Cannabis Use Disorder: Changing trends & Treatment approaches

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ISSUP INTERNATIONAL SOCIETY OF SUBSTANCE USE PROFESSIONALS
NIGERIA chapter

No Disclosures

Don't own any stock in cannabis products

Objectives – Part 1

- Understand the Prevalence and Trends of Cannabis Use
- Outline short-term and long-term health effects of cannabis use
- Identify the diagnostic criteria for CUD according to DSM-5, ICD-11
- Describe evidence-based treatment options for CUD, including behavioural therapies

Cannabis Use In Numbers

- Cannabis grows in nearly every country in the world.
- Cannabis was used by an estimated 192 million people worldwide in 2016, approximately 3.9% of the global population age 15 to 64 years (16% increase since 2016)
- Cannabis use is most prevalent in West and Central Africa (13.2 %), North America (12.9), and Oceania (11.0 %), and least prevalent in East and South-East Asia (0.6 %), Eastern and South-Eastern Europe (2.4 %), the Caribbean (2.2 percent), and Central America (2.8%)

https://www.uptodate.com/contents/cannabis-use-and-disorder-epidemiology-comorbidity-health-consequences-and-medico- legal-status

What is Marijuana?

- Is a plant –
- Two species of Cannabis exist:
  - **Cannabis Indica**
    - Generally, it is more sedating
  - **Cannabis Sativa**
    - Generally, is more stimulating

- Contains MANY cannabinoid chemicals
- Delta-9-tetrahydrocannabinol (THC)
- Cannabidiol (CBD)

https://www.freepik.com/free-photo/cannabis-marijuana-leaf-closeup_5218112.htm#query=cannabis%20shadow&position=49&from_view=search&track=ais &uuid=672db24f-cd56-4daf-8e2f-24668d3b166f

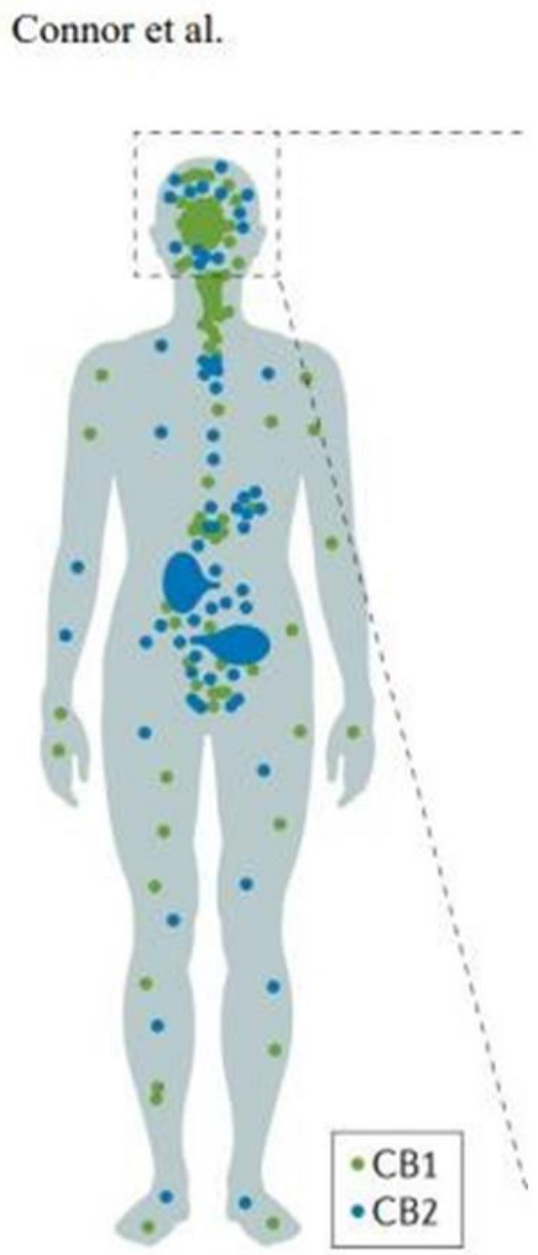
Cannabis - Facts

- World's most commonly used controlled substance worldwide.
- Highly lipophilic
- Persists in bodily fluids for extended period of time - Excreted slowly
- Chronic user, UDS (+) THC up to 1 month!!
- Higher rates of mental illness and suicide Attempts
- Gateway drug - 74% with CUD uses another substance

https://www.freepik.com/free-photo/marijuana-buds-with-marijuana-joints-cannabis-oil_7365453.htm#query=cannabis&position=23&from_view=search&track=sph&uuid=3d21bac4-6784-4f6d-bad3-2b20e2828ac0

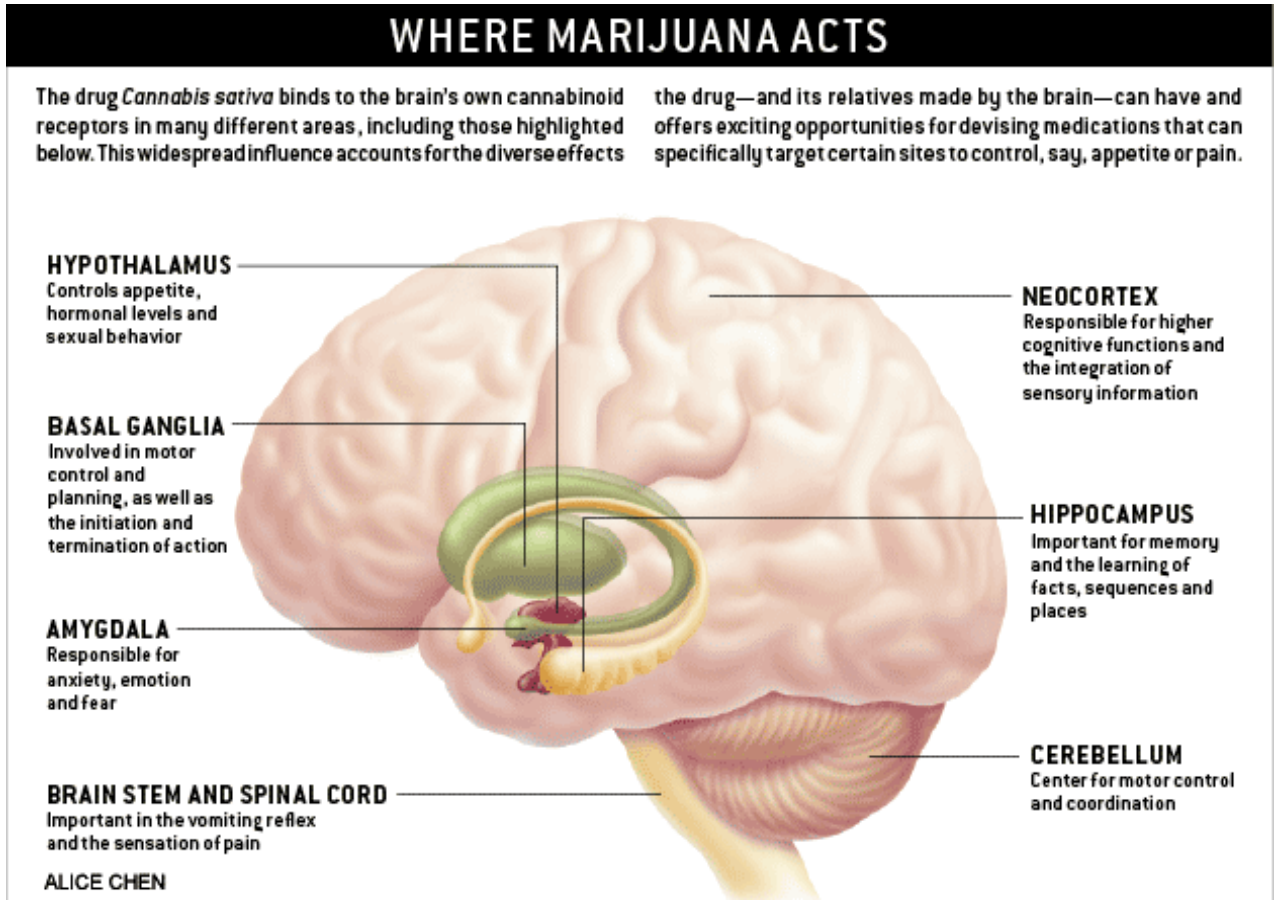
Distribution of CB receptors in the Brain

