

Cannabis and Mental Health

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Conflicts of Interest

None

Outline

- **Background on cannabis, cannabis use and Cannabis Use Disorder**
- **Endocannabinoid system**
- **Endocannabinoid system and mental health**
- **Cannabis use and mental health**

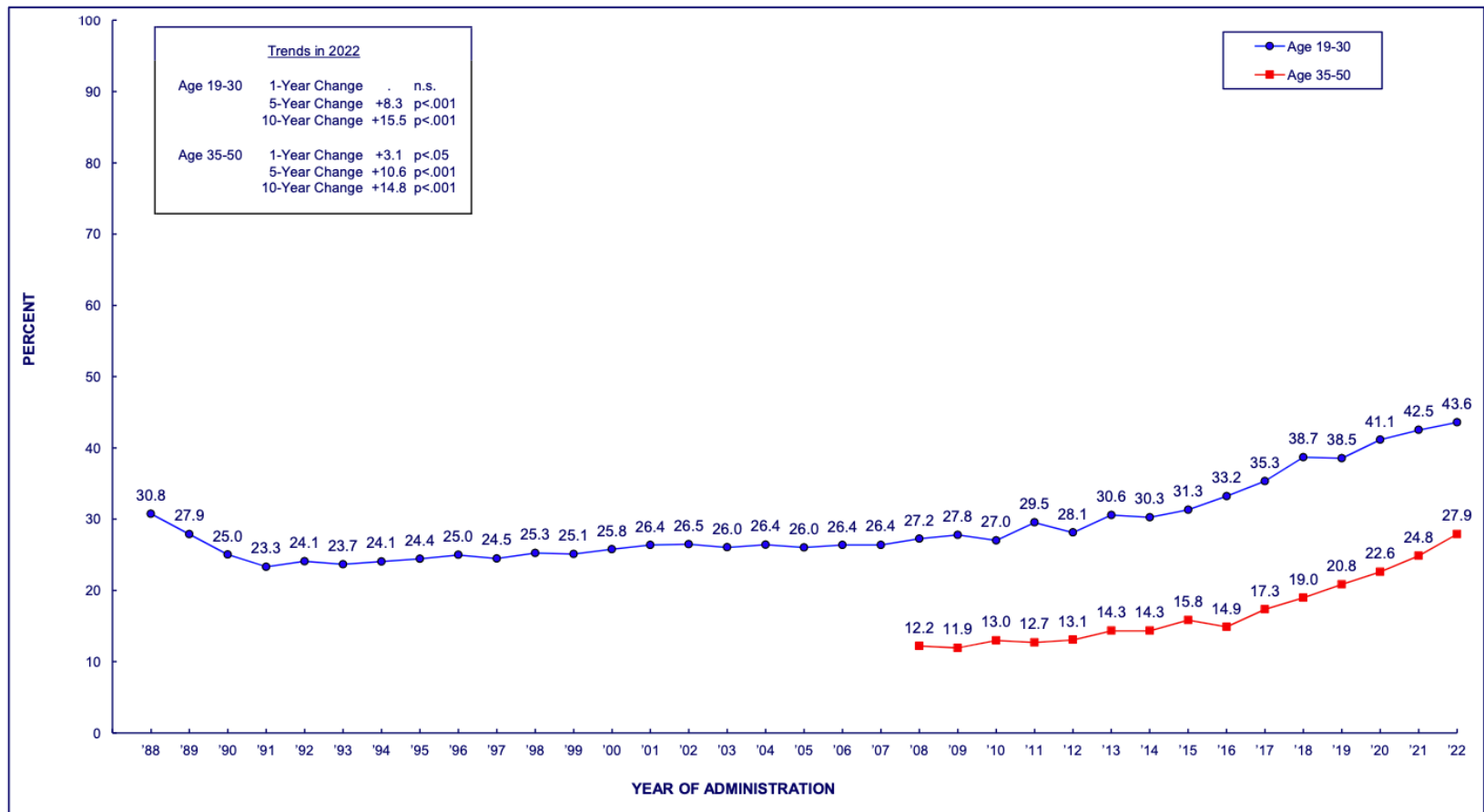
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- **Background on cannabis, cannabis use and Cannabis Use Disorder**
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Background

- Cannabis is the most commonly used illegal drug in the U.S.
- In 2022, cannabis use reached the highest levels ever recorded among young adults (aged 19-30) and adults (aged 35-50):

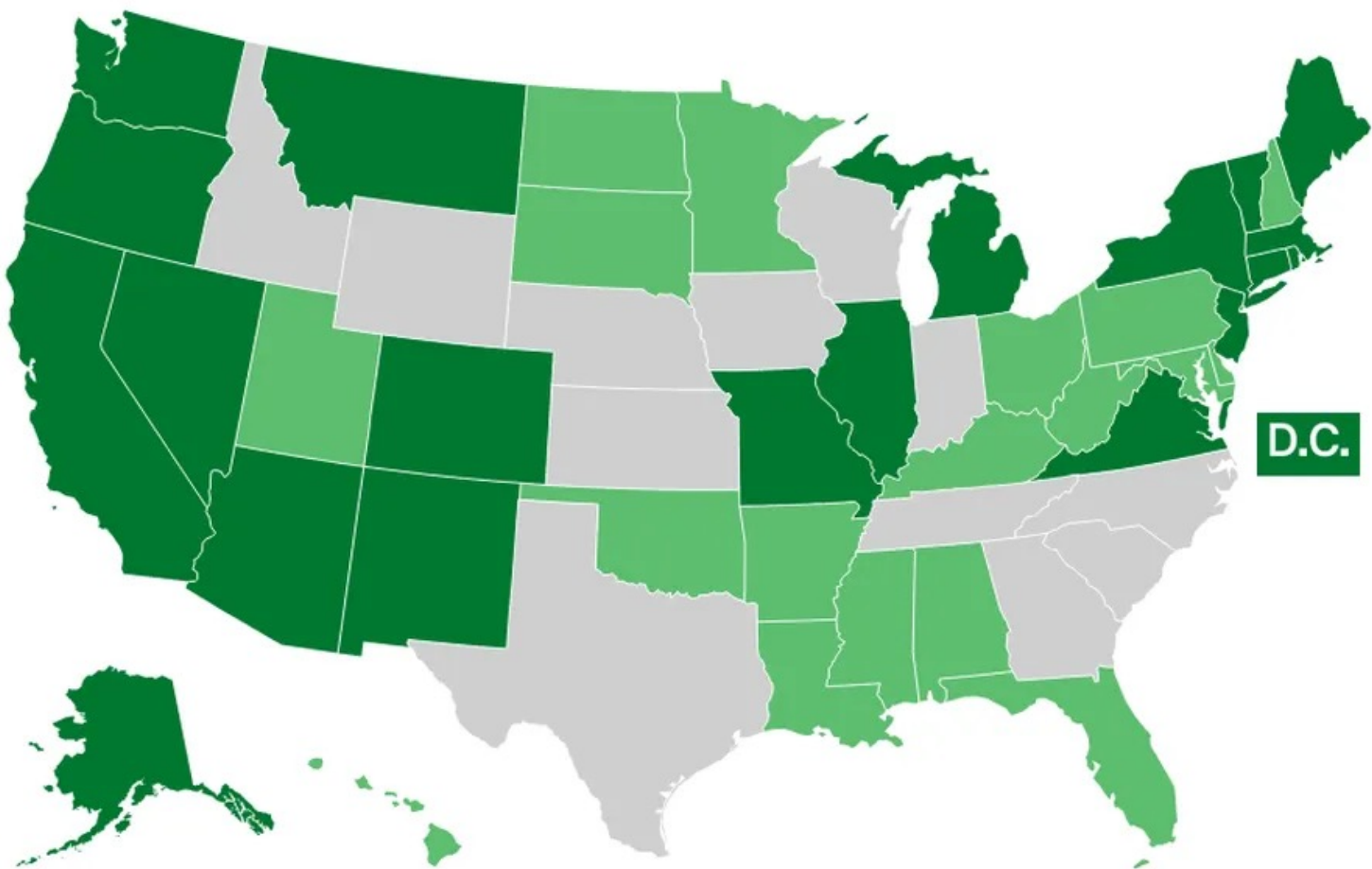
Trends in 12-Month Prevalence
among Respondents of Modal Ages 19 through 50, by Age Group



Marijuana legalization by state

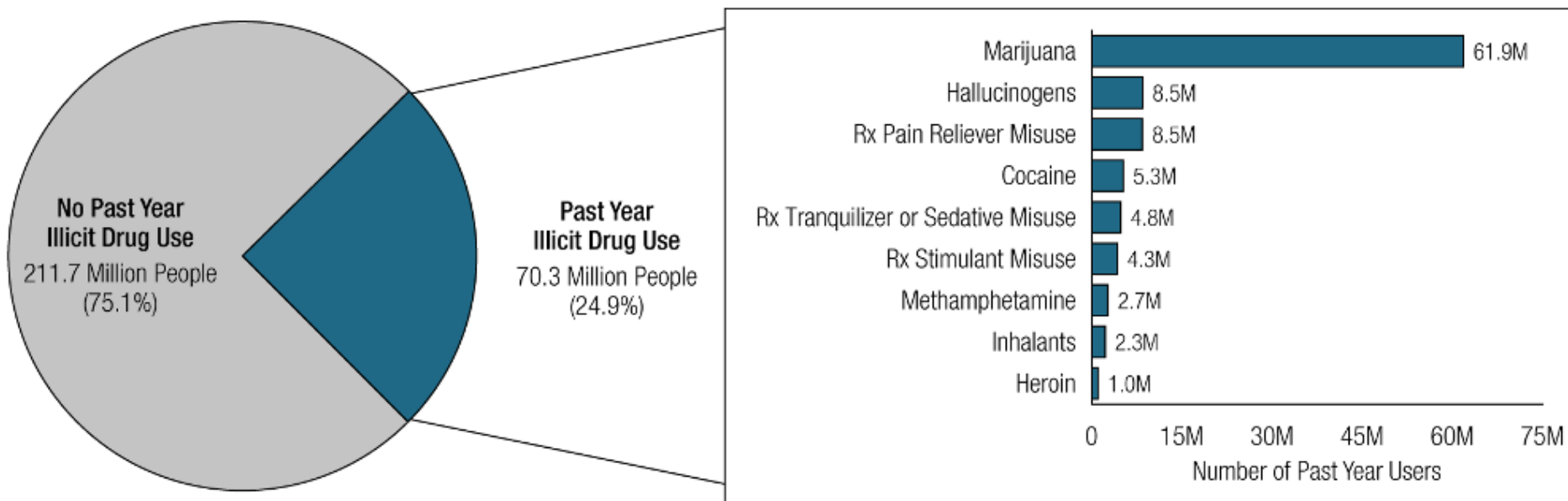
As of April 2023

Legal Medical Illegal*



Key Substance Use and Mental Health Indicators in the United States: Results from the 2022 National Survey on Drug Use and Health

