

Cannabis Use/Disorder in the Patient with OUD

Presented By:

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Disclosures

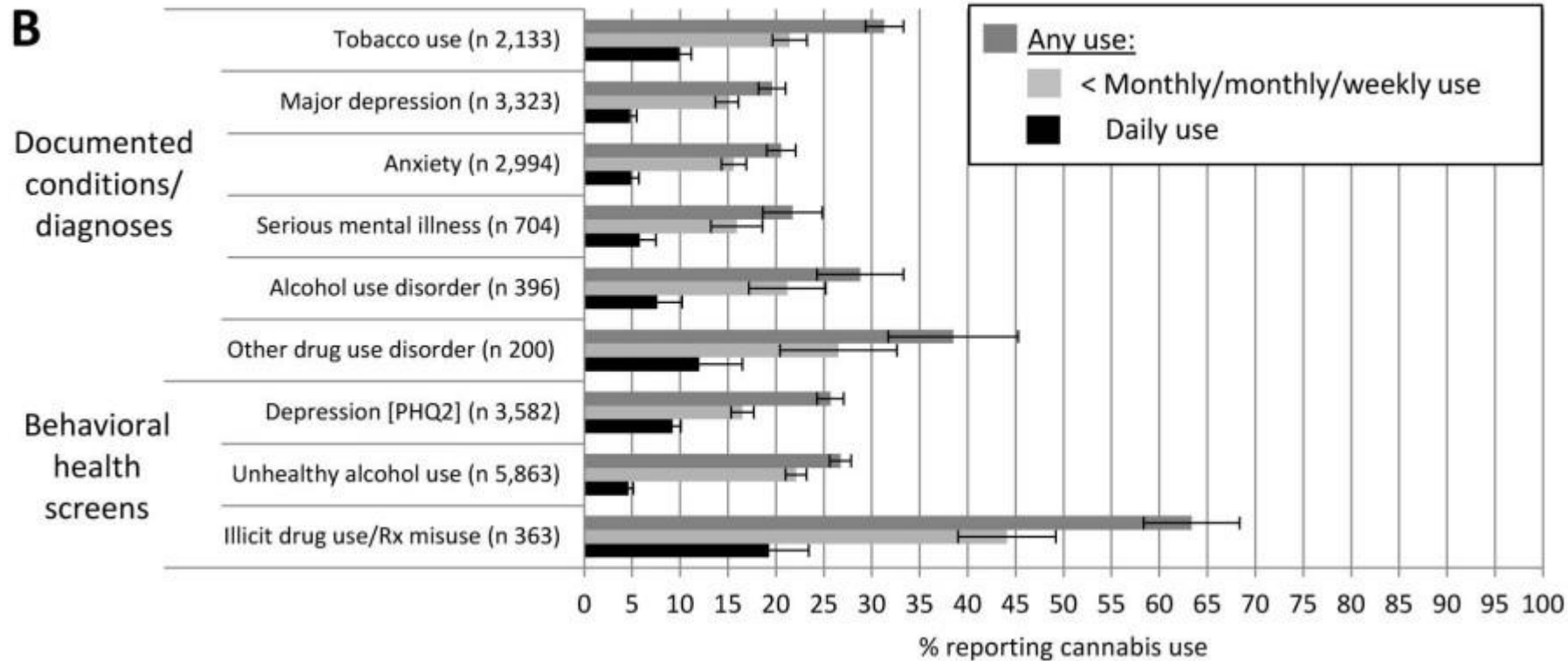
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Objectives

- Identify the prevalence of cannabis use in the U.S.
- Discuss the benefits and risks of cannabis use
- Distinguish the components of cannabis and their expected effects
- Summarize available literature on cannabis use in OUD and the implications of legalization
- Explain the role of the general practitioner in assessing for and reducing the risk of cannabis use
- Apply principles of harm reduction in talking to patients about cannabis use

Cannabis Use in the U.S.



Prevalence of cannabis use in patients with OUD is 51%; 28% meet criteria for cannabis use disorder

Lapham GT, et al. *J Am Board Fam Med.* 2017 Nov-Dec;30(6):795-805.

Lake S, et al. *Clin Psychol Rev.* 2020 Dec;82:101939.

Rosic T, et al. *Subst Abuse Treat Prev Policy.* 2021 Apr 13;16(1):34.

