# Cannabis:
# What you need to know

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# Topics we will cover (in 20 min!)

- What is cannabis and how is it used? (CB1, CB2, THC, CBD)
- Changing landscape of cannabis today (highly potent products!)
- Special considerations for youth, who are at greatest risk for harms
- Is dispensary cannabis “medicine”? (Spoiler… *probably not*)

# What is Cannabis?

- Dry, shredded mix of leaves, flowers, stems, and seeds, usually from *Cannabis sativa* or *Cannabis indica* plant
- Both are common subspecies of the hemp plant, which is common throughout the world
- Contains over 400 chemical compounds

# How is Cannabis Used?

| SMOKED | VAPORIZED | EATEN/DRUNK |
| --- | --- | --- |
| Smoked in a pipe, bowl, cigarette | Inhaled through machine that converts active compounds into inhalable form | Consumed as ingredient in baked goods, candies, sodas |
| Rapid effects | Rapid effects | Takes time to reach brain, so effects are delayed |

# Endocannabinoid System

- The ECS is a complex **cell-signaling system** involved in maintaining **homeostasis**.
- **Key Components:**
  - **Endocannabinoids:** Anandamide (AEA) and 2-Arachidonoylglycerol (2-AG)
  - **Cannabinoid Receptors:** CB1 and CB2
  - **Enzymes:** FAAH (breaks down AEA) and MAGL (breaks down 2-AG)
- **Functions:** Regulation of **mood, appetite, pain, immune response, and cognition**.
- The neuron's "volume control" system: dials down neuron activity when too strong
- Regulates neurotransmitters that affect pleasure, mood, pain, appetite, motivation, memory

# Endocannabinoid System

- Shapes brain development by…
  - guiding neurons to grow to the right places in the brain for correct function
  - controlling neuron activity, thereby affecting brain wiring (“neurons that fire together, wire together”)
  - supporting myelin growth on neurons

# Cannabinoid receptors identified: CB1 and CB2

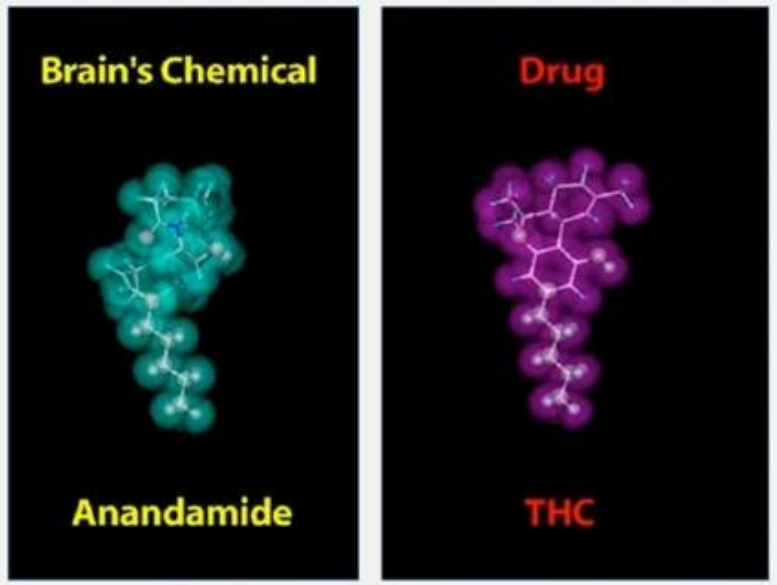
- **CB1 Receptors:**
  - Located primarily in the **central nervous system (CNS)**.
  - Found in the **brain (hippocampus, cerebellum, basal ganglia), spinal cord, and peripheral tissues**.
  - Involved in **mood, memory, motor function, and appetite**.
  - **Target of THC's psychoactive effects**.
- **CB2 Receptors:**
  - Mostly in the **immune system and peripheral organs**.
  - Found in the **spleen, tonsils, and immune cells**.
  - Modulates **inflammation and immune response**.
  - **Limited psychoactive effects**.

# Differences Between THC and CBD

- **Tetrahydrocannabinol (THC):**
  - **Partial agonist** of **CB1 and CB2 receptors**.
  - Produces **psychoactive effects** (euphoria, altered perception, relaxation).
  - Impacts **memory, coordination, and mood**.
  - Associated with **addictive potential and cognitive effects**.
- **Cannabidiol (CBD):**
  - The pharmacology of CBD is **complex**, as CBD is thought to be a weak inverse agonist of CB2 receptors, as well as an allosteric modulator of many other molecular targets.
  - **Indirect modulator** of **CB1 and CB2** (low binding affinity).
  - Acts on **serotonin, TRPV1, and adenosine receptors**.
  - **Non-psychoactive** (does not cause a “high”).
  - **Anti-inflammatory, neuroprotective, and anxiolytic properties?**