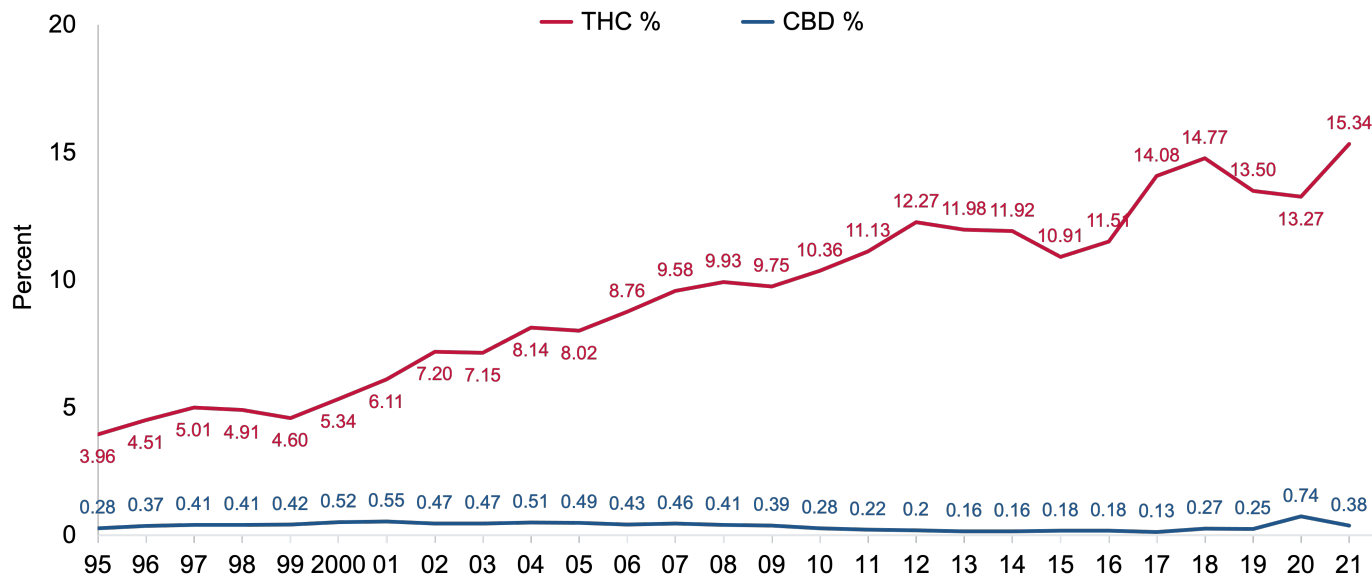
Past Year Illicit Drug Use: Among People Aged 12 or Older; 2022



Background

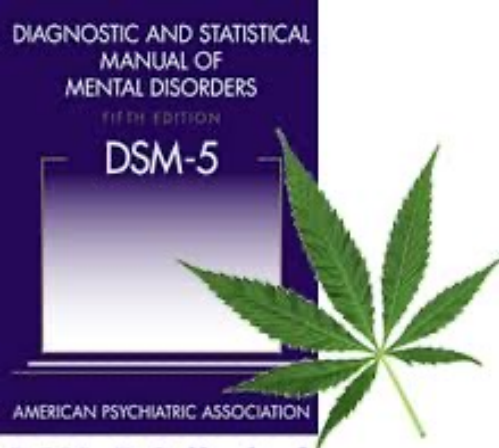
- Over 500 different compounds & >100 cannabinoids in cannabis
 - Δ^9 -tetrahydrocannabinol (THC)
 - Cannabidiol (CBD)
- The ratio of THC and CBD has drastically changed

Percentage of THC and CBD in Cannabis Samples Seized by the DEA, 1995-2021



SOURCE: U Miss, Potency Monitoring Project

- Cannabis is addictive: 3 out of 10 users develop problematic use



DSM-5 Criteria for Cannabis Use Disorder

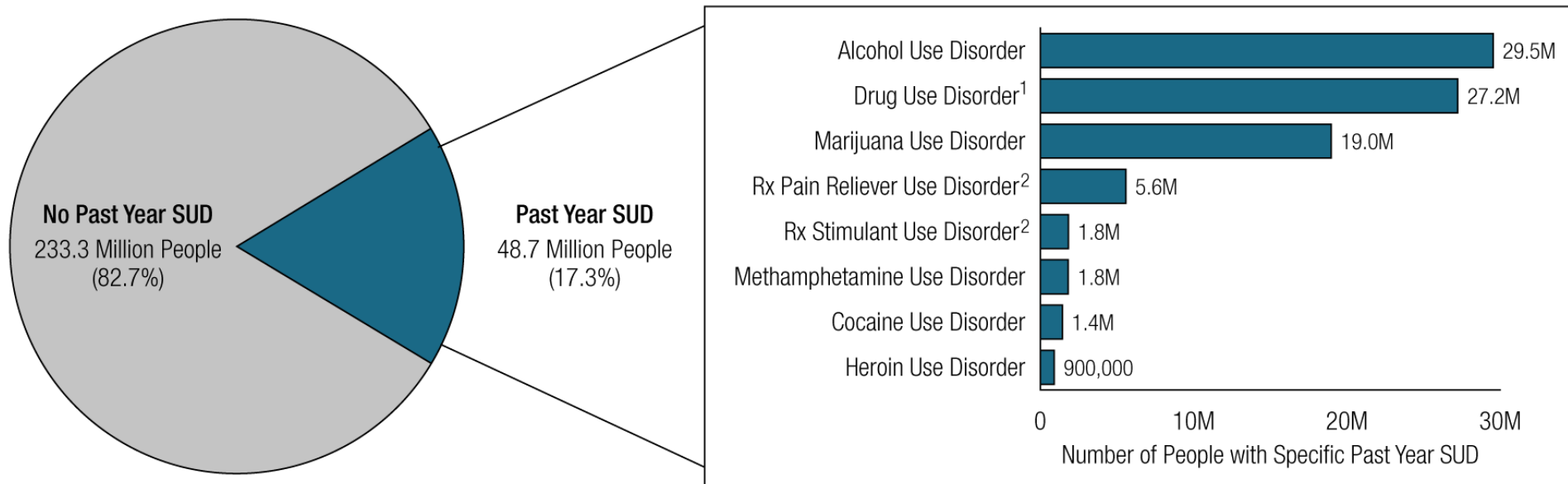
Defining Substance Use Disorder

	MILD			MODERATE			SEVERE				
NUMBER OF SYMPTOMS	1	2	3	4	5	6	7	8	9	10	11

- 1 Using more or using the substance longer than intended.
- 2 Persistent desire for it or unsuccessful effort to cut back.
- 3 Spending a lot of time to obtain the substance, use it or recover from it.
- 4 Craving or desiring it strongly.
- 5 Recurring use causes failure to fulfill major obligations at work, school or home.
- 6 Use continues despite persistent or recurring social or interpersonal problems.
- 7 Giving up social, occupational or recreational activities due to use.
- 8 Recurring use in situations in which it's physically hazardous.
- 9 Use continues despite knowing it causes physical or psychological problems
- 10 Developing tolerance (diminished effect or needing more)
- 11 Experiencing withdrawal symptoms or using the substance to avoid them.

Key Substance Use and Mental Health Indicators in the United States: Results from the 2022 National Survey on Drug Use and Health

Past Year Substance Use Disorder (SUD): Among People Aged 12 or Older; 2022



Rx = prescription.

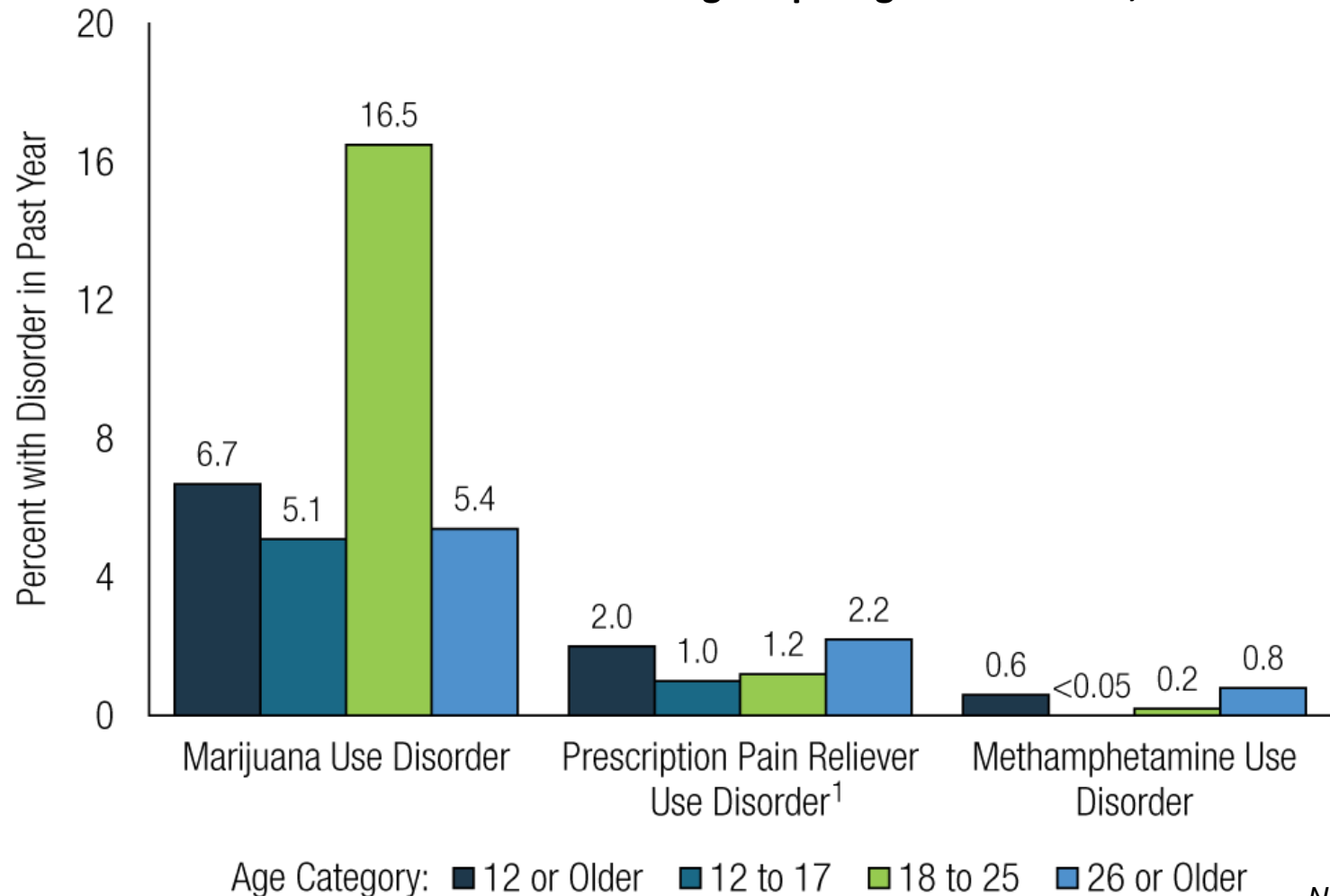
Note: The estimated numbers of people with SUDs are not mutually exclusive because people could have use disorders for more than one substance.

¹ Includes data from all past year users of marijuana, cocaine, heroin, hallucinogens, inhalants, methamphetamine, and prescription psychotherapeutic drugs (i.e., pain relievers, tranquilizers, stimulants, or sedatives).

