Medicinal Marijuana: Closing the gap between anecdotal benefits and evidence-based research

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Presenter Disclosure

• Presenter: Jonathan Kiesman
• Relationship with Commercial interest:
  • Employed as a Pharmacist at CanniMed Ltd.
Mitigating Potential Bias

• Jonathan is a Pharmacist with 20 years experience in outpatient Pharmacy settings.

• Prairie Plant Systems Inc, parent company of CanniMed Ltd, has been working with and providing medical marijuana to Health Canada since 2000.

• The parent company has provided product for clinical trials and have on-going clinical trials.

• Generic names will be used.
Female Cannabis Flowers

Page, 2014
Introduction

• Marijuana (cannabis) contains compounds called cannabinoids. (THC and CBD)

• Perceived association of cannabinoids = recreational marijuana gives rise to a lot of misconception

• It wasn’t until the mid-1990s that scientists discovered why marijuana is reported to work so well, and for so many different illnesses. The discovery was a natural system in the human body called the endo-cannabinoid system.

• The body produces many of it’s own endogenous cannabinoid signalling molecules, 2 most studied are:
  • Anandamide (AEA)
  • 2-AG
Introduction

• The endo-cannabinoid system is similar to the body’s opioid system:
  • natural endorphins (natural opioids), act on opioid receptors, same as synthetic drugs: morphine, hydromorphone, oxycodone, etc.
  • Similarly, AEA and 2-AG (natural CB’s) attach to the body’s endo-cannabinoid receptors, same as cannabinoids found in medical cannabis.

• The main cannabinoid receptors in the body are CB1 and CB2 receptors.
Cannabis (marijuana) supplied by medication (nabilone, sativex) or medical plant-based cannabis. Cannabinoid receptors found in brain, CNS, liver, kidney, pancreas. Effects on human body.
The (Phyto) cannabinoids

• There are more than 110 known cannabinoids, and 400 molecules identified in the cannabis plant

• The major cannabinoids are:
The two most researched substances in medical marijuana are:

- Delta-9-tetrahydrocannabinol (THC)
- Cannabidiol (CBD)

- Consistent THC/CBD ratio = Consistent health benefits
- **THC**: Literature cited for psychoactive, immunosuppressive, anti-inflammatory and analgesic properties of medical marijuana.
- **CBD**: Responsible for anti-inflammatory, analgesic, anti-nausea, anti-emetic, anti-psychotic, anti-ischemic, anxiolytic, and anti-epileptic effects.
Δ⁹-Tetrahydrocannabinol (THC)

- The main active ingredient in drug forms of cannabis (marijuana) is Δ⁹-tetrahydrocannabinol (THC)

- A CB1-receptor antagonist
- THC produces many of the psychoactive effects of cannabis
- Suggested therapeutic effects
  - Analgesic
  - Antiemetic
  - Appetite stimulant
  - Anti-spastic activity

Gaoni and Mechoulam, 1964; Joy et al, 1999
Cannabidiol (CBD)

- A CB2 receptor agonist
- Second most important cannabinoid after THC
- Literature cited indications:
  - Anti-inflammatory
  - Neuro-protective
  - Anxiolytic
  - Anti-epileptic
  - Antipsychotic
- May attenuate memory-impairment effects of THC
- Role in treating pediatric epilepsy? (Dravet syndrome)

Cannabinoid Indications

- **Off-label indications/emerging evidence:**
  - Nausea and vomiting from chemotherapy
  - Chronic pain (neuropathic pain in MS and cancer)
  - Anorexia associated with HIV/AIDS
  - PTSD
  - Anxiety
  - Insomnia
  - Spasticity
  - Lower Urinary tract symptoms (MS)
  - Improving bladder symptoms associated with MS
  - Neuropathic/nociceptive/mixed pain
  - Chronic daily headache
  - Fibromyalgia
  - Anorexia and cachexia
  - Spasticity
  - Epilepsy
Dosing and Administration

• Cannabis requires heat to “activate” THC and CBD
• General principle: “start low/go slow”
  • Keep dose as low as possible using the least amount necessary to control symptoms and titrate slowly

• 1.5 grams/day is the average daily dose as seen at CanniMed (Health Canada indicated 1-1.25 grams/day)
  • Using 12% THC material = 50mg THC/day
Dosing and Administration

• Inhaled
  • Smoking (not recommended)
  • Vaporizing (recommended)
  • Fastest onset of action (5 min-1/2 hr) for both smoking and vaporizing.
  • Shorter duration of action

• Oral and Edibles
  • Prescription cannabinoid capsules: Cesamet (Nabilone)
  • Ingested via tinctures, teas, oils, baking
  • Slower onset of action (1-3)
  • Longer duration of action (8-12 hrs)

• Spray
  • Sativex (“nabiximols” 1:1 ratio of THC: CBD) Sprayed under the tongue or inside of cheek.
  • Max effect at 1-2 hrs.
Vaporizing vs Smoking

• Ideal and fast for those in pain.
• Rapid onset and short duration only achieved through inhaled delivery
Vapourizing in Hospital settings?