# How Does THC Affect the Brain?

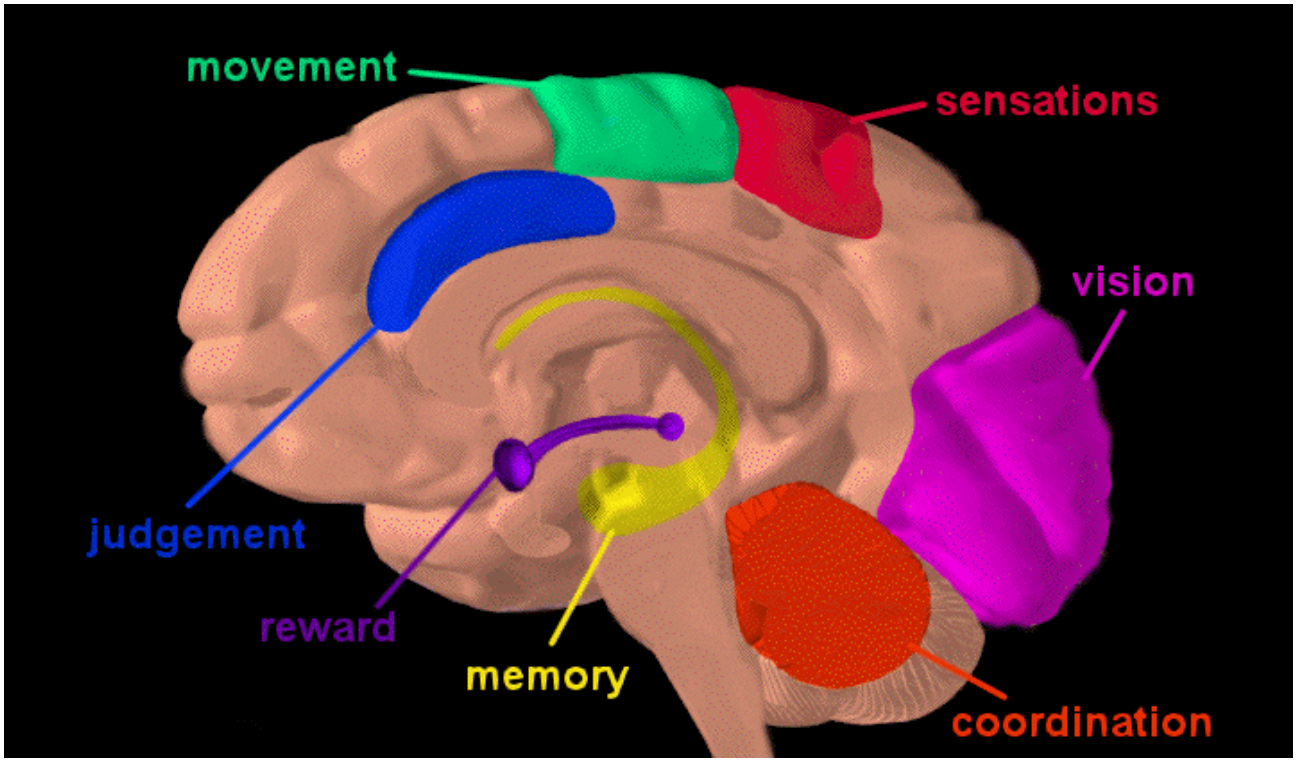
- THC rapidly passes from lungs into the bloodstream, carries chemicals to the brain
- Absorbed more slowly when ingested in food or drink.
- THC acts on molecular targets called cannabinoid receptors.
- These receptors are ordinarily activated by chemicals similar to THC that naturally occur (such as anandamide) and are part of a neural communication network called the endocannabinoid system.



