Update on Medicinal Cannabis: Incorporating Cannabinoid Therapeutics into Your Practice: What You Need to Know About Both Recreational and Medical Marijuana Use and Availability in the State of Washington

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"Hemp is of first necessity to the wealth & protection of the country."- Thomas Jefferson

- Many cannabis based medications were produced by Eli-Lilly, Parke Davis, and Sharp Dohme (now Merck Sharp Dohme).
- Tinctures; Pills; Liniments
- Widely prescribed by physicians 1890-1937

Cannabis for Neuralgia 1925

the Endocannabinoid system

- is intricately involved in normal human physiology, specifically in the control of movement, pain, memory, mood, motor tone, and appetite, among others.
- Cannabinoid receptors are found in the brain and peripheral tissues.
- Dense receptor concentration in the cerebellum, basal ganglia, and hippocampus
- Few cannabinoid receptors in the respiratory areas in brainstem
- The cannabinoid receptors CB1 and CB2, two G protein-coupled receptors that are located in the central and peripheral nervous systems.

The Endocannabinoid System

- endocannabinoids are both neuromodulators and immunomodulators
- Controls pain, appetite, mood, sleep,
- gut motility, muscle coordination, short term memory
- Inflammatory levels – cannabinoids suppress inflammation
- activation of cannabinoid receptors leads to activation of GTPases in macrophages, neutrophils, and B/T cells.
- CB2 receptors regulate migration of B cells and maintain healthy IgM levels.

Botanical cannabis

- 3 species of cannabis: sativa, indica, and ruderalis
- sativa grows 5-18 feet, few branches.
- indica grows 2-4 feet tall, compactly branched.
- > 700 strains of cannabis: Some are strains of 1 of the 3 subspecies. Many are crossbred hybrids.

Natural vs compounded

- Natural cannabis contains over 100 cannabinoids, most of the non-psychoactive yet therapeutic
- NATURAL CANNABIS IS 15% THC AT BEST – recreational uses like/want THC
- CANNABIS GROWN ON FEDERAL FARMS IN MISSISSIPPI FOR DRUG TRIALS IS 3% THC
- Delta-9-tetrahydrocannabinol (THC): in PURE FORM is a schedule 3 drug (MARINOL)
- –NATURAL CANNABIS, at 3 - 15% THC is schedule I, dangerous, no medical use –

cannabinoids

- Cannabidiol (CBD): analgesia; moderates effects of THC
- Cannabinol (CBN): anticonvulsant
- Tetrahydrocannabivarin (THCV): anti-inflammatory
- Cannabichromene (CBC): mixed effects
- Cannabicyclol (CBL)
- Plus 80-100 other cannabinoids –
- THESE CANNABINOIDS ARE NOT INTOXICATING
- new strain in Israel with no THC but potential medical use

CLINICAL PHARMACOLOGY OF CANNABIS & CANNABINOIDS

- ***95-99% plasma protein bound - hydroxylation, oxidation, and conjugation for rapidly clearance from plasma***
- ***First-pass metabolism (after PO admin) to 11-OH-THC***
- ***Elimination is slow: days to weeks 20-35% found in urine; 65-80% found in feces; stored in adipose;***
- ***Pregnancy Category C: in breast milk***

