

SCI Wellness Summit: The Use of Medical Marijuana to Manage Symptom Burden in Spinal Cord Injury

- **Speaker: Gregory T. Carter, MD, MS**
- **Medical Director, St Luke's Rehabilitation Institute**
- **Spokane, WA ; Faculty, University of Washington School of Medicine**
- **Saturday, June 07, 2014**
- **3:45-4:30 pm.**

This presentation is supported by

- Research and Training grant from the Washington State Office of the Attorney General - Bob Ferguson
- Project Title: Chronic Pain Management and Marijuana Use: Science-Based Education in Times of Legalization.
- Principal Investigator: Beatriz H. Carlini, PhD, MPH, Research Scientist; Alcohol and Drug Abuse Institute, University of WA
- Grant manager: Sharon Garrett, MPH

Overview

- A brief overview of the history
- Pharmacological Research Summary
- Clinical Applications in Spinal Cord Injury
- Future directions

Brief Historical Overview

- **Oldest known psychoactive plant** - documented use as medicine > 5000 years ago in China - Cannabis is one of the 50 fundamental herbs of traditional Chinese medicine
- 3,000-year-old Egyptian mummies contain cannabis traces (still active!)
- Introduced into Western medicine in 1840's by Dr. W.B. O'Shaughnessy
- Important crop in early USA: cultivated for fiber, rope, clothing, seeds for oil and fuel

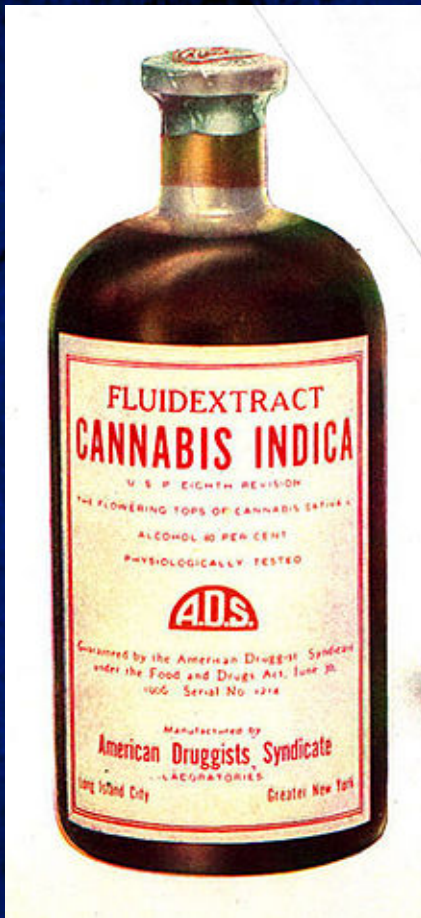
"Hemp is of first necessity to the wealth & protection of the country." - Thomas Jefferson

- 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 Tincture, circa 1910, Parke Davis




"The prestige of government has been lowered considerably by the prohibition of cannabis. Nothing is more destructive of respect for the government and the law of the land than passing laws which cannot be enforced."- Albert Einstein



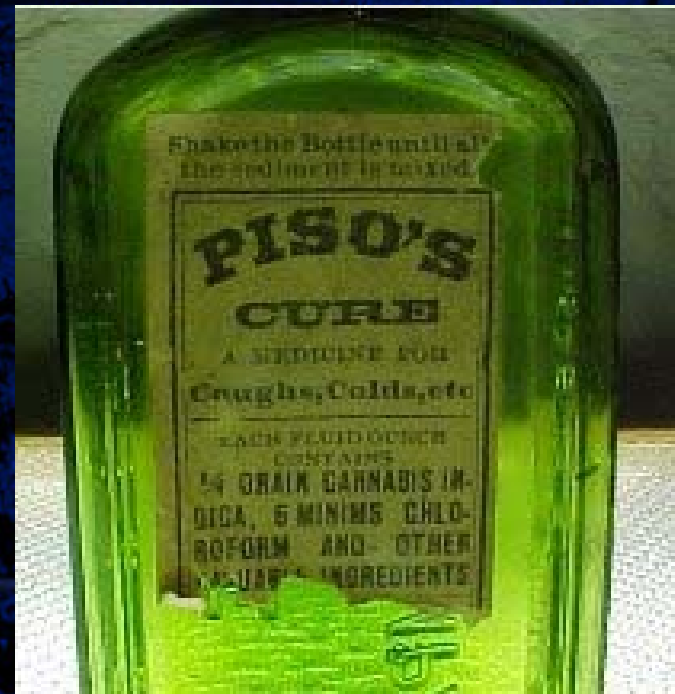
CANNABIS AMERICANA
U. S. P.
Physiologically Tested

OUR American variety is the answer to the question which has so long troubled manufacturers. With our material a finished product can be turned out at a reasonable cost.

