

# Cannabis: What Does it Mean for Your Practice?

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# Disclosures

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- ❑ Speakers bureau: Allergan, Amgen & Lilly Pharmaceuticals
- ❑ Any unlabeled/unapproved uses of drugs or products referenced will be disclosed.
- ❑ Covering a very **LARGE** topic in a short amount of time.

# Learning Objectives

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- 1) Review the history of cannabis in medicine.
- 2) Explore the current research.
- 3) Review practical clinical basics & safety considerations.

# Is this really a big deal?

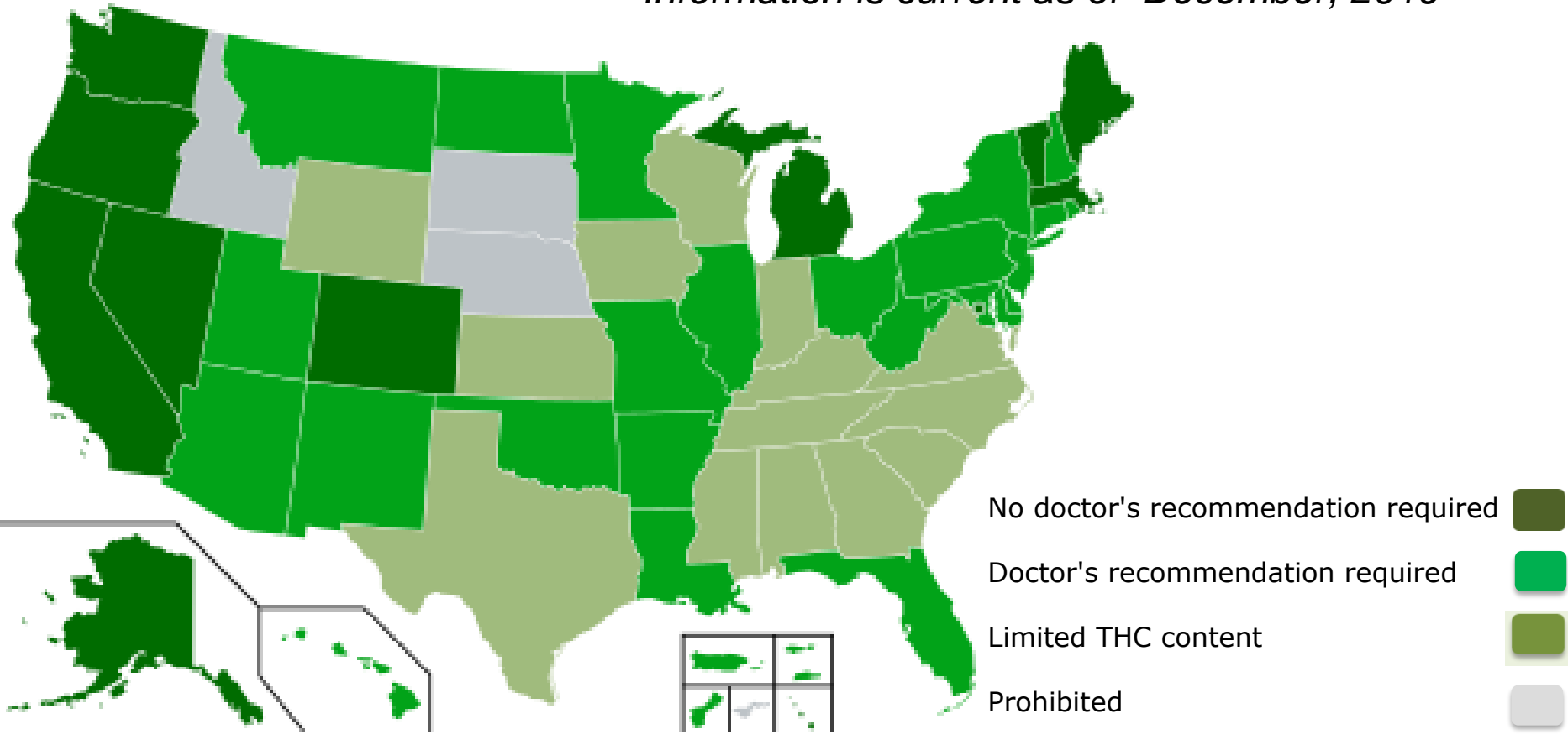
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- Most states (Guam & DC) in the US that have legislation allowing for the medicinal use of cannabinoids.
- Federally illegal! Major confusion?!
- Canada → Cannabis Act
- UK → Legalize medicinal marijuana
- FDA 2018 approved EPIDIOLEX® (cannabidiol) oral solution, schedule V.
- Global financial impact

# Is this really a big deal?

Map shows current state laws and recently-approved ballot measures legalizing marijuana for medical or recreational purposes.

*Information is current as of December, 2019*



# Cannabis Through History

Earliest writings of cannabis use.

**Asia/Europe**

2700 B.C.



**U.S. Pharmacopeia**

1800's

1850-1942

**Dr. William Brooke O'Shaughnessy**

Introduced cannabis into western medicine.