IN THE MEDIA:

- Charles Bury's marijuana use in Quebec hospital stirs debate
  - Charles Bury, long-time editor of Sherbrooke Record, vaporizes marijuana to deal with Stage 4 liver cancer. Bury uses medically prescribed marijuana in his hospital room with a vaporizer, which emits little odour and no smoke, to help curb his anxiety.
  - CBC News Posted: Jan 09, 2014 10:52 AM ET Last Updated: Jan 09, 2014 3:44 PM ET

- Canadian Hospitals Prepare To Allow Medical Marijuana
  - Huffington Post/Metro/CBC/Leaf Science, Jan. 9, 2014

- Alberta Health Services: “AHS is looking at developing a process to support patients who are treated with medical marijuana in our facilities”
  - Huffington Post/Metro/CBC/Leaf Science, jan.9, 2014

- Currently is accommodated in a negative-pressure room, which are currently rarely available in most Canadian hospitals.
• Start low and go slow
• Average dose: 1 to 2 grams daily when smoked or vapourized
• Vapourization: At a lower temperature, cannabinoids are vapourized without burning plant matter. The Volcano® Medic is the only vapourizer approved as a medical device by Health Canada
Dosing considerations

• Inhaled delivery:
  • more desirable for acute symptoms: nausea, appetite stimulation, sleep initiation, seizures, spontaneous neuropathic pain episodes

• Oral, edibles and spray delivery:
  • More desirable for persistent symptoms: chronic pain, sleep maintenance, spasticity
  • Patient must consume approx. 2.5X more for same effect as inhalation\(^4,5\)

Possible side effects

Risk of serious side effects are relatively low compared with other prescription drugs. However, evaluating safety data has been complicated due to the illegal status of cannabis.

- Drowsiness
- Dizziness
- Dry mouth
- Fatigue
- Increased heart rate
- Postural hypotension
- Delayed fetal growth
- Excreted in breast milk
- Caution driving under the influence
Contraindications

• Contraindications
  • Hypersensitivity to any cannabinoid
  • Hypersensitivity to smoking
  • Psychotic disorders (particularly schizophrenia)

• Warnings
  • Pregnant or nursing women—highly recommended **not** to use cannabinoids as it may effect development of the fetus and nervous system
  • Potential for dependence and abuse
  • Do not drive or operate machinery
Those who are:

• Are nursing, pregnant, or planning to conceive are highly recommended not to use cannabinoids
Use with Caution in patients with:

- Cardiac disorder (hypertension, hypotension,
- History of substance abuse or dependency
- Mania or depression
- Multiple drug therapy (may be a CYP 3A4 and CYP2C9 liver enzyme inhibitor?)
- Respiratory illness
- Pediatric and elderly populations (due to lack of knowledge/experience about use)
Addiction Potential of Cannabis?

• Thought to have a high abuse potential

• Ability to produce dependence is less than alcohol or nicotine and some drugs such as diazepam, morphine and phenobarbital \(^{21}\)

• Approx. 10% of regular cannabis users become addicted \(^{21}\)

• Addiction potential may be even less when cannabis is used for medical purposes, similar to some other drugs with addiction potential.

Cohen, PJ. Medical Marijuana: the conflict between scientific evidence and political ideology Part one of two. J Pain Palliat Care Pharmacother. 2009; 23:4-25
Research and Evidence
Limitations of Available Data

• Most studies are small, much data is anecdotal, pre-clinical, animal/in vitro.

• Number of studies which actually use medical cannabis plant as opposed to a commercially available THC/CBD product is low. It is not known if this data can be extrapolated to medical cannabis?

• Difficulty for researchers to get approval to work with cannabis due to it’s illegal status.

• No controlled trials comparing smoked cannabis with oral THC or other analgesic agents
Results: “a single inhalation of 25mg of 9.4% THC herbal cannabis three times a day for 5 days reduced intensity of pain, improved sleep and was well tolerated.”