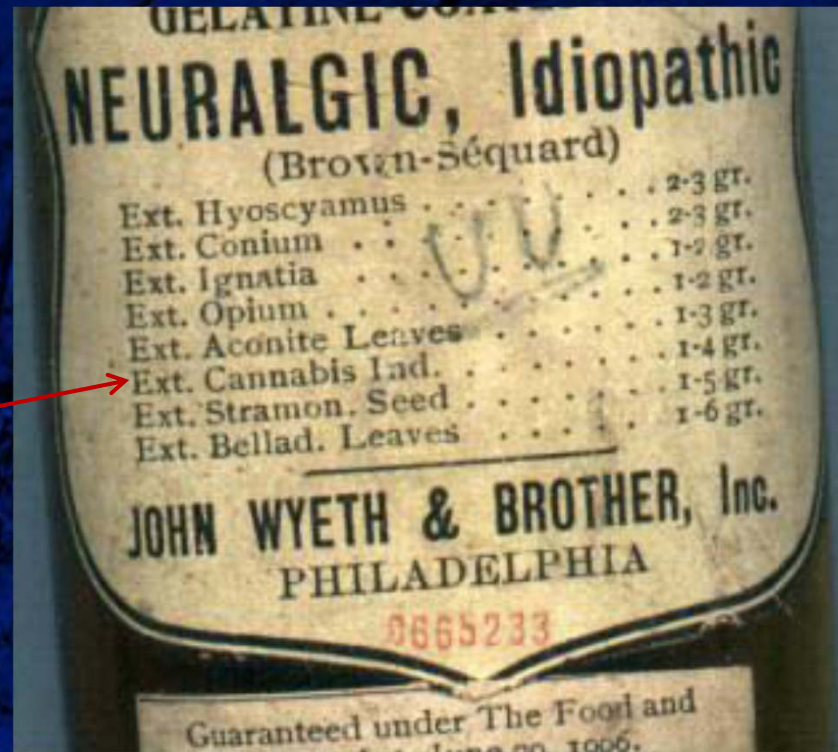


IT is no longer necessary to depend on the foreign variety which is of high cost and slightly superior. The uncertainty of further supplies of it is another factor favoring the American product.

J. L. HOPKINS & CO., 106 W. 23rd St., New York



Cannabis for Neuropathic Pain 1906



Cannabis for Neuralgia 1925



Marijuana

- All use of marijuana was made illegal in the late 1930s
- Against the advice of the AMA
- Included hemp for the use of clothing, food, fibers, and fuel

Suggested reading for historical reference

- 1) Herer J. "The Emperor Wears No Clothes". AH HA Publishing; 11th edition; 2000
- 2) Gieringer D, Rosenthal E, Carter GT. "Marijuana Medical Handbook: A Practical Guide to the Therapeutic Uses of Marijuana". Quick Trading Publishing, 3rd edition; 2008
- Fox S, Armentano P, Tvert M. "Marijuana is Safer: So Why Are We Driving People to Drink?" Chelsea Green Publishing; 1st edition; 2009
- Martin M, Rosenthal E, Carter GT. Medical Marijuana 101, Quick American Press 2010

Times are changing...

- Government-appointed commissions on cannabis that have issued favorable findings: 1) The Nixon appointed Shafer Commission in 1972; 2) The U.S. Institute of Medicine in 1982; 3) The Australian National Task Force on Cannabis in 1994; 4) The U.S. National Institutes of Health Workshop on Medical Marijuana in 1997 ; The National Academy of Sciences, the Institute of Medicine, and the American College of Physicians have all issued cautiously affirmative statements
- Legal for medicinal use in 20 states
- Legal for recreational use in 2 states