The “What” of Cannabis Use and its Benefits



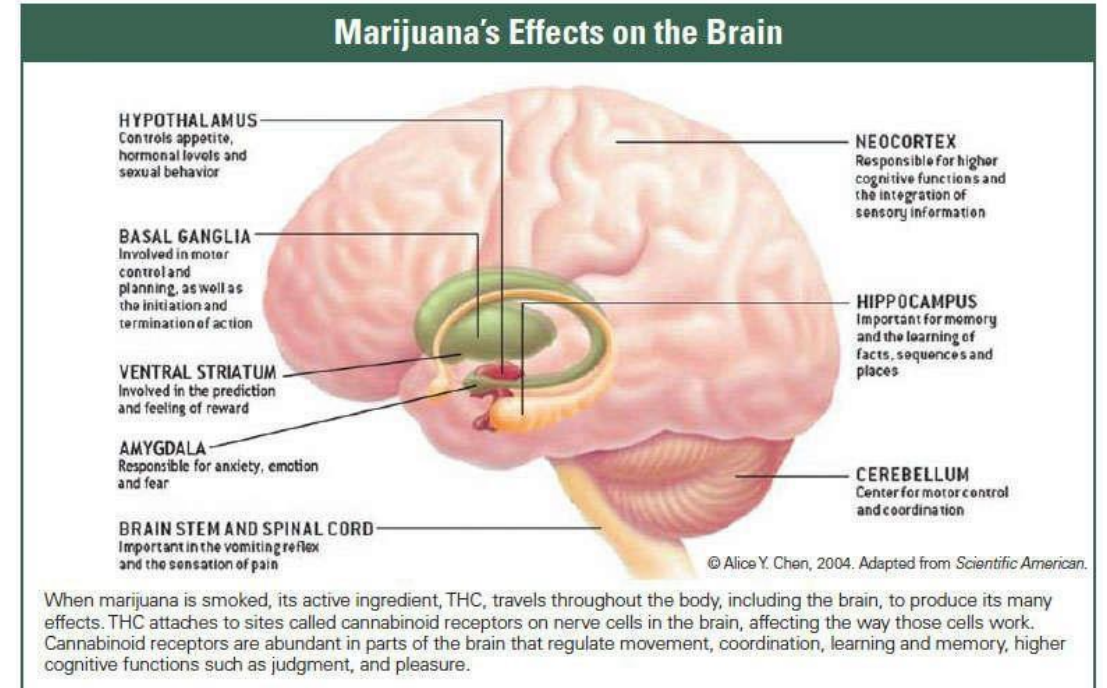
Cannabis Products



<https://yourlocalcannabis.com/cannabis-products-2022/>

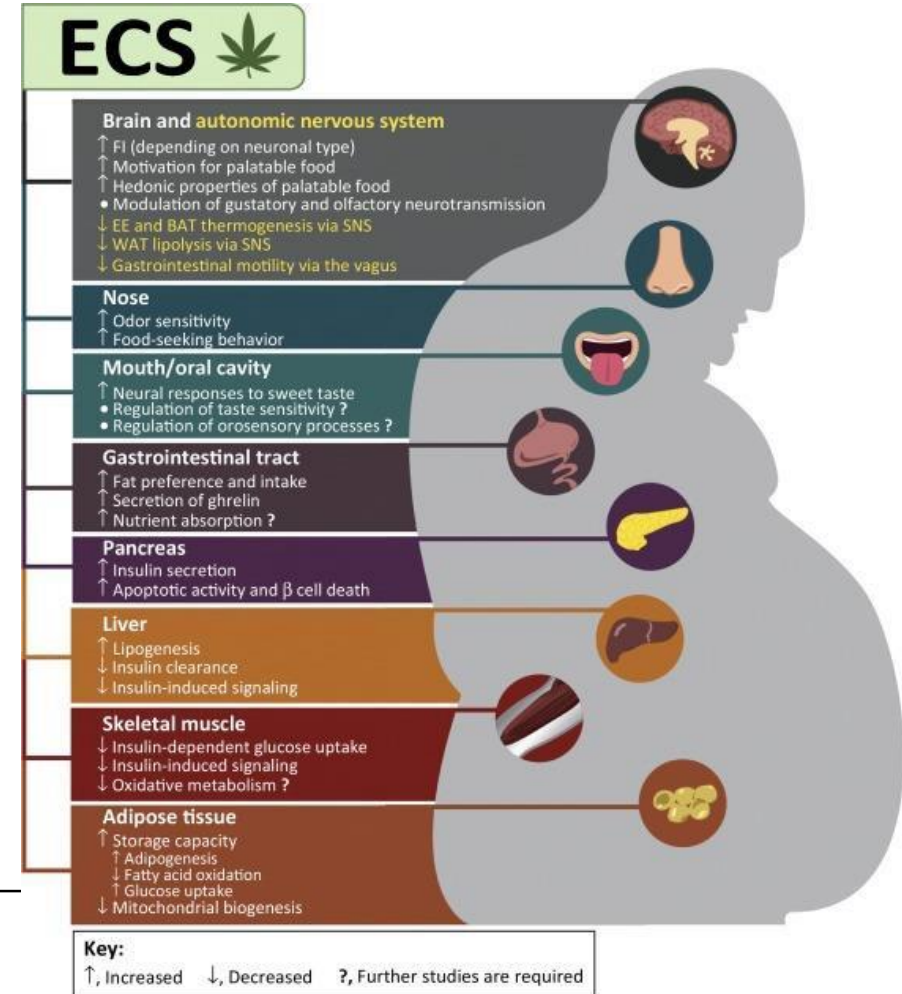
Cannabinoid Receptors

- CB₁
 - Psychoactive; mostly in brain/CNS
 - Found on GABA interneurons and glutamatergic neurons
 - Low density in brainstem → no overdose risk
- CB₂
 - Found on peripheral immune cells (T cells, B cells, macrophages, etc)
 - Also on microglial, dendritic, and endothelial cells in the brain
 - Relief of pain



ECS Function – Body’s “Supercomputer”

- “Steadies the temperature in every room in the body’s house”
- Regulates the flow and balance of all organ systems
- Basic functions
 - Relaxing, eating, sleeping, forgetting, protecting our organs

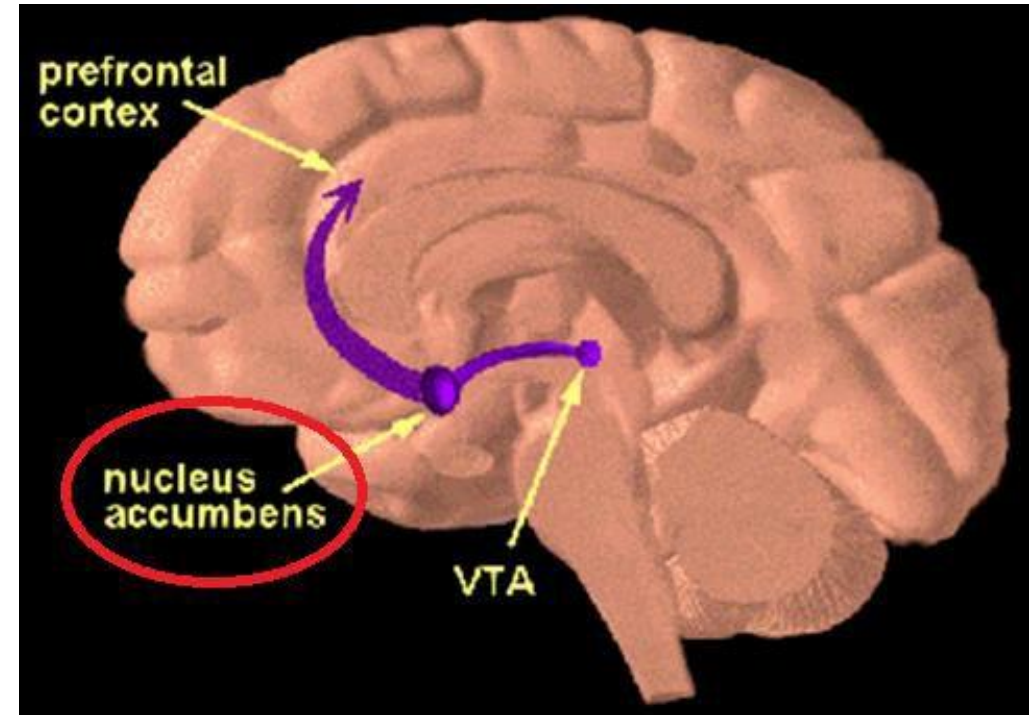
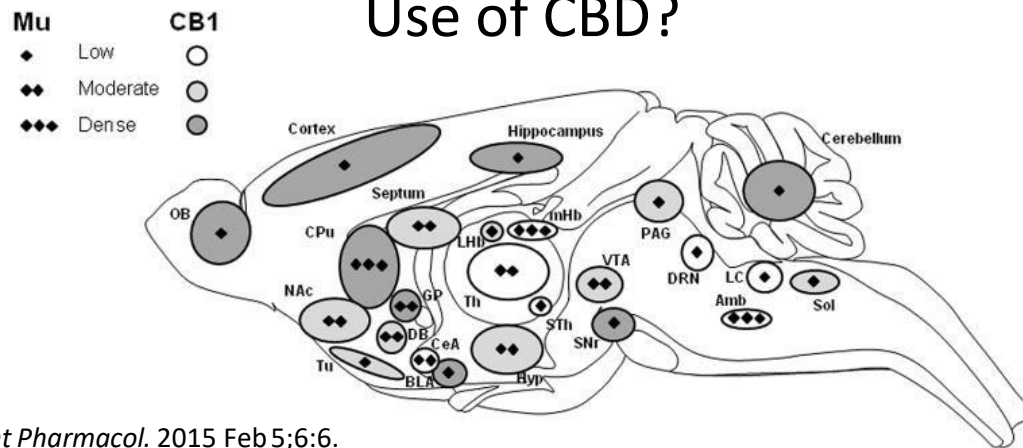