- CB1 (green) is primarily in the brain and binds to our own endocannabinoids (i.e. anandamide)
- CB2 (blue) are primary on immune cells



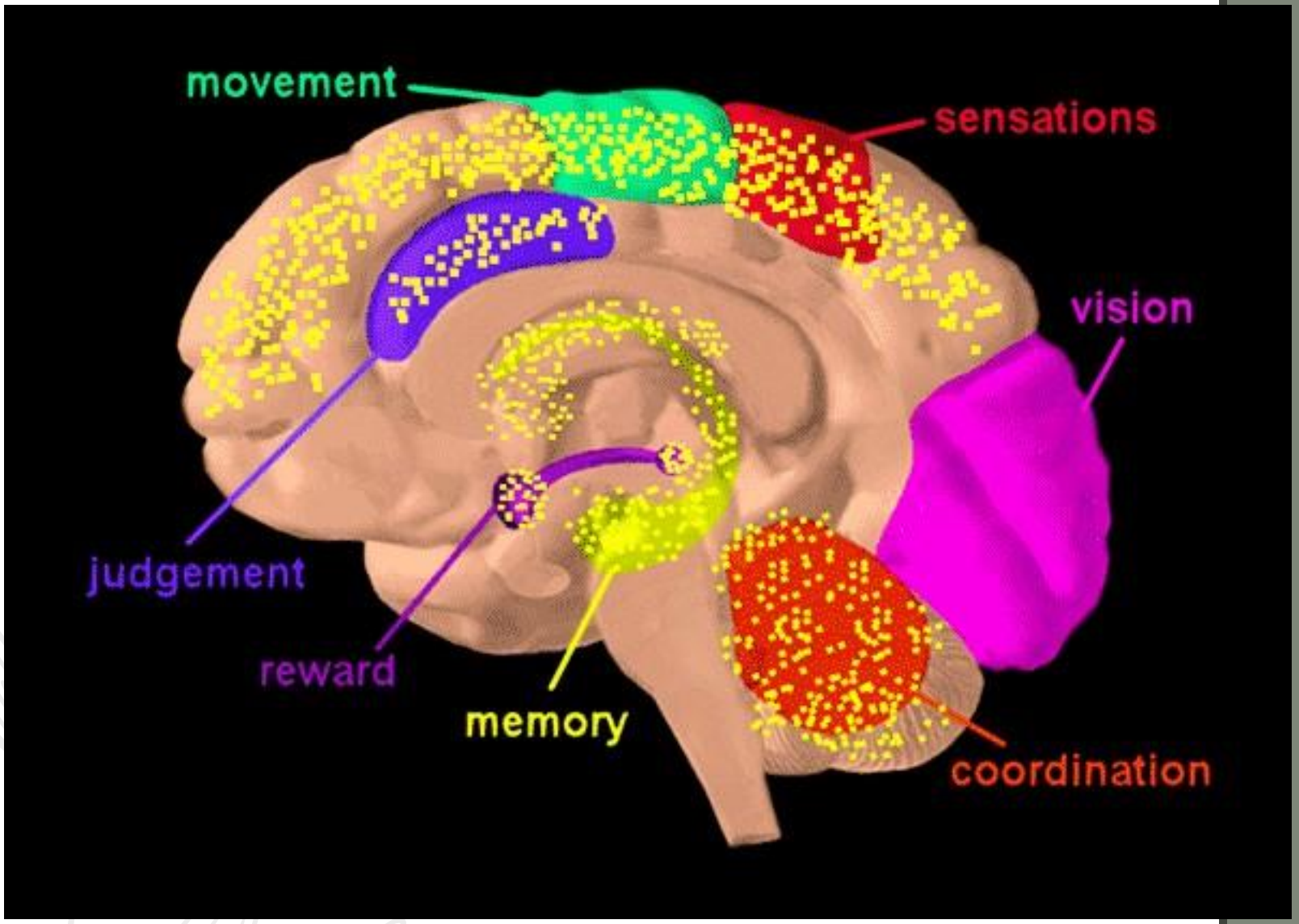
Connor JP, Stjepanović D, Le Foll B, Hoch E, Budney AJ, Hall WD. Cannabis use and cannabis use disorder. Nat Rev Dis Primers. 2021 Feb 25;7(1):16. doi: 10.1038/s41572-021-00247-4. PMID: 33627670; PMCID: PMC8655458.

The Endocannabinoid System



Receptor location can determine how activation or deactivation affects the body:

Midbrain = Pain
Peripheral tissues = Immunomodulation
Basal ganglia = Sedation and motor
Hippocampus = Cognition and memory
Hypothalamus =Appetite



Area of the brain with CB1 receptors - affected by cannabis (THC)

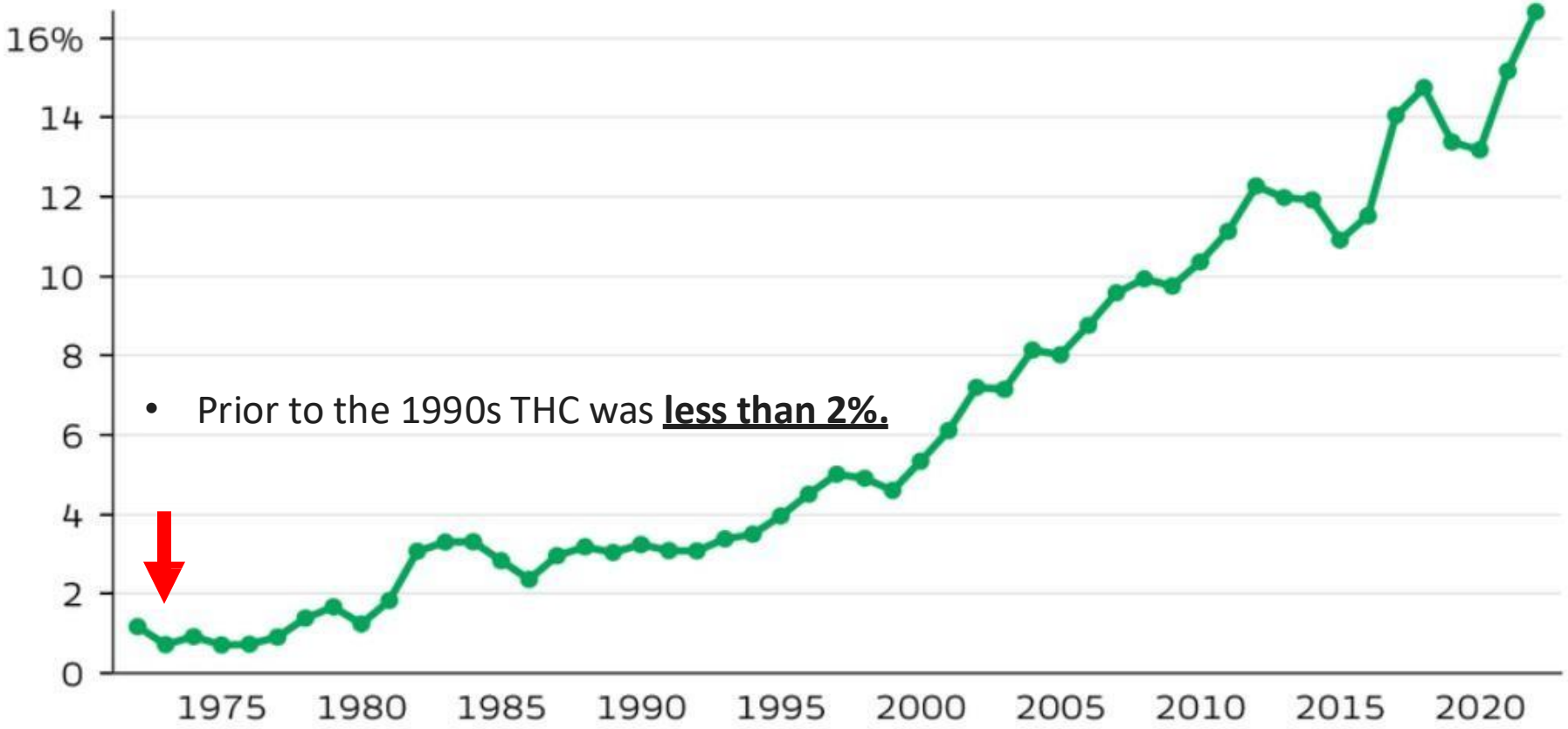
https://nida.nih.gov/publications/drugfacts/cannabis-marijuana

