



Medical Efficacy of Cannabis Therapeutics: Focus on Pain Management

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Disclosure

- Speakers bureau: Allergan & Pernix Pharmaceuticals
- Any unlabeled/unapproved uses of drugs or products referenced will be disclosed



Learning Objectives

- Define the endocannabinoid system
- Discuss the medicinal use of cannabinoids in pain
- Explore the current research in pain



Condition of the times

- Why is this lecture being presented at PAINWeekEnd 2018?
- Why is it a timely topic in pain management?
- What are the 3 key takeaways today?
 - Where to start the discussion
 - How to counsel patients about dosing
 - The best resources to provide



Background

- USP 1850-1942
- 1930s U.S. Federal Bureau of Narcotics sought to portray marijuana as a “gate-way” drug to narcotics addiction
- 1937 Marijuana Tax Act
- The Controlled Substances Act of 1970
- The Compassionate Investigational New Drug Program (1978), federally sponsored program allowing a limited number of patients to use medical marijuana grown at the University of Mississippi



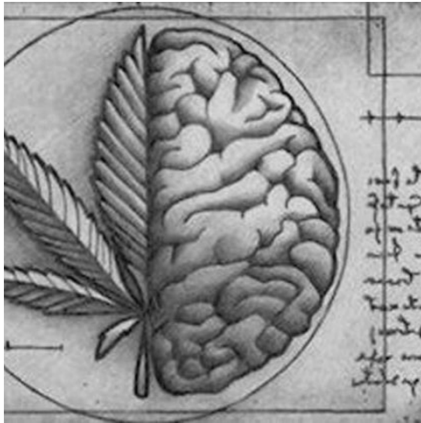
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Milestones in Cannabinoid Science

1964	Δ^9 -THC synthesized and structure identified	(Raphael Mechoulam)
1980s	Synthetic cannabinoids	
1988	CB1 receptor identified	
1989	(Howlett & Devane @St. Louis University Medical School)	
1990	CB1 receptor cloned	
1992	CB2 receptor	
1992	Anandamide	(Raphael Mechoulam)
1993	CB2 receptor cloned	
1995	2-arachidonylglycerol (2AG) identified	
1994-7	Receptor antagonists	
1998	Endogenous ligands shown to be analgesic	
2001	Noladin ether identified	
2000+	Synthetic cannabinoids, more on the endogenous system, biosynthesis and degradation, delivery systems	

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Endocannabinoid System (ECS)



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

ECS (cont'd)

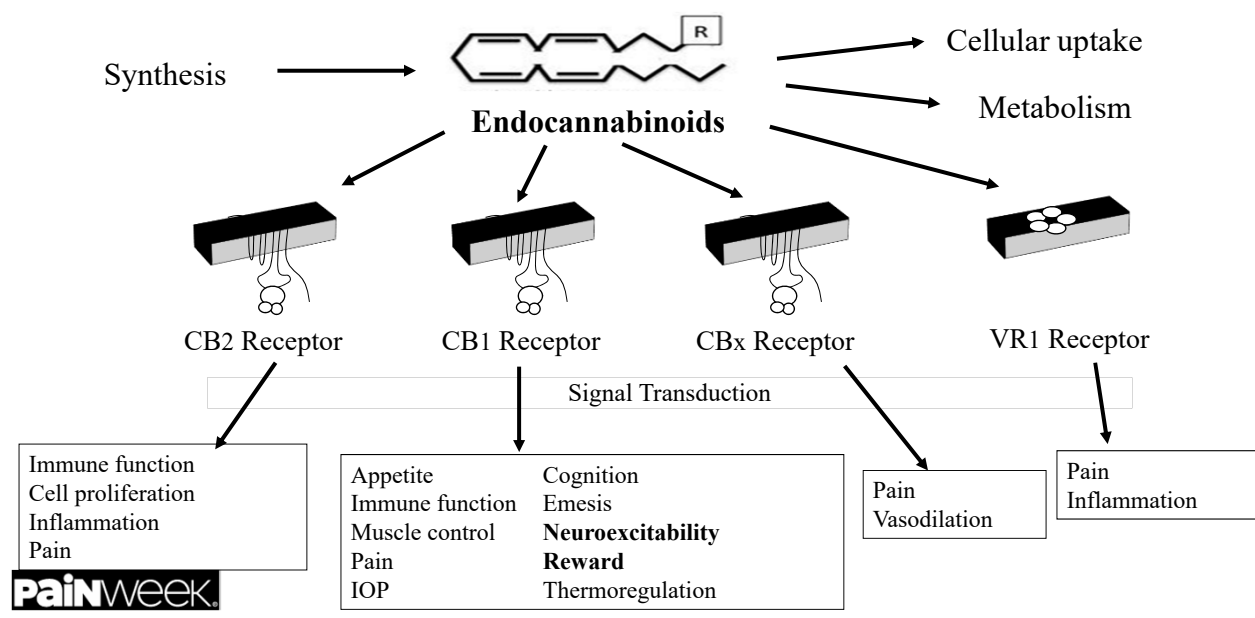
Endogenous - homeostatic regulatory system inherited by all mammals

