Cannabis and Pain: Past, Present and Future

Mark A. Ware
McGill University
Montreal, Quebec, Canada
Disclosures

• Dr. Ware is Executive Director of the Canadian Consortium for the Investigation of Cannabinoids (CCIC) and receives a monthly stipend
  – CCIC has contracts and grants with governments, agencies, industry
  – CCIC is member of UN Vienna NGO Committee with interests in international scheduling of cannabinoids

• Grant funding from CanniMed for clinical trial
Objectives

• Appreciate the trajectory of the development of cannabis in therapeutics
• Understand the current evidence for cannabis and cannabinoids in pain management
• Consider limitations of current research on its efficacy, effectiveness, and safety considerations (at work or home)
• Reflect on future research opportunities and challenges in the use of cannabinoids and pain
2 case studies

• 62y female with radiation-induced neuropathic pain of the anterior chest for 5 years

• 42y female with diffuse body pain for 20 years, recently diagnosed with rheumatoid arthritis
# The “cannabis curriculum”

<table>
<thead>
<tr>
<th>Topic</th>
<th>Learning objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of medical cannabis</td>
<td>Describe the historical perspective of medical cannabis use and the effects of cannabis policy on research and drug development. Comparison with opioid drug development may be useful.</td>
</tr>
<tr>
<td>Botany of Cannabis sativa</td>
<td>Describe the plant based production of cannabinoids and other aromatic ingredients; describe genetic and phenotypic interspecies differences.</td>
</tr>
<tr>
<td>Biology of the endocannabinoid system</td>
<td>Describe the identity, location and functional characteristics of cannabinoid receptors and endogenous ligands; endocannabinoid synthesis and metabolism; mechanism of action and role of endocannabinoids in normal physiology.</td>
</tr>
<tr>
<td>Pharmacology of cannabinoids</td>
<td>Describe the clinical pharmacology (absorption, distribution, metabolism and elimination) of cannabinoid molecules; potential drug-drug interactions.</td>
</tr>
<tr>
<td>Cannabinoid administration</td>
<td>Compare the pharmacokinetics of cannabinoid administration methods (oral, inhaled, topical, sublingual, rectal).</td>
</tr>
<tr>
<td>Efficacy of cannabinoids in clinical conditions</td>
<td>Critically appraise clinical trial data: strengths, weaknesses, need for further study; clinical conditions studied to date; identify gaps in research knowledge.</td>
</tr>
<tr>
<td>Safety of medical cannabis use</td>
<td>Discuss known adverse effects of acute and chronic cannabis use; consideration of differences between safety of medical and recreational cannabis use; methods of studying cannabis safety; absolute and relative contraindications.</td>
</tr>
<tr>
<td>Cannabis misuse and abuse</td>
<td>Recognize and discuss cannabis use disorder characteristics and treatment.</td>
</tr>
<tr>
<td>Legal considerations in medical cannabis</td>
<td>Discuss medical cannabis policy: international, national and local concerns; identify pragmatic factors in medical cannabis authorization (where legally possible).</td>
</tr>
<tr>
<td>Communicating with patients about medical marijuana</td>
<td>Discuss the stigma of medical cannabis; establishing therapeutic relationship and goals of treatment; use of treatment agreements and compliance.</td>
</tr>
</tbody>
</table>
Cannabinoids and Opioids: An Historical Perspective

Cannabinoids

- First evidence of medicinal use in China 3000 BC
- Earliest known reference for opium-based elixir 500 BC
- W.B. O’Shaughnesssey’s work popularizes cannabis use 1800’s
- Medicinal cannabis use declines 1804
- 9-THC identified as main psychoactive agent in Cannabis sativa plant 1817
- Morphine extracted from opium poppy plant 1804
- Paracelsus reference to “laudanum”, opium-based elixir, as a potent painkiller 1522
- 1874: Morphine first marketed in Germany as analgesic
- 1874: Diacetylmorphine (heroin)
- 1817: Morphine first marketed in Germany as analgesic
- 1900’s: Codeine, dihydromorphine, oxycodone, pethidine, oxymorphone
- 1988: CB₁ receptor identified. 1990: CB₁ receptor cloned
- 1992: Anandamide discovered, CB2 receptor identified
- 1993: CB2 receptor cloned
- 1998: Endogenous cannabinoid ligands shown to be analgesic