Cannabis Use & Trends

- THC percentage is indicative of how potent the effects are in a sample of cannabis.
  - Samples of cannabis taken in the 1960's typically contained no more than 3-4% THC
  - The concentration of THC has markedly increased from the 1960's to the present day.
- You would have to smoke 15 joints of 1960's marijuana to achieve the THC level in 1 joint of today's marijuana

Unfortunately not what your grandma used…different species!

THC content – then and now….

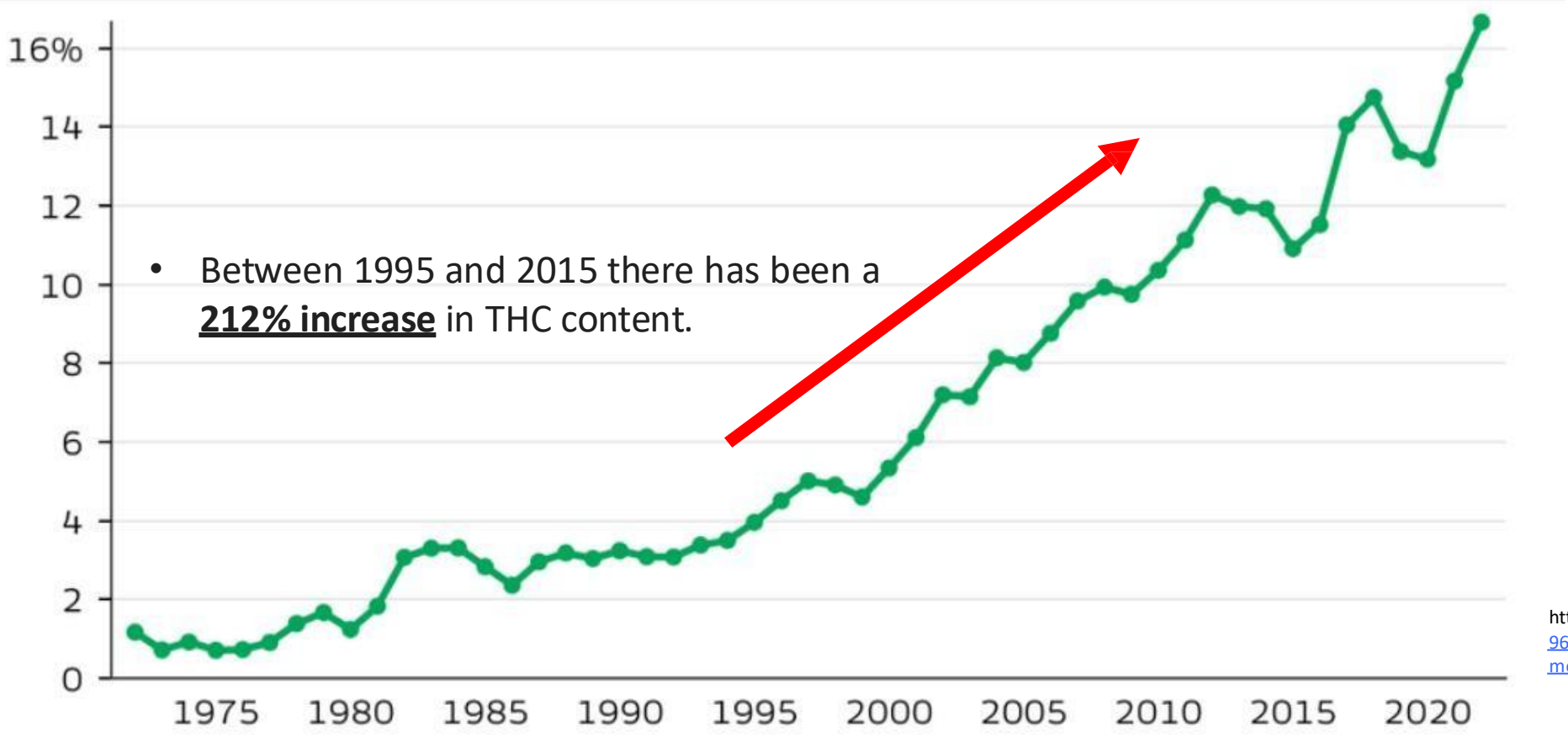


- Prior to the 1990s THC was **less than 2%.**

https://www.newscientist.com/article/2396976-is-cannabis-today-really-much-more-potent-than-50-years-ago/

Unfortunately not what your grandma used…different species!

THC content – then and now….



SOURCE: NIDA POTENCY MONITORING PROGRAM, UNIVERSITY OF MISSISSIPPI

https://www.newscientist.com/article/2396976-is-cannabis-today-really-much-more-potent-than-50-years-ago/

