

Cannabis and Dementia — What We Need To Know

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Outline

- Medical Cannabis and legalization
- Cannabinoids, Medical Marijuana, and Medical Cannabinoids
- Safety and Efficacy of Cannabinoids In Older Adults
- Cannabinoids In Dementia – Mechanism Of Action
- Cannabinoids For Behavioural Symptoms of Alzheimer's Disease
- Medical Cannabinoids for Other Conditions In Older Adults
- Known Harms and Contraindications
- Take Home Messages



Medical Cannabis- Historical perspective

- ▶ Cannabis used therapeutically for almost 5,000 years
- ▶ 2700 BC – Earliest evidence in Chinese pharmacopeia
- ▶ 1841 – Medical Cannabis introduced into Western medicine
- ▶ Late 19th century – Medical Cannabis widely disseminated in the Americas for managing pain-related conditions
- ▶ 1930-1940 – Fell from favour, triggered by concerns about violence and crimes from recreational use
- ▶ Prohibitive legislation leading to world-wide ban
- ▶ 2001 – Medical Marijuana Access Program by Health Canada

Medical Cannabis- Historical perspective

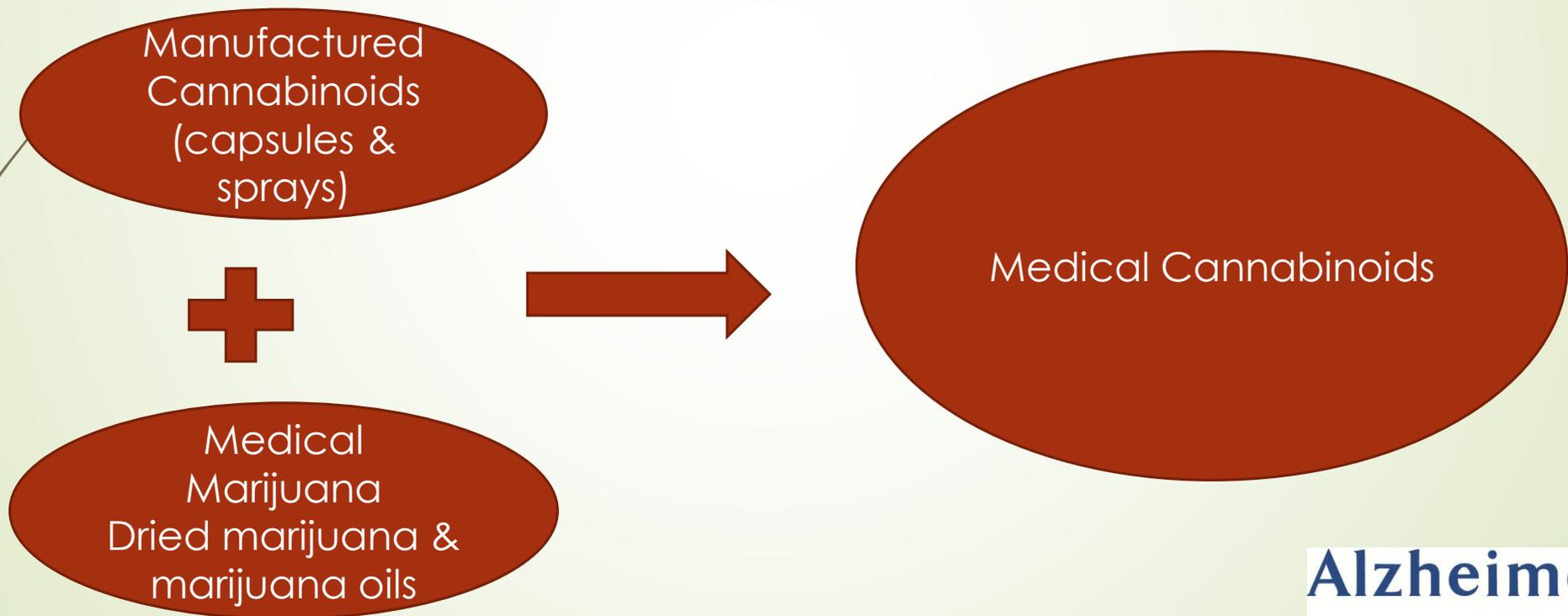


- ▶ 2003 & 2004 – Failed decriminalization bill
- ▶ 2007 – National Anti-drug strategy
- ▶ 2009- Bill C-15/S-10 Mandatory Minimum for Cannabis
- ▶ April 2014 – Marijuana for Medical Purposes Regulations replaced Medical Marijuana Access Program
Now access to medical cannabis under Part 14 of the New Cannabis regulation
- ▶ June 2015 – Expanded definition of medical cannabis to include all forms of the drug
- ▶ June 2016 – Task Force on Cannabis Legalization and Regulation
- ▶ April 2017 – Cannabis Act
- ▶ June 2018 – Final Legalization

Medical Cannabinoids



- Cannabinoids are bioactive components of Cannabis plant (Cannabis Sativa & Indica)
- Over 100 Cannabinoids, including Tetrahydrocannabinol (THC), and Cannabidiol (CBD)
- THC has therapeutic and psychoactive effects; CBD has potential therapeutic effects, and no psychoactive effects
- Medical Cannabinoids include manufactured cannabinoids and medical marijuana



Characteristics Of Medical Cannabinoid Consumers



- ▶ The number of registered medical marijuana users in Canada has tripled every year since 2014 from 7914 in 2014 to 201,398 in 2017
- ▶ 1.7% of Albertans are registered users of medical marijuana