1937

**Marijuana Tax Act**

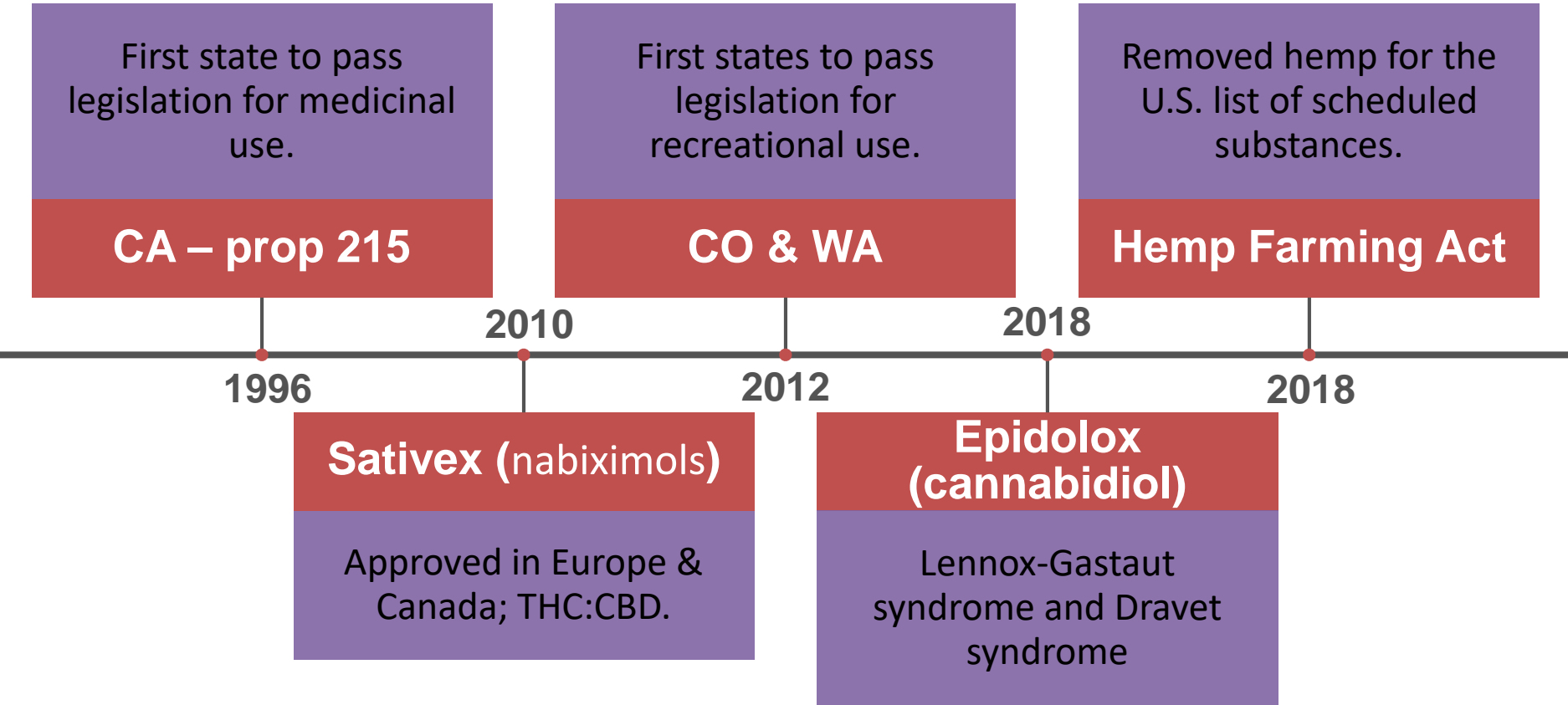
1930s U.S. Federal Bureau of Narcotics  
"Marijuana is a gateway drug to narcotics addiction."

Marijuana a CS I: Having no medicinal value.

**Controlled Substance Act**

1970

# Cannabis Through History



# Hemp Farming Act 2018

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- Removed hemp for the US list of scheduled substances.
- Did not remove hemp derived cannabinoids from the list of scheduled I substances.
- Amended the definition of marijuana → included an exemption for hemp → defined as “any part” of the *Cannabis sativa* L. plant → containing no more than 0.3% THC.
- Ongoing legislation → federal & regulatory agency guidance.
- States setting their own rules for the hemp industry.
- USDA has broad regulatory “authority” over hemp industry.



# Endocannabinoid System

Endogenous – homeostatic - regulatory system inherited by all mammals.

