

# Cannabis and Dementia — What We Need To Know

Paul Bartel MSW, RSW

Padmaja Genesh BSc, MBBS, BA (Gerontology)



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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 19<sup>th</sup> 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

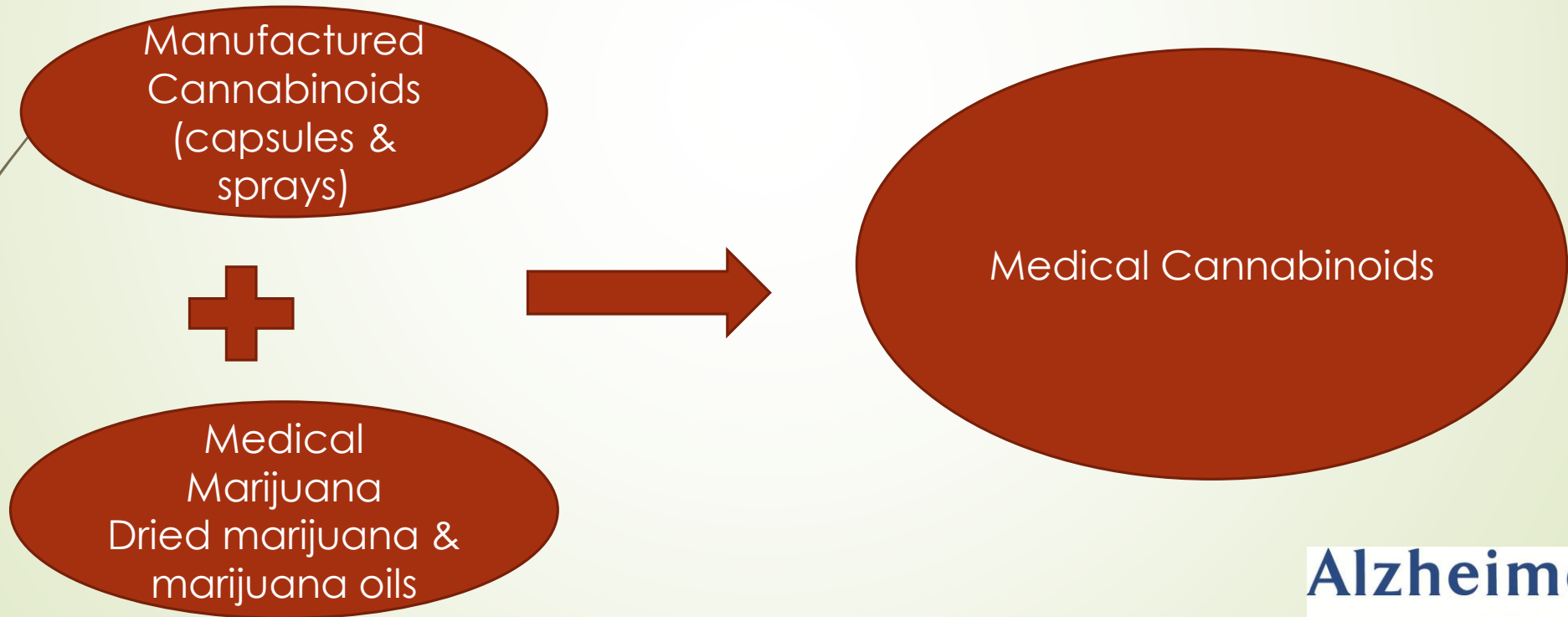


- 2003 & 2004 – Failed decriminalization bill
- 2007 – National Anti-drug strategy
- 2009- Bill C-15/S-10 Mandatory Minimum for Cannabis
- April 2014 – Marijuana for Medical Purposes Regulations replaced Medical Marijuana Access Program  
Now access to medical cannabis under Part 14 of the New Cannabis 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  $\geq 65$  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<br>(Derived from the plant)<br>THC, CBD etc. | Endogenous<br>(Produced in bodies of animals and humans)<br>Anandamide, 2-AG etc. | Synthetic<br>(produced in laboratory)<br>(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/<br>Controls          | Number Needed<br>to Treat        | Quality of<br>Evidence |
|--|---------------------------------------|-------------------------------|----------------------------------|------------------------|
| ≥ 30% ↓ in<br>Neuropathic +Cancer      | 39%                                   | 30%                           | 11                               | Very low               |
| ≥ 30% ↓ in<br>Neuropathic pain         | 38%                                   | 30%                           | 14                               | Very low               |
| ≥ 30% ↓ in Palliative<br>pain          | 30%                                   | 23%                           | Not statistically<br>significant | Very low               |
| Change in Chronic<br>Pain Scale (0-10) | Baseline ≈ 6<br>Decreased 1.2-<br>1.6 | Baseline ≈ 6<br>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/<br>Controls   | Number Needed<br>to Treat | Quality of<br>Evidence |
|---|--------------|------------------------|---------------------------|------------------------|
| Control of nausea & vomiting<br>(Cannabinoids vs Placebo)       | 47%          | 13%                    | 3                         | Moderate               |
| Control of nausea & vomiting<br>(Cannabinoids vs. Neuroleptics) | 31%          | 16% (vs. Neuroleptics) | 7                         | Low                    |

