Is it High-Time for Medical Cannabis: Doobie-ous Evidence or Smokin’ Results?

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Faculty/Presenter Disclosure

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What is presently happening,...

- Canada: Any Cannabis Use 43% and this year ~12%.
- Patients with conditions like chronic pain or MS, ~15-20% use Cannabis.
- Most common reason: Pain (58-84% of medical use).

![Number of Canadians on Licensed MM](image)


Some of the promoted medical uses for Cannabinoids

1. Tourette Syndrome
2. Amyotrophic Lateral Sclerosis
3. Huntington’s Disease
4. Parkinson’s Disease
5. Dystonia
6. Glaucoma
7. Traumatic Brain Injury/Intracranial Hemorrhage
8. Addiction
9. Anxiety
10. Depression
11. Sleep Disorders
12. Posttraumatic Stress Disorder
13. Schizophrenia and Other Psychosis
14. Osteoarthritis
15. Fibromyalgia
16. Neuropathic Pain
17. HIV Pain
18. Dementia
19. Cancer
20. Chemotherapy-Induced Nausea and Vomiting
21. Anorexia and Weight Loss
22. Irritable Bowel Syndrome
23. Epilepsy
24. Spasticity Associated with Multiple Sclerosis or Spinal Cord Injury
Examples of Poor Research

- Glaucoma: 1 RCTs with 6 people (no effect)
- Anxiety: 1 RCT of 24 patients tested for simulated public speaking found more improvement on mood visual analogue scale.
- IBS: 1 RCT of 36 pts given dronabinol for 2.5, 5mg or placebo BID x2 days: Focused on transit times.


Two Primary Problems.

- Blinding: Attempted but rarely tested
  - In 2 Inhaled cannabis cross-over RCTs
    - 1st: 57% identified all 6 phases
    - 2nd: 90% identified active vs cannabis cigs without THC/CBD
  - Dronabinol, 95% of patients identified active (as did 85% of nurses. (nabilone study similar)
- Inclusion: Previous users often focused on.
  - Of 6 inhaled RCTs: 3 required past use, 2 no limitation and 1 did not report.
  - In Nausea/vomiting, previous use led to great response
  - Naive users (not past report psychosis).
- Together, these introduce profound bias

Can Fam Physician 2018 (submitted)
Pain Outcomes: 30% pain reduction & others

<table>
<thead>
<tr>
<th>Type of Pain</th>
<th>Risk Ratio</th>
<th>Cannabis</th>
<th>Placebo</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Pain</td>
<td>1.23 (0.98-1.56)</td>
<td>37%</td>
<td>31%</td>
<td>~19</td>
</tr>
<tr>
<td>Smoked, Neuropathic</td>
<td>1.62 (1.24-2.12)</td>
<td>47%</td>
<td>29%</td>
<td>6</td>
</tr>
<tr>
<td>Neuropathic</td>
<td>1.34 (1.04-1.74)</td>
<td>38%</td>
<td>30%</td>
<td>14</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.35 (0.63-2.09)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Palliative</td>
<td>1.34 (0.96-1.86)</td>
<td>30%</td>
<td>23%</td>
<td>~15</td>
</tr>
<tr>
<td>Chronic Pain</td>
<td>1.37 (1.14-1.64)</td>
<td>39%</td>
<td>30%</td>
<td>11</td>
</tr>
</tbody>
</table>

- On a 0-10 point scale: Baseline ~6/10.
  - Placebo reduces things ~0.8
  - Cannabinoids: 0.2 to 0.8

What factors influence Cannabinoid pain effect?

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Subgroup</th>
<th>Risk Ratios</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Cannabinoid</td>
<td>Inhaled</td>
<td>1.52 (1.17-1.99)</td>
<td>P=0.34</td>
</tr>
<tr>
<td></td>
<td>Buccal</td>
<td>1.28 (1.02-1.61)</td>
<td></td>
</tr>
<tr>
<td>Size of RCT</td>
<td>&lt;150</td>
<td>1.56 (1.26-1.92)</td>
<td>P=0.03</td>
</tr>
<tr>
<td></td>
<td>&gt;150</td>
<td>1.09 (0.86-1.39)</td>
<td></td>
</tr>
<tr>
<td>Duration of RCT</td>
<td>&lt;1 week</td>
<td>1.58 (1.13-2.20)</td>
<td>P=0.01</td>
</tr>
<tr>
<td></td>
<td>2-5 wks</td>
<td>1.79 (1.32-2.43)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9-15 wks</td>
<td>1.07 (0.87-1.32)</td>
<td></td>
</tr>
</tbody>
</table>

**Bottom-Line:** When you examine higher quality studies (larger & longer), cannabinoids do not appear to have an effect on pain.