## **Includes:**

➤ CB1 (CNS) & CB2 (immune & organs) receptor sites

{CBx & VR1}

➤ *Endocannabinoids*

➤ *Anandamide*

➤ *2-arachidonylglycerol (2AG)*

➤ *Nolan ether*

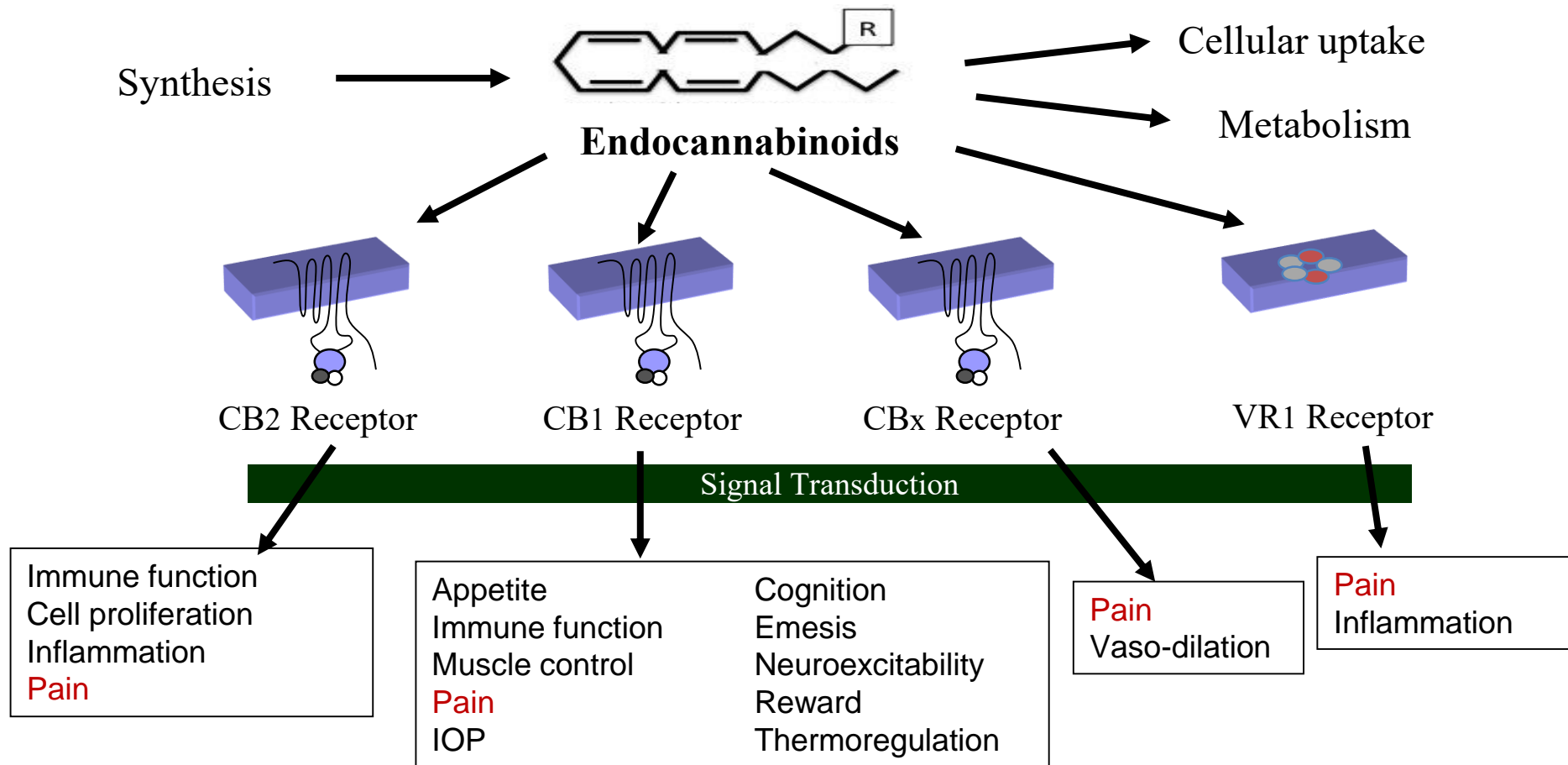
➤ *Virodhamine*

➤ *NADA*

➤ Synthesizing & degrading enzymes

- Cognition & memory
- Appetite & digestion
- Stress response
- Inflammation
- Motor control
- Sleep
- Exploration, social behavior, & anxiety
- Immune/Endocrine function
- Autonomic nervous system
- Antinociception

# Endogenous Cannabinoid System



Courtesy of Donald Abrams, MD

# Clinical Endocannabinoid Deficiency

Ethan Russo, MD (2004/2016)

- The ECS theory of disease.
- Lack of sufficient endocannabinoids/ dysregulation of the ECS.
- Result in higher susceptibility (fibromyalgia, irritable bowel syndrome, depression, anxiety, migraine).
- Phytocannabinoids (THC, CBD) can bind to the cannabinoid receptor sites (CB1, CB2), and mimic the physiological processes seen with binding of the endocannabinoids.



