

# Clinical Perspective of Cannabis

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## Acknowledgments

**No disclosures or potential conflicts of interest related to this topic**

**Medical cannabis is not FDA approved**

**Cannabis remains Schedule I class in the Controlled Substance Act**

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## Objectives

- Describe regulatory climate
- Discuss approach to patient certification process
- Review evidence for medical cannabis
- Identify possible side effects and harms
- Illustrate approach to caring for patients using cannabis



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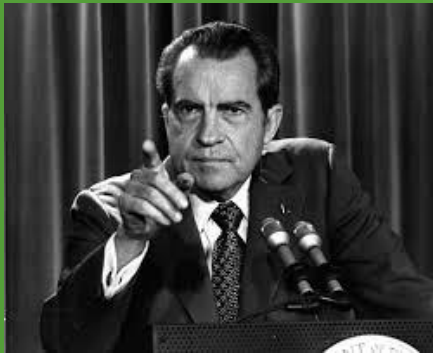
## Cannabis

- Standard terminology within scientific and scholarly communities
- Describes products derived from *cannabis sativa* plant
- For medical, industrial, and social purposes



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# CSA 1970: Marijuana (cannabis) is Schedule I substance



High potential for abuse

No currently accepted medical use in  
 treatment in US

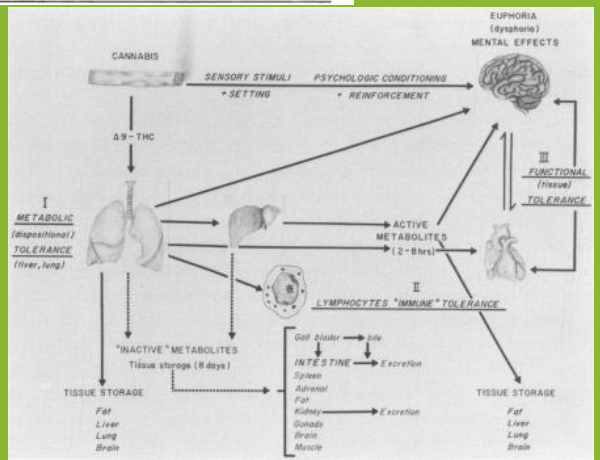
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## marihuana: a signal of misunderstanding


First Report  
 of the National  
 Commission on  
 Marihuana and  
 Drug Abuse  
 March 1972

Shafer Commission, formally  
 known as National  
 Commission on Marijuana  
 and Drug Abuse  
 Appointed by Nixon, chaired  
 Raymond Shafer  
 In 1972 called for  
 decriminalization of  
 marijuana possession in  
 United States  
 Rejected by Nixon  
 administration

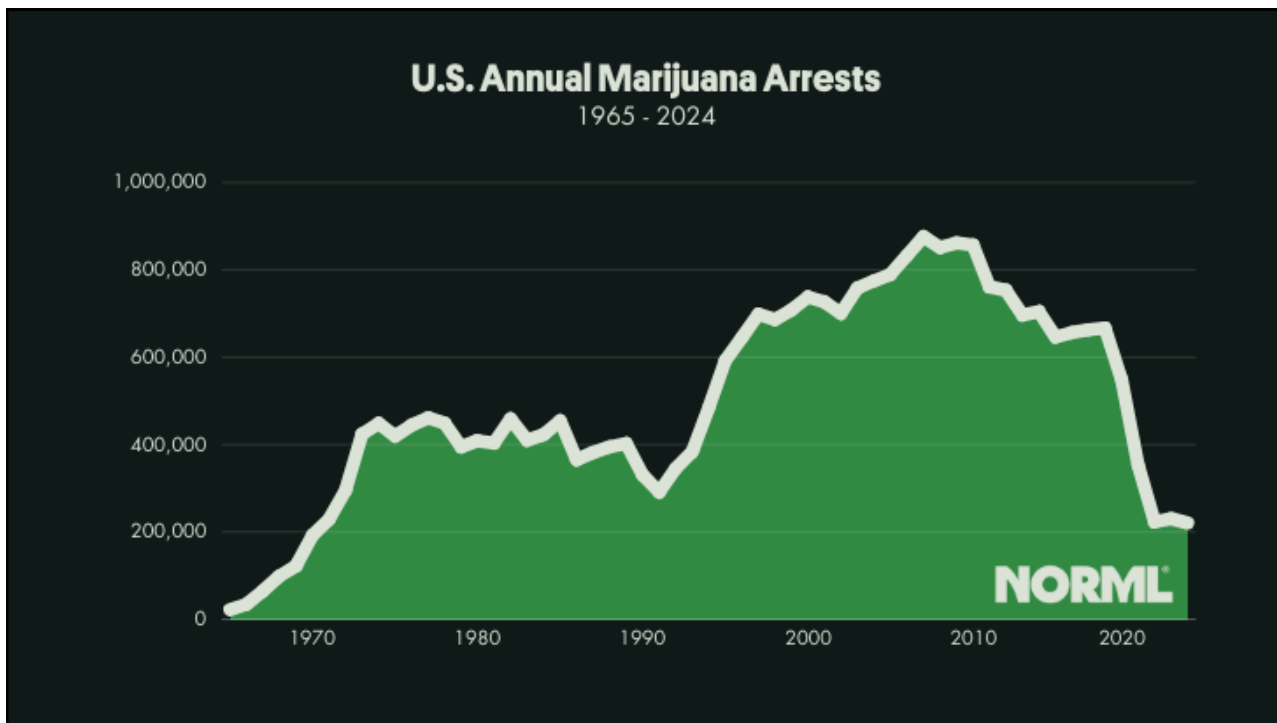
Type of user	Frequency of use	Numbers in total population
Experimental	Once a month or less	24,000,000 people over 11 years of age —14% of all aged 12-17 —15% of adults over 18
Intermittent	2-10 times per month	7,750,000 teenagers and adults
Moderate	11 times per month to once daily	4,500,000 users
Heavy	Several times daily	500,000 users
Very heavy	Almost constantly intoxicated with pot- tent preparations— brains rarely free from drug	"Very small fraction" of the 500,000 heavy users



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<b>Schedule 1</b> <ol style="list-style-type: none"><li>1. Marijuana</li><li>2. Heroin</li><li>3. Mescaline</li><li>4. Lysergic acid diethylamide (LSD)</li><li>5. Methylenedioxymethamphetamine (MDMA)</li><li>6. Methaqualone</li></ol>	<b>Schedule 2</b> <ol style="list-style-type: none"><li>1. Fentanyl</li><li>2. Oxycodone</li><li>3. Morphine</li><li>4. Methylphenidate</li><li>5. Hydromorphone</li><li>6. Amphetamine</li><li>7. Methamphetamine</li><li>8. Pentobarbital</li><li>9. Secobarbital</li></ol>	
<b>Schedule 3</b> <ol style="list-style-type: none"><li>1. Anabolic steroids</li><li>2. Testosterone</li><li>3. Ketamine</li><li>4. Buprenorphine</li></ol>	<b>Schedule 4</b> <ol style="list-style-type: none"><li>1. Diazepam</li><li>2. Alprazolam</li><li>3. Tramadol</li></ol>	

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## ROOTS IN RACISM



**Harry Anslinger, first director Federal Bureau of Narcotics, 1930s:**

“There are 100,000 total marijuana smokers in the US, and most are Negroes, Hispanics, Filipinos, and entertainers. Their Satanic music, jazz and swing, results from marijuana use. This marijuana causes white women to seek sexual relations with Negroes, entertainers and others.”