Includes:

- CB1 & CB2 receptor sites (CBx receptor & VR1 receptor)
- Endocannabinoids (anandamide, 2AG, Nolan 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

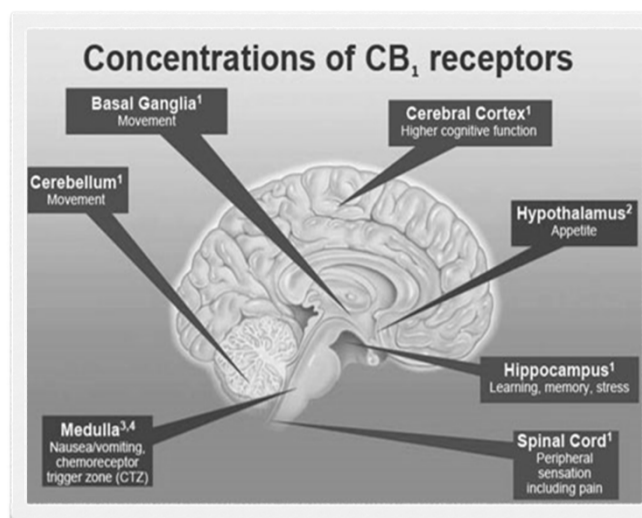
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Endogenous Cannabinoid System

