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

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- **Saturday, June 07, 2014**
- **3:45-4:30 pm.**
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- 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 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Suggested reading for historical reference

- 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

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

References:
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

- **Anandamide**: Endogenous, phospholipid-derived metabolites that bind to and activate cannabinoid receptors
- **2-Arachidonoyl-glycerol**

**CB₁ receptor**

**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

Difference Between Classical and Retrograde Neurotransmission

Classical neurotransmitter

Presynaptic

Postsynaptic

Retrograde neurotransmitter

Presynaptic

Postsynaptic

• 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
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

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.
EBM Class One Human Clinical trials


More EBM Class One Clinical trials


• Ware et al. 2010. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ 182: 694-701.

Cochrane reviews of human data


- 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**
"Smoke two joints, and call me in the morning!"