We discovered 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

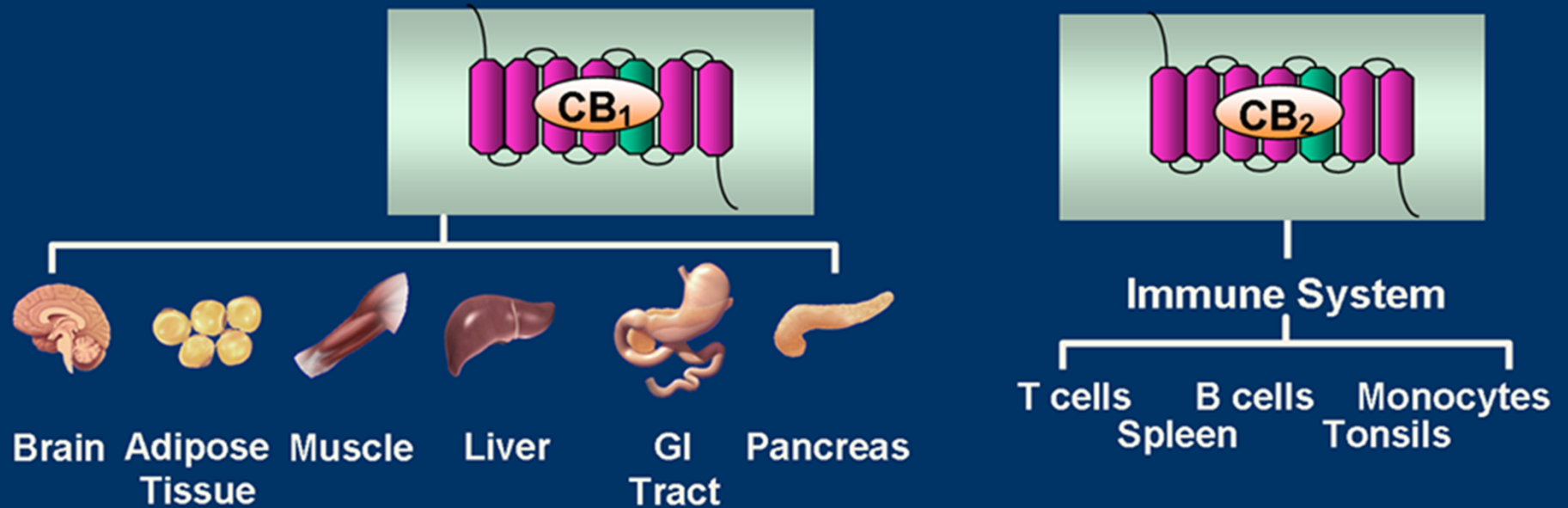
- endocannabinoids are both neuromodulators and immunomodulators
- Controls pain, appetite, mood, sleep,
- gut motility, muscle coordination, short term memory
- Inflammatory levels – cannabinoids suppress inflammation
- activation of cannabinoid receptors leads to activation of macrophages, neutrophils,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

Physiological Effects of Endocannabinoids

- Endocannabinoids are often produced as an adaptive response to cellular stress, aimed at reestablishing cell homeostasis
- Endocannabinoids affect a large number of physiologic processes including
 - Feeding behavior
 - Energy balance, metabolism, and GI function
 - Pain perception
 - Motor control and posture
 - Learning, memory, and emotions
 - Immune and inflammatory responses
 - Cardiovascular function
 - Reproduction
 - Bone formation

Cota D, Woods S. *Curr Opin Endocrinol Diabetes*. 2005;12:338-351; De Petrocellis L et al. *Br J Pharmacol*. 2004;141:765-774; Pagotto U et al. *Endocr Rev*. 2006;27:73-100; Ameri A. *Prog Neurobiol*. 1999;58:315-348; Cota D et al. *J Clin Invest*. 2003;112:423-431; Di Marzo V, Matias I. *Nat Neurosci*. 2005;8:585-589; Kershaw EE, Flier JS. *J Clin Endocrinol Metab*. 2004;89:2548-2556; Correa F et al. *Mini Rev Med Chem*. 2005;5:671-675; van der Stelt M et al. *Embo J*. 2005;24:3026-3037; Wang H et al. *Endocr Rev*. 2006;27:427-448; Idris AI et al. *Nat Med*. 2005;11:774-779; de Oliveira Alvares L et al. *Brain Res*. 2006;1075:60-67; Arenos JD et al. *Eur J Pharmacol*. 2006;539:177-183; Mikics E et al. *Behav Pharmacol*. 2006;17:223-230; Guindon J et al. *Pain*. 2006;121:85-93.

