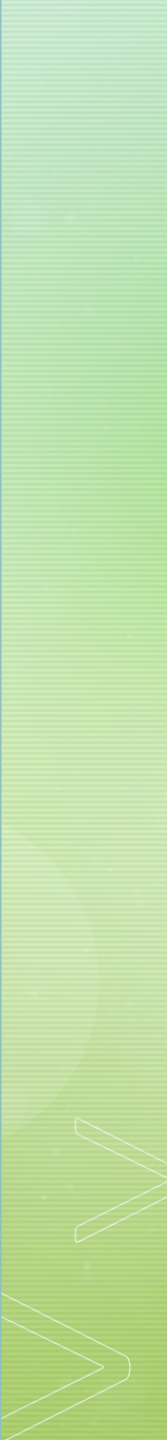# Learning Objectives

By the end of this presentation, participants should be able to:

- Outline diagnostic features of Cannabis Use Disorder and Withdrawal

- Develop understanding of cannabis use prevalence and means of consumption

- Conceptualize pharmacokinetics and pharmacodynamics of Delta-9-tetrahydrocannabinol (THC)

- Justify interventions to improve patient outcomes

Disclosure

- No affiliation with cannabis industry or any pharmaceuticals

- I currently have no relationship of any kind with any company whose products or services mentioned in any way relate to the practice of medicine, medical education or research.

A Quick Poll

How many of you have seen someone with a psychiatric disorder who uses cannabis (a.k.a. marijuana) products such as Delta-9-tetrahydrocannabinol (THC)?

A. Yes, I have.

B. I do not ask individuals about cannabis use.

C. No, I have not.

Clinical correlations

- A 24 F presents to clinic with 3 years of worsening auditory hallucinations

  - Has smoked cannabis nearly every day since age 13

- Patient presents with severe anxiety and insomnia

  - Smokes 2g cannabis throughout the day and waking up to use overnight

- 54 M presents with c/f undiagnosed ADHD

  - Smokes 1/8 oz cannabis daily

- Patient presents with uncontrolled chronic pain

  - Using cannabis vape pens daily

A Visual Guide to Cannabis Quantities

one gram eighth ounce quarter ounce

half ounce one ounce

1 oz = 28.35 g
1/2 oz = 14 g
1/4 oz = 7 g
1/8 oz = 3.5 g
1g = 1,000 mg

one gram

half gram

Note: size dependent on flower density.

Seed Supreme

Cannabis Plant

Goertzen, J. (2017, June 12). Do you know the anatomy of a marijuana plant? *The Orange County Register*.

Traditional means of use

Pipes/Bowls

Joints

Water Bong

Blunts

How it is ingested today

Butane Hash Oil (BHO)

Flower

Tinctures

Edibles

Transdermal

Cannabis Use Disorder[1]

A problematic pattern of cannabis use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. Cannabis is often <u>taken in larger amounts or over a longer period than was intended</u>.

2. There is a persistent desire or <u>unsuccessful efforts to cut down</u> or control cannabis use.

3. A great deal of time is spent in activities necessary to obtain cannabis, use cannabis, or recover from its effects.

4. <u>Craving</u>, or a strong desire or urge to use cannabis.

5. Recurrent cannabis use resulting in a <u>failure to fulfill major role obligations</u> at work, school, or home.

6. Continued cannabis use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of cannabis.

7. Important social, occupational, or recreational <u>activities are given up or reduced</u> because of cannabis use.

8. Recurrent cannabis use **<u>in situations in which it is physically hazardous</u>**.

9. Cannabis 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 cannabis.

Cannabis Use Disorder[1]

10. <u>Tolerance</u>, as defined by either of the following:

   1. A need for markedly increased amounts of cannabis to achieve intoxication or desired effect.

   2. Markedly diminished effect with continued use of the same amount of cannabis.

11. <u>Withdrawal</u>, as manifested by either of the following:

   3. The characteristic withdrawal syndrome for cannabis.

   4. Cannabis (or a closely related substance) is taken to relieve or avoid withdrawal symptoms

Cannabis Withdrawal[2]

A. Cessation of cannabis use that has been heavy and prolonged (i.e., usually daily or almost daily use over a period of at least a few months).

B. **Three (or more)** of the following signs and symptoms develop **within approximately 1 week** after Criterion A:

1. Irritability, anger, or aggression.

2. Nervousness or **anxiety**.

3. **Sleep difficulty** (e.g., insomnia, disturbing dreams).

4. **Decreased appetite** or weight loss.

5. Restlessness.

6. **Depressed mood**.

7. At least one of the following physical symptoms causing significant discomfort: abdominal pain, shakiness/tremors, sweating, fever, chills, or headache.

C. The signs or symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Legalization in Missouri

- Date of medical legalization: December 6th, 2018.[3]

- As of December 8th, 2022, consumers at least 21 years of age are legally allowed to possess up to 3 oz of marijuana.[3]

- There are over 190 cannabis dispensaries in the state of Missouri[4]

Prevalence?

Who is consuming cannabis?

Prevalence?

1/3 Veterans

Data are incomplete due to limited research

- Among U.S. veterans[5]:

  - 32.5% reported use of cannabis

  - 5.7% have/had cannabis use disorder

- The U.S. *National Poll on Healthy Aging*[6] for individuals aged 50-80

  - 2006: 2.8% reported use in past year

  - 2021: 12.1% reported use in past year

    - 34.2% said they use 4 or more days per week
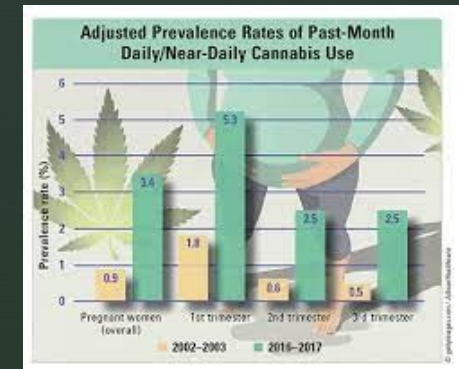

e.g. Willie Nelson

Vulnerable populations

A couple struggling to pay bills

Highest rate of use:

- **low income**

- having **psychiatric diagnosis**

- in a state with medical MJ legalization laws[3]

Pregnant individuals have been using cannabis products increasingly from 2002-2020[6]