- ▶ Older Adults account for 7% to 33% of medical cannabinoid consumers world-wide
- ▶ Canadian stats for older adult consumers not available
- ▶ Most common indications- chronic pain (58-84%), cancer, spasticity in MS, arthritis, sleep disorders, anxiety and depression
- ▶ Majority of older consumers using a mixture of cannabis strains
- ▶ Common Routes of administration- smoking, vaporization, and oil



Medical Cannabinoids- Safety & Efficacy In Older Adults

- ▶ High quality systematic studies lacking
- ▶ A prospective study of patients ≥ 65 years of age who received medical cannabinoids from January 2015 to October 2017 reported:
 - ▶ Medical Cannabis fairly safe and efficacious
 - ▶ Significant reduction in intensity of pain (from 8 to 4 on a scale of 0-10)
 - ▶ Improvement in quality of life (from 79% reporting bad or very bad to 59% reporting good or very good), reported after six months of treatment
 - ▶ Reduction in the use of other prescription medicines, including opioids

**Population Study – ✓
Observational, short duration, mixed
strains, absence of RCTs
Evidence: Weak**



The Dementia scenario

- ▶ Dementia: Chronic degenerative condition affecting the brain, characterized by a progressive decline in cognitive and functional abilities.
- ▶ The most common forms :
 - ▶ Alzheimer's Disease (AD) 60% -70%
 - ▶ Vascular Dementia (VaD)
 - ▶ Dementia with Lewy Body (DLB)
 - ▶ Dementia in Parkinson's Disease (PDD)
 - ▶ Frontotemporal Dementia (FTD)
- ▶ Dementia Stats: to triple from 47 million in 2016 to 131 million in 2050
- ▶ Behavioural and Psychological Symptoms of Dementia (BPSD):
 - ▶ $\geq 50\%$
 - ▶ caregiver distress, early placement, rapid progression, and higher costs

Dementia Treatment Scenario



- ▶ Licensed medications (Aricept, Exelon, Reminyl & Ebixa) available only for AD and PDD
- ▶ Modest benefit for cognitive symptoms, no effect on behavioural symptoms
- ▶ Behavioural and psychological symptoms managed using antipsychotic drugs, such as Risperidone, with variable, modest benefit and serious side effects, including death
- ▶ A range of non-pharmacological interventions (music, art, virtual reality etc.) used, with varied and modest benefits
- ▶ Need for new, safe, and more effective treatments for dementia and its associated symptoms



