Marijuana in GI diseases: problem or panacea?

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Objectives

At the end of this presentation, learners will be able to:

a) Recognize the prevalence and patterns of use of cannabis by patients with GI diseases
b) Assess the evidence base for cannabinoid use in GI disorders
c) Discuss the barriers and facilitators for authorizing the clinical use of cannabinoids in GI disease
Two clinical cases

- 29 y male with known Crohn’s disease referred by gastroenterologist because patient reports using cannabis to relieve nausea and abdominal pain
- 23y female with cyclical vomiting syndrome referred by GP because “cannabis is reportedly the only thing that helps”
Cannabis in Gastroenterology

Constantine Soulellis
Disclosure Statement

• No relevant financial relationship(s) exist
History and Origins

• Cannabis use for medicinal purpose dates back at least 3500 years

• Various papyri from ancient Egypt describe medical cannabis
  – Ramesseum III Papyrus 1700 BC
  – Ebers Papyrus 1550 BC
  – Berlin Papyrus 1300 BC

Source: Wikipedia.com
History and Origins

- Ancient Greeks and ancient Indians used cannabis to treat wounds and sores on horses, ease childbirth, expel tapeworms, treat otitis, cure dysentery, sharpen appetite, etc.

Source: Wikipedia.com
History and Origins

• Well-documented use for anesthesia by famed Chinese Surgeon Hua Tuo in 140 AD (credited as the first anesthesiologist)

• Today, the Chinese term for anesthesia “mazui” literally means cannabis intoxication
History and Origins

• By the mid-19th century, medicinal cannabis was commonplace, thanks to William Brooke O’Shaughnessy, assistant surgeon at the Medical College of Calcutta

• Began treating muscle spasms, abdominal cramps, and generalized pain

Source: Wikipedia.com
History and Origins

• By the 1960’s, benefits in intraocular pressure (glaucoma) were established

• By the 1970’s, the first wave of modern synthetic cannabis extracts became available – ie. Canasol (glaucoma) and Marinol (appetite in AIDS cachexia)

Source: Wikipedia.com
Legal Status in Canada

• At the moment, no consensus on legal status of cannabis – technically a controlled drug/substance with criminal implications despite multiple (failed) decriminalization bills in the 2000’s

• However, superior and appellate courts have declared the cannabis laws of no effect with prescription as per the Marihuana for Medical Purposes Regulations issued by Health Canada (2014)
Legal Status in Canada

• Patient interest and consideration for cannabis steadily increasing due to
  – Proliferation of medical marijuana programs in the US
  – Decriminalization in more than 15 states
  – Campaign promises by the current Canadian administration to decriminalize cannabis

• More in Dr. Ware’s presentation to follow
Data on Digestive Disorders

• Most of the accrued data from the last 15 years

• Given the illegalities surrounding cannabis, difficult to develop controlled studies with proper dose titration, etc

Source: Vice.com
Data on Digestive Disorders

• Observational data exists demonstrating that IBD patients use more cannabis and start at younger ages compared with age-matched healthy controls (Weiss and Friedenberg, 2015)

• Small pilot study from 2011 also suggests that quality of life is improved with inhaled cannabis use in IBD patients (Lahat et al, 2012)
  – Less physical pain, less depression
  – Increased willingness to work
Data on Digestive Disorders

• Naftali et al in 2011 demonstrated in a small retrospective observational study that the majority of IBD patients that began using cannabis for their disease improved
  – Reduction of other IBD medications
  – Decreased need for surgery
  – Improvement in disease indices (Harvey Bradshaw index)
Data on Digestive Disorders

- Currently there are 5 proper randomized controlled trials pertaining to marijuana on the gastrointestinal tract
Appetite and Intake


- Six male volunteers were placed in a residential laboratory for 13 days – two groups of 3 randomized to 2.3% THC containing cigarettes versus placebo
Appetite and Intake

• Group that smoked marijuana had a 40% increase in caloric intake through increased consumption of sweet solid snack foods
• Statistically significant increase in body weight, greater than predicted by caloric intake alone
Appetite and Intake


• Dronabinol (0,10,20,30 mg po) and smoked marijuana (0%, 1.8%, 2.8%, 3.9% THC) compared to placebo in 30 HIV+ subjects, 15 with and 15 without AIDS wasting
Appetite and Intake

• Compared with placebo, both Dronabinol and smoked marijuana resulted in significantly increased caloric intake in the AIDS-wasting HIV+ group

• Side effects were minimal with the exception of the highest dose of Dronabinol, which resulted in excess nausea and vomiting, along with reportedly uncomfortable level of intoxication
Appetite and Intake

