Cannabis: Evidence vs No Evidence

Stewart Cameron MD, CCFP, FCFP, MAEd
Dr. Stewart Cameron

I HAVE/HAD an affiliation (financial or otherwise) with a pharmaceutical, medical device or communications organization.

<table>
<thead>
<tr>
<th>I am a member of an advisory board or equivalent with a commercial organization.</th>
<th>Company/Organization</th>
<th>Details</th>
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| I am a member of a speakers bureau. | Yes, the Canadian Consortium for the Investigation of Cannabinoids, a non-profit educational and research organization | I have received payments to give seminars and workshops on cannabinoid prescribing over the last 5 years |

| I have received payment from a commercial organization (including gifts or other consideration or “in kind” compensation). | No | |

| I hold a patent for a product referred to in the CPD program or that is marketed by a commercial organization. | No | |

| I hold investments in a pharmaceutical organization, a medical device company or communications firm. | No | |

| I am currently participating in or have participated in a clinical trial within the past two years. | No | |
Agenda

• A short history of the cannabis plant
• The laws around cannabis
• The science of cannabis
• Cannabis as medicine
• General discussion
Cannabis - History

4000 BC – Cultivated in China

3000 BC - First evidence of medicinal use in China for malaria, constipation, rheumatic pains, “female disorders”

1800s  W.B. O’Shaughnessey’s work popularizes cannabis for rheumatism, convulsions, muscular spasms in rabies and tetanus

1900s  Cannabis use declines

Decreased Medicinal Use of Cannabis

- Lack of standardized product
- Synthetic drugs e.g. aspirin, penicillin
- Development of hypodermic needle and morphine
- “Reefer Madness”

Cannabis Criminalized

• Cannabis was made illegal in Canada in 1923 through the “Act to Prohibit the Improper Use of Opium and other Drugs”

• Cannabis put on schedule 1 in 1937 in the USA despite opposition of AMA

http://www.cbc.ca/news/health/marijuana-was-criminalized-in-1923-but-why-1.2630436
Cannabis Made Legal for Medical Use

- Patients allowed to possess medical marijuana in 2001 under the MMAR
- An application was needed, requiring a doctor’s endorsement
- Ottawa permitted personal production for authorized patients
- This could be delegated to others, or you could buy from a federal supplier
Disease Distribution of 2604 Patients with MMAR Category 1 Approvals (Up to Feb 6, 2009)

- Severe Arthritis: 36%
- Epilepsy: 3%
- Cancer: 6%
- Spinal Cord Disease: 10%
- Multiple Sclerosis: 14%
- AIDS/HIV Infection: 15%
- Spinal Cord Injury: 16%

Personal Communication – Suzanne Desjardins, Health Canada
The Changing Environment

- June 2013: the *Marihuana for Medical Purposes Regulations (MMPR)*
- Got Ottawa out of the production business
- Forbids users from growing their own
- Doctors are required to authorize applications
The Changing Environment

- 19 American states have permitted medical cannabis use
- 4 states, Alaska, Washington, Colorado, and Oregon, have voted to legalize *recreational* use
- The prime minister-designate, Justin Trudeau has vowed to legalize cannabis in Canada
The Science of Cannabis

• 1964 $\Delta^9$-THC shown to be the main psychoactive ingredient of the Cannabis sativa plant
• 1988 $\text{CB}_1$ receptor identified
• 1990 $\text{CB}_1$ is found in the brain
• 1992 Anandamide is discovered
  • $\text{CB}_2$ receptor is identified
• 1998 cannabinoids shown to relieve pain
Cannabis Receptors

• Extremely common in the brain
• 10 times more abundant than opioid receptors
• Very few in the brain stem
• The brain stem controls breathing

This image is licensed under the Creative Commons Attribution 3.0 Unported license. Anatomy & Physiology, Connexions Web site. http://cnx.org/content/col11496/1.6/
Cannabis as Medicine

- **On-label indications for Cannabinoids:**
  - Cancer pain, neuropathic pain in MS, chemotherapy-associated nausea and vomiting, anorexia in HIV/AIDS

- **Off-label use and emerging evidence**
  - Rheumatoid arthritis, epilepsy, spinal cord injury, spasticity, chronic non-cancer pain, fibromyalgia, PTSD, insomnia, anxiety...