Opioids

- 1804: Morphine extracted from opium poppy plant
- 1874: Diacetylmorphine (heroin)
- 1900’s: Codeine, dihydromorphine, oxycodone, pethidine, oxymorphone
- 1970s: Discovery of opioid receptors – µ (mu), κ (kappa), δ (delta)
- 1975: Discovery of endogenous opioid peptides - endorphins

References:
The draft genome and transcriptome of *Cannabis sativa*
Cannabis botany

- Cuticle
- Cavity accumulating resin (terpenes & cannabinoids)
- Cells synthesizing terpenes and cannabinoids

Genet Resour Crop Evol
DOI 10.1007/s10722-015-0254-2
Major constituents

- >100 cannabinoids
  
  THC, CBD, CBN, CBC, CBG (resins)
- 120 terpenoids: aromatic compounds
- 21 flavonoids: antioxidants
- 11 plant sterols (seed)
- 22 fatty acids (ω3,6,9)

C21 group of compounds

Side-chain (n-pentyl or n-propyl)

Cyclization
THC and CBD in Canadian regulated cannabis
Distribution of CB1 receptors

- **Cerebral cortex**
  - Decision making, cognition, and emotional behavior
- **Caudate nucleus**
  - Learning & memory system
- **Putamen**
  - Regulate movements & influence various types of learning
- **Globus pallidus**
  - Regulate voluntary movements
- **Amygdala**
  - Responsible for anxiety & stress, emotion & fear, pain
- **Hypothalamus**
  - Body temperature, feeding, neuroendocrine function
- **Hippocampus**
  - Memory & learning
- **Substantia nigra**
  - Important role in reward, addiction, & movement
- **Cerebellum**
  - Motor control & coordination
Cannabinoids as ‘synaptic circuit-breakers’

*Nat Med* 2008;14(9):923-30
Peripheral neuropathic pain models

• Nerve injury
  – Chronic constriction injury
  – Sciatic nerve ligation
  – Brachial plexus avulsion
  – Trigeminal neuralgia

• Diabetes
  – Streptozotocin

• Chemotherapy
  – Paclitaxel
  – Cisplatin
  – Vincristine

• HIV neuropathy
...and other pain models

- Spinal cord injury
- Multiple sclerosis
- Cancer pain
- Osteoarthritis
- Visceral pain
- Inflammatory, nociceptive pain
- Muscle pain
Prescription cannabinoids

Dronabinol (Δ-9 tetrahydrocannabinol – THC) (2.5 - 10mg)
- Oral capsule
- Approved for **chemotherapy-induced nausea and vomiting** and **anorexia associated with HIV/AIDS**

Nabilone (0.25 - 1.0mg)
- Oral capsule
- Approved for **chemotherapy-induced nausea and vomiting**

Nabiximols (2.7mg THC + 2.5mg CBD)
- Oromucosal spray
- Approved in Canada for **multiple sclerosis-associated neuropathic pain, spasticity and advanced cancer pain**

Herbal cannabis (varying THC levels)
- State programs (USA)
- Federal programs (Canada, Holland, Israel)
- **No formal ‘approval’**
Pharmacokinetics: THC:CBD 1:1

Mean plasma THC after administration of THC:CBD 1:1 (n=12)

Vaporization as a Smokeless Cannabis Delivery System: A Pilot Study

DI Abrams¹,²,³, HP Vizoso¹,³, SB Shade¹,³, C Jay⁴,⁵, ME Kelly¹,²,³ and NL Benowitz³,⁶

[Diagram of a vaporization device]

Plots showing plasma THC levels over time for 1.7%, 3.4%, and 6.8% THC.

- 1.7% THC
  - Smoked
  - Vaporized

- 3.4% THC
  - Smoked
  - Vaporized

- 6.8% THC
  - Smoked
  - Vaporized
The Pharmacokinetics, Efficacy, Safety, and Ease of Use of a Novel Portable Metered-Dose Cannabis Inhaler in Patients With Chronic Neuropathic Pain: A Phase 1a Study

15 mg herbal cannabis; 19% THC
Single inhalation using inhaler
N=10 neuropathic pain patients
Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials

Mary E. Lynch & Fiona Campbell

1Department Anesthesia, Psychiatry, Dalhousie University, Halifax, Canada, and 2Department of Anaesthesia and Pain Medicine, Hospital for Sick Children, University of Toronto, Toronto, Canada