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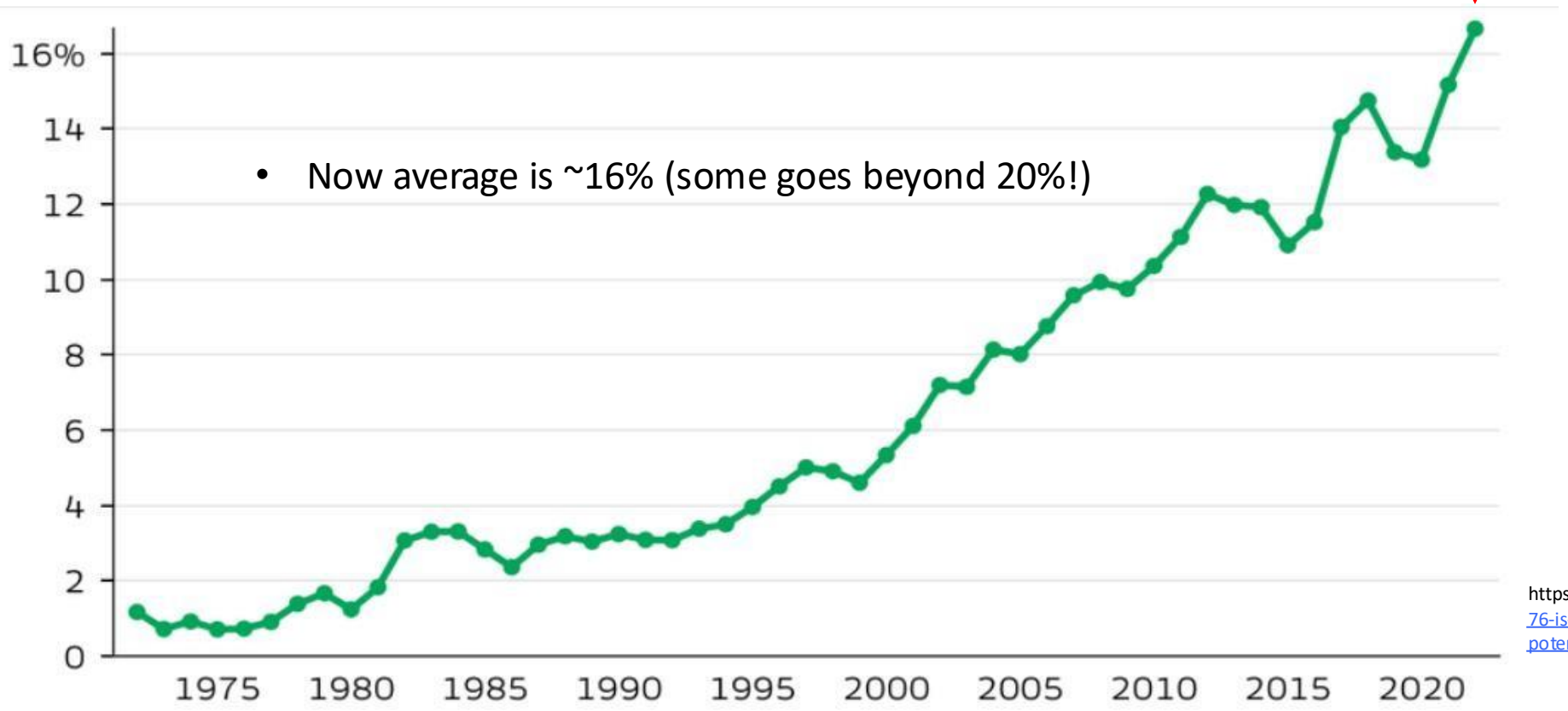
THC content – then and now….



- Now average is ~16% (some goes beyond 20%!)

https://www.newscientist.com/article/2396976-is-cannabis-today-really-much-more-potent-than-50-years-ago/

Delta 8 THC

- It is not found in significant amounts in the Cannabis sativa plant. As a result, concentrated amounts are typically manufactured.

- Between December 2020 and July 2021, the FDA received reports of 22 patients consuming delta-8 THC products (e.g., brownies, gummies), with 19 experiencing adverse events such as vomiting, hallucinations, difficulty standing, and loss of consciousness

- National poison control centers received 661 exposure cases of delta-8 THC products between January 2018 and July 31, 2021; 39% less than 18 years, 18% required hospitalization including children who required ICU admission.

Meier MH, et al (2012): **Persistent cannabis users show neuropsychological decline from childhood to midlife.** Proceedings of the National Academy of Sciences Plus 109:2657-2664

Meier et al. (2017). **Associations between adolescent cannabis use and neuropsychological decline: a longitudinal co-twin control study.** Addiction, 113:257-265

Why is Delta 8 THC more dangerous than Delta 9 THC

- Marketed as being **milder, legal** even where marijuana is not
- Delta-8 THC products often involve use of potentially harmful chemicals to create the concentrations of delta-8 THC claimed in the marketplace

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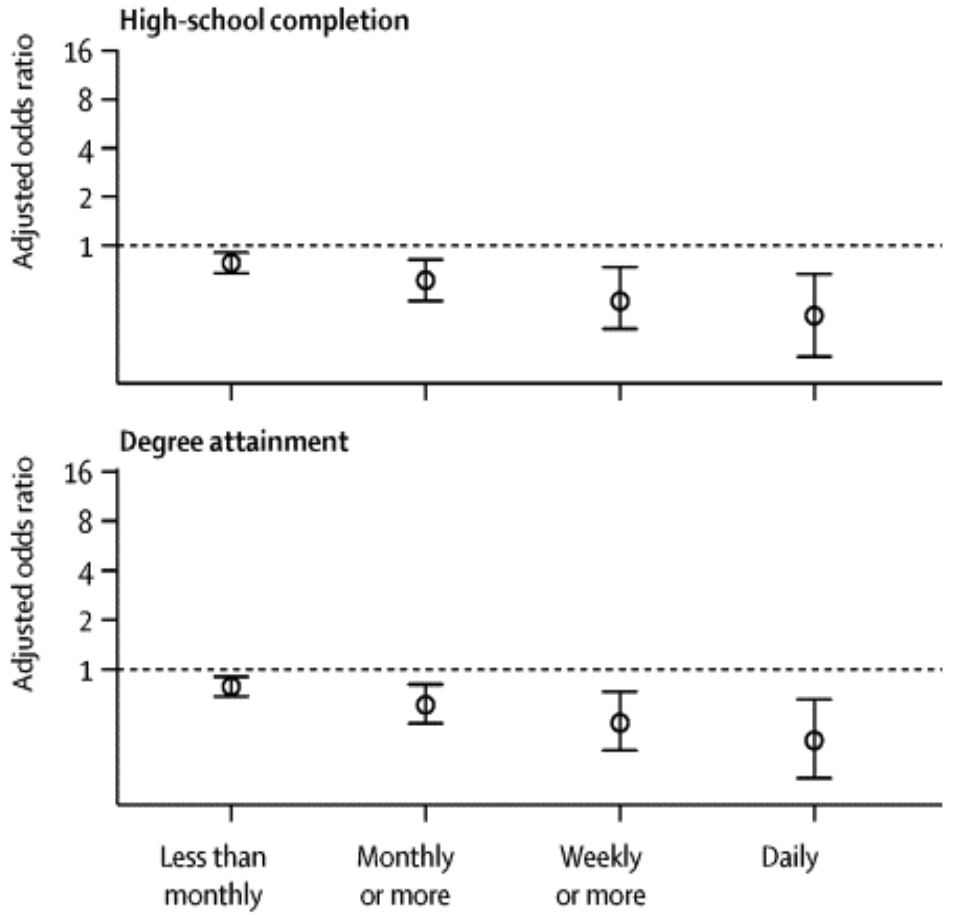
Meier et al. (2017). **Associations between adolescent cannabis use and neuropsychological decline: a longitudinal co-twin control study.** Addiction, 113:257-265

Cannabis Motivation and Educational Attainment

Unadjusted odds ratios (log scale) between maximum frequency of cannabis use before age 17 years and young adult outcomes in combined data, compared with individuals who have never used cannabis



Three large, long-running longitudinal studies from Australia and New Zealand: the Australian Temperament Project, the Christchurch Health and Development Study, and the Victorian Adolescent Health Cohort Study

Sillins E et al: Young adult sequelae of adolescent cannabis use: an integrative analysis. Lacet Psychiatry 2014 vol1

Adolescent Brain and Cannabis use

- Cannabis exposures during adolescent **adversely impact synaptic pruning and white matter development**
  - These alterations may cause cognitive and emotional deficits in adolescent cannabis users
- Prolong cannabis use during adolescent will result in a **disruption** in the normal neuromaturation processes.