**John Erlichman, senior Nixon advisor, 1970s (quote from 1990s):**

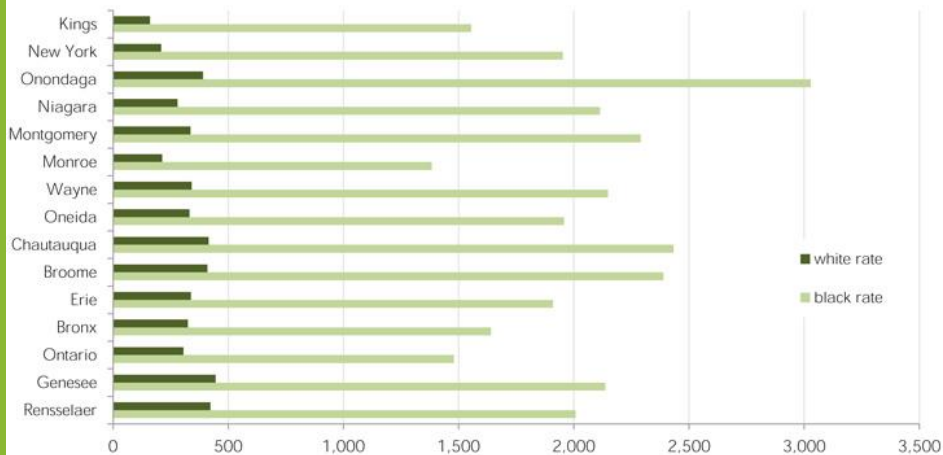
“We knew we couldn’t make it illegal to be against the war or black, but by getting the public to associate the hippies with marijuana and blacks with heroin, and then criminalizing both heavily, we could disrupt those communities. We could arrest their leaders, raid their homes, break up their meetings, and vilify them night after night on the evening news. Did we know we were lying about the drugs? Of course we did.”

**Jeff Sessions, Attorney General, 2016:**

“Good people don’t smoke marijuana.”

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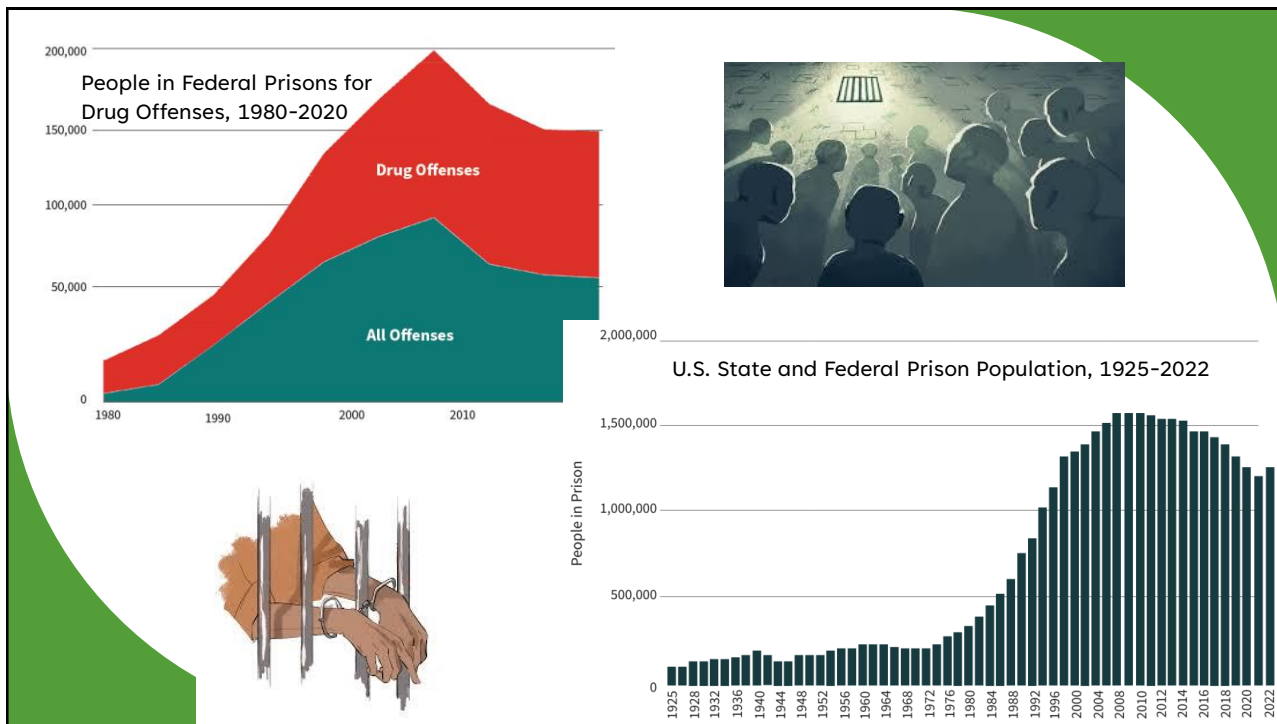
Counties with the Largest Racial Disparity in Marijuana Arrests  
 New York State



NOTE: Population Size > 30,000 and Black Population Percentage Share > 2 percent.  
 Ordered by highest racial disparity (Kings) to 15th highest in New York State (Rensselaer). Rates equivalent to arrests per 100,000 residents in population.  
 Source: FBI/Uniform Crime Reporting. Data include arrests and summonses for P.L. 221.05, 221.10 and 221.15. "White" rates include Latino residents.

NYCLU, 2013.

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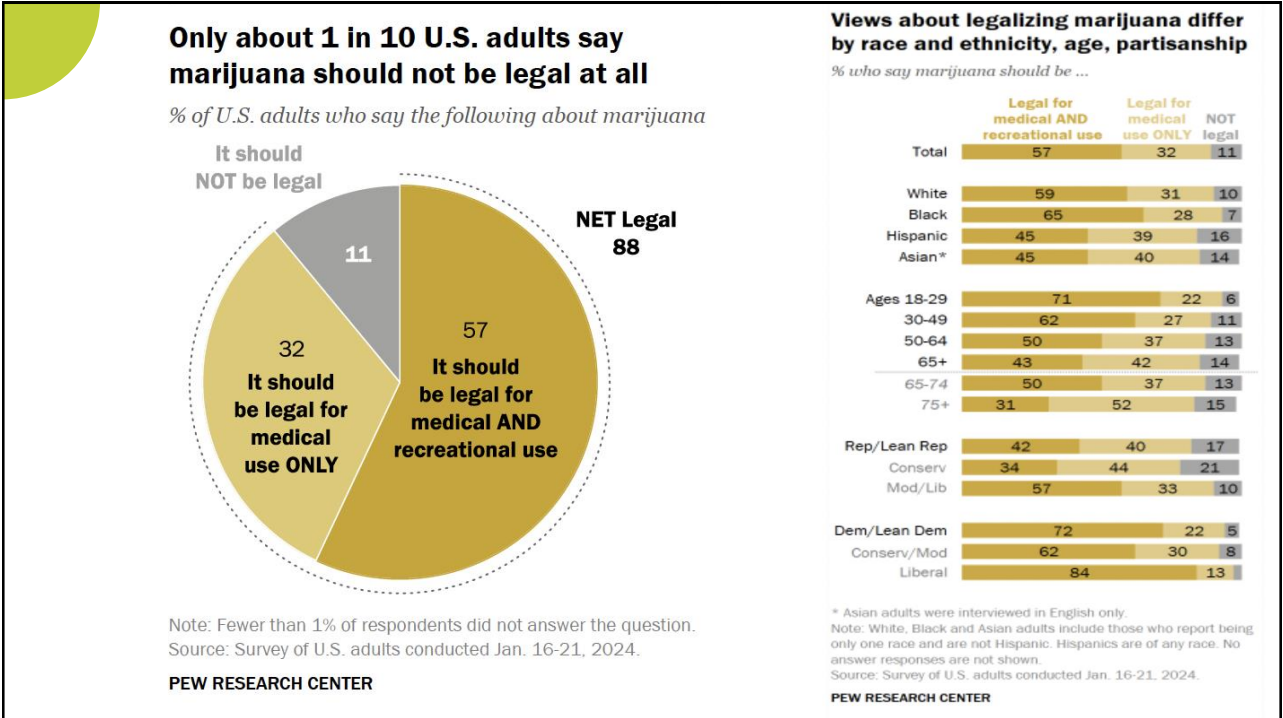


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# 193+ million cannabis users worldwide

~10% fit criteria for cannabis use disorder (CUD)

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## Farm Bill 2014

### Removed hemp from CSA

Hemp = cannabis w/THC content < 0.3% dry weight

Hemp cultivated for production of wide range of products

# FARM BILL

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# THC ANALOGS

2018 Farm Bill Loop Hole:  
*hemp-derived cannabinoids,  
CBD-derived cannabinoids,  
hemp-derived isomers, THC  
isomers, synthetic cannabinoids,  
and semi-synthetic  
cannabinoids.*

