Practical Cannabis for Patients with Palliative Needs

Project ECHO
Palliative Care - Canada
BY
Pallium Canada

Host and Moderator: Jeffrey Moat, CM
Presenter: Craig Goldie, MD, CCFP(PC), FRCPC
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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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Thank You

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Introductions

Host & Moderator

Jeffrey Moat, CM
CEO, Pallium Canada

Presenter

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

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

Presenter

- Craig Goldie–No financial conflicts of interest
- Kingston site investigator on cannabis oil trial (CAFCARS – BC Cancer Agency)

Welcome and Reminders

- Please introduce yourself in the chat!
- Your microphones are muted. There will be time during this session for questions and discussion. Please add your questions in the Q&A function
- Use the chat function if you have any comments or are having technical difficulties.
- 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 CNS
  - Basal ganglia, hippocampus
  - Cerebral cortex, cerebellum
  - Spinal cord, primary afferent nociceptors
  - Integrated vomiting center*
- CB2: Periphery
  - Immune and hematopoetic systems
  - Spleen, tonsils, Mast cells

Endogenous Cannabinoids

- Anandamide (AEA)
  - Similar effect to THC
- 2-AG (2-arachidonoylglycerol)
  - Primary endogenous agonist (CB1 and CB2)
- Akin to endogenous opioid peptides (e.g. β-endorphin, enkephalins and dysnorphins)
- Very primitive system, found in most vertebrates

Exogenous Cannabinoids

- Phytocannabinoids
  - Cannabis plant
  - 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, can 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:
  - Cannabinol (CBN), Cannabichromene (CBC), Cannabigerol (CBG) etc.
  - Uncertain clinical properties
- Terpenes
  - 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

- Probably helpful for neuropathic pain.
- 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

- No trials
- But sleep subscales/scores on other trials (e.g. pain trials) look promising

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”

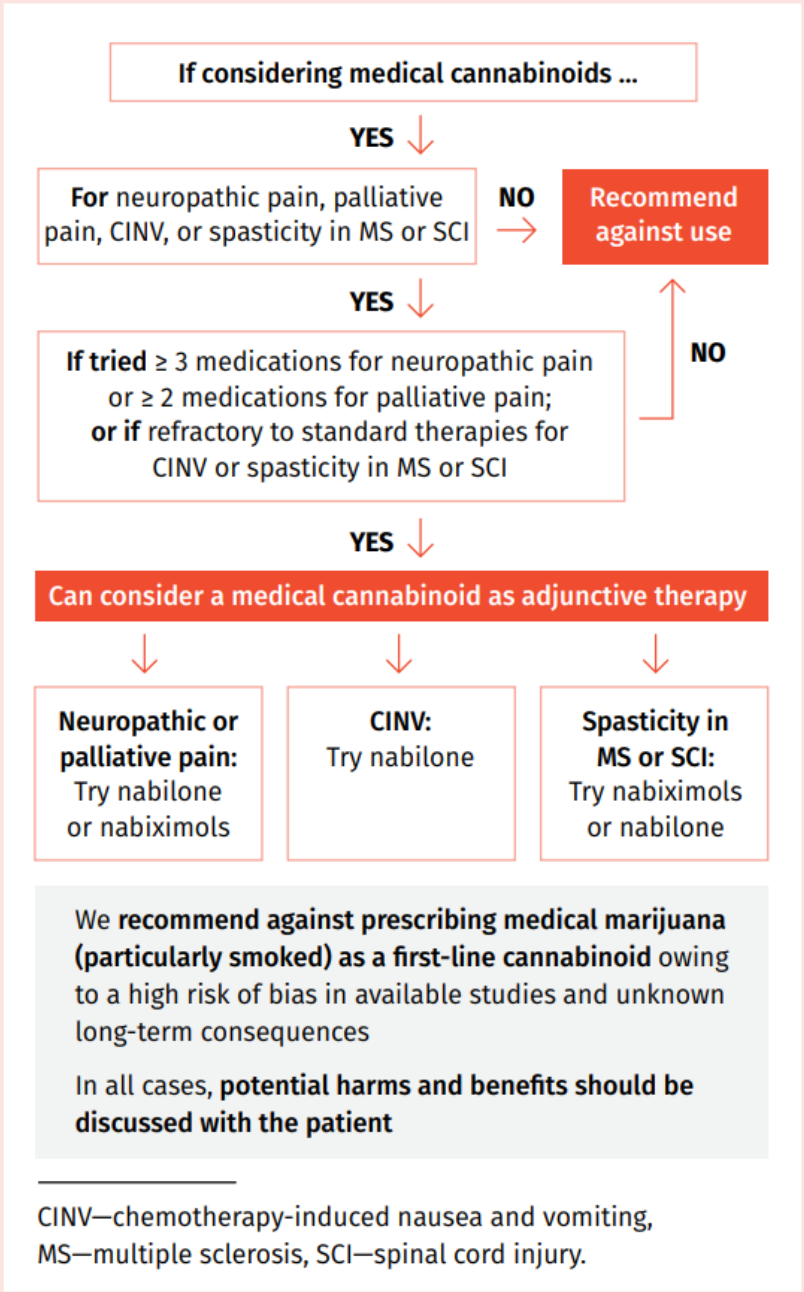
Medical Evidence – CBD alone

- No evidence for CBD alone for cancer pain, nausea, sleep, mood, spasticity, anorexia
- Pending palliative care trial (Good et al. 2019) – no data yet
- 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

Medical Evidence - Combined

- Systematic Reviews:
  - 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

Figure 1. Medical cannabinoid prescribing algorithm



CINV—chemotherapy-induced nausea and vomiting, MS—multiple sclerosis, SCI—spinal cord injury.