Medical Cannabinoids In Dementia

- ▶ Cannabis plant used for centuries to treat a wide range of conditions in older people, such as pain, depression, sleep disturbances, and loss of appetite
- ▶ The broad therapeutic applications due to its bioactive components- cannabinoids
- ▶ Growing interest in medical applications of Cannabis in older adults with dementia, based on positive attitude of older adults towards medical cannabis, as elicited by surveys (Banwell 2016, Gazibara 2017)
- ▶ 3 general classes of cannabinoids

| Cannabinoids | | |
|---|---|--|
| Herbal (Derived from the plant) THC, CBD etc. | Endogenous (Produced in bodies of animals and humans) Anandamide, 2-AG etc. | Synthetic (produced in laboratory) (Nabilone, Nabiximols etc.) |

How Medical Cannabinoids work



- Cannabinoids exert their effects through endocannabinoid system (ECS)
- ECS Comprised of:
 - Endogenous cannabinoids (produced in the body)
 - Cannabinoid receptors (mainly CB1 and CB2)
 - Enzymes involved in synthesis and degradation of endocannabinoids
- CB1 receptors present throughout the central nervous system, especially hippocampus
 - CB2 receptors present in the peripheral tissues, especially immune cells
- Cannabinoids bind to the CB1 and CB2 receptors, modulate the way the neurons communicate with each other, and modulate behaviour

Medical Cannabinoids- Mechanism of Action



- CB1 Mediated:
 - Neurotransmitter release – Improves memory and cognition, reduces pain and, behaviour symptoms
 - Glutamate production and oxidative stress – Reduces amyloid plaque, tau tangles, neurodegeneration
 - Energy balance and metabolism- Improves neuron survival
- CB2 Mediated
 - Reduces neuroinflammation – Neuroprotection
 - Facilitates neuron survival – Slowing neurodegeneration

Population Studies – X
Animal studies, cell studies- ✓
Evidence: Weak

Cannabinoids In Behavioural Symptom Management



- Behavioural Symptoms: Depression, Anxiety, Agitation, Aggression, Irritability, Hallucinations, Delusions, Sleep disorders etc .
- Synthetic THC (Nabilone, Dronabinol, Nabiximols):
 - Disease-modifying action – Significant improvement in behavioral symptoms in LOAD
 - Analgesic, anxiolytic actions – Persistent Reduction in night-time agitation, and motor activity
 - Improvement in sleep duration, and food consumption
- Studies Published: 7
 - 1 retrospective chart review, 3 small randomized controlled trials, one pilot study, and one case report

Population Studies – ✓
Few studies, Small Size, Short Duration, Lack of placebo control
Evidence: Weak

Medical Cannabinoids for Chronic Pain (Median follow-up 4 weeks)



► Nabiximols has better evidence than Nabilone

| Chronic Pain | Cannabinoids | Placebo/ Controls | Number Needed to Treat | Quality of Evidence |
|--|---------------------------------------|-------------------------------|----------------------------------|------------------------|
| ≥ 30% ↓ in Neuropathic +Cancer | 39% | 30% | 11 | Very low |
| ≥ 30% ↓ in Neuropathic pain | 38% | 30% | 14 | Very low |
| ≥ 30% ↓ in Palliative pain | 30% | 23% | Not statistically significant | Very low |
| Change in Chronic Pain Scale (0-10) | Baseline ≈ 6 Decreased 1.2- 1.6 | Baseline ≈ 6 Decreased 0.8 | | Very low |

From TOP Cannabinoid Prescribing Information 2018

Medical Cannabinoids For Chemotherapy-Induced Nausea & Vomiting



Median follow-up 1 day)

➔ **Prescribe Nabilone if considering a medical cannabinoid**

| | Cannabinoids | Placebo/ Controls | Number Needed to Treat | Quality of Evidence |
|---|--------------|------------------------|---------------------------|------------------------|
| Control of nausea & vomiting (Cannabinoids vs Placebo) | 47% | 13% | 3 | Moderate |
| Control of nausea & vomiting (Cannabinoids vs. Neuroleptics) | 31% | 16% (vs. Neuroleptics) | 7 | Low |

From TOP Cannabinoid Prescribing Information 2018

Medical Cannabinoids For Spasticity (Median Follow-up 6 weeks)



- Prescribe Nabiximols if considering medical cannabinoids.