Additional Variables in Pain

- Nabilone (oral): 2 best trials
  - RCT Fibromyalgia 40 patients, 1mg PO BID x4 wks
    - 14.6 more than placebo on 100mm VAS.
  - RCT: 73 x3 wks, 500 μg v 60 mg dihydrocodeine QID.
    - 10 on 100mm VAS: 19% dihydrocodeine vs 5% nabilone.

- Rheumatologic Pain: Insufficient evidence
- Acute Pain: decrease (1), worse (1) & no effect (5)
- Function not reported and QoL unchanged.


Pain Summary

- Bottom-line: At best, medical cannabinoids reduce pain ≥30% for one in 11 patients suffering from neuropathic pain (vs placebo).
  - This includes highly biased research, meaning the effect is likely exaggerated.
  - It is very unclear if one type medical cannabinoids is better but the best research is on nabiximol.
Nausea & Vomiting

Absence Nausea & Vomiting from Chemotherapy

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Outcome</th>
<th>Rate Ratio</th>
<th>Cannabis</th>
<th>Control</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vs Placebo</td>
<td>Control Sx*</td>
<td>3.60 (2.55 - 5.09)</td>
<td>47%</td>
<td>13%</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Pt Preference</td>
<td>4.82 (1.74 - 13.36)</td>
<td>72%</td>
<td>18%</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Pt Preference</td>
<td>5.67 (3.95 - 8.15)</td>
<td>76%</td>
<td>13%</td>
<td>2</td>
</tr>
<tr>
<td>Vs Neuroleptics</td>
<td>Control Sx*</td>
<td>1.85 (1.18 - 2.91)</td>
<td>31%</td>
<td>16%</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Pt Preference</td>
<td>2.76 (1.88 - 4.03)</td>
<td>63%</td>
<td>19%</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Pt Preference</td>
<td>2.39 (2.05 - 2.78)</td>
<td>61%</td>
<td>26%</td>
<td>3</td>
</tr>
</tbody>
</table>

* Done by us

Additional Variables

- Most trials followed patients 1 day (after chemo)
- Patient preference higher than effectiveness (preference ~75% while effectiveness 47%)
  - Maybe preference based on more than effectiveness
- Medical Cannabinoids for nausea/vomiting are primarily oral agents like Nabilone (& delisted dronabinol).


Nausea & Vomiting Summary

- Bottom-Line: Although biases, likely works, preventing nausea/vomiting in 47% vs 13% (on placebo).
- Medical cannabinoids will prevent nausea/vomiting in 31% vs 16% (Vs neuroleptics like prochlorperazine)
- Patients like it,
  - More than it works
Spasticity

How well it works

<table>
<thead>
<tr>
<th>Rate Ratio</th>
<th>Cannabis</th>
<th>Placebo</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥30% Improvement in Spasticity</td>
<td>1.43 (0.99-2.08)</td>
<td>35%</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>1.37 (1.07-1.76)</td>
<td>35%</td>
<td>25%</td>
</tr>
<tr>
<td>Global Impression of Change (by us)</td>
<td>1.45 (1.08 – 1.95)</td>
<td>50%</td>
<td>35%</td>
</tr>
</tbody>
</table>

- Spasticity score from 0-10, Mean score: 6.2,
  - Placebo improved spasticity 0.95
  - Cannabinoid improved spasticity, over placebo, by 0.31 – 0.76

Spasticity Summary

- Bottom-Line: Medical Cannabinoids reduce spasticity for 50% of patients compared to 35% of those on placebo (as assessed by patient global assessment of improvement).