Cannabinoid Receptors



- G-protein-coupled receptors
- CB₁ receptors highly expressed in the brain
 - CB₁ receptors also found in adipose tissue, liver, muscle, the gastrointestinal tract, pancreas, as well as reproductive and cardiovascular tissues
- CB₂ receptors are expressed primarily in immune cells
 - CB₂ receptor expression in neurons is being studied

Devane WA et al. *Mol Pharmacol*. 1988;34:605-613.

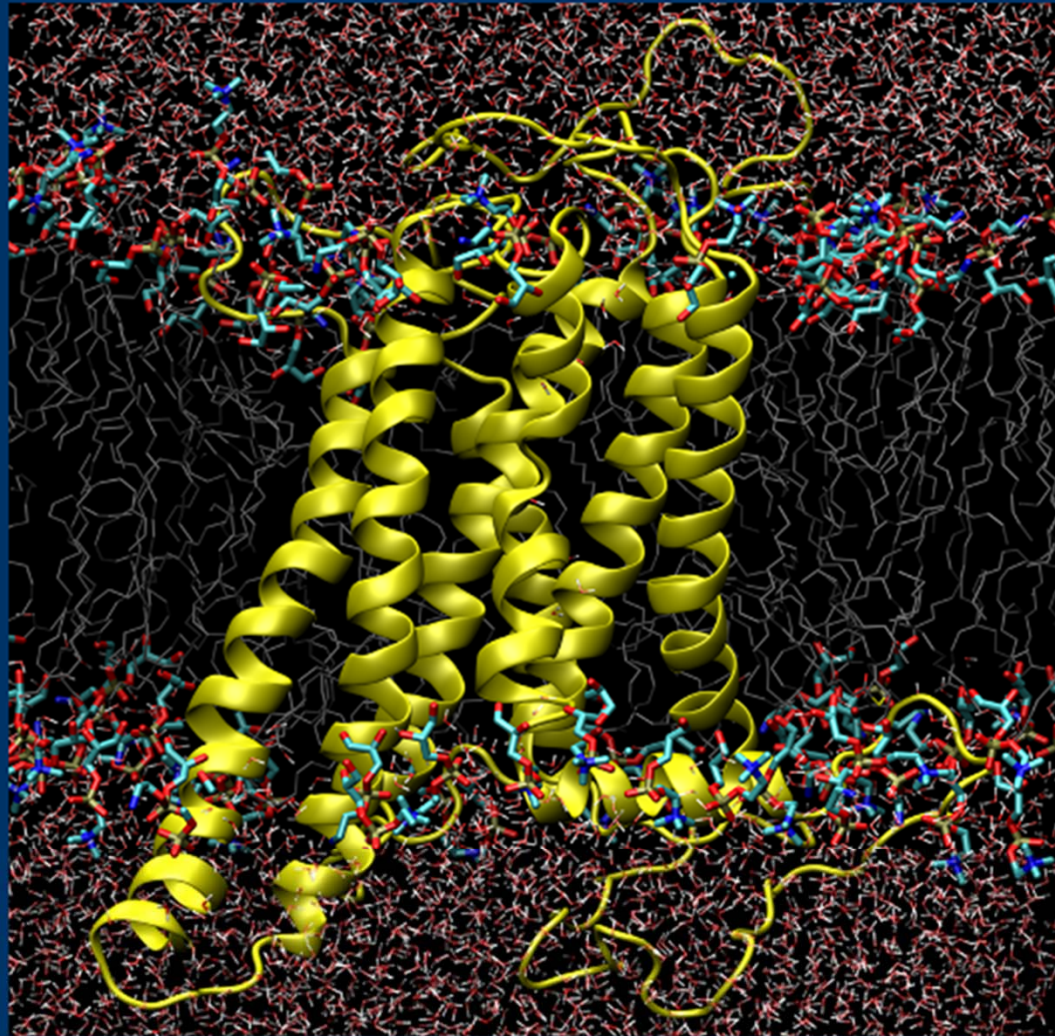
Munro S et al. *Nature*. 1993;365:61-65.

Ameri A. *Prog Neurobiol*. 1999;58:315-348.

Osei-Hyiaman D, DePetrillo M, Pacher P, et al. *J Clin Invest*. 2005;115:1298-1305.