| | Cannabinoids | Placebo/ Controls | Number Needed to Treat | Quality of Evidence |
|--------------------------------|---|---------------------------------|---------------------------|------------------------|
| Global Impression Of Change | 50% | 35% | 7 | Low |
| ≥ 30% ↓ in Spasticity | 35% | 25% | 10 | Low |
| Change in Spasticity (0-10) | Baseline ≈ 6.2 Decreased 1.3- 1.7 | Baseline ≈ 6.2 Decreased 1.0 | | Very low |

From TOP Cannabinoid Prescribing Information 2018

Medical Cannabinoids- Known Adverse Events

- Risk of adverse events (Cannabinoids vs. Placebo): 80% versus 60%
- Withdrawal due to adverse events (Cannabinoids vs. Placebo): 11% versus 3%
- Common Adverse Events:

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| Adverse Event | Cannabinoids | Placebo |
|--------------------------------|---------------------|----------------|
| Feeling high | 35% | 3% |
| Sedation | 50% | 30% |
| Dysphoria | 13% | 0.3% |
| Trouble speaking | 32% | 7% |
| Memory Problems | 11% | 2% |
| Psychosis | 17% | 5% |
| Disturbed/Disconnected thought | 17% | 2% |
| Dizziness | 32% | 11% |
| Hypotension | 25% | 11% |
| Disorientation/Confusion | 9% | 2% |

Is CBD superior to THC



- ▶ THC is the psychoactive component of Cannabis
- ▶ CBD has a lower risk of psychoactive side effects
- ▶ Medical Cannabinoids contain varying combinations of THC and CBD
- ▶ THC has greater affinity for Cannabinoid receptors compared to CBD
- ▶ 4 studies available to compare the benefits/harms of CBD versus THC/CBD , or THC versus THC/ CBD were inconclusive
- ▶ At this point it is unclear if using CBD alone, instead of THC/CBD combination would be more beneficial

Medical Cannabinoids- Contra-indications



- History of psychosis
- Bipolar Disorder
- History of Cannabis allergies
- History of unstable angina or pre-existing heart disease
- Risk of interaction with other drugs that influence the hepatic CYP family enzymes
- **Current evidence in elderly population is scarce, extensive research imperative**

Medical Cannabinoids



Daily doses and costs

| Drug | Daily Dose ² | Approximate cost/month |
|-----------------------------------|--------------------------------|-------------------------------------|
| Nabilone* ¹ | 2 to 6 mg | \$94 to \$305 |
| Nabiximols* | 4 to 12 sprays | \$226 to \$903 |
| Medical Marijuana <i>Dried</i> | 1 to 3 g <i>typical use</i> | \$250 to \$750 Based on \$8.37/g |

*Manufacturer list price, does not reflect pharmacy dispensing fees.

¹Only generic nabilone covered by most provincial drug plans.

²Studied doses: Nabilone 0.5mg to 8mg/day, nabiximols 4 to 48 sprays/day, smoked marijuana had THC concentrations ranging 1 to 8% up to three times a day as tolerated. Daily doses from drug monographs and Health Canada.