Cannabinoid and Opioid Receptors Distributed in Same Regions of CNS

Analgesic synergy?

Use of cannabis to spare-opioid consumption in OUD has had conflicting results

Use of CBD?



Befort K. *Front Pharmacol.* 2015 Feb 5;6:6.

Cannabis Benefits

Known

- **Chronic Pain**
 - Neuropathic, fibromyalgia
- **Nausea and vomiting**
 - Rx: dronabinol, nabilone
- Cachexia – appetite stimulant
- Spasticity from Multiple Sclerosis
- Resistant Epilepsy
 - Rx: Cannabidiol

Possible

- **Reduction in long-term use of opioids and opioid withdrawal**
- Dystonia
- Glaucoma

Inconclusive

- **Anxiety and depression**
- Alzheimer disease
- Parkinson's Disease
- Antitumor
- Inflammatory bowel diseases
- Heart failure
- Hepatitis C
- Ischemia/Reperfusion injury
- Sleep

Page RL, et al. *Circulation*. 2020 Sep 8;142(10):e131-e152.

Cannabis Components

Delta-9-Tetrahydrocannabinol (THC)

- Pros
 - Analgesic (refractory chronic pain)
 - Antiemetic (FDA-approved formulation)
 - Muscle relaxant
 - Appetite stimulant (FDA-approved formulation)
- Cons
 - Psychosis
 - Risk of worsened co-morbid OUD and associated consequences
 - Risk of dependence → addiction
 - Euphoria
 - Cannabinoid Hyperemesis Syndrome

Cannabidiol (CBD)

- Pros
 - Analgesic?
 - Anti-seizure (FDA-approved formulation)
 - Anxiolytic and antipsychotic?
 - Neuroprotective
- Cons
 - Decreased appetite
 - Diarrhea
 - Liver impairment

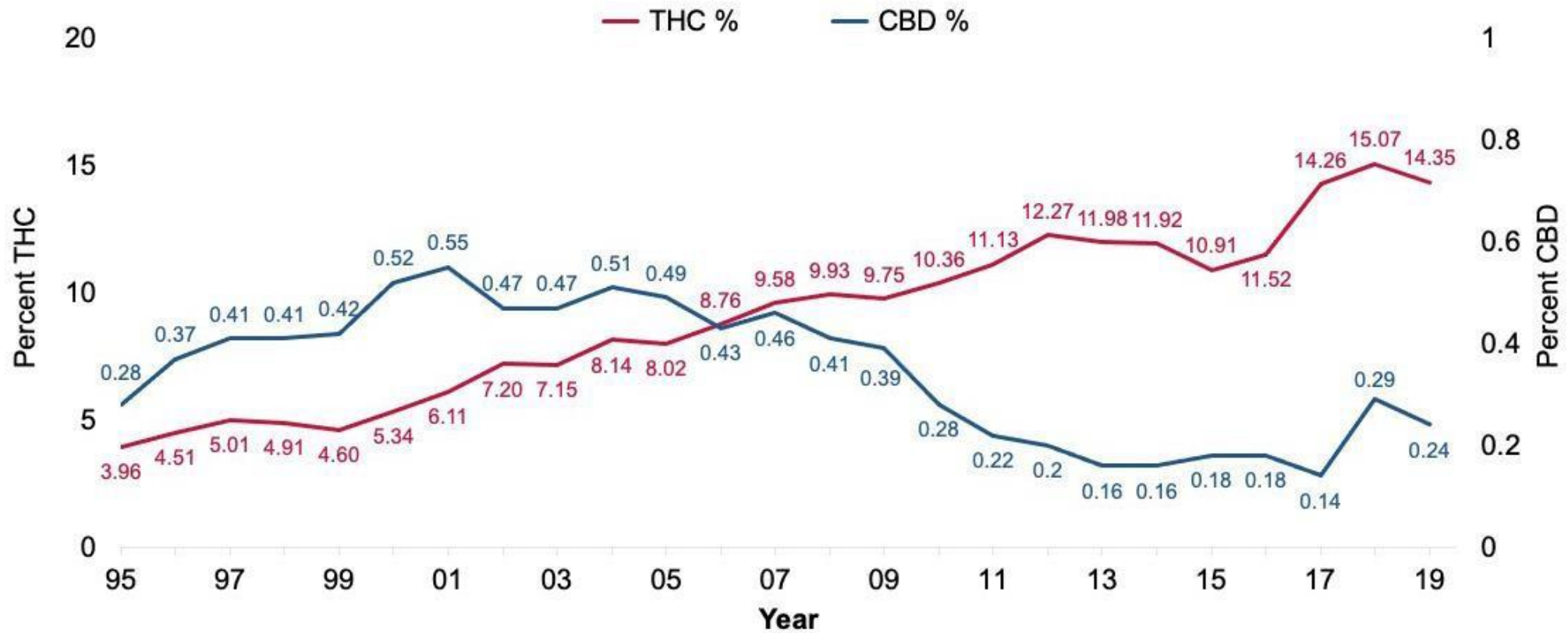
Many drug interactions and additive effects

Clinical Resource, *Comparison of Cannabinoids. Pharmacist's Letter/Prescriber's Letter*. September 2018.

