Cannabis for pain: from pills to pot?

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Adapted with permission from Dr. Daniel J. Clauw.
Disclosures

■ None
14 OLYMPIC GOLD MEDALS
37 WORLD RECORDS.
2 AWESOME LUNGS.

Unlike heavy tobacco smokers, heavy marijuana smokers exhibit no obstruction of the lung's small airway. That indicates that people will not develop emphysema from smoking marijuana. For more information visit clubfbi.com/marijuana.

Don't let the government fool you

LEGALIZE MARIJUANA
Authorised by the High design Studio, Sydney, Australia.
A VICIOUS RACKET WITH IT'S ARMS AROUND YOUR CHILDREN!

THE TRUTH ABOUT MARIJUANA

THE SMOKE OF HELL!

"DEVIL'S HARVEST"

SIN

DEGREDATION

VICE

INSANITY

DEBAUCHERY

http://66.media.tumblr.com/tumblr_mbxx10s2D51qapk
myo1_500.jpg
HIGH TIMES

MEDICAL CANNABIS CUP

FIRST EVER MEDICAL PATIENT ONLY EVENT

AUTO CITY SPEEDWAY

CLIO, MICHIGAN       JUNE 11-12       #CANNABISCUP

TICKETS ON SALE NOW AT CANNABISCUP.COM

https://www.leafly.com/cannabis-events/michigan-medical-cannabis-cup
Medical cannabis in US

SCHEDULE 1
Medical cannabis in Michigan

Michigan Medical Marihuana Act of 2008:
- Many conditions/symptoms covered
- In 2016: 80% of the 218,556 patients in Michigan have their license for severe and chronic pain

Is cannabis appropriate for pain?
Which kinds of pain? Any other uses?

1: 2016 Medical Marihuana Act Statistical Report, Michigan
Big Decline in Opioid Use by Marijuana Users

March 23, 2016

Medical Pot Is Our Best Hope to Fight the Opioid Epidemic
"There are direct reasons why [cannabis] could actually help people get off of opioids," says one leading marijuana researcher.

Could Medical Cannabis Break the Painkiller Epidemic?
A body of research suggests yes, but scientists are having to fight red tape to study whether medical marijuana could substitute for opioid drugs.

One way to fight the marijuana.
An innovative, but evidence-based, idea.
Cannabis as an opioid substitute for chronic pain?

- Cannabis as a synergist with opioids\(^1,2\)

- State-wide analyses\(^3-5\)
  - Importance of Dispensaries in these studies (Powell et al, 2018)

- Cross-sectional\(^6-8\) and longitudinal support\(^9-11\)

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Cannabis and Cannabinoids

- Definitions and Background
- Overview of Risks and Benefits of Cannabinoids
- Role in Pain Management
  - Acute vs. Chronic
- Summary
Definitions

- **Cannabis** - indica, sativa, and ruderalis

- **Cannabinoids:**
  - Endocannabinoids
  - Phytocannabinoids – plant origin
  - Synthetic cannabinoids – e.g. dronabinol and Nabilone
Endocannabinoid system - I
A set of receptors and their naturally occurring ligands (endocannabinoids) and enzymes regulating control

Endocannabinoid system

Endocannabinoid system - II

Some known functions of the endocannabinoid system:

- **Functions:** “Relax, eat, sleep, forget, protect”
- Memory
- Neurogenesis
- Analgesia
- Immune function
- Stress
- Appetite


Figure from Crowe et al, 2014.
Cannabis-derived cannabinoids

- **Tetrahydrocannabinol (THC)**
  - Analgesic, mood-altering, appetite stimulating
  - Partial agonist of CB1 and CB2

- **Cannabidiol (CBD)**
  - Does not bind with significant affinity to CB receptors
  - Non-intoxicating, potentially protective against psychoactive effects of THC
  - Anti-inflammatory, peripheral pain effects

- Other cannabinoids: CBN, CBG, CBC, etc. – The "Entourage Effect"

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**CBD Biscuits**

For small to medium dogs (9-44lbs)  
For medium to large dogs (45-120lbs)

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**CBD Extracts**

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Pharmacokinetics

Route of administration influences THC pharmacokinetics, left = 5 mg i.v. injection, center = smoking 13.0 mg, or right = consuming cookie with 20 mg (Agurell et al. 1986).

Feelings of ‘high’ from different administration routes

U-Shaped Curve for cannabis effects

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Known benefits of Cannabinoids

- Antiemetic and anorexia\textsuperscript{1-4} – dronabinol and nabilone are FDA-approved (Schedule II + III) in US.\textsuperscript{6}

- Nabiximols: Anti-spasticity agent, used for MS\textsuperscript{4,5,6}

- Analgesia\textsuperscript{6}: Strongest evidence in chronic neuropathic pain

- Recent trial of CBD for Osteoarthritis

- Epilepsy: CBD found to reduce seizure frequency in Dravet Syndrome, Lennox-Gastaut, and other epileptic disorders

Contraindications of medical cannabinoids

- Poor data available on herbal cannabis

- Dronabinol contraindications:
  - Disulfiram or Metronidazole use in past 14 days
  - History of substance abuse
  - Pregnancy
  - Psychiatric disorder
  - Cardiovascular disease
  - History of seizures

- Nabiximols contraindications:
  - Known or suspected allergy to cannabinoids, propylene glycol, ethanol or peppermint oil,
  - Patients with significant hepatic or renal impairment
  - Patients with serious cardiovascular disease such as ischaemic heart disease, arrhythmias, poorly controlled hypertension or severe heart failure,
  - Patients with a history of schizophrenia or any other psychotic disorder,
  - Children under 18 years of age;
  - Women of child-bearing potential not on a reliable contraceptive or men intending to start a family, and in pregnant or nursing women.

