

# Medical and Legalized Marijuana

*From pain relief to recreational use...*

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Dr. White, a practicing family physician in Kansas City, MO, walks into an examination room and meets a 31 y/o female named Rachel. Rachel has a 3 year history of multiple sclerosis (MS). She was born in KC, MO and now lives in California. She has been in town visiting family and friends for the past 2 weeks.

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Ethical

Clinical

Legal

# Session Objectives

After attending the CME session on Medical and Legalized Marijuana, you will be able to:

1. Compare and contrast the known effects of tetrahydrocannabinol (THC) and cannabidiol (CBD).
2. Identify symptoms that may be relieved by treatment with marijuana or other cannabinoids
3. Identify applicable medical marijuana laws in states in which you have a medical license.

# Exogenous cannabinoids

- Extracted from the marijuana plant *Cannabis sativa* or *Cannabis indica*



- Over 100 cannabinoids have been identified in the marijuana plant

## Tetrahydrocannabinol (THC)

- Major psychoactive component in marijuana
- *Cannabis sativa*

## Cannabidiol (CBD)

- Doesn't produce any of the psychoactive effects of THC
- Doesn't make you high, paranoid, hallucinate
- *Cannabis indica*

# Receptors that bind exogenous cannabinoids

## CB1 receptors

- CNS neurons in the basal ganglia, limbic system, cerebellum, cortex
- Activation causes psychotropic effects, dependence, and cognitive impairment

## CB2 receptors

- Distribution predominantly in cells and tissues of the immune system (thymus, tonsils, B & T lymphocytes, macrophages, monocytes, NK cells)
- Expressed in microglial cells (CNS version of immune cells) during various states of inflammation
- Activation largely devoid of psychotropic effects

Serotonin receptors, GPR-55, TRVP1 receptor, others...

# Effects of THC and CBD

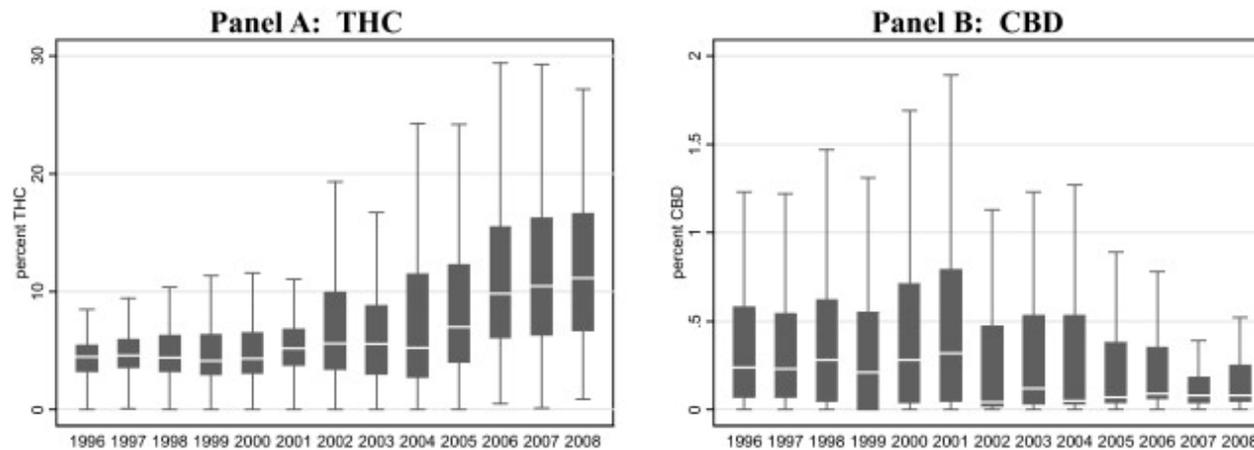
## THC

- CB1 and CB2 receptor partial agonist
- Responses strongly influenced both by the expression level and signaling efficiency of CB1/CB2 receptors and by ongoing endogenous cannabinoid release

## CBD

- High potency as an antagonist of CB1/CB2 receptor agonists in CB1- and CB2-expressing cells or tissues
- Antagonist actions helps explain its ability to inhibit evoked immune cell migration
- May prevent THC from acting as agonist (hallucinogenic effects)

# What are the components of marijuana?



Heterogeneity in the composition of marijuana seized in California

- THC levels have risen consistently since the mid 1990s
- As the desire for marijuana with high hallucinogenic effects increased, CBD levels decreased