THC

Lubman DI, Cheetham A, Yücel M. Cannabis and adolescent brain development. *Pharmacol Ther*. 2015;148:1-16. doi:10.1016/j.pharmthera.2014.11.009
https://www.freepik.com/free-photo/surgical-procedure-made-by-doctor-special-equipment_14008909.htm#fromView=search&page=1&position=15&uuid=b0c27d76-d37d-4bc6-a747-ac5611f6c886 https://www.freepik.com/free-photo/close-up-ax-log-mountain_9201862.htm#fromView=search&page=1&position=4&uuid=6a318f12-cb71-48d2-afe9-16c6e7cef376

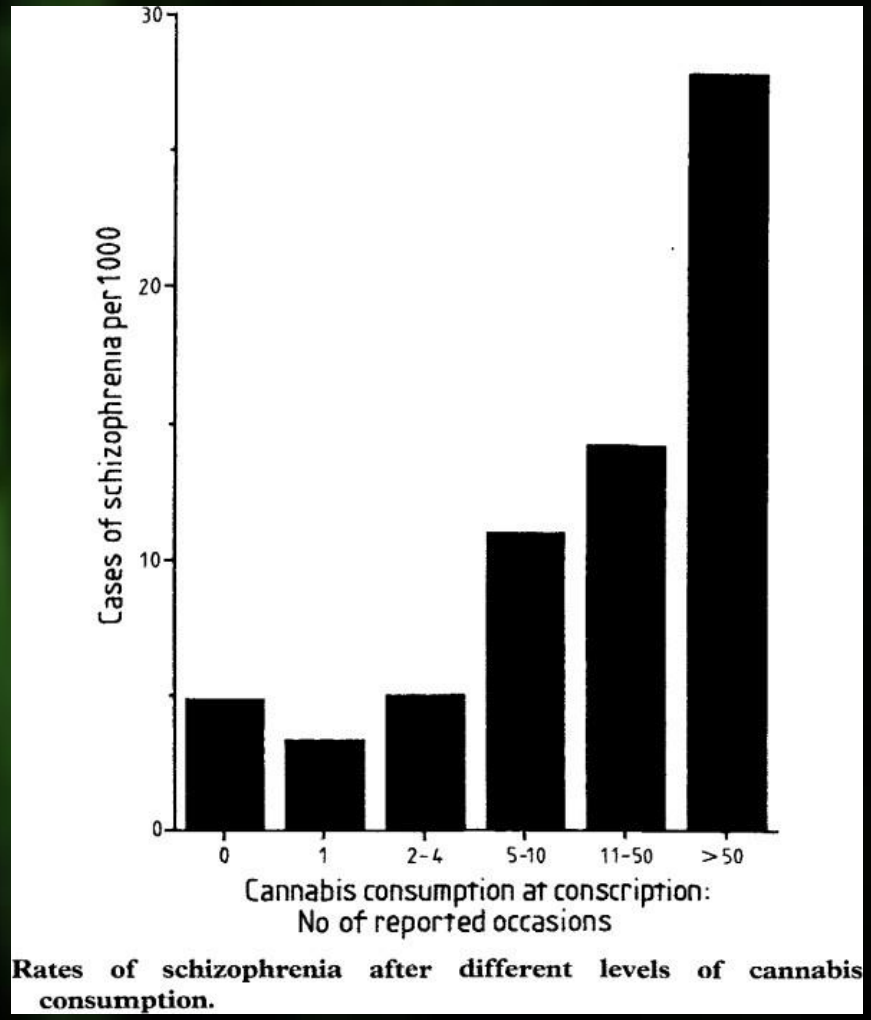
Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study

Louise Arseneault, Mary Cannon, Richie Poulton, Robin Murray, Avshalom Caspi, Terrie E Moffitt

- Using cannabis in adolescence **increases the likelihood of experiencing symptoms of schizophrenia in adulthood.**
  - Early cannabis use (by age 15) confers greater risk for schizophrenia outcomes than later cannabis use (by age 18).
- ~10% cannabis users by age 15 in this study sample (3/29) developed schizophreniform disorder by age 26 compared with 3% of the remaining cohort (22/730)

TABLE I—CANNABIS CONSUMPTION AND SCHIZOPHRENIA

Consumption (no of occasions)	No (%)	Cases of schizophrenia	Relative risk	95% CI
0	41 280 (90·6)	197	1 0	–
1–10	2836 (6·2)	18	1 3	0 8–2·2
11–50	702 (1·5)	10	3 0	1 6–5·5
>50	752 (1·7)	21	6·0	4·0–8·9

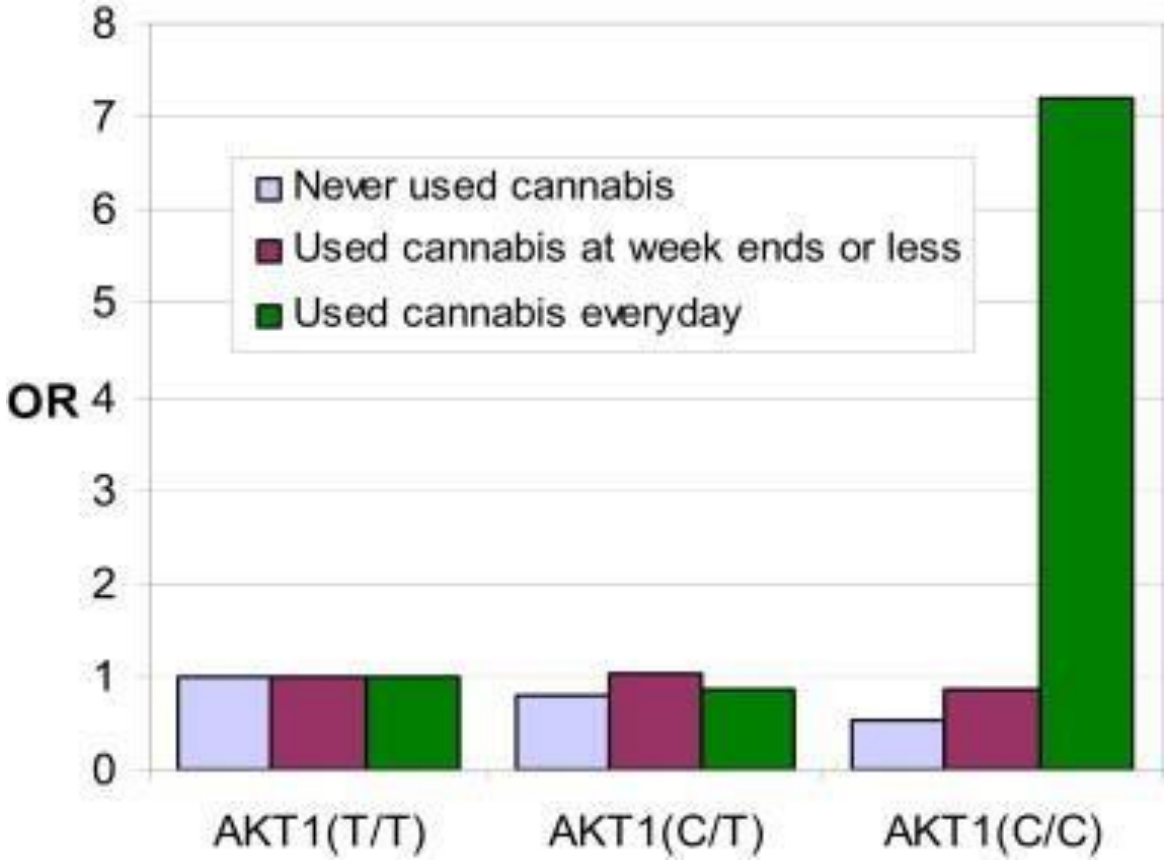


Rates of schizophrenia after different levels of cannabis consumption.