Cota D, Woods SC. *Curr Opin Endocrinol Diabetes*. 2005;12:338-351.

The CB₁ Receptor

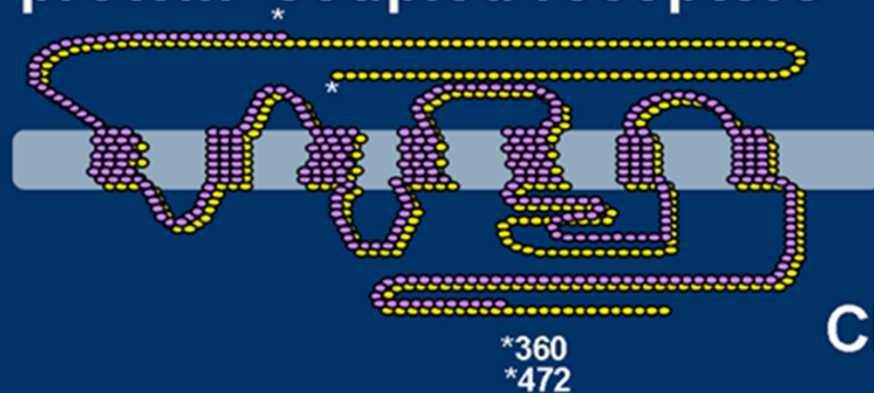


The CB₁ receptor consists of 7 transmembrane helices

Courtesy of Patricia Reggio, PhD

Key ECS Elements

Cannabinoid receptors are
G-protein-coupled receptors



Endocannabinoids



Endogenous, phospholipid-derived metabolites
that bind to and activate cannabinoid receptors

CB₂ receptor

- Central nervous system
 - Hippocampus
 - Basal ganglia
 - Cortex
 - Cerebellum
 - Hypothalamus
 - Limbic structures
 - Brainstem
- GI tract (myenteric neurons and epithelial cells)
- Liver (hepatocytes)
- Adipose tissue
- Muscle
- Pancreas (α -cells)

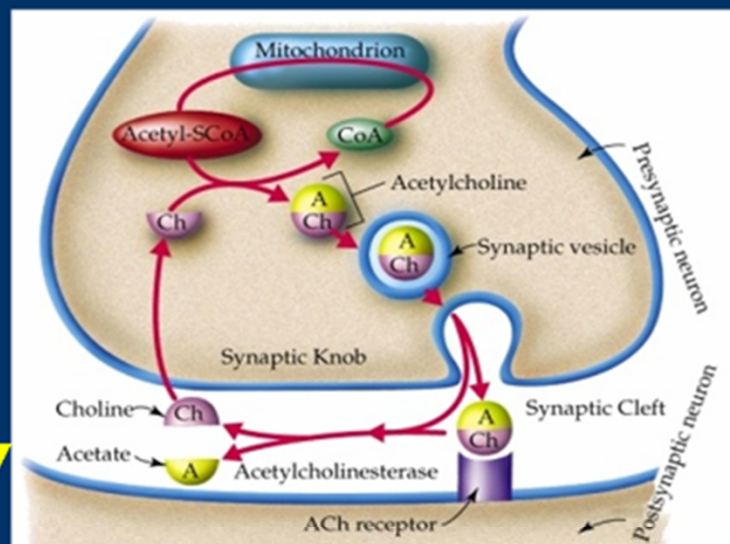
- Immune cells and tissues
 - T cells, B cells
 - Macrophages
 - Dendritic cells
 - Spleen, tonsils
 - Adipose tissue

De Petrocellis et al. *Br J Pharmacol.* 2004;;141:765-774.
Pertwee et al. *Pharmacol Ther.* 1997;74:129-180.
Roche R et al. *Histochem Cell Biol.* 2006;126(2):177-187.

