Stanford HEALTH CARE

Medical and Recreational Cannabis:
What's a Clinician to Do?

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Disclosures

- Speakers bureau: Amgen & Lilly Pharmaceuticals
- Any unlabeled/unapproved uses of drugs or products referenced will be disclosed.

Objectives

1) Define the endocannabinoid system.
2) Explore the current research.
3) Review practical clinical basics & safety considerations.

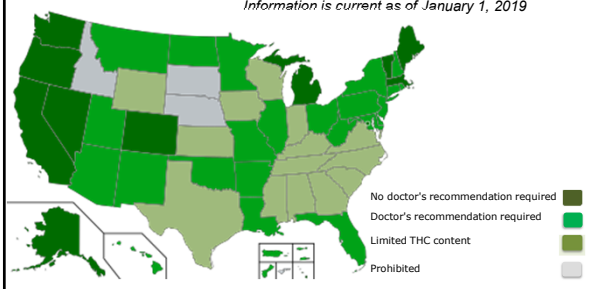
Is this really a big deal?

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

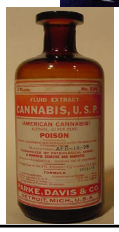
Information is current as of January 1, 2019



https://en.wikipedia.org/wiki/Medical_cannabis_in_the_United_States

Background

- USP 1850-1942
- 1930s U.S. Federal Bureau of Narcotics "Marijuana is a gate-way drug to narcotics addiction."
- 1937 Marijuana Tax Act
- The Controlled Substances Act of 1970
- Hemp Farming Act 2018



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

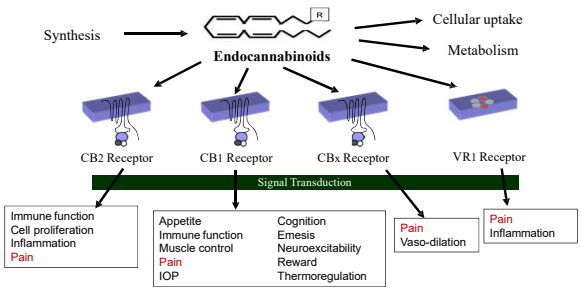
Endogenous – homeostatic - regulatory system inherited by all mammals.

Includes:

- CB1 (CNS) & CB2 (immune & organs) receptor sites
  {CBx & VR1}
- *Endo*cannabinoids
  - *Anandamide*
  - *2-arachidonylglycerol (2AG)*
  - *Nolan ether*
  - *Virodhamine*
  - *NADA*
- Synthesizing & degrading enzymes

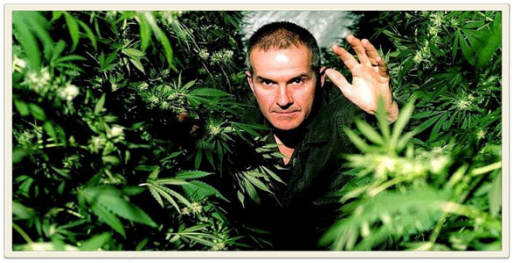
- Cognition & memory
- Appetite & digestion
- Stress response
- Inflammation
- Motor control
- Sleep
- Exploration, social behavior, & anxiety
- Immune/Endocrine function
- Autonomic nervous system
- Antinociception

Endogenous Cannabinoid System

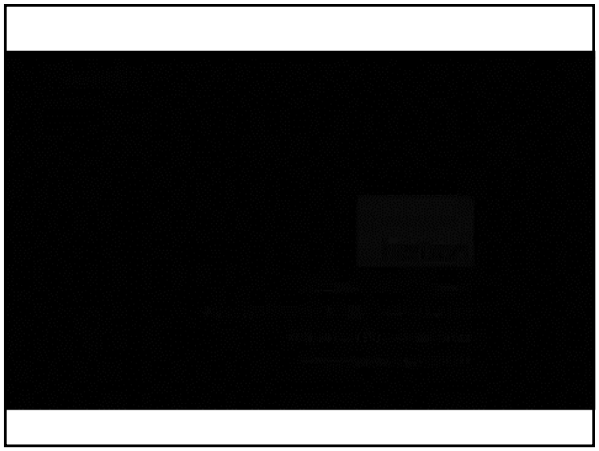


Courtesy of Donald Abrams, MD

YouTube - Cannabinoid Receptors - Horizon: Cannabis - The Evil Weed



http://youtu.be/QGKpbqXwg84



Clinical Endocannabinoid Deficiency:

Ethan Russo, MD (2004/2016)

- The CED 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)?