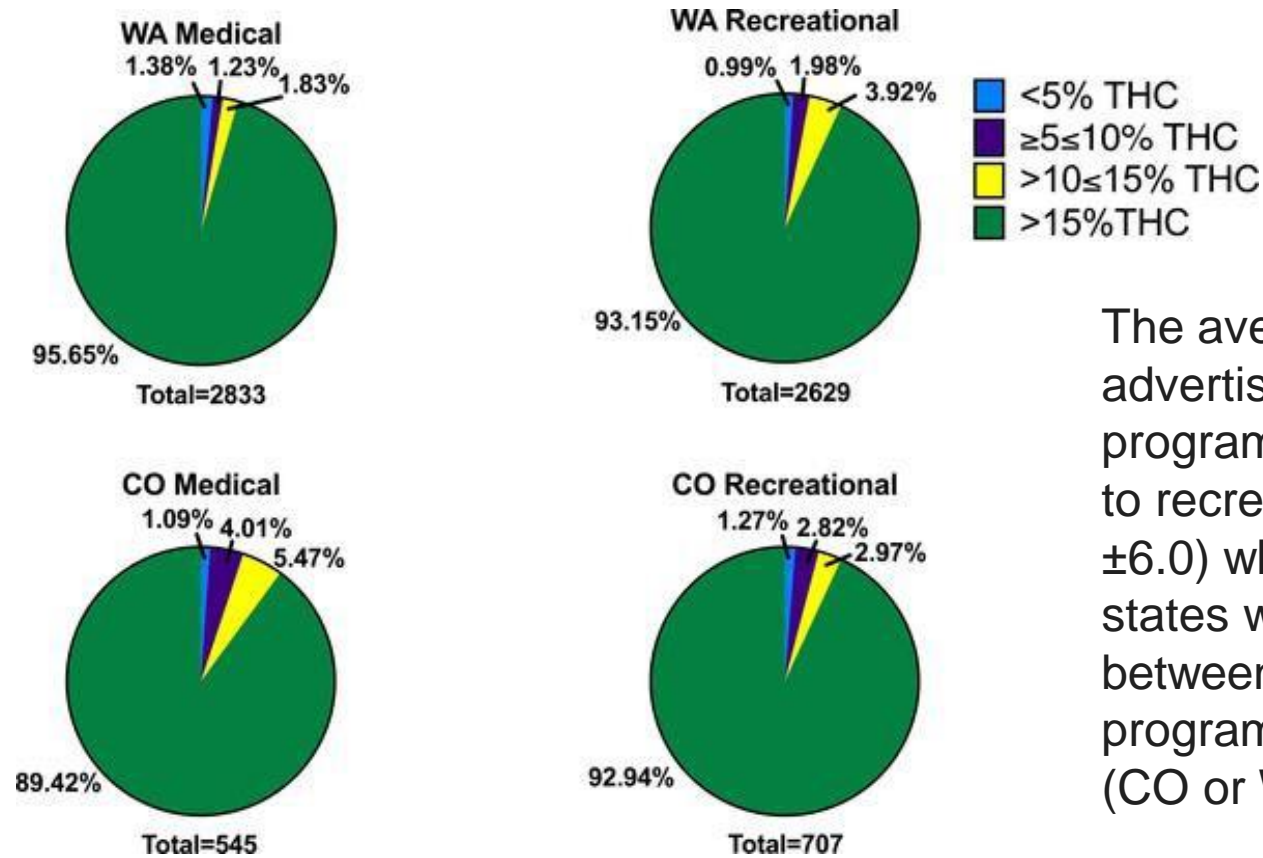
Risk of THC



Historical Timeline of THC vs. CBD Content



Proportion of Products of Different Levels of THC



The average THC concentration advertised online in medicinal programs was similar ($19.2\% \pm 6.2$) to recreational programs ($21.5\% \pm 6.0$) when compared between states with different programs, or between medicinal and recreational programs within the same states (CO or WA).

Cash MC, Cunnane K, Fan C, Romero-Sandoval EA (2020) Mapping cannabis potency in medical and recreational programs in the United States. PLOS ONE 15(3): e0230167. <https://doi.org/10.1371/journal.pone.0230167>