DELTA 8 THC

DELTA 9 THC

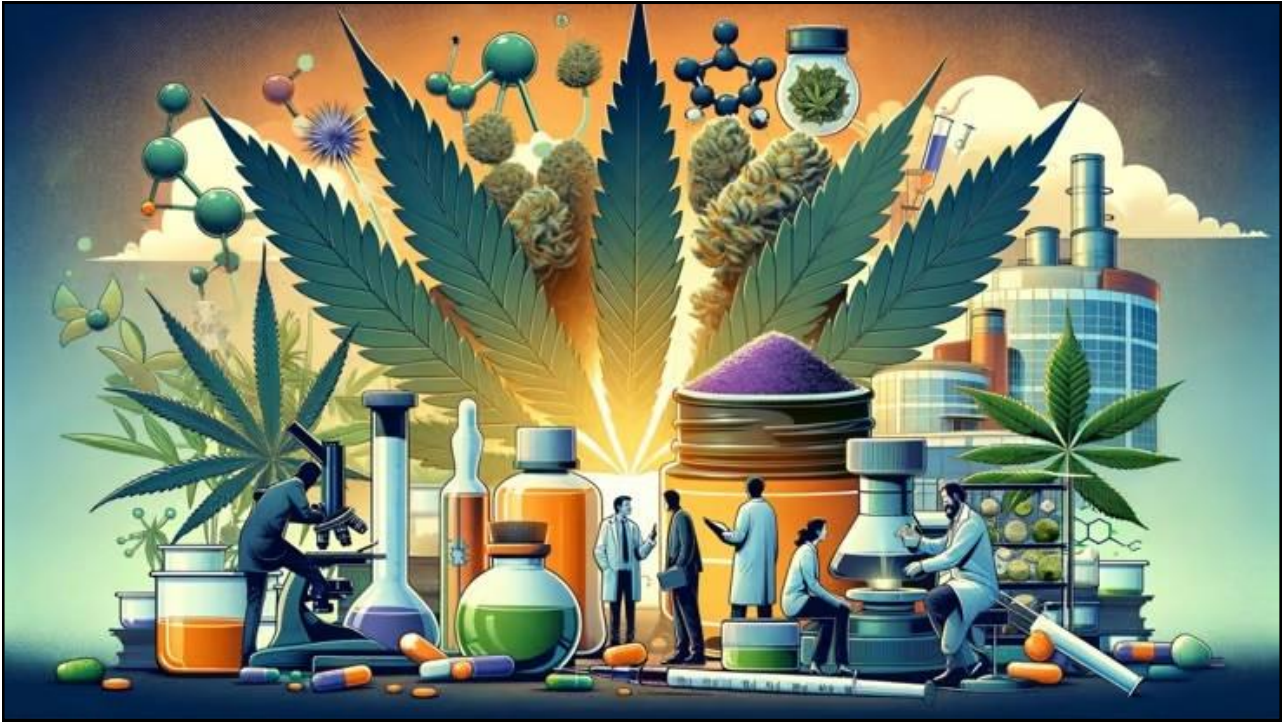
DELTA 10 THC

THC-O

THC-V

THC-P

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Most commonly used federally illegal drug in US, about 19% of Americans (52.2 million) have used at least once since 2021

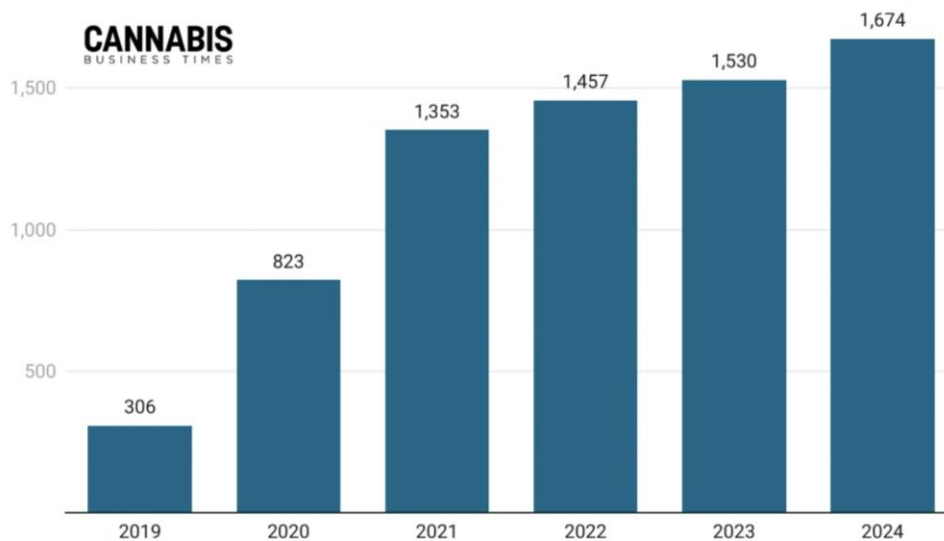


California was 5<sup>th</sup> largest economy in world in 2023, remains world's largest cannabis economy with adult use and medical > \$4.7 billion

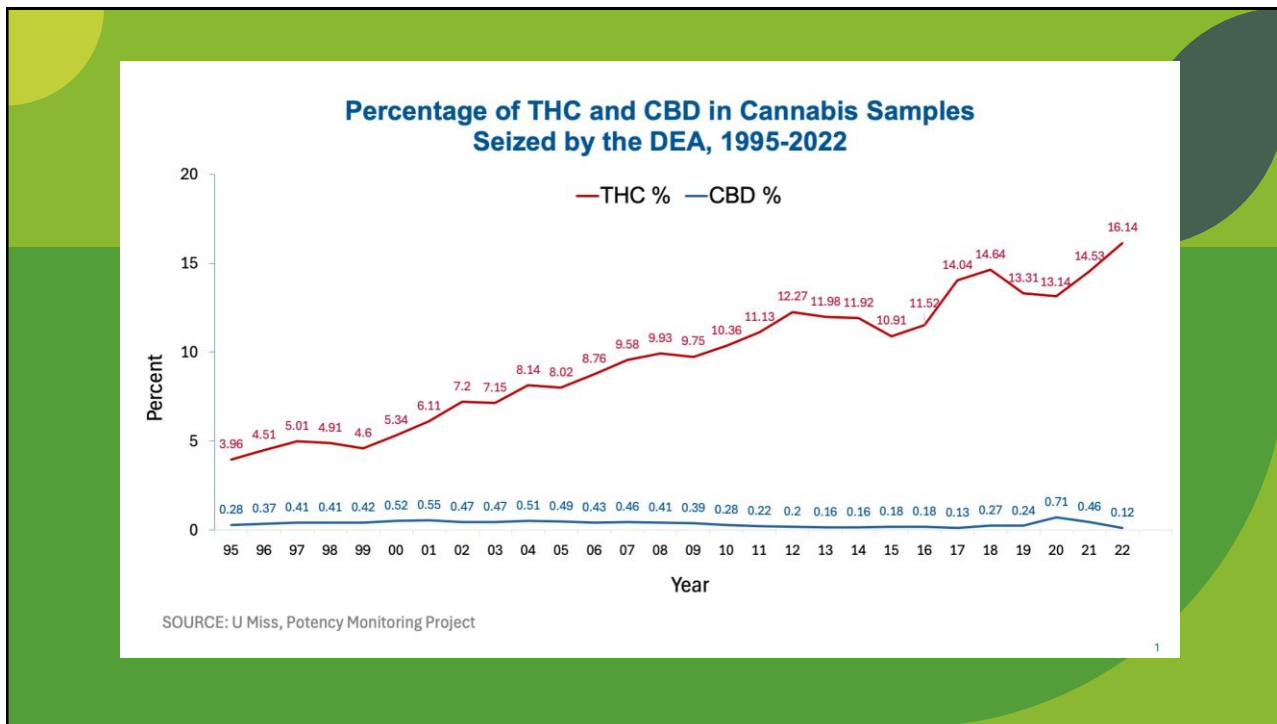
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### Pennsylvania Medical Cannabis Sales

Figures are in millions of dollars. (Pennsylvania dispensaries are projected to record nearly \$1.7 billion in 2024 medical cannabis sales.)