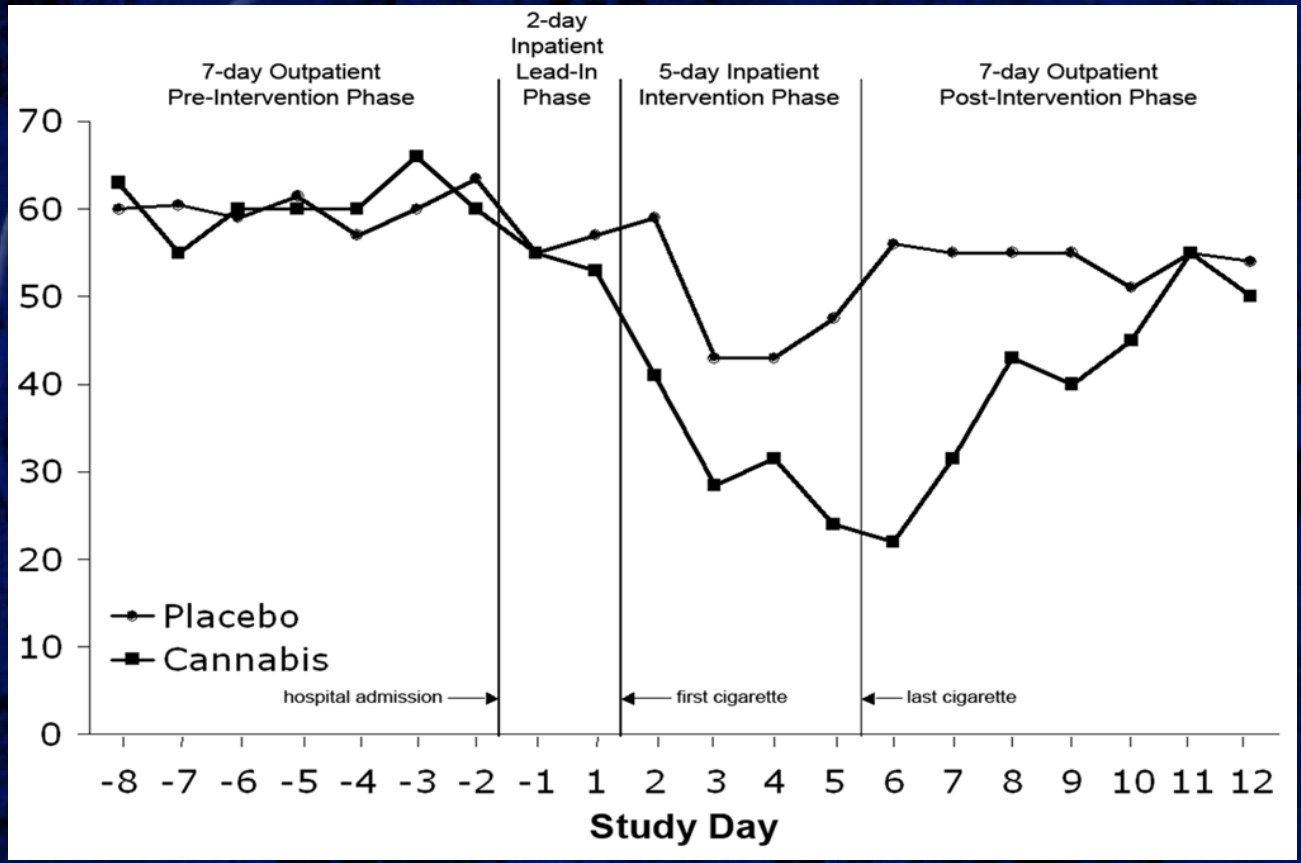
Clinical Pearl – know this

- SAFE, NO OVERDOSE, WELL TOLERATED –
- NO CONSTIPATION
- NO RESPIRATORY SUPPRESSION
- RELIEVES PAIN, IMPROVES SLEEP
- IMPROVES APPETITE
- DECREASES NEED FOR OPIOIDS
- WORKS SYNERGISTICALLY WITH OPIOIDS

History of human research

- Studies have tended to be small, imperfectly controlled, using smoked cannabis-limited by regulations
- Feds require using Mississippi cannabis of poor composition and irregular bioavailability. Delivered as "joints"
- evaluation of medicinal cannabis in humans is still evolving – don't have pharma funding though
- the discovery of the endocannabinoid system has stirred research

Abrams DI, Rowbotham MC, Petersen KL, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology 2007; 68(7):515-21.



EBM Class One Human Clinical trials

- Abrams DI, Jay CA, Shade SB, Vizoso H, Reda H, Press S, Kelly ME, Rowbotham MC, Petersen KL. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology 2007; 68(7):515-21.

- Ellis RJ, Toperoff W, Vaida F, van den Brande G, Gonzales J, Gouaux B, Bentley H, Atkinson JH. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropsychopharmacology 2009;34(3):672-80.

- Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology 2005; 65(6):812-9.

More EBM Class One Clinical trials

- Wallace et al. 2007. Dose-dependent effects of smoked cannabis on Capsaicin-induced pain and hyperalgesia in healthy volunteers Anesthesiology 107: 785-796.
- Wilsey et al. 2008. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. Journal of Pain 9: 506-521.
- Ware et al. 2010. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ 182: 694-701.
- Johnson et al. 2009. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety and tolerability of THC: CBD extract in patients with intractable cancer-related pain. Journal of Symptom Management 39: 167-179.

Cochrane reviews of human data

- Phillips TJ, Cherry CL, Cox S, Marshall SJ, Rice AS. Pharmacological treatment of painful HIV-associated sensory neuropathy: a systematic review and meta-analysis of randomised controlled trials. ***PLoS One*** 2010; 28;5(12):e14433.
- Martín-Sánchez E, Furukawa TA, Taylor J, Martin JL. Systematic review and meta-analysis of cannabis treatment for chronic pain. ***Pain Med*** 2009; 10(8):1353-68.
- Campbell FA, Tramèr MR, Carroll D, Reynolds DJ, Moore RA, McQuay HJ. Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. BMJ 2001; 323(7303):13-6.
- Machado Rocha FC, Stéfano SC, De Cássia Haiek R, Rosa Oliveira LM, Da Silveira DX. Therapeutic use of Cannabis sativa on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. Eur J Cancer Care 2008;17(5):431-43.