High-Potency Cannabis and Risk for Psychotic Disorder

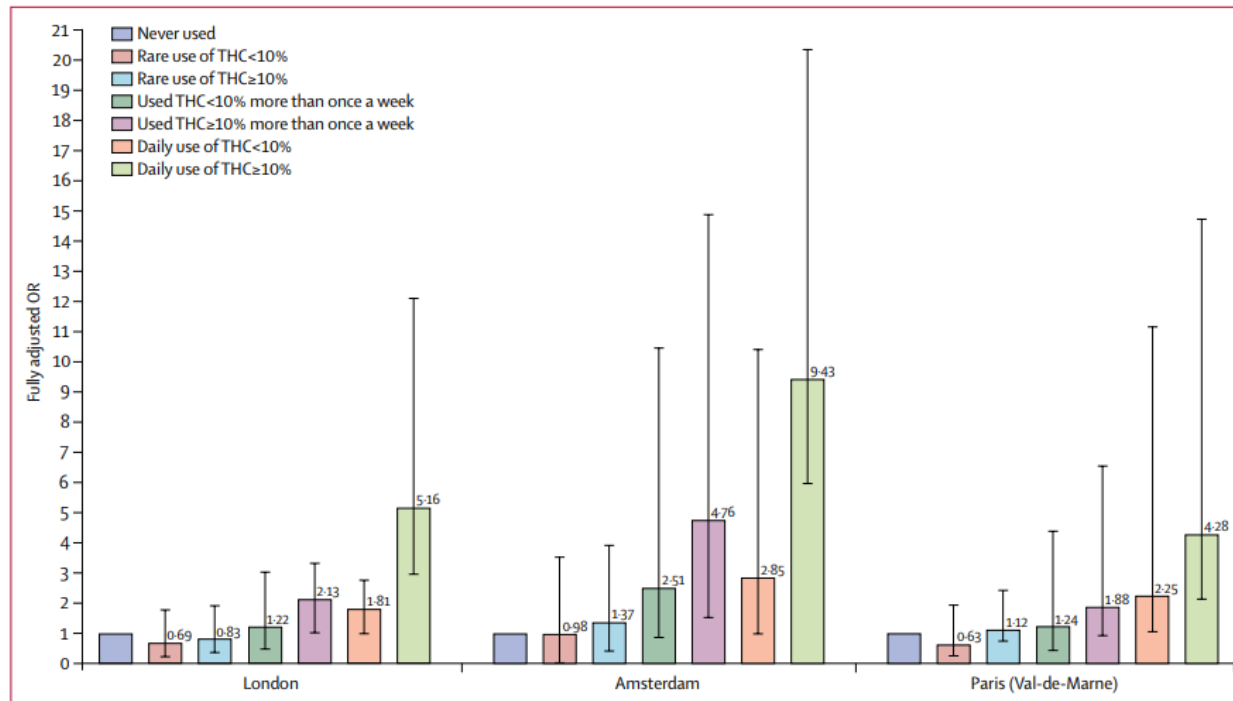


Figure 2: Fully adjusted ORs of psychotic disorders for the combined measure of frequency plus type of cannabis use in three sites
 Data are shown for the three sites with the greatest consumption of cannabis: London (201 cases, 230 controls), Amsterdam (96 cases, 101 controls), and Paris (54 cases, 100 controls). Error bars represent 95% CIs. OR=odds ratio.

- 4x greater in Paris
- 5x greater in London
- >9x in Amsterdam
- High correlation between amount of drug used, age at first use, and genetic vulnerability

Di Forti, et al. *Lancet Psychiatry*. 2019 May;6(5):427-36.
<https://www.drugabuse.gov/publications/research-reports/marijuana/there-link-between-marijuana-use-psychiatric-disorders#:~:text=Recent%20research%20suggests%20that%20smoking,who%20have%20never%20used%20marijuana.&text=The%20amount%20of%20drug%20used,shown%20to%20influence%20this%20relationship.>

Causal Link Between Cannabis and Psychosis?

- Meta-analysis of 18 studies showed that there is a positive dose-dependent relationship of cannabis use to psychosis
 - OR of 3.90 (95% CI 2.84 to 5.34) for the risk of schizophrenia amongst heaviest cannabis users
- **Population-Attributable Risk Fraction (PARF)** for Cannabis Use Disorder in Schizophrenia
 - Large longitudinal population-based study of over 7 million in Denmark from 2001 to 2017
 - Increased from 2% → 6-8% since 2019
 - 3-4-fold increase in PARF score
- Daily cannabis use was associated with increased odds of first-episode psychotic disorder, ↑ up to 5-fold amongst high-potency cannabis across Europe in a multicenter case-control study
 - 3-5 fold increase
 - 12.2% PARF

Marconi A, et al. *Schizophr Bull.* 2016 Sep;42(5):1262-9.
Hjorthoj C, et al. *JAMA Psychiatry.* 2021;78(9):1013-19.
Di Forti M, et al. *Lancet Psychiatry.* 2019 May 6(5):427-36.

Cannabinoid Hyperemesis Syndrome

- **Chronic cannabis use** leading to cyclic, recurrent episodes of severe nausea/vomiting and abdominal pain
- 3 phases: Prodromal, hyperemetic, and recovery
- Relief can be achieved by “hot bathing”
- True resolution of the problem: Stopping cannabis use
- Cause???
- Misdiagnosis is high

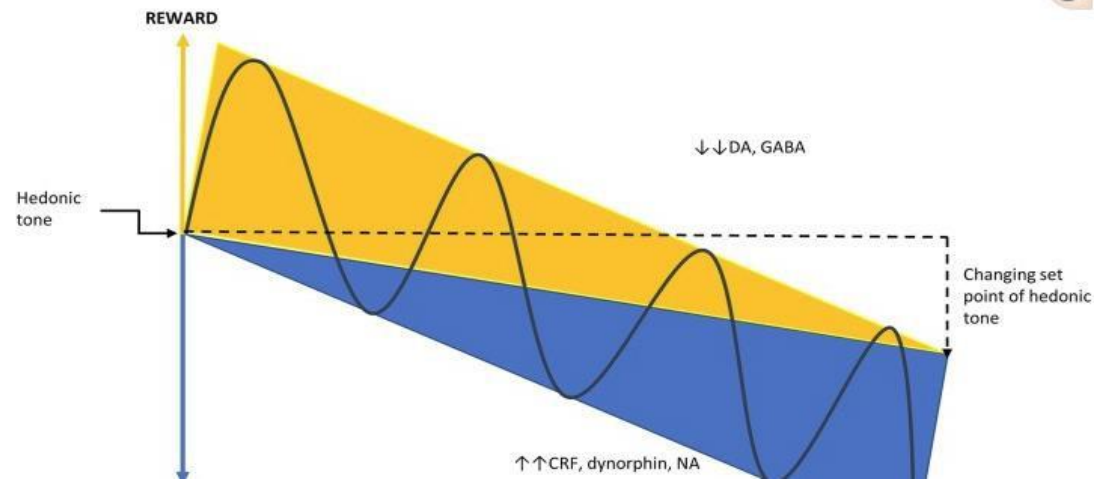


Galli JA, et al. *Curr Drug Abuse Rev.* 2011 Dec;4(4):241-49.

Cannabis Withdrawal → Link to a Use Disorder?

- Anger
- Anxiety
- Disturbed sleep
- Restlessness
- Depressed mood
- Strange dreams
- Decreased appetite
- Weight loss
- Headache
- Night sweats

- Not as:
 - Painful as heroin withdrawal
 - Dangerous as alcohol withdrawal
 - Long-lasting as cocaine withdrawal



Less production of internal endocannabinoids!

Kakko J, et al. *Front Psychiatry*. 2019 Aug 30;10:592.

Page RL, et al. *Circulation*. 2020 Sep 8;142(10):e131-e152.

