Medical Marijuana as Pain Management

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Cannabis (sativa, indica, rduealis)

Cannabis—a brief history

- Originated in Central Asia
- Has been used as a source of fiber, food, and medicine for millennia
- Records and evidence show it’s use by H. sapiens for at least 12,000 years
- Use in the ancient world was widespread (Egypt, Greece, China)
- First Chinese pharmacopeia by emperor Chen Nung 5,000 years ago describes use of Cannabis to treat a variety of aliments

History of Cannabis cont.

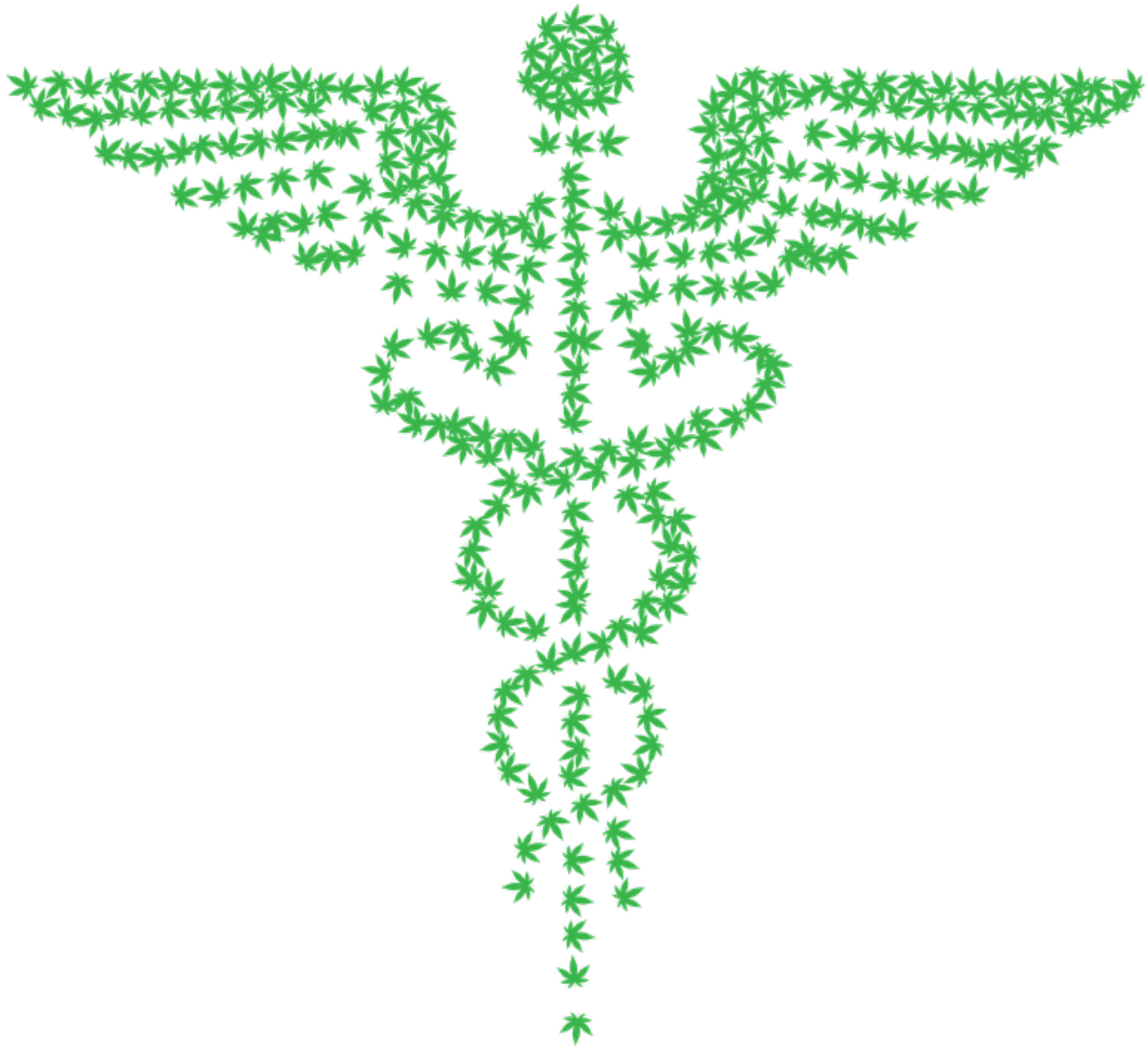
- Introduction to Europe
- Widespread cultivation and commercialization by Italians in the Middle Ages
- In 1484, Pope Innocent VIII issued a papal bull condemning the use of Cannabis to achieve altered mental states
- Brought to the Americas by European colonists

History of Cannabis cont.