- **Cannabis reported useful for pain, sleep, mood, spasm, seizures by patients with**
  - HIV/AIDS, MS, arthritis, epilepsy, chronic pain

Forms of Cannabis

- Pill - Nabilone or Cesamet: 1 cannabinoid
- Spray - Nabiximols or Sativex: THC and CBD
- Oils - dozens of cannabinoids
- Herb - dozens of cannabinoids
Levels of Evidence

- Randomized Controlled Trials
- Case Control Trials
- Observational Studies
- Anecdotal
Randomized Controlled Trials Cannabinoids

Nabilone
- Neuropathic pain (Frank 2008)
- Fibromyalgia pain (Skrabek 2008) and sleep (Ware 2010)
- Spinal cord injury (Pooyania 2010)
- Diabetic neuropathy (Toth 2012)

Dronabinol
- MS spasticity (Svensen 2004)
- Chronic pain + opioids (Narang 2008)
- Spinal cord injury (Rinatla 2010)

Cannador (2.5mg THC + 1.2mg CBD)
- Spasticity in MS (Zajicek 2003, 2005, 2012)

Nabiximols (2.5mg THC + 2.5mg CBD)
- Brachial plexus avulsion (Berman 2004)
- Rheumatoid arthritis (Blake 2005)
- MS neuropathic pain (Rog 2007)
- MS Spasticity (Novotna 2011)
- Cancer pain (Portnoy 2012)

Herbal cannabis (1.8-9.4% THC)
- HIV neuropathy (Abrams 2007, Ellis 2009)
- Neuropathic pain (Wilsey 2009, 2012)
- Post traumatic neuropathy (Ware 2010)
- MS spasticity (Corey-Bloom 2012)
• There is emerging evidence for cannabinoids as effective treatment options for a number of patients and conditions

• Cannabinoid drugs can be legally prescribed for several approved indications

• They are typically third or fourth line agents used in pain management
<table>
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<tr>
<th>Author (Date)</th>
<th>Population(n) Design</th>
<th>Results</th>
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<tr>
<td>Ware et al. (2010)</td>
<td>Fibromyalgia (32)</td>
<td>Nabilone is effective in improving sleep and is well tolerated.</td>
</tr>
<tr>
<td>Skrabek et al. (2008)</td>
<td>Fibromyalgia (40)</td>
<td>Nabilone improved symptoms and was well tolerated.</td>
</tr>
<tr>
<td>Frank et al. (2008)</td>
<td>Chronic neuropathic pain (96)</td>
<td>Dihydrocodeine provided better pain relief than Nabilone.</td>
</tr>
<tr>
<td>Redmond et al. (2008)</td>
<td>Experimental heat pain, healthy volunteers (17)</td>
<td>Nabilone failed to produce analgesic effect and did not interact with descending pain inhibitory systems. Significant difference was observed in effects between men and women.</td>
</tr>
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<td>Pinsger et al. (2006)</td>
<td>Chronic pain (30)</td>
<td>Nabilone caused a significant reduction in pain and improvement in quality of life.</td>
</tr>
<tr>
<td>Beaulieu et al. (2006)</td>
<td>Post operative pain (41)</td>
<td>Nabilone did not reduce 24hr morphine consumption or improve effects of morphine. Nabilone did increase pain scores.</td>
</tr>
<tr>
<td>Wissel et al. (2006)</td>
<td>MS, spasticity related pain (11)</td>
<td>Significant reduction of pain, but not spasticity, motor function, or activities of daily living.</td>
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</table>
Clinical Evidence: Nabilone

References:
# Clinical Evidence: THC/CBD

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<td>Centonze (2009)</td>
<td>CNP and spasticity in patients with MS (20)</td>
<td>THC/CBD failed to reduce pain and spasticity</td>
</tr>
<tr>
<td>Nurmikko (2007)</td>
<td>Neuropathic pain with allodynia (63)</td>
<td>THC/CBD significantly better than placebo in reducing pain</td>
</tr>
<tr>
<td>Blake (2006)</td>
<td>Rheumatoid arthritis (58)</td>
<td>Significant reduction in pain and sleep disturbance</td>
</tr>
<tr>
<td>Rog (2005)*</td>
<td>Central pain in MS (64) parallel group</td>
<td>Significant reductions in pain (NRS, NPS) and sleep disturbance (NRS)</td>
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<td>Berman (2004)</td>
<td>Neuropathic pain brachial plexus avulsion (48) crossover</td>
<td>Significant reductions in pain and sleep disturbance (NRS) but not to the full 2 point reduction (NNT $\geq 1=3$, NNT $\geq 2=7.5$)</td>
</tr>
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*Rog 2005 - open extension 2 years; continued effect, no tolerance and only mild-moderate side effects
Clinical Evidence: THC/CBD

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# Clinical Evidence: THC/CBD

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<td>Wade (2004)</td>
<td>MS (160) parallel group</td>
<td>No significant difference in pain scores (VAS) between active and placebo all decreased. There was a significant reduction in spasticity scores.</td>
</tr>
<tr>
<td>Notcutt (2004)</td>
<td>Chronic pain (34) “N of 1” 2 week open/RCT 1 week Rx periods x 2 for each CBME</td>
<td>Significant reduction in pain (VAS) for THC and THC/CBD</td>
</tr>
</tbody>
</table>

Why so little research?