Difference Between Classical and Retrograde Neurotransmission

Classical neurotransmitter

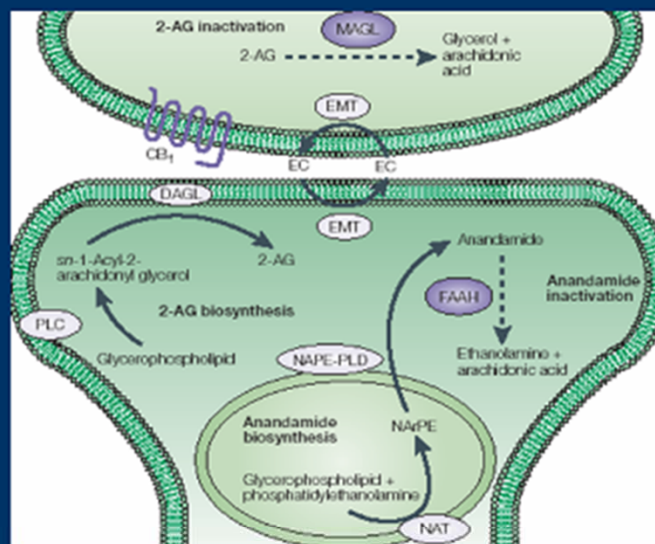
Presynaptic



Postsynaptic

Retrograde neurotransmitter

Presynaptic



Postsynaptic

Di Marzo V, Matias I. *Nat Neurosci.* 2005;8:585-589.
 Di Marzo Vet al. *Nat Rev Drug Discov.* 2004;3:771-784.
 Wilson RI, Nicoll RA. *Nature.* 2001;410:588-592.
 Vaughan CW, Christie MJ. 2005:367-383.

CLINICAL PHARMACOLOGY OF CANNABIS

- *95-99% plasma protein bound - hydroxylation, oxidation, and conjugation for rapid 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*

How does it help in SCI?

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

Medical cannabis = low THC, high in other 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

Cannabinoids have suppressed neuropathic nociception in 9 different animal models of SCI and other nerve injury

- Spinal cord injury
- Chronic constriction injury: infraorbital nerve, saphenous nerve
- Partial nerve ligation: sciatic, saphenous
- Spinal nerve ligation: L5
- Spared nerve injury
- Tibial nerve injury
- Streptozotocin-induced diabetic neuropathy

Rahn EJ and Hohmann AG. Cannabinoids as Pharmacotherapies for Neuropathic Pain: From the Bench to the Bedside. Neurotherapeutics 2009. 7:4, 713-737.

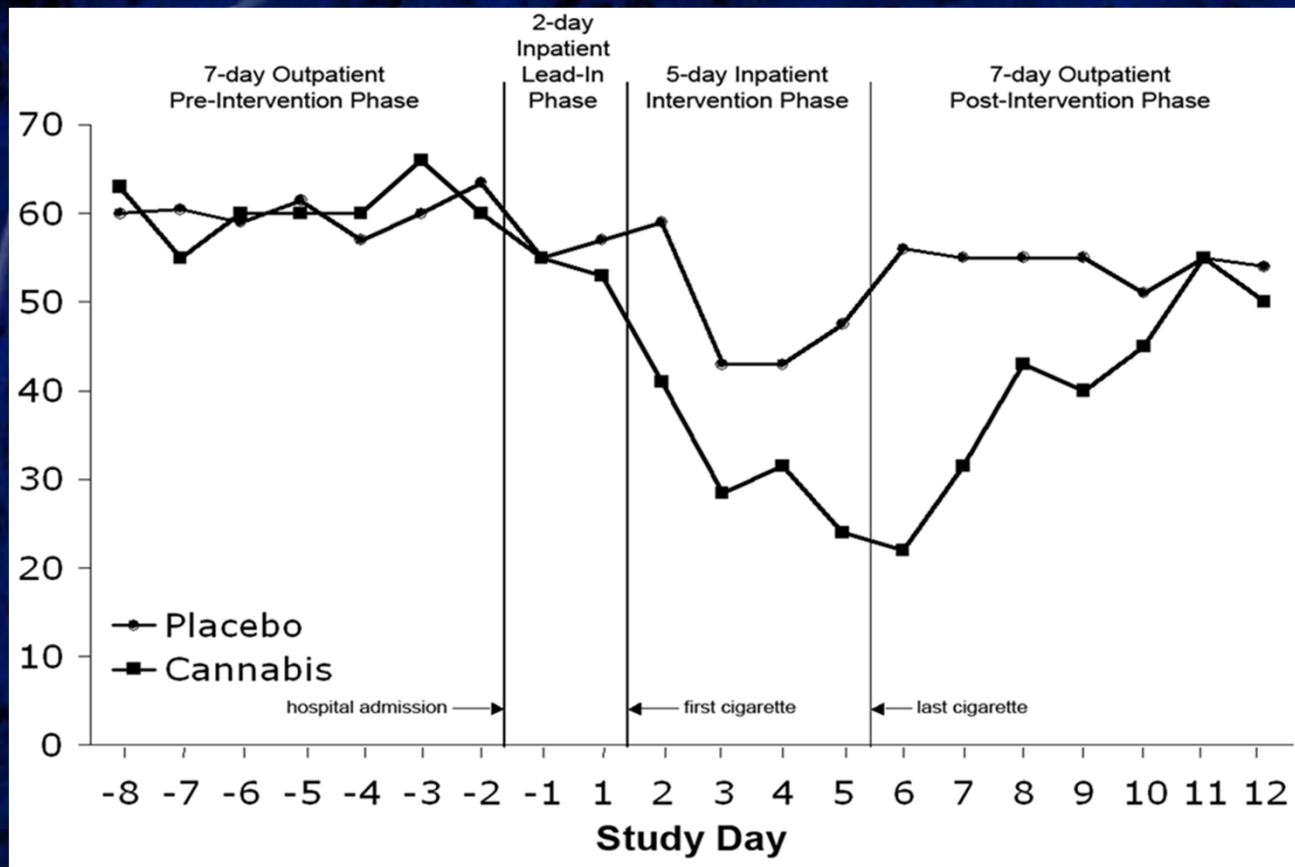
More on Cannabinoid Suppression of Neuropathic Pain – animal models