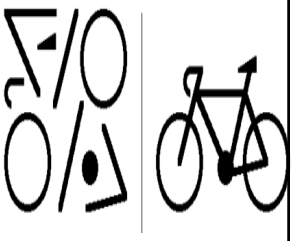
It is a Plant w/over 400 different chemicals:

- >60 types of *phyto*-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

- 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

https://clinicaltrials.gov/

ClinicalTrials.gov Search Results 01/18/2019: 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-Tetrahydrocannabino •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 cap
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 THC •Drug: Smoked Placebo Cannabis L 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 Schmidlkofer, 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

Cochrane Library
Cochrane Database of Systematic Reviews

Cannabis-based medicines for chronic neuropathic pain in adults (Review) 2018

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

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

Cochrane Library
Cochrane Database of Systematic Reviews

Cannabis-based medicines for chronic neuropathic pain in adults (Review) 2018

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

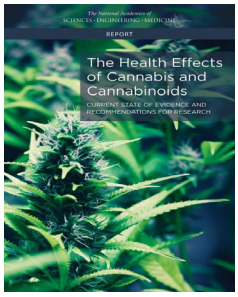
All cannabis-based medicine pooled together were NO better than placebo:

- 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.



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"

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

Is Cannabis a Rational Solution to the Opioid Crisis, or Leading us Down the Rabbit Hole?

Pro/Advocates

- 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.

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)

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.

Cannabinoid: Opioid Interaction Trial: Objectives

- Evaluate effect of vaporized cannabis on blood levels of prescribed opioids:
  - Sustained release morphine
  - Sustained release oxycodone
- Adverse effects of co-administration & pain relief.
- Improved pain relief, no change in opioid serum levels, no increase in cardiovascular or respiratory AEs

(Abrams et al., 2011: Funded in part by NIDA and NIH CRC grants)

CBD for Addiction & OUD?

- CBD has been shown to reduce the rewarding aspects of multiple drugs of abuse, such as cocaine, amphetamine and nicotine (*Parker, et al. 2004; Budzyn, et al. 2009*).
- Pilot clinical studies have shown that in individuals recently abstinent from heroin, CBD reduces heroin craving (*Hurd, et al. 2015*).

Psychopharmacology (Berl). 2004;175:360–366.
Pharmacol Rep. 2009;61:304–310.
Neurotherapeutics. 2015;12:807–815.

Recreational versus Medicinal Cannabis, What are the Differences?

Practical & Theoretical differences

Recreational user

- Reasons other than
- Higher THC content
- "Get High"
- Buying & Selling
- Addiction traits
- 21 y/o

Medicinal user

- Medical purposes
- Lower THC content
- Prefers minimal altered cognition
- Obtain state authorized card
- Obtains products from dispensary
- 18 y/o
- Lower costs and taxes
- Higher quantity restrictions

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.
- Share the extend of the research that is known.
- Provide website resources.
- Discuss drug to plant interactions, side effects, risk of addiction.
- Do Not: Recommend products & dispensaries.

Mental Health

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

Evidence for cannabis dependence from epidemiological studies (Miller & Plant 1996; Malhotra & Biswas 2006).

irritability, anxiety, disturbed sleep, craving

Mental wellness

Worsen sub-clinical, stable mental illness

Effective motivation

Psychosis in genetically susceptable 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, weak partial agonist at CB1 & CB2
- 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
- t1/2 occasional users is 1-2 days, daily users up to 2 weeks

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).

How to Shop for CBD

Consumer Reports

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/

Stirring the Pot: Potential Drug Interactions

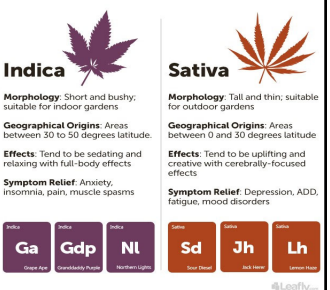
- CYP450 Enzymes: 1A2, 3A4, 2C9, 2C19.
- CNS depressants, antidepressants, central nervous system drugs – potentiate effects of THC.
- Any medications that are metabolized through the same pathways could result in less or more of the drug's effects.
- For scientific reviews: *Drug Metabolism Reviews*.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

Chemical Varieties/"chemovars"

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

- Cannabis Sativa
- Cannabis Indica
- Cannabis Ruderalis

www.leafly.com



Http://www.safeaccessnow.org/using_medical_cannabis

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

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

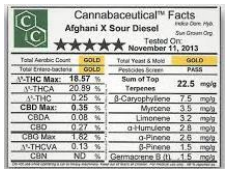
- Dose, variety
- Route (Inhalation, oral, transmucosal, transdermal, topical)
- Timing
- General health (medical co-morbidities), Age
- Use of other substances/medications
- Chronic user of cannabis versus naive

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

Practical Dosing

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).



