Cannabis in Palliative Care: Exploring Benefits and Considerations

Project ECHO
Palliative Care - Canada
BY Pallium Canada

Host: Diana Vincze
Presenter: Craig Goldie, MD, CCFP(PC), FRCPC
Date: December 15, 2023

Territorial Honouring

The Palliative Care ECHO Project

The Palliative Care ECHO Project is a 5-year national initiative to cultivate communities of practice and establish continuous professional development among health care providers across Canada who care for patients with life-limiting illness.

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The Palliative Care ECHO Project is supported by a financial contribution from Health Canada. The views expressed herein do not necessarily represent the views of Health Canada.

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Project ECHO Palliative Care - Canada BY Pallium Canada

LEAP Core

- Interprofessional course that focuses on the essential competencies to provide a palliative care approach.
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- Accredited by the CFPC and Royal College.

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Introductions

Host

Diana Vincze
Palliative Care ECHO Project Manager,
Pallium Canada

Presenter

Craig Goldie, MD, CCFP(PC), FRCPC
Assistant Professor, Queen's University

Support

Aliya Mamdeen
Program Delivery Officer, Pallium Canada

Conflict of Interest

Pallium Canada

- Non-profit
- Partially funded through a contribution by Health Canada
- Generates funds to support operations and R&D from course registration fees and sales of the Pallium Pocketbook

Host/Presenter

- Diana Vincze: Nothing to disclose.
- Craig Goldie–No financial conflicts of interest
  Kingston site investigator on cannabis oil trial (CAFCARS – BC Cancer Agency)

Welcome and Reminders

- For comments, please use the chat function.
- Please introduce yourself in the chat! Let us know what province you are joining us from, your role and your work setting.
- For questions, please use the Q&A function, these questions will be addressed at the end of the session.
- This session is being recorded and will be emailed to registrants within the next week.
- Remember not to disclose any Personal Health Information (PHI) during the session.

Practical Cannabis for Patients with Palliative Needs

Overview

- Basics of the Endocannabinoid System
- Rapid review of the literature
- Forms of cannabis administration
- Basic principles for safety
- Questions and Cases

Endocannabinoid System

- Mediated by CB1 and CB2 receptors
  - CB1: Mainly located in Central Nervous System (brain, spinal cord)
  - CB2: Mainly located in the immune system and blood cells
- Stimulated by endogenous (‘home grown’) cannabinoids:
  - 2-AG (full agonist)
  - AEA (CB1 agonist)
-

Exogenous Cannabinoids

- Plant-derived [Phytocannabinoids]
  - Cannabis sativa, Cannabis indica.
  - Nabiximols (botanical drug/extract) (i.e. Sativex)
- Synthetic cannabinoids
  - Marinol (pure isomer of THC)
  - Nabilone (synthetic THC mimic)

Cannabis Plant

(Δ9)-THC

- Partial Agonist at CB1 and CB2 receptors
  - Psychoactive, analgesic, antiemetic, muscle relaxant, anti-spasmotic, anti-inflammatory
- Agonism at several TRP receptors

Cannabadiol (CBD)

- CBD
  - Non-psychoactive, anti-inflammatory, ?anti-anxiety, ?anti-psychotic, anti-convulsant, inhibits metabolism of THC, potentially reduce psychoactive effects of THC (as well as sedation, tachycardia, anxiety)
- Does not directly bind CB1/CB2
  - Mechanism of action not well understood:
    - Non-competitive negative allosteric modulator of CB1
    - Reduces efficacy and potency of THC/AEA
    - Binds to TRPV1
    - Inhibit AEA uptake

Other Compounds

- Other cannabinoids (150+):
  - Cannabinol (CBN), Cannabichromene (CBC), Cannabigerol (CBG) etc.
  - Uncertain clinical properties
- Terpenes (dozens)
  - Myrcene (clove/hops)
  - Limonene (citrus)
  - Linalool (floral/lavender)
  - Carophyllene (spice/pepper)
  - Pinene (pine)