Lynch ME, Campbell F. Cannabinoids for Treatment of Chronic Non-Cancer Pain; a Systematic Review of Randomized Trials. Br J Clin Pharmacol 2011 2(5):735-44 PMID: 21426373

- systematic review of RCTs for cannabis treating chronic non-cancer pain: neuropathic pain, fibromyalgia, rheumatoid arthritis, and mixed chronic pain.
- quality of trials = excellent;
- 15 of the 18 trials showed significant analgesic effect of cannabis
- No serious adverse effects; only a few withdrawals from the studies
- Overall evidence indicates that cannabinoids are safe and effective

Hill KP. Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems: A Clinical Review. JAMA 2015; 23-30;313(24): 2474-83.

- Use of marijuana for chronic pain, neuropathic pain, and spasticity due to multiple sclerosis is supported by high-quality evidence.
- Six trials that included 325 patients examined chronic pain
- 6 trials that included 396 patients investigated neuropathic pain
- 12 trials that included 1600 patients focused on multiple sclerosis
- “Several of these trials had positive results, suggesting that marijuana or cannabinoids may be efficacious for these indications”

Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, et al. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. JAMA 2015; 23-30;313(24):2456-73.

- 79 trials (6462 participants) were included
- Most trials showed improvement in symptoms associated with cannabinoids nausea and vomiting
- reduction in pain
- reduction in spasticity
- Common AEs included dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, and hallucination.

So how does this all work in real life clinical medicine?

- Methods of Use
- Dosing paradigms
- Patient instructions
- What clinicians should know

Use in clinical setting

- DO NOT SMOKE – USE VAPORIZER FOR FAST EFFECT; INGESTION FOR LONGER EFFECT; TOPICAL FOR LOCAL EFFECT
- USE LOW DOSES OF CANNABIS THAT HAS HIGH CBD/CBN AND LOW THC
- DO NOT NEED TO BE HIGH TO GET PAIN RELIEF

Vaporization of cannabis – safe alternative to smoking

- examples

How do vaporizers work?

- When cannabinoids are heated to between 285 °F (140 °C) and 392 °F (200 °C) they literally boil and vaporize.
- Studies show that vaporization is most effective at around 338 °F (170 °C)
- A vaporization temperature over 392 °F (200 °C) will burn the cannabis, creating unwanted smoke.

Dosing

- START LOW; GO SLOW
- 2-3 inhalations, stop, wait ten minutes
- Do not need to be high to get pain relief
- Ingestion takes about an hour to get effects so harder to dose but lasts longer
- Transdermal works well as a linament
- No current injectable forms

SIDE EFFECTS

- Disinhibition, relaxation, drowsiness
- Feeling of well being, exhiliration, euphoria
- Sensory - perceptual changes
- Recent memory impairment
- Balance/stability impaired
- Decreased muscle strength, small tremor
- Poor on complex motor tasks (e.g., driving)

Effects on behavior

- can get impaired judgement
- Slowed reaction time
- Motor impairment
- disorganized thoughts, confusion
- May get paranoia, agitation

Do Not Drive!

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Advising the patient

- Adverse effects: mainly seen in new users
- Start low, go slow and easy
- These are reversible, short lived effects (3-4 hours max)
- Serious adverse effects NOT seen in chronic users

CLINICAL PEARLS

- FOR CHRONIC PAIN? ***Screen patient*** – do the risk screening tools –
- if the patient is legit, try the standard non-opioid drugs first
- If the standard first line meds do not work then consider cannabis
- Starting patient on opioids may pose considerably higher risk for dependency and dose escalation

Why Cannabis?

- It works, Not many drug-drug interactions
- Side effects mild; low toxicity, NO LD50
- Cannabis has other potential benefits: reduce inflammation, neuroprotective, anti-tumor properties
- You still need to monitor the patient!
- They may still ask you for opioids…but not all will, and you have leverage

Is Cannabis for everyone? NO!