AKT-1 Gene Variants and Psychosis

- The AKT-1 gene governs an enzyme that affects DA brain signaling leading to psychosis.
- Variant C/C, if daily user, 7x high odds of developing psychosis

- Blue: never used cannabis
- Purple: used 1x or less per week
- Green: daily user



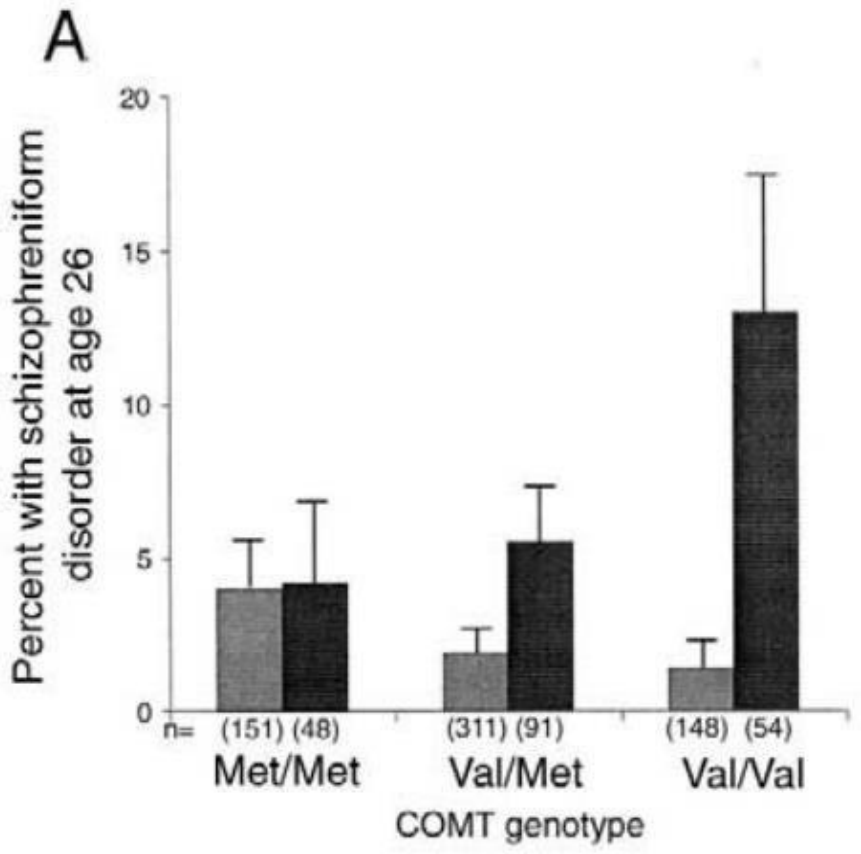
Di Forti M, Iyegbe C, Sallis H, et al. Confirmation that the AKT1 (rs2494732) genotype influences the risk of psychosis in cannabis users. *Biol Psychiatry*. 2012;72(10):811-816. doi:10.1016/j.biopsych.2012.06.020

COMT Gene Variants and Schizophreniform disorders

- Adolescent cannabis use was associated with increased risk of schizophreniform disorder in adulthood among Val/Val individuals (Odds ratio 10,9!!) and Val/Met (OR 2.5)

- Gray: non-adolescent cannabis users
- Black: adolescent cannabis users

Caspi A, Moffitt TE, Cannon M, et al. Moderation of the Effect of Adolescent-Onset Cannabis Use on Adult Psychosis by a Functional Polymorphism in the Catechol-O-Methyltransferase Gene: Longitudinal Evidence of a Gene X Environment Interaction. *Biological psychiatry (1969).* 2005;57(10):1117-1127. doi:10.1016/j.biopsych.2005.01.026



The Dunedin Study:

Persistent cannabis users show neuropsychological decline from childhood to midlife

- Study design:
  - 1,037 individuals followed from birth (1972/1973) to age 38 y.
  - Cannabis use was ascertained in interviews at ages 18, 21, 26, 32, and 38 y.
  - Neuropsychological testing was conducted at age 13 y, before initiation of cannabis use, and again at age 38 y
- Results:
  - Persistent cannabis use was associated with neuropsychological decline broadly across domains of functioning, even after controlling for years of education

Madeline H. Meier, Avshalom Caspi, Antony Ambler, HonaLee Harrington, Renate Houts, Richard S. E. Keefe, Kay McDonald, Aimee Ward, Richie Poulton, and Terrie E. Moffitt

Screening

- No consensus on screening recommendations for general population
- US Preventive Services Task Force recommends:
  - Screening for illicit drug use in adults ≥18 years
  - Pregnant and postpartum women
  - Adolescents age 12-17 (if follow-up care can be offered)
- AAP recommends screening adolescents.
- Screening higher-risk populations is good practice

Meier MH, et al (2012): **Persistent cannabis users show neuropsychological decline from childhood to midlife.** Proceedings of the National Academy of Sciences Plus 109:2657-2664

Meier et al. (2017). **Associations between adolescent cannabis use and neuropsychological decline: a longitudinal co-twin control study.** Addiction, 113:257-265

The Cannabis Use Disorder Identification Test - Revised (CUDIT-R)

Have you used any cannabis over the past six months? Yes_____ No _____

If you answered "Yes" to the previous question, please answer the following questions about your cannabis use. Circle the response that is most correct for you in relation to your cannabis use over the *past six months*.

1. How often do you use cannabis?

Never	Monthly or less	2-4 times a month	2-3 times a week	4+ times a week
0	1	2	3	4

2. How many hours were you "stoned" on a typical day when you had been using cannabis?

Less than 1	1 or 2	3 or 4	5 or 6	7 or more
0	1	2	3	4

3. How often during the past 6 months did you find that you were not able to stop using cannabis once you had started?

Never	Less than monthly	Monthly	Weekly	Daily/almost daily
0	1	2	3	4

4. How often during the past 6 months did you fail to do what was normally expected from you because of using cannabis?

Never	Less than monthly	Monthly	Weekly	Daily or almost daily
0	1	2	3	4

5. How often in the past 6 months have you devoted a great deal of your time to getting, using, or recovering from cannabis?

Never	Less than monthly	Monthly	Weekly	Daily/almost daily
0	1	2	3	4

6. How often in the past 6 months have you had a problem with your memory or concentration after using cannabis?

Never	Less than monthly	Monthly	Weekly	Daily or almost daily
0	1	2	3	4

7. How often do you use cannabis in situations that could be physically hazardous, such as driving, operating machinery, or caring for children?

Never	Less than monthly	Monthly	Weekly	Daily/almost daily
0	1	2	3	4

8. Have you ever thought about cutting down, or stopping, your use of cannabis?

Never	Yes, but not in the past 6 months	Yes, during the past 6 months
0	2	4

This questionnaire was designed for self-administration and is scored by adding each of the 8 items:

Question 1-7 are scored on a 0-4 scale
Question 8 is scored 0,2, or 4

Score: _____

Scores of 8 or more indicate hazardous cannabis use, while scores of 12 or more indicate a possible cannabis use disorder for which further intervention may be required.