# What is cannabis sativa (aka marijuana)?

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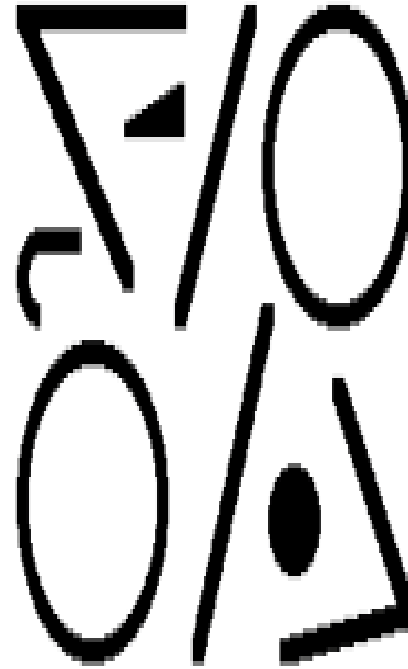
It is a Plant w/over 400 different chemicals:

- >60 types of cannabinoids
  - delta-9-tetrahydrocannabinol (THC)
  - Cannabidiol (CBD)
  - Cannabinol (CBN)
  - Cannabichromene (CBC)
  - Cannabigerol (CBG)
  - Tetrahydrocannabivarin (THCV)
- Flavonoids, Terpenes, Terpenoids
- Fungus? Bacteria? Pesticides?
- Byproducts of manufacturing (solvents, heavy metals)



# Entourage effect: sum of the parts

- The entourage effect is a proposed mechanism by which cannabis compounds act to modulate the overall physiological effects of the plant.



- Example: CBD + THC = mitigating some of the psychosis-like effects of THC.

- Cannabis is a multimodal treatment. It can be used to treat multiple symptoms & conditions concurrently, which can therefore help to reduce polypharmacy burden.

# Research

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- Center for Medicinal Cannabis Research
- National Center for Natural Products Research (NCNPR) at the University of Mississippi
- National Institute on Drug Abuse (NIDA)
- National Institutes of Health (NIH)
  
- Canadian Institutes of Health Research
- Canadian Consortium for the Investigation of Cannabinoids (CCIC)

## Europe

- The Medicinal Cannabis Research Foundation (MCRF): UK
- Spain, Germany, Italy
- ICRS: [http:// www.cannabinoidsociety.org](http://www.cannabinoidsociety.org)

<https://clinicaltrials.gov/>

# Cannabinoids for Medical Use

## A Systematic Review and Meta-analysis

Penny F. Whiting, PhD; Robert F. Wolff, MD; Sohan Deshpande, MSc; Marcello Di Nisio, PhD; Steven Duffy, PgD; Adrian V. Hernandez, MD, PhD; J. Christiaan Keurentjes, MD, PhD; Shona Lang, PhD; Kate Misso, MSc; Steve Ryder, MSc; Simone Schmidtkofer, MSc; Marie Westwood, PhD; Jos Kleijnen, MD, PhD

- Moderate-quality evidence support use of cannabinoids in chronic pain & spasticity.
- Low-quality evidence: CINV, HIV weight loss, insomnia, Tourette's.
- Use of cannabinoids were associated with increased risk of short-term adverse effects.

# Selective Cannabinoids for Chronic Neuropathic Pain: A Systematic Review and Meta-analysis

Howard Meng, MD,\* Bradley Johnston, PhD,†‡§|| Marina Englesakis, MLIS,¶ Dwight E. Moulin, MD,# and Anuj Bhatia, MBBS, MD, FRCPC, FRCA, FFPMRCA, FIPP, EDRA, CIPS\*

- Selective cannabinoids provided a small benefit in chronic neuropathic pain.
- High degree of heterogeneity amongst included publications.
- Need for additional: well designed, large, RCT to better assess dosage/duration/effects on physical & psychological function.



High-quality evidence is lacking.

All cannabis-based medicine pooled together were better than placebo:

- Reducing pain intensity
- Reports of moderate pain relief
- Improvement in sleep
- Improvement in psychological distress
- Global improvement

Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W

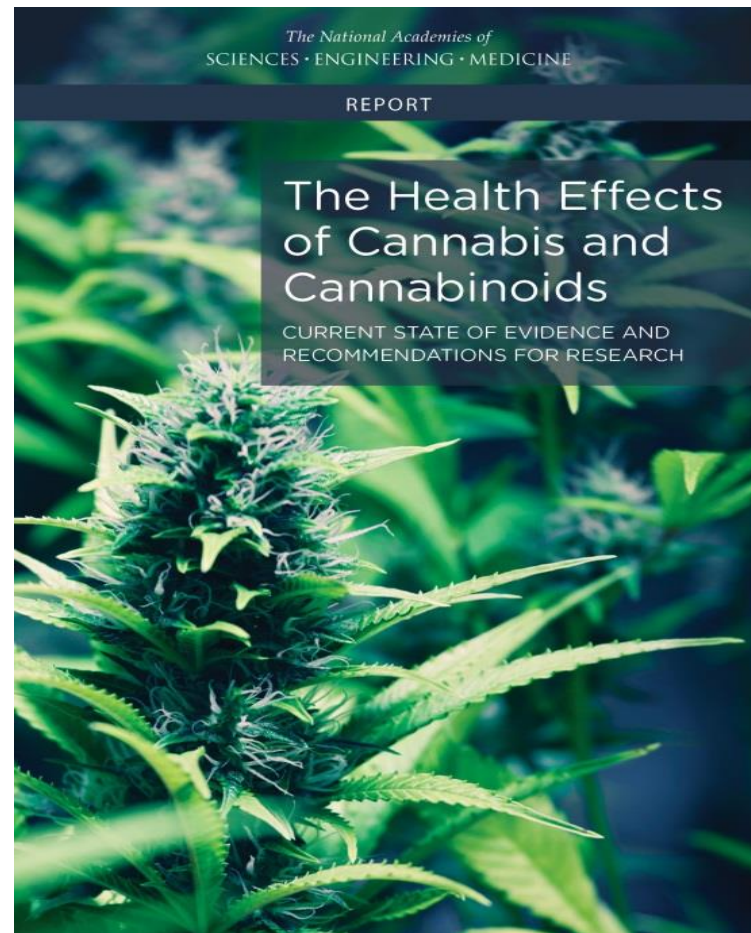
All cannabis-based medicine pooled together were NO better than placebo:

