medication Trials with Negative Primary Outcome Results		
Fully Powered Controlled Trials		
Dronabinol	Venlafaxine	Buspirone
Lofexidine + Dronabinol	N-Acetyl-Cysteine (NAC) (ages > 21)	
Pilot Controlled Trials		
Divalproex	Buproprion SR	Nefazodone
Atomoxetine	Escitalopram	Lithium
Vilazodone	Nabilone	
Human Laboratory Controlled Studies		
Buproprion SR	Nefazodone	Divalproex
Baclofen	Mirtazapine	Naltrexone
Quetiapine	Cannabidiol	Tiagabine

Summary: Medications targeting cannabinoid, GABAergic, glutamatergic, and neurohormonal systems have shown early promise for treating CUD.

adapted from Gray, 2020