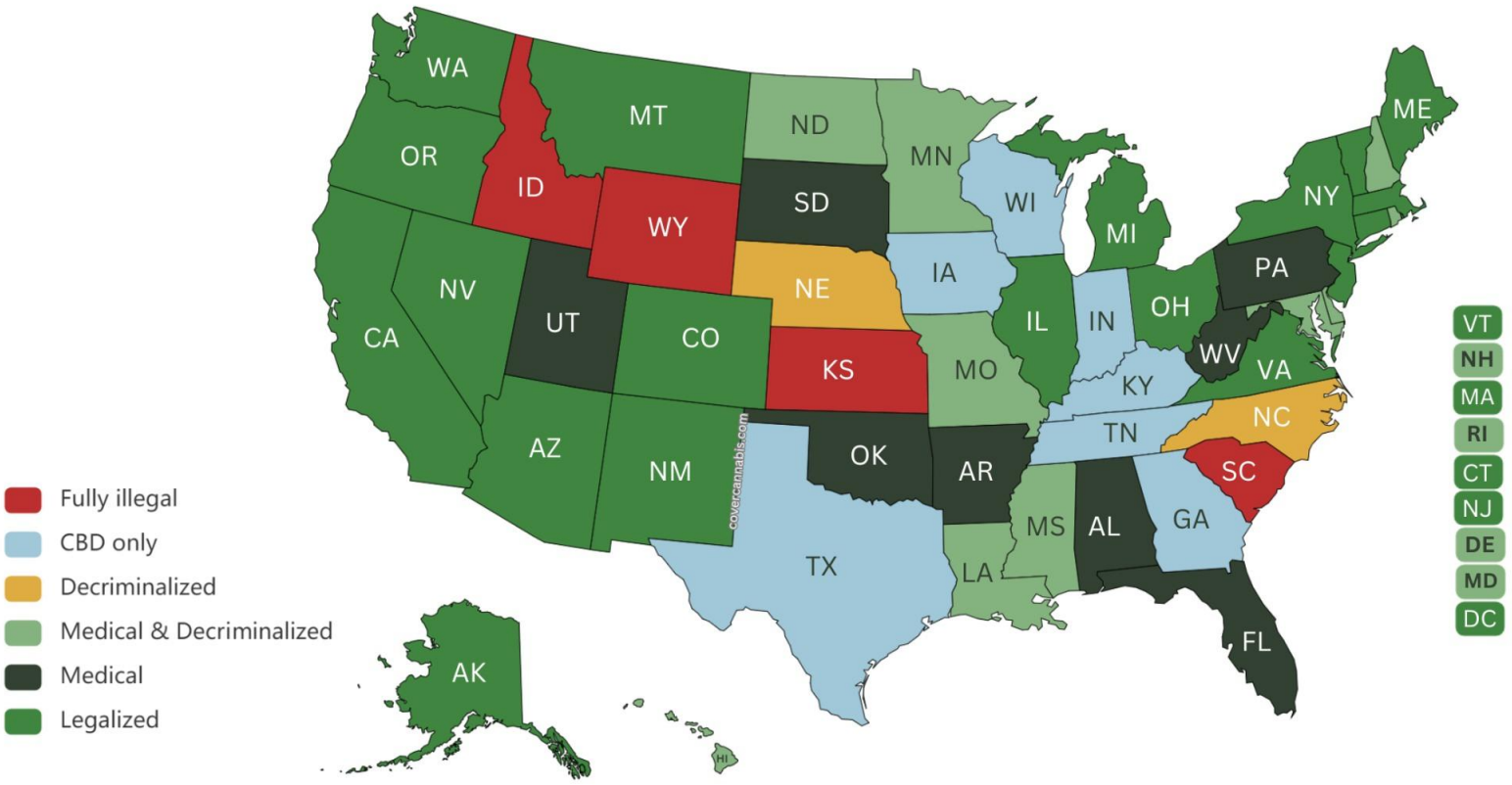

**THC's chemical structure is like the brain chemical anandamide. Similarity in structure allows drugs to be recognized by the body and to alter normal brain communication**

*THC has a MUCH STRONGER, LONGER effect than anandamide on brain cells*

# What is affected by THC?



# Landscape of Cannabis Today




In the United States, cannabis is legal in 39 states for medical use and 24 states for recreational use.