- some people cannot tolerate it or it does not work for them
- There is a risk for psychological addiction
- Minimal physical dependence (withdrawal is mainly irritability, depression)
- Tolerance may develop in heavy, long term users - may need higher doses
- Patient/family will have to purchase or grow it

Is Cannabis the cure for everything? No! …but it works well for:

- Chronic pain – particularly neuropathic
- Chronic muscular pain/fibromyalgia
- Pain associated with sleep disorder, loss of appetite, dysthymia
- Pain associated with inflammation, including inflammatory bowel disease, bronchial spasms in asthma

CLINICAL PEARL If you choose to recommend ***medicinal cannabis…***

- FOLLOW THE LAW
- Properly counsel the patient and family
- Patient should use high quality cannabis to improve efficacy: high CBD, CBN, lower THC – do not need to be high to get pain relief and use a delivery route that maximizes benefits and minimizes side effects

SB 5052 – Cannabis Patient Protection Act

- This act creates licensing and regulation of all marijuana producers, processors and retail stores under the oversight of the renamed Washington State Liquor and Cannabis Board (LCB).
- Mandates contracting with a third party to create and administer a medical marijuana authorization database;
- Adopting rules relating to the operation of the database;
- Adopting rules regarding products sold to patients and their designated providers;
- Consulting with the LCB about requirements for a retail store to get a medical marijuana endorsement;
- Creating a medical marijuana consultant certification program;

SB 5052 – Cannabis Patient Protection Act

- Developing and approving continuing education for healthcare practitioners who authorize the medical use of marijuana; and
- Making recommendations to the legislature about establishing medical marijuana specialty clinics.

SB 5052 – Cannabis Patient Protection Act

- Post-traumatic stress disorder and traumatic brain injury are added as qualifying conditions.
- A qualifying condition must be severe enough to significantly interfere with the patient's activities of daily living and ability to function, which can be objectively assessed and evaluated.
- All new authorizations must be written on a form developed by the department and printed on tamper-resistant paper.
- Patient examinations and re-examinations must be performed in person at the healthcare practitioner's permanent business location.
- Healthcare practitioners who write more than 30 authorizations per month must report the number to the department.

SB 5052 – Cannabis Patient Protection Act

- Healthcare practitioners cannot have a practice that consists primarily of authorizing the medical use of marijuana.
- No more than 15 plants may be grown in a single housing unit even if multiple patients or designated providers reside there.
- Butane extraction is prohibited unless the person is a processor licensed by the LCB
- All marijuana producers, processors and retail stores must be licensed by the LCB.
- All marijuana and marijuana products must be tested for safety and THC/CBD levels, accurately labeled, and sold in child-resistant packaging.
- Licensed retail stores may apply for and get a medical marijuana endorsement.

SB 5052 – Cannabis Patient Protection Act

- All authorizations must be written on a form developed by the department and printed on tamper-resistant paper. All other forms of documentation are no longer valid.
- Patients under 18 years of age must have permission from a parent or guardian, and must participate in treatment.
- The database becomes operational.
- Patients and designated providers may be entered into the database by presenting their authorization to a licensed retail store with a medical marijuana endorsement.

SB 5052 – Cannabis Patient Protection Act

- Possession amounts change depending on whether the patient or designated provider is entered into the database:
- If entered: May purchase up to three times the current limits at licensed retail store with a medical marijuana endorsement and may possess six plants and eight ounces of useable marijuana; healthcare practitioner may authorize additional plants to a maximum of 15; purchases at retail stores with a medical marijuana endorsement are not subject to sales tax; provides arrest protection.
- If not entered: Patient or designated provider can be arrested but has an affirmative defense to criminal prosecution for possession of up to four plants and six ounces of useable marijuana; may not participate in cooperatives; purchases at retail stores limited to amounts for all adults and are subject to sales tax.

SB 5052 – Cannabis Patient Protection Act

- Up to four patients and designated providers may form a cooperative at the residence of one of the members and may grow the total authorized amount for the four members. Cooperatives must be registered with the LCB.
- A healthcare practitioner may sell or donate to patients topical products that have less than 0.3 percent THC.
- Collective gardens under the old law are no longer allowed. New language allows for cooperatives with specific restrictions

Decision from the Washington Supreme Court - May 2015

- Chapter 69.51A RCW doesn't legalize the medical use of marijuana. It only provides qualified patients holding a valid recommendation and their designated providers with an affirmative defense to criminal prosecution
- State of Washington v. William Michael Reis

Cat 1 CME education on-line

- http://adai.uw.edu/mcacp/
- Medicinal cannabis and chronic pain project
- UW ADAI – PI: Beatriz Carlini, Ph.D., M.P.H.; Research Scientist, Alcohol & Drug Abuse Institute, UW
- Co-investigators
- Gregory Carter, M.D.
- Roger Roffman, Ph.D.
- Reinaldo Naoto Takahashi, Ph.D.
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Thank you

- Questions?
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- Special Thank you to Gregory T Carter, MD who provided presentation slides for me to adapt for this presentation.
- E-mail: gtcarter@uw.edu