



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

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Disclosure

Speakers Bureau: Allergan, Amgen, & Lilly Pharmaceuticals

Any unlabeled/unapproved uses of drugs or products
referenced will be disclosed.



Learning Objectives

- Define the endocannabinoid system
- Discuss evidence for cannabinoids in pain management
- Review practical clinical basics & safety considerations



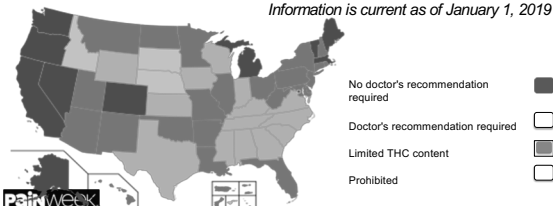
Is this really a big deal?

- Most states (Guam & DC) in the US that 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 – World Economics Forum
- Federally illegal! Major confusion?!



Is this really a big deal? (cont'd)

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



Background

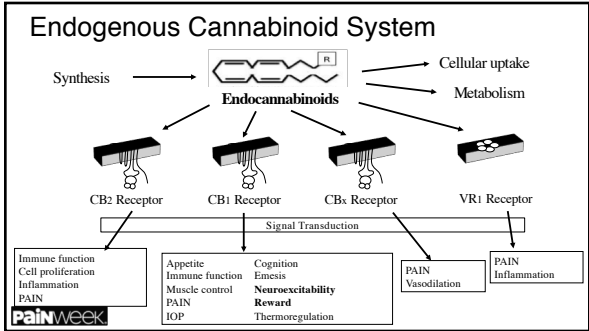
- USP 1850-1942
- 1930s U.S. Federal Bureau of Narcotics sought to portray marijuana "gate-way" drug to narcotics addiction
- 1937 Marijuana Tax Act
- The Controlled Substances Act of 1970
- Agriculture Act 2014 – Hemp Farming Act 2018



Endocannabinoid System


- Endogenous - homeostatic regulatory system inherited by all mammals
- Includes:
 - CB1 & CB2 receptor sites {CBx Receptor & VR1 Receptor}
 - Endocannabinoids {anandamide, 2AG, Nolan ether, NADA virodhamine}
 - Synthesizing and degrading enzymes
- Cognition & memory
- Appetite & digestion
- Stress response
- Inflammation
- Motor control
- Sleep
- Exploration, social behavior, & anxiety
- Immune/endocrine function
- Autonomic nervous system
- Antinociception

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Clinical Endocannabinoid Deficiency

Ethan Russo, MD (2004)




- 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

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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



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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)



clinicaltrials.gov/cannabis

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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 Niso, 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

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


■ META-ANALYSIS Anesth Analg 2017;125:1638-52.

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, FPMRCA, 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

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 **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

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 **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:

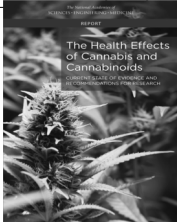
- Improving health-related QOL
- Stopping medication because it was not effective
- Frequency of serious side effects

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.

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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"

Research
Original Investigation

JAMA Intern Med. doi:10.1001/jamainternmed.2014.4005
Published online August 25, 2014.

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% lower mean annual opioid overdose mortality rate compared with states without medical cannabis laws."

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Is Cannabis a Rational Solution to the Opioid Crisis?

<p>Pro/Advocates</p> <ul style="list-style-type: none"> ▪ Reasonable 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 	<p>Con/Critics</p> <ul style="list-style-type: none"> ▪ Substitution of one addictive substance for another ▪ Side effects underrecognized (eg, psychosis) ▪ Evidence hasn't proven benefit for pain
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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-tetrahydrocannabinol (delta-9-THC) is 3.6 times lower than the of morphine alone.
- For codeine administered in combination with delta-9-THC was 9.5 times lower than of codeine alone.



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

CBD for Addiction & OUD

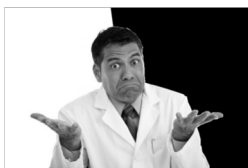
▪ CBD has been shown to reduce the rewarding aspects of multiple drugs of abuse, such as cocaine, amphetamine and nicotine (*Parker, et al. 2004; Budzyn, et al. 2009*).

▪ 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.



I know nothing about cannabis!



Important Talking Points

- Encourage open 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 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 subclinical, 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
- >65% excreted in the feces, ~20% urine
- t1/2 occasional users is 1-2 days, daily users up to 2 weeks

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Cannabidiol (CBD)

<p>Defining Terms:</p> <ul style="list-style-type: none"> ▪ CBD from hemp ▪ CBD from cannabis sativa ▪ Hemp oil <p>▪ Safety: Dosing toxicity? Anti-inflammatory effects? CYP450 metabolism</p> <p>▪ Side effects: Fatigue, diarrhea, changes of appetite/weight, dry mouth. Transaminase elevations (reported in Epidiolex studies)</p>	<p>Research:</p> <ul style="list-style-type: none"> – Epidiolex® – Other - preliminary research included studies of anxiety, cognition, movement disorders, and pain (anti-inflammatory) – Efficacy most antidotal (discuss current animal studies)
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Stirring the Pot: Potential Drug Interactions

- CYP450 enzymes: 1A2, 3A4, 2C9, 2C19
- CNS depressants, antidepressants, central nervous system drugs – potentiate effects of THC


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

Varieties/Strains

- Though cannabis is biologically classified as the single species Cannabis Sativa, there are at least 3 distinct plant varieties:
 - Cannabis Sativa
 - Cannabis Indica
 - Cannabis Ruderalis
- www.leafly.com
- http://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

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

Ga
Green Apple

Gdp
Guadalupe Dope

NI
Northern Lights

Sd
Super Diesel

Jh
Jack Herer

Lh
Lemon Haze

@Leafly...

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 comorbidities), age
 - Use of other substances/medications
 - Chronic user of cannabis vs naive

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

Practical Dosing (cont'd)

Average adult dosing of THC for:

- Cannabis-naïve individuals 2.5-5 mg
- Daily to weekly users 10-20 mg
- Daily+ 25 mg+

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

Average adult dosing of CBD:

- 300-1500 mg/day

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



Practical Dosing (cont'd)

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 & clinicians

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)



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
- 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 ...



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 (eg, FL)



Resources (cont'd)

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): <http://icrs.co/>
International Cannabis & Cannabinoid Institute: <https://www.icci.science/en/>

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>



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 (pain management, palliative care, etc)

NPs: OR, WA, NY, MA, NM



THANK YOU

Questions?



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