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

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”.


SFGATE

BAY AREA & STATE SUBSCRIBE

7 Californians hospitalized in ICU after vaping cannabis or CBD oils

Mike Moffitt, SFGATE | on August 16, 2019

Photo: Contributed Photo

LACK OF STARDIZATION 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
- Go **s**low
- **S**upplement as needed

(Erowid & Erowid, 2011)

Tips

- Familiarize yourself with
  - THC, CBD dosing.
  - drug : drug (plant) interactions, side effects, withdrawal.
  - local dispensaries and counsel patient to accordingly.
- **Consider The Treatment Agreement.**
- Continue to remember Federally illegal.
- Informed about state laws.
- Mindful of addiction, abuse, mental health issues.

Final Takeaways

- Cannabinoids emerging as valid option for refractory chronic pain management.
- Innovative solutions to opioid crises needed.
- Cannabinoid-opioid synergy deserves attention.
- Clinical trials challenging to design but necessary to conduct.
- Can no longer refuse to discuss.
- State laws …

Ohio (embraces?) Medical Cannabis

- June 8, 2016, H.B. 523 signed into law - making Ohio the 25th state to adopt medical marijuana.
- Regulatory oversight will be shared among three agencies:
  - The Department of Commerce - oversee cultivators and testing labs.
  - The Board of Pharmacy - oversee the patient registry and dispensaries.
  - State Medical Board of Ohio - oversee physicians.

https://www.medicalmarijuana.ohio.gov/
https://www.medicalmarijuana.ohio.gov/faqs
https://www.mpp.org/states/ohio/

Ohio (embraces?) Medical Cannabis

- **Qualifying Medical Conditions:**
  - AIDS, Alzheimer's disease, amyotrophic lateral sclerosis, cancer, chronic traumatic encephalopathy, Crohn's disease, epilepsy or another seizure disorder, fibromyalgia, glaucoma, hepatitis C, inflammatory bowel disease, multiple sclerosis, chronic or intractable pain, Parkinson's disease, positive status for HIV, PTSD, sickle cell anemia, spinal cord disease or injury, Tourette's syndrome, traumatic brain injury, and ulcerative colitis. …
- **Usage Limitations:** Patients will have access to medical marijuana, including whole plant, extracts, and infused products such as food items.
  - Raw cannabis may not be smoked, but may be vaporized.
  - Patients will be limited to a 90-day supply of medical marijuana.

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)

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

www.ccic.net

International Cannabinoid Research Society (ICRS):
www.icrs2014.org

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

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

http://adai.uw.edu/mcacp/index.htm

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.)

NPs: OR, WA, NY, MA, NM, ME, NJ

http://adai.uw.edu/mcacp/index.htm

MediHuanna - Medicinal Cannabis Education

- Introduction to Medical Cannabis (Module 1) - The Endocannabinoid System
https://youtu.be/6EolVjb1Q5o

- Introduction to Medical Cannabis (Module 2) - Pharmacology & Phytocannabinoids
https://youtu.be/pltZWVsfbS4

- Introduction to Medical Cannabis (Module 3) - Chronic Pain, Palliation & Case Studies
https://youtu.be/DNrHvOQYyFw

- Introduction to Medical Cannabis (Module 4) - CINV & Epilepsy
https://youtu.be/Pubo9AwY7Hq

- Introduction to Medical Cannabis (Module 5) - Adverse Effects & Potential Drug Interactions
https://youtu.be/aao2LVXBTT8

- Introduction to Medical Cannabis (Module 6) - Patient Care, Dosing & Titration
https://youtu.be/_7l_hBm3kUY

THANK YOU

Questions?

References

1. Abrams DI, Couey P, Shade SB, et al. Cannabinoid-opioid interaction in chronic pain. *Clin Pharmacol Ther.* 2011 Dec;90(6):844-51.
2. 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.
3. Andreae MH, Carter GM, Shaparin N, et al. Inhaled Cannabis for Chronic Neuropathic Pain: A Meta-analysis of Individual Patient Data. J Pain. 2015 Dec;16(12):1221-32.
4. 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.
5. Burstein S. Cannabidiol (CBD) and its analogs: a review of their effects on inflammation. Bioorg Med Chem. 2015 Apr 1;23(7):1377-85.
6. Carter G, Weydt P, Kyashna- Tocha M, Abrams D. Medicinal Cannabis: Rational guidelines for dosing. *IDrugs: The Investigational Drugs Journal* 2004;7(5):464-70.
7. Croxford J. Therapeutic potential of cannabinoids in CNS disease. *CNS Drugs* 2003;17(3):179-202.
8. Di Marzo V. The endocannabinoid system: its general strategy of action, tools for its pharmacological manipulation and potential therapeutic exploration. *Pharmacol Res* 2009;60(2):77-84.
9. Erowid E, Erowid F. "The L.E.S.S. Method: A Measured Approach to Oral Cannabis." *Erowid Extracts* Nov 2011;21:6-9.

