

Medical Efficacy of Cannabis Therapeutics: Focus on Pain Management PAINWeek-End 2018

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Disclosure

Speakers bureau Allergan, Amgen & Pernix
Pharmaceuticals

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



Condition of the times

- Why is this lecture being presented at PWEnd 2018?
- Why is it a timely topic in pain management?
- What are the three key take a ways today:
 - Where to start the discussion
 - How to counsel patient's about dosing
 - The best resources to provide



Learning Objectives

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



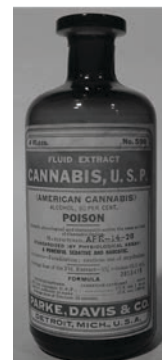
Is this really a big deal?

- 29 states, as well as DC, Guam & Puerto Rico, that have legislation for the “legal” use of medicinal marijuana.
- 8 states & DC “legalized” recreational use.
- Global financial impact
- Canada = Cannabis Act
- UK = Legalize medicinal marijuana
- FDA just approved EPIDIOLEX® (cannabidiol) oral solution, pending DEA scheduling action.
- Federally illegal! Major confusion?!

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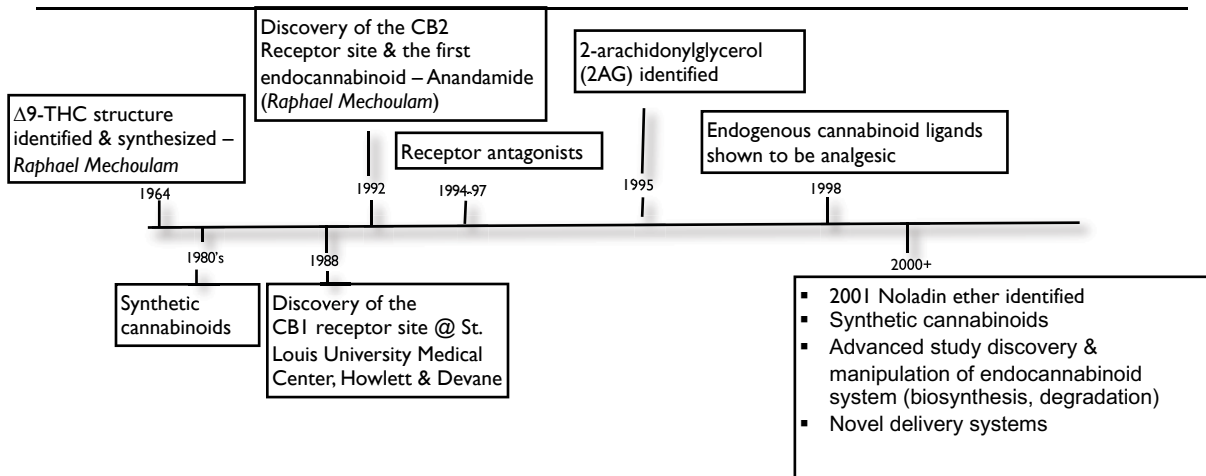
Background

- 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



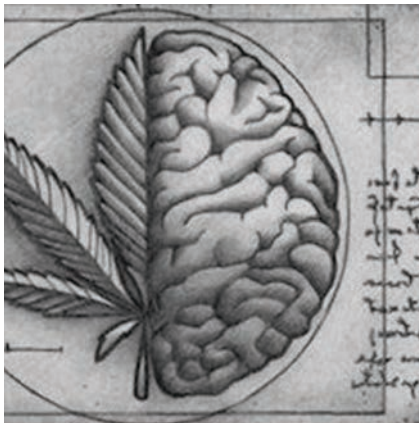
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Milestones in Cannabinoid Science



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Endocannabinoid System (ECS)



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<http://herb.co/2016/07/28/endocannabinoid-system-dummies/>

Endocannabinoid System

Endogenous - homeostatic regulatory system inherited by all mammals.

