

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

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Painweek

Disclosure

Speakers Bureau: Allergan, Amgen, Lilly Pharmaceuticals

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

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Learning Objectives

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

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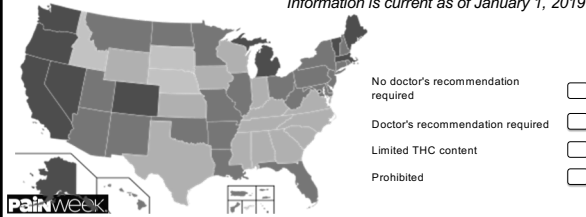
Is this really a big deal?

- 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

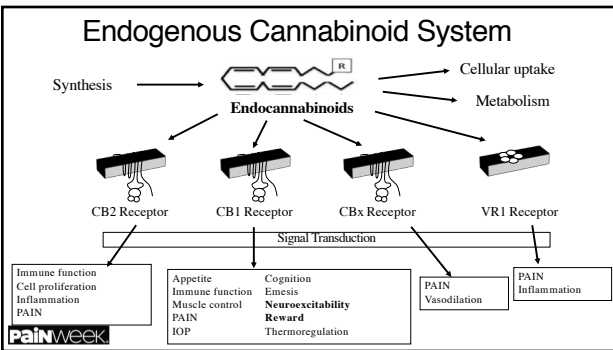
Endogenous - homeostatic regulatory system inherited by all mammals

Includes:

- CB1 & CB2 receptor sites
- CBx Receptor & VR1 Receptor
- Endocannabinoids
- anandamide, 2AG, Nolen 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



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



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 Kilgipen, 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 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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 **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

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 **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:

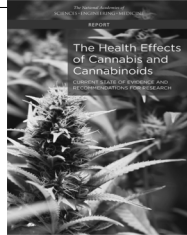
- Improving health-related QOL
- Stopping medication because it was not effective
- Frequency of serious side effects

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



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?

Pro/Advocates

- 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 (Dr. Cunningham at Albert Einstein).

Con/Critics

- Substitution of one addictive substance for another.
- Side effects under recognized (eg, 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-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.

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


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

Marcus A. Bachhuber, MD, Brendan Saloner, PhD, Chiraz 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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I know nothing about cannabis!



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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 and 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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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 out 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

PainWeek <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



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

Indica
Ga
Orange Ace

Indica
Gdp
Goldberry Pops

Indica
Nl
Norman Light

Sativa
Sd
Straw Diesel

Sativa
Jh
Jack Herer

Sativa
Lh
Lemon Head

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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/6802>

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)



Final Takeaways

- Cannabinoids emerging as valid option for refractory chronic pain management
- Innovative solutions to opioid crises needed
- Cannabinoid-opioid synergy deserves attention
- Consider "Treatment Agreement"
- Mindful of addiction, abuse, mental health issues
- 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/mcaco/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 (eg, pain management, palliative care)

NPs: OR, WA, NY, MA, NM



THANK YOU

Questions?