- Improving health-related QOL
- Stopping medication because it was not effective
- Frequency of serious side effects

More people reported sleepiness, dizziness, cognitive problems and dropped out of studies because of side effects with all cannabis-based medicines pooled together versus placebo.

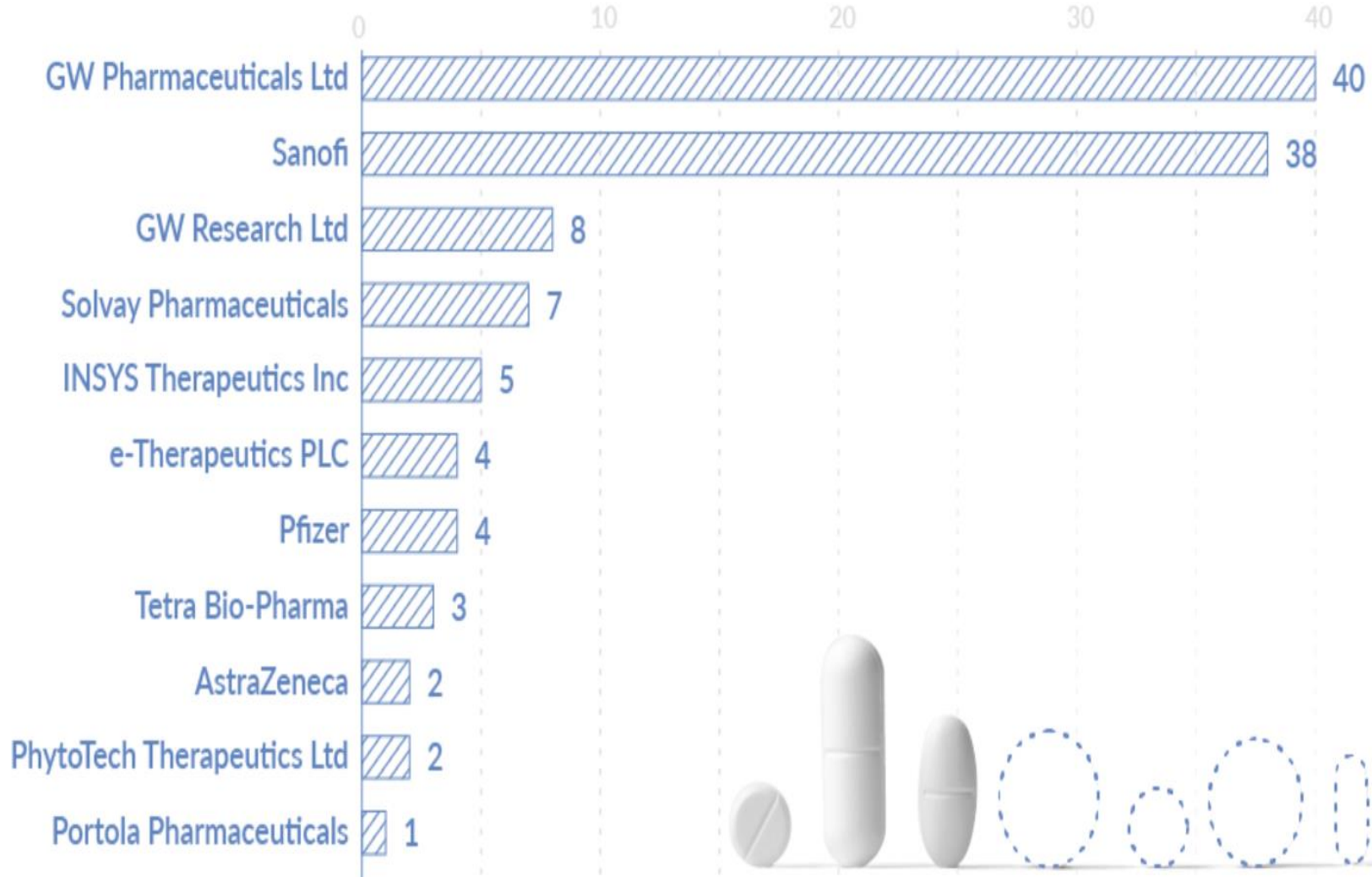
# The Health Effects of Cannabis and Cannabinoids: Current State of Evidence and Recommendations for Research (2017)

- In adults with chemotherapy induced N/V, oral cannabinoids are effective antiemetics.
- Adults with chronic pain are more likely to experience clinically significant pain relief.
- Adults with MS related spasticity reported improvement of spasticity symptoms.