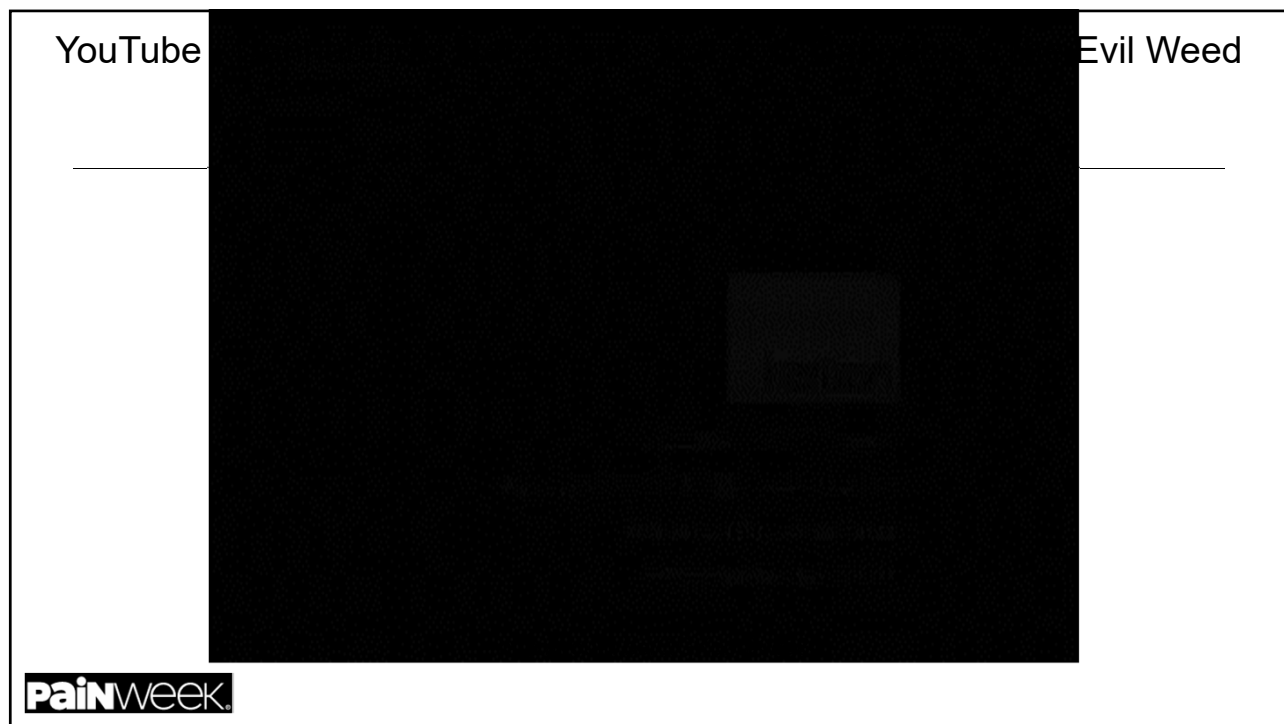


High density of receptor sites in the CNS, account for the effects seen by (THC)

- Euphoria
- Anxiety
- Anxiolysis
- Coordination
- Antinociception
- Cognitive disturbances



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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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Endocannabinoid System (modulation/manipulation)

- Enhancing the ESC through inhibiting the breakdown of endocannabinoids (EC)
- Supporting EC viability/action/more selective
- Supplementation with phytocannabinoids (CBD/THC), role of terpenes

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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?



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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/us/nj_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

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

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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

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Pharmacodynamics delta-9-tetrahydrocannabinol

- Cannabinoids appear to effect the same reward systems as alcohol, cocaine, and opioids
- Evidence for cannabis dependence is now available from epidemiological studies of long-term users (Miller & Plant 1996; Malhotra & Biswas2006)
- Symptoms such as irritability, anxiety, craving, and disturbed sleep have been reported in 60% to 90% of cannabis users during abstinence
- Cannabis and mental illness
 - Worsen underlying (subclinical), previously stable chronic mental illness
 - Effect motivation
 - Psychosis in genetically susceptible individuals

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Pharmacodynamics

delta-9-tetrahydrocannabinol (cont'd)

Tolerance to cannabis:

- Mood, sleep
- Psychomotor performance
- Arterial pressures
- Antiemetic properties

Common adverse effects:

- Anticholinergic effects (dry mouth, blurry vision, urinary retention, tachycardia, hypertension)
- CNS effects (ataxia, cognitive dysfunction, hallucinations)



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 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)

(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

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Lack of Standardization Makes Dosing a Challenge for Patients and 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 low
- Establish potency
- Go slow
- Supplement as needed

(Erowid & Erowid, 2011)

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Practical Dosing: RX

Dronabinol (Marinol) – Schedule III drug: Chemical Formula C21-H30-O2

- A prescribed capsule, used to treat nausea and vomiting caused by chemotherapy and loss of appetite and weight loss in people who have acquired immunodeficiency syndrome (AIDS). It is a synthetic version of THC suspended in sesame oil and does not contain CBD (cannabidiol) or other cannabinoids. *Recommended dosing oral 2.5-10 mg twice daily*

Nabilone (Cestamet) – Schedule II drug: Chemical Formula C24-H36-O3

- A prescribed capsule, used to treat nausea and vomiting caused by chemotherapy. It is a synthetic version of THC suspended in sesame oil and does not contain CBD (cannabidiol) or other cannabinoids. *Recommended dosing oral 1-2 mg twice daily. 20% bioavailable after first-pass.* An analog of dronabinol (synthetic THC).



Practical Dosing: RX (cont'd)

Nabiximol (Sativex) – not available in US: chemical formula C42-H60-O4

- An oromucosal (mouth) spray to alleviate various symptoms of MS and cancer, including neuropathic pain, spasticity, overactive bladder, and other symptoms, depending on the country
- Derived from 2 strains of cannabis, the principal active cannabinoid components are THC and CBD suspended in ethanol
- *Each spray of Sativex delivers a fixed dose of 2.7 mg THC & 2.5 mg CBD*



Stirring the Pot: Potential Drug Interactions

Smoking more than 2 joints weekly is likely to increase the risk of drug-related interactions. (Horn & Hansten, 2014; Jusko, 1979)