- Added to the U.S. Pharmacopeia and National Formulary (USP-NF) in 1850 for use as an anti-inflammatory, anti-emetic, anti-convulsant, and analgesic agent.
- 20th Century—changes
- Banned from the British pharmacopeia in 1932
- United States—Marijuana Tax Act of 1937—imposes tax of persons who sell, acquire, or possess Marijuana
- Opposed by AMA because tax put financial burdens on physicians who grew/sold/prescribed cannabis

History of Cannabis cont.

- Effect of Act was to criminalize Cannabis cultivation and use
- Act overturned in 1969 (Leary v. United States)
- Comprehensive Drug Abuse Prevention and Control Act of 1970 classified cannabis as a Schedule 1 substance (high potential for abuse, lack of accredited safety, and no accredited medical use)



History of Cannabis cont.

- Recent changes (state-level only!)
- As of January 2019, 33 states and the district of Columbia have passed laws, many via state-wide referendums, that legalize marijuana in some form (medicinal and/or recreational).
- A recent national survey of U.S. adults (16,280, response rate of 55.3%) reported that approx. 15% of respondents used cannabis in the past year. 81% believed cannabis was beneficial for a variety of conditions, including pain, anxiety, stress, and depression. (Keyhani S. et all, Ann Intern Med 2018)

History of Cannabis cont.

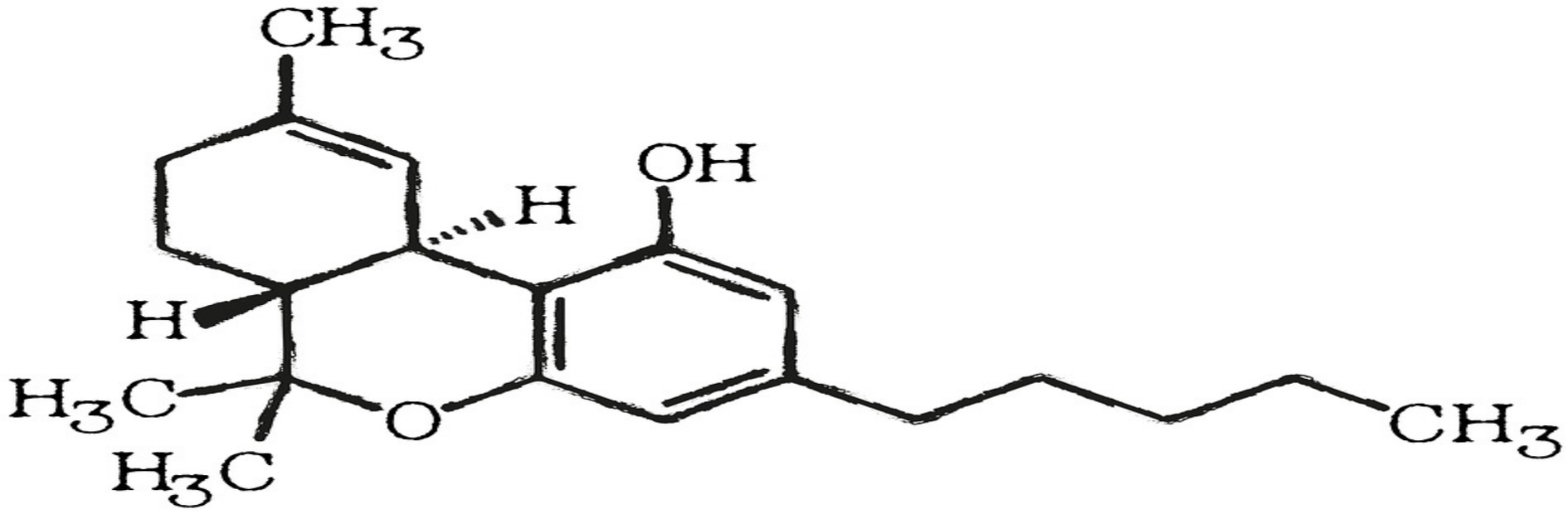
- 20 question survey given to 150 seniors in New York and Minnesota (m/f, age 61-70) who used cannabis in various forms (pills, oil, smoking) for treatment of chronic pain. Majority of users reported significant decreases in pain (9 to 5.6). (Martins-Welch, D. American Geriatric Society Meeting, Orlando Fl 2018).
- In New York and Illinois, legislators have changed state laws so that patients with opioid prescriptions can now instead use that script to buy cannabis products at a registered dispensary.
- Has the Legalization of Cannabis outpaced the science?