- Believed to be due to increased access and overall decrease in perceived risk throughout the population
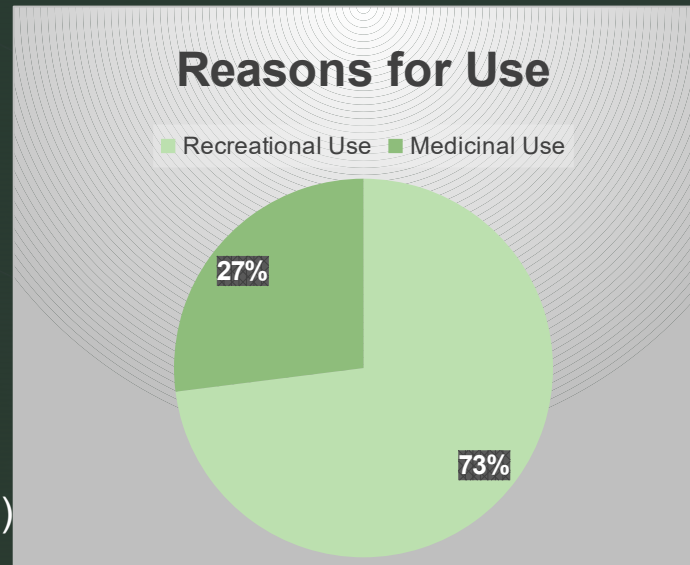

Prevalence among pregnant individuals has more than doubled in the past 20 years

Why do people use it?

Self-Reported Reasons for Cannabis Use[7]

- 27% report using for medical purposes
  - **Physical Health**
    - **Manage pain** (53%)
    - **Sleep** (46%)
    - Headaches/Migraines (35%)
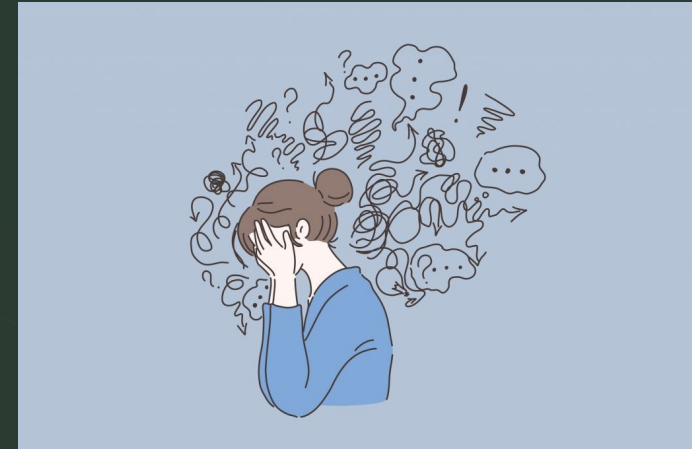   - Appetite (22%)
    - Nausea/Vomiting (21%)

Reasons for Use

Recreational Use Medicinal Use

27%

73%

Pain

Insomnia

Reasons for use

Self-Reported Reasons for Cannabis Use[7]

- 27% report using for medical purposes

  - **Mental Health**

    - **Anxiety** (52%)

    - Depression (40%)

    - PTSD/Trauma (17%)

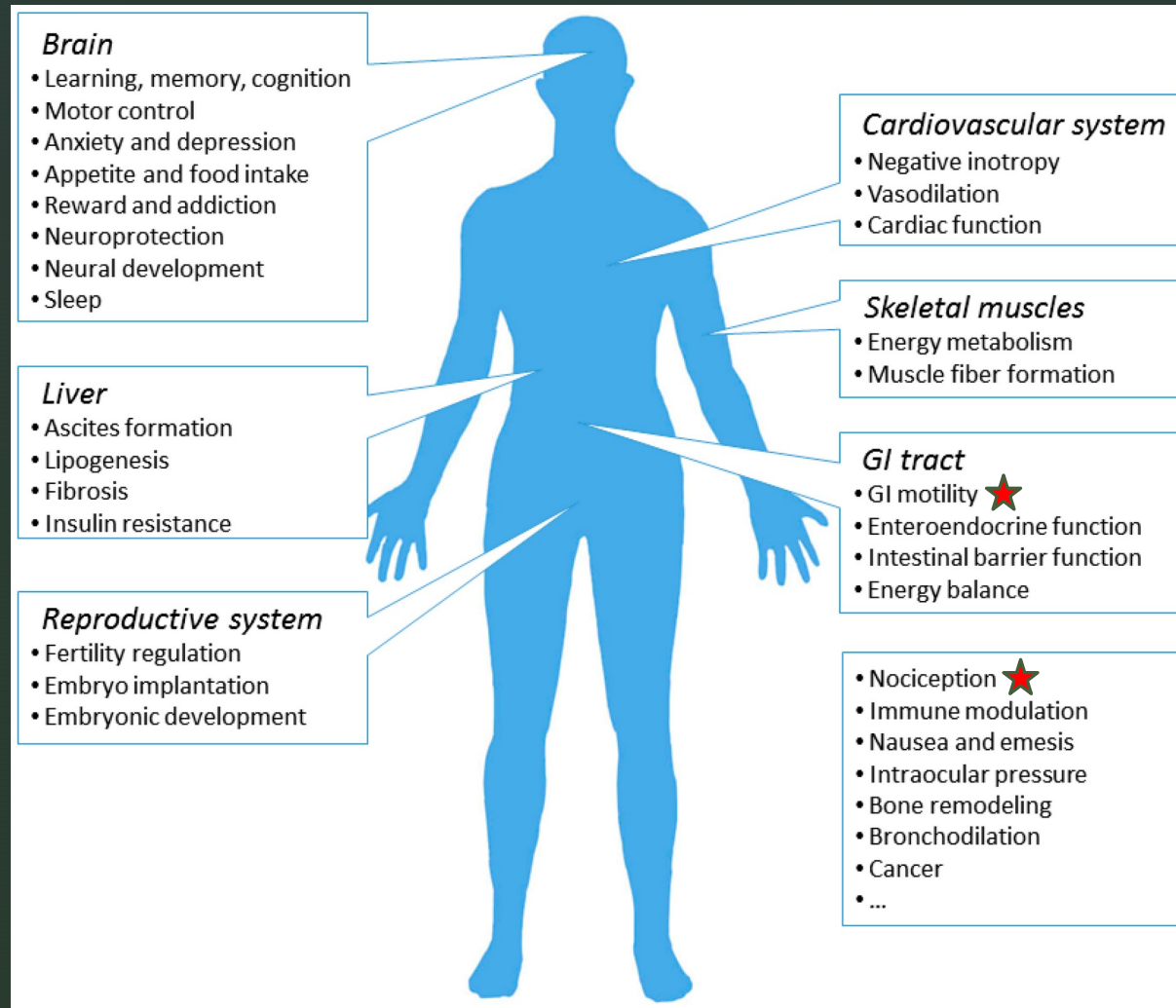   - Other drug or alcohol use (11%)