CYP450 enzymes: 1A2, 3A4, 2C9, 2C19

- CNS depressants – potentiate effects
- Antidepressants, sympathomimetics - depression, anxiety, mania, tachycardia, hypertension
- Antiepileptic drugs (AEDs)
- Other (lithium, valproate, warfarin, theophylline, antiretroviral, protease inhibitors) - increased serum levels
- Disulfiram (Antabuse) - hypomania, agitation, and irritability

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Cannabis: Pregnancy

- Affects on neonatal brain functional connectivity (Salzwedel AP, et al. J Neurosci. 2015;35:5860-5869)
- New study shows “no associated rates of birth defects when used by pregnant ♀” (Mark K, et al. Arch Womens Ment Health. 2015)
- Cannabinoid in pregnancy - dronabinol category C

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Tips

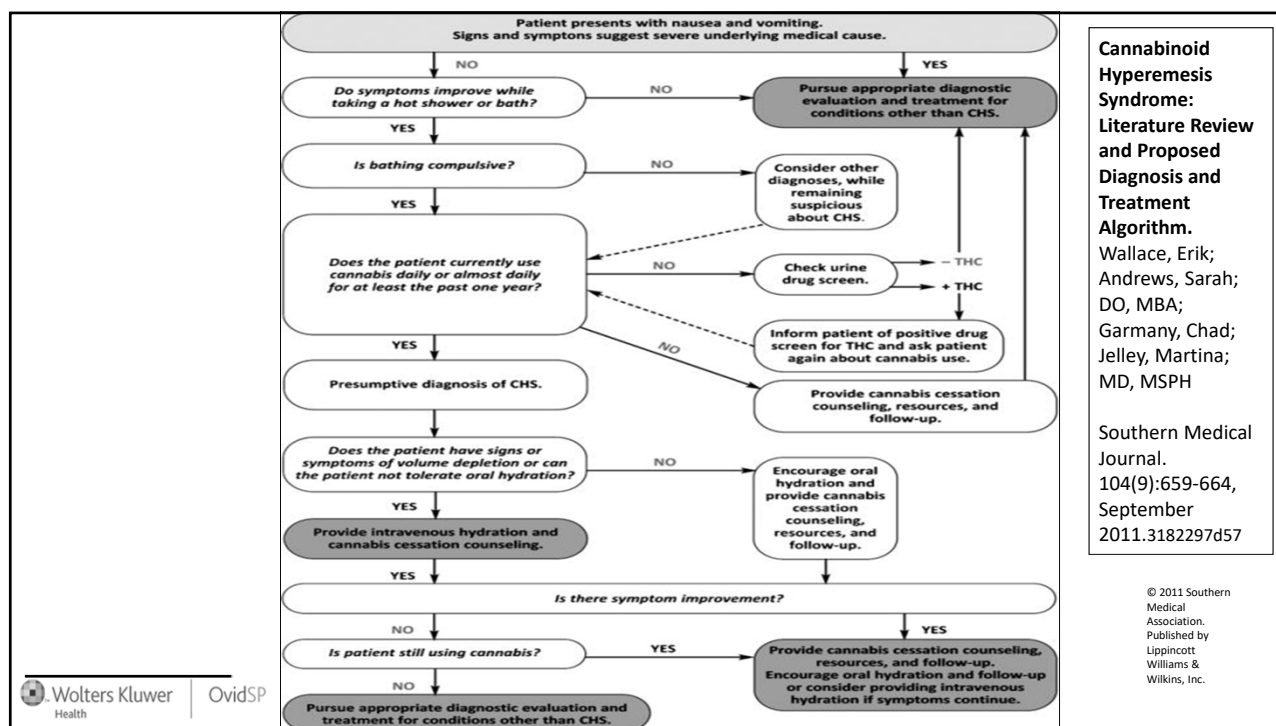
- Familiarize yourself with THC, CBD dosing
- Familiarize yourself with drug : drug (plant) interactions, side effects, withdrawal
- Familiarize yourself with local dispensaries and refer patient to accordingly
- Consider The Treatment Agreement

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Cannabinoid Hyperemesis Syndrome (CHS)

- What is it?
- Is it really that common?
- Why now?
- Treatment?