- SCI model—mechanical allodynia was reduced with chronic administration of WIN (mixed CB agonist) with no decrease in effectiveness, unlike morphine
- CB2 receptor immunoreactivity is increased in the ipsilateral dorsal horn after L5 spinal nerve transection
- Saphenous partial nerve ligation increased u-opioid, CB1, and CB2 receptor protein levels in ipsilateral/contralateral hind paw skin, DRG, and ipsilateral/contralateral L-cord (1-7 days post-surgery)
- Tibial nerve injury → upregulation of CB1 receptor mRNA in the contralateral thalamus, 1 day post-surgery

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

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.

But how do I know how much to use??



- START LOW; GO SLOW
- 2-3 inhalations, stop, wait ten minutes
- Do not need to be high to get pain relief

Other ways to use medicinal cannabis?



- Ingestion? Takes about an hour to get effects so harder to dose but lasts longer
- Transdermal? Yes! Works well as a linament
- Injectable: NO!

SIDE EFFECTS

- Disinhibition, relaxation, drowsiness
- Feeling of well being, exhilaration, 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!

For the SCI patient to know

- 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

Why Use Cannabis?

- It works for pain, spasticity/spasms and not many drug-drug interactions
- Side effects mild; low toxicity, NO LD50
- Cannabis has other potential benefits: reduce inflammation, neuroprotective, anti-tumor properties

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

Marinol? No...but Sativex? Sure, it's a step in the right direction

- 1:1 combination from two clonal cannabis cultivars yielding a high THC extract (Tetranabinex®) and a high CBD extract (Nabidiolex®).
- a botanical drug substance (BDS) of defined composition with controlled reproducibility batch to batch.
- THC and CBD comprise some 70% (w/w) of the total BDS, with minor cannabinoids (5 – 6%), terpenoids (6 – 7%, most GRAS), sterols (6%), triglycerides, alkanes, squalene, tocopherol, carotenoids and other minor components (also GRAS).
- each 100 µL pump-action spray provides 2.7mg of THC and 2.5mg of CBD, the minor components, plus ethanol: propylene glycol excipients, and 0.05% peppermint as flavouring.
- Intermediate onset: 15-40 minutes
- Allows dose titration; Reduces first pass metabolism
- MUCH BETTER THAN MARINOL



If you choose to recommend *medicinal cannabis...*

- **FOLLOW THE LAW**
- use high quality cannabis to improve efficacy: high CBD, CBN, lower THC
- do not need to be high to get pain relief
- use a delivery route that maximizes benefits and minimizes side effects

Consider the evidence



- *“Change is the essential process of all existence”.*
- *Lieutenant Commander Spock, Chief Science Officer; Starship Enterprise, StarFleet Division of the United Federation of Planets*

What would Dr. McCoy do?

- *before*



- *after*



The End

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"SMOKE TWO JOINTS, AND CALL ME IN
THE MORNING."