Correspondence
Dr Mary E. Lynch, MD, FRCPC, Pain Management Unit, Queen Elizabeth II Health Sciences Centre, 4th Floor Dickson Centre, Room 4086, Halifax, Nova Scotia, B3H 1V7, Canada.
Tel.: +1 902 473 6428
Fax: +1 902 473 4126
E-mail: mary.lynch@dal.ca

Keywords
cannabinoids, chronic non-cancer pain, neuropathic pain, systematic review

Received
22 December 2010

Accepted
7 March 2011

Accepted Article
23 March 2011
Summary of 2011 review

• 18 trials
  – 15 in neuropathic pain
  – 2 in mixed chronic pain
  – 1 each in fibromyalgia, rheumatoid arthritis, mixed chronic pain on opioids

• Drugs evaluated
  – Nabiximols (7)
  – Cannabis (4)
  – Nabilone (4)
  – Dronabinol (2)
  – Ajulemic acid (CT-3) (1)

• No serious adverse events

Lynch & Campbell BJCP 2011
Cannabinoids for the Treatment of Chronic Non-Cancer Pain: An Updated Systematic Review of Randomized Controlled Trials

M. E. Lynch¹,³ • Mark A. Ware²

• 11 trials involving 1185 subjects
  – Nabilone (4)
  – Nabiximols (3)
  – Smoked/vapourized cannabis (2)
  – FAAH inhibitor (1)

• 7 trials showed positive outcomes

• Serious adverse events
  – 3 on cannabis extract (UTI, TBI, interstitial lung disease)
  – 2 on nabiximols (disorientation and suicidal ideation)
  – 1 on nabilone (delirium)
Conclusions of 2015 review

- Studies generally short, small, with modest effect sizes
- “cannabinoids are safe, demonstrate a modest analgesic effect and provide a reasonable treatment option for the treatment of chronic non-cancer pain.”
CONSENSUS STATEMENT

Pharmacological management of chronic neuropathic pain: Revised consensus statement from the Canadian Pain Society

DE Moulin MD, A Boulanger MD, AJ Clark MD, H Clarke MD PhD, T Dao DMD PhD, GA Finley MD, A Furlan MD PhD, I Gilron MD MSc, A Gordon MD, PK Morley-Forster MD, BJ Sessle MDS PhD, P Squire MD, J Stinson RN PhD, P Taenzer PhD, A Velly DDS PhD, MA Ware MD, EL Weinberg MD, OD Williamson MBBS

Moulin DE et al PR&M 2014
Synthetic pharmaceutical approaches

• FAAH inhibition
  – Pfizer compound failed in OA knee trial (Huggins 2012)
• Peripherally restricted CB1 agonist
  – AstraZeneca compound status unknown (Yu 2010)
• CB2 agonists
  – GSK compound failed in 3rd molar extraction trial (Ostenfeld 2011)
• CB1 antagonists
  – Rimonabant approved in Europe for obesity and smoking cessation
  – Withdrawn for safety concerns (depression and suicidality)
Amygdala activity contributes to the dissociative effect of cannabis on pain perception

Michael C. Lee a,d,*, Markus Ploner a,b, Katja Wiech a, Ulrike Bingel a,c, Vishvarani Wanigasekera a, Jonathan Brooks a, David K. Menon d, Irene Tracey a
Table 1. Adverse Effects of Short-Term Use and Long-Term or Heavy Use of Marijuana.

**Effects of short-term use**
- Impaired short-term memory, making it difficult to learn and to retain information
- Impaired motor coordination, interfering with driving skills and increasing the risk of injuries
- Altered judgment, increasing the risk of sexual behaviors that facilitate the transmission of sexually transmitted diseases
- In high doses, paranoia and psychosis

**Effects of long-term or heavy use**
- Addiction (in about 9% of users overall, 17% of those who begin use in adolescence, and 25 to 50% of those who are daily users)*
- Altered brain development*
- Poor educational outcome, with increased likelihood of dropping out of school*
- Cognitive impairment, with lower IQ among those who were frequent users during adolescence*
- Diminished life satisfaction and achievement (determined on the basis of subjective and objective measures as compared with such ratings in the general population)*
- Symptoms of chronic bronchitis
- Increased risk of chronic psychosis disorders (including schizophrenia) in persons with a predisposition to such disorders

* The effect is strongly associated with initial marijuana use early in adolescence.
Adverse effects of medical cannabinoids: a systematic review