Adamson SJ, Kay-Lambkin FJ, Baker AL, Lewin TJ, Thornton L, Kelly BJ, and Sellman JD. (2010). An Improved Brief Measure of Cannabis Misuse: The Cannabis Use Disorders Identification Test – Revised (CUDIT-R). *Drug and Alcohol Dependence* 110:137-143.

Cannabis Withdrawal

- Three or more of the following signs and symptoms that develop after the cessation of prolonged cannabis use
  - Irritability, anger, or aggression
  - Nervousness or anxiety
  - Sleep difficulty
  - Decreased appetite or weight loss
  - Restlessness
  - Depressed mood
- At least one of the following physical symptoms that causes discomfort: abdominal pain, shakiness/tremors, sweating, fever, chills, or headache
- Withdrawal symptoms may be present within the first 24 hours.
- Overall, they peak within the first week and persist up to 1 month following the last use of cannabis.

Treatment of Withdrawal

- In absence of medical and psychiatric comorbidities, withdrawal does not pose serious risk
- Psychoeducation and coping skills training
- Dronabinol and nabiximols improved multiple withdrawal symptoms, including craving
- Quetiapine, zolpidem, and mirtazapine may help with withdrawal-induced sleep disturbances
- Combining dronabinol and lofexidine was superior to placebo in reducing withdrawal symptoms and improving sleep

Cannabis Use Disorder

- Approximately 9% of those who experiment with marijuana will become addicted
- Greater frequency of cannabis use increases the likelihood of developing problem cannabis use.
- Initiating cannabis use at a younger age increases the likelihood of developing problem cannabis use

Table 2. Level of Confidence in the Evidence for Adverse Effects of Marijuana on Health and Well-Being.

Effect	Overall Level of Confidence*
Addiction to marijuana and other substances	High
Abnormal brain development	Medium
Progression to use of other drugs	Medium
Schizophrenia	Medium
Depression or anxiety	Medium
Diminished lifetime achievement	High
Motor vehicle accidents	High
Symptoms of chronic bronchitis	High
Lung cancer	Low

* The indicated overall level of confidence in the association between marijuana use and the listed effects represents an attempt to rank the strength of the current evidence, especially with regard to heavy or long-term use and use that starts in adolescence.

Volkow N et al: Adverse Health Effects of Marijuana use. The New England Journal of Medicine. 2014;370:2219-27. DOI: 10.1056/NEJMra1402309

Diagnostic Criteria for Cannabis Use Disorder

	12-month period.	period		continuously over a period of at least one month.
1	No equivalent criterion – mentioned in text	Craving or a strong desire or urge to use the substance	A strong desire or sense of compulsion to take the psychoactive substance (craving or compulsion)	1. Impaired control over substance use – in terms of the onset, level, circumstances or termination of use, and often, but not necessarily, accompanied by a subjective sensation of urge or craving to use the substance.
2	There is persistent desire or unsuccessful attempts to cut down or control substance use	There is persistent desire or unsuccessful efforts to cut down or control substance use	No equivalent criterion but text states that the subjective awareness of compulsion is most commonly seen during attempts to stop or control substance use.	
3	The substance is often taken in larger amounts or over a longer period of time than was intended	The substance is often taken in larger amounts or over a longer period than was intended	Difficulties in controlling substance-taking behaviour in terms of its onset, termination, or levels of use *(loss of control)*	
4	Important social, occupational or recreational activities are given up or reduced because of drinking or psychoactive substance use.	Recurrent substance use resulting in a failure to fulfil major role obligations at work, school or home	Progressive neglect of alternative pleasures and responsibilities because of psychoactive substance use, or increased amount of time necessary to obtain or take the substance or to recover from its effects.	2. Substance use becomes an increasing priority in life such that its use takes precedence over other interests or enjoyments, daily activities, responsibilities, or health or personal care. It takes an increasingly central role in the person's life and relegates other areas of life to the periphery. Substance use often continues despite the occurrence of problems.
5	A great deal of time is spent in activities necessary to obtain the substance, use the substance or recover from its effects.	A great deal of time is spent in activities necessary to obtain the substance, use the substance or recover from its effects	Subsumed in the above criterion.	
6.	The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance	Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance.	Persisting with substance use despite clear evidence of overtly harmful consequences.	
6.	Tolerance: as defined by either (a) a need for markedly increased amounts of the substance to achieve the desired effects or (b) markedly diminished effect with continued use of the same amount of the substance.	Tolerance is defined by either of the following: a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect b) a markedly diminished effect with continued use of the same amount of the substance	Tolerance: such that increased doses of the psychoactive substances are required in order to achieve effects originally produced by lower doses.	3. Physiological features (indicative of neuroadaptation to the substance) as manifested by (i) tolerance, (ii) withdrawal symptoms following cessation or reduction in use of that substance, or (iii) repeated use of the substance (or pharmacologically similar substance) to prevent or alleviate withdrawal symptoms. Withdrawal symptoms must be characteristic for the withdrawal syndrome for that substance and
7.	Withdrawal as manifested by either (a) the characteristic withdrawal syndrome for the substance or (b) the same (or a	Withdrawal is manifested by either of the following: a)the characteristic withdrawal syndrome for the substance, or	A physiological withdrawal state when substance use has ceased or been reduced, as evidenced by the characteristic withdrawal	
	closely related) substance is taken to relieve or avoid withdrawal symptoms.	b) the substance (or a closely related substance) is taken to relieve , or avoid withdrawal symptoms	syndrome for the substance; or use of the same (or a closely related substance) with the intention of relieving or avoiding withdrawal symptoms.	must not simply reflect a hangover effect.
9. Former DSM-IV abuse	Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g. arguments with spouse about consequences of intoxication, physical fights)	Substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by that substance	To some extent subsumed in criterion no. 4.	To some extent subsumed in criterion no. 2.
10.	Recurrent substance use in	Recurrent use in situations in	No equivalent criterion	No equivalent criterion

Treatment Options: Psychotherapy

- Motivational enhancement treatment (MET), cognitive behavioral therapy (CBT), and contingency management (CM) have demonstrated effectiveness in reducing frequency and quantity of cannabis use
- Abstinence rates remain modest and decline after treatment
- Generally, MET is effective at engaging individuals who are ambivalent about treatment; CM incentivizes abstinence; and CBT can work to enhance abstinence following treatment
- Longer duration of psychotherapy is associated with better outcomes
- Adolescent Community Reinforcement Approach for adolescents

Adolescent cannabis use disorder treatment

- Individual

- **Adolescent community reinforcement approach** – increase adolescent's engagement in their community and find activities to replace the use
- **Cognitive behavior therapy** – concentrates on identifying patterns of substance use and learn/apply skills to reduce the use
- **Contingency management**
- **Motivational enhancement/cognitive behavior therapy** – use MI to resolve ambivalence and increase motivation to reduce substance use

Adams ZW, Marriott BR, Hulvershorn LA, Hinckley JD. Treatment of Adolescent Cannabis Use Disorders. *The Psychiatric clinics of North America*. 2023;46(4):775-788. doi:10.1016/j.psc.2023.03.004

Adolescent cannabis use disorder treatment

-Family therapy

- **Brief strategic family therapy** – focus on family function
- **Functional family therapy** – modify maladaptive family patterns and use cognitive behavioral technique
- **Multidimensional family therapy** – focus on 4 domains – adolescent, parent, family environment and relationships and also extrafamilial
- **Multisystemic therapy** – address individual, family, peers, school, and community factors to reduce the use
- **Risk reduction through family therapy** – integrative treatment to address co-occurring trauma-related s/s and risk behaviors