² Includes data from all past year users of the specific prescription drug.

Key Substance Use and Mental Health Indicators in the United States: Results from the 2022 National Survey on Drug Use and Health

Marijuana Use Disorder, Prescription Pain Reliever Use Disorder, or Methamphetamine Use Disorder in the Past Year: Among People Aged 12 or Older; 2022

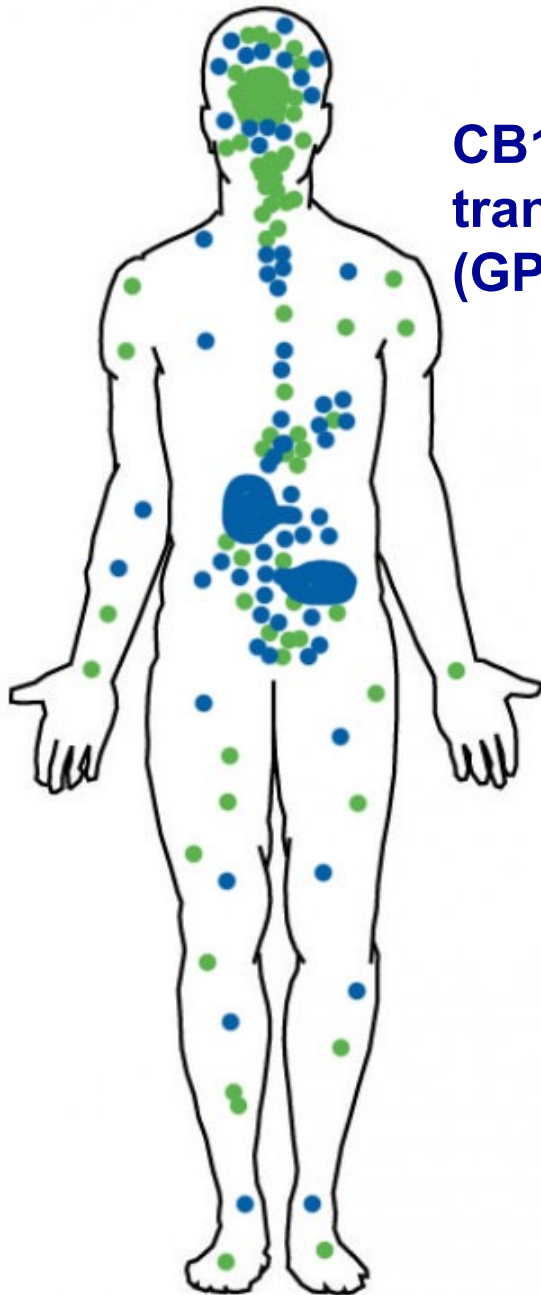


¹ Includes data from all past year users of prescription pain relievers.

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- **Endocannabinoid system**
- Endocannabinoid system and mental health
- Cannabis use and mental health

CB1 and CB2 receptors belong to the family of 7-transmembrane-spanning G-protein-coupled receptors (GPCRs)



CB₁

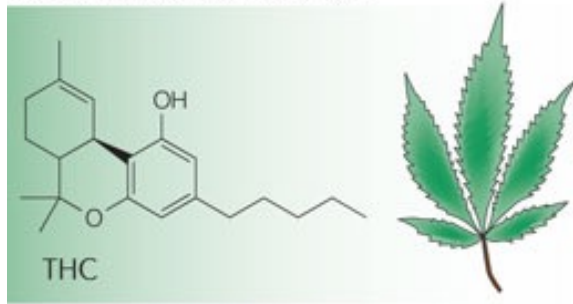
- **CB₁ mostly in the brain and CNS, also present in nerves and some organs**

CB₂

- **CB₂ mostly in PNS and organs in the body, especially in cells associated with the immune system**

What Binds to CB Receptors?

Plant-derived cannabinoid



Endogenous cannabinoids

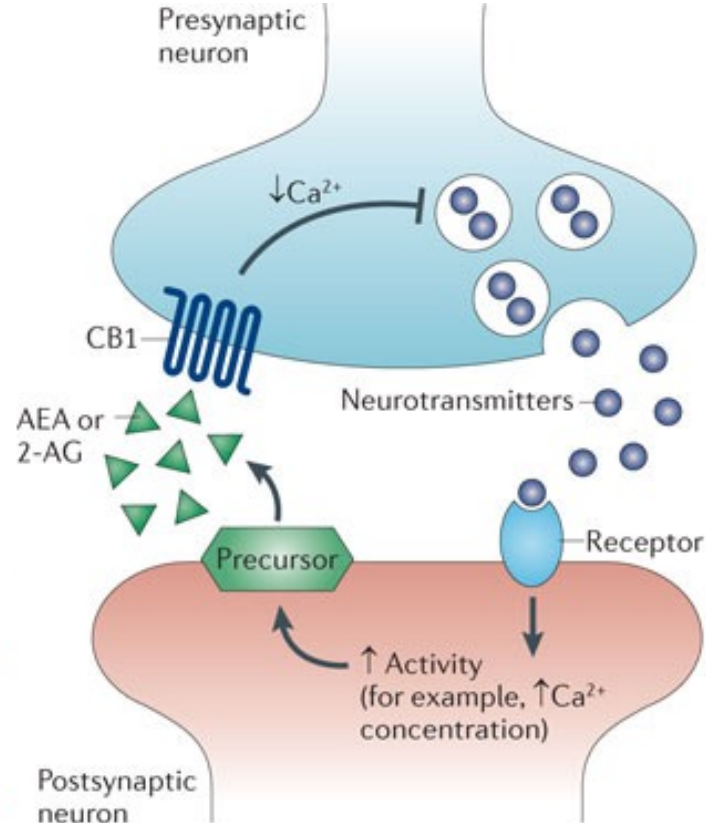
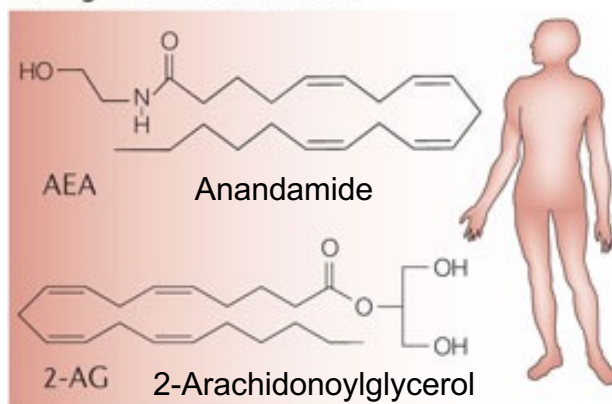


Figure from Velasco et al, 2012

Nature Reviews | Cancer

- **Endocannabinoids made 'on demand' in postsynaptic cell**
- **Work as retrograde synaptic messengers through binding to the CB receptors on the presynaptic terminal of neurons**
- **Activation of cannabinoid receptors in turn inhibits the release of many neurotransmitters (e.g., serotonin, glycine, gamma-aminobutyric acid, cholecystikinin)**

“Complexity, redundancy, and promiscuity of the endocannabinoid system”

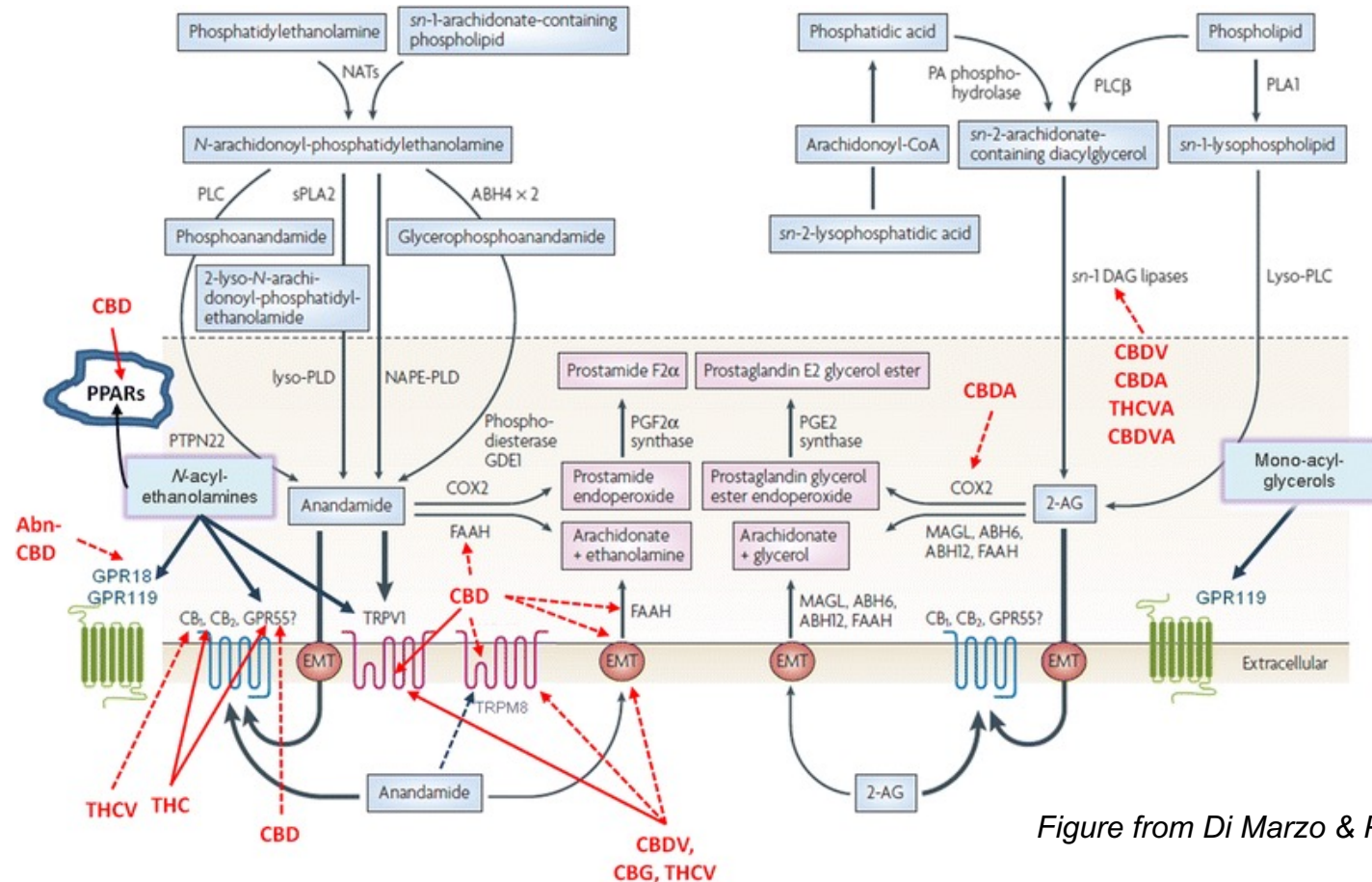


Figure from Di Marzo & Piscitelli, 2015

- Other targets including orphan G-protein-coupled receptors (GPR55, GPR18, GPR119); the transient receptor potential of vanilloid-type 1 (TRPV1) channel; and peroxisome proliferator-activated nuclear receptors (PPARs)
- Yet-to-be-characterized endocannabinoid membrane transporter (EMT) may facilitate reuptake

