




Cutting Through the Hype: Cannabis in Clinical Practice

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Disclosures

- Speakers bureau: Allergan & 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

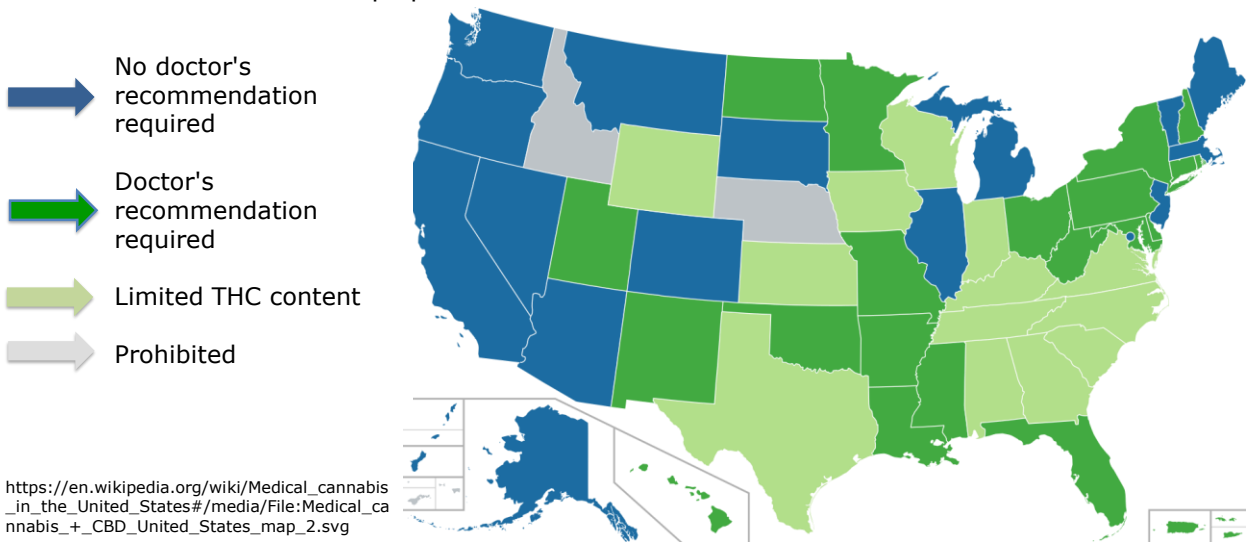
- Define the endocannabinoid system.
- Discuss the medicinal use of cannabinoids, supported by the research.
- Review practical clinical basics & safety considerations.

Is this really a big deal?

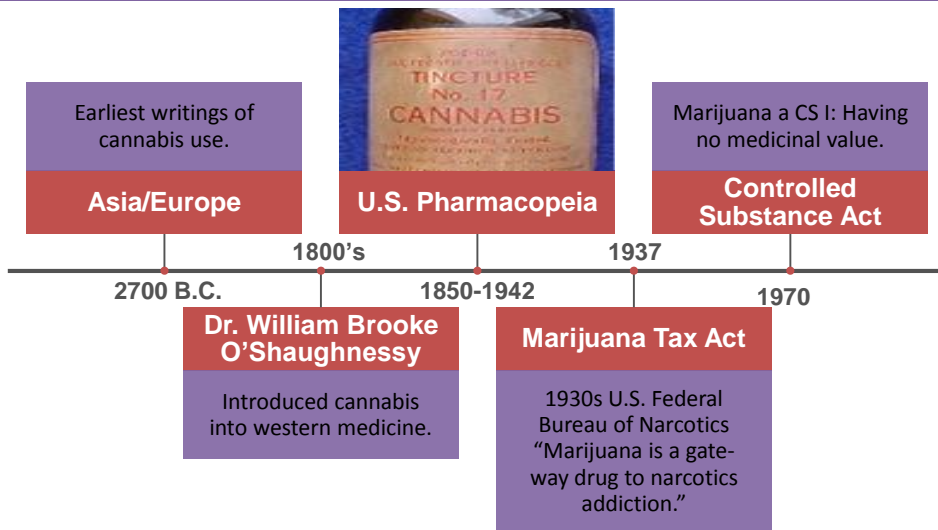
- Most states (Guam & DC) in the U.S. have legislation allowing for the medicinal use of cannabinoids.
- Canada → Cannabis Act (2019)
- UK → Legalize medicinal marijuana (2018)
- FDA 2018 approved EPIDIOLEX® (cannabidiol) oral solution, schedule V.
- Global financial impact - Cannabis Conclave (2019)
- Federally illegal! Major confusion?!