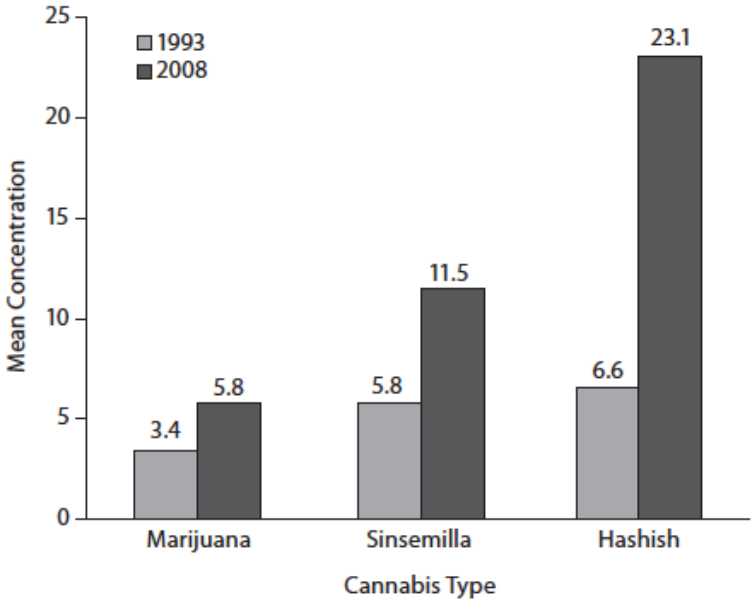
# Cannabis until the 2000's: THC 1-3%



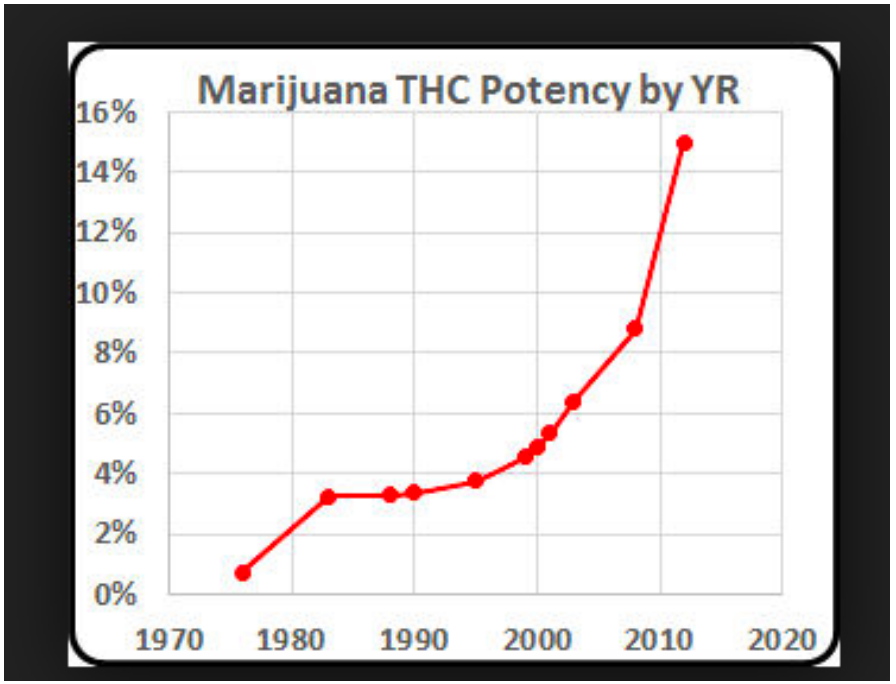



# THC Potency Increased Over Ten-Fold in Flower-Based Products

**Figure 1. Mean $\Delta^9$-THC[b] Potency by Cannabis Type[a]**




[a]Data from Mehmedic et al.[31]
[b]Abbreviation: $\Delta^9$-THC = delta 9 tetrahydrocannabinol.



# Cannabis is not “just a plant” anymore – derivatives contain up to 98% THC

*“Green Crack” wax*

*“Ear Wax”*

Butane Hash Oil (BHO)

Hash Oil Capsules

*“Budder”*



*“Shatter”*

# THC Oil in a JUUL Pod


**Novel forms of  THC delivery are the new norm, yet use is difficult to detect**

# Creation of a New Market of Cannabis Edibles


Borodovsky et al., 2016; Schauer, King et al., 2016; Wang et al., 2016; Weiss, 2015