# Pharmaceutical Companies & Medical Cannabis

Number of Cannabinoid Clinical Trials Registered with FDA by Company  
*as of June 2018*



# Pharmaceutical Companies & Medical Cannabis



Source: Clinical Trials, Cannabis Business Executive

In 2019, 33 states and the District of Columbia have legalized marijuana for medical use.

Its potential for pain management has led some experts to recommend it as an alternative to addictive painkillers.

# Is Cannabis a Rational Solution to the Opioid Crisis?

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## Pro/Advocates

- Excellent alternative, less addictive, less likely to result in death.
- “Alternatives to Opioids Act of 2018” - Illinois
- NY - “adding any condition for which an opioid could be prescribed as a qualifying condition for medical marijuana.”
- The National Institutes of Health recently awarded a 5-year \$3.8 million grant. [*Albert Einstein College of Medicine - Chinazo Cunningham, M.D.*]

## Con/Critics

- Substitution of one addictive substance for another.
- Side effects under recognized (e.g. psychosis).
- Evidence hasn't proven benefit for pain.

# Opioid-Sparing Effect of Cannabinoids: A Systematic Review and Meta-Analysis (2017)

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Purpose: Determine the opioid-sparing potential of cannabinoids.

Results: Studies included in qualitative synthesis (n = 28)

- Median effective dose of morphine administered in combination with delta-9-THC is 3.6 times lower than the of morphine alone.
- Codeine administered in combination with delta-9-THC was 9.5 times lower than of codeine alone.

Original Investigation

# Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999-2010

Marcus A. Bachhuber, MD; Brendan Saloner, PhD; Chinazo O. Cunningham, MD, MS; Colleen L. Barry, PhD, MPP

The enactment of statewide medicinal marijuana laws is associated with significantly lower state-level opioid overdose mortality rates, according to data published in August 2014 in JAMA Internal Medicine.

Researchers reported, “States with medical cannabis laws had a 24.8 percent lower mean annual opioid overdose mortality rate compared with states without medical cannabis laws.”



# I know nothing about cannabis!

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# Important Talking Points

- Encourage open/non-judgmental dialogue.
- Driving “under the influence”.
- Recommend obtaining medical marijuana card issued by state.
- Traveling considerations.
- Share the extend of the research that is known.
- Provide website resources.
- Discuss drug to plant interactions, side effects, risk of addiction.
- Issues with recommending products & dispensaries.



# Mental Health

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Cannabinoids (THC) appear to effect the same reward system as alcohol, cocaine, opioids.

Evidence for cannabis dependence from epidemiological studies

➤ irritability, anxiety, disturbed sleep, craving

Mental wellness

- Worsen sub-clinical, stable mental illness
- Effective motivation
- Psychosis in genetically susceptible individuals

# Tolerance & Adverse Effects (AEs)

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## Tolerance

- Mood, sleep
- Psychomotor performance
- Arterial pressure
- Antiemetic properties

## Common AEs

- **Anticholinergic effects** (dry mouth, blurry vision, urinary retention, tachycardia, constipation, hypertension).
- **CNS effects** (ataxia, cognitive dysfunction, hallucination).

## Cannabis Hyperemesis Syndrome

# Pharmacokinetics: delta-9-tetrahydrocannabinol

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- THC psychoactive cannabinoid
- Highly lipophilic
- Rapidly absorbed through lungs after inhalation, quickly reaching high serum concentration
- Systemic bioavailability is ~23-27% for daily users, ~10-14% occasional users
- Extensive liver (first pass) metabolism; cytochrome P450
- >65% excreted in the feces, ~20% urine
- $t_{1/2}$  occasional users is 1-2 days, daily users up to 2 weeks

# Stirring the Pot: Potential Drug Interactions

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- CYP450 Enzymes: 1A2, 3A4, 2C9, 2C19.
- CNS depressants, antidepressants, central nervous system drugs – potentiate effects of THC.
- Any medications that are metabolized through the same pathways could result in less or more of the drug's effects.
- For scientific reviews: *Drug Metabolism Reviews*.
- Epocrates is a good quick reference for cannabidiol and synthetic THC.


# Oral versus Inhaled

	INHALED	ORALLY INGESTED
Peak Blood Levels (min)	3-10	60-120
Bioavailability (%)	10-40	<15
Time to peak psychoactive activity (min)	20	120-240

# Practical Dosing

Recommend only products that are properly labeled.

- Label information should include the ingredients and the milligrams of each cannabinoid per dose.
- Recommend only products from companies that test for potency, pesticides, mold, and bacteria.
- Mindful of byproducts of production (e.g. solvents).



