Chronic pain and Mary Jane: Are cannabinoids the “high”way to relief?

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What is pain?

“An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”

-International Association for the Study of Pain (IASP)
The two faces of pain: Protection and disease

Normal

Protective

Acute → Prolonged

Reflexes → Inflammation and repair

Abnormal

Non-protective

Chronic (Pain as Disease)

Therapeutic goal:
Eliminate abnormal pain without interfering with normal, protective pain
Chronic pain is a highly prevalent problem worldwide.
The body interprets pain using a simple neural pathway.
Chronic pain is poorly treated

• 82% of chronic pain patients reported that their pain was “treated poorly” (National Pain Foundation, 2014).

• Over 50% of chronic pain patients complain that they have no control over managing their pain (National Pain Foundation, 2014).

• Females suffer disproportionately than males from chronic pain disorders— in some cases over 3x more (Mogil, 2012).

Current treatment options (e.g., opioids) leave millions of people untreated.
Side effects of opioid analgesics limit their use

Miosis (pin point pupil)
Out of it (sedation)
Respiratory depression
Physical dependence
Histamine release (excessive itch)
Increased intracranial pressure
Nausea
Uphoria
Bench-to-bedside translation of analgesics is SLOW

Illustration by Erinn Acland

Acland, 2016, Pain Research Forum

Illustration by Erinn Acland
Medical marijuana laws reduce opioid prescriptions

Average numbers of daily doses filled for prescription drugs annually per physician in states with a medical marijuana law, by condition categories studied, compared to the average numbers in states without a law.

- Anxiety: -562
- Depression: -265
- Glaucoma: 35
- Nausea: -541
- Pain: -1,826
- Psychosis: -519
- Seizures: -486
- Sleep disorders: -362
- Spasticity: -32

Bradford and Bradford, 2016, *Health Affairs*
Cannabis contains 100+ cannabinoids (537 constituents total)

(a) $\Delta^9$-Tetrahydrocannabinol
(b) Cannabidiol
(c) Cannabielsoin
(d) Cannabitriol
(e) Cannabichromene
(f) Cannabigerol
(g) $\Delta^8$-Tetrahydrocannabinol
(h) Cannabinol and Cannabinodiol
(i) Cannabicyclol

Nascimento et al., 2015, *Analytical Methods*
Clinical pharmacology of *Cannabis* is complex

- Elimination is slow: days to weeks; 20-35% found in urine; 80% found in feces; stored in adipose

- Fast absorption if vaporized, slower if ingested or topical

  ✓ No constipation or respiratory suppression

  ✓ No $LD_{50}$

Lindgren et al., 1981, *Psychopharmacology*
Cannabinoid/pain research is very new

Publication info gathered from MEDLINE, National Institutes of Health
How do cannabinoids provide pain relief?

Hosking and Zajicek, 2008, Br J Anaesth
Cannabinoid-based therapies are currently on the market

- Dronabinol (Marinol): $\Delta^9$-tetrahydrocannabinol (Schedule III)
- Nabilone (Cesamet): Synthetic $\Delta^9$-tetrahydrocannabinol (Schedule II)
- Nabiximols (Sativex): $\Delta^9$-tetrahydrocannabinol/cannabidiol (Schedule IV)
- Medical marijuana: $\Delta^9$-tetrahydrocannabinol/cannabidiol/others (Schedule I)
Cannabinoids provide relief against multiple types of pain

- Myofascial pain syndrome
- Diabetic neuropathy
- Neuropathic pain syndrome
- Central pain syndrome
- Phantom pain
- Spinal cord injury
- Fibromyalgia
- Osteoarthritis
- Rheumatoid arthritis
- Discogenic back pain
- HIV-associated neuropathy
- Malignant pain
- Cancer pain
- Headaches/Migraine
- Muscle cramps
Characteristics of migraine

Before an attack
- Yawning
- Fatigue
- Food cravings
- Drowsiness or depression
- Irritability or tension
- Occurs 24-48 h before attack

During an attack
- Nausea, vomiting
- Sweating or cold hands
- Sensitivity to light and sound
- Scalp tenderness or extracephalic allodynia
- Throbbing, unilateral pain
- Can last from 4-72 h

After an attack
- “Hungover”
- Weakness
- Tiredness
- Mood changes
- Can last for hours to days after attack is over
Where do headaches come from?

Ray and Wolff, 1940, Archives of Surgery
Migraine art
$\Delta^9$-THC analgesia against migraine is not perfect

Kandasamy et al., in preparation
$\Delta^9$-THC analgesia against migraine is not perfect

Kandasamy et al., in preparation
What is fibromyalgia?

“Fibromyalgia makes your skin hurt just by the touch of your clothes. It makes your skin burn with pain.”
Cannabis is more effective against fibromyalgia pain

National Pain Foundation survey, 2014
What is neuropathic pain?

- Caused by a problem with one or more nerves such that the nerve sends pain messages to the brain in the absence of any stimulus.

Cannabinoids may be effective for neuropathic pain

- Opioid analgesics are ineffective due to depletion of opioid receptors in the spinal cord following nerve injury.

- However, there is an upregulation of CB₁ receptors in the thalamus which may increase analgesic efficacy.

Rice et al., 2002, Prostagl Leukot Essent Fatty Acids; Siegling et al., 2001, Eur J Pharmacol
Females suffer disproportionately from chronic pain.

Mogil et al., 2012, Nat Rev Neurosci
Females are more sensitive to $\Delta^9$-THC analgesia
Males are more sensitive to *Cannabis* analgesia

Cooper and Haney, 2016, *Drug Alcohol Depend*
Advantages of cannabinoids over traditional analgesics

- Minimal side effects (no constipation or respiratory depression)
- At least 1 year of use is not associated with long-term negative consequences in adults
- No LD$_{50}$
- *Cannabis* use for pain is not associated with increased vascular, metabolic, blood, renal, musculoskeletal, gastrointestinal, pulmonary, or immune system disorders
Unanswered questions surrounding CB analgesia

- Limit psychoactivity?
- Peripherally-restricted CB agents?
- Cannabinoid x opioid synergy?
- Legal status?
- **Is marijuana** a ‘magic bullet’ for chronic pain patients?
Questions?