Eighth Annual Dartmouth Symposium on Substance Use

Medical Marijuana: Compassionate Care or Oxymoron?

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Cannabinoid Pharmacology and Clinical Promise
Endocannabinoid system

- **Receptors**
  - CB1 – Mostly in the brain
  - CB2 – Mostly out of the brain

- **Molecules that activate the receptors (endocannabinoids)**
  - Anandamide
  - 2-Arachidonoylglycerol

- **Molecules that degrade endocannabinoids**
  - Fatty acid amide hydrolase (FAAH)
  - Monoacylglycerol lipase (MAGL)
Cannabinoid Receptors

- Tetrahydrocannabinol (THC) is the major active ingredient of marijuana.
  - Binds mostly to CB1 receptors

- In the brain, CB1 receptors are found in high concentrations in areas that influence pleasure, memory, thought, concentration, sensory and time perception, appetite, pain, and movement coordination.

- CB1 receptors are not present in cardiopulmonary centers in the brain.

- Patients with Huntington Disease show a reduction of brain CB1.

- CB1 receptors are expressed in brain areas that control pain.
Endocannabinoids and Pain

- Analgesic effects by actin in the brain and out of the brain
- Endocannabinoids are elevated in areas that process pain signals
- Mediate stress-induced analgesia
- The elevation of endocannabinoids reduces pain
  - By the blockade of the molecules that degrade endocannabinoids
Chronic pain affects 100 million

Costs $635 billion annually

Following common surgeries:
  - Persistent pain in 10-50%
  - Disability in 2-10%

Mechanisms responsible for the transition from acute to chronic pain are unknown
Pain processing
Postoperative pain and ECBs in spinal cord

Alkaitis et al., PLoS One 2010
Paw Incision: CB1 expression

*\( p < 0.05 \) vs. Naive Control

Alkaitis et al., PLoS One 2010
Paw Incision: CB2 expression

*p<.05 vs. Naive Control

Alkaitis et al., PLoS One 2010
CB1 cellular expression

CB1 receptor

Alkaitis et al., PLoS One 2010
CB2 cellular expression

CB2 receptor

Neurons

Microglia

Astrocytes

Perivascular

Alkaitis et al., PLoS One 2010
Cannabinoid Pharmacology

- Smoked Marijuana
- Specific chemicals found in marijuana
- Chemicals that mimic marijuana’s chemicals
- Chemicals that modulate the ECB system
The cannabis plant contains active ingredients with therapeutic potential for relieving:

- Pain
- Spasticity
- Controlling nausea
- Stimulating appetite
- Decreasing ocular pressure.
Cannabinoid Pharmacology

Alternatives for smoking marijuana

- Sativex
- Dronabinol (Marinol, synthetic THC)
- Nabilone (Cesamet, synthetic cannabinoid, mimics THC)

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- Rimonabant (Acomplia, CB1 ANTAGONIST)
Cannabinoids - Drugs

- **Smoked marijuana (Cannabis Sativa)**
  - According to DEA, it is an illegal Schedule I drug with no accepted medical use.
  - Potential of abuse, no medical use, lack of safety to be prescribed by doctors
  - It has 460 known compounds
  - 60 of these compounds are cannabinoid (unique to cannabis)
  - The main psychoactive compound if delta-9-tetrahydrocannabinol (THC)
  - Other major component is cannabidiol

- The use of medical marijuana is currently legal in 16 states and the D.C.
Cannabinoids - Drugs

- **Dronabinol (Marinol, synthetic THC)**
  - Schedule III (medical use and less risk of abuse)
  - Approved by FDA in 1985
    - Nausea and vomiting caused by chemotherapy
  - Approved by FDA in 1992
    - Loss of appetite and weight loss in AIDS patients

- Major concerns
  - Some patients describe a strong effect at first, and then wore off quickly.
  - It is very expensive ($200-800 monthly)
  - Difficult for nauseous patients to consume the pill.
Cannabinoids - Drugs

- **Nabilone (Cesamet, synthetic cannabinoid, mimics THC)**
  - Schedule II (risk of abuse, with medical use)
  - Approved by FDA in 1985 but it was first marketed in 2006.
    - Nausea and vomiting caused by cancer chemotherapy
    - It is also used for loss of appetite and weight loss in AIDS patients
  - Adjunct analgesic for neuropathic pain in Mexico.
Cannabinoids - Drugs

- **Sativex (THC-cannabidiol, 1:1. Nabiximols in US)**
  - Oromucosal mouth spray
  - FDA issued an investigational new drug (IND) application for Sativex in 2006
    - IND allows Sativex to be studied for potential approval for marketing if it is deemed safe and effective.