Exogenous cannabinoids

- Only THC and THCV (Δ^9 -tetrahydrocannabivarin) are capable of binding with high affinity to CB1 and CB2 receptors
 - THC- agonist
 - THCV- antagonist

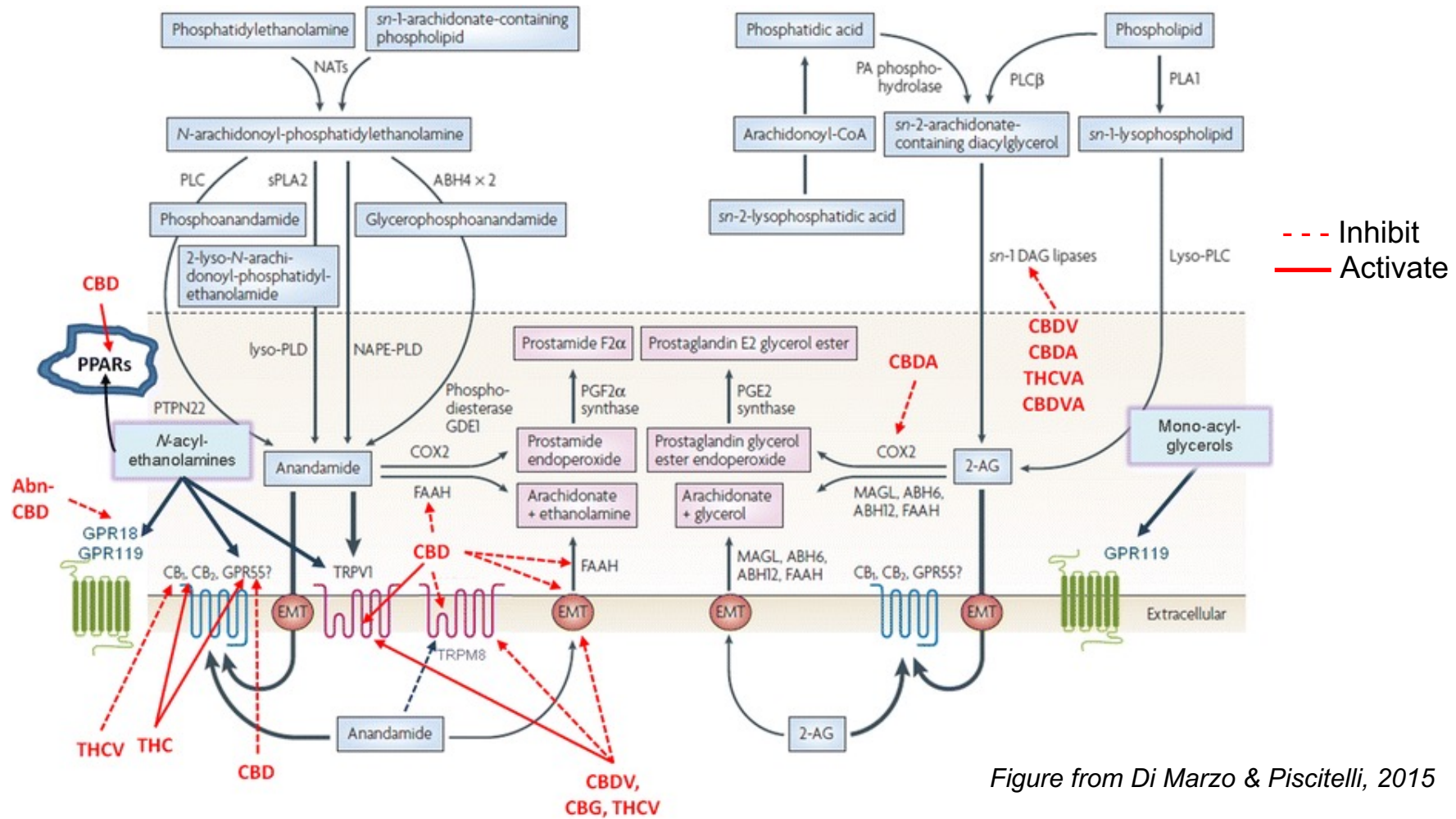


Figure from Di Marzo & Piscitelli, 2015

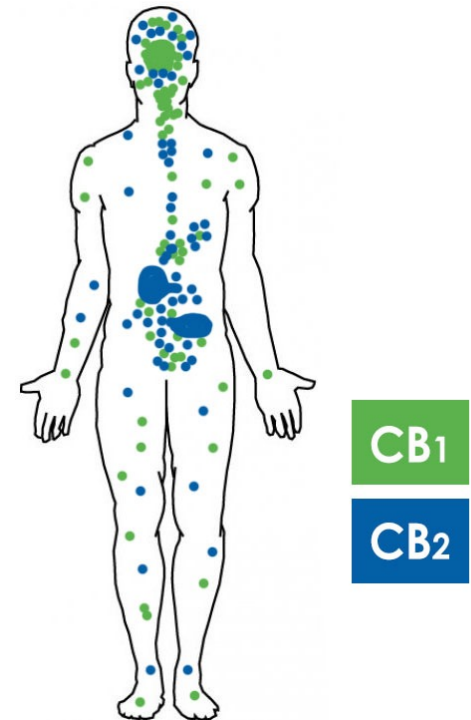
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- **Endocannabinoid system and mental health**
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Cannabinoids

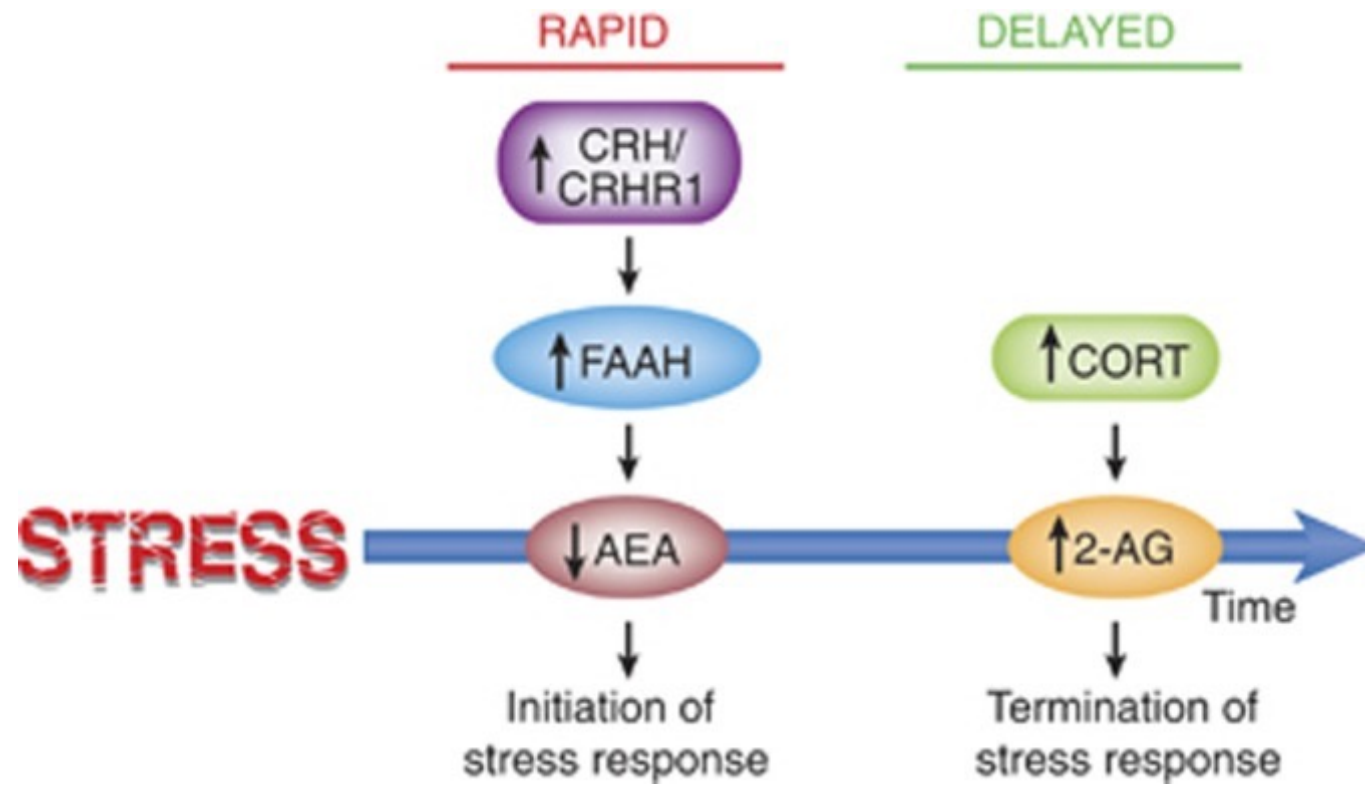
- **Cannabinoids bind to the endocannabinoid system in the body involved in:**

- | | | |
|------------|----------|-------------------------|
| - Pain | - Mood | - Metabolism |
| - Memory | - Stress | - Immune function |
| - Appetite | - Sleep | - Reproductive function |

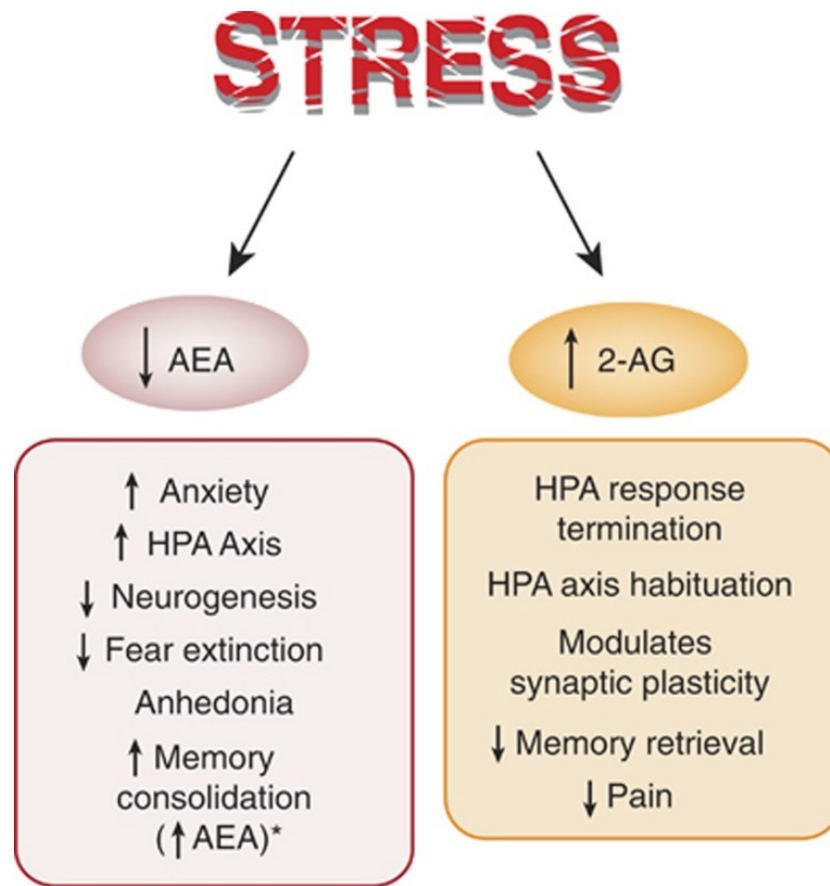


- **Cannabinoids are effective for reducing:**
 - Chronic pain
 - Nausea and vomiting during chemotherapy
FDA approved Rx Marinol (THC)
 - Self-reported spasticity in Multiple Sclerosis (MS)
 - Rare childhood onset seizures disorders
(Dravet and Lennox-Gastuat Syndromes):
FDA approved Rx Epidiolex (CBD)