Overwhelming thoughts

Endocannabinoid System

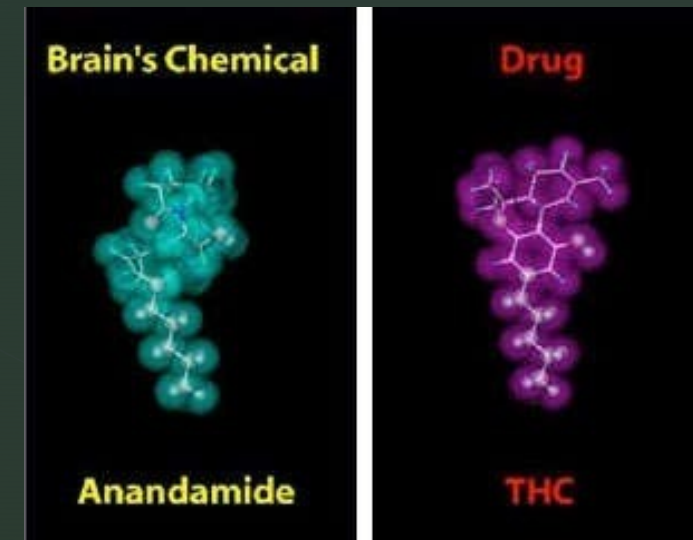Why do humans have cannabis receptors?

Endocannabinoid System

Zou, S., & Kumar, U. (2018). Cannabinoid receptors and the endocannabinoid system: signaling and function in the central nervous system. *International journal of molecular sciences*, *19*(3), 833.

Cannabinoids

- **<u>Anandamide</u>** (from Sanskrit *ananda* meaning "bliss") – Endogenous; first identified endocannabinoid molecule inherent to vertebrates

- **<u>Delta-9-tetrahydrocannabinol (THC)</u>** – Exogenous, primary psychoactive molecule from marijuana products, mimics anandamide

- THC analogs

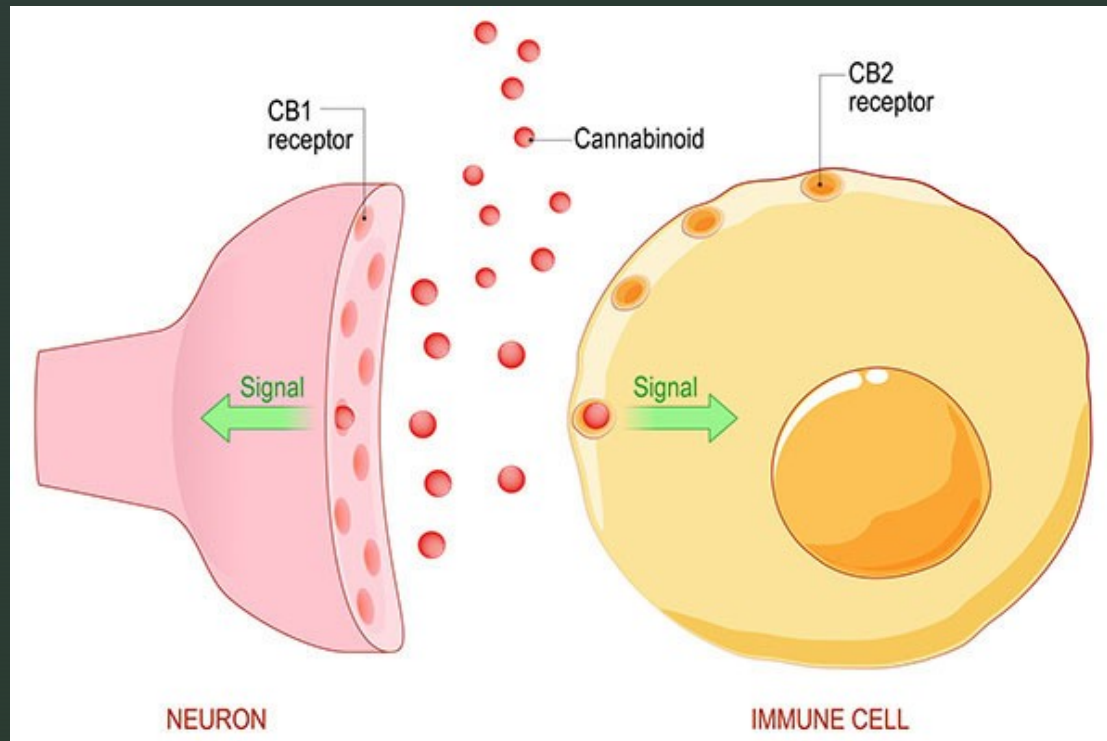 - THC metabolites or byproducts

  - Synthetic "spice" or K2

Grinspoon, P. (2021). The endocannabinoid system: essential and mysterious.

Molecular structures

Endocannabinoid system

Grinspoon, P. (2021). The endocannabinoid system: essential and mysterious.

Comprised of cannabinoid molecules and G-Protein coupled receptors

Cannabinoid 1 (**CB1**) receptors
- **Neurotransmitter regulation**
  - Effects: sleep, alertness, memory, learning, body temperature, pain perception, hunger, and **emotion**
- Target for cannabis use disorder

CB2 receptors
- **Immune system modulation**
- Does not cause "high" effect
- Has been shown to modulate intestinal inflammation, contractility, and pain in IBD conditions.
  - Target of drug development

CB1 in the amygdala

- CB1 receptor activation in the amygdala **affects functional connectivity** to the PFC

