Cannabis and Dementia — What We Need To Know
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Home Care Assistance
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

Manufactured Cannabinoids (capsules & sprays)

Medical Marijuana
Dried marijuana & marijuana oils

Medical Cannabinoids
Characteristics Of Medical Cannabinoid Consumers

- The number of registered medical marijuana users in Canada has tripled every year since 2014 from 7,914 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 worldwide.
- 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):
  - ≥ 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

<table>
<thead>
<tr>
<th>Cannabinoids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herbal (Derived from the plant)</td>
</tr>
<tr>
<td>THC, CBD etc.</td>
</tr>
</tbody>
</table>
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

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

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

<table>
<thead>
<tr>
<th>Control of nausea &amp; vomiting (Cannabinoids vs Placebo)</th>
<th>Cannabinoids</th>
<th>Placebo/Controls</th>
<th>Number Needed to Treat</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control of nausea &amp; vomiting (Cannabinoids vs Neuroleptics)</td>
<td>47%</td>
<td>13%</td>
<td>3</td>
<td>Moderate</td>
</tr>
<tr>
<td>Control of nausea &amp; vomiting (Cannabinoids vs Neuroleptics)</td>
<td>31%</td>
<td>16% (vs. Neuroleptics)</td>
<td>7</td>
<td>Low</td>
</tr>
</tbody>
</table>

From TOP Cannabinoid Prescribing Information 2018
Medical Cannabinoids For Spasticity (Median Follow-up 6 weeks)

- Prescribe Nabiximols if considering medical cannabinoids.

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

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:

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Cannabinoids</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeling high</td>
<td>35%</td>
<td>3%</td>
</tr>
<tr>
<td>Sedation</td>
<td>50%</td>
<td>30%</td>
</tr>
<tr>
<td>Dysphoria</td>
<td>13%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Trouble speaking</td>
<td>32%</td>
<td>7%</td>
</tr>
<tr>
<td>Memory Problems</td>
<td>11%</td>
<td>2%</td>
</tr>
<tr>
<td>Psychosis</td>
<td>17%</td>
<td>5%</td>
</tr>
<tr>
<td>Disturbed/Disconnected thought</td>
<td>17%</td>
<td>2%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>32%</td>
<td>11%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>25%</td>
<td>11%</td>
</tr>
<tr>
<td>Disorientation/Confusion</td>
<td>9%</td>
<td>2%</td>
</tr>
</tbody>
</table>

From TOP Cannabinoid Prescribing Information 2018
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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily Dose</th>
<th>Approximate cost/month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nabilone*1</td>
<td>2 to 6 mg</td>
<td>$94 to $305</td>
</tr>
<tr>
<td>Nabiximols*</td>
<td>4 to 12 sprays</td>
<td>$226 to $903</td>
</tr>
<tr>
<td>Medical Marijuana</td>
<td>1 to 3 g typical use</td>
<td>$250 to $750</td>
</tr>
<tr>
<td><em>Dried</em></td>
<td></td>
<td>Based on $8.37/g</td>
</tr>
</tbody>
</table>

*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.
Medical cannabinoid prescribing algorithm

If Considering Medical Cannabinoids

YES

For: Neuropathic Pain, Palliative Pain, Spasticity in Multiple Sclerosis (MS) or Spinal Cord Injury (SCI), Chemotherapy-induced Nausea/Vomiting (CINV)

YES

If tried: ≥3 medications for neuropathic pain or ≥2 medications for palliative pain; or if refractory to standard therapies for CINV or spasticity in MS or SCI

YES

May consider a medical cannabinoid as adjunctive therapy:

- Neuropathic or Palliative Pain: Try nabilone or nabiximols
- Chemotherapy-induced Nausea/Vomiting: Try nabilone
- Spasticity in MS or SCI: Try nabilone or nabiximols

NO

Recommend Against Use

We recommend against prescribing medical marijuana (particularly smoked) as a first-line cannabinoid due to a high risk of bias in available studies and unknown long-term consequences.

In all cases, potential harms and benefits should be discussed with the patient.
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
References

- AIA Ahmed, MA Va Der Marck, GAH Van Der Elsen and MGM Olde Rikkert. Cannabinoids in Late-Onset Alzheimer’s Disease, from Clinical Pharmacology & Therapeutics Vol 97 Number 6/June 2015
- Celina S. Liu, Sarah A. Chau, Myuri Ruthirakuhhan, Krista L. Lactot, and Nathan Herrmann. Cannabinoids for the Treatment of Agitation and aggression in Alzheimer’s Disease. Published online: 14 August 2015© Springer International Publishing Switzerland 2015


Pauline Anderson. Marijuana Doesn’t Curb Agitation, Aggression in Dementia, Medscape- May 21, 2015

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Medical Cannabinoids

Questions?