Endocannabinoid system involved in the stress response



Endocannabinoids and Stress



Endocannabinoid Modulation of Brain Reward Circuitry

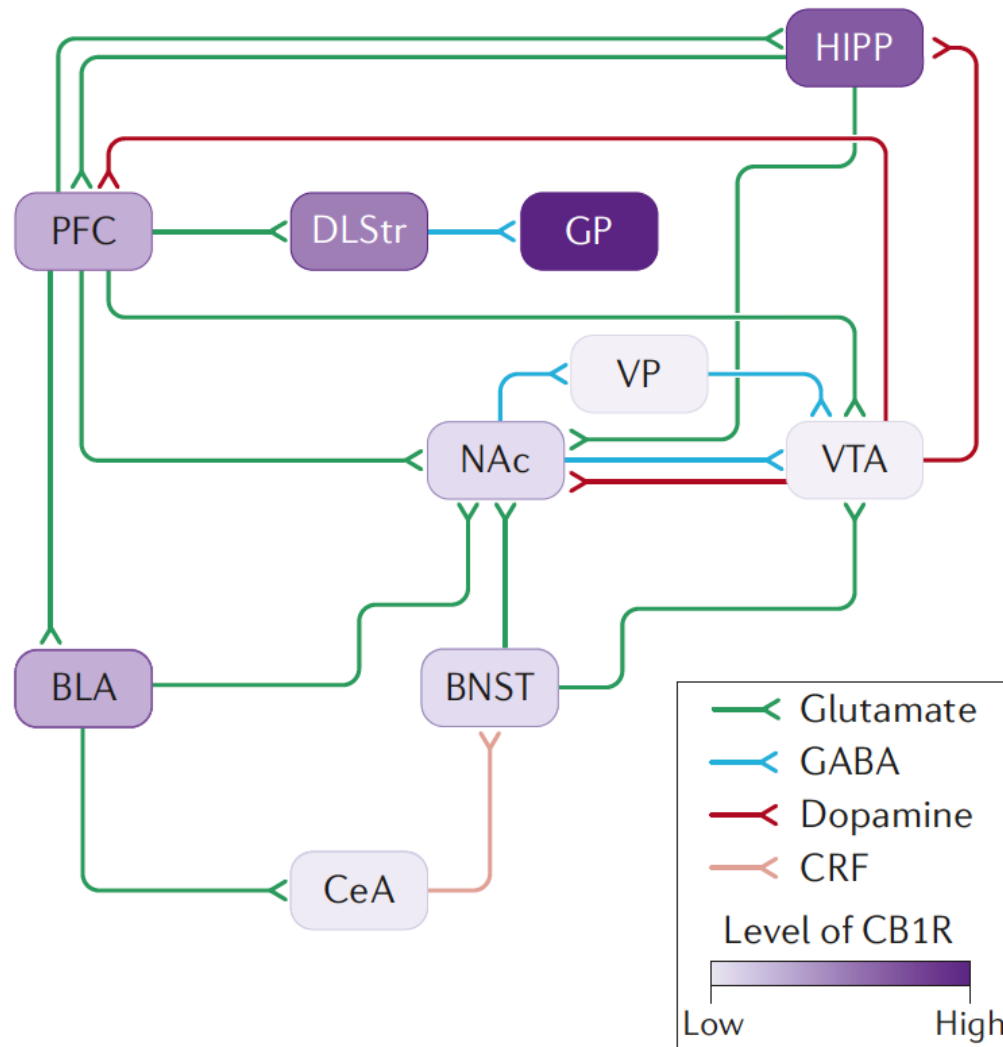


Figure from Parsons & Hurd, 2015

CB1 receptors support drug-seeking behavior

- **THC/agonists**
 - Reinstate extinguished seeking of cannabinoids, opioids, ethanol, nicotine, cocaine
- **CB1 antagonists**
 - Attenuate cue- or drug-induced reinstatement of THC, heroin, ethanol, nicotine, and cocaine
- **Inverse agonist rimonabant – clinical trials for metabolic syndrome, smoking cessation**
 - Halted due to anxiety, depression, suicidal ideation side effects
- **Neutral agonists looked to for effects on food intake, reward seeking**
 - Phytocannabinoid THCV (Δ^9 -tetrahydrocannabivarin) under investigation

Endocannabinoid System Implicated in Mental Health

- **The endocannabinoid system has been implicated in many mental health disorders, including mood disorders, anxiety disorders, stress disorders, and psychosis**
- **Preclinical evidence**
 - **Reduced endocannabinoid signaling may contribute to anhedonic depression**
 - **Inhibition or removal of the CB1 receptor in rodents results in decreased motivation to consume sucrose, while activation of CB1 receptors in rodents results in increased sucrose drinking**
 - **CB1 manipulation has bidirectional effect on anxiety-related behavior**
 - **CB1 activation decreases anxiety at lower doses, but anxiogenic effects occur at higher doses or after CB1 blockade**
- **In humans**
 - **Lower 2-AG in major depression compared to matched controls**
 - **Higher AEA in untreated and treated patients with schizophrenia compared to controls (and among individual at risk for psychosis)**

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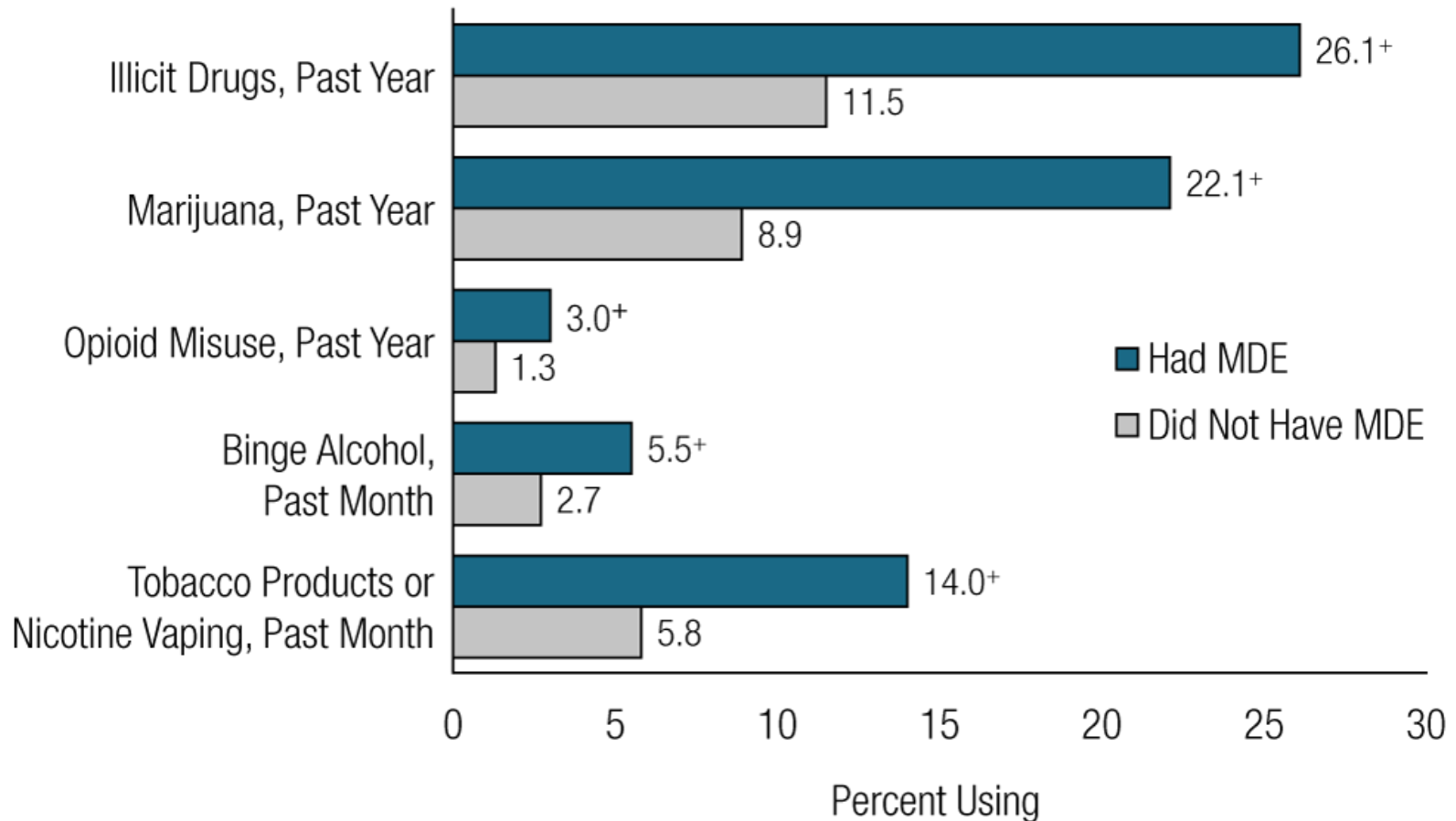
Cannabis Use Controversies

- **Inconclusive or negative data (or no data) for medicinal use**
- **Regulatory issues**
 - Barriers to research
 - Potency
 - Accuracy of labels at dispensaries
- **Public health issues:**
 - Increased cannabis use and rates of Cannabis Use Disorder
 - Cannabis use among vulnerable populations
 - Increased risk of motor vehicles crashes
 - Poorer cognitive functioning in users
 - Worse respiratory symptoms and more chronic bronchitis episodes



Key Substance Use and Mental Health Indicators in the United States: Results from the 2022 National Survey on Drug Use and Health

Past Year or Past Month Substance Use: Among Adolescents Aged 12 to 17; by Past Year Major Depressive Episode (MDE) Status, 2022