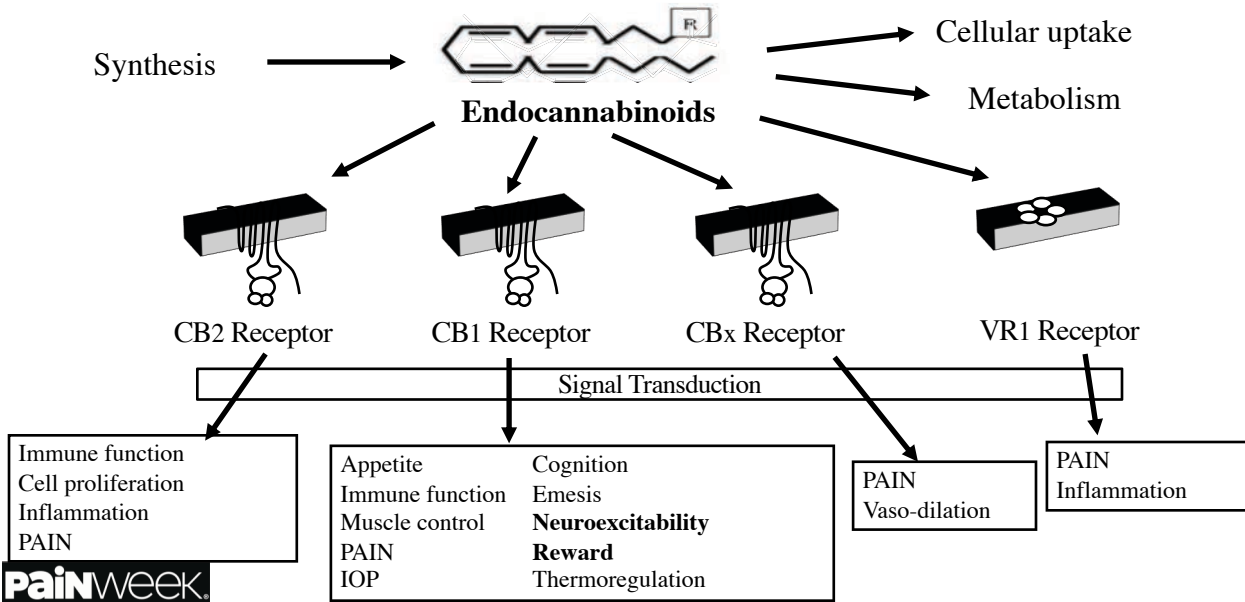
Includes:

- CB1 & CB2 receptor sites {CBx Receptor & VR1 Receptor}
- Endocannabinoids {anandamide, 2AG, Nolen ether, virodhamine, NADA}
- 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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Endogenous Cannabinoid System





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.

What is 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?



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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)



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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 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.

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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, FRCP, 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.

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

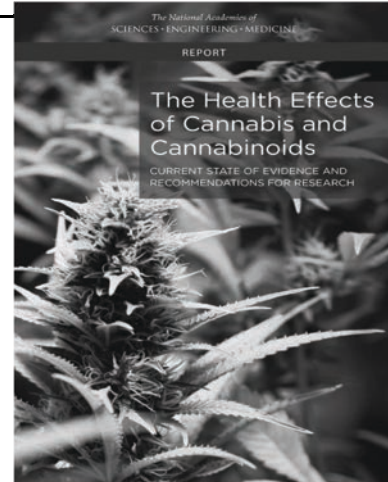
- Improving health-related QOL
- Stopping medication because it was not effective
- Frequency of serious side effects

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"

CONSENSUS STATEMENT

Pharmacological management of chronic neuropathic pain: Revised consensus statement from the Canadian Pain Society

DE Moulin MD, A Boulanger MD, AJ Clark MD, H Clarke MD PhD, T Dao DMD PhD, GA Finley MD, A Furlan MD PhD, I Gilron MD MSc, A Gordon MD, PK Morley-Forster MD, BJ Sessle MDS PhD, P Squire MD, J Stinson RN PhD, P Taenzer PhD, A Velly DDS PhD, MA Ware MD, EL Weinberg MD, OD Williamson MBBS

Pain Res Manag
2014;19(6):328-335

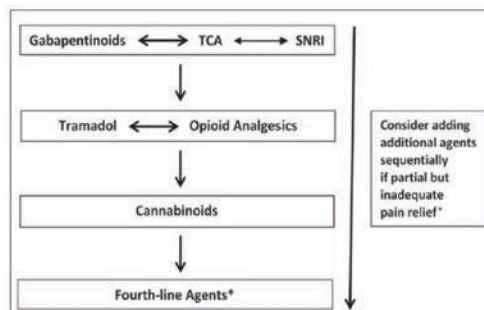


Figure 1) Algorithm for the pharmacological management of neuropathic pain. *Topical lidocaine (second line for postherpetic neuralgia), methadone, lamotrigine, lacosamide, tapentadol, botulinum toxin; *Limited randomized controlled trial evidence to support add-on combination therapy. TCA Tricyclic antidepressants; SNRI Serotonin noradrenaline reuptake inhibitors

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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.