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



- **Prescribe Nabiximols if considering medical cannabinoids.**

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

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# 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 |
|--------------------------------|--------------|---------|
| <b>Feeling high</b>            | <b>35%</b>   | 3%      |
| <b>Sedation</b>                | <b>50%</b>   | 30%     |
| Dysphoria                      | 13%          | 0.3%    |
| <b>Trouble speaking</b>        | <b>32%</b>   | 7%      |
| Memory Problems                | 11%          | 2%      |
| Psychosis                      | 17%          | 5%      |
| Disturbed/Disconnected thought | 17%          | 2%      |
| <b>Dizziness</b>               | <b>32%</b>   | 11%     |
| <b>Hypotension</b>             | <b>25%</b>   | 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 <sup>2</sup>        | Approximate cost/month              |
|-----------------------------------|--------------------------------|-------------------------------------|
| Nabilone* <sup>1</sup>            | 2 to 6 mg                      | \$94 to \$305                       |
| Nabiximols*                       | 4 to 12 sprays                 | \$226 to \$903                      |
| Medical Marijuana<br><i>Dried</i> | 1 to 3 g<br><i>typical use</i> | \$250 to \$750<br>Based on \$8.37/g |

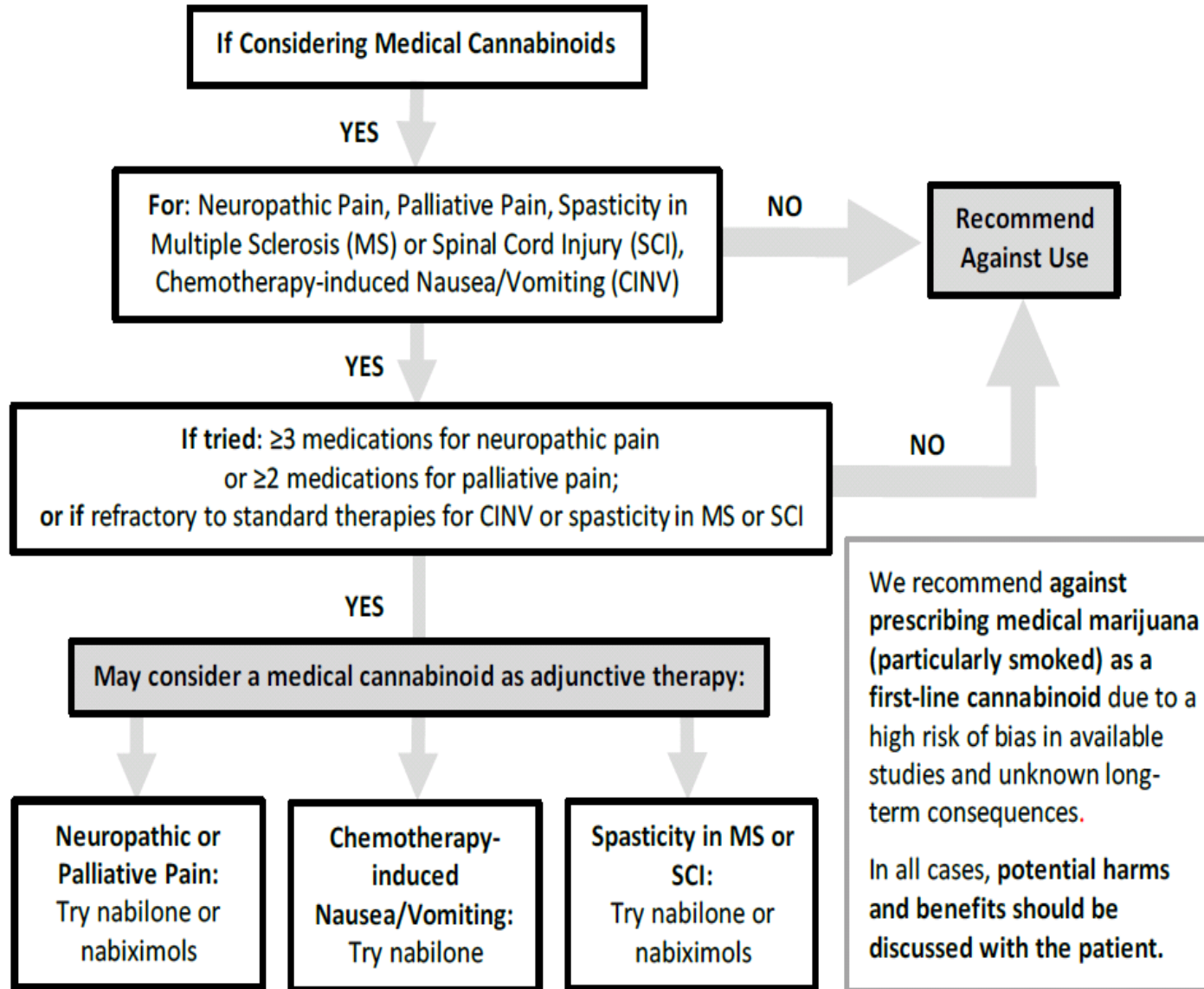
\*Manufacturer list price, does not reflect pharmacy dispensing fees.

<sup>1</sup>Only generic nabilone covered by most provincial drug plans.

<sup>2</sup>Studied 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.

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# 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?