The Science behind Cannabis

- Currently, there are 480 phytochemicals identified in the Cannabis plant, of which 66 have been identified as cannabinoids—chemicals unique to Cannabis.

Cannabis science (cont.)

- 1964—Gaoni and Mecholam isolated the first phytocannabinoid, D9-THC (delta-9-tetrahydocannabinol), which is the phytochemical primarily responsible for the psychoactive properties of cannabis.



Cannabidiol

Most abundant cannabinoid –40%

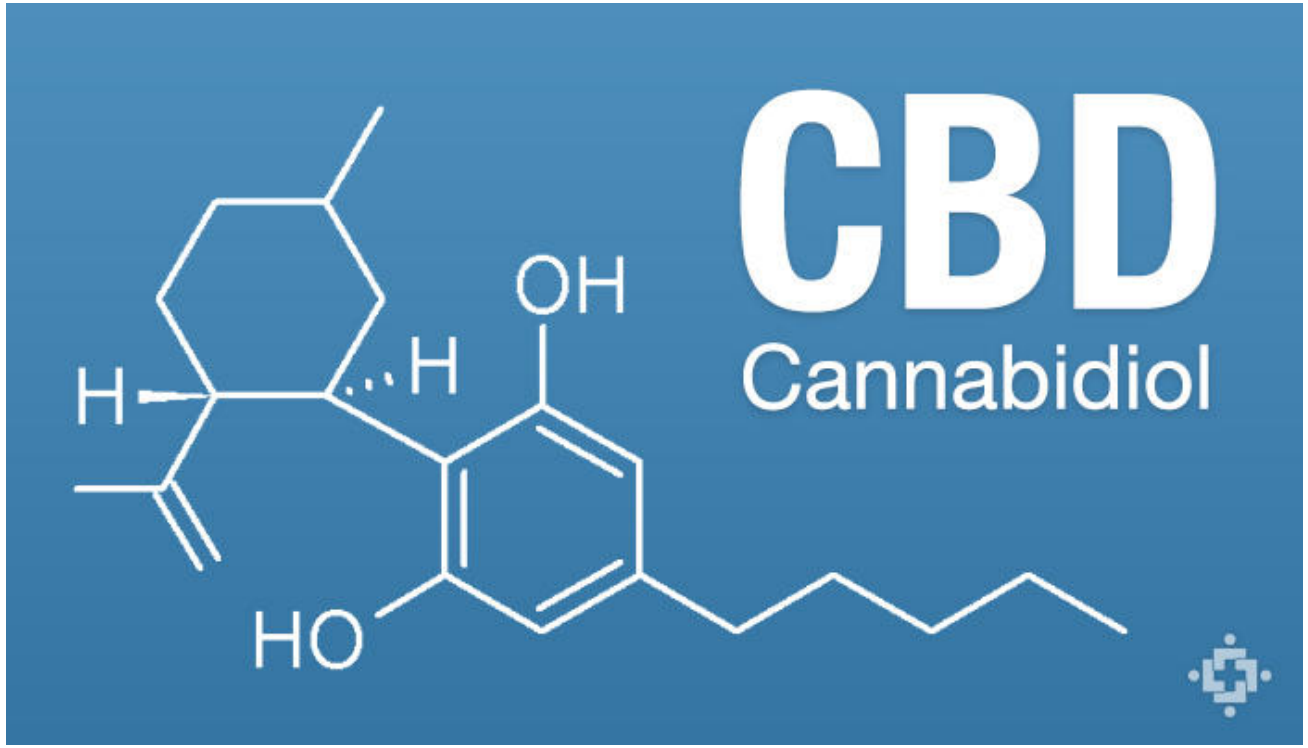
Multiple medical claims made for CBD:

Pain modulation

Anxiety relief

Seizure reduction

Inhibits growth of cancer cells



Other Cannabinoids

- Cannabinol (CBN)
- Cannabigerol
- Tetrahydrocannabivarin (THCV)
- Few, if any, studies on the above compounds
- Terpenes—compounds found in plants that give them their aroma and taste. Receptors for terpenes have been found in animal models.
- FDA has approved the synthetic drugs Dronabinol and Nabilone to treat nausea, vomiting, and anorexia, and Epidiolex for epilepsy.

Endocannabinoid system (eCBs)

- Discovered in 1990s
- Signaling system that plays multiple roles, including:
- Inflammation
- Pain
- Memory
- Regulation of Stress
- Called the “eat, sleep, relax, forget, and protect” system

The Endocannabinoid System (cont.)