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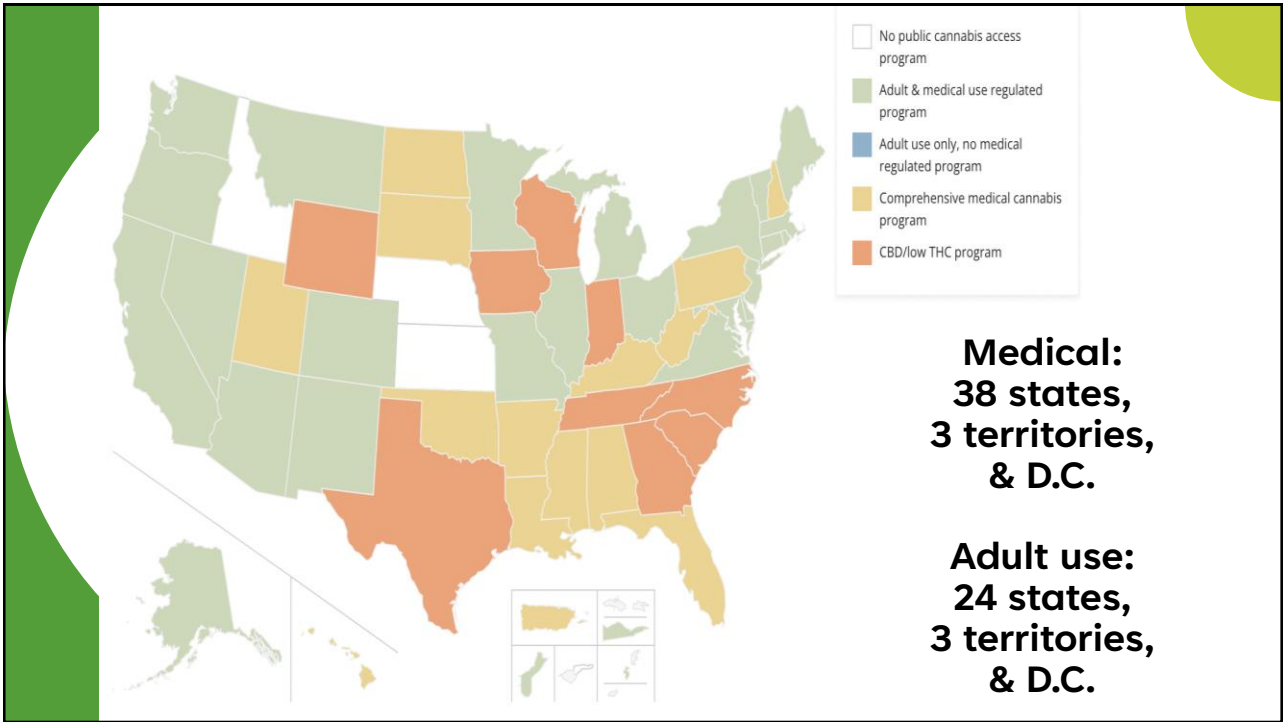
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- Schedule I since Controlled Substances Act (CSA) enacted in 1970
- October 2022, Statement from President Biden on Marijuana Reform,  
“Too many lives have been upended because of our failed approach to marijuana. It’s time that we right these wrongs.”
- Aug 2023, HHS rec’d DEA to reschedule marijuana from I to III under CSA based off FDA review of marijuana
- Reports April 2024 DEA planned to move from schedule I to III



## Rescheduling?

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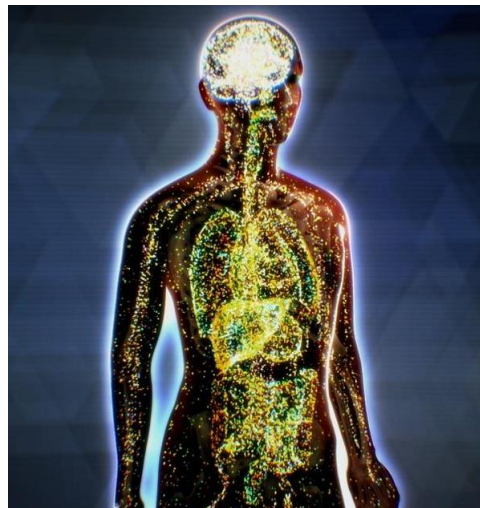
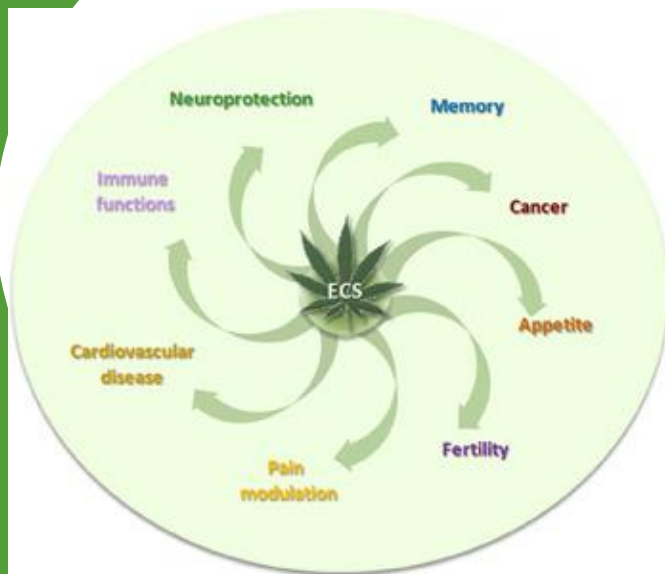
# Cannabis = Controversial Topic

Every guideline or recommendation says...  
Need more research!

US Pharmacopeia 1850-1942

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## Endocannabinoid System(ECS)



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## Endocannabinoid System

Nearly all animals except of Phyla *Protozoa* and *Insecta*

Unknown to scientists until mid-1990s

Maintains homeostasis for number of organ systems

Modulation of nervous and immune systems through complex system of receptors and signaling molecules

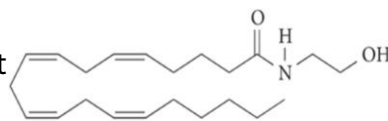
Numerous essential biologic processes, eg, neuronal plasticity, pain, anxiety, inflammation, neuro-inflammation, immune function, metabolic regulation, and bone growth



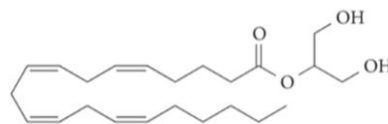
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## Endogenous Cannabinoids

- Bind CB1 and CB2 receptors
  - CB1 – AEA partial agonist & 2-AG full agonist
  - CB2 – 2-AG higher affinity than AEA
- CB1 receptors mediate neurotransmitters by inhibiting presynaptic release
- CB2 receptors up/down regulate cytokine release
  - ↓ Th1 cytokines II-2, IFN $\gamma$ , TNF $\alpha$
  - ↑ Th2 cytokines II-5, II-6, II-10
- Breakdown AEA w/fatty acid amide hydrolase (FAAH) & 2-AG w/monoacylglycerol lipase (MAGL)



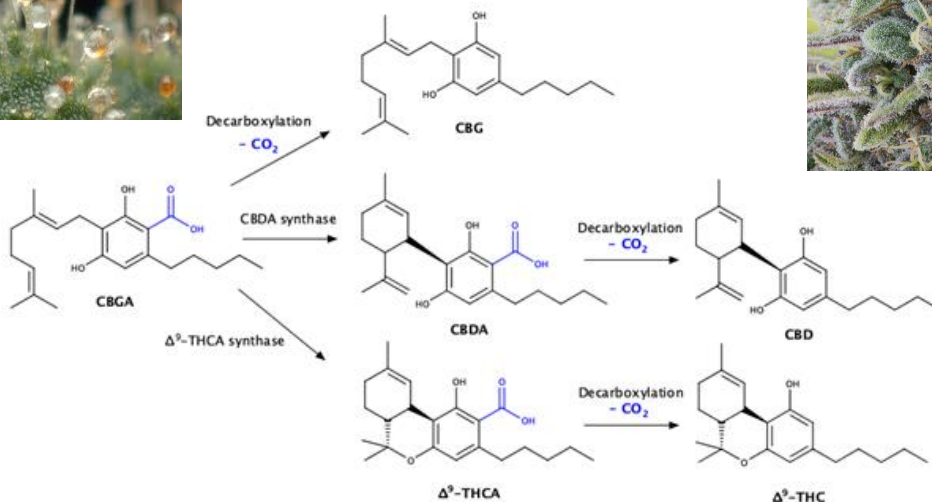
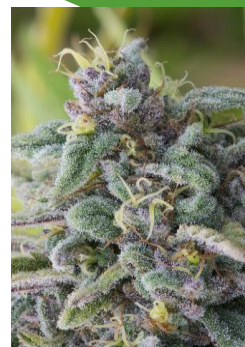
Arachidonoyl ethanolamide (AEA)