Allan et al. Retrieved from http://www.cfp.ca/content/cfp/64/2/111.full.pdf

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

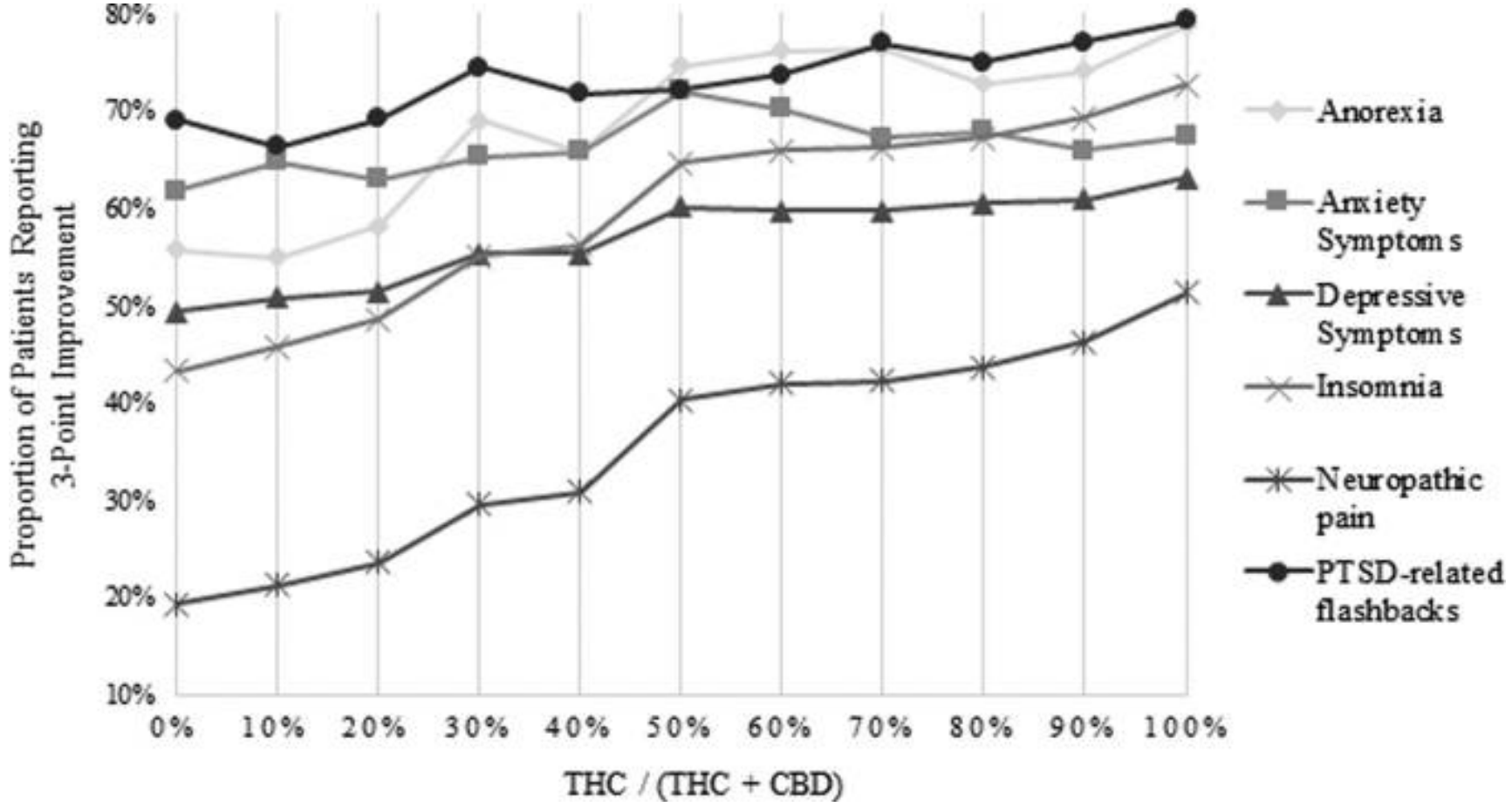
- Financial harms
- Avoidance of ‘regular’ medications with solid evidence base + experience
- Inability to drive
- Avoidance or delay of cancer-directed treatments

“Evidence” – Crowd-sourced

- Benefit of Tetrahydrocannabinol versus Cannabidiol for Common Palliative Care Symptoms
  - J Palliat Med. 2019 Oct 1; 22(10): 1180–1184.

- Used crowd-source data from smartphone app ”Strainprint” to look at 6 symptoms:
  - Neuropathic pain
  - Anorexia
  - PTSD-related flashbacks
  - Insomnia
  - Anxiety symptoms
  - Depressive symptoms

“Evidence” – Crowd-sourced



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 is preferred:
  - Rapid and predictable absorption
  - Reduced airway irritation
  - Less 11-OH-THC metabolite (less likely to have psychoactive effects)
  - 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 2.5mg THC/CBD per ingestion (preferably sublingual oil)
- Typically works out to ~0.1-0.5ml per ingestion.

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.

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 replicatable
- **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 ~30mg 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 (relatively few)

Questions?

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