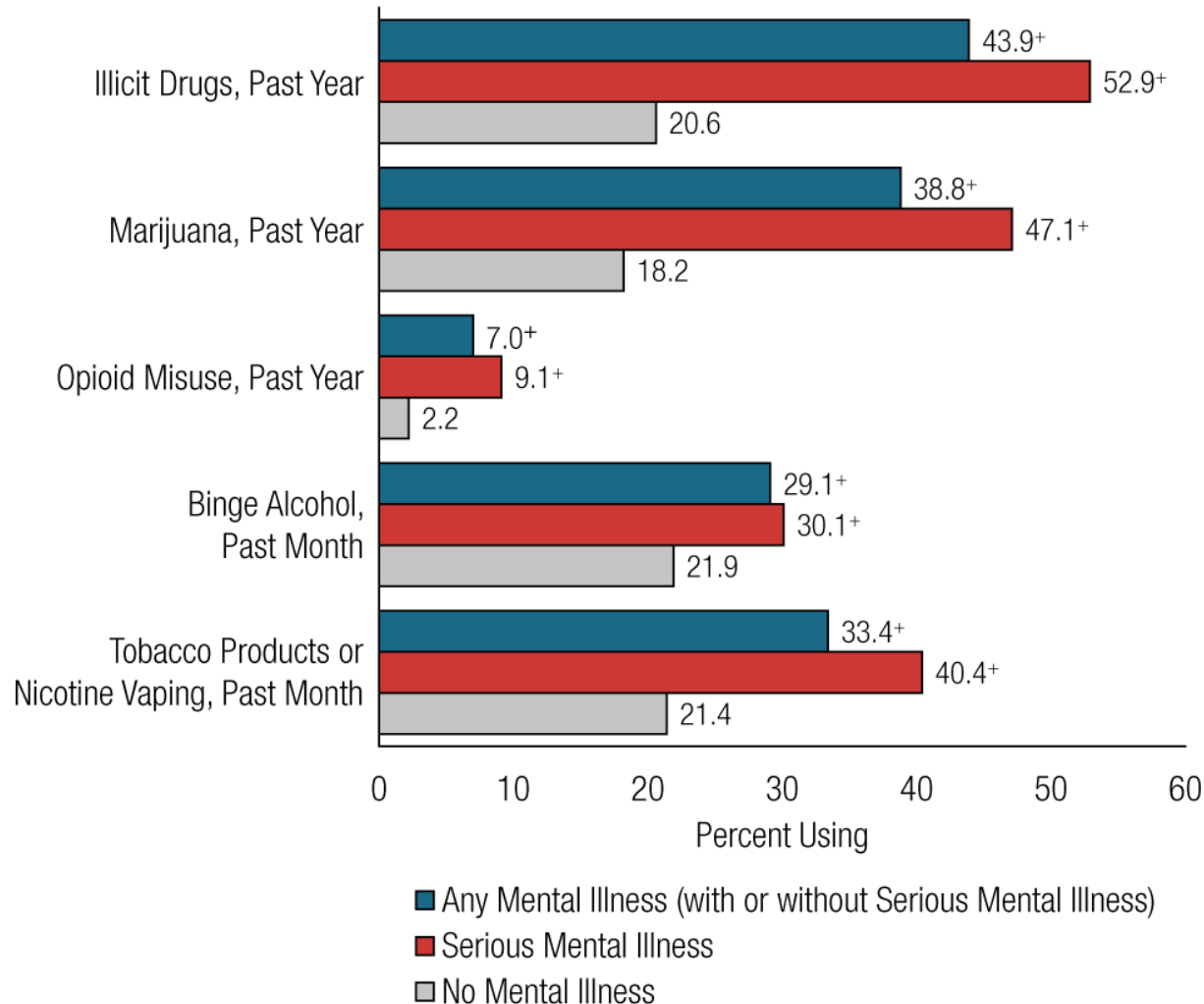


+ Difference between this estimate and the estimate for adolescents who did not have MDE is statistically significant at the .05 level.

Note: Adolescent respondents with unknown MDE data were excluded.

Key Substance Use and Mental Health Indicators in the United States: Results from the 2022 National Survey on Drug Use and Health

Past Year or Past Month Substance Use: Among Adults Aged 18 or Older; by Past Year Mental Illness Status, 2022

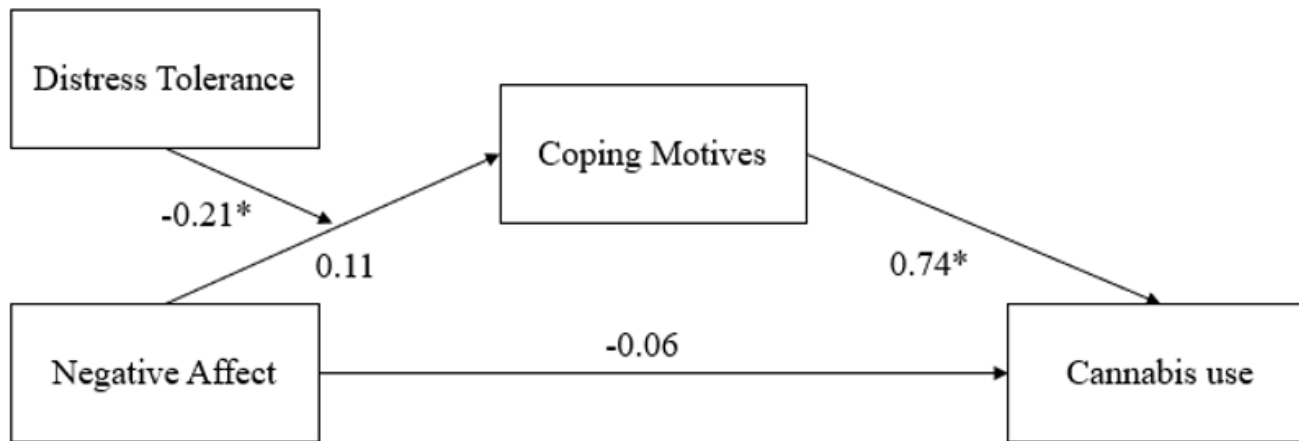


+ Difference between this estimate and the estimate for adults aged 18 or older with no mental illness is statistically significant at the .05 level.

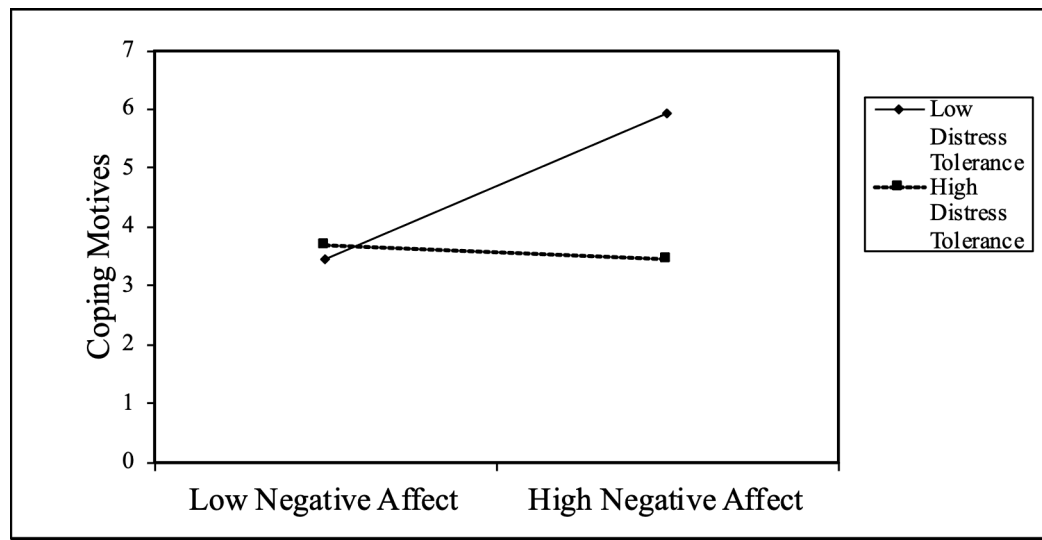
Cannabis Use Motives



Katie Paige, MA
Clinical Psychology
Intern



- Late adolescents and young adults with high negative affect and difficulties withstanding distress (low distress tolerance) are more likely to use cannabis to cope with negative affect**





Rebecca Denson, MA
Clinical Psychology
PhD Student

Association between affect and cannabis use varies by social context

Rebecca K. Denson^a  , Donald Hedeker^b, Robin J. Mermelstein^{a,c}

- **Positive affect is elevated at cannabis use times regardless of social context**
 - **Negative affect is reduced at cannabis use times when individuals are with others**
 - **Negative affect is elevated at cannabis use times when individuals are alone**
 - **Higher cannabis use disorder symptoms are related to less negative affect at cannabis use times**
-
- **Some evidence that individuals with higher depression symptoms feel more positive affect after using a THC-dominant cannabis product**