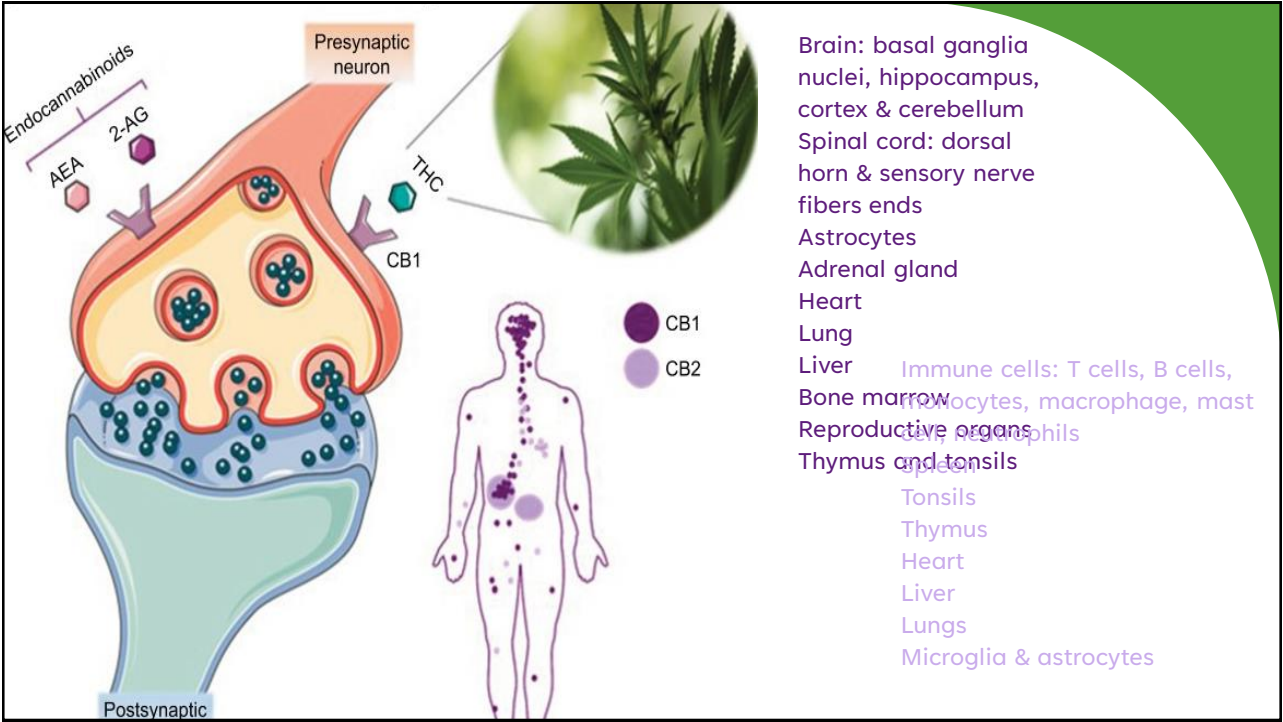
2-Arachidonoyl glycerol (2-AG)

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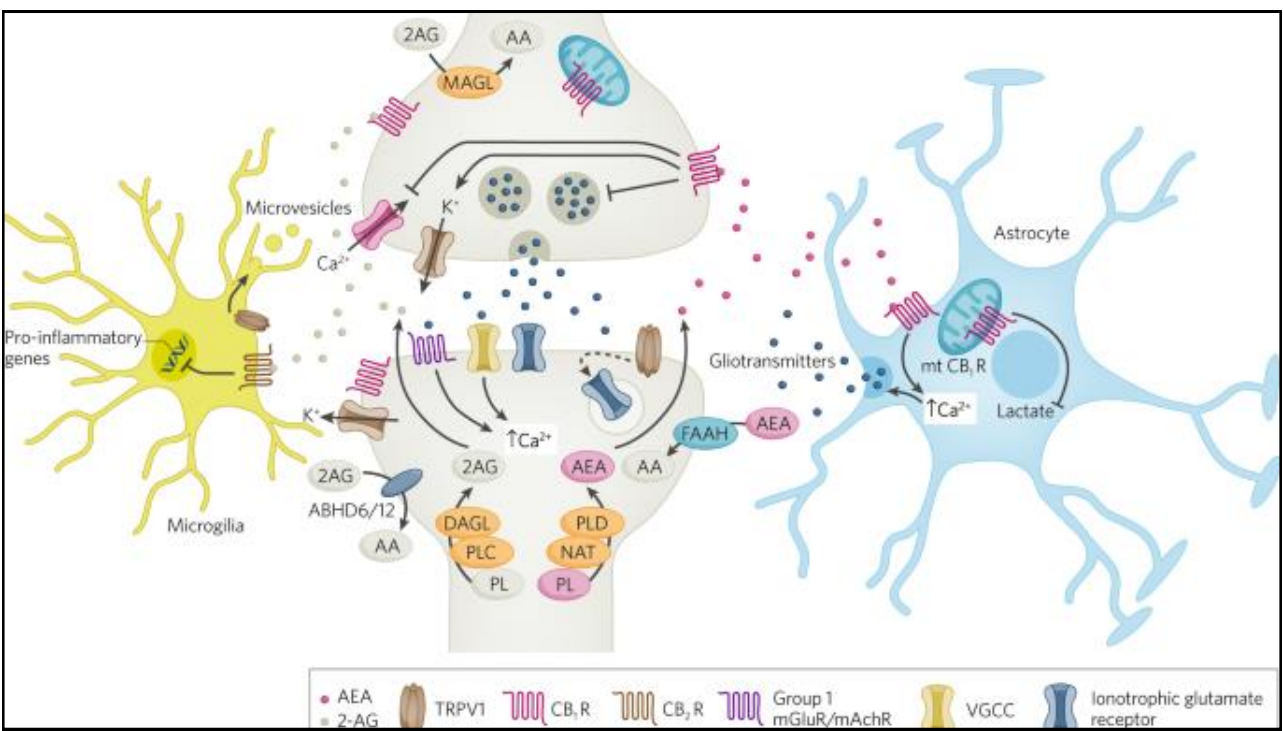
## Cannabigerolic acid (CBGa)