Appetite and Intake

- 243 adults with cancer, cachexia, significant weight loss, and low ECOG status were randomized to one of three groups:
  - 1. Cannabis extract (2.5 mg THC and 1 mg CBD)
  - 2. 2.5 mg THC alone
  - 3. Placebo

- Twice daily orally, for 6 weeks
Strasser F, Luftner D, Possinger K et al. *J Clin Oncol* 2006; 24: 3394 – 400
Strasser F, Luftner D, Possinger K et al. J Clin Oncol 2006; 24: 3394 – 400
Appetite and Intake

• No significant differences reported for adverse effects between the three arms as well

• Authors report an independent data review board recommended termination of study recruitment due to insufficient differences between the study arms
Appetite and Intake


- 10 HIV+ marijuana smokers were each exposed to two 16 day inpatient phases where they were given 4 days of either oral Dronabinol 5 mg, Dronabinol 10 mg, or smoked marijuana 2% THC or marijuana 3.9% THC, with placebo washout between each drug and dosage change
Appetite and Intake

• Only 1 drug was active per day, preserving double-blind dosing
• Compared with placebo, body weight and caloric intake improved significantly for all marijuana and Dronabinol groups
• Intoxication was rated positively and there were no adverse effects reported
Appetite and Intake


• 21 patients were recruited, all with a CDAI score between 250-400, having failed at least one form of medical treatment of the disease (mesalamine, steroids, thiopurines, MTX, or anti-TNF)
Appetite and Intake

• Patients were randomized to cigarettes with 115 mg THC versus placebo cigarettes

• Followed for 8 weeks and 2 additional washout weeks
  – Medical interview and physical exam
  – CDAI, blood tests (including CRP)
Appetite and Intake

• 5 patients from the cannabis group achieved clinical remission (symptomatically only) versus 1 from placebo group – not SS
• No difference in blood parameters or CRP between the groups
• Significant increase in quality of life reported for the cannabis group, compared with none for the placebo group
  – Less pain
  – Improved appetite
  – Higher satisfaction
Cause for Caution

- Storr et al, Inf Bowel Dis 2013 – 313 patients with IBD treated in Calgary completed a questionnaire on cannabis use specifically for their disease
- Vast majority of patients reported improved abdominal and joint pain, diarrhea
- > 6 months of continuous use was a predictor of requiring surgery (OR 5) even after controlling for duration of disease, SES, tobacco use
Cause for Caution

- Allen et al, Gut 2004 first described Cannabinoid Hyperemesis Syndrome, afflicting around 50% of cannabis users
- Cyclical vomiting, up to 20 times daily that resolved with cessation of use
- Nearly 15 papers (mainly case series) describing the syndrome and its defining features since then
Cause for Caution

• Cannabis induced pancreatitis has been proposed as a new diagnostic entity in several papers (Grant 2004, Dembinski 2006, Belze 2011, Bournet 2008, Akkacuk 2015)

• Hezode et al, Gastroenterology 2011 – 313 patients with untreated Chronic Hepatitis C were biopsied
  – Significant increase in steatosis seen in daily users (double the OR) compared with infrequent users
Final Thoughts

• Widespread media attention = increase awareness, public/professional interest, and funding for cannabis research

• With time, the role of cannabis in GI diseases and the proper indications and side effect profiles with be determined

• Regardless of the legal issues surrounding cannabis, widespread use means more studies required to address efficacy and safety
Marijuana in GI diseases: basic science and practicalities

Dr. Mark A. Ware
Disclosures

• Executive Director of Canadian Consortium for the Investigation of Cannabinoids (CCIC)

• Grant from CanniMed for RCT of vapourised cannabis for OA of the knee
The draft genome and transcriptome of *Cannabis sativa*
Non-psychoactive phytocannabinoids
Other cannabis constituents

- **Myrcene**
  - Analgesic effect
    - Blocked by naloxone or yohimbine
  - Anti-inflammatory effect
    - Through PGE2 inhibition
- **Linalool**
  - Possible reduction of stress
- **Limonene**
  - Adenosine agonist
- **Caryophyllene**
  - CB2 agonist
  - Anti-inflammatory
  - Beta-caryophyllene is an FDA approved dietary supplement
- **Humulene**
  - Anti-inflammatory
  - Effects similar to dexamethasone
  - Inhibits TNFα and IL1B
Cannabinoids as ‘synaptic circuit-breakers’

Nat Med 2008;14(9):923-30
THC and CBD in Canadian regulated cannabis
Defining “medical cannabis”

• “the use of cannabis under ongoing medical supervision, with an established diagnosis of the target symptom-disease complex...used in conjunction with, or in consideration of, other pharmacological and non-pharmacological approaches and with the goal of reaching pre-specified treatment outcomes”