Is this really a big deal?

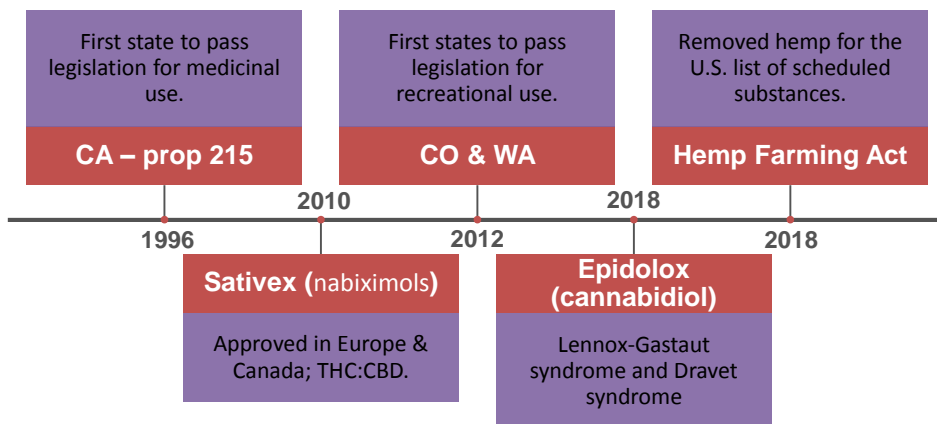
Map shows current state laws and recently-approved ballot measures legalizing marijuana for medical or recreational purposes. *Information is current as of November 2020*



Cannabis Through History



Cannabis Through History



Hemp Farming Act 2018

- 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

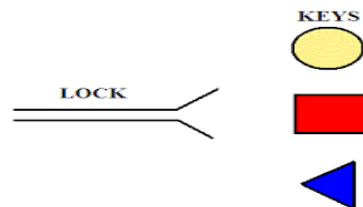
➤ Molecule - Endocannabinoids

- *Anandamide*
- *2-arachidonylglycerol (2AG)*
- *Nolan ether*
- *Virodhamine*
- *NADA*

➤ Synthesizing & degrading enzymes

➤ Receptor Sites

- CB1 (CNS)
- CB2 (immune & organs)
- CBx & VR1



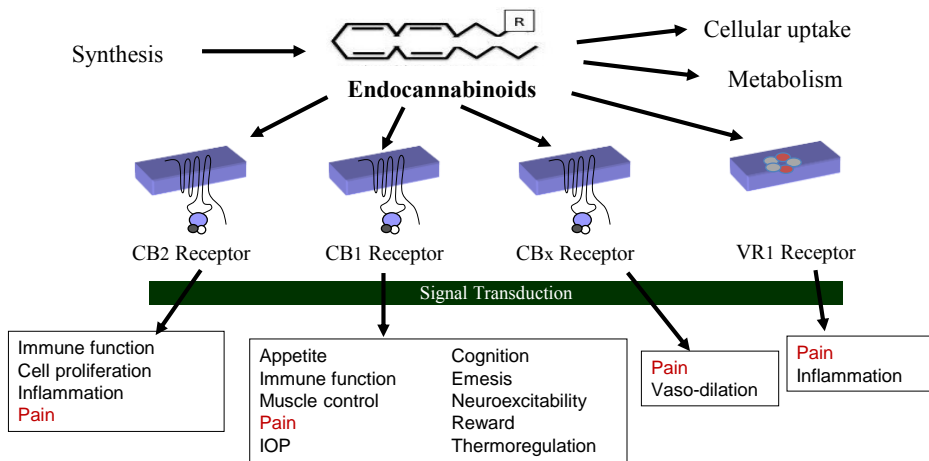
Endocannabinoid System

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

Basic Principals:

