Chronic pain and Mary Jane: Results from research

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I have nothing to disclose.
Learning objectives

1. Understand the definition and mechanisms of pain and its prevalence

2. Identify the pain conditions where medical marijuana is effective

3. Identify current and future directions for research surrounding the use of cannabinoids for the treatment of pain
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
Ausea
Euphoria
Current opioid policies affect patients’ qualities of life

Dialogue, Dialogue, Dialogue: Strategies to Facilitate Translation

The development of new and effective analgesics requires ongoing, productive, back-and-forth communication between basic scientists and clinicians

by Ram Kandasamy on 30 Aug 2016

Dialogue between clinicians, scientist & Please do NOT forget to include genuine Pain patients whos rights have've been stripped right now in the name of "addicts".there's NO other efficient pain treatment for them to be able to just make it through their day.

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Kandasamy, 2016, Pain Research Forum
Bench-to-bedside translation of analgesics is SLOW

Illustration by Erinn Acland

Acland, 2016, Pain Research Forum
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
Many arguments oppose the clinical use of Cannabis

- Chemical composition of Cannabis is complex, variable, unknown; thus, predicting effects are not possible

- Cannabis is harmful to individual and public health

- The push for medical cannabis is part of a well-structured and funded strategy to legalize Cannabis for general use

- Smoking Cannabis may be harmful because of products of combustion
Cannabis contains 100+ cannabinoids (537 constituents total).

(a) Δ⁹-Tetrahydrocannabinol
(b) Cannabidiol
(c) Cannabinol
(d) Cannabigerol
(e) Cannabichromene
(f) Cannabichromene
(g) Δ⁸-Tetrahydrocannabinol
(h) Cannabinol and Cannabinol
(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
Cannabis is more effective against fibromyalgia pain
“Throbbing, pulsating, stabbing. On a bad day, I have difficulty leaving my bed, let alone my home. I cannot go to work on almost half of a month, cannot enjoy playing with my children or even meeting friends for a coffee. There are weeks during which I barely manage to keep my place in order. Darkness and silence are my friends of late. I basically don’t recognize myself anymore.”

-Anonymous migraine patient, describing her illness
**Cannabis and migraine: Anecdotes vs. research**

- Dr. Cledinning in London first prescribed cannabis for migraine in the 1840’s.

- Dr. Farlow described marijuana as having “few equals in its power over headaches” in 1889.

- Cannabis preparations were taken off the *US Pharmacopoeia* in 1941; however, Dr. Fishbein recommended oral cannabis for menstrual migraine in 1942.

- Smoked cannabis terminates migraine attacks within 5 min of inhalation and restore complete function within 15 min.

- Frequency of migraine headache was decreased with medical marijuana use.

Baron, 2015, *Headache*; Rhyne et al., 2016, *Pharmacotherapy*
What is neuropathic pain?

- Neuropathic pain is 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.

Females suffer disproportionately from chronic pain.
Males are more sensitive to *Cannabis* analgesia
Advantages of cannabinoids over traditional analgesics

- Minimal side effects (no constipation or respiratory depression)
- Chronic use (1 year min.) 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

Ware et al., 2015, *J. Pain.*
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?