## CBD may be the real star

- CBD has gained particular interest recently as a constituent in the medication Sativex, which has been found to alleviate spasticity associated with MS, cancer pain in opioid-treated patients, and marijuana withdrawal
- CBD is under investigation in assorted clinical trials as an anti-epileptic
- Preclinical studies reported that CBD elicits anticonvulsant, anti-inflammatory, and anti-tumorigenic effects.
- <http://www.ncbi.nlm.nih.gov/pubmed>

Clinical conditions with symptoms that may be relieved by treatment with marijuana or other cannabinoids

# Glaucoma

- Marijuana can cause a transient decrease in intraocular pressure (1970s, 1980s)
- Other, standard treatments are currently more effective
- More research is needed to establish whether molecules that modulate the endocannabinoid system may not only reduce intraocular pressure but also provide a neuroprotective benefit in patients with glaucoma

# Nausea

- Treatment of the nausea and vomiting associated with chemotherapy was one of the first medical uses of THC and other cannabinoids
- THC is an effective antiemetic agent in patients undergoing chemotherapy, but patients often state that marijuana is more effective in suppressing nausea
- Other, unidentified compounds in marijuana may enhance the effect of THC (as appears to be the case with THC and CBD)
- Paradoxically, increased vomiting (hyperemesis) has been reported with repeated marijuana use

# AIDS-associated anorexia and wasting syndrome

- Smoked or ingested cannabis improves appetite and leads to weight gain and improved mood and quality of life among patients with AIDS
- However, there is no long-term or rigorous evidence of a sustained effect of cannabis on AIDS-related morbidity and mortality, with an acceptable safety profile, that would justify its incorporation into current clinical practice for patients who are receiving effective antiretroviral therapy
- Data from the few studies that have explored the potential therapeutic value of cannabinoids for this patient population are inconclusive

# Chronic pain

- Marijuana has been used to relieve pain for centuries
- Studies have shown that cannabinoids acting through central CB1 receptors and possibly peripheral CB1 and CB2 receptors play important roles in modeling nociceptive responses in various models of pain
- Marijuana has been shown to be effective in ameliorating neuropathic pain at very low levels of THC (1.29%)
- Both marijuana and dronabinol (synthesized THC) decrease pain, but dronabinol may lead to longer-lasting reductions in pain sensitivity and lower ratings of rewarding effects

# Inflammation

- THC and CBD have substantial anti-inflammatory effects because of their ability to induce apoptosis, inhibit cell proliferation, and suppress cytokine production
- CBD has attracted particular interest as an anti-inflammatory agent because of its lack of psychoactive effects
- Animal models have shown that CBD is a promising candidate for the treatment of rheumatoid arthritis and for inflammatory diseases of the gastrointestinal tract (e.g., ulcerative colitis and Crohn's disease)

# Multiple sclerosis

- Nabiximols (Sativex), an oromucosal spray that delivers a mix of THC and CBD, appears to be an effective treatment for neuropathic pain, disturbed sleep, and spasticity in patients with multiple sclerosis
- Sativex is available in the United Kingdom, Canada, and several other countries and is currently being reviewed in phase 3 trials in the United States in order to gain approval from the Food and Drug Administration
- The National Multiple Sclerosis society supports the rights of people with MS to work with their MS health care providers to access marijuana for medical purposes in accordance with legal regulations in those states where such use has been approved ([www.nationalmssociety.org](http://www.nationalmssociety.org))

# Epilepsy

- In a recent small survey of parents (19 families) who use marijuana with a high CBD content to treat epileptic seizures in their children:
  - 11% reported complete freedom from seizures
  - 42% reported a reduction of more than 80% in seizure frequency
  - 32% (6 families) reported a reduction of 25 to 60% in seizure frequency
- Although such reports are promising, insufficient safety and efficacy data are available on the use of cannabis botanicals for the treatment of epilepsy
- There is increasing evidence of the role of CBD as an antiepileptic in animal models

# Clinical trials

- 80 total studies for cannabidiol (CBD)
- 132 total studies for tetrahydrocannabinol (THC)
- Conditions involved
  - Epilepsy
  - Substance abuse
  - Pain
  - Autoimmune diseases
  - Demyelinating diseases
  - Multiple sclerosis
  - Psychiatric disorders
- [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

## 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.

Compared to adverse effects from current therapy options?