- Endocannabinoids are made on demand
→ responding to needs of the individual.
- Adaptive
- Effected/modulated/influenced by exposure to exogenous cannabinoids (cannabis).
- THC → CB1 ← anandamide
 ↑
 2AG

Endogenous Cannabinoid System



Courtesy of Donald Abrams, MD

Clinical Endocannabinoid Deficiency

Ethan Russo, MD (2004/2016)

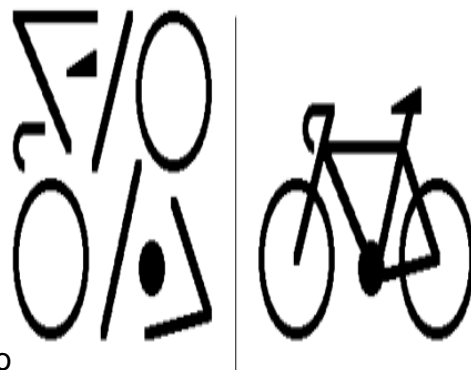
- The ECS theory of disease.
- Lack of sufficient endocannabinoids/
dysregulation of the ECS.
- Result in higher susceptibility
(fibromyalgia, irritable bowel syndrome,
depression, anxiety, migraine).

- Phytocannabinoids (THC, CBD) can
bind to the cannabinoid receptor sites
(CB1, CB2), and mimic the physiological
processes seen with binding of the
endocannabinoids.



Entourage effect: sum of the parts

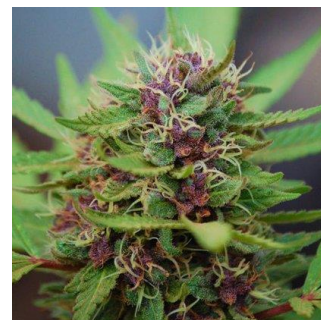
- The entourage effect is a proposed mechanism by which cannabis compounds act synergistically to modulate the overall physiological effects of the plant.
- Example: CBD + THC = possibly mitigating some of the psychosis-like effects of THC.
- Cannabis is a multimodal treatment. It can be used to treat multiple symptoms & conditions concurrently, which can therefore help to reduce polypharmacy burden.



What is cannabis sativa (aka marijuana)?

It is a Plant w/over 400 different chemicals:

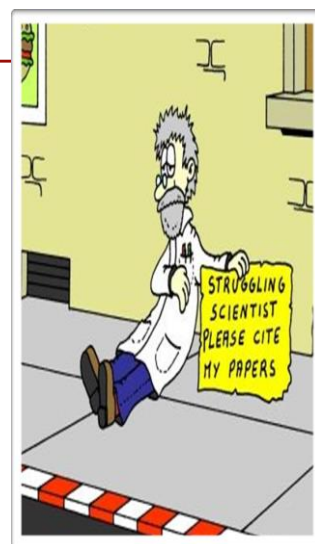
- >60 types of cannabinoids
 - delta-9-tetrahydrocannabinol (THC)
 - Cannabidiol (CBD)
 - Cannabinol (CBN)
 - Cannabichromene (CBC)
 - Cannabigerol (CBG)
 - Tetrahydrocannabivarin (THCV)
- Flavonoids, Terpenes, Terpenoids
- Fungus? Bacteria? Pesticides?
- Byproducts of manufacturing (solvents, heavy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