Ware MA, Encyclopedia Brittanica 2014
http://www.britannica.com/science/medical-cannabis
Canada’s Marihuana for Medical Purposes Regulations: a synopsis for health professionals

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Table 1. Key points from the MMPR for HCPs

1. HCPs (licensed physicians and nurse practitioners) have the authority to provide a medical document for a patient to legally access dried cannabis.
2. Patients accessing cannabis for therapeutic purposes under these regulations are referred to as “clients”.
3. Patients require a medical document from a HCP as part of their registration with a LP to become a client.
4. The medical document requires both the HCP and client’s names and contact information, the location of the consultation and the daily quantity of dried cannabis for the patient (in grams).
5. Only an original medical document can be accepted by an LP, and if a client changes to a different LP, then a new medical document will be required.
6. HCPs should be aware that LPs are obliged to keep information on their registered clients, including their medical document, and to provide information to Health Canada for auditing or upon legal request for an investigation.
7. HCPs should also be aware that information on serious adverse events must be recorded by the LP and kept for 25 years.
8. Cannabis will be shipped directly to the client, unless specified that a HCP will receive it on their behalf (extra conditions apply in situations like this and reviewing the full regulations is recommended).
9. The regulations clearly state that cannabis must not be sold or provided with any additives or in any dosage forms, but a recent exemption has been issued to allow LPs to prepare and provide oils and fresh leaves.
10. HCPs should be aware that a client may not possess more than 30 times the daily quantity of cannabis up to a maximum of 150 g.
The Medicinal Cannabis Treatment Agreement

Providing Information to Chronic Pain Patients Through a Written Document

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Secure storage
Functional outcomes
Precautions
  Pregnancy
  Heart disease
  Serious mental illness
Avoid smoking
Wait 3-4h before driving

“Start low, go slow”
Try prescription cannabinoids
Withdrawal syndrome
Regular re-evaluation
No use in public
Awareness of positive UDT
Reduce opioid/benzo/alcohol

(Clin J Pain 2015;31:1087–1096)
Data collection

- Clinical data
  - Diagnosis
  - Symptom
  - Cannabis producer
  - Strain/THC:CBD profile
- Patient reported outcomes
  - BPI
  - ESAS
  - Stanford Presenteeism Scale (function)/EQ5D
- Adverse events
- Data collected every three months for two years
Participating in the Registry

- Physicians interested in recruiting study participants must:
  - Submit a request to access the protected documents of the site
  - Sign the confidentiality agreement
  - Access the protected resources of the site
    - Training videos and to the Study startup material.
  - Authorization to begin recruitment

- Eligible patients must sign an information and consent form and answer a short survey.
- The treating physician will proceed to the evaluation of the patient and will record the information on a case report form (CRF).
- The case report form must be faxed to the Central registration office.
- The treating physician will receive an acknowledgement of receipt of the CRF.
- Participating physicians will receive reminders to complete the follow-up questionnaires.
Vapourization 101

Solvents
- Naphtha
- Butane
- Ethanol
- CO₂

Device constituents
- Heat source
- Thermoplastics
- Screens

Control
- Temperature
- Dose
Knowledge gaps

- Cannabidiol
- Basic pharmacology of ‘entourage effect’
- Opioid sparing effects
- Cannabis in the workplace
- Functional outcomes
- Pharmacovigilance
- Genetic control of pain response and psychiatric effects
- Imaging: effects on brain, mechanisms of pain/reward
Cannabinoid research capacity in Canada

**BC**
- Botany
- Harm reduction
- Policy research
- Patient-centered research
- Palliative care/oncology
- Pain management
- Veterinary medicine
- HIV/AIDS
- Neuroscience

**Alberta**
- Mental health
- Neurology
- Gastroenterology
- Pain management

**Manitoba**
- Palliative care
- Pain management
- Spasticity/SCI

**Ontario**
- Mental health & addiction
- Driving
- Pharmacology/neuroscience
- Pediatrics
- Epilepsy
- Pain management
- Emesis/GI
- Osteoporosis

**Saskatchewan**
- Cannabis genomics

**Quebec**
- Pain management
- Pharmacology
- Neurology/ALS
- Epidemiology
- Medical education
- Inflammation

**New Brunswick**
- Spasticity/SCI
- Nursing research

**Nova Scotia**
- Glaucoma
- Pain management
- Arthritis
- Pharmacology
- Neuroscience
Resources

• CFPC Preliminary Guidance Document
• CMPA position
• Collège des médecins du Québec policy
• Health Canada Information for Health Care Professionals
Canadian Consortium for the Investigation of Cannabinoids

www.ccic.net

Promoting education and research on the role of cannabinoids in health and disease.

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CIHR IRSC

QUEBEC PAIN RESEARCH NETWORK

DOULEUR PAIN