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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

- Medicinal Cannabis Research Foundation (MCRF): UK
- Spain, Germany, Italy
- ICRS: [http:// www.cannabinoidsociety.org](http://www.cannabinoidsociety.org)



Stakeholder Meeting for the
National Academies' Report:

The Health Effects of Cannabis and Cannabinoids:

The Current State of
Evidence and
Recommendations for
Research

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Health Effects of Cannabis and Cannabinoids

Therapeutics

- In adults with chemotherapy induced nausea and vomiting, oral cannabinoids are effective antiemetics.
- In adults with chronic pain, patients who were treated with cannabis or cannabinoids are more likely to experience a clinically significant reduction in pain symptoms
- In adults with multiple sclerosis (MS) related spasticity, short-term use of oral cannabinoids improves patient-reported spasticity symptoms.
- For these conditions the effects of cannabinoids are modest; for all other conditions evaluated there is inadequate information to assess their effects.

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Cannabinoids and Pain

- Elevated levels of the CB1 receptor—like the opioid—are found in areas of the brain that modulate nociceptive processing
- CB1 & CB2 agonists have peripheral analgesic actions
- Cannabinoids may also exert anti-inflammatory effects
- Analgesic effects not blocked by opioid antagonists
- Combination of THC & CBD

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Research in Pain Management

Intervention	Quality of Evidence	Additional Comments
Neuropathic Pain	High	i. Andreae MH et al. 2015 ii. Moulin D et al. 2014 iii. Nugent S et al. 2017 <u>CPS Consensus Statement:</u> <i>I. Gabapentinoids, TCAs, SNRIs</i> <i>II. Tramadol, SR opioids</i> <i>III. Cannabinoids</i>
Inflammatory Pain	Low	i. Burstein S. 2015 ii. Oláh A et al. 2014 iii. Blake DR et al. 2006
Chronic Pain	High	i. Nugent S et al. 2017 ii. Hill K et al. 2015 iii. Aggarwal SK et al. 2013 iv. Lynch ME et al. 2011 v. Martin-Sanchez E et al. 2009

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Cannabinoid: Opioid Interactions

- Share several pharmacologic properties:
 - Antinociception
 - Hypothermia
 - Sedation
 - Hypotension
 - Inhibition of intestinal motility and locomotion
- Cannabinoids interact with kappa and delta receptors in production of pain relief
- Analgesic effects of opioids mediated by mu receptors, but may be enhanced by cannabinoid effects (CB1)

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Cannabinoid: Opioid Interactions (cont'd)

- Cannabinoid: opioid interaction may occur at the level of their signal transduction mechanisms:
 - Receptor activation for both leads to decreased cAMP production via G protein activation
 - Some evidence that cannabinoids might increase production or release of endogenous opioids

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Cannabinoid: Opioid Interactions (cont'd)

- In mice and rats, THC greatly enhances analgesic effect of morphine in a synergistic fashion
- Increased potency of other mu opioids (hydromorphone and oxymorphone) seen with oral- Δ -9-THC in mouse models
- Possibility of enhanced and persistent analgesic effect at lower opioid doses

(Lucas, 2012)

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Cannabinoid: Opioid Interaction Trial—Objectives

- Evaluate effect of vaporized cannabis on blood levels of prescribed opioids
 - Sustained release morphine
 - Sustained release oxycodone
- Determine the short-term side-effects of co-administration of cannabis and opioids
- Assess effect of vaporized cannabis on level of chronic pain

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

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Cannabinoid-Opioid Interaction in Chronic Pain

- Question: The potential pharmacokinetics and the safety of the combination of opioids and cannabis in humans
- (Abrams et al., 2011)

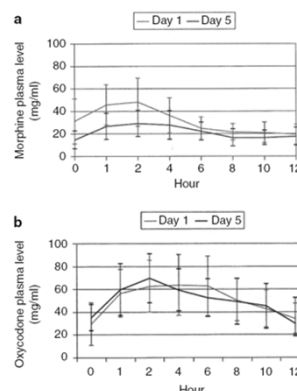
	Morphine group	Oxycodone group
<i>n</i>	10	11
Women	4	6
Caucasian	8	9
Mean age (range)	42.9 (33–55)	47.1 (28–61)

Vaporized cannabis administered 3 times a day on the steady-state pharmacokinetics of sustained-release morphine and oxycodone administered at 12-h intervals

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Plasma concentration–time curves for sustained-release (a) morphine & (b) oxycodone before & after exposure to inhaled cannabis.