Adolescents & Young Adults May be Particularly Vulnerable to Cannabis' Effects

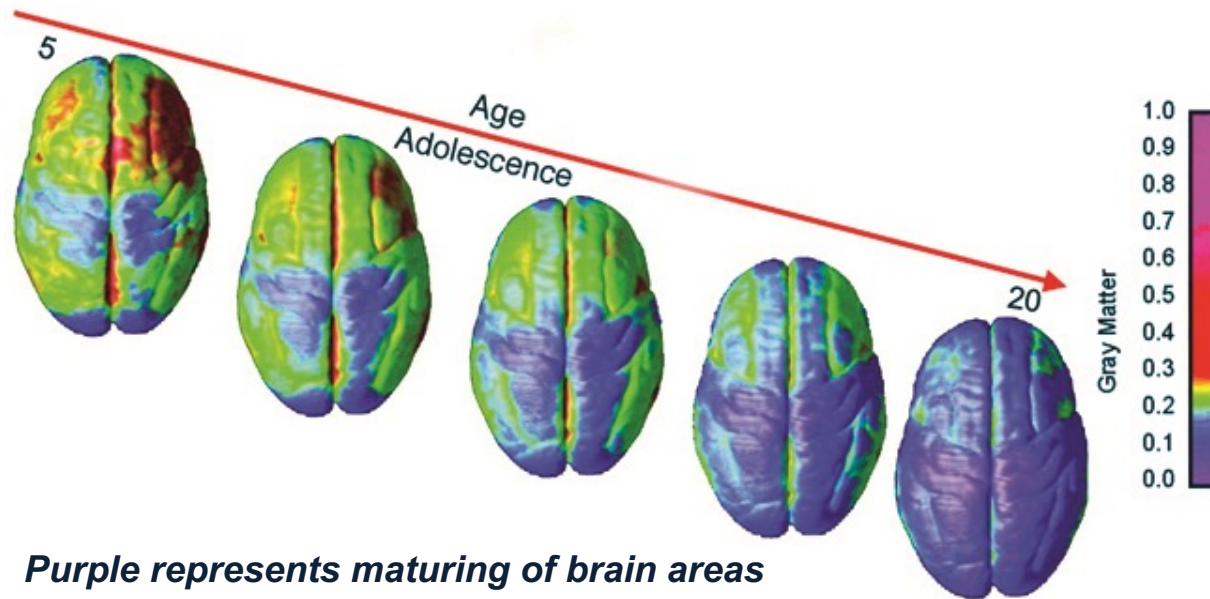
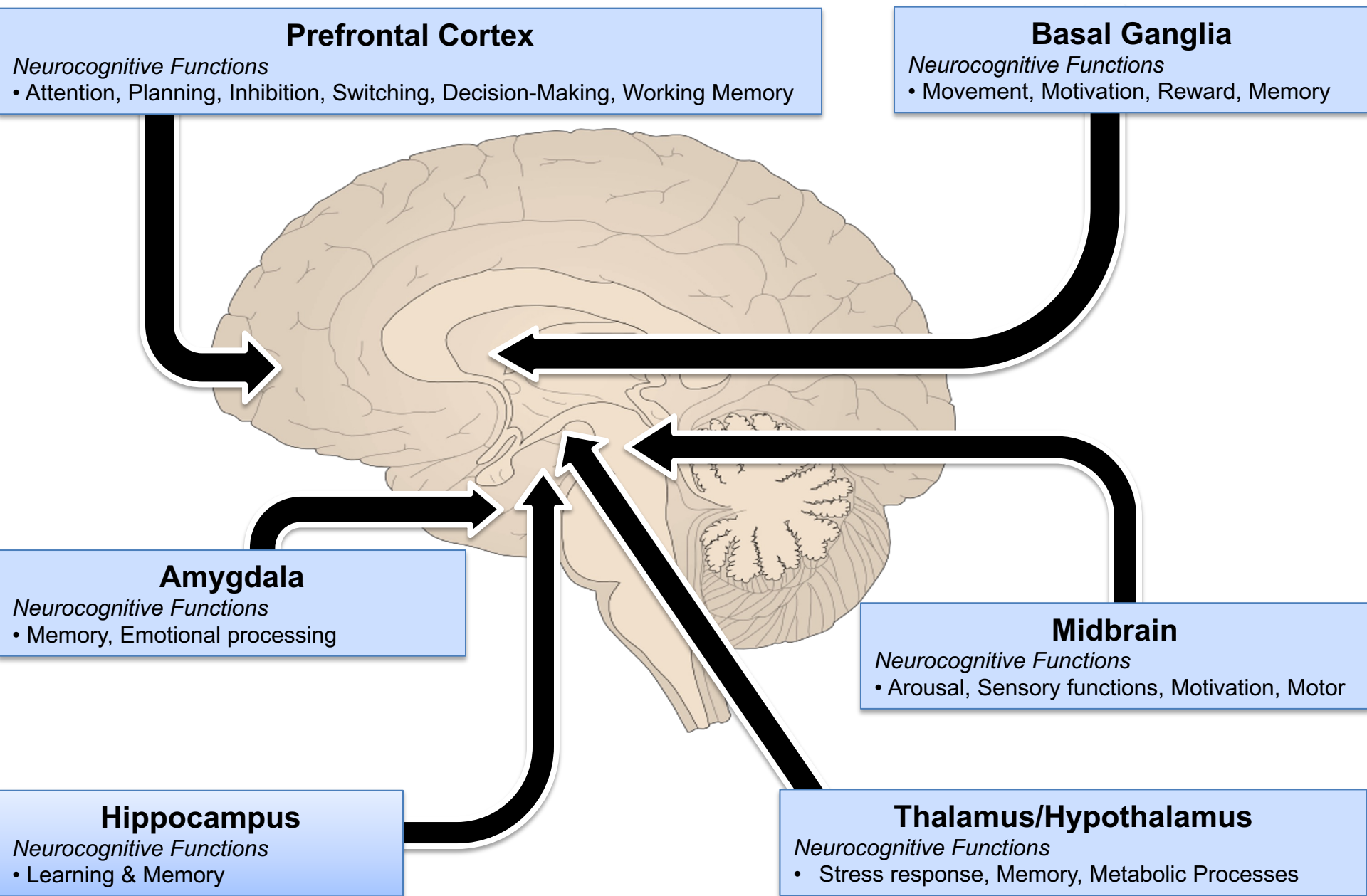


Figure from Gogtay et al., 2004, *PNAS*

- Cannabis use during adolescence may result in additive structural brain abnormalities and poorer cognitive functioning
- Cannabis acts on the endocannabinoid system in the brain
 - involved in neuromaturation and synaptic pruning
- Animal studies show THC exposure during adolescence can have lasting functional and structural brain changes



Negative Outcomes of Cannabis Use


- **Regular cannabis use, especially during adolescence and young adulthood**
 - **Poorer school performance and increased drop-out rates**
 - **Increased risk for later psychotic disorder in adulthood**
 - **Increased symptoms of affective disorders (MDD, Bipolar Dx), anxiety, personality disorders**
 - **Increased suicidal ideation and suicide attempts**
 - **Increased prevalence of nearly all other substance use**
 - **Increased sexual risk behaviors**
 - **Increased disability in adulthood**



REVIEW ARTICLE



Consensus paper of the WFSBP task force on cannabis, cannabinoids and psychosis

Deepak Cyril D'Souza^{a,b,c} , Marta DiForti^{d,e}, Suhas Ganesh^{a,b,c} , Tony P. George^{f,g} , Wayne Hall^h , Carsten Hjorthøj^{i,j}, Oliver Howes^{k,l}, Matcheri Keshavan^m, Robin M. Murray^k , Timothy B Nguyen^{d,l}, Godfrey D. Pearson^{n,c}, Mohini Ranganathan^{a,b,c} , Alex Selloni^{b,c}, Nadia Solowij^{o,p} and Edoardo Spinazzola^k

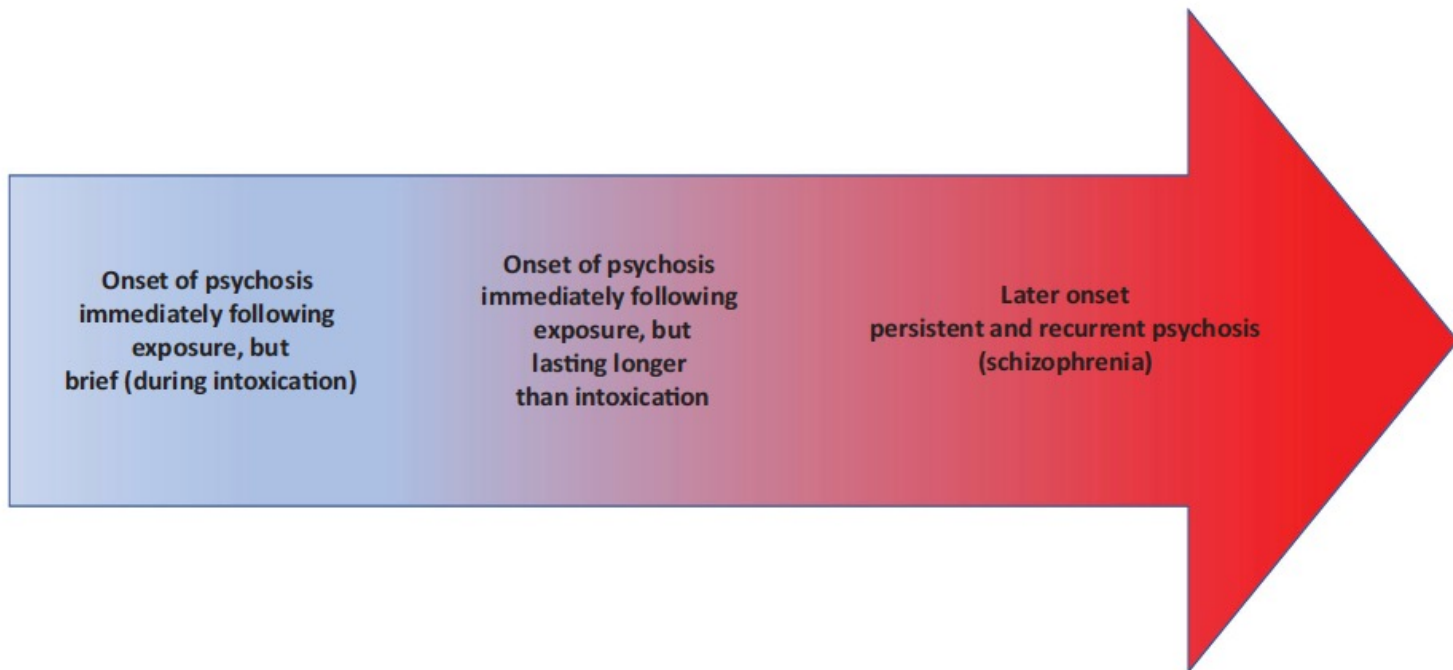


Figure 1. Temporal relationships between cannabis and psychosis.

Figure from D'Souza et al., 2022

Cannabis Use and Psychosis

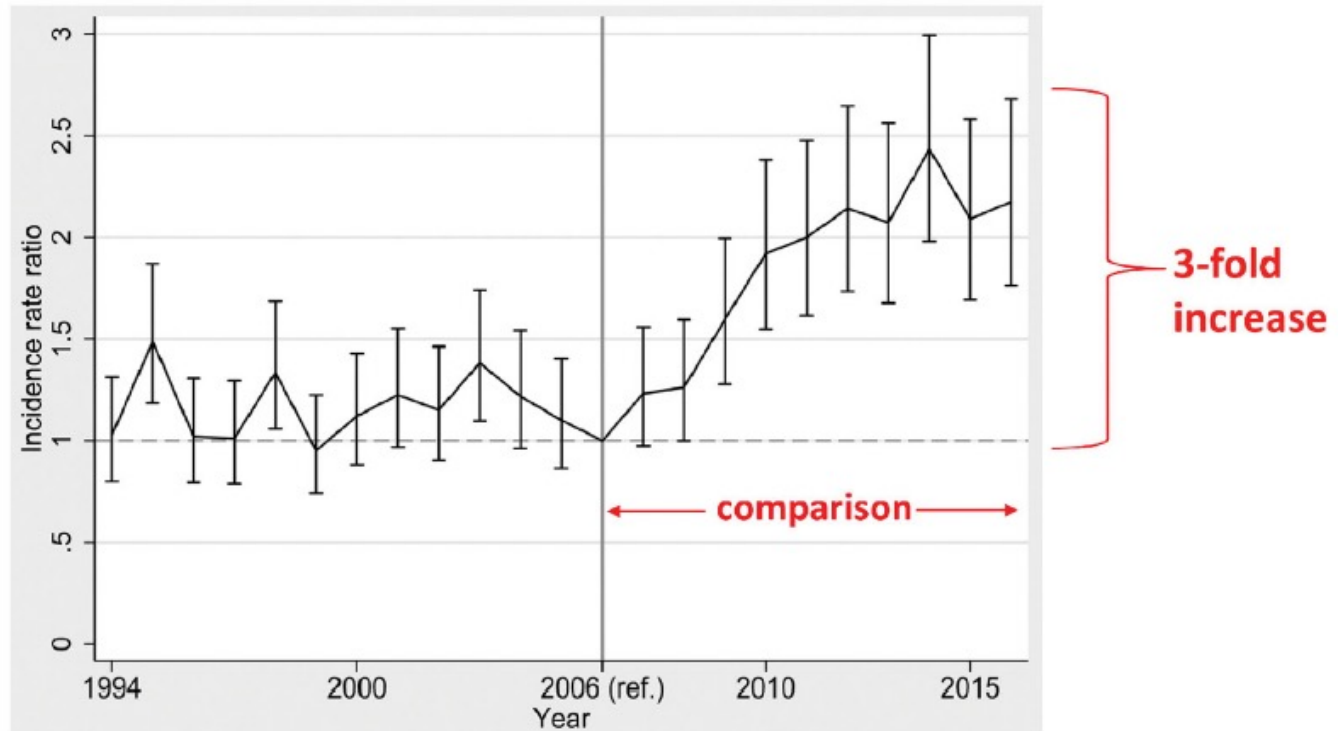


Figure 3. Increasing rates of cannabis-induced psychosis in Denmark.