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# Marijuana in the 1600-1800s

American production of hemp was encouraged by the government in the 17th century for the production of rope, sails, and clothing

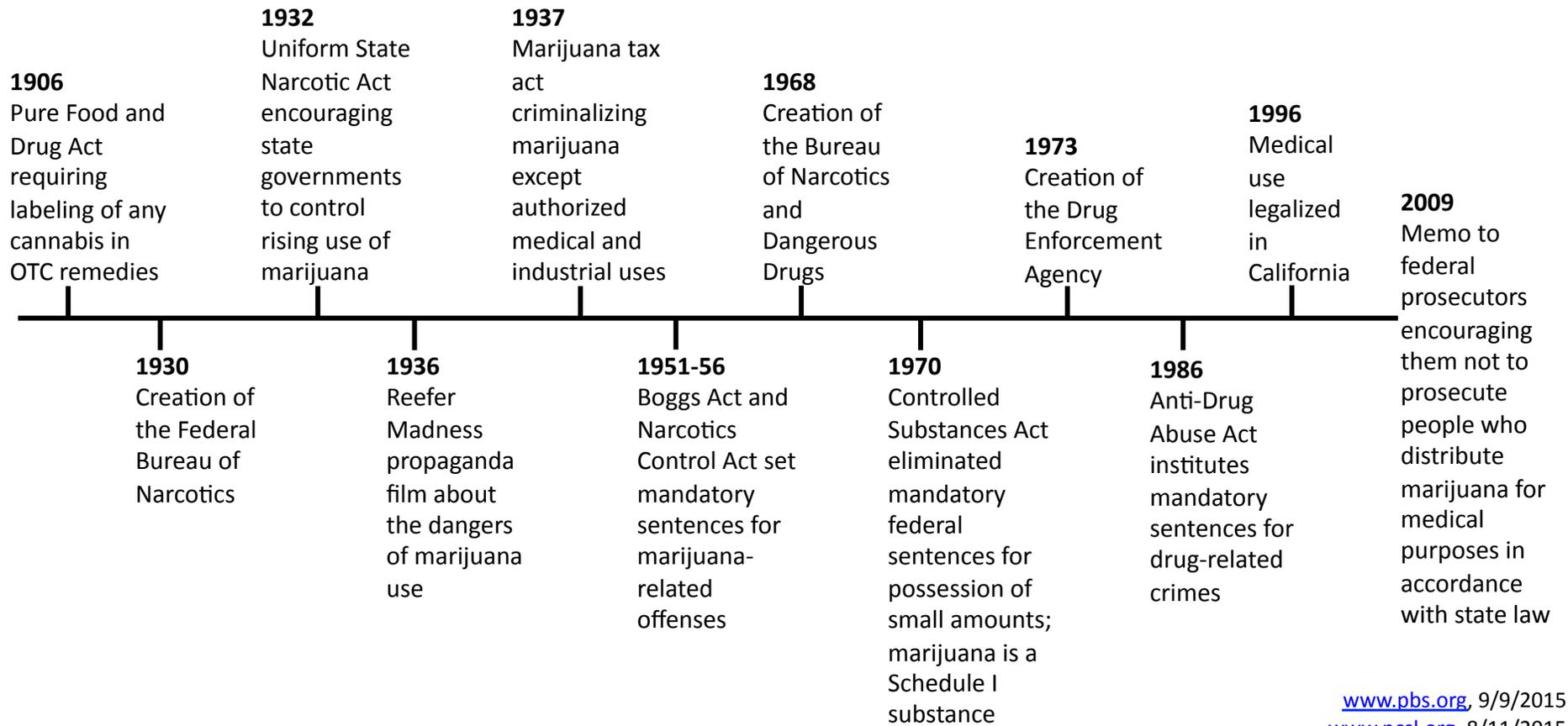


In 1619 the Virginia Assembly passed legislation requiring every farmer to grow hemp. Hemp was allowed to be exchanged as legal tender in Pennsylvania, Virginia, and Maryland

Domestic production flourished until after the Civil War, when imports and other domestic materials replaced hemp for many purposes

In the late nineteenth century, marijuana became a popular ingredient in many medicinal products and was sold openly in public pharmacies

# Brief history of marijuana regulation



# Federal perspective – a mixed message?

Marijuana is a Schedule I substance under the Controlled Substances Act

- Considered to have a high potential for dependency and no accepted medical use
- Distribution of marijuana is a federal offense.

October 2009

- Obama Administration sends a memo to federal prosecutors encouraging them not to prosecute people who distribute marijuana for medical purposes in accordance with state law

August 2013

- USDOJ announces update to their marijuana enforcement policy
- USDOJ expects states like CO and WA to create "strong, state-based enforcement efforts.... and will defer the right to challenge their legalization laws at this time."
- USDOJ reserves the right to challenge the states at any time they feel it's necessary.