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## Major Cannabinoids

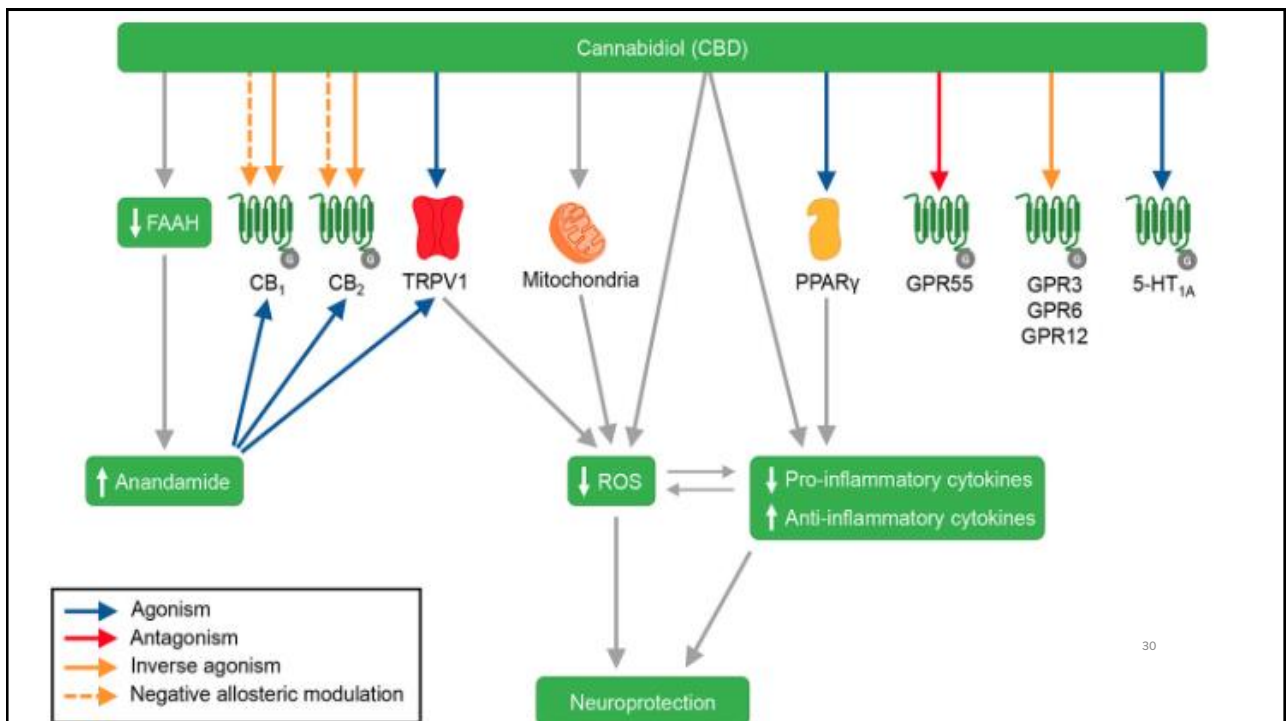
### $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC) – discovered 1964

Psychoactive effects, non-psychoactive THCA precursor  
Partial agonist CB1 and CB2; mimics AEA and 2-AG  
Allosteric modulator delta & kappa opioid receptors  
Agonist GPR55, GPR18, TRPV2, TRPV3, TRPV4, TRPA1; antagonist TRPM8, 5HT<sub>3A</sub>  
Anti-inflammatory, neuroprotective, analgesic, antiemetic  
11- OH -THC, metabolite s/p CYP3A4 & CYP2C19, ↑ potency

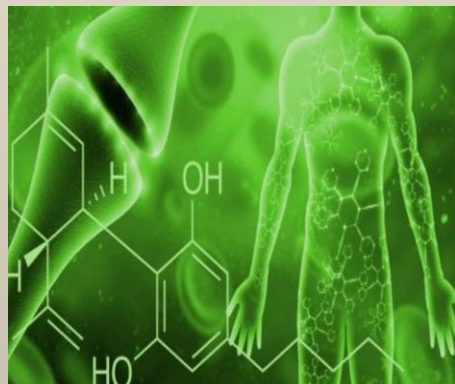
### Cannabidiol (CBD) – discovered 1940

Non-intoxicating, no significant affinity for binding sites of CB1 or CB2  
Negative allosteric modulator CB1 and CB2  
Inhibits cellular uptake of anandamide (AEA)  
Activates A<sub>1A</sub> adenosine receptors  
Blocks formation of THC metabolite, potent CYP450 inhibitor  
Pleiotropic

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Cannabinol (CBN) –weak agonist CB1, high affinity CB2, potent agonist TRPA1 and antagonist TRPM8

Cannabigerol (CBG) -low affinity CB1 and CB2, inhibits anandamide (AEA) uptake, possible activation  $\alpha$ 2 adrenergic receptor, block  $5HT_{1A}$ , TRPV1 & TRPV2 agonist, potent TRPM8 agonist, potent TRPA1 agonist

Cannabichromene (CBC) – no significant CB1/CB2 affinity, inhibits anandamide uptake, potent agonist TRPA1 channels, can activate TRPV3 & TRPV4, block TRPM8

$\Delta^9$ -Tetrahydrocannabivarin ( $\Delta^9$  THCV)- antagonist/inverse agonist CB1 (low dose) with agonism higher dose?, CB2 partial agonist, partial agonist GPR55, activate  $5HT_{1A}$

Cannabivarin (CBV) – unknown pharmacology

Cannabidivarin (CBDV) – weak affinity CB1 and CB2, potent activation TRPA1 channel, weak agonist TRPV1, TRPV2, and TRPV3 cation channel

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## How do physicians certify patients for cannabis?



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# Laws vary by state for medical use

Patient under care of physician  
Multitude of diagnoses recognized  
Exam depends on state  
Copies of medical records



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## PA Act 16 legislatively-approved diagnoses

Amyotrophic Lateral Sclerosis;  
**Anxiety (2019')**;  
Autism;  
Cancer, including remission therapy;  
**Chronic hepatitis C (2021)**;  
Crohn's Disease;  
**Dyskinetic and spastic movement disorders (2018)**;  
Damage to the nervous tissue of the spinal cord with objective neurological indication of intractable spasticity, and other associated neuropathies;  
Epilepsy;  
Glaucoma;  
HIV / AIDS;  
Huntington's Disease;  
Inflammatory Bowel Disease

Intractable Seizures;  
Multiple Sclerosis;  
**Neurodegenerative Disorders (2018)**;  
Neuropathies;  
**Opioid Use Disorder for which conventional therapeutic interventions are contraindicated or ineffective, or for which adjunctive therapy is indicated in combination with primary therapeutic interventions (2018)**;  
Parkinson's Disease;  
Post-traumatic Stress Disorder;  
Severe chronic or intractable pain of neuropathic origin or severe chronic or intractable pain;  
Sickle Cell Anemia;  
Terminal Illness; and/or  
**Tourette Syndrome (2019)**

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**Marinol<sup>®</sup> or Syndros<sup>®</sup> (dronabinol) semi-synthetic  $\Delta$ -9 THC liquid Schedule III**  
FDA-approved for **chemotherapy-related nausea/vomiting & AIDS-associated anorexia/weight loss**

**Cesamet<sup>®</sup> (nabilone) synthetic  $\Delta$ -9 THC powder Schedule II**  
FDA-approved for **chemotherapy-related nausea/vomiting**

**Epidiolex (purified whole plant CBD extract) Schedule V**  
FDA approved for **Dravet syndrome** and **Lennox-Gastaut syndrome**, and neonatal hypoxic-ischemic encephalopathy.

**Sativex<sup>®</sup> (nabiximols) – no FDA approval**  
Standardized whole-plant extract, 25+ countries, metered dose oromucosal spray for **cancer associated pain** and **MS spasticity/symptoms**

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# Cannabis-based medical products (CBMPs)

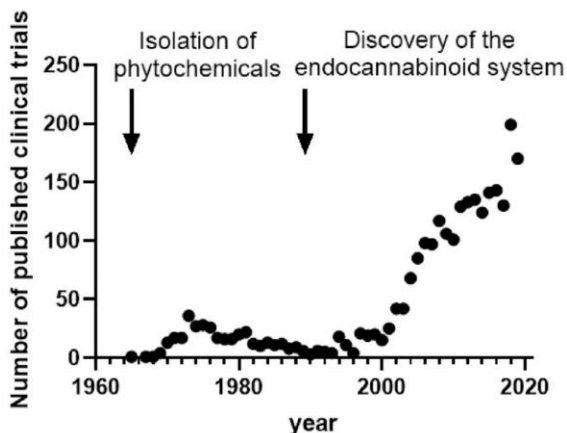


Fig. 1. Number of published clinical trials.

Vary from purified single compounds (THC or CBD) to complex mixtures of hundreds molecules, in multiple formulations with multiple delivery mechanisms.