- Major receptors:
- CB1 (cannabinoid type 1)—most abundant G-protein-coupled receptors in the body; found predominantly in brain and nervous system
- CB2 (cannabinoid type 2)—receptors predominantly found in peripheral organs and immune cells

The Endocannabinoid System (cont.)

- CB1 and CB2 are activated by naturally occurring endogenous cannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG) as well as THC and CBD.
- THC—high affinity for CB1 receptors
- CBD—high affinity for CB2 receptors
- CBD does not cause a “high”, and the ratio of THC to CBD in cannabis plants determines the psychogenic potency of the plant

Scientific Studies on Cannabis

- Hampered by continued classification of Cannabis as a Schedule 1 substance by the federal government
- Few rigorous, double-blinded, randomized, placebo-controlled trials
- Spasticity
- Nausea/Vomiting
- Pain

Safety issues

- No known lethal overdose
- THC—linked to increases in anxiety, psychosis, and schizophrenia
- Conflicting data on BP, heart rate in humans
- Some studies show decreased driving performance
- CBD—No significant changes in psychomotor and psychological functions
- No significant changes in HR, BP

Cannabis and pain

- Randomized, controlled trial of cannabis to treat central pain in patients with MS (Rog DJ et al, Neurology 2005)
- 5 week, RDBPC trial in 66 m/f patients with MS and chronic pain
- Cannabis oromucosal spray containing THC/CBD (2.7 mg/2.5 mg); pts could self-titrate up to 48 sprays daily (129.6/120)
- Number of sprays used daily at end of trial was an average of 9.6 for those in treatment group and 19.1 for placebo users
- Cannabis users reported better reduction in pain and sleep disturbances
- Side effects were dizziness, dry mouth, fatigue, and loss of long-term memory

Cannabis and pain cont.

- Retrospective study on treating chronic pain with cannabis capsules (Bellnier et al., Mental Health Clinician, 2018).
- 29 patients, m/f age 51-70. Various disease processes contributing to pain (spinal cord trauma, neuropathies, cancer, IBD).
- Pain measured by 2 pain scales (European Quality of Life 5 dimension scale and Pain Quality Assessment Scale
- Therapy was 10 mg cannabis capsules, THC/CBD at 1:1 ratio, taken every 8-12 hours; breakthrough pain was treated with THC/CBD inhaler (20:1 ratio) every 4-6 hours as needed

Chronic pain study cont.

- Pain surveys given at baseline and at 3 months
- Results showed that cannabis use decreased pain and improved quality of life
- Only adverse SE reported was dry mouth

Cannabis and headache pain

- RDBC trial of 30 patients, m/f, age 35-65, with treatment refractory medication overuse headache (Pini LA et al., Jour Headache Pain 2012)
- Study used Nabilone, a synthetic CB1 receptor agonist
- 16 week study; patients either took 400 mg ibuprofen or nabilone 0.5 mg daily for 8 weeks, then had one week washout period, then switched medications.

Cannabis and headache pain cont

- Results showed that patients taking nabilone had greater reduction in pain intensity and improved quality of life.

Cannabis and chronic non-cancer pain

- 4 year prospective study in Australia on effect of cannabis use among 1,514 patients (m/f, age 48-70) with chronic non-cancer pain who used opioids.(Campbell G et al., The Lancet 2018).
- Results showed that after 4 years, cannabis use was common (66%) among chronic pain patients. Researchers found no difference in pain severity ratings between cannabis and non-cannabis users; in addition, they found no decrease in the use of opioids in cannabis vs. non-cannabis users.
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Review Articles on Cannabis and Pain

- 2009 systematic review and meta-analysis of cannabis treatment for chronic pain that included 18 trials (Sanchez EM et al. Amer Acad Pain Med 2009)
- Authors concluded that cannabis use (capsules, oromucosal spray) is moderately efficacious for the treatment of chronic pain, but that its use may be significantly offset by side effects, including blurred vision, confusion, psychosis)

Cannabis and pain cont.

- 2011 article from the *British Journal of Clinical Pharmacology*; systematic review of randomized trials examining the use of cannabinoids for the treatment of chronic non-cancer pain.
- Types of Cannabis included smoked, oromucosal spray, nabilone, and dronibinol.
- Authors reported that 15 of the 18 trials examined demonstrated a significant effect of cannabis on pain as compared to placebo.
- Concluded that cannabinoids are safe and moderately effective in the treatment of chronic non-cancer pain.