- Cannabis augments the analgesic effects of opioids
- Less pain after 5 days of inhaling vaporized cannabis
- Mechanism by which cannabis augments the analgesic effects of opioids could be pharmacokinetic and/or pharmacodynamic



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Conclusions

- Co-administration of vaporized cannabis with oral sustained release opioids is safe
- Co-administration of vaporized cannabis in subjects on stable doses of morphine or oxycodone appears to enhance analgesia
- Co-administration of vaporized cannabis trends towards lowering concentration of the opioids:
 - The PK effects would be expected to reduce the analgesic effects of the opioids
 - The effect of vaporized cannabis to enhance opioid analgesia occurs by a pharmacodynamic, not a pharmacokinetic mechanism

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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.”

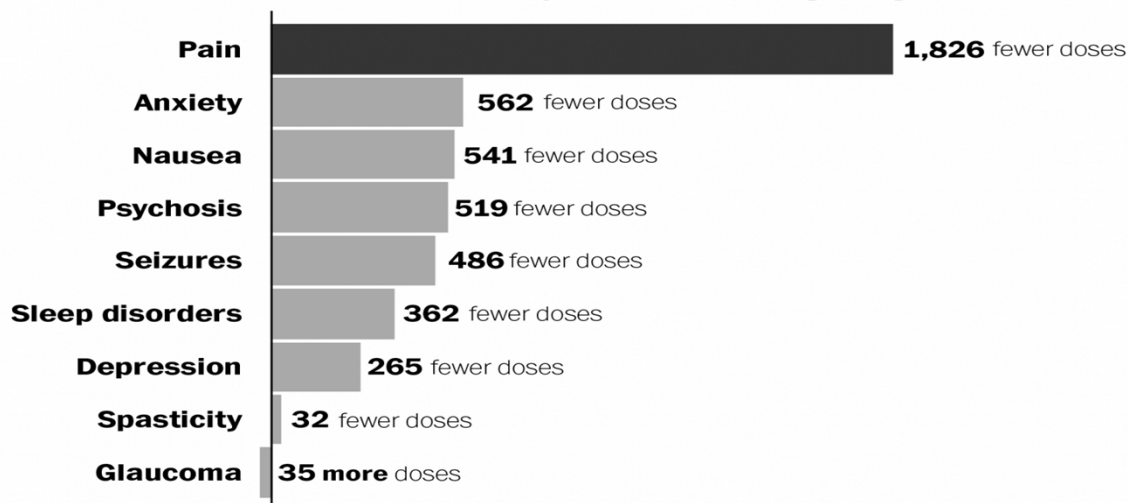


Principal investigator Chinazo Cunningham, MD, MS

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Fewer pills prescribed in medical ☐ states

Difference between annual drug doses prescribed per physician in medical marijuana states, and in states without medical marijuana laws, by drug category



WAPO.ST/**WONKBLOG**

Source: Bradford and Bradford, Health Affairs, July 2016

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."

Summary

- Cannabis has been around for centuries
- Long track record of safety
- Avoid in patients with mental health issues and adolescents
- Dealers' choice what is on the market (buyer beware)
- Combination THC/CBD effective in neuropathic pain
- Need for more clinical trials



Dispensary Information

Patient Focused Certification

<http://patientfocusedcertification.org/certification/>

- Addresses product and 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/>

THE HEALTH EFFECTS OF CANNABIS AND CANNABINOIDS: National Academies of Science

https://www.nap.edu/resource/24625/Cannabis_chapter_highlights.pdf

Requirements for California Cards

California Department of Public Health website

<https://www.cdph.ca.gov/Programs/CHSI/Pages/Medial-Marijuana-Identification-Card.aspx>



Patients out of Time

Conferences and resources

www.medicalcannabis.com

PROCON

<http://medicalmarijuana.procon.org/>

THE HEALTH EFFECTS OF CANNABIS AND CANNABINOIDS: National Academies of Science

https://www.nap.edu/resource/24625/Cannabis_chapter_highlights.pdf

Canadian Consortium for the Investigation of Cannabinoids (CCIC)

- Accredited cannabinoid education (ACE) programs
- Interactive
- 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



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