- Lack of funding
- Lack of supply
- Stigma
Off-Label Use of Cannabinoids

• Chronic pain guidelines support the off-label use of cannabinoids

• Fourth-line analgesic in the treatment of chronic neuropathic pain
  – Moulin DE et al. CPS consensus statement 2007

• 2\textsuperscript{nd}/3\textsuperscript{rd} line use in Central Neuropathic Pain of MS
  – Attal et al. EFNS 2007.

• Consider when other therapies fail or cause unacceptable side effects


THC/CBD Indication

- Adjunctive treatment for the management of neuropathic pain in adults with MS
- Adjunctive analgesic treatment in adult patients with advanced cancer pain
- NOC/c status: marketing authorization with conditions reflecting promising nature of clinical evidence and the need for confirmatory studies to verify clinical benefit
- Patients should be advised of conditional nature of the indication

Emerging Evidence

- There is some good quality evidence that cannabinoids boost the effect of opioids

- This may allow a reduction in opioid dose for chronic opioid users

- Why is this important?

www.hc-sc.gc.ca/dhp-mps/marihuana/index-eng.php
Opioid Overdose

• Kills 16,000 people annually in the US
• States with medical cannabis laws had a 24.8% lower mean annual opioid overdose mortality rate
• In 2010, this translated to an estimated 1729 (95% CI, 549 to 3151) fewer deaths than expected.

Cannabis Toxicity

- Generally very low toxicity/lethality
- Legalization is associated with an increase in child intoxication
Herbal Cannabis

• Many patients are already using it and want a legal supply
• Some have heard about it and want to try it
• Some patients desire to avoid pharmaceuticals and use a “natural” product
• Some may be recreational users who want a safe, legal supply
• Those who want to divert it
Herbal Cannabis

• General population considerations:
  – Other illnesses (medical and psychiatric)
  – Use of other medications
  – Abuse issues

• General drug considerations:
  – Most effects short-term
  – Experienced users report fewer side effects
  – Most common: dizziness, dry mouth, drowsiness

Connecticut’s Law

- Restricts marijuana to residents who are over 18 and have received a physician’s certification that they have one of the 11 conditions that marijuana might soothe:
  - Cancer, glaucoma, H.I.V. or AIDS, Parkinson’s, multiple sclerosis, spinal cord nerve damage, epilepsy, Crohn’s disease, cachexia, wasting syndrome and post-traumatic stress disorder.

Colorado’s Law

- Restricted to those age 21 or older
- Maximum one ounce for recreation
- Maximum 2 ounces for medical purposes
- Permitted to cultivate 6 plants
- No driving under the influence
- Not allowed for export
Dangers

• What about abuse?
• What about driving?
• What about smoking?
• What about seniors?
Cannabis Dependence (Recreational Users)

Percentage of people who have ever used drug

- Tobacco: 76%
- Alcohol: 92%
- Marijuana (Cannabinoids): 46%
- Tranquilizers (and other prescription drugs): 13%
- Cocaine: 16%
- Heroin: 2%

Percentage of users who became dependent

- Tobacco: 32%
- Alcohol: 15%
- Marijuana (Cannabinoids): 9%
- Tranquilizers (and other prescription drugs): 9%
- Cocaine: 17%
- Heroin: 23%

Rx Cannabinoids and Abuse Potential

- Evidence shows prescription cannabinoids generally have low potential for abuse
  - Dronabinol
  - Nabilone
- THC/CBD has not yet been evaluated for abuse potential, but there is no evidence of tolerance
- Thorough evaluation and screening for risk factors should help identify high-risk patients

What about Driving?

• Cannabis use impairs driving ability
• The number of accident victims with cannabis in their blood increases after legalization
• What do you think will happen to traffic deaths after legalization?
Anderson DM, Hansen B, Rees DI. Medical marijuana laws, traffic fatalities, and alcohol consumption.

_The Journal of Law & Economics_
Vol. 56, No. 2 (May 2013), pp. 333-369
Smoking your Medicine?

- Smoking is a poor way to deliver a drug
- The oils in herbal cannabis vaporize before they burn
- The vapors can be inhaled without the products of combustion
- There are numerous vaporizers available
- Volcano Medic has been approved as a medical device

Geriatric Use

- Limited data in geriatric populations
- Should be used with caution in the elderly
- Greater risk of falling (particularly in patients with dementia)
- Elderly may be more susceptible to side effects:
  - neurological
  - psychoactive
  - blood pressure effects

Medical Cannabis Contraindications

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

• Warnings
  – Pregnant or nursing women
  – Potential for dependence and abuse
  – Do not drive or operate machinery

www.hc-sc.gc.ca/dhp-mps/marihuana/index-eng.php
Medical Cannabis Contraindications

