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

Theresa Mallick-Searle, MS, ANP-BC
Stanford Health Care, Division Pain Medicine
Tmallick@stanfordhealthcare.org

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 takeaways 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?!

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
Milestones in Cannabinoid Science

- **1964**: \(\Delta 9\)-THC structure identified & synthesized – Raphael Mechoulam
- **1988**: Discovery of the CB2 Receptor site & the first endocannabinoid – Anandamide (Raphael Mechoulam)
- **1992**: CB1 receptor site discovered @ St. Louis University Medical Center, Howlett & Devane
- **1992**: Discovery of the CB2 receptor site & the first endocannabinoid – Anandamide (Raphael Mechoulam)
- **1995**: Receptor antagonists
- **1998**: 2-arachidonylglycerol (2AG) identified
- **2000+**: Endogenous cannabinoid ligands shown to be analgesic

- 2001 Noladin ether identified
- Synthetic cannabinoids
- Advanced study discovery & manipulation of endocannabinoid system (biosynthesis, degradation)
- Novel delivery systems

Endocannabinoid System (ECS)

http://herb.ca/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, Nolan ether, virodhamine, NADA)
- Synthesizing and degrading enzymes

Endogenous Cannabinoid System

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

Synthesis → Endocannabinoids → Cellular uptake, Metabolism

CB2 Receptor → CB1 Receptor → CBx Receptor → VR1 Receptor

Signal Transduction

- Appetite
- Immune function
- Muscle control
- PAIN
- IOP
- Thermoregulation
- Cognition
- Emesis
- Neuroexcitability
- Reward
- PAIN
- Vaso-dilation
- Inflammation
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)
  - Tetrahydrocannabinol (THCV)

- Flavonoids
- Terpenes, Terpenoids
- Fungus? Bacteria? Pesticides?

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
Cannabinoids for Medical Use
A Systematic Review and Meta-analysis

- 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.

Selective Cannabinoids for Chronic Neuropathic Pain: A Systematic Review and Meta-analysis

- 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.
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

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.

- 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.


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, TD Dao DDS PhD, GA Finley MD, AF Furlan MD PhD, I Gilron MD NSc, A Gordon MD, PK Morley-Forster MD, BJ Saslo MDS PhD, P Sepire MD, J Stinson RN PhD, P Taenzer PhD, A Velly DDS PhD, MA Ware MD, E Weinberg MD, OD Williamson MBBS

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

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

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.”


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

- 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.”

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).

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

<table>
<thead>
<tr>
<th>Tolerance &amp; Adverse Effects (AEs)</th>
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<tbody>
<tr>
<td><strong>Tolerance</strong></td>
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<tr>
<td>- Mood, sleep</td>
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<td>- Psychomotor performance</td>
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<td>- Arterial pressure</td>
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<td>- Antiemetic properties</td>
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<tr>
<td><strong>Common AEs</strong></td>
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<tr>
<td>- Anticholinergic effects (dry mouth, blurry vision, urinary retention, tachycardia, constipation, hypertension).</td>
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<tr>
<td>- CNS effects (ataxia, cognitive dysfunction, hallucination)</td>
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<tr>
<td><strong>Cannabis Hyperemesis Syndrome</strong></td>
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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
- **t1/2** occasional users is 1-2 days, daily users up to 2 weeks
### Inhaled versus Oral

<table>
<thead>
<tr>
<th></th>
<th>INHALED</th>
<th>ORALLY INGESTED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak Blood Levels (min)</td>
<td>3-10</td>
<td>60-120</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>10-40</td>
<td>&lt;15</td>
</tr>
<tr>
<td>Time to peak psychoactive activity (min)</td>
<td>20</td>
<td>120-240</td>
</tr>
</tbody>
</table>

### 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.leafly.com)

[http://www.safeaccessnow.org/using_medical_cannabis](http://www.safeaccessnow.org/using_medical_cannabis)
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

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 Low
- Establish potency
- Go slow
- Supplement as needed

(Erowid & Erowid, 2011)

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**Practical Dosing: RX**

<table>
<thead>
<tr>
<th>Drug Description</th>
<th>Dosage &amp; Details</th>
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<tbody>
<tr>
<td>dronabinol (Marinol/Syndros) – Schedule III drug</td>
<td>A synthetic version of THC &amp; does not contain CBD (cannabidiol) or other cannabinoids. <strong>Recommended dosing oral 2.5-10 mg twice daily.</strong></td>
</tr>
<tr>
<td>nabilone (Cesamet) – Schedule II drug</td>
<td>A synthetic cannabinoid agonist (an analog of dronabinol) &amp; does not contain CBD (cannabidiol) or other cannabinoids. <strong>Recommended dosing oral 1-2 mg twice daily.</strong></td>
</tr>
<tr>
<td>nabiximols (Sativex) – Not available in US</td>
<td>An oromucosal spray → fixed dose of 2.7mg THC &amp; 2.5mg CBD.</td>
</tr>
<tr>
<td>cannabidiol (Epidiolex) – Approved FDA</td>
<td>Muscle stiffness/spasm due to multiple sclerosis.</td>
</tr>
<tr>
<td></td>
<td>CBD pure-plant-derived product for epilepsy.</td>
</tr>
<tr>
<td></td>
<td>2.5mg/kg – 10mg/kg taken twice daily.</td>
</tr>
<tr>
<td>Smoking</td>
<td>Vapourisation</td>
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<tr>
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<tr>
<td>- Most common route of administration, but not recommended (joints, bongs, pipes, etc.)</td>
<td>- Heats cannabis at 160–230 °C. Reduced CO, but not complete elimination of PAH demonstrated to date.</td>
</tr>
<tr>
<td>- Combustion at 600–900 °C producing toxic products: tar, PAH (polyaromatic hydrocarbons), carbon monoxide (CO), ammonia (NH3)</td>
<td>- Vapourisation produces significantly less harmful products than smoking.</td>
</tr>
<tr>
<td>- Chronic use associated with respiratory symptoms (bronchitis, cough, phlegm), but not lung cancer nor COPD (if cannabis only).</td>
<td>- Decreased pulmonary symptoms reported compared to smoking.</td>
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<tr>
<td>- Patients may mix with tobacco increasing respiratory/cancer risk.</td>
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<tr>
<td>- 20–50% of cannabis is lost to 'side-stream' smoke</td>
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**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/

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**PainWeek**
Resources

Canadian Consortium for the Investigation of Cannabinoids (CCIC)

- Accredited cannabinoid education (ACE) programs
- Informed by needs assessments, expert faculty
  www.ccic.net


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

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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/DNrhvQQYvFw

- Introduction to Medical Cannabis (Module 4) - CINV & Epilepsy by Dr. The
  https://youtu.be/Pubo9AwY7Hg

- Introduction to Medical Cannabis (Module 5) - Adverse Effects & Potential Drug Interactions
  https://youtu.be/ao2LVXBTT8

- Introduction to Medical Cannabis (Module 6) - Patient Care, Dosing & Titration by Dr. The
  https://youtu.be/_7l_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

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.
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.

THANK YOU

Questions?
Selected References


Selected References