Cannabis Use Disorder – DSM 5

- Using cannabis for a minimum of one year with the presence of at least two of the following symptoms accompanied by serious impairment of functioning and agitation:
 - Used in larger amounts over a longer time than what was intended
 - Repeatedly tried to stop or lessen the amount of cannabis used
 - Unusual amount of time is spent trying to get, use and/or recover from cannabis effects
 - Having cravings for cannabis, such as thoughts and images, dreams, and perceiving its smell because of an obsession with it
 - Keep on using cannabis even in light of the fact that it has negative consequences, such as others warning to leave the relationship or being left by a partner or friends, poor job performance, and criminal charges
 - Using cannabis is more important than other areas of life—job, school, hygiene, and responsibilities to family members and friends
 - Using cannabis and taking dangerous risks, such as driving a car
 - Using cannabis even though the person is aware of the physical and psychological problems they have because of it (lack of motivation, chronic cough)
 - Builds a tolerance to cannabis—taking larger amounts to get the psychoactive effect experienced when it was first used
 - Cannabis is used to halt the symptoms of withdrawal

Who's at Greatest Risk?

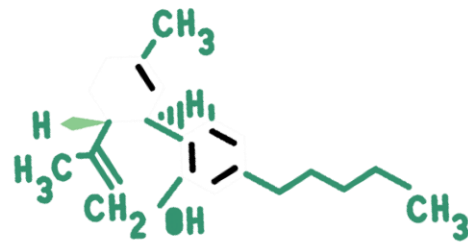
- Adolescents
 - Those under the age of 18
- People with:
 - Polysubstance use – cigarette smoking?
 - Co-occurring mental health disorders
 - Pregnant
- Those with frequent use

Treatment for Cannabis Use Disorder

- Psychotherapy
- No FDA-approved medication for the treatment of cannabis use disorder
 - Topiramate? Gabapentin? Naltrexone?
 - GABAergic mechanism
 - Some medications may help with cannabis withdrawal but not with recurrence
 - Zolpidem
 - Mirtazapine
 - Quetiapine
 - Oral THC-Rx products – dronabinol/nabilone?

Brezing CA, et al. *Neuropsychopharmacology*. 2018 Jan;3(1):173-94.

The Impact of Cannabis Use on Opioid Use Disorder



Effect of Cannabis and Patient Outcomes in those on MOUD

- Systematic review of 41 studies
- Primary outcome relationship
 - Opioid use, treatment adherence, treatment retention
- Majority showed no statistical significance
- Called for more studies looking at adjunctive effects of cannabis use on opioid craving and withdrawal
- Prospective cohort study of 211 participants found that the odds of same-day opioid use with cannabis was nearly 2 (aOR 1.86 95% CI 1.44-2.41) relative to opioid use on days without cannabis use
 - Cannabis not used as a substitute

Lake S, et al. *Clin Psychol Rev.* 2020 Dec;82:101939.

Gorfinkel LR, et al. *Addiction.* 2021 May;116(5):1113-1121.

Effect of Cannabis and Patient Outcomes in those on MOUD

- Prospective observational study of n=2,315 patients from community-based SUD treatment clinics in Ontario, Canada receiving methadone or buprenorphine over 3-month period
 - Past-month cannabis use = 51% of participants
 - Any cannabis use compared to non-use not associated with more or less opioid use
 - Daily cannabis use associated with lower odds of opioid use when compared to occasional use (OR=0.61; CI 0.47-0.79;p<0.001); older age also with lower odds of opioid use
 - 75% perceived no impact of cannabis use on their OUD treatment

Table 3 Multivariable model of cannabis-use characteristics associated with opioid use, amongst cannabis users (n = 1154)

Characteristic	OR	95% CI	p
Age of onset of cannabis use in years (for every 1 year increase in age)	0.97	0.94, 0.99	0.032
Non-daily cannabis use	[reference]		
Daily cannabis use	0.60	0.46, 0.78	<0.001
Marijuana Cravings Questionnaire Score (for each 10-point increase)	1.06	0.98, 1.14	0.144
No side effects from cannabis reported	[reference]		
Side effects from cannabis reported	0.66	0.52, 0.84	0.001

OR odds ratio, CI confidence interval

Model is adjusted for age, sex, type of MAT, dose, and years in treatment

Rosic T, et al. *Harm Reduct J.* 2021

Opioid and Cannabis Co-Use and Association with Substance Misuse, Mental Health, and Pain

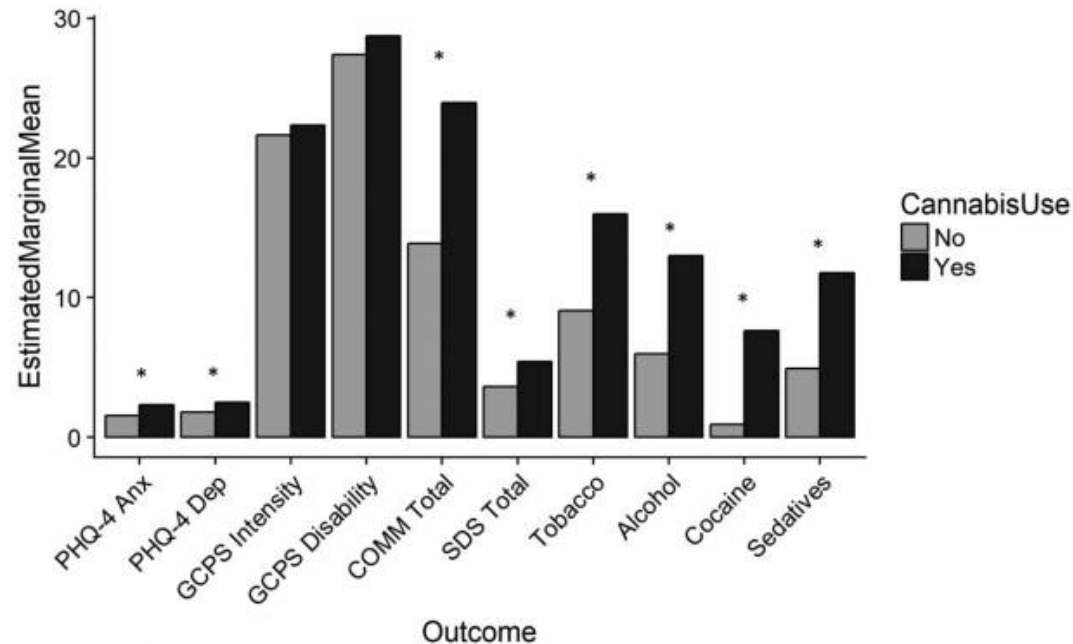


FIGURE 1. Group Estimated Marginal Mean Comparison. Note: * indicates a significant difference at the $P < 0.005$ level. PHQ-4 Anx—Anxiety, PHQ-4 Dep—Depression, GCPS Intensity—pain intensity, GCPS Disability—pain disability, COMM Total—Current Opioid Misuse, SDS Total—Severity of Opioid Dependence.