- **Multiple Sclerosis (UK, Spain, Canada and New Zealand)**
- **Cancer pain (Canada)**
- **Neuropathic pain (Canada)**

- **Problems**
  - Cost (1 vial for 10 days costs $125 in Canada; 125 pounds in UK)
Cannabinoid Pharmacology

- **Rimonabant (Acomplia, CB1 ANTAGONIST)**

  - Anti-obesity drug, reduces appetite (Europe).
  - Withdrawn from market due to side-effects (depression and suicidal thoughts)
  - Potential efficacy for smoke cessation (under study)
Cannabinoid Clinical Promise

Potential safer alternatives for marijuana

- **Tetracan**
  - Medical marijuana patch (Medical Marijuana Delivery Systems, MMDS) LLC.
  - May be marketed for dispensaries soon.

- **Synthetic activators of CB receptors (agonists)**
  - CB1 or non-selective agonists
  - CB2 agonists

- **Compounds that enhance endocannabinoids (natural/biological agonists).**
  - Blockers of endocannabinoids degradative molecules
Cannabinoid Clinical Promise

CB1 or non-selective activators

- Effectively block pain responses in virtually every pain model
  - Acute inflammatory, cancer, chronic neuropathic, surgical, etc.
  - Effects were independent of route of administration

- Limitations: Consistently produced psychotropic effects (brain actions)
  - Catalepsy and reduced motor activity.
  - The long term administration produces tolerance.
Cannabinoid Clinical Promise

CB1 or non-selective activators

- Alternative: Avoid brain actions by targeting sites out of the brain (periphery).
  - It has been shown that CB1 activators that do not act in the brain are effective in several types of pain experimentally (inflammation, nerve injury or cancer).
  - Thus, drugs that do not enter the brain could be ideal for certain types of pain in which brain circuits are not essential
    - Prevention to transition from acute to chronic pain
    - Postoperative pain at the time of surgery
    - Inflammatory pain of short duration

- Precautions:
  - CB1 activators may regulate immune responses: potential risk of infection or wound healing.
Cannabinoid Clinical Promise

CB1 or non-selective activators

Clinical studies – Acute pain

- THC or nabilone (THC analogue) has not proven to reduce acute pain in humans (postoperative).

- In some cases analgesic effects were achieved with doses that enhanced frequency and intensity of side effects.

- In other cases CB1 agonists induced higher pain intensities.

- There is a clear disconnection between experimental studies and human trial results.

Conclusion

- CB1 agonists cannot be recommended for this condition.
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CB1 or non-selective activators

Clinical studies – Chronic pain

- Pain in Multiple Sclerosis
  - Dronabinol and Cannabidiol have shown efficacy in reducing MS pain.
  - Dronabinol improved functional tests in MS patients.
  - CB1 or non-selective activators are recommended as second line therapy for pain and spasticity in MS patients.
  - Potential risk of abuse and psychiatric adverse events due to long term treatment.

- Neuropathic Pain (NP, due to nerve damage)
  - THC or sativex have shown about 30% improvement in these patients: peripheral nerve lesions or HIV-associated NP.
  - These types of pain are resistant to common treatments for NP.
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CB1 or non-selective activators

Clinical studies – Chronic pain

- Cancer Pain, Rheumatoid Arthritis or Fibromyalgia syndrome
  - THC, cannabidiol, dronabinol and nabilone have shown about 30% relief.
  - These drugs also improved mood, sleep and coping.
  - In Fibromyalgia patients cannabinoids were more effective in patients with depression than in patients without depression. Suggesting that an action into the brain is important (high potential of side effects!)

- Combination with opioids
  - Dronabinol as adjuvant therapy seems to synergistically reduce pain with opioids. Additionally, dronabinol seems to reduce opioid tolerance (open-label clinical trial).

- Conclusions
  - Cannabinoids induce mild-moderate pain relief (about 30%), they are not more effective than current treatments. They improve mood and sleep quality. Recommended as second-line or for some individuals.
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CB2 selective activators

- They have shown to reduce pain responses in neuropathic, cancer and postoperative pain and in some types of inflammatory pain experimentally.