# High Potency Cannabis is Associated with Increased Risk of Psychosis

***In Amsterdam, half of all new cases of psychosis were linked with high potency use***

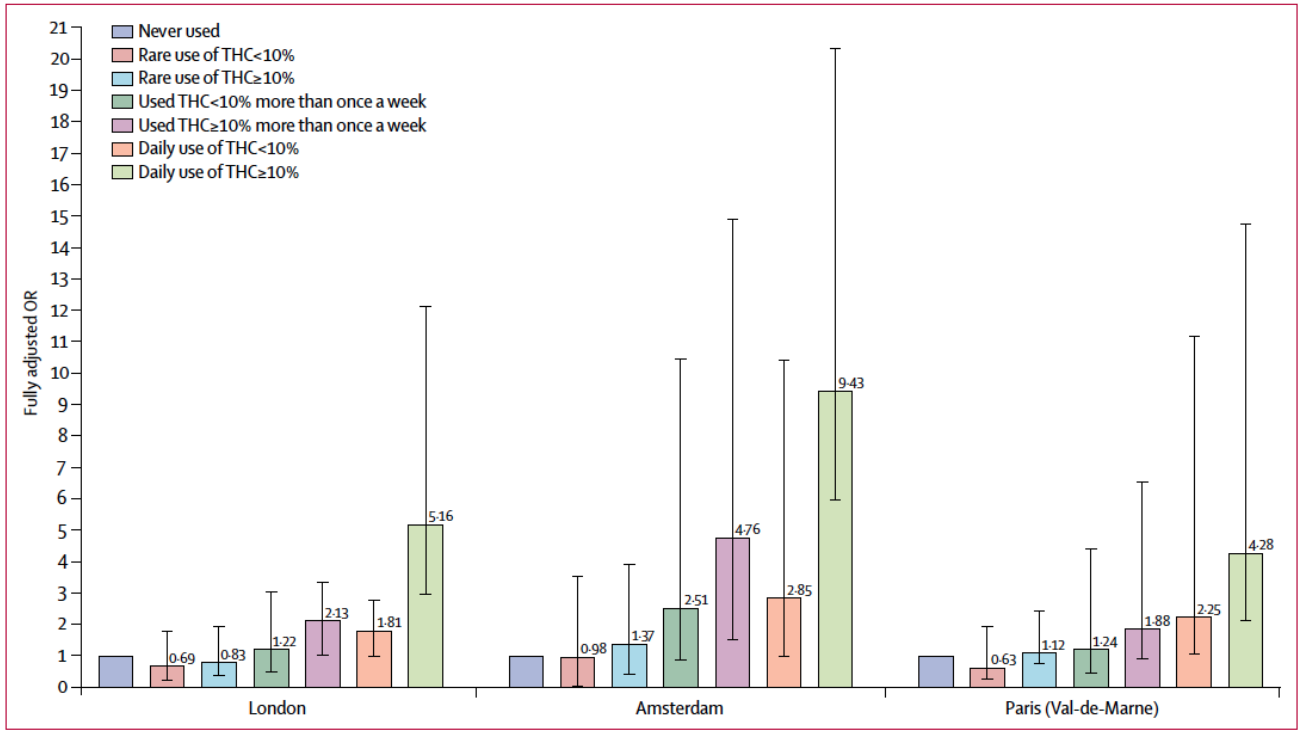
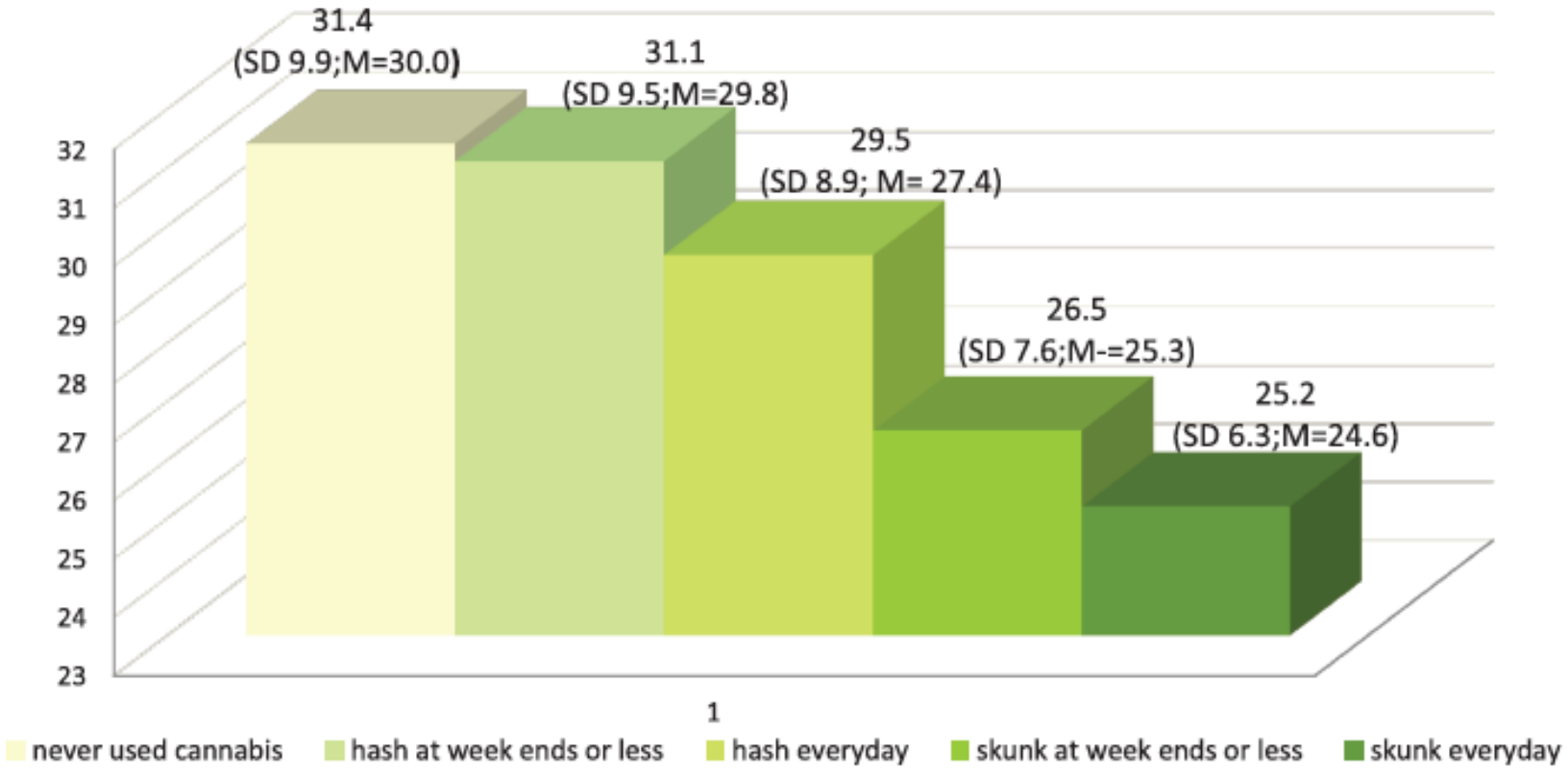
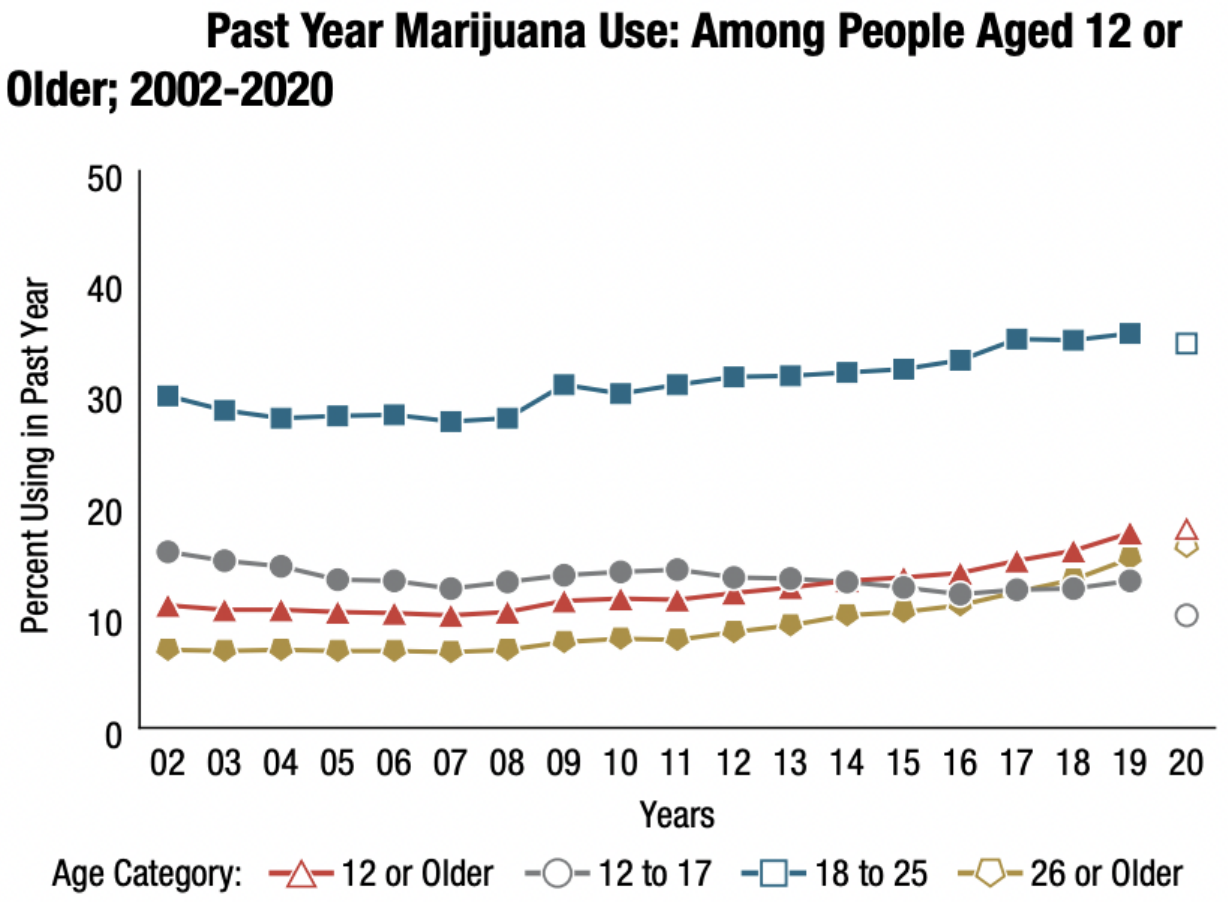