Cochrane Review on Cannabinoids for fibromyalgia pain

- 2016 report; included 2 studies with a total of 72 participants. (Walitt B et al., Cochrane Database Syst Rev 2016)
- One study was cross-over, the other parallel group design, with study durations of 4-6 weeks.
- Both studies used nabilone at 1 mg/day.
- Authors concluded that use of nabilone has no value in treating fibromyalgia pain.

Effects of Cannabis Among Adults with Chronic Pain

- 2017 review article in Annals of Internal Medicine (Nugent et al, Ann Int Med 2017)
- Examined 13 systematic reviews and 62 primary studies; all intervention trials and observational studies
- Studies that used synthetic cannabinoid preparations (dronabinol, nabilone) were excluded; preparations included oralmucosal spray (THC 2.7 mg/CBD 2.5 mg) oils, and plant parts
- Concluded that there is low-strength evidence that cannabis alleviates neuropathic pain but that there was insufficient evidence in other pain populations.

Chronic pain and Cannabis cont.

- Worrisome side effects included increased risk for motor vehicle accidents, short term cognitive impairment, and psychotic symptoms.

2017 Study on Cannabinoid medications and acute pain

- Studies included only randomized controlled trials.
- Seven studies included in review ; 611 patients
- Cannabinoids examined included Nabilone, THC capsules, Dronabinol, and Levonantradol
- Results: In 5 studies, cannabinoids were no better than placebo in providing pain control; in one study, cannabinoids were superior to placebo and in one study cannabinoids were inferior to placebo
- Conclusions: Cannabinoids have no role in acute pain treatment (Stevens AJ, Higgins MD. Acta 2017)

Cannabis for neuropathic pain

- 2018 Cochrane Report
- Randomized, double-blind studies using medicinal cannabis or plant derived/synthetic cannabis medications.
- Included 16 studies with 1,750 participants (15 with placebo control, one with analgesic control), 2-26 weeks in duration; 10 oromucosal THC/CBD mix, 2 using nabilone, 2 using inhaled cannabis, 2 using dronabinol
- Outcomes: Cannabis-based medications may increase the number of people achieving 50% or greater pain relief vs. placebo

Cannabis for Neuropathic Pain cont.

- Psychiatric disorders occurred among 17% of cannabis users vs. 5% placebo users
- Conclusions of authors: “The potential of cannabis-based medicine in chronic neuropathic pain might be outweighed by their potential harms.”

Medical Cannabinoids for pain, nausea, vomiting, and spasticity

- 2018 Review article (Allan GM et al. Can Fam Physician 2018)
- Included systematic reviews of RCTs examining MC for pain, nausea, vomiting and spasticity. 31 reviews were examined. Included plant-based as well as synthetic cannabinoids.
- Conclusions of authors: Cannabinoids have a moderate efficacy in combating nausea and vomiting after chemotherapy; they might improve spasticity in patients with MS; there is uncertainty if they improve pain.
- Common side effects include dizziness, sedation, confusion, and dissociation.

Cannabis for other Medical Issues

- Epilepsy: 3 month study of 175 child and adults with treatment resistant epilepsy. Tx consisted of Epidiolex. 50% of the patients reported a reduction in seizure activity and frequency. (Amer Acad Neurology 2015 Annual Meeting)

- Spasticity due to MS or paraplegia: A 2017 systematic review and meta-analysis included 16 trials (2,597 patients). The authors concluded that there was moderate evidence indicating that cannabinoids significantly decreased spasticity

Cannabis for other Medical Uses cont.

- Glaucoma: Some evidence shows that cannabinoids may decrease intraocular pressure, but not to the extent of approved medications.

- Nausea and Vomiting: Treatment of chemotherapy-induced nausea and vomiting was one of the first FDA-approved uses of synthetic cannabis (dronabinol)
- Parkinson's disease: A small (21 patients) placebo-controlled study from 2014 showed that CBD at 300 mg/day increased the quality of life (mobility, ADLs, cognition) in patients with PD

Where we stand today…

Take home messages

- In conclusion:
- There is some reasonable evidence that cannabis and cannabis-based products may help for some medical issues (n/v, spasticity), with weaker evidence for its use in pain (chronic and acute); therefore, if patients have failed to control their issues with conventional treatment, then it may be appropriate to discuss a cannabis-based approach with them. The time of “don’t ask, don’t tell” is over.
- Patients should have no known substance abuse or psychotic illness

Take home message cont.

- As Osteopathic physicians, we need to develop basic competence in recognizing issues with cannabis use, its potential risks, and be able to discuss this openly with our patients.