- In some cases CB2 activators can also interact with opioid receptors.

- They do not produce classic psychotropic cannabinoid effects (dependent on CB1 activation).
  - No catalepsy, reduction in motor activity or tolerance.

- The efficacy of CB2 agonist is not as high as CB1 agonists experimentally.

- Precautions:
  - CB2 activators strongly regulate immune responses: potential risk of infection or wound healing delay.
Cannabinoid Clinical Promise

CB2 selective agonists

Clinical studies

- **Acute Pain**
  - Cannabinor (Pharmos Corporation) did not show efficacy in acute pain (capsaicin) or postoperative pain (molar extraction).
  - GW842166 (GSK) has failed to reduce tooth extraction-induced postoperative pain in patients.

- **Conclusion**
  - CB2 selective agonist cannot be recommended for acute pain conditions.
Cannabinoid Clinical Promise

ECB enhancers – blockers of ECB degradative molecules

- URB597 or PF-04457845 inhibits the enzyme that degradates anandamide.
- JZL184 inhibits the enzyme that degrates 2-AG.
- Effective experimentally in osteoarthritis, inflammatory pain, visceral pain, diabetic neuropathy, neuropathic pain, bone cancer pain
- They do not induce cannabinoid-like psychotropic effects.

Theoretical Advantages:
- ECBs are produced on-demand, therefore the inhibition of their degradative molecules would enhance ECBs only at sites where they are needed and important. This may explain the lack of cannabinoid-side effects in pain conditions experimentally.
Cannabinoid Clinical Promise

ECB enhancers – enzyme inhibitors

Clinical studies

- PF-04457845 effectively induced an increase in anandamide in humans.
- PF-04457845 failed to relieve pain in patients with osteoarthritis.

Conclusion

- ECB enhancers are not recommended for OA pain. Some weaknesses of this clinical trial is the type of pain chosen: OA has a minimal inflammatory component.
Cannabinoid Clinical Promise

**ECB enhancers – enzyme inhibitors**

**Clinical Promise?**

- ECBs drive the resolution of postoperative acute pain experimentally.

Alkaitis et al., PLoS One 2010
Cannabinoid Clinical Promise

Other conditions

- Obesity
  - Drugs that modulate ECBs outside the brain seem a safer strategy (URB 447 peripherally restricted CB1 antagonist).

- Anxiety

- Cardiovascular conditions (atherosclerosis, blood pressure, heart function).

- Memory

- Gut microbiota

- Nicotine withdrawal
Cannabinoid Clinical Promise

Conclusions

- CB1 or non-selective activators cannot be recommended for acute pain.

- CB1 or non-selective activators induce mild-moderate pain relief (about 30%), but they are not more effective than current treatments. They improve mood and sleep quality. Recommended as second-line therapy specially for MS pain. For other chronic pain they could be useful for some individuals.

- CB analgesic effects are not sufficient for severe pain conditions. But their other neurologic effects may be beneficial as co-analgesics or as an adjuvant for multimodal therapeutic approaches for individual patients or certain type of patient groups.

- Precautions should be taken for CB1 activators when given for long term: Potential risk of abuse, psychiatric adverse events or tolerance formation.
Cannabinoid Clinical Promise

Conclusions

- CB2 activators cannot be recommended for acute pain conditions.
- ECB enhancers are not recommended for OA pain.
- Since CB1 activators compounds are more potent than CB2 activators or ECBs, the clinical promise of these compounds is not clear, and it remains to be determined for other conditions (chronic pain or inflammatory conditions).
- The enhancement of ECBs may be beneficial in patients with risk to develop chronic pain following injuries or surgeries. The identification of patients with that risk remains elusive.
- More research on cannabinoids is necessary.
Cannabinoid Clinical Promise

Conclusions

- Cannabis is claimed to produce a stronger analgesic effect than synthetic cannabinoids. This may be due to a complex combination of several components in the plant.

- More studies are needed to compare cannabis effect vs. synthetic compounds.

- The regulation of marijuana plant as a medicine seems difficult. This is due to the complexity in regulating exact chemical contents and in the logistic of production. Not to mention the federal government policy of zero-tolerance toward illicit drugs.
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Thanks