***Figure 2:*** **Fully adjusted ORs of psychotic disorders for the combined measure of frequency plus type of cannabis use in three sites**
Data are shown for the three sites with the greatest consumption of cannabis: London (201 cases, 230 controls), Amsterdam (96 cases, 101 controls), and Paris (54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

# Mean age of onset of psychosis depends on degree of exposure to cannabis



# Use in Adolescents and Young Adults




Note: There is no connecting line between 2019 and 2020 to indicate caution should be used when comparing estimates between 2020 and prior years because of methodological changes for 2020. Due to these changes, significance testing between 2020 and prior years was not performed.

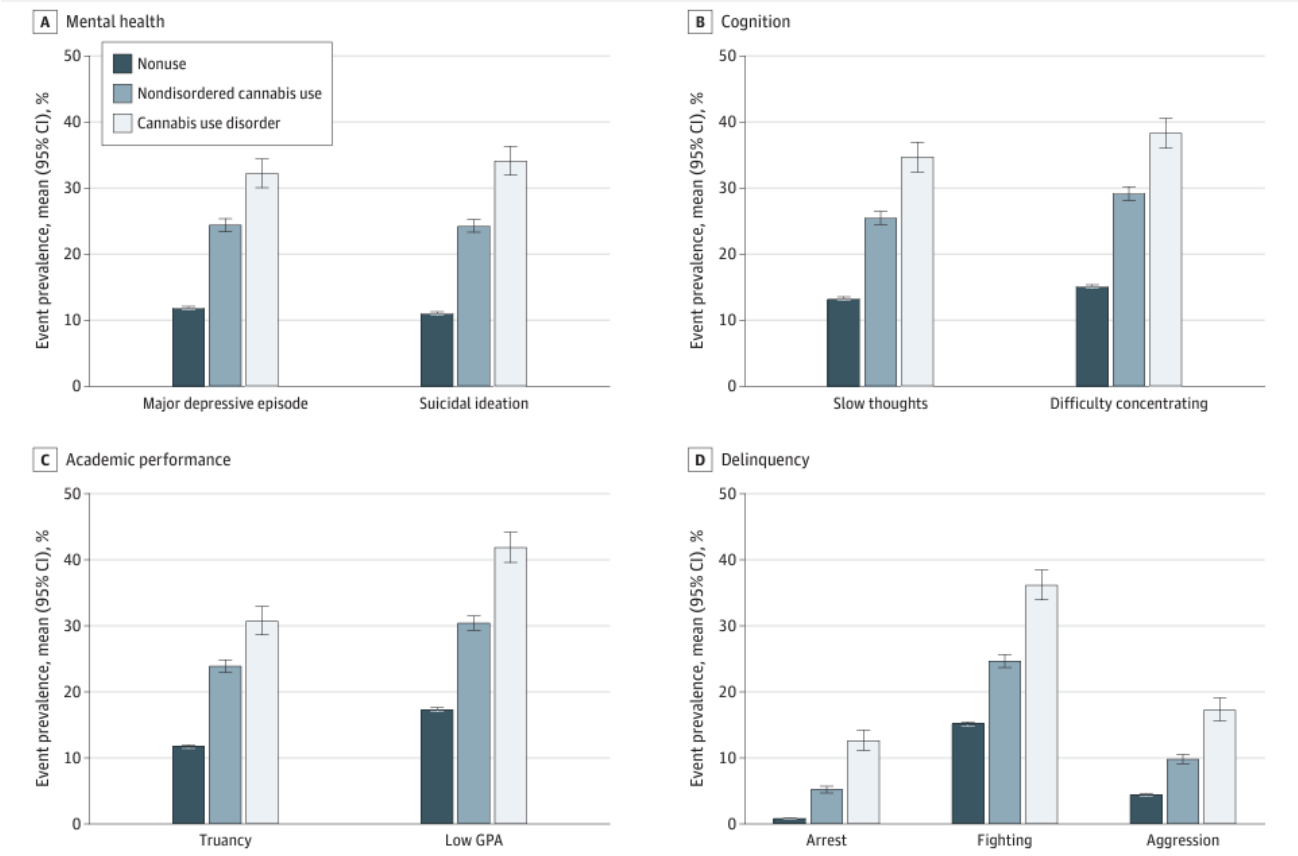
# Earlier Use is Worse

- Regular cannabis use during adolescence is associated with:
  - worse IQ, attention, memory,
  - changes in brain structure and function
  - greater difficulty on tasks requiring judgment, planning and inhibitory function

| STUDIES | Cognitive | Brain Structure | Brain Function Effects |
|---|---|---|---|
| Meier et al., 2012 | ↓ IQ | | |
| Pope et al., 2003 | ↓ IQ | | |
| Ehrenreich et al., 1999 | ↓ attention | | |
| Huestegge et al., 2002 | ↓ visual search | | |
| Fontes et al., 2011 | ↓ executive functioning | | |
| Solowij et al., 2012 | ↓ executive functioning | | |
| Churchwell et al., 2010 | | ↓ prefrontal cortex volume | |
| Gruber et al., 2011 | ↑ impulsivity | ↓ white matter integrity in prefrontal cortex | |
| Lopez-Larson et al., 2011 | | ↓ prefrontal cortex thickness | |
| Wilson et al., 2000 | | ↓ total gray matter, | |
| Becker et al., 2010a | | | ↑ prefrontal cortex activity during working memory task |
| Gruber et al., 2012 | | | ↓ anterior cingulate activity during inhibition task |
| Jager et al., 2010 | | | ↑ prefrontal cortex activity during in working memory |

# Cannabis Use In Adolescents Is Associated With Mental Health Risks

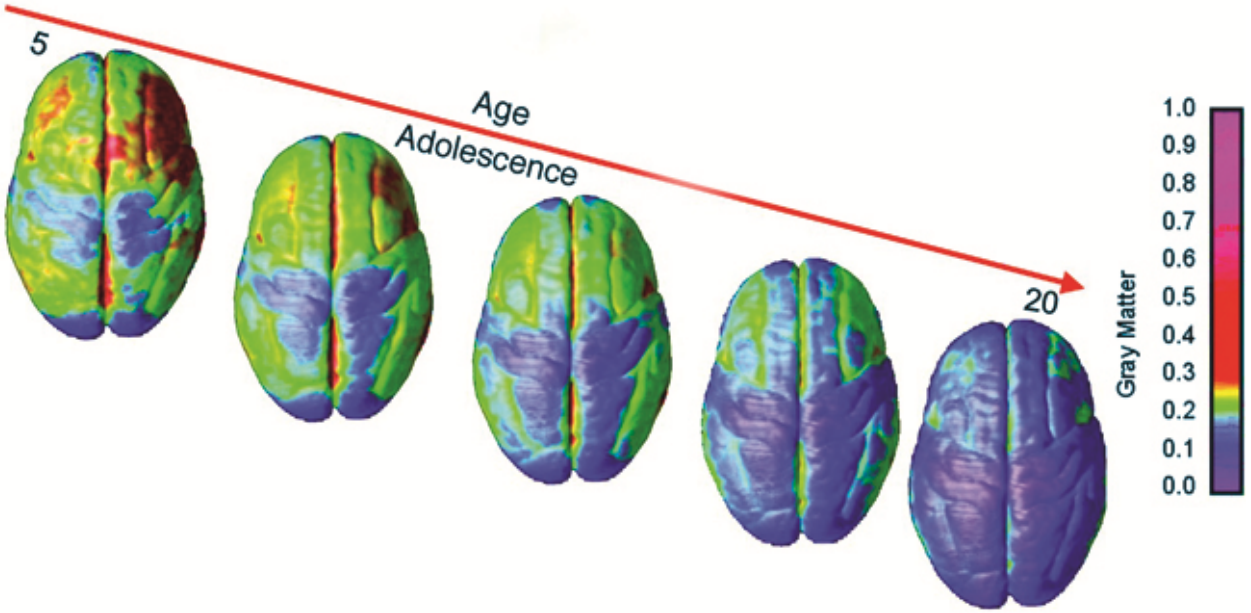
Individuals with NDCU had approximately past-year 2 to 4 times greater odds of ALL adverse psychosocial events examined, including major depression, suicidal ideation, slower thoughts, difficulty concentrating, truancy, low grade point average, arrest, fighting, and aggression.




Non-disordered Cannabis Use Among US Adolescents • May 3, 2023; JAMA Network Open

# Why is early use worse?

- Adolescence: a developmentally vulnerable period during which the brain is undergoing global cortical development
- Synaptic pruning of gray matter density occurs last in higher-order association areas such as the prefrontal cortex: helps make brain more efficient



# Now let’s talk about ‘medical’ cannabis…

- Gold standard: double-blind, placebo-controlled clinical trials
- Few exist for dispensary cannabis products
- Clinical trials have been small, largely unsuccessful

# FDA Approval Process

- Medicines go through a rigorous process of testing in human subjects for
  - safety
  - efficacy
  - long term effects
  - side effects
  - *Testing for a single medical condition*,
  - many other standards, including:
    - measuring shelf life, gauging manufacturing and labeling practices, inspections of the cleanliness of the facilities in which the drug is manufactured, etc.