Figure from D'Souza et al., 2022

- Increased incidence of psychosis parallels increases in THC potency in cannabis products
- Evidence supporting hypothesis that high THC cannabis increases the risk of psychosis

Cannabis Use and Psychosis

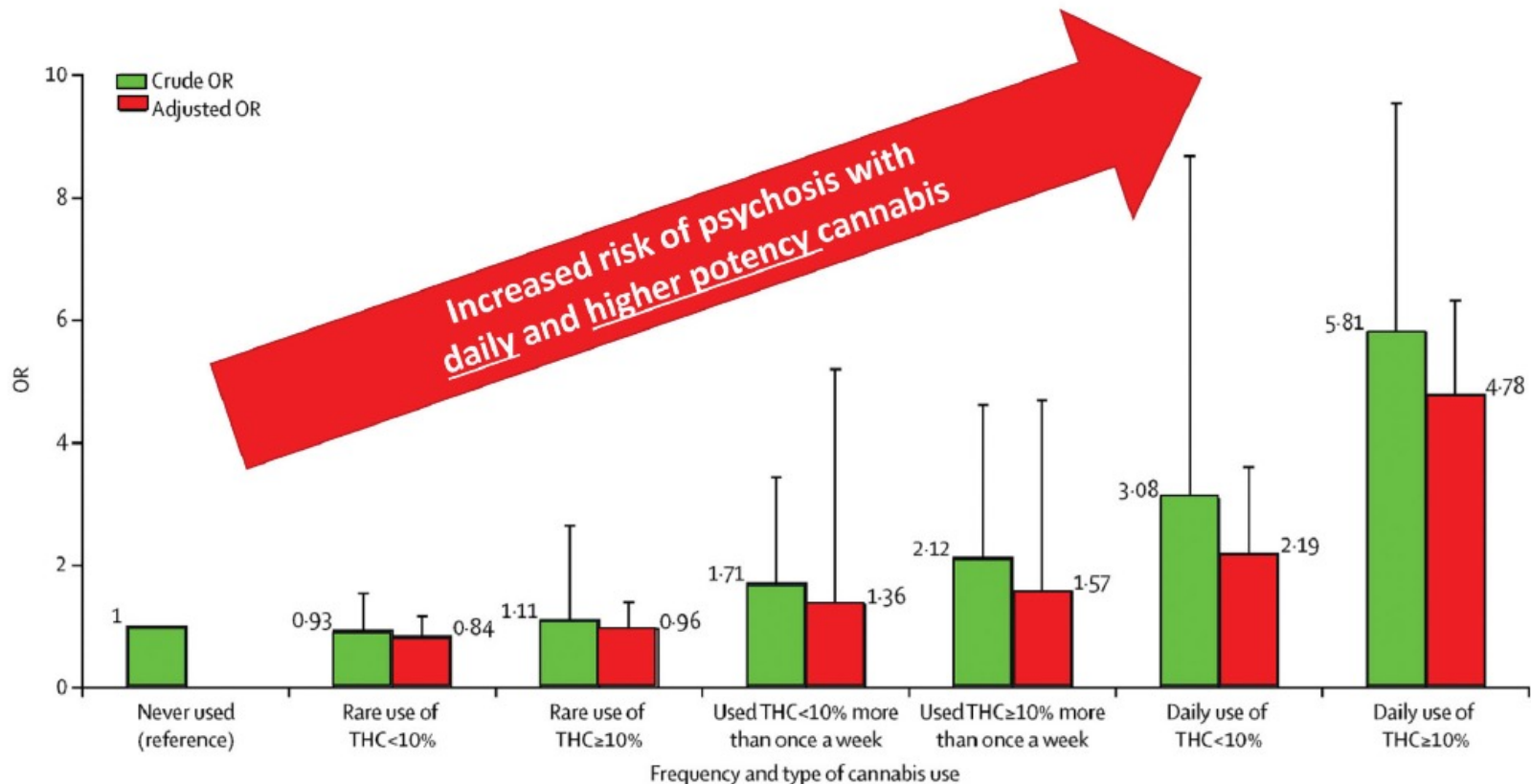


Figure 5. Increased risk of psychosis with daily and more potent cannabis.

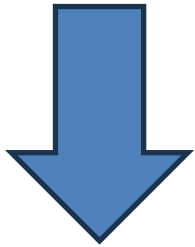
Figure from D'Souza et al., 2022

Greater risk:

- Earlier age of initiated use
- Higher THC content
- Heavier/more frequent use of high THC cannabis

2018 Farm Bill

>0.3%
Delta-9-THC
by dry weight

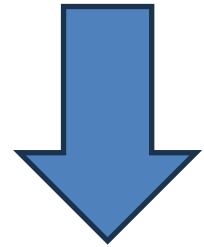


CANNABIS

- Federally illegal (Schedule 1)
- Regulated by states that have policies in place

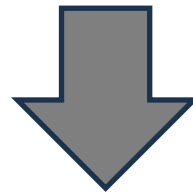


≤0.3%
Delta-9-THC
by dry weight



HEMP

- Federally legal
- Regulated federally as an agricultural plant



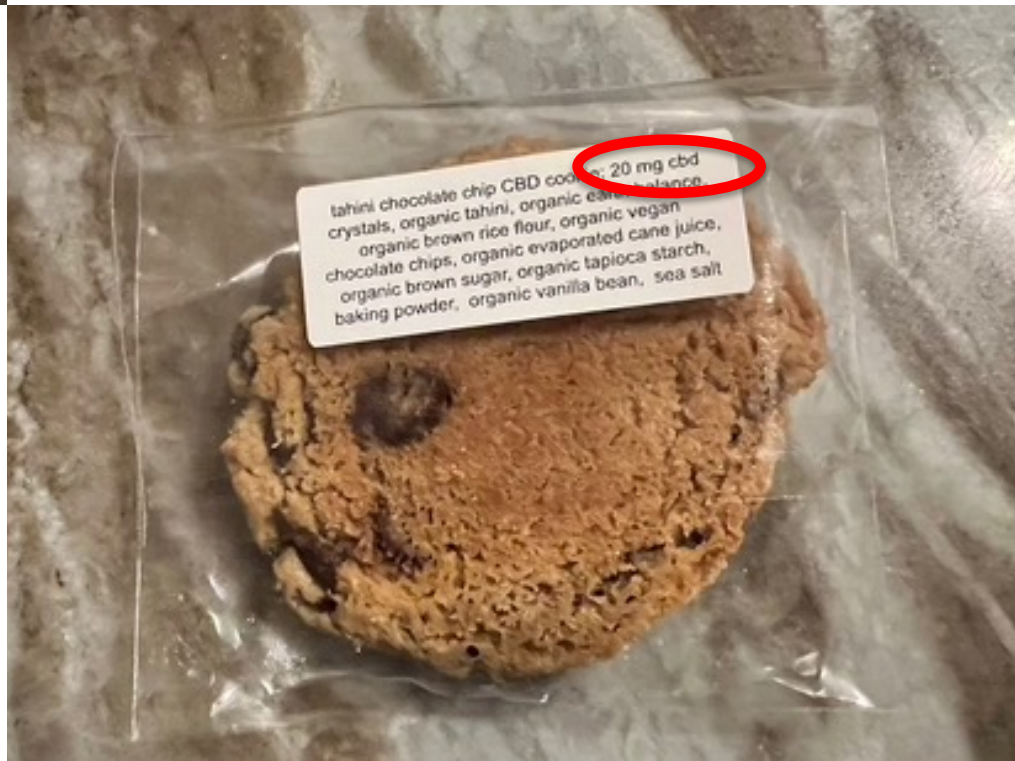
Products containing: Delta-9-THC, Delta-8-THC, CBD, CBN, CBG, etc.



Woman Owned Since 2007
Organic - Vegan - Gluten-Free

BOT
BAKERY

773-495-4615
7100 S South Shore Drive
Chicago, Illinois 60649



tahini chocolate chip CBD cookie: 20 mg cbd
crystals, organic tahini, organic extra virgin olive oil,
organic brown rice flour, organic vegan
chocolate chips, organic evaporated cane juice,
organic brown sugar, organic tapioca starch,
baking powder, organic vanilla bean, sea salt

Effects of Cannabidiol in Adolescent and Young Adult Depressive and Anxiety Disorders: A Systematic Review of Clinical and Preclinical Research

Author(s): Rebecca K. Denson* , Julia Brooks, Graziano Pinna and Natania A. Crane

Volume 13, Issue 3, 2023



Rebecca Denson, MA
Clinical Psychology
PhD Student

- **Preclinical evidence for CBD effects on depression-like behavior mixed**
 - Differ by sex, early life stress, and duration of use
 - No human studies on the effects of CBD on depression to date
- **CBD may reduce symptoms of anxiety in adolescents and young adults, especially for social anxiety disorder**
 - No evidence for anxiolytic effects of CBD in adolescent preclinical models
- **Further research is needed to understand the potential benefits and/or harms of CBD for depression and anxiety disorders**

Conclusions

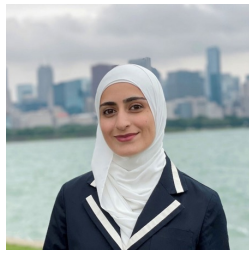
- **Cannabis use is prevalent in the U.S., especially among adults**
- **Cannabis has changed drastically over the past 40 years**
- **Endocannabinoid system is involved in many processes including mood, stress, reward, sleep, and immune function**
- **Endocannabinoid system is implicated in many many health disorders including mood disorders, anxiety disorders, stress disorders, and psychosis**
- **Regular cannabis use, especially during adolescence and young adulthood, is associated with several negative health and mental health outcomes**
 - **Higher THC cannabis associated with higher risk**
 - **Less is known about other cannabinoids**

REWARD LAB

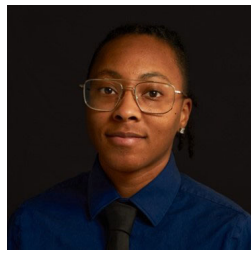
RESEARCH EXAMINING WHAT DRIVES ADDICTION RISK AND COMORBID DEPRESSION



Zoa Glab, BA, BS
Research Assistant



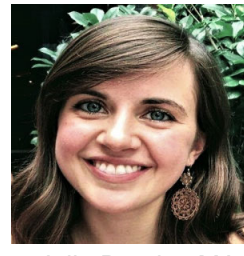
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Anthony Robinson, MA
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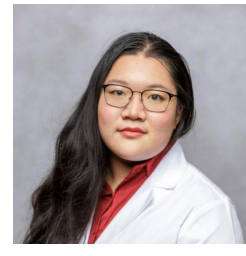
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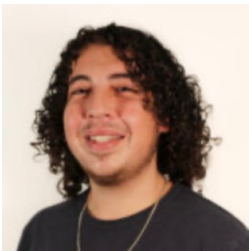
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- Harriet de Wit, PhD- Univ. of Chicago
- K. Luan Phan, MD- Ohio State University
- Scott Langenecker, PhD- Univ. of Utah
- Stewart Shankman, PhD- Northwestern Univ.

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