“Pre-clinical studies provide robust evidence of the opioid-sparing effect of cannabinoids.”



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

JAMA Internal Medicine | Original Investigation | HEALTH CARE POLICY AND LAW

Association Between US State Medical Cannabis Laws and Opioid Prescribing in the Medicare Part D Population

Ashley C. Bradford, BA; W. David Bradford, PhD; Amanda Abraham, PhD; Grace Bagwell Adams, PhD

- From 2010 to 2015 there were 23.08 million daily doses of any opioid dispensed per year in the average state under Medicare Part D.
- Prescriptions for all opioids ↓ by 2.11 million daily doses per year, when a state instituted medical cannabis law.
- Prescriptions for all opioids ↓ by 3.742 million daily doses per year, when medical dispensaries opened.

“Medical cannabis policies may be one mechanism that can encourage lower prescription opioid use & service as a harm abatement tool in the opioid crisis.”



JAMA Intern Med. 2018;178(5):667-672.

Research

JAMA Internal Medicine | Original Investigation | HEALTH CARE POLICY AND LAW

Association of Medical and Adult-Use Marijuana Laws With Opioid Prescribing for Medicaid Enrollees

Hefei Wen, PhD; Jason M. Hockenberry, PhD

- Population-based, cross-sectional study using the all-capture Medicaid opioid prescription data for 2011 to 2016.
- Medical marijuana laws & adult-use marijuana laws were associated with lower opioid prescribing rates (5.88% & 6.38% lower, respectively).

JAMA Intern Med. 2018 May 1;178(5):673-679

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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; 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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The National Institutes of Health recently awarded a 5-year \$3.8 million grant to Albert Einstein College of Medicine and Montefiore Health System

- To determine if medical marijuana reduced opioid consumption in specific patient groups.
- “There is a lack of information about the impact of medical marijuana on opioid use in those with chronic pain. We hope this study will fill in the gaps and provide doctors and patients with some much-needed guidance.”



Principal Investigator
Chinazo Cunningham, MD, MS

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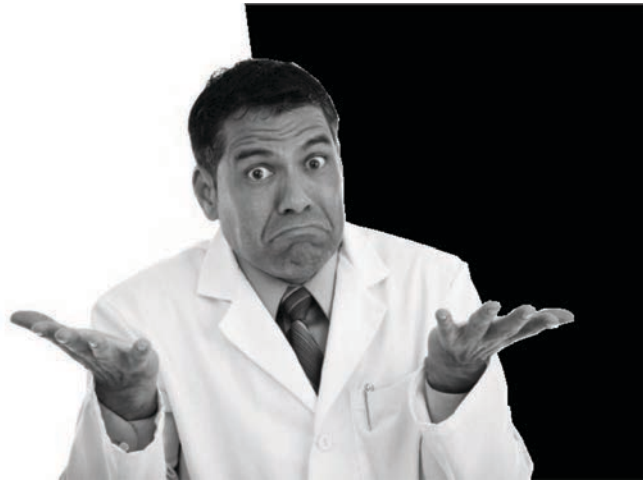
Provision added to Illinois Compassionate Use of Medical Cannabis Pilot Program – SB336 “Alternatives to Opioids Act of 2018”

Treating physician to refer a patient to the “Opioid Alternative Pilot Program” for conditions where an opioid might otherwise be prescribed.

- Written certification to the Department of Public Health (patient & physician).
- Clear documentation of medical need and ongoing treating relationship.
- Patients must be at least 21 y/o, register with a licensed dispensary.
- Limited to 2.5 ounces every 14 days, cannot exceed 90 days per MD certification.