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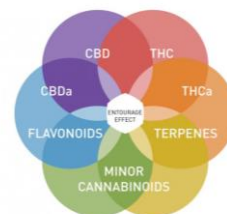
## The Entourage Effect

### Terpenoids

- Limonene (citrus)
- Myrcene (hops)
- Pinene (pine)
- Linolool (lavender)
- Beta Caryophyllene (pepper)
- Terpeneol (lilac)
- Nerolidol (ginger)
- Borneol (rosemary)
- Eucalyptol (eucalyptus)

### Cannabinoids

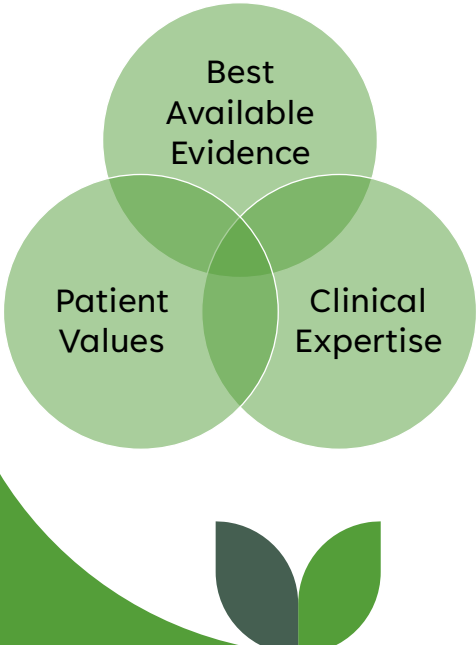
- Cannabigerol (CBG)
- Cannabinol (CBN)
- $\Delta^9$ -Tetrahydrocannabivarin ( $\Delta^9$  THCV)
- Cannabichromene (CBC)
- Cannabivarin (CBV)
- Cannabidivarin (CBDV)
- 100+ cannabinoids



### Flavonoids

- Cannaflavins A, B, & C
- Beta-sitosterol
- Vitexin
- Isovitexin
- Apigenin
- Kaempferol
- Quercetin
- Luteolin
- Orientin

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## How to navigate evidence-based practice for patients using cannabis?


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## Pain?

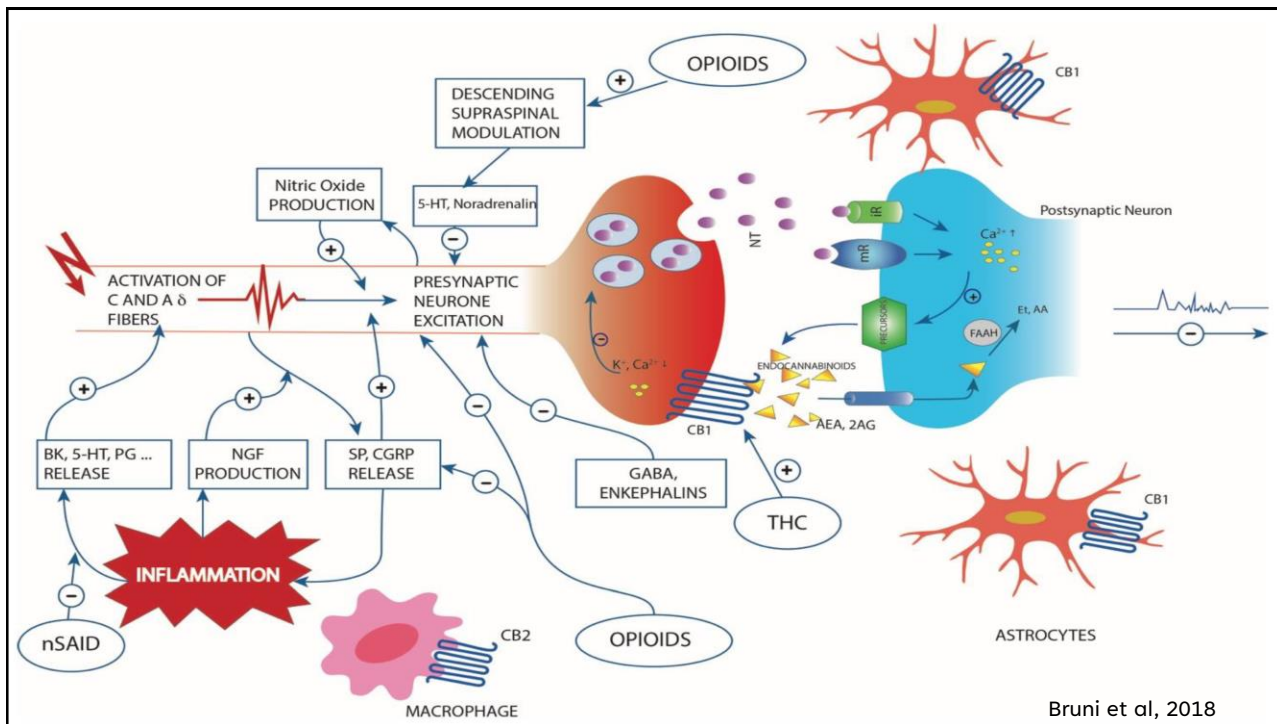
**JAMA 2015 (79 trials, 6462 participants)**  
**Moderate-quality evidence** to support use of cannabinoids in **chronic pain and spasticity**

**NASEM 2017 (consensus report)**  
There is **conclusive or substantial evidence** that cannabis or cannabinoids are effective for the treatment for **chronic pain in adults**. **Moderate evidence** for improving short-term sleep outcomes in individuals with sleep disturbance associated with OSA, fibromyalgia, chronic pain, & MS.

**BMJ 2021 (32 trials, 5174 participants)**  
Oral cannabinoids w/ moderate-high certainty evidence of **small to very small** improvement in pain, physical function, and sleep in **chronic pain**



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## Anxiety?

APA 2019: There is no current scientific evidence that cannabis is in any way beneficial for the treatment of any psychiatric disorder. In contrast, current evidence supports, at minimum, a strong association of cannabis use with the onset of psychiatric disorders. Adolescents are particularly vulnerable to harm, given the effects of cannabis on neurological development.

- No relationship between cannabis use and anxiety disorders (5 studies)
- Self-medication hypothesis (8 studies)
- Cannabis use causes anxiety (9 studies)
- Anxiety disorders predispose to cannabis use (8 studies)
- Common factor theory (5 studies)

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## Opioid Use Disorder?

**CBD** (Epidiolex™) (dbRCT, n=42) reduced cue-induced craving and anxiety, also heart rate and cortisol levels, in heroin withdrawal (Hurd et al., 2019)

**Dronabinol** (dbRCT, n=60) reduced severity of early opioid withdrawal but had no effect on treatment retention with naltrexone (Bisaga et al., 2016)

**Dronabinol** (dbRCT, n=12) produced modest opioid withdrawal suppression and demonstrated abuse liability (Lofwall et al. 2016)

**ASAM 2020  
Healthcare  
professionals  
should not  
recommend  
cannabis use for  
treatment of OUD**

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## ASAM 2020 Policy Statement Updates

- Cannabis used for medical purposes should be rescheduled from Schedule 1 of the Controlled Substances Act to promote more clinical research and Food and Drug Administration (FDA) oversight.
- Cannabis and cannabis-derived products recommended for medical indications should be subject to FDA review and approval to ensure their safety and effectiveness.
- Healthcare professionals who recommend non-FDA-approved cannabis products for medical use should be required to complete training on risk mitigation and the prevention, diagnosis, and management of cannabis use disorder and other substance use disorders.
- Healthcare professionals who recommend non-FDA approved cannabis should do so only within the context of a bona fide patient-clinician relationship and only if there is evidence that the potential benefits outweigh the potential harms.
- Non-FDA-approved cannabis recommended by clinicians should be reported to Prescription Drug Monitoring Programs (PDMPs).

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# Patient-centered care



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Patients are using cannabis and may disclose this information, ask!  
Lack of guidance from healthcare professionals can be problematic  
Safety of cannabis use should be assessed regardless of legal or illicit source  
Screen for precautions and contraindications, possible CYP450 interactions

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## THINGS TO CONSIDER

Can medical cannabis be safely used by this patient?

What strategies can be used to mitigate potential harms of medical cannabis?

Safety-focused framework for medical cannabis initiation and utilization.

Provide clear recommendations, precautions, contraindications, drug interactions.