# The Elephant in the Room Regarding Cannabis Products from Dispensaries

- ***The science to support effectiveness and safety, the dual standards for an approved medicine, does not yet exist.***

- Medical cannabis has been “legalized” by voting on a ballot or by legislatures, not by scientifically testing whether it meets standards for medicinal use.

# 2018 Cochrane Review of Cannabinoids for Pain

Cochrane Library
Trusted evidence.
Informed decisions.
Better health.

Cochrane Database of Systematic Reviews

[Intervention Review]

## Cannabis-based medicines for chronic neuropathic pain in adults

Martin Mücke[1], Tudor Phillips[2], Lukas Radbruch[1], Frank Petzke[3], Winfried Häuser[4]

[1]Department of Palliative Medicine, University Hospital of Bonn, Bonn, Germany. [2]Pain Research and Nuffield Department of Clinical Neurosciences (Nuffield Division of Anaesthetics), University of Oxford, Oxford, UK. [3]Pain Clinic, Universitätsmedizin Göttingen, Göttingen, Germany. [4]Department of Psychosomatic Medicine and Psychotherapy, Technische Universität München, München, Germany

- Selected randomized, double-blind controlled trials of plant-derived and synthetic cannabis-based medicines against placebo or any other active treatment of conditions with chronic neuropathic pain in adults, with a treatment duration of at least two weeks and at least 10 participants per treatment arm.
- Rated the quality of the evidence according to GRADE: (Grading of Recommendations Assessment, Development and Evaluation) used to rate the overall quality of the evidence for risk of bias, publication bias, imprecision

# Most Trials Were Flawed…

**Summary of findings 1. Cannabis-based medicines compared with placebo for chronic neuropathic pain**

**Cannabis-based medicines compared with placebo for chronic neuropathic pain**

**Patient or population**: adults with chronic neuropathic pain

**Settings**: outpatient study centres and hospitals in Europe and North America

**Intervention**: cannabis-based medicines (smoked cannabis; oral plant-based (dronabinol) or synthetic tetrahydrocannabinol (THC) (nabilone); oromucosal spray of THC and cannabidiol (CBD))

**Comparison**: placebo

| Outcomes | Probable outcome with intervention 95% CI | Probable outcome with placebo | Relative effect Risk difference (95% CI) | No. of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| **Participant-reported pain relief of 50% or greater** | 209 per 1000 (196 to 222) | 173 per 1000 | 0.05 (0.00 to 0.09) | 1001 (8 studies) | ⊕⊕⊙⊙ **low** [1,2] | NNTB 20 (11 to 100) |
| **Patient Global Impression of Change much or very much improved** | 261 per 1000 (246 to 276) | 211 per 1000 | 0.09 (0.01 to 0.17) | 1092 (6 studies) | ⊕⊙⊙⊙ **very low** [1,3,4] | NNTB 11 (6 to 100) |
| **Withdrawals due to adverse events** | 104 per 1000 (99 to 107) | 47 per 1000 | 0.04 (0.02 to 0.07) | 1848 (13 studies) | ⊕⊕⊕⊙ **moderate** [1] | NNTH 25 (16 to 50) |
| **Serious adverse events** | 66 per 1000 (63 to 69) | 52 per 1000 | 0.01 (-0.01 to 0.03) | 1876 (13 studies) | ⊕⊕⊙⊙ **low** [1,2] | NNTH not calculated |
| **Participant-reported pain relief of 30% or greater** | 377 per 1000 (358 to 396) | 304 per 1000 | 0.09 (0.03 to 0.15) | 1586 (10 studies) | ⊕⊕⊕⊙ **moderate** [1] | NNTB 11 (7 to 33) |
| **Specific adverse events: nervous system disorder** | 611 per 1000 (576 to 644) | 287 per 1000 | 0.38 (0.18 to 0.58) | 1304 (9 studies) | ⊕⊕⊙⊙ **low** [1,3] | NNTH 3 (2 to 6) |

# Most Trials Were Flawed…

- Methodological weaknesses:
  - failure to appropriately handle withdrawals
  - selective outcome reporting
  - inadequate description of methods of randomization, allocation concealment, and blinding
  - High-quality evidence means that they are very confident in the results.
  - There was **no high-quality evidence.**

# Take-home Points

- The endocannabinoid system is critical for brain development and supports functions including mood, motivation, appetite, and cognition.
- This system includes CB1 receptors, primarily in the central nervous system, and CB2 receptors, primarily involved in immune function.
- THC is the primary psychoactive component of cannabis, while CBD has been proposed to have anxiolytic and anti-inflammatory properties.
- Today's cannabis products are highly potent, widely available, and increasingly used by adolescents during a vulnerable period of brain development.
- Adolescent cannabis use is associated with poorer cognitive outcomes and increased risk of psychopathology.
- There is limited evidence that dispensary cannabis provides meaningful benefit for most medical symptoms.