Medical Evidence - Cancer/Chronic Pain

- Possibly helpful/opioid-sparing, for cancer/chronic pain.
- Helpful for sleep
- Important papers:
  - Nabilone: Maida (2008) for cancer pain
  - Nabiximols: Johnson (2010), Porteno (2012), Lichtman (2018) for cancer pain
  - Cannabis oil: Kahwa (2021) for chronic pain
  - Nabiximols: Ueberall (2019) for chronic pain
- Systematic Reviews/Meta-analysis:
  - Wang (BMJ 2021): Medical cannabis or cannabinoids for chronic non-cancer and cancer-related pain
  - Noori (BMJ Open 2021): Opioid-sparing effects of medical cannabis or cannabinoids for chronic pain

Medical Evidence – Neuropathic Pain

- Possibly helpful for some types of neuropathic pain in some patients.
- Important papers:
  - Smoked cannabis: Abrams (2007)/Ellis (2009) for HIV-associated neuropathy
  - Dronabinol: Svendsen (2004) for MS-associated central neuropathic pain
  - Nabiximols: Nurmikko (2007) for peripheral neuropathic pain
  - Nabilone: Ueberall (2019) for chronic pain
- Systematic Reviews/Meta-analysis:
  - Cochrane Review (2018): Cannabis-based medicines for chronic neuropathic pain in adults

Medical Evidence - Nausea

- Helpful for chemotherapy-induced nausea/vomiting
- Preferred by patients
- Systematic Reviews/Meta-analysis:
  - Tramer (2001)
  - Machado Rocha (2008)
  - Cochrane Review (2015)

Medical Evidence – Cancer Anorexia

- Not really helpful
- Possibly improves “chemosensory perception” (e.g. taste/smell of food)
- Important papers:
  - Cannabis extracts: Strasser (2006)
  - Dronabinol: Brisbois (2011)
  - Dronabinol: Jatoi (2002)

Medical Evidence - Sleep

- Eight RCTs and 8 non-randomized trials
- Small studies, but relatively positive (THC/nabilone/THC:CBD)

Medical Evidence - Spasticity

- In Multiple Sclerosis or Spinal Cord Injury: Probably helpful
- Probably mostly patient perception
- Important Papers:
  - Cannabis Extract: Zajicek (2005) for MS spasticity
- Systematic Reviews/Meta-Analysis:
  - Wade (2010) for MS spasticity with nabiximols
  - Neilsen (2018): “The Use of Cannabis and Cannabinoids in Treating Symptoms of Multiple Sclerosis: a Systematic Review of Reviews”

Medical Evidence – Anti-cancer

- Cancer treatment or cure: No good evidence in humans for treating cancer / increasing survival, or curing cancer.
- Preclinical data is promising: cancer cell lines (CB1/CB2 receptors) and mouse models
- Given possible immune-modulating properties (and success of immunotherapy treatments) – theoretically could be helpful.
- Important papers:
  - Nabiximols: Twelves (2021) - Phase 1b trial (glioblastoma) with temozolamide
- Important problems:
  - “Rick Simpson Oil”, “Phoenix Tears”

Medical Evidence – CBD alone

- No evidence for CBD alone for cancer pain, nausea, sleep, mood, spasticity, anorexia
- Pending rheumatoid arthritis + ankylosing spondylitis (Hendricks et al. 2019) – no data yet
- Hand osteoarthritis + psoriatric arthritis trial
- Good data for pediatric epilepsy
- Mixed data for psychiatric illness (schizophrenia, anxiety, social phobia, addictions)
- Very tiny studies in Parkinson's disease, Crohn's, chronic pain (in kidney transplant patients)
- Important paper:
  - Gulbransen (2020) - Cannabidiol prescription in clinical practice: an audit on the first 400 patients in New Zealand

original reports

Phase IIb Randomized, Placebo-Controlled, Dose-Escalating, Double-Blind Study of Cannabidiol Oil for the Relief of Symptoms in Advanced Cancer (MedCan1-CBD)