Research

- 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/>

ClinicalTrials.gov Search Results: pg 1 of 8

Title	Status	Study Results	Conditions	Interventions
Treatment of Chronic Pain With Cannabidiol (CBD) and Delta-9-tetrahydrocannabinol (THC)	Recruiting	No Results Available	•Chronic Pain, Widespread	•Drug: Delta-9-Tetrahydrocannabinol •Drug: Cannabidiol •Drug: Placebos
Bioequivalence Assessment of Oral Administration Vs. Oral Spray of a Cannabinoids (Tetrahydrocannabinol and Cannabidiol)	Completed	No Results Available	•Pain	•Drug: Sativex buccal spray •Drug: CBD-THC-Piperine-PNL caps
Characterization of the Analgesic Effect of CBD in Healthy, Normal Volunteers	Active, not recruiting	No Results Available	•Pain	•Drug: Cannabidiol •Drug: Placebo
Cannabis Oil for Chronic Non-Cancer Pain Treatment	Not yet recruiting	No Results Available	•Chronic Non-cancer Pain	•Drug: CBD •Drug: CBD+THC •Other: Placebo
Investigation of Cannabis for Chronic Pain and Palliative Care	Not yet recruiting	No Results Available	•Chronic Pain	•Drug: Smoked Cannabis High CBD/l THC •Drug: Smoked Placebo Cannabis Lc CBD/low THC
Marijuana in Combination With Opioids in Palliative and Hospice Patients	Enrolling by invitation	No Results Available	•Pain Management in Terminally Ill Patients Receiving Scheduled Opioid Therapy	•Drug: Medical Marijuana
A Study to Evaluate the Effects of Cannabis Based Medicine in Patients With Pain of Neurological Origin	Completed	Has Results	•Pain •Multiple Sclerosis	•Drug: GW-1000-02 •Drug: Placebo
Pain Research: Innovative Strategies With Marijuana	Recruiting	No Results Available	•Chronic Pain •Chronic Low Back Pain •Cannabis Use	•Drug: Cannabis Edible
Effect of Cannabis and Endocannabinoids on HIV Neuropathic Pain	Recruiting	No Results Available	•Cannabis •HIV Neuropathy	•Drug: Cannabis

Original Investigation

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.

JAMA. 2015;313(24):2456-2473. doi:10.1001/jama.2015.6358

■ META-ANALYSIS

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.

Anesth Analg 2017;125:1638-52

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

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

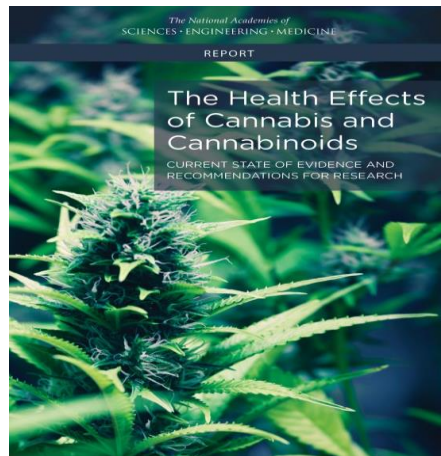
- Improving health-related QOL
- Stopping medication because it was not effective
- Frequency of serious side effects

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.

The National Academies of
SCIENCES • ENGINEERING • MEDICINE



Suggested citation: National Academies of Sciences, Engineering, and Medicine. 2017. *The health effects of cannabis and cannabinoids: Current state of evidence and recommendations for research*. Washington, DC: The National Academies Press. "Used with permission"

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

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.

Neuropsychopharmacology. 2017 Aug;42(9):1752-1765.



Research

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!