Approval for Sativex with conditions. Bayer, 2005. Epocrates Online, Marinol
Risks of cannabinoids (recreational)

Long term:
- Respiratory effects
- Dependence and addiction
- Psychotic illnesses: 1.5-2.4x rate developed under age of 25
- Long term effects on memory and brain structure

Acute:
- Common: Dizziness, somnolence, euphoria, light-headedness, anxiety, and others
- Uncommon: Vomiting, hallucinations, paranoia, seizures
- Uncertain quality of herbal preparation
- Vehicle accidents

The map displays the United States for all contiguous states and offset images for noncontiguous states. Colors denote relative increase in traffic risks on April 20 compared with control days exactly 1 week earlier and later. Green corresponds to increased relative risk, yellow to neutral relative risk, and brown to decreased relative risk (spectrum scaled by logarithm transformation). Findings show that 30 states had a relative risk point estimate greater than unity (e.g., Hawaii), while only 18 states had an estimate less than unity (e.g., Minnesota), and 2 states had an estimate of exactly unity (e.g., Montana).
Risks of cannabinoids: medical use

- Much less data on risks of medical use, though similar profile in elderly adults as younger medical users. 3,4
- In observational trial of smoked medical cannabis: Increased minor adverse events, no increase in serious adverse events 2

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Role of Cannabinoids in Pain Management

- Mechanisms of pain
  - Preclinical models, mechanisms of action

- Clinical trials in chronic pain states
- Efficacy
## Mechanistic Characterization of Pain

Any combination may be present in a given individual.

### Peripheral (nociceptive)
- Inflammation or mechanical damage in tissues
- NSAID, opioid responsive
- Responds to procedures

### Peripheral Neuropathic
- Damage or dysfunction of peripheral nerves
- Responds to both peripheral (NSAIDs, opioids, Na channel blockers) and central (TCA's, neuroactive compounds) pharmacological therapy

### Centralized Pain
- Characterized by central disturbance in pain processing (diffuse hyperalgesia/allodynia)
- Responsive to neuroactive compounds altering levels of neurotransmitters involved in pain transmission

### Classic examples
- Acute pain due to injury
- Osteoarthritis
- Rheumatoid arthritis
- Cancer pain
- Diabetic neuropathic pain
- Carpal tunnel
- Sciatica
- Fibromyalgia
- Irritable bowel syndrome
- TMJD
- Tension headache

### Mixed Pain States
Preclinical models of pain

- Animal models of pain with CB1 agonists, CB2 agonists and mixed CB1/CB2 agonists

- Because of CNS actions, compounds with CB1 activity cause more "off-target" side effects

- THC reduces connectivity between limbic and sensory brain regions, and thus unpleasantness of pain (may be mechanism with nausea)

- Selective CB2 agonists (e.g., ajulemic acid) should have considerably less CNS effects

- Good for nociceptive or inflammatory mechanisms of pain

- Not good for pain of CNS origin

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https://www.corbuspharma.com/pipeline/lenabasum
Role of Cannabinoids in Pain Management

- Preclinical models
- Mechanisms of action
- Clinical trials in chronic pain states
  - Efficacy
Cannabis clinical trials for chronic pain

- Limited: short length and small sample size
  - Many used THC alone or THC + CBD
- Most support for use of cannabinoids in neuropathic pain (THC+CBD).
- Increased risk of short term AEs (mostly minor) for study participants

Cannabinoid for acute and surgical pain

A systematic review of the analgesic efficacy of cannabinoid medications in the management of acute pain

A. J. Stevens¹ and M. D. Higgins²

¹St Vincent’s Hospital Melbourne, Fitzroy, Vic., Australia
²Flinders Medical Centre, Bedford Park, SA, Australia

- Meta-analysis of 7 clinical trials: **Cannabinoids mostly equivalent (n=5) or inferior (n=1) to placebo**
  - All trials limited in length
  - No trials used CBD

- Recent observational study of recovery from musculoskeletal trauma²:
  - Users report reduced pain and need for opioids

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What to do when candidate for surgery discloses cannabis use?

- No need to alter typical analgesic regimen.
- Use best judgment
- No evidence for cannabinoids in surgical setting or for acute pain.
- Given length of in-patient stay, don’t really do anything for any user if patients are there for more than 1-2 days.
Summary

- Endocannabinoid system: plausibility as analgesic at right dose and in right person

- Cannabinoids can exert analgesic effects in the periphery and CNS

- For treatment of clinical pain with cannabinoids:
  - Better evidence for efficacy in chronic neuropathic pain: May be reasonable to use in place of opioids for *chronic pain* when all else has failed, but NOT in a surgical context.
  - No evidence for efficacy in acute/surgical pain. No clinical trial data on recovery from surgical pain
Questions?