Tongtong Wang MSc, Jean-Paul Collet PhD MD, Stan Shapiro PhD, Mark A. Ware MBBS MSc

CMAJ 2008;178:1629
<table>
<thead>
<tr>
<th>Study</th>
<th>Rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oromucosal spray cannabis extract v. control</strong></td>
<td></td>
</tr>
<tr>
<td>Berman et al.</td>
<td>2.42 (1.33-4.41)</td>
</tr>
<tr>
<td>Blake et al.</td>
<td>1.75 (0.85-3.59)</td>
</tr>
<tr>
<td>Collin et al.</td>
<td>1.86 (1.35-2.55)</td>
</tr>
<tr>
<td>Nurmikko et al.</td>
<td>2.55 (1.77-3.67)</td>
</tr>
<tr>
<td>Rog et al.</td>
<td>2.09 (1.31-3.33)</td>
</tr>
<tr>
<td>Tomida et al.</td>
<td>1.50 (0.51-4.43)</td>
</tr>
<tr>
<td>Wade et al.</td>
<td>0.74 (0.41-1.34)</td>
</tr>
<tr>
<td>Wade et al.</td>
<td>2.11 (1.52-2.93)</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>1.88 (1.48-2.39)</td>
</tr>
<tr>
<td><strong>Oral Δ9-tetrahydrocannabinol-cannabinol v. control</strong></td>
<td></td>
</tr>
<tr>
<td>Carroll et al.</td>
<td>2.53 (1.39-4.60)</td>
</tr>
<tr>
<td>Killestein et al.</td>
<td>2.31 (1.20-4.42)</td>
</tr>
<tr>
<td>Strasser et al.</td>
<td>1.12 (0.77-1.63)</td>
</tr>
<tr>
<td>Vaney et al.</td>
<td>0.56 (0.37-0.86)</td>
</tr>
<tr>
<td>Zajicek et al.</td>
<td>1.36 (1.25-1.48)</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>1.31 (0.88-1.96)</td>
</tr>
<tr>
<td><strong>Oral Δ9-tetrahydrocannabinol v. control</strong></td>
<td></td>
</tr>
<tr>
<td>Buggy et al.</td>
<td>1.08 (0.79-1.47)</td>
</tr>
<tr>
<td>Frytak et al.</td>
<td>3.70 (2.34-5.85)</td>
</tr>
<tr>
<td>Killestein et al.</td>
<td>0.69 (0.30-1.62)</td>
</tr>
<tr>
<td>Naef et al.</td>
<td>4.39 (2.91-6.62)</td>
</tr>
<tr>
<td>Nethart et al.</td>
<td>1.90 (1.38-2.61)</td>
</tr>
<tr>
<td>Noyes et al.</td>
<td>4.54 (2.73-7.55)</td>
</tr>
<tr>
<td>Noyes et al.</td>
<td>2.50 (1.98-3.15)</td>
</tr>
<tr>
<td>Orr et al.</td>
<td>8.44 (4.23-16.85)</td>
</tr>
<tr>
<td>Strasser et al.</td>
<td>1.40 (0.97-2.03)</td>
</tr>
<tr>
<td>Svendsen et al.</td>
<td>2.63 (1.81-3.82)</td>
</tr>
<tr>
<td>Timpone et al.</td>
<td>1.24 (0.54-2.85)</td>
</tr>
<tr>
<td>Zajicek et al.</td>
<td>1.32 (1.21-1.43)</td>
</tr>
<tr>
<td>Petro et al.</td>
<td>0.50 (0.03-7.98)</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>2.18 (1.59-2.99)</td>
</tr>
</tbody>
</table>

**Figure 2:** Incidence rates and rate ratios (random-effects model) for nonserious adverse events among participants assigned to medical cannabinoid therapy or control in 23 randomized controlled trials. Dotted vertical line represents no difference between the intervention and the control. CI = confidence interval.
Precautions and contraindications

• Contraindications:
  – psychosis
  – unstable heart disease
  – pregnancy

• Precautions
  – History of legal issues/criminal charges
  – Screen for cannabis use disorder
  – Validate that desire for cannabis is ‘medical’
Cannabis use disorder (DSM-V)