  - Influences ability to **cope with stress**

  - **Extinction of fear memories**

  - Has been shown to **impair learning**, **attention**, and **motivation**

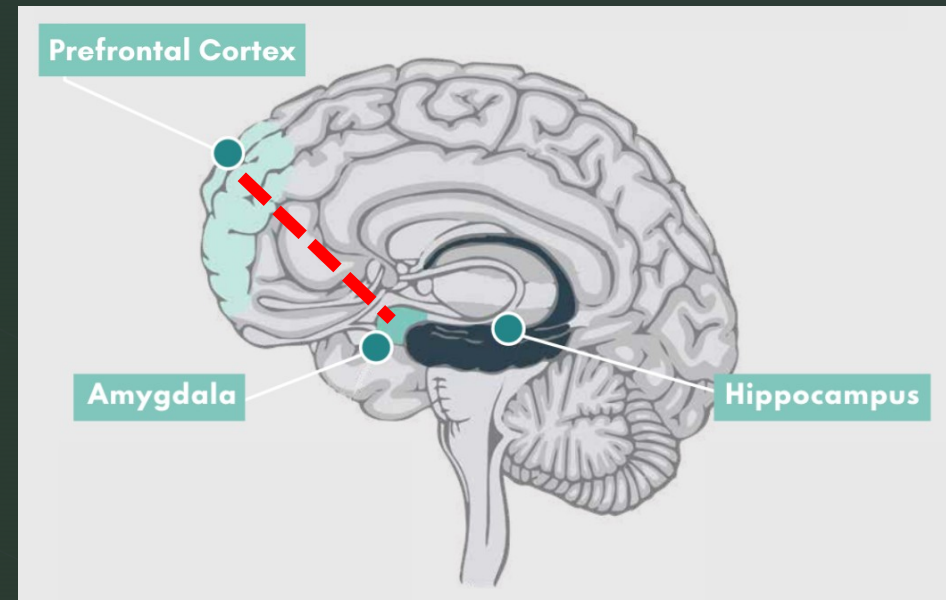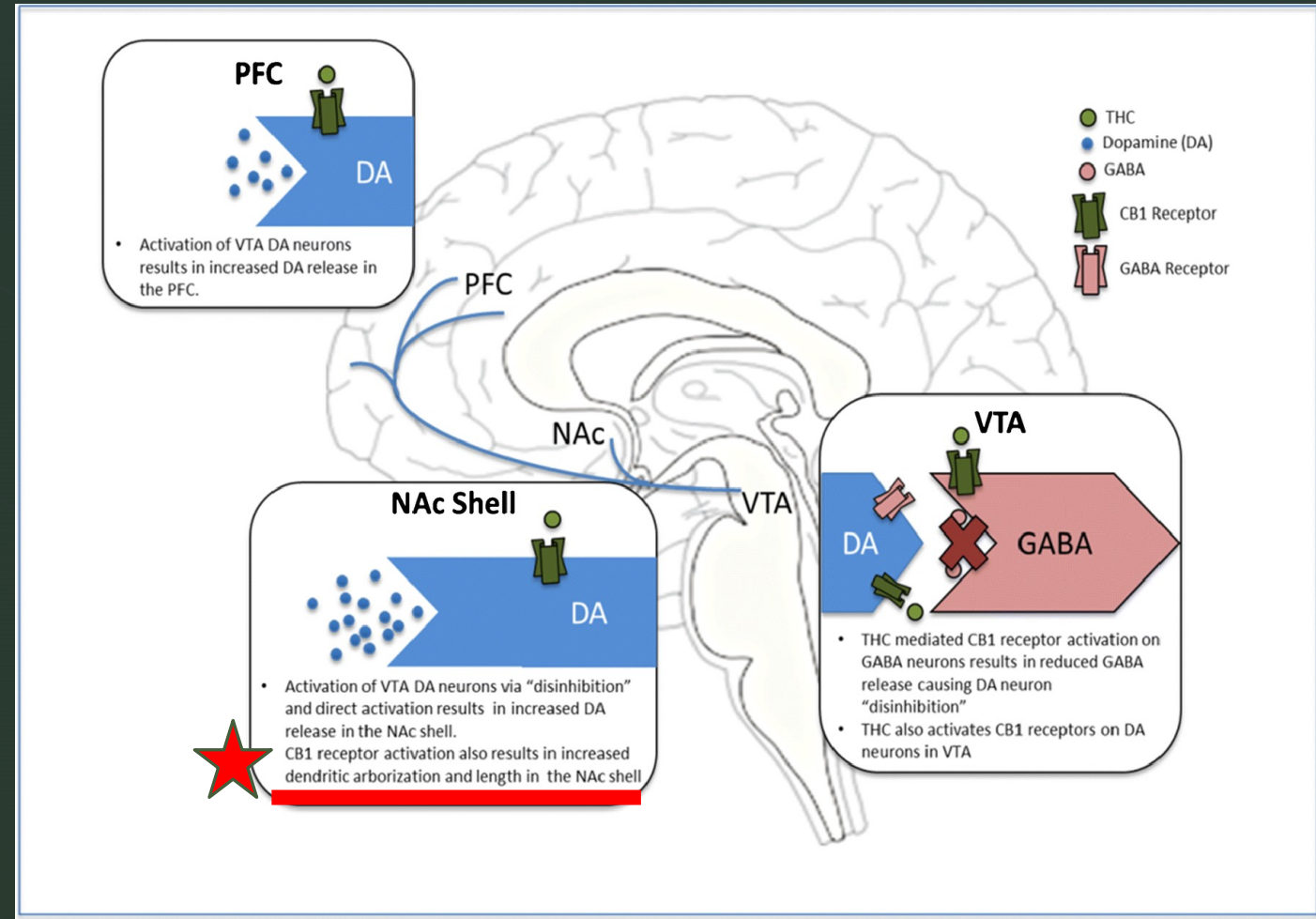- Potential drug target for PTSD or anxiety disorders

Image: Sarah. (2023, July 19). *Trauma and how it impacts the brain: Lotus: Sexual assault center: Sexual abuse resources: Kentucky*. Lotus | Sexual Assault Center | Sexual Abuse Resources | Kentucky. https://hopehealgrow.org/trauma-and-how-it-impacts-the-brain/

Mayo, L. M., Rabinak, C. A., Hill, M. N., & Heilig, M. (2022). Targeting the endocannabinoid system in the treatment of posttraumatic stress disorder: A promising case of preclinical-clinical translation?. *Biological psychiatry*, *91*(3), 262-272.

THC/Anandamide Effects on Dopamine

The Brain's Reward Circuitry:

- **Ventral Tegmental Area**[12] (~60% DA neurons)
    - Learning
    - Memory
    - Reward/addiction

- **Nucleus Accumbens**[13]
    - Limbic-Motor interface
    - Translates motivation into action