Examined use of opioids alone compared to use of opioid and cannabis co-use in a **cross-sectional** study.

Opioid and cannabis co-use associated with increased anxiety and depression symptoms, as well as tobacco, alcohol, cocaine, and sedative use problems, but not pain experience.

Rogers AH, et al. *J Addict Med.* Jul/Aug 2019;13(4):287-94.

Impact of Legalization on Cannabis Use



Association Between Recreational Cannabis Legalization and Changes in Cannabis Use/Disorder

- 506,000 respondents comparing cannabis use before and after legalization of recreational cannabis across several states

Table 2. Past-Month Marijuana Use, Frequent Marijuana Use, and CUD in the Past 12 Months Among 495 796 Respondents Before vs After RML Enactment From 2008 to 2016^a

Age Group, y	Marijuana Use						CUD in the Past 12 mo		
	Past Month			Frequent			% Who Met Criteria for CUD		
	Before RML ^b	After RML ^c	AOR (95% CI) ^d	Before RML ^b	After RML ^c	AOR (95% CI) ^d	Before RML ^b	After RML ^c	AOR (95% CI) ^d
12-17	4.76	5.28	1.12 (0.97-1.28)	1.07	1.19	1.12 (0.87-1.43)	2.18	2.72	1.25 (1.01-1.55)
18-25	13.06	14.03	1.09 (0.99-1.20)	4.64	5.08	1.10 (0.97-1.25)	3.62	3.48	0.96 (0.80-1.14)
≥26	5.65	7.10	1.28 (1.16-1.40)	2.13	2.62	1.24 (1.08-1.41)	0.90	1.23	1.36 (1.08-1.71)

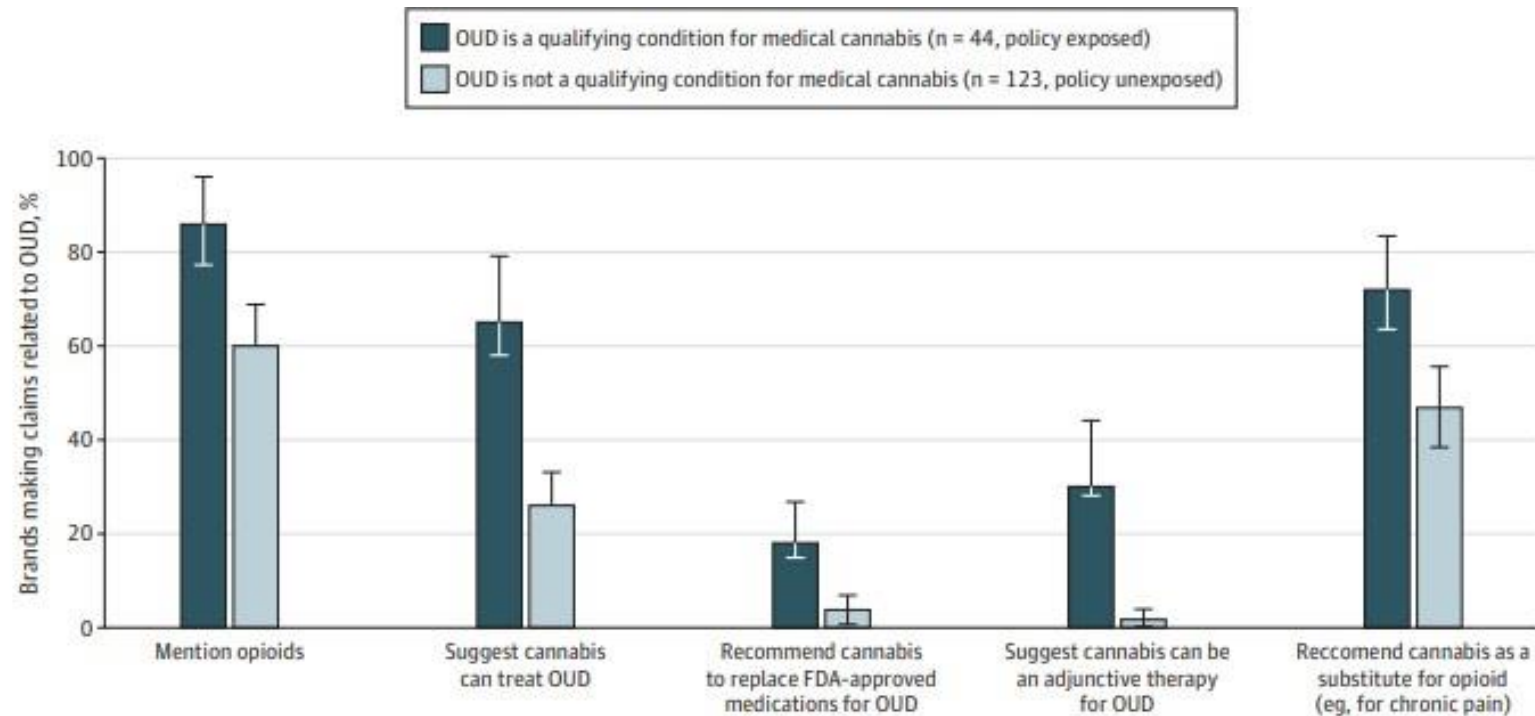
Data from the National Survey on Drug Use and Health

Cerda M, et al. *JAMA Psychiatry*. 2020 Feb 1;77(2):165-71.