Adverse Events:
Cannabis is Natural and therefore Safe
<table>
<thead>
<tr>
<th>Type of AE</th>
<th>Cannabinoid Event Rate</th>
<th>Placebo Event Rate</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>81%</td>
<td>62%</td>
<td>6</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>11%</td>
<td>~3%</td>
<td>14</td>
</tr>
<tr>
<td>Ataxia/Muscle Twitching</td>
<td>30%</td>
<td>11%</td>
<td>6</td>
</tr>
<tr>
<td>Blurred Vision/ Visual Hallucination</td>
<td>6%</td>
<td>0%</td>
<td>17</td>
</tr>
<tr>
<td>Central Nervous System</td>
<td>60%</td>
<td>27%</td>
<td>4</td>
</tr>
<tr>
<td>Disorientation/Confusion</td>
<td>9%</td>
<td>2%</td>
<td>15</td>
</tr>
<tr>
<td>Dissociation/ Acute Psychosis</td>
<td>5%</td>
<td>0%</td>
<td>20</td>
</tr>
<tr>
<td>Disturbance attention/ disconnected thought</td>
<td>17%</td>
<td>2%</td>
<td>7</td>
</tr>
<tr>
<td>Dizziness</td>
<td>32%</td>
<td>11%</td>
<td>5</td>
</tr>
<tr>
<td>Dysphoria</td>
<td>13%</td>
<td>0.3%</td>
<td>8</td>
</tr>
<tr>
<td>Euphoria</td>
<td>15%</td>
<td>2%</td>
<td>9</td>
</tr>
<tr>
<td>&quot;Feeling High&quot;</td>
<td>35%</td>
<td>3%</td>
<td>4</td>
</tr>
<tr>
<td>Hypotension</td>
<td>25%</td>
<td>11%</td>
<td>8</td>
</tr>
<tr>
<td>Impaired Memory</td>
<td>11%</td>
<td>2%</td>
<td>NS (12)**</td>
</tr>
<tr>
<td>Numbness</td>
<td>21%</td>
<td>4%</td>
<td>6</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>17%</td>
<td>5%</td>
<td>9</td>
</tr>
<tr>
<td>Sedation</td>
<td>50%</td>
<td>30%</td>
<td>5</td>
</tr>
<tr>
<td>Speech Disorders</td>
<td>32%</td>
<td>7%</td>
<td>5</td>
</tr>
</tbody>
</table>

**Adverse Events**

- **Bottom-Line:**
  - Versus placebo, medical cannabinoids cause multiple different adverse events in patients, from visual disturbance or hypotension (1 in 3-10) to hallucination or paranoia (1 in 20).
  - Stopping due to adverse effects occurs in 1 in every 8-20 patients.
  - Regardless of the type of medical cannabinoid used, adverse events are common and likely underestimated.
  - Given the extensive harms, potential benefits must be impressive to warrant a trial of therapy.

Summing Up

From CMAJ 2017 (Point 2),...

1. Despite widespread availability, medical cannabinoids are still experimental
2. Most clinical trials use pharmaceutical cannabinoids rather than smoked THC.
3. Although ~40% of strains from licensed producers contain a potency of ≥15% THC, 9.4% is the highest percentage studied.
4. Smoked THC as a mode of delivery is not superior to oromucosal sprays based on current evidence, and may result in dose variability and unforeseen individual responses.

Pain: Recommendations

- Do not prescribe Cannabinoids for chronic pain first or second line.
  - Try at least 3 prescription drugs first.
- The best of worst evidence is for neuropathic
  - Even then, it appears less effect than others.
- For cancer/palliative, may be more reasonable as long term risk gone but effectiveness appears poor.
- Avoid prescribing smoked as long term health effects unknown.

Pharmacotherapy for Treatment of Neuropathic Pain
Outcome: Meaningful Improvement in Pain
Ordered by Efficacy

Opioids*
Venlafaxine
Pregabalin
Gabapentin
Duloxetine
Cannabinoids
Amitriptyline

Legend
Better with Treatment
Better without Treatment
No Meaningful Improvement

*60mg-110mg oral morphine per day
For Spasticity or Nausea/Vomiting

• For Nausea and Vomiting of Chemotherapy, cannabinoids may be reasonable if Refractory.
  – Nabilone is reasonable here.

• For Spasticity (generally of MS), cannabinoids may be a reasonable if Refractory.
  – In this case the best evidence is with Nabiximol.

The End