- **Prefrontal Cortex**[14]
    - Executive functioning
    - Engaging in goal-directed behaviors
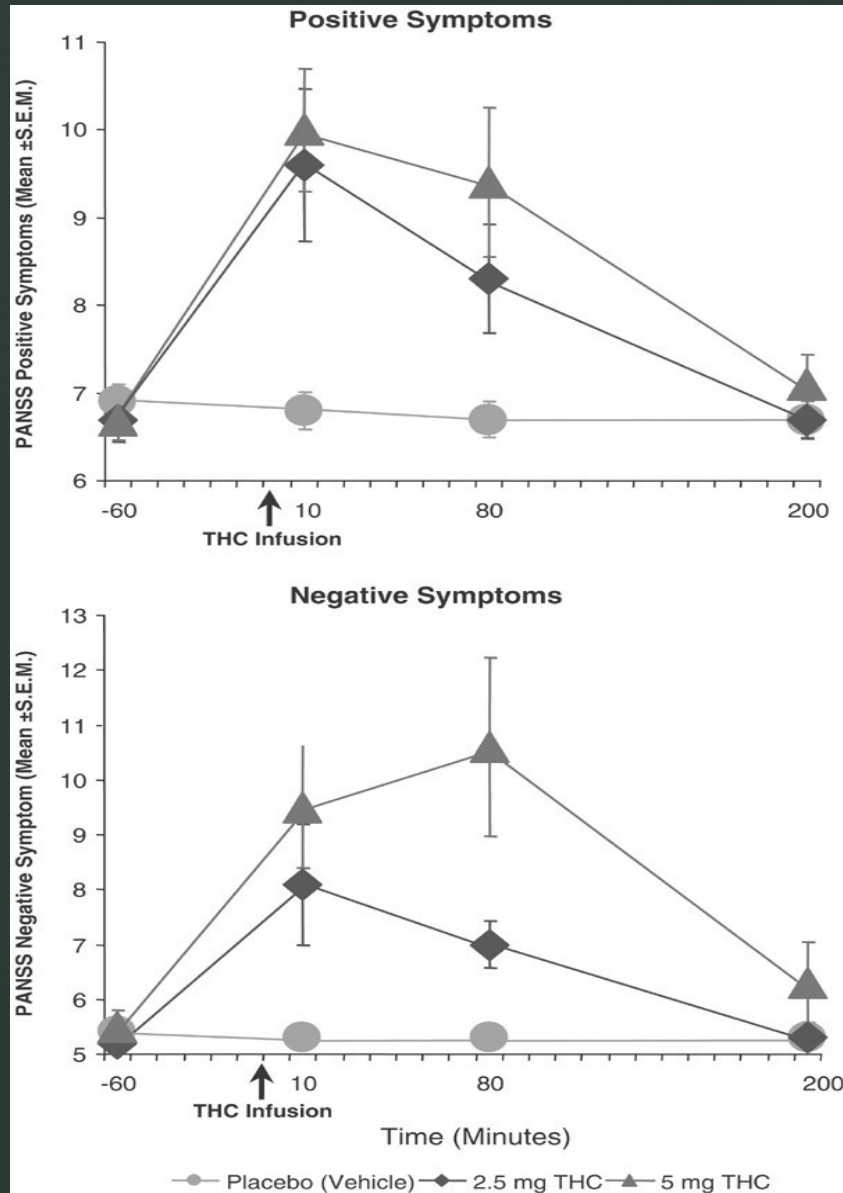   - Sustained attention

Fischer, A. S., Tapert, S. F., Louie, D. L., Schatzberg, A. F., & Singh, M. K. (2020). Cannabis and the developing adolescent brain. *Current treatment options in psychiatry*, 7, 144-161.
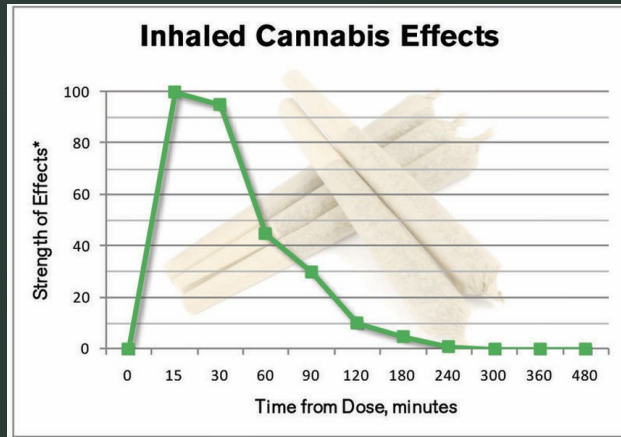
THC and Psychosis

D'Souza, D. C., Perry, E., MacDougall, L., Ammerman, Y., Cooper, T., Wu, Y. T., ... & Krystal, J. H. (2004). The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology*, *29*(8), 1558-1572.
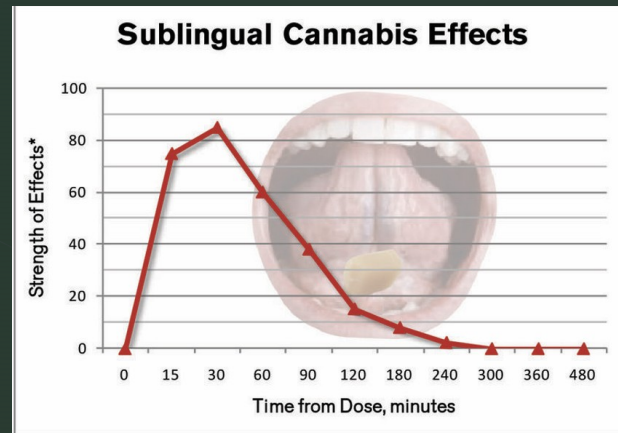
22 Healthy individuals given IV THC
- Positive and Negative Syndrome Scale (PANSS) used to measure symptoms related to schizophrenia.

<u>Schizophrenia Spectrum Disorder</u>
- **66.2%** lifetime prevalence of cannabis use among 229 participants followed over 10 years

- Cannabis use doubled the risk of psychotic disorder onset (HR = 1.97) compared to matched non-users

- Increased symptoms correlated with higher use; decreased symptoms with lower use (P < 0.0125)[15]
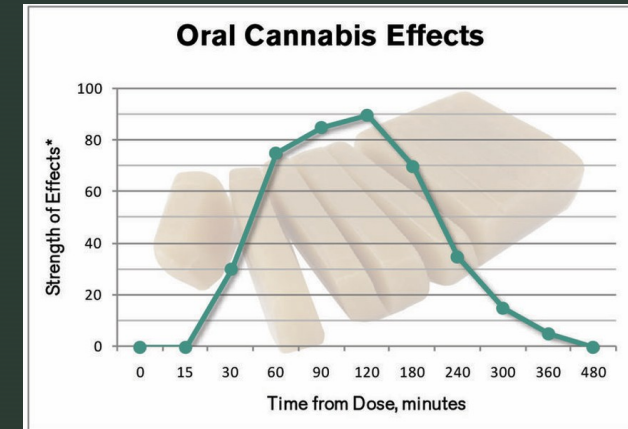
Absorption and Metabolism*

- Absorption rate similar to IV administration
- Rapid time to peak concentration (minutes)

- Not fully subject to first-pass metabolism
- May be partially swallowed
- Bioavailability between Inhaled and Oral

- Subject to first-pass metabolism
    - Lower bioavailability than inhaled
- Delayed onset

***Metabolism varies** and **elimination** is slower among heavy users with higher lipid concentrations and with combined CBD use

Lucas, C. J., Galettis, P., & Schneider, J. (2018). The pharmacokinetics and the pharmacodynamics of cannabinoids. *British journal of clinical pharmacology*, *84*(11), 2477-2482.