Important Talking Points

- Encourage open/non-judgmental dialogue
- Driving “under the influence”
- Recommend obtaining medical marijuana card issued by state
- Traveling considerations
- Provide website resources
- Share the extend of the research that is known
- Discuss drug to plant interactions, side effects, risk of addiction
- Do Not: Recommend products & dispensaries



Drug Testing for Cannabis

Many factors:

- Route of administration (inhaled, oral, topical)
 - Duration of use (acute v/s chronic usage)
 - Blood, sweat, tears (hair, saliva)
 - Sensitivity of the test (immunoassay – screening;
v/s GC-MS – confirmatory)
 - Genetics – CYP450 variations, adipose tissue
- In general, the detection time is longest in hair→ urine, sweat, oral fluid & blood.
- The average limit or cut-off level for testing positive on a drug test for marijuana (THC) is 50 ng/ml (15 ng/ml for GC-MS).

Drug Testing for Cannabis

Cannabinoid Test Results

12/01/2018

Cannabinoid analysis utilizing High Performance Liquid Chromatography (HPLC, QSP 5-4-4-4)

	mg/g	%	LOD mg/g	LOQ mg/g
THC	ND	ND	0.000034	0.001
THCa	ND	ND	0.000066	0.001
CBD	10.797	1.0797	0.000057	0.001
CBDa	ND	ND	0.000038	0.001
CBN	ND	ND	0.000029	0.001
CBDV	0.049	0.0049	0.000065	0.001
CBDVa	ND	ND	0.00003	0.001
CBG	ND	ND	0.000086	0.001
CBGa	ND	ND	0.000072	0.001
THCV	ND	ND	0.000035	0.001
$\Delta 8$ - THC	ND	ND	0.000083	0.001
CBC	ND	ND	0.000095	0.001
Sum of Cannabinoids:	10.846	1.0846	845.988 mg/Unit	
Total THC ($\Delta 9$ THC+0.877*THCa)	ND	ND		ND
Total CBD (CBD+0.877*CBDa)	10.797	1.0797	842.166 mg/Unit	

Mental Health

Cannabis (THC) appear to affect the same reward system as alcohol, cocaine, opioids.

Evidence for cannabis physiological & psychological dependence:

- irritability, anxiety, disturbed sleep, craving

Mental wellness

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

Tolerance & Adverse Effects (AEs)

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

- 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

- CYP450 → Main metabolic pathway for cannabinoids
- Studies of THC, CBD, and CBN inhibition and induction of major human CYP-450 isoforms generally reflect a low risk of clinically significant drug interactions with most use, but specific human data are lacking. (Stout & Cimino, 2014)
- 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 <small>Hydro-Cann. Hyb.</small> <small>Sun Green Corp.</small>	
		Tested On: November 11, 2013	
Total Aerobic Count	GOLD	Total Yeast & Mold	GOLD
Total Enterobacteria	GOLD	Pesticides Screen	PASS
Δ⁹-THC Max:	18.57 %	Sum of Top Terpenes	22.5 mg/g
Δ ⁹ -THCA	20.89 %	β-Caryophyllene	7.5 mg/g
Δ ⁹ -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 ⁹ -THCVA	0.13 %	Germacrene B (t)	1.5 mg/g
CBN	ND %		

Chemical Varieties/”chemovars”

Though cannabis is biologically classified as a single species: *Cannabis Sativa*, there are at least three distinct plant varieties:

- Cannabis Sativa
- Cannabis Indica
- Cannabis Ruderalis

(Pennisi, 2017)

www.leafly.com

www.safeaccessnow.org/using_medical_cannabis

Indica



Morphology: Short and bushy; suitable for indoor gardens

Geographical Origins: Areas between 30 to 50 degrees latitude.

Effects: Tend to be sedating and relaxing with full-body effects

Symptom Relief: Anxiety, insomnia, pain, muscle spasms

↓THC ↑CBD

Sativa



Morphology: Tall and thin; suitable for outdoor gardens

Geographical Origins: Areas between 0 and 30 degrees latitude

Effects: Tend to be uplifting and creative with cerebrally-focused effects

Symptom Relief: Depression, ADD, fatigue, mood disorders

↑THC ↓CBD

Cannabidiol (CBD)

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

- 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.