Cannabaceutical™ Facts		Afghani X Sour Diesel		Tested On: November 11, 2013	
Total Aerobic Count	<b>GOLD</b>	Total Yeast & Mold	<b>GOLD</b>		
Total Enterobacteria	<b>GOLD</b>	Pesticides Screen	<b>PASS</b>		
Δ <sup>9</sup> -THC Max:	18.57 %	Sum of Top Terpenes	22.5 mg/g		
Δ <sup>9</sup> -THCA	20.89 %	β-Caryophyllene	7.5 mg/g		
Δ <sup>9</sup> -THC	0.25 %	Myrcene	3.5 mg/g		
CBD Max:	0.35 %	Limonene	3.2 mg/g		
CBDa	0.08 %	α-Humulene	2.8 mg/g		
CBD	0.27 %	α-Pinene	2.6 mg/g		
CBG Max:	1.82 %	β-Pinene	1.5 mg/g		
Δ <sup>9</sup> -THCVA	0.13 %	Germacrene B (tl)	1.5 mg/g		
CBN	ND %				



# Cannabidiol (CBD)

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## Defining Terms:

- CBD from Hemp (↑contaminants, ↓THC)
- CBD from cannabis sativa (↑THC, ↑purity)
- Hemp Oil (seeds of hemp plant, no CBD, no THC, +essential fatty acids, +omega three)

## Research:

- Epidiolex®
- Other - preliminary research included studies of anxiety, cognition, movement disorders, and pain (anti-inflammatory).
- Efficacy most antidotal (discuss current animal studies).

**Safety:** Dosing toxicity? Anti-inflammatory effects? CYP450 metabolism.

**Side Effects:** Fatigue, diarrhea, changes of appetite/weight, dry mouth. Transaminase elevations (reported in Epidiolex studies).

# FDA Warns of CBD's Potential Harm

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- The FDA has approved only one CBD product, a prescription drug product to treat two rare, severe forms of epilepsy.
- Illegal to market CBD by adding it to a food or labeling it as a dietary supplement.
- Limited data about CBD safety:
  - ***Liver Injury***
  - ***Drug Interactions***
  - ***Male Reproductive Toxicity***
- Some CBD products are being marketed with unproven medical claims and are of unknown quality.

# FDA warns 15 companies

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- Koi CBD LLC, of Norwalk, California
- Pink Collections Inc., of Beverly Hills, California
- Noli Oil, of Southlake, Texas
- Natural Native LLC, of Norman, Oklahoma
- Whole Leaf Organics LLC, of Sherman Oaks, California
- Infinite Product Company LLLP, doing business as Infinite CBD, of Lakewood, Colorado
- Apex Hemp Oil LLC, of Redmond, Oregon
- Bella Rose Labs, of Brooklyn, New York
- Sunflora Inc., of Tampa, Florida/Your CBD Store, of Bradenton, Florida
- Healthy Hemp Strategies LLC, doing business as Curapure, of Concord, California
- Private I Salon LLC, of Charlotte, North Carolina
- Organix Industries Inc., doing business as Plant Organix, of San Bernardino, California
- Red Pill Medical Inc., of Phoenix, Arizona
- Sabai Ventures Ltd., of Los Angeles, California
- Daddy Burt LLC, doing business as Daddy Burt Hemp Co., of Lexington, Kentucky

# How to Shop for CBD

- 1. Decide Why You Want to Use CBD, and in What Form**
- 2. Consider How Much THC the Product Contains**
- 3. For Products From Hemp, Find Where It Was Grown**
- 4. Ask for Test Results**
- 5. Look for Products That List the CBD Amount**
- 6. Know What Other Terms on the Label May Mean**
- 7. Avoid Products That Make Sweeping Health Claims**
- 8. Watch Out for Vaping Products With Propylene Glycol**

# Hemp CBD Scorecard: An Evaluation of Hemp CBD Producers

## HEMP CBD SCORECARD

GRADE	COMPANY
A	   
B	       
C	         
D	       
F	         

Center for Food Safety (CFS) is a national non-profit public interest and environmental advocacy organization

<https://www.centerforfoodsafety.org/reports/5719/hemp-cbd-scorecard-an-evaluation-of-hemp-cbd-producers>

Created an expert CBD Board – To enhance safety & ensure appropriate regulation of CBD products.

- CBA is NOT a government agency

**Grocery Manufacturers Association (GMA): survey of 2,056 U.S. adults (age 18 and older)**

- 1:3 of Americans use a CBD product
- 76% assume that CBD products are subject to federal regulations and safety oversight
- 66% believe CBD is safe
- >50% pain, anxiety, sleep
- 39% believe that CBD is just another name for marijuana

<https://progressivegrocer.com/gma-consumers-confused-about-cbd>

# CBD Drug Development Pipeline

Pharmaceutical Company	Medical Indication	Status
Echo Pharmaceuticals (Netherlands)	Rett syndrome Schizophrenia	Phase 1 Phase 1
GW Pharmaceuticals	Neonatal hypoxic-ischemic encephalopathy	Phase 1
STI Pharmaceuticals (United Kingdom)	Marijuana-induced subjective effects	Phase 2
INSYS Pharmaceuticals	Infantile spasms Prader-Willi syndrome Childhood absence epilepsy	Phase 3 Phase 2 Phase 2
Zynerba Pharmaceuticals	Fragile X & other epileptic neurological indications	Phase 2

# The Vape Pen

- Avoid with products that contain propylene glycol (solvent).
- Propylene glycol can degrade to formaldehyde.
- Recommend vape pens that contain “solvent-free oils”.