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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 & dispensaries

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

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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

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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.
- Smoking more than two joints weekly is likely to increase the risk of drug-related interactions. (*Horn & Hansten, 2014*)

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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
- t_{1/2} occasional users is 1-2 days, daily users up to 2 weeks

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Inhaled versus 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 three distinct plant varieties:

- *Cannabis Sativa*
- *Cannabis Indica*
- *Cannabis Ruderalis*

www.leafly.com

http://www.safeaccessnow.org/using_medical_cannabis

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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



Leafly.com

Practical Dosing

(Thank you to Mariavittoria Mangini, PhD, FNP)

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 naïve



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

Practical Dosing

(Thank you to Mariavittoria Mangini, PhD, FNP)

Average adult dosing of THC for:

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

To convert % cannabinoids & terpenoids/gram to milligrams, move the decimal one place to the right

- 20% THC = 200 mg THC/gram of cannabis
- 2% CBD = 20 mg CBD/gram of cannabis
- 0.20% β -caryophyllene = 2.0 mg/gram of cannabis



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 **L**ow
- Establish potency
- Go **s**low
- Supplement as needed



(Erowid & Erowid, 2011)

Practical Dosing: RX

dronabinol (Marinol/Syndros) – Schedule III drug

A synthetic version of THC & does not contain CBD (cannabidiol) or other cannabinoids. *Recommended dosing oral 2.5-10 mg twice daily*

nabilone (Cesamet) – Schedule II drug

A synthetic cannabinoid agonist (an analog of dronabinol) & does not contain CBD (cannabidiol) or other cannabinoids. *Recommended dosing oral 1-2 mg twice daily.*

nabiximols (Sativex) – Not available in US

- An oromucosal spray → fixed dose of 2.7mg THC & 2.5mg CBD.
- Muscle stiffness/spasm due to multiple sclerosis.

cannabidiol (Epidiolex) – Approved FDA

- CBD pure-plant-derived product for epilepsy.
- 2.5mg/kg – 10mg/kg taken twice daily.



 Contents lists available at ScienceDirect European Journal of Internal Medicine journal homepage: www.elsevier.com/locate/ejim Review Article Practical considerations in medical cannabis administration and dosing Caroline A. MacCallum^{a,*}, Ethan B. Russo^b 			
Table 1 Cannabis routes of administration. European Journal of Internal Medicine 49 (2018) 12–19			
Cannabis routes of administration			
Smoking	Vaporisation	Oral	Other routes
• Most common route of administration, but not recommended (joints, bongs, pipes, etc.) • Combustion at 600–900 °C producing toxic biproducts: tar, PAH (polycyclic aromatic hydrocarbons), carbon monoxide (CO), ammonia (NH₃). • Chronic use associated with respiratory symptoms (bronchitis, cough, phlegm), but not lung cancer nor COPD (if cannabis only). • Patients may mix with tobacco increasing respiratory/cancer risk • 30–50% of cannabis is lost to 'side-stream' smoke	• Heats cannabis at 160–230 °C. Reduced CO, but not complete elimination of PAH demonstrated to date. • Vaporisation produces significantly less harmful biproducts vs. smoking. • Decreased pulmonary symptoms reported compared to smoking.	• Oils, capsules and other po routes increasingly popular due to convenience and accuracy of dosing. • Edibles (brownies/cookies) may be more difficult to dose. • Juicing and cannabis teas do not allow for adequate decarboxylation of raw plant • Nabiximols oromucosal spray is currently the only cannabis-based prescription that delivers standardised dosage of CBD/THC in a 1:1 ratio with extensive research • Tinctures and lozenges intermediate onset with limited research	• Topicals ideal for localised symptoms (dermatological conditions, arthritis), with limited research evidence • Suppositories possibly indicated for specific populations (cancer, GI symptoms, young/elderly, etc.) with variable absorption. THC-hemisuccinate may allow for best absorption with limited research. • Recreational routes include 'shatter', 'dabs', concentrates. Deliver very high doses of THC with high risk of euphoria, impairment, reinforcement, toxic psychosis, orthostatic hypotension. Inappropriate for medical application.

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/>

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



MediHuanna - Medicinal Cannabis Education

- Introduction to Medical Cannabis (Module 1) - The Endocannabinoid System by Dr. Towpik
<https://youtu.be/6EolVjb1Q5o>
- Introduction to Medical Cannabis (Module 2) - Pharmacology & Phytocannabinoids by Dr. Towpik
<https://youtu.be/pltZWVsfbS4>
- Introduction to Medical Cannabis (Module 3) - Chronic Pain, Palliation & Case Studies by Dr. Towpik
<https://youtu.be/DNrHvOQYyFw>
- Introduction to Medical Cannabis (Module 4) - CINV & Epilepsy by Dr. The
<https://youtu.be/Pub09AwY7Hg>
- 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 by Dr. The
 https://youtu.be/7I_hBm3kUY

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: CA, OR, WA, NY, MA, NM

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Tips

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

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Conclusion

- 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.



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THANK YOU

Questions?



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