<https://www.fda.gov/consumers/consumer-updates/what-you-need-know-and-what-were-working-find-out-about-products-containing-cannabis-or-cannabis>

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**

<https://www.consumerreports.org/marijuana/how-to-shop-for-cbd/>

Consumer Brands Association



- 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)

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

- 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

Practical Dosing

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

https://www.colorado.gov/pacific/sites/default/files/MED%20Equivalency_Final%2008102015.pdf

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

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

LACK OF STANDARDIZATION MAKES DOSING A CHALLENGE FOR PATIENTS & PRACTITIONERS

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 **L**ow

- **E**stablish potency
- **G**o **s**low
- **S**upplement as needed

(Erowid & Erowid, 2011)

Final Takeaways

- Familiarize yourself with
 - THC, CBD dosing
 - drug : drug (plant) interactions, side effects, withdrawal
 - local dispensaries & 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

Resources

Dispensary Information: 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.

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

- More and more states are mandating certification and regulated licensures from dispensaries (e.g. FL).

Resources

Canadian Consortium for the Investigation of Cannabinoids (CCIC): www.ccic.net

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

International Cannabinoid Research Society (ICRS): <https://icrs.co/>

International Association for Cannabinoid Medicine (IACM): www.cannabis-med.org

University of Washington & Alcohol and Drug Abuse Institute (ADAI)

<http://adai.uw.edu/mcaccp/index.htm>

Society of Cannabis Clinicians: www.cannabisclinicians.org

Physician/Clinician Training

New York:

https://www.health.ny.gov/regulations/medical_marijuana/practitioner/

Florida:

http://www.flhealthsource.gov/ommu/physician_requirements

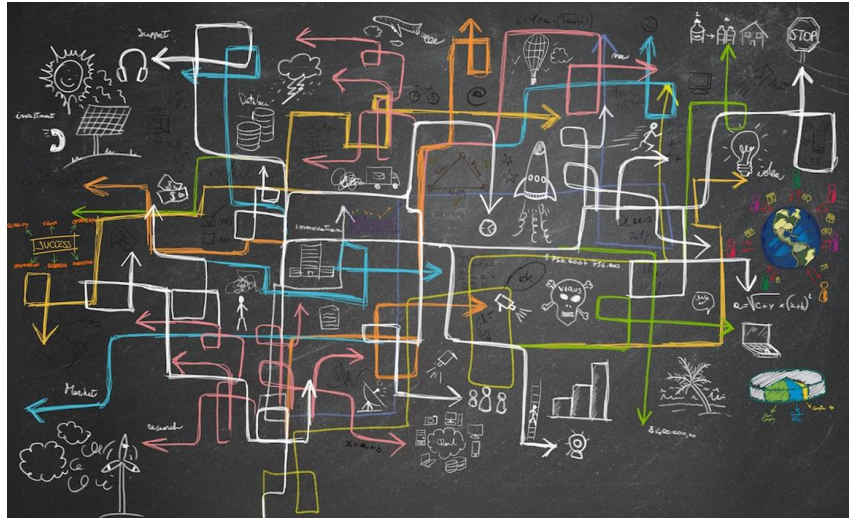
All licensed MDs/DOs – some states require specialty practice (e.g. pain management, palliative care, etc.)

MS in Medical Cannabis Science and Therapeutics at the School of Pharmacy should contact msmedicalcannabis@rx.umaryland.edu

PAs: state specific

Thank You

Questions?