Image source

Tolerance with Chronic Use

Figure 1. When fewer *neurotransmitter* receptors are formed, it is called **downregulation**.
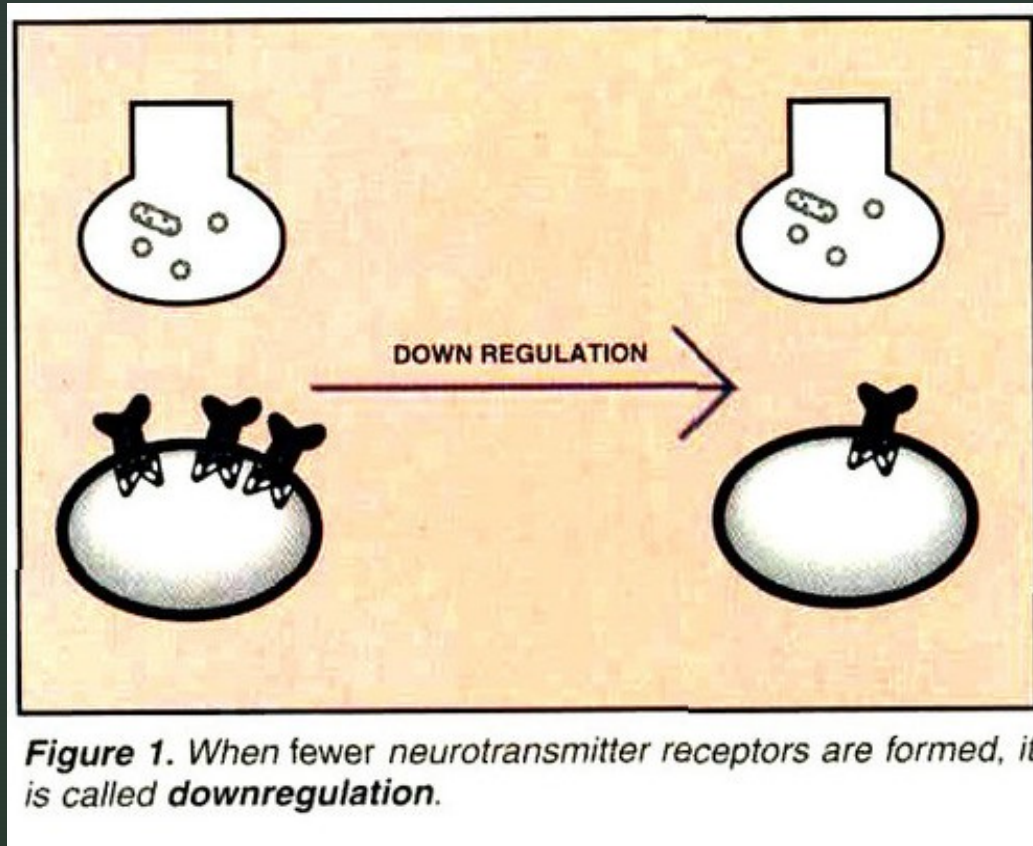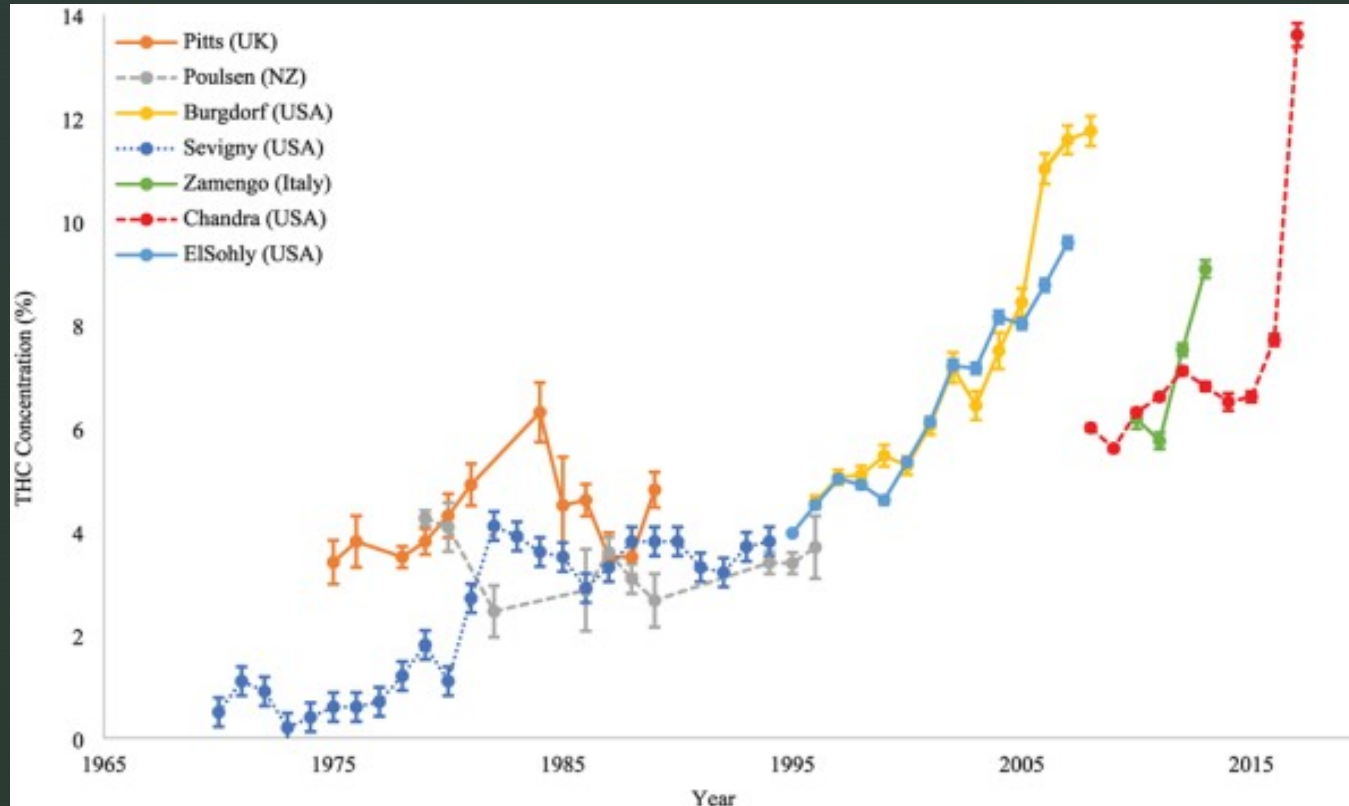
Figure 1

Zhang-James, Y., Wyon, E., Grapsas, D., & Johnson, B. (2023). Daily cannabis use may cause cannabis-induced hyperalgesia. *The American Journal on Addictions*, *32*(6), 532-538.

Strength over time

- THC concentrations in herbal cannabis, on average, have increased by 0.29% annually between 1970 and 2017.