Cannabis...may be useful in alleviating a wide variety of single or co-occurring symptoms often encountered in the palliative care setting; these symptoms include intractable nausea and vomiting associated with chemotherapy or radiotherapy, anorexia/cachexia, severe intractable pain, severe depressed mood, and insomnia. The use of cannabinoids for palliative care may also result in a decrease in the number of medications used by this patient population.

Taken from Health Canada’s: Information for Health Care Professionals: Cannabis (marihuana, marijuana) and the cannabinoids, pg.34.

Cannabis in Palliative Medicine: Improving Care and Reducing Opioid-Related Morbidity

AM J HOSP PALLIAT CARE August 2011 vol. 28 no. 5 297-303

Abstract

Unlike hospice, long-term drug safety is an important issue in palliative medicine. Opioids may produce significant morbidity. Cannabis is a safer alternative with broad applicability for palliative care. Yet the Drug Enforcement Agency (DEA) classifies cannabis as Schedule I (dangerous, without medical uses). Dronabinol, a Schedule III prescription drug, is 100% tetrahydrocannabinol (THC), the most psychoactive ingredient in cannabis. Cannabis contains 20% THC or less but has other therapeutic cannabinoids, all working together to produce therapeutic effects. As palliative medicine grows, so does the need to reclassify cannabis. This article provides an evidence-based overview and comparison of cannabis and opioids. Using this foundation, an argument is made for reclassifying cannabis in the context of improving palliative care and reducing opioid-related morbidity.
Nausea and vomiting

• Health Canada Page 35:
  “While chemotherapy-induced vomiting generally appears to be well-controlled with current first-line therapies, the associated acute, delayed, or anticipatory nausea remain more poorly controlled and the use of cannabis/cannabinoids may provide some measure of benefit in certain cases.” 88,192

Nausea and Vomiting

• Health Canada Page 36:

• “Patients who smoked cannabis showed a 70-100% relief from nausea and vomiting, while those who used a Δ9-THC capsule experienced 76-88% relief (191). Plasma levels of >10ng/mL Δ9-THC were associated with the greatest suppression of nausea and vomiting, although levels ranging between 5 and 10 ng/mL were also effective.” 191

Cancer Pain

• Health Canada, Page 51:
• “The opioid-sparing effect refers to the ability of a non-opioid medication to confer adjunctive analgesia with the use of a lower dose of the opioid thereby decreasing opioid-associated side effects. While there are some pre-clinical data supporting such an effect for cannabinoids, this is less well-established in published clinical studies.”
Cancer Pain continued.

• Health Canada, Page 51:

• “Findings suggest the existence of cross-talk between the cannabinoid and opioid systems. Furthermore, pre-clinical studies using a combination of different opioids (morphine, codeine) and cannabinoids (THC), at acute or sub-effective doses, have reported additive and even synergistic analgesic effects (515,516,517,518,519,520).”

CANCER THERAPY

• Pre-clinical evidence that CB may inhibit tumor growth.

• J.P. Marcu, et al: THC and CBD work together to slow tumour growth more effectively than when they are applied individually.

• “Delta(9)-THC and cannabidiol acted synergistically to inhibit cell proliferation. The treatment of glioblastoma cells with both compounds led to significant modulations of the cell cycle and induction of reactive oxygen species and apoptosis as well as specific modulations of extracellular signal-regulated kinase and caspase activity.”

Cancer Therapy continued

• “Delta(9)-Tetrahydrocannabinol inhibited tumour-cell proliferation in vitro and decreased tumour-cell Ki67 immuno-staining when administered to two patients.”

  • M.Guzman et al.

Summary and Concluding remarks

• Therapeutic cannabinoids may be a safe and effective option to consider for patients experiencing chronic pain, cancer-associated anorexia, or nausea and vomiting associated with cancer chemotherapy.

• Additive effects may allow for dose reduction of concomitant analgesics such as opioids.

• Abuse potential is relatively low. (approx. 10% of users)

• New evidence is emerging, pointing to efficacy of CB to treat conditions such as epilepsy, spasticity, headache, PTSD, anxiety, and insomnia.
Summary and Concluding remarks

- Medical cannabis should be considered when conventional medicine is not enough

- Cannabis should be considered in same context as other pharmaceuticals, opioids for example, that have:
  - Important medical value
  - However also may have significant side effects and potential for abuse.
Resources

Health Canada information about the new regulations is available at: http://www.hc-sc.gc.ca/dhp-mps/marihuana/transition/index-eng.php


www.ccic.net

www.cannabis-med.org
Questions?

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