Selected References

1. Aggarwal SK et al. Cannabinergic pain medicine: a concise clinical primer and survey of randomized-controlled trial results. *Clin J Pain*. 2013. Feb;29(2):162-71.
2. Alsherbiny MA & Li CG. Medicinal Cannabis—Potential Drug Interactions. *Medicines (Basel)*. 2019 Mar; 6(1): 3.
3. Baron EP. Medicinal properties of cannabinoids, terpenes, and flavonoids in cannabis, and benefits in migraine, headache, and pain: An update on current evidence and cannabis science. *Headache Currents*. July/August 2018: 1139-1158.
4. Bergamaschi MM, Queiroz RHC, Zuardi AW, et al. Safety and side effects of cannabidiol, a Cannabis sativa constituent. *Current drug safety*. 2011;6:237-249.
5. Blake DR et al. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology (Oxford)* 2006;45:50–2.
6. Bonnet U & Preuss UW. The cannabis withdrawal syndrome: current insights. *Subst Abuse Rehabil*. 2017 Apr 27;8:9-37.
7. Burstein S. Cannabidiol (CBD) and its analogs: a review of their effects on inflammation. *Bioorg Med Chem*. 2015;23(7):1377-85.
8. Devinsky O, Cilio MR, Cross H, et al. Cannabidiol: Pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia*. 2014;55(6): 791–802.
9. Erowid E, Erowid F. "The L.E.S.S. Method: A Measured Approach to Oral Cannabis." *Erowid Extracts* Nov 2011;21:6-9.

Selected References

10. Fine PG et al. The endocannabinoid system, cannabinoids, and pain. *Rambam Maimonides Med J*. 2013 Oct 29;4(4):e0022.
11. Guindon J & Hohmann A. The endocannabinoid system and pain. *CNS Neurol Disord Drug Targets* 2009;8:403-421.
12. Hill KP. Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems: A Clinical Review. *JAMA*. 2015 Jun 23-30;313(24):2474-83.
13. Laprairie RB, Bagher AM, Kelly ME, Denovan-Wright EM. Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor. *British Journal of Pharmacology*. 2015;172(20):4790-4805.
14. MacCallum CA & Russo EB. Practical considerations in medical cannabis administration and dosing. *European Journal of Internal Medicine* 2018;49:12–19.
15. Martin-Sanchez E et al. Systematic review and meta-analysis of cannabis treatment for chronic pain. *Pain Med*. 2009Nov;10(8):1353-68.
16. Moulin D et al. Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. *Pain Res Manag*. 2014 Nov-Dec; 19(6):328-35.
17. Nugent S, Morasco B, O'Neil M, et al. The effects of cannabis among adults with chronic pain and an overview of general harms. *Annals of Internal Medicine* 2017;167(5):319-332.
18. Pennisi E. A new neglected crop: cannabis. *Science*. 2017;356(6335):232-233.
19. Rani Sagar D, Burston JJ, Woodhams SG, Chapman V. Dynamic changes to the endocannabinoid system in models of chronic pain. *Philos Trans R Soc Lond B Biol Sci*. 2012 Dec 5;367(1607):3300-11.

Selected References

20. Rhyne DN, Anderson SL, Gedde M, Borgelt LM. Effects of Medical Marijuana on Migraine Headache Frequency in an Adult Population. *Pharmacotherapy*. 2016 May;36(5):505-10.
21. Russo E. Cannabinoids in the management of difficult to treat pain. *Ther Clin Risk Manag* 2008;4(1):245-259.
22. Russo EB. Clinical Endocannabinoid Deficiency Reconsidered: Current Research Supports the Theory in Migraine, Fibromyalgia, Irritable Bowel, and Other Treatment-Resistant Syndromes. *Cannabis and Cannabinoid Research* 2016 1(1):154-165.
23. Russo EB. Cannabidiol Claims and Misconceptions. *Trends Pharmacol Sci*. 2017 May;38(5):499.
24. Stout SM & Cimino NM. Exogenous cannabinoids as substrates, inhibitors, and inducers of human drug metabolizing enzymes: a systematic review. *Drug Metab Rev*. 2014 Feb;46(1):86-95.
25. Walsh Z, Gonzalez R, Crosby K, et al. Medical cannabis and mental health: a guided systematic review. *Clin Psychol Rev* 2017;51:15-29.