- **Higher THC concentrations increase risk of addiction and mental health disorders.**

Freeman, T. P., Craft, S., Wilson, J., Stylianou, S., ElSohly, M., Di Forti, M., & Lynskey, M. T. (2021). Changes in delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) concentrations in cannabis over time: systematic review and meta-analysis. *Addiction*, *116*(5), 1000–1010. https://doi.org/10.1111/add.15253

What happens if we block CB1 Receptors?

Rimonabant

- Designed as a weight-loss drug

- Highly effective in reducing appetite and causing weight loss

- Had to *emergently* be pulled from the market after discovering it caused suicidality
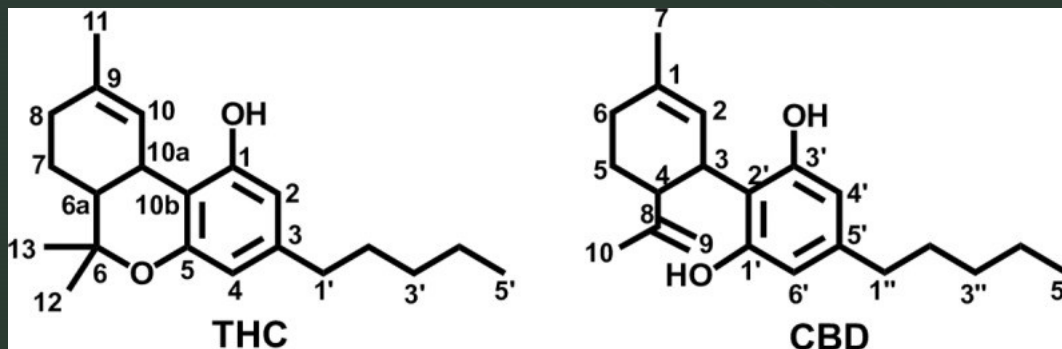
Acomplia

Grinspoon, P. (2021). The endocannabinoid system: essential and mysterious.

Treatment Recommendations
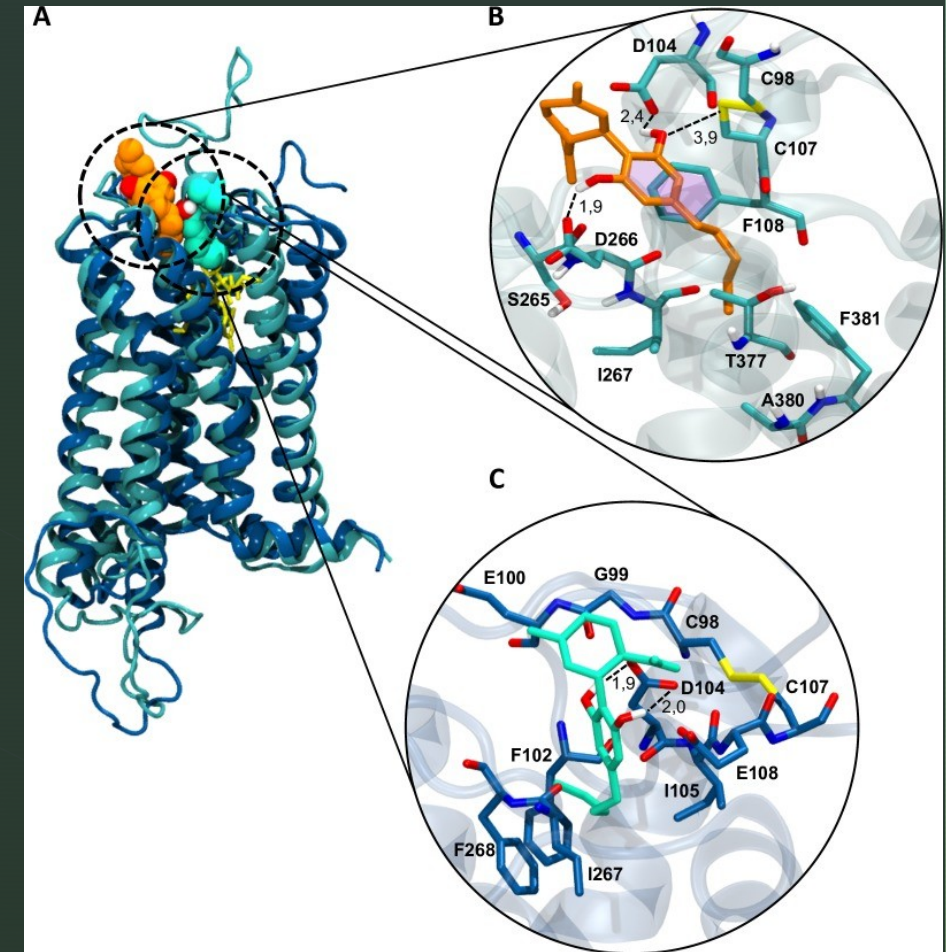
- Currently low strength of evidence for any pharmacological treatment for cannabis use disorder (CUD) to date[9]

- **Just Say No** … to abstinence-only counseling

  - Treatment preferences among individuals with CUD[10]

    - Decreasing use as goal

    - One-on-one outpatient care

    - Contingency management (reinforcement for evidence of improvement)

- Motivational interviewing

Treatment Recommendations

Harm reduction counseling: Reduce THC % and add CBD to mitigate potency[11]