<table>
<thead>
<tr>
<th>Table 3. Clinical features of cannabis use disorder in patients with chronic pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Insists on a medical document for dried cannabis rather than trying other treatments known to be effective for his or her condition</td>
</tr>
<tr>
<td>• Uses cannabis daily or almost daily, spending considerable non-productive time on this activity</td>
</tr>
<tr>
<td>• Has poor school, work, and social functioning</td>
</tr>
<tr>
<td>• Is currently addicted to or misusing other substances (other than tobacco)</td>
</tr>
<tr>
<td>• Has risk factors for cannabis use disorder: is young, has current mood or anxiety disorder or a history of addiction or misuse</td>
</tr>
<tr>
<td>• Reports having difficulty stopping or reducing use</td>
</tr>
<tr>
<td>• Reports cannabis withdrawal symptoms after a day or more of abstinence: intense anxiety, fatigue</td>
</tr>
<tr>
<td>• Has friends or family members concerned about his or her cannabis use</td>
</tr>
</tbody>
</table>

CFPC Preliminary Guidance document 2014
Abuse potential of nabiximols
Non-Smoker Exposure to Secondhand Cannabis Smoke. I. Urine Screening and Confirmation Results

Edward J. Cone¹, George E. Bigelow¹, Evan S. Herrmann¹, John M. Mitchell², Charles LoDico³, Ronald Flegel³ and Ryan Vandrey¹

¹Behavioral Pharmacology Research Unit, Johns Hopkins University School of Medicine, Baltimore, MD, USA, ²RTI International, Research Triangle Park, NC, USA, and ³Division of Workplace Programs (DWP), Substance Abuse and Mental Health Services Administration (SAMHSA), Rockville, MD, USA
Sample Medical Document for the *Marihuana for Medical Purposes Regulations*

This document may be completed by the applicant’s authorized health care practitioner as defined in the *Marihuana for Medical Purposes Regulations*. An authorized health care practitioner includes physicians in all provinces and territories, and nurse practitioners in provinces and territories where prescribing dried marihuana for medical purposes is permitted under their scope of practice. If another document is used, it must contain all of the information below.

**Patient’s Given Name and Surname**

Daily quantity of dried marihuana to be used by the patient: _______ g/day

The period of use is _____ day(s) _____ week(s) _____ month(s).

**Health Care Practitioner’s Business Address**

Full business address of the location at which the patient consulted the health care practitioner
(if different than above):

**Phone Number:**
**Fax Number (if applicable):**
**Email Address (if applicable):**
**Province(s) Authorized to Practice in:**
**Health Care Practitioner’s Licence number:**

**By signing this document, the health care practitioner is attesting that the information contained in this document is correct and complete.**

Health Care Practitioner’s Signature: ____________________________________________

Date Signed (DD/MM/YYYY): ____________________________________________
• “Physicians must be familiar with the existing program for patients currently accessing medical marijuana and must also familiarize themselves with the new regulations.

• Physicians are expected to know and comply with the regulations and policies of their College.”
• 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.

http://www.cmpa-acpm.ca/cmpapd04/docs/resource_files/web_sheets/2013/com_w13_005-e.cfm
Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999-2010

Marcus A. Bachhuber, MD; Brendan Saloner, PhD; Chinazo O. Cunningham, MD, MS; Colleen L. Barry, PhD, MPP

Figure 1. Mean Age-Adjusted Opioid Analgesic Overdose Death Rate

Figure 2. Association Between Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in Each Year After Implementation of Laws in the United States, 1999-2010

Published online August 25, 2014.
Communication

• The language of cannabis (weed, pot, joints, blunts, dabs, doobs, herb, grass, bud, hash, wax, shatter...)

• Cannabis has a stigma... and an odor

• Cannabis patients feel stigmatized

• Treatment agreement (Grant et al 2014)

• Setting goals

• Alternative delivery systems

• “Bona fide relationship”
Education of health care professionals

Canadian Consortium for the Investigation of Cannabinoids (CCIC)
- Accredited cannabinoid education (ACE) programs
- Interactive
- Informed by needs assessments, expert faculty
- www.ccic.net

International Cannabinoid Research Society (ICRS)
- 25th Annual Symposium
- July 2015, Halifax, Nova Scotia
- www.icrs2014.org

International Association for Cannabinoid Medicine (IACM)
- www.cannabis-med.org

Patients out of Time
- Conferences and resources
- www.medicalcannabis.com

The Answer Page
- www.theanswerpage.com
- online CME, accredited by Massachusetts Medical Society
Financial support