Use with caution in patients with:
- Cardiac disorder
- History of substance abuse or dependency
- Mania or depression
- Concomitant therapy affecting CNS therapy
- Multiple drug therapy
- Respiratory
- Pediatric and elderly populations

www.hc-sc.gc.ca/dhp-mps/marihuana/index-eng.php
Take Home Messages

• Cannabis compounds have been shown to relieve several types of pain, nausea from chemotherapy and spasticity
• Evidence is lacking for other uses
• Legalization of cannabis is associated with
  – Lower death rates for opioid overdose and
  – Lower death rates for traffic fatalities
More Recent Publications


More Recent Publications

The Canadian Medical Protective Association

- Physicians should only sign medical documents when they have the necessary clinical knowledge to engage in a meaningful consent discussions with patients.
- Physicians requested to provide a medical document should discuss with the patient the lack of information available to date.
- All consent-related discussions should be documented in the patient’s medical record. The discussion should include:
  - information provided about what is known, and not known, regarding the risks and benefits of using marijuana for medical purposes.
- …the CMPA no longer advises physicians to ask patients to sign a release when assisting with a request under the new regulations.

The Canadian Medical Protective Association

Minimising risk

• Have conventional treatments failed or been considered inappropriate for the patient?
• Does the physician’s College have a policy, statement, or guidelines on the use of marijuana?
• Has the patient been made aware of the extent of scientific knowledge about marijuana, such as that found on the Health Canada website?
• Does the physician have sufficient knowledge about the use of marijuana for treatment of the patient’s condition to complete the medical document and provide the information the patient needs in order to give an informed consent?
CFPC Recommendation 1

- There is no research evidence to support the authorization of dried cannabis as a treatment for pain conditions commonly seen in primary care, such as fibromyalgia or low back pain.
- Authorizations for dried cannabis should only be considered for patients with neuropathic pain that has failed to respond to standard treatments.

Recommendation 2

• If considering authorizing dried cannabis for treatment of neuropathic pain, the physician should first consider
  – adequate trials of other pharmacologic and nonpharmacologic therapies and
  – an adequate trial of pharmaceutical cannabinoids
Recommendation 3

• Dried cannabis is not an appropriate therapy for anxiety or insomnia
Recommendation 4

Dried cannabis is not appropriate for patients who:

• a) Are under the age of 25
• b) Have a personal history or strong family history of psychosis
• c) Have a current or past cannabis use disorder
• d) Have an active substance use disorder
• e) Have cardiovascular disease (angina, peripheral vascular disease, cerebrovascular disease, arrhythmias)
• f) Have respiratory disease or
• g) Are pregnant, planning to become pregnant, or breastfeeding
Recommendation 5

Dried cannabis should be authorized *with caution* in those patients who:

- a) Have a concurrent active mood or anxiety disorder
- b) Smoke tobacco
- c) Have risk factors for cardiovascular disease or
- d) Are heavy users of alcohol or taking high doses of opioids or benzodiazepines or other sedating medications prescribed or available over the counter
Recommendation 7

- Physicians should assess and monitor all patients on cannabis therapy for potential misuse or abuse.
Recommendation 8

Before signing a medical document authorizing dried cannabis for pain, the physician should do all of the following:

• a) Conduct a pain assessment
• b) Assess the patient for anxiety and mood disorders
• c) Screen and assess the patient for substance use disorders
Recommendation 9

The physician should regularly monitor the patient’s response to treatment with dried cannabis, considering the patient’s function and quality of life in addition to pain relief.

• The physician should discontinue authorization if the therapy is not clearly effective or is causing the patient harm.
Recommendation 10

Patients taking dried cannabis should be advised not to drive for at least:

- a) Four hours after inhalation
- b) Six hours after oral ingestion
- c) Eight hours after inhalation or oral ingestion if the patient experiences euphoria
Recommendation 11

When authorizing dried cannabis therapy for a patient, the physician should advise the patient of harm reduction strategies.
Recommendation 12

The physician should manage disagreements with patients about decisions around authorization, dosing, or other issues with unambiguous, evidence-based statements.
Recommendation 13

The physician who is authorizing cannabis for a particular clinical indication must be primarily responsible for managing the care for that condition and following up with the patient regularly.
Recommendation 13 continued

- Physicians seeking a second opinion on the potential clinical use of cannabis for their patient should only refer to facilities that meet standards for quality of care typically applied to specialized pain clinics. In both instances, it is essential that the authorizing physician, if not the patient’s most responsible health care provider, communicate regularly with the family physician providing ongoing comprehensive care for the patient.
Recommendation 14

Given the weak evidence for benefit and the known risks of using cannabis, the only sensible advice for physicians involved with authorizing dried cannabis is the maxim “Start low, and go slow”.

Recommendation 15

Although it is not required by the MMPR, physicians should specify the percentage of THC on the medical document for all authorizations for dried cannabis, just as they would specify dosing when prescribing any other analgesic.