Janet Hardy, MD, FRACP[1,2]; Ristan Greer, PhD[2,3]; Georgie Huggett, BN[1]; Alison Kearney, FRACP[4,5]; Taylan Gurgenci, FRACGP[1,2]; and Phillip Good, PhD, FRACP[1,2,6]

Medical Evidence - Combined

- Systematic Reviews:
  - Doppen (2022 JPSM): Cannabis in Palliative Care: A Systematic Review of Current Evidence
  - Whiting (2015 JAMA): Cannabinoids for Medical Use
- Systematic Review of Systematic Reviews:
  - Allan (2018): Systematic review of systematic reviews for medical cannabinoids: Pain, nausea and vomiting, spasticity, and harms.
- Canadian Clinical Guidelines:
  - Allan (2018 CFP): Simplified guideline for prescribing medical cannabinoids in primary care

Review Article

Cannabis in Palliative Care: A Systematic Review of Current Evidence

Marjan Doppen, MCSc, Stacey Kung, PhD, Ingrid Maijers, MSc, Mary John, MBChB, Harriette Dunphy, MBChB, Hermaleigh Townsley, MBChB, BMedSc(Hons), Allie Eathorne, Bsc, Alex Semprini, PhD, and Irene Braithwaite, PhD, MD

Medical Research Institute of New Zealand, (M.D., S.K., I.M., M.J., H.D., A.E. A.S., I.B.) Wellington, New Zealand; Capital and Coast District Health Board, (H.T.) Wellington, New Zealand

Medical Evidence - Harms

- Adverse effects:
  - Generally mild and acceptable but up 10% of patients withdrew from trials due to adverse events (~3x higher than placebo rate)
  - Most common:
    - Dizziness (~30%), dry mouth (~30%), sedation (~50%), feeling high (~35%)
  - Most problematic:
    - Dizziness (5), Confusion (4), Somnolence (3), Drowsiness (3.6), Disorientation (5.4), Balance (2.6), Paranoia (2)
  - Overall:
    - Number needed to harm (with AE) 6, to withdraw due to AE (14)

Medical Evidence - Harms

- Financial harms
- Avoidance of ‘regular’ medications with solid evidence base + experience
- Inability to drive
- Avoidance or delay of cancer-directed treatments

Medical Evidence – Potential Harms

- May affect immunotherapy [“checkpoint inhibitors”] – reduce efficacy of cancer treatment

- Drug interactions (CYP450 system)
  - THC inhibits CYP1A2, CYP2B6, CYP2C9, **CYP2D6**
  - CBD inhibits **CYP3A4**, CYP2B6, CYP2C9, **CYP2D6**

Supportive Care in Cancer (2023) 31:202
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REVIEW

MASCC guideline: cannabis for cancer-related pain and risk of harms and adverse events

Josephine To[1] · Mellar Davis[2] · Andrea Sbrana[3] · Bryony Alderman[4] · David Hui[5] · Sandip Mukhopadhyay[6] · Carole Bouleuc[7] · Amy A. Case[8,9] · Koji Amano[10] · Gregory B. Crawford[11] · Giulia de Feo[12] · Kimberson Tanco[5] · Jessica Garsed[13]

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Forms of Cannabis Administration

- Inhaled (Smoking or Vaporizing): dried plant, vape liquid, concentrates
- Ingestion
  - Oil or alcohol-based tincture
  - Edibles or beverages
- Sublingual
  - Oil or alcohol-based spray
- Topical
- Transdermal

Onset/ Duration of Effects

- Inhaled: ~ 5 minutes / 4-6 hours
- Ingestion: ~ 60 minutes / 8-12 hours
- Sublingual:~30 minutes / 4-6 hours
- Topical: Rapid local effect (minutes), duration unclear
- Transdermal: ~15 minutes / continuous effect for 72 hours