Study included >500,000 respondents

RML = Recreational Marijuana Legalization

Association of State Policies Allowing Medical Cannabis for OUD And Dispensary Marketing

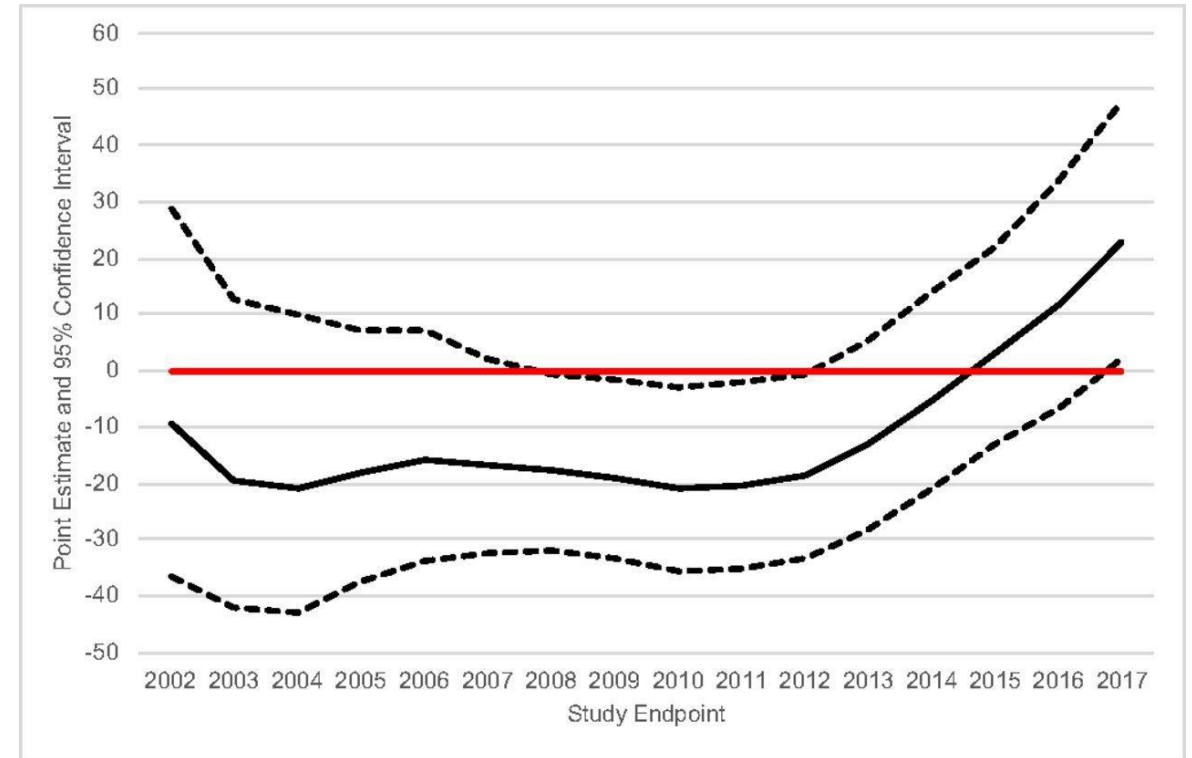


Whiskers indicate 95% CIs. FDA indicates US Food and Drug Administration.

Shover CL, et al. *JAMA Netw Open*. 2020 Jul;1:3(7):e2010001.

Trend Towards Increase in Opioid Overdose Deaths

- Bachhuber, et al –
 - 1999-2010 – states enacting medical cannabis laws had lower-than-expected opioid overdose mortality rates (24.8% reduction)
- Shover, et al -
 - 2010-2017 – 32 states enacted medical cannabis laws, including 17 allowing only low levels of THC
 - 8 states enacted recreational cannabis laws
 - 23% increase in opioid overdose deaths



Bachhuber MA, et al. *JAMA Intern Med.* 2014;174(10):1668-1673.

Shover CL, et al. *Proc Natl Acad Sci USA.* 2019 Jun 25;116(26):12624-12626.

Synthetic Cannabinoids



- Not detected by standard tests
- Cross-sectional study of patient with OUD: detected in 4.3% of individuals
- Missing the “Entourage Effect”

Alias-Ferri, et al.

The “How” of Cannabis Use



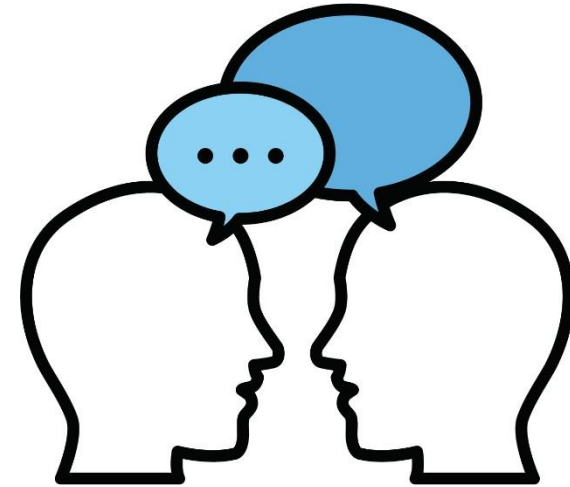
Approaching the Patient on Cannabis Use

Opening the dialogue to cannabis



Cannabis Use – Talking Points

- General use
 - Is it being used alternatives to treat your indication?
- Indication for use
- Route of use – how do you use it?
 - Affects onset of action
 - Dabbing?
- Quantity and **frequency of use**
- Source of use
- What do you enjoy/don't enjoy about using cannabis?
- Would there be benefit to stopping, what would be hard about stopping?



Be patient-centered

Harm Reduction

- Focus on reducing the negative consequences of cannabis use vs. cannabis use is "bad"
- Emphasize the importance of knowing the content and concentration of the cannabis product
- Set patient-centered goals
- Need to continue to develop therapeutic relationship



DON'T EXPECT THE CONVERSATION TO BE FINISHED
ALL IN ONE VISIT

Jaffe SL. *Emerging Trends in Drugs, Addictions, and Health*. 1 (2021) 100011.

Key Points to Understand as a Provider

- Synthesize the available information in an unbiased way
- Discuss the risks of use of cannabis
 - At what point do you bring up the negative consequences or bring up cannabis use overall?
- Emphasize that a cannabis-approved qualifying condition does NOT mean it is proven to treat a specific disease
- Understand that many studies have variable outcome measures
 - Difficulty in studying due to Scheduled I controlled substance status

Summary

- The growth of highly potent THC-containing products is fraught with risks
 - Products with greater composition of CBD likely to be of benefit?
- The medical literature for cannabis has not kept up with the fervor of cannabis use resulting from both legalization and commercialization
- Gaps exist particularly related to:
 - Appropriate dosing
 - Content of THC vs. CBD
 - Route of administration and associated bioavailability
- Harm reduction strategies are essential
 - People who frequently use
 - Those with history/risk of schizophrenia/psychotic disorder

Questions & Discussion



Thank you to everyone
who joined and
participated today!