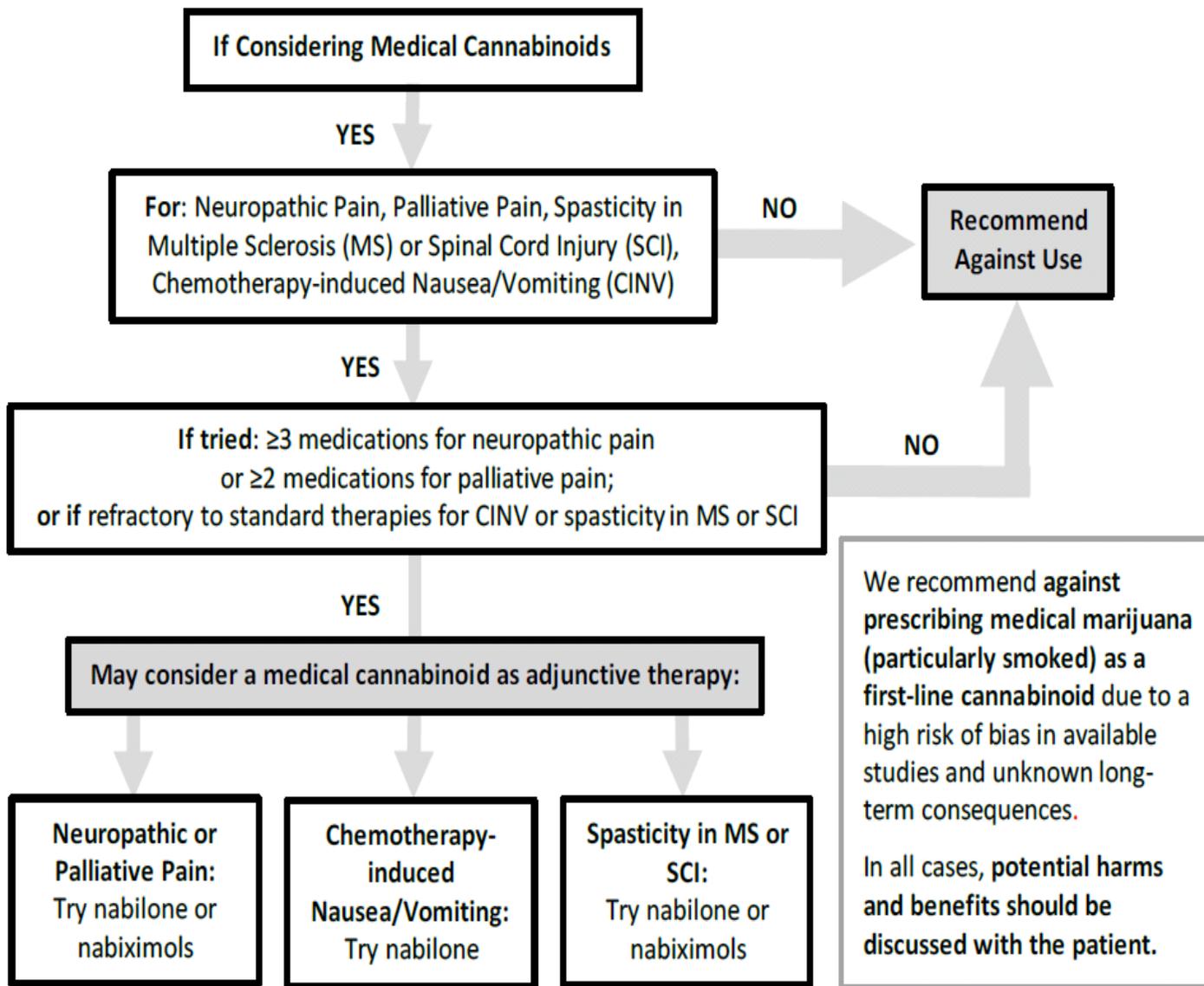
From TOP Cannabinoid Prescribing Information 2018

Alzheimer Society

CALGARY

30+
years

Medical cannabinoid prescribing algorithm



Factors affecting the potency and effects of Cannabis



- Potency/ dose of THC
- Route of administration – inhalation versus oral
- Concomitant use of other substances – alcohol, tobacco etc.
- Concomitant use of other medications
- Duration and frequency of use

Medical Cannabinoids: Take Home



Messages

- Medical Cannabinoids include medical Marijuana and manufactured cannabinoids
- Cannabinoids may help people with chronic pain, muscle spasticity caused by MS or spinal cord injury, and chemotherapy-induced nausea and vomiting. Evidence is weak.
- Cannabinoids could theoretically benefit people with Alzheimer's disease, but current evidence is weak due to absence of high quality studies
- Side effects and drug interactions are common while using Cannabinoids

Medical Cannabinoids: Take Home Messages



- Clearance of Cannabis from the body slowed by decreased liver and kidney function, and increased body fat in older adults
- Long-term harms are unknown
- Well-conducted high quality studies to assess safety, efficacy, and drug metabolism in the body required before Cannabinoids can be safely prescribed for older adults.
- Discuss with your physician about potential benefits, risks and known harms before taking cannabinoids
- If considering Cannabis, a trial of pharmaceutical cannabinoids preferred to medical marijuana

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Medical Cannabinoids



➤ Questions?