# What is legal and what is not?

National Conference of State Legislatures – [www.ncsl.org](http://www.ncsl.org)

- State medical marijuana/cannabis program laws
- Limited access marijuana product laws (low THC/high CBD)
- Links to legal documentation
- State vs. federal perspective

Marijuana Policy Project – [www.mpp.org](http://www.mpp.org)

- Federal and state policies
- Ballot initiatives

# State medical marijuana/cannabis program laws

23 states, the District of Columbia and Guam now allow for comprehensive public medical marijuana and cannabis programs

## Comprehensive program

- Protection from criminal penalties for using marijuana for a medical purpose
- Access to marijuana through home cultivation, dispensaries or some other system that is likely to be implemented
- It allows a variety of strains, including those more than "low THC"
- It allows either smoking or vaporization of some kind of marijuana products, plant material or extract

## State medical marijuana/cannabis program laws

State	Statutory Language (year)	Patient Registry or ID cards	Allows Dispensaries	Specifies Conditions	Recognizes Patients from other states	State Allows for Retail Sales/Adult Use
Arizona	Proposition 203 (2010)	Yes	Yes	Yes	Yes	
Colorado	Amendment 20 (2000)	Yes	Yes	Yes	No	Amendment 64 (2012)
California	Proposition 215 (1996) SB 420 (2003)	Yes	Yes (cooperatives and collectives)	No		
Michigan	Proposal 1 (2008)	Yes	Not in state law, but localities may create ordinances to allow them and regulate them.	Yes	Yes	

Alaska, Connecticut, Delaware, DC, Guam, Hawaii, Illinois, Maine, Maryland, Massachusetts, Minnesota, Montana, Nevada, New Hampshire, New Jersey, New Mexico, New York, Oregon, Rhode Island, Vermont, Washington

# Variability from state to state

“Serious medical condition”:

- Acquired immune deficiency syndrome (AIDS)
- Anorexia
- Arthritis
- Cachexia
- Cancer
- Chronic pain
- Glaucoma
- Migraine
- Severe nausea
- Persistent muscle spasms, including, but not limited to, spasms associated with multiple sclerosis
- Seizures, including, but not limited to, seizures associated with epilepsy.
- Any other chronic or persistent medical symptom that either: (A) Substantially limits the ability of the person to conduct one or more major life activities as defined in the Americans with Disabilities Act of 1990. (B) If not alleviated, may cause serious harm to the patient's safety or physical or mental health.



# Variability from state to state

“Debilitating medical condition”:

- Cancer
- multiple sclerosis
- HIV
- AIDS
- The treatment of these conditions, if the disease or the treatment results in severe, persistent, and intractable symptoms; OR

- a disease, medical condition, or its treatment that is chronic, debilitating, and produces severe, persistent, and one or more of the following intractable symptoms:

- Cachexia or wasting syndrome
- Severe pain
- Severe nausea
- Seizures



# Limited access marijuana product laws

17 states allow use of "low THC, high cannabidiol (CBD)" products for medical reasons in limited situations or as a legal defense

State	Program Name and Statutory Language (year)	Patient Registry or ID cards	Dispensaries or Source of Product(s)	Specifies Conditions	Recognizes Patients from other states	Definition of Products Allowed	Allows for Legal Defense	Allowed for Minors
Missouri	HB 2238 (2014)	Yes	Yes, creates cannabidiol oil care centers and cultivation and production facilities/ laboratories.	Yes, intractable epilepsy that has not responded to three or more other treatment options.	No	"Hemp extracts" equal or less than .3% THC and at least 5% CBD by weight.	Yes	Yes

Alabama, Florida, Georgia, Iowa, Kentucky, Louisiana, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Utah, Virginia, Wisconsin, Wyoming

# Variability from state to state

State	Specifies Conditions	Definition of Products Allowed
Missouri	Yes, intractable epilepsy that has not responded to three or more other treatment options.	"Hemp extracts" equal or less than .3% THC and at least 5% CBD by weight.
Alabama	Yes, debilitating epileptic conditions or life-threatening seizures.	Extracts that are low THC= below 3% THC
Florida	Yes, cancer, medical condition or seizure disorders that chronically produces symptoms that can be alleviated by low-THC products	Cannabis with low THC= below .8% THC and above 10% CBD by weight
Georgia	Yes, end stage cancer, ALS, MS, seizure disorders, Crohn's, mitochondrial disease, Parkinson's, Sickle Cell disease	Cannabis oils with low THC= below 5% THC and at least an equal amount of CDB.
Iowa	Yes, intractable epilepsy	"Cannabidiol- a non-psychoactive cannabinoid" that contains below 3% THC, no more than 32 oz, and essentially free from plant material.
Kentucky	Intractable seizure disorders	No, only "cannabidiol"

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