**BAY AREA & STATE** SUBSCRIBE

## 7 Californians hospitalized in ICU after vaping cannabis or CBD oils

Mike Moffitt, SFGATE | on August 16, 2019

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Photo: Contributed Photo  



# Practical Dosing

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**Regardless of the specific physiological system, the effects of cannabis are dependent on many factors:**

- Dose, variety
- Route (Inhalation, oral, transmucosal, transdermal, topical)
- Timing
- General health (medical co-morbidities), Age
- Use of other substances/medications
- Chronic user of cannabis versus naive

# Practical Dosing

## Average adult dosing of THC:

- Cannabis-naïve individuals 2.5-5 mg
- Daily - weekly users 10-20 mg
- Daily+ 25 mg+
- Doses exceeding 20–30 mg/day may increase adverse events or induce tolerance without improving efficacy.

<https://www.leafly.com/news/cannabis-101/cannabis-edibles-dosage-guide-chart>

MacCallum & Russo, 2018

## Average adult dosing of CBD:

- 300-1500 mg/day

<https://www.webmd.com/vitamins/ai/ingredientmono-1439/cannabidiol>

MacCallum & Russo, 2018

# Practical Dosing

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**Sativex®** (1:1 THC/CBD): Spasticity due to multiple sclerosis.

➤ 2.7mg/2.5mg BID

(max 32.4mg/30mg/day)

<https://www.medicines.org.uk/emc/product/602>

**Epidiolex®** (CBD): Seizures (Dravet/Lennox-Gastaut)

➤ 5 mg/kg oral BID

(max 20 mg/kg/day)

[https://www.epidiolex.com/sites/default/files/EPIDIOLEX\\_Full\\_Prescribing\\_Information.pdf](https://www.epidiolex.com/sites/default/files/EPIDIOLEX_Full_Prescribing_Information.pdf)

# LACK OF STANDARDIZATION MAKES DOSING A CHALLENGE FOR PATIENTS & PRACTITIONERS

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## **Overconsumption:**

- Re-dosing too soon
- Delayed on-set with oral dosing (>120 minutes)
- Hostile behavior/erratic speech/mild psychosis

**The L.E.S.S. Method:** A measured approach to oral cannabis dosing

**Start Low**

- **Establish potency**
- **Go slow**
- **Supplement as needed**

(Erowid & Erowid, 2011)

# Final Takeaways

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Familiarize yourself with

- THC, CBD dosing.
- drug : drug (plant) interactions, side effects, withdrawal.
- local dispensaries and counsel patient to accordingly.

## **Consider The Treatment Agreement.**

<file:///C:/Users/s0040168/AppData/Local/Microsoft/Windows/INetCache/IE/ROXKFXQ6/treatmentagreement.pdf>

- Continue to remember Federally illegal.
- Informed about state laws.
- Mindful of addiction, abuse, mental health issues.

# Dispensary Resources

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## Voluntary Patient Focused Certification

<http://patientfocusedcertification.org/certification/>

- Addresses product & distribution safety
- Based on quality standards for medical cannabis products and businesses issued by the **American Herbal Products Association** (AHPA) and the **American Herbal Pharmacopoeia** (AHP) Cannabis monograph

## Association of Canadian Cannabis Retailers

<http://camcd-acdcm.ca/>

# Resources

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Canadian Consortium for the Investigation of Cannabinoids (CCIC): [www.ccic.net](http://www.ccic.net)

- Accredited cannabinoid education (ACE) programs
- Informed by needs assessments, expert faculty

- International Cannabinoid Research Society (ICRS): [www.icrs2014.org](http://www.icrs2014.org)
- International Association for Cannabinoid Medicine (IACM): [www.cannabis-med.org](http://www.cannabis-med.org)
- University of Washington & Alcohol and Drug Abuse Institute (ADAI): <http://adai.uw.edu/mcacp/index.htm>
- Society of Cannabis Clinicians: [www.cannabisclinicians.org](http://www.cannabisclinicians.org)

# Physician/Clinician Training

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All licensed MDs/DOs – some states require specialty practice (e.g. pain management, palliative care, etc.)

New York: [https://www.health.ny.gov/regulations/medical\\_marijuana/practitioner/](https://www.health.ny.gov/regulations/medical_marijuana/practitioner/)

Florida: [http://www.flhealthsource.gov/ommu/physician\\_requirements](http://www.flhealthsource.gov/ommu/physician_requirements)

MS in Medical Cannabis Science & Therapeutics at the University of Maryland - School of Pharmacy  
[msmedicalcannabis@rx.umaryland.edu](mailto:msmedicalcannabis@rx.umaryland.edu)

PAs: state specific



# Thank You

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