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. Hazekamp A, & Fischedick J. Cannabis – from cultivar to chemovar. *Drug Testing and Analysis* 2012;4(special issue):660-667.
13. 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.
14. Hua T, Vemuri K, Pu M, et al. Crystal Structure of the Human Cannabinoid Receptor CB1. Cell 2016;167:750–762.
15. Janero D & Makriyannis A. Cannabinoid receptor antagonists: pharmacological opportunities, clinical experieince, and translational prognosis. *Expert Opinion On Emerging Drugs* 2009;14(1):43-65.
16. Johnson JR et al. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. J Pain Symptom Manage. 2010 Feb;39(2):167-79.
17. Kahan M et al. Prescribing smoked cannabis for chronic noncancer pain: preliminary recommendations. Can Fam Physician. 2014 Dec;60(12):1083-1090.
18. Lynch ME et al. Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. Br J Clin Pharmacol. 2011 Nov;72(5):735-44.

References

19. MacCallum CA & Russo EB. Practical considerations in medical cannabis administration anddosing. *European Journal of Internal Medicine* 2018;49:12–19.
20. Malhotra A & Biswas P. Cannabis Use and Performance in Adolescents. *Journal of Indian Associationfor Child and Adolescent Mental Health* 2006;2(2):59-67.
21. Martin-Sanchez E et al. Systematic review and meta-analysis of cannabis treatment for chronic pain. Pain Med. 2009Nov;10(8):1353-68.
22. McPartland J. Phylogenomic and chemotaxonomic analysis of the endocannabinoid system. *Brain Res Rev* 2004;45(1):18-29.
23. Melton S. Stirring the Pot: Potential Drug Interactions with Marijuana. …
24. Miller P & Plant M. Drinking, smoking, and illicit drug use among 15 and 16 year olds in the United Kingdom. *BMJ* 1996 Aug 17;313(7054):394-7.
25. 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.
26. Murry R, Quigley H, Quattrone D, et al. Traditional marijuana, high-potency cannabinoid and synthetic cannabinoids: increasing risk for psychosis. *World Psychiatry* 2016;15(3):195-204.
27. 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.
28. Oláh A, Tóth BI, Borbíró I, et al. Cannabidiol exerts sebostatic and antiinflammatory effects onhuman sebocytes. J Clin Invest. 2014 Sep;124(9):3713-24.

References

28. Pacher P, Batkai S, & Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. *Diabetes* 2006;55(3):389-462.
29. Price M, Baillie G, Thomas A, et al. Allosteric modulation of the cannabinoid CB1 receptor. *Mol Pharmacol* 2005;68(5):1484-95.
30. Rani Sagar D, Burston JJ, Woodhams SG, Chapman V. Dynamic changes to the endocannabinoid systemin models of chronic pain. Philos Trans R Soc Lond B Biol Sci. 2012 Dec5;367(1607):3300-11.
31. Rom S & Persidsky Y. Cannabinoid receptor 2: Potential role in immunomodulation and neuroimflammation. J *Neuroimmune Pharmacol* 2013;8:608-620.
32. Russo E. Clinical endocannabinoid deficiency (CECD): Can this concept explain therapeutic benefitsof cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment resistant conditions? *Neuroendocrinol Lett* 2004;25(1-2):31-39.
33. Russo EB. Clinical Endocannabinoid Deficiency Reconsidered: Current Research Supports the Theoryin Migraine, Fibromyalgia, Irritable Bowel, and Other Treatment-Resistant Syndromes. *Cannabis and Cannabinoid Research* 2016 1(1):154-165.
34. Russo E. Cannabinoids in the management of difficult to treat pain. *Ther Clin Risk Manag* 2008;4(1):245-259.
35. Sorensen CJ, DeSanto K, Borgelt L, et al. Cannabinoid Hyperemesis Syndrome: Diagnosis, Pathophysiology, and Treatment-a Systematic Review. J Med Toxicol. 2017, 13(1):71-87.
36. Walsh Z, Gonzalez R, Crosby K, et al. Medical cannabis and mental health: a guided systematicreview. *Clin Psychol Rev* 2017;51:15-29.
37. Wilkerson J & Milligan E. The central role of glia in pathological pain and the potential of targeting the cannabinoid 2 receptor for pain relief. *ISRN Anesthesiol* 539894:2011