Preferred Administration

- Sublingual oil or sprays are preferred:
  - Rapid and predictable absorption
  - Reduced airway irritation
  - Less 11-OH-THC metabolite (less likely to have psychoactive effects)
  - More rapid onset (and shorter duration of action) (better for prn usage)

- Downsides of sublingual:
  - Can be hard to hold sublingually, can irritate the mucosa (esp alcohol-based)
  - Harder to measure/administer (draw up oil in syringe, dropper)

Dosing

- Individualized, relies on (self) titration
- “Start low, go slow”, lower THC content balanced with CBD (~1:1). Can titrate the quantity (in mg) or potency (in %)
- Reasonable starting dose 2.5-5mg THC/CBD per ingestion (preferably sublingual oil)

Dosing- Maximum

- Majority of studies were of THC <= ~30mg per day (or equivalent)
  - Nabilone: 3mg a day (divided)
  - Nabiximols: Less than 12 sprays a day
  - Marinol: 20mg a day (divided)

- CBD maximum unclear: usually similar to THC doses (e.g. in nabiximols)
  - Phase 1 trial (Taylor et al 2018) showed doses up to 6000mg

Cannabis Access

- ACMPR (“Access to Cannabis for Medical Purposes Regulation”
  - Licensed Producers
- Prescription cannabinoids
  - Nabilone
  - Nabiximols (Sativex)
- Recreational cannabis
- Home grown
- Grey-market cannabis

Who might ask for medical RX?

- Those who can receive drug coverage for their cannabis or get it reimbursed by a Health Spending account.
- It can be written off a medical expense on tax returns
- Those who want it to be clear they are using cannabis for a medical purpose rather than recreational.
- Those who hope the “medical” stream of cannabis will become refined with regards to standardized strains with medical evidence, capsules or other reliable delivery mechanism.

What is the cost?

- Nabilone: Covered by most provincial drug plans ($1.90 for 0.5mg cap, $3.70 for 1mg cap)
- Nabiximols: Approx $2.50 per spray (average use 6 sprays / d = ~$15/d); covered by private drug plans
- Cannabis oil:
- Licensed Producers: $80 for 40ml bottle (20mg/mL) – $0.50 per ‘dose’ of 5mg
- Recreational Producer: $33 for 30ml bottle (28mg/mL) - $0.20 per ‘dose’ of 5mg

Basic Principles of Safety

- Cannabis has weak evidence for use in palliative care, but this is mostly due to limited high-quality trials, often of alternative products (e.g. nabilone, Marinol, nabiximols)
  - The plural of “anecdote” is not “evidence”
  - Lack of evidence does not = lack of efficacy
- Many trials failed hard endpoints but demonstrated patient preference, sometimes other benefits (e.g. sleep), or improvement in well-being/quality of life.
- Appropriate to trial if conventional medications are either not tolerated or effective, particularly for difficult-to-treat pain and symptom constellations (e.g. pain with sleep interruption)

Basic Principles of Safety

- Trial low-dose cannabis, preferably oil or capsules:
- Start with balanced THC:CBD strain, approximately 2.5mg per dose, q4h prn for whatever symptom it is being trialed for:
  - E.g. q4h prn for pain, q4h prn for appetite (take before meals), qhs prn (for sleep), q4h prn (for nausea).
  - Sublingual administration is more predictable and replicable
- **No driving while using cannabis** (within 6 hours of sublingual, or 12 hours of oral)
- Careful moving (with respect to dizziness, hypotension)
- If any psychoactive effects, reduce dose or discontinue

Basic Principles of Safety

- Monitor effects closely (follow-up within ~7 days)
- My usual maximum dose for cannabis is ~30-40mg THC/day total
- Reassess benefits routinely and objectively (e.g. using ESAS scores, symptom diary, other medication use e.g. PRN use of opioids or antiemetics).
- Consider drug interactions

Q&A

Session Wrap Up

- Thank you for joining us!
- Please fill out the feedback survey following the session—a link has been added into the chat.

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Thank You

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