Risk mitigation – chemovar selection, route of admin, and dosing

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## Pharmacokinetics

Lipophilic, crosses BBB and placenta, in breast milk

95-99% protein bound

Metabolized in the liver by cytochrome p450 (drug interactions)

THC – CYP2C9 & CYP3A4

CBD – CYP2CP & CYP3A4 & CPY2C19

Highly variable half-life and dose response

Long term storage in adipose tissue – no acute testing for intoxication

Elimination: feces (65%) and urine (25%) also sweat, oral fluid, hair

Variable elimination, may take days to weeks



CANN-DIR CANNabindoid Drug Interaction  
Review: <https://cann-dir.psu.edu>

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## Common Adverse Reactions

### THC

- Drowsiness, fatigue
- Dry mouth
- Cough, phlegm, bronchitis (inhaled)
- Anxiety, confusion, cognitive effects, panic
- ↑ HR, ↑ BP, +/- cardiac contractility
- Nausea
- Blurred vision, irritated eyes
- Headache

### CBD

- Somnolence
- Gastrointestinal distress
- Irritability, agitation
- Liver injury
- Male reproductive toxicity, infertility
- Drug interactions (CYP450)
- Unknowns

Many side effects are THC dose dependent & mitigated by slow titration or dose reduction.

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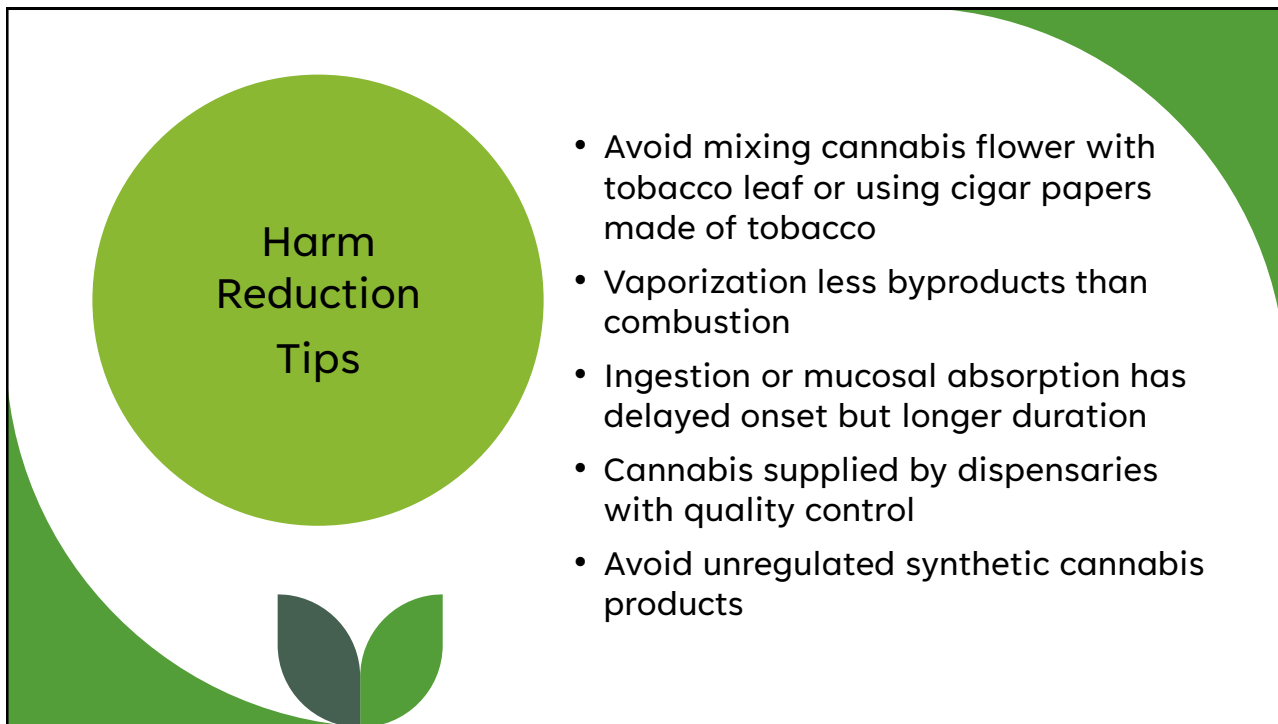
## Caution Cannabis Use



Uncontrolled mental health conditions, especially w/risk for psychosis or schizophrenia  
Unstable cardiac, pulmonary, hepatic, and/or renal function  
Currently pregnant, breastfeeding, or planning to conceive  
Exposure during brain development, children and adolescents  
If harmful CYP450 interactions occur

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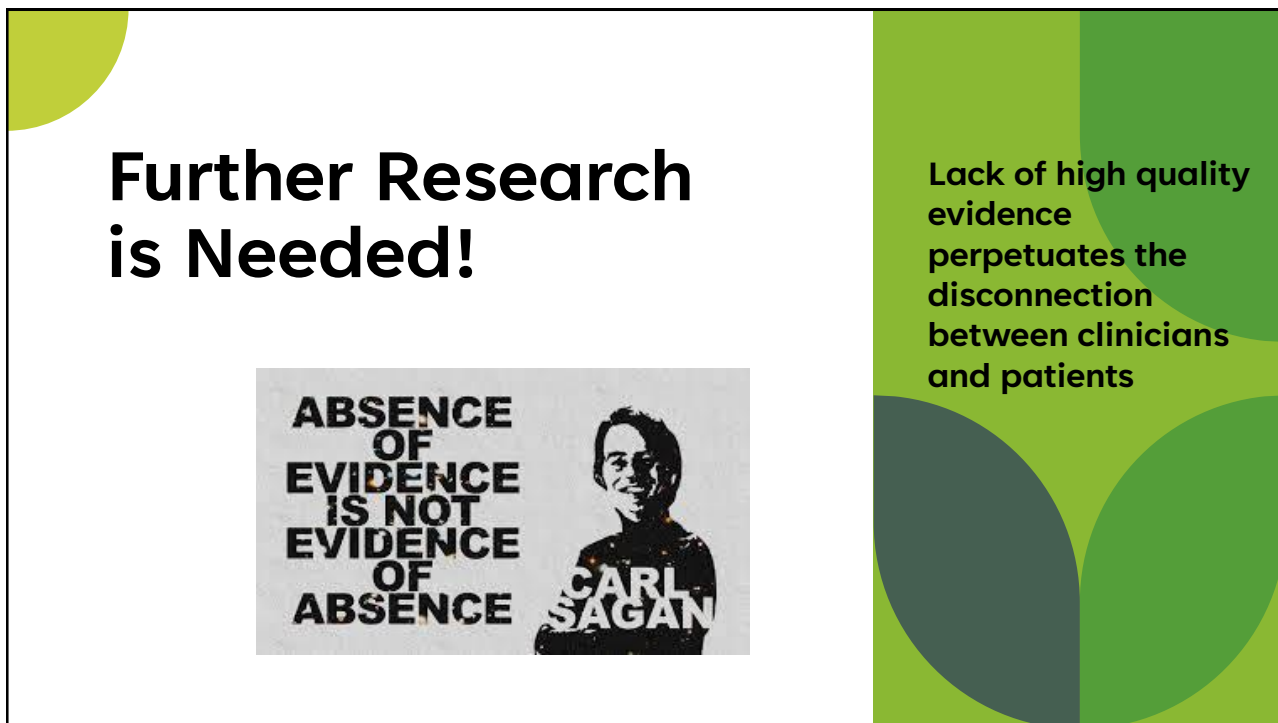


A slide titled "Harm Reduction Tips" with a green circular graphic on the left containing the title. To the right is a bulleted list of six tips. At the bottom center is a small graphic of two leaves.

## Harm Reduction Tips

- Avoid mixing cannabis flower with tobacco leaf or using cigar papers made of tobacco
- Vaporization less byproducts than combustion
- Ingestion or mucosal absorption has delayed onset but longer duration
- Cannabis supplied by dispensaries with quality control
- Avoid unregulated synthetic cannabis products

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A slide with the heading "Further Research is Needed!". Below the heading is a quote by Carl Sagan: "ABSENCE OF EVIDENCE IS NOT EVIDENCE OF ABSENCE". To the right of the quote is a small portrait of Carl Sagan. On the right side of the slide, there is a vertical green bar with white text: "Lack of high quality evidence perpetuates the disconnection between clinicians and patients".

## Further Research is Needed!

**ABSENCE OF EVIDENCE IS NOT EVIDENCE OF ABSENCE**

**CARL SAGAN**

Lack of high quality evidence perpetuates the disconnection between clinicians and patients

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# Thank you kindly!

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