Adams ZW, Marriott BR, Hulvershorn LA, Hinckley JD. Treatment of Adolescent Cannabis Use Disorders. *The Psychiatric clinics of North America*. 2023;46(4):775-788. doi:10.1016/j.psc.2023.03.004

Treatment Options: Medication Strategies

- No FDA-approved pharmacological agents
- Off-label use of medications is available
- Treatment should target withdrawal symptoms, aim to initiate abstinence and prevent relapse, and treat psychiatric comorbidity and symptoms that may be driving cannabis use

Abstinence Initiation and Relapse Prevention

- Gabapentin 1200 mg/day reduced quantitative THC urine levels and improved cognitive functioning (in addition to decreasing withdrawal)
  - One mechanism by which gabapentin might facilitate cannabis abstinence is by producing effects that overlap with those of cannabinoids.
- Topiramate up to 200 mg/day resulted in significantly decreased grams of cannabis used but no difference in percent days used or proportion of positive urine drug screens
- In a small clinical trial, reductions in cannabis use were seen with oxytocin in combination with MET

Sherman BJ, Baker NL, McRae-Clark AL. Effect of oxytocin pretreatment on cannabis outcomes in a brief motivational intervention. *Psychiatry Res.* 2017;249:318-320

Abstinence Initiation and Relapse Prevention: NAC

- N-acetylcysteine (NAC), a prodrug of the naturally occurring amino acid cysteine. Through normalization of the cysteine-glutamate exchange process, NAC has been shown to reduce the reinstatement of drug seeking in animal models.
- An open-label trial of NAC in 24 young (aged 18-21 years) cannabis users demonstrated reductions in self-report of cannabis use and cannabis craving
- A follow up larger placebo-controlled study conducted in 116 participants showed that participants receiving NAC, when paired with brief counseling and CM to promote abstinence, had more than twice the odds of having negative urine cannabinoid tests
- **In contrast, there is no evidence that NAC 1200 mg twice daily plus CM is differentially efficacious for CUD in adults when compared to placebo plus CM**

Gray KM, Carpenter MJ, Baker NL, et al. A double-blind randomized controlled trial of N- acetylcysteine in cannabis-dependent adolescents.
The American Journal of Psychiatry. 2012; 8:805–12. [PubMed: 22706327]
Gray, KM, et al: A randomized placebo-controlled trial of N-acetylcysteine for cannabis use disorder in adults. Drug and Alcohol Dependence, Volume 177, 2017. Pages 249-257

Abstinence Initiation and Relapse Prevention: Naltrexone

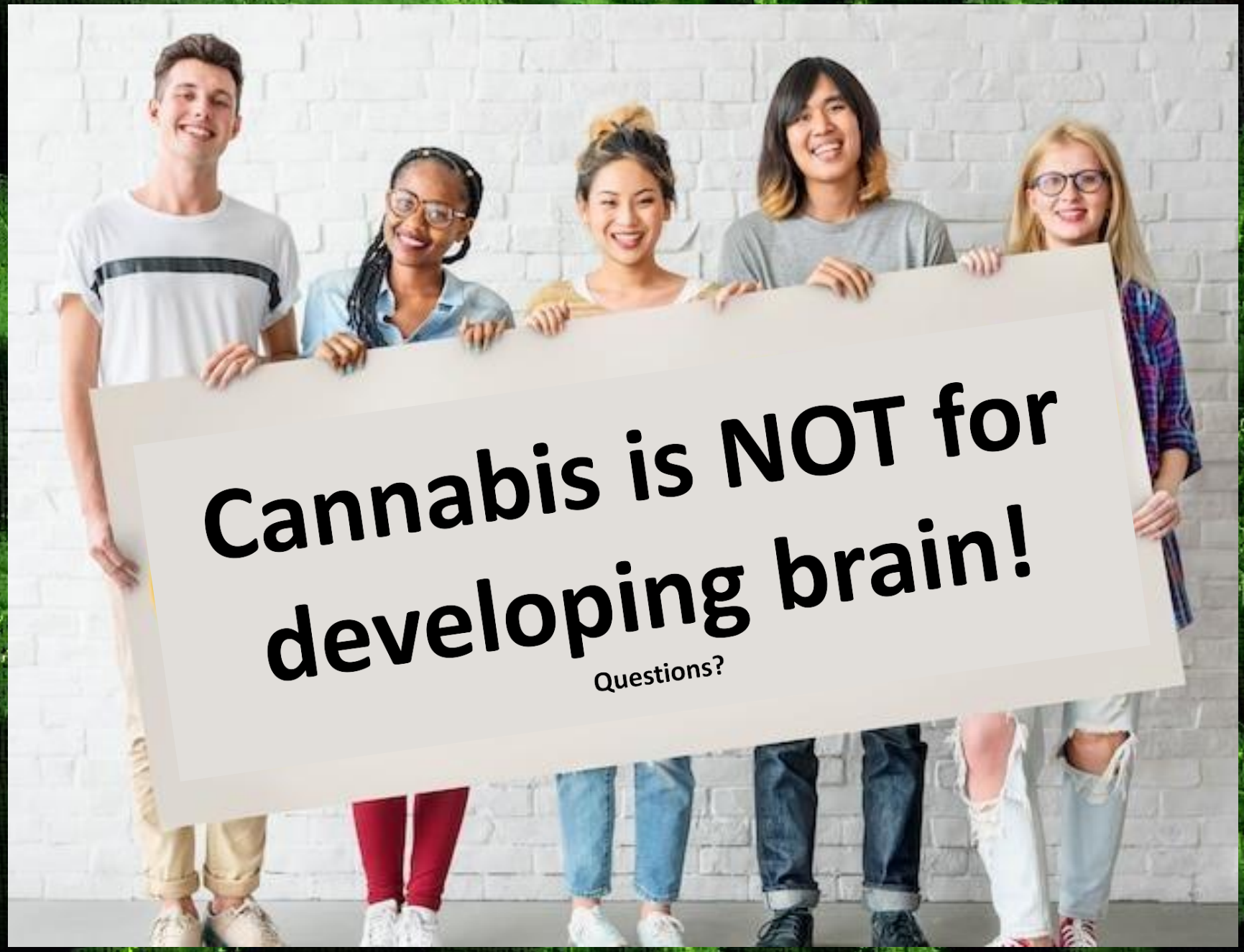
- In a human lab study, naltrexone 50mg significantly reduced both active cannabis self-administration and its positive subjective effects ('good effect') in Nontreatment-seeking, daily cannabis smokers compared to placebo.

- Small Open label study found that injectable naltrexone reduced cannabis use in individuals with CUD (N of 12)

- Haney, M., Ramesh, D., Glass, A. et al. Naltrexone Maintenance Decreases Cannabis Self-Administration and Subjective Effects in Daily Cannabis Smokers. Neuropsychopharmacol 40, 2489–2498 (2015)
- Daniel P. Notzon, Meredith A. Kelly, C. Jean Choi, Martina Pavlicova, Amy L. Mahony, Daniel J. Brooks, John J. Mariani & Frances R. Levin (2018) Open-label pilot study of injectable naltrexone for cannabis dependence, The American Journal of Drug and Alcohol Abuse, 44:6, 619-627

Conclusion

- The most efficacious treatments to date include a combination of MET/CBT/CM and computer-delivered treatments
- **Gabapentin, naltrexone, and possibly N-acetylcysteine** in adolescents only show the greatest promise in the off-label treatment of cannabis use disorders
- Medication cost need to be factored into the decision-making
- Combination medication and psychotherapy approaches may work the best


Cannabis is NOT for developing brain!
Questions?