CBD (orange) binding to inactive (blue) CB1R superimposed with THC (aqua) and active (cyan) CB1R
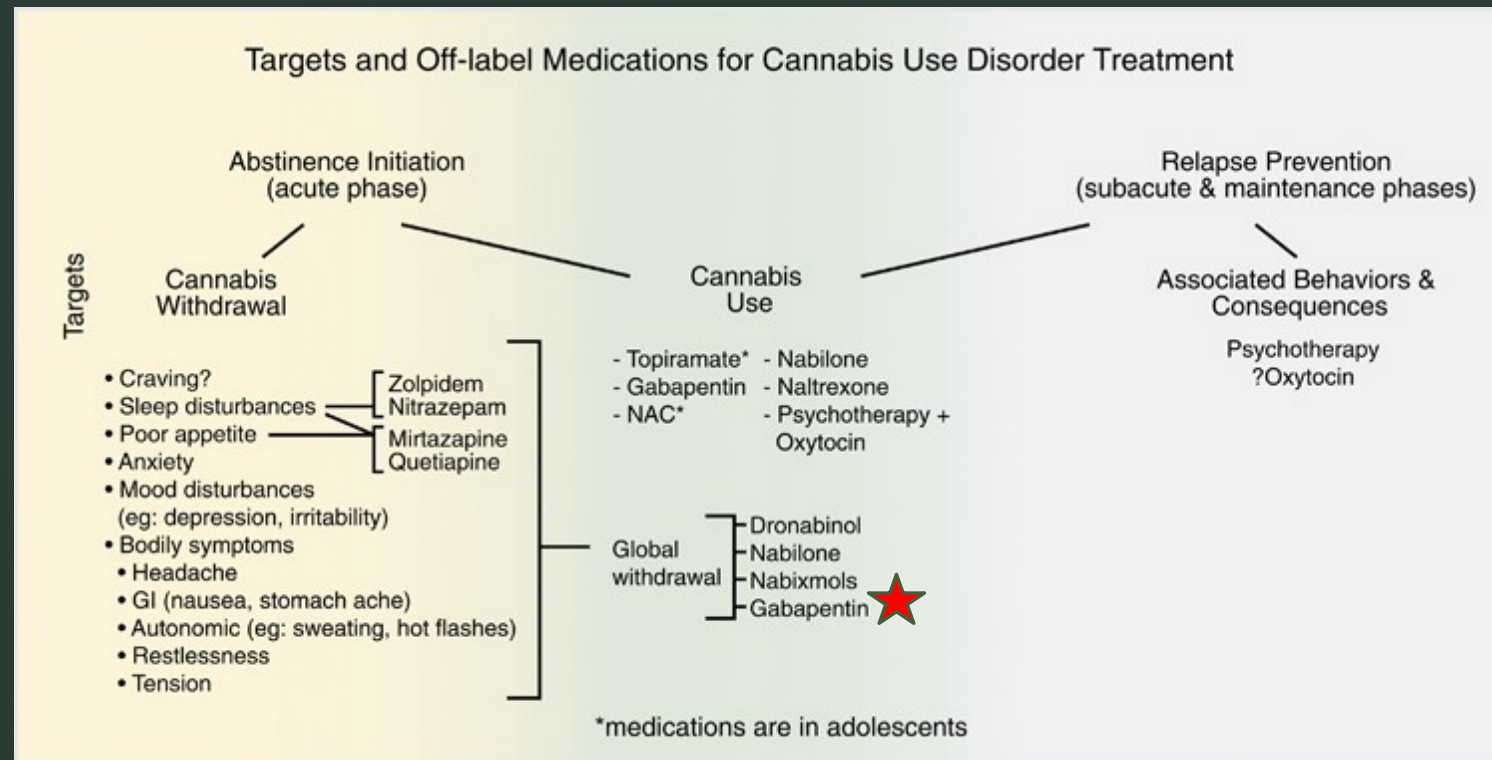
Chung, H., Fierro, A., & Pessoa-Mahana, C. D. (2019). Cannabidiol binding and negative allosteric modulation at the cannabinoid type 1 receptor in the presence of delta-9-tetrahydrocannabinol: An In Silico study. *PloS one*, *14*(7), e0220025.

Treatment Recommendations

Targets and Off-label Medications for Cannabis Use Disorder Treatment

Brezing, C., Levin, F. The Current State of Pharmacological Treatments for Cannabis Use Disorder and Withdrawal. *Neuropsychopharmacology Reviews*. **43**, 173–194 (2018). https://doi.org/10.1038/npp.2017.212

Conclusions

- What to expect in the long run

    - Increase in cannabis use nationwide

    - Potential neurodevelopmental issues for children with in-utero exposure

    - More CUD and withdrawal symptoms presenting to psychiatry

- Take-home actions

    - Educate yourself and your patients

    - Take a risk-reduction approach

References

1. Desk Reference to the Diagnostic Criteria from DSM-5-TR. (2022). American Psychiatric Association Publishing. pg. 197-198.

2. Desk Reference to the Diagnostic Criteria from DSM-5-TR. (2022). American Psychiatric Association Publishing. pg. 199-200.

3. Division of Cannabis Regulation. (n.d.). *Adult use faqs*. Adult Use FAQs | Medical Marijuana | Health Services Regulation | Health & Senior Services. https://health.mo.gov/safety/cannabis/faqs-adultuse.php

4. *Dispensaries near me in Missouri*. Missouri Cannabis Information Portal. (n.d.). https://missouristatecannabis.org/dispensaries#

5. Browne, K. C., Stohl, M., Bohnert, K. M., Saxon, A. J., Fink, D. S., Olfson, M., ... & Hasin, D. S. (2022). Prevalence and correlates of cannabis use and cannabis use disorder among US veterans: results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC-III). *American Journal of Psychiatry*, *179*(1), 26-35.

6. Fernandez, A. C., Coughlin, L., Solway, E. S., Singer, D. C., Kullgren, J. T., Kirch, M., & Malani, P. N. (2023). Prevalence and Frequency of Cannabis Use Among Adults Ages 50–80 in the United States. *Cannabis and cannabinoid research*.

7. Hayes, S., Delker, E., & Bandoli, G. (2023). The prevalence of cannabis use reported among pregnant individuals in the United States is increasing, 2002–2020. *Journal of Perinatology*, *43*(3), 387-389–389. https://doi.org/10.1038/s41372-022-01550-y

8. Leung, J., Chan, G., Stjepanović, D., Chung, J. Y. C., Hall, W., & Hammond, D. (2022). Prevalence and self-reported reasons of cannabis use for medical purposes in USA and Canada. *Psychopharmacology*, *239*(5), 1509-1519.

9. Kondo, K. K., Morasco, B. J., Nugent, S. M., Ayers, C. K., O'Neil, M. E., Freeman, M., & Kansagara, D. (2020). Pharmacotherapy for the treatment of cannabis use disorder: a systematic review. *Annals of internal medicine*, *172*(6), 398-412.

10. Lile, J. A., Turner, B. W., Cox, D. H., Bonn-Miller, M. O., Katz, N. R., Shellenberg, T. P., ... & Strickland, J. C. (2023). Cannabis use disorder treatment preferences: a pilot survey in current users of cannabis. *Journal of addiction medicine*, *17*(2), e87-e93.

11. Niesink, R. J., & van Laar, M. W. (2013). Does cannabidiol protect against adverse psychological effects of THC?. *Frontiers in psychiatry*, *4*, 130.

12. Cai, J., & Tong, Q. (2022). Anatomy and function of ventral tegmental area glutamate neurons. *Frontiers in Neural Circuits*, *16*, 867053.

13. Fernández-Espejo E. (2000). Cómo funciona el nucleus accumbens? [How does the nucleus accumbens function?]. *Revista de neurologia*, *30*(9), 845–849.

14. Siddiqui, S. V., Chatterjee, U., Kumar, D., Siddiqui, A., & Goyal, N. (2008). Neuropsychology of prefrontal cortex. *Indian journal of psychiatry*, *50*(3), 202.

15. Foti, D. J., Kotov, R., Guey, L. T., & Bromet, E. J. (2010). Cannabis use and the course of schizophrenia: 10-year follow-up after first hospitalization. *American Journal of Psychiatry*, *167*(8), 987-993.

Questions?

Thank you!