CANNABIDIOL IN THE TREATMENT OF CHRONIC NEUROPATHIC PAIN IN CANCER PATIENTS

Antonio Vigano, MD, MSc
Attending Physician, Supportive and Palliative Care Division, McGill University Health Centre (MUHC)
Associate Professor, Department of Oncology, McGill University
Director, Cancer Rehabilitation Program (CAREPRO), MUHC
Research Director, Sante' Cannabis.

MASCC/ISOO Annual Meeting on Supportive Care in Cancer
Vienna, June 29th 2018
## Faculty Disclosure

<table>
<thead>
<tr>
<th>Company Name</th>
<th>Honoraria/ Expenses</th>
<th>Consulting/ Advisory Board</th>
<th>Funded Research</th>
<th>Royalties / Patent</th>
<th>Stock Options</th>
<th>Ownership/ Equity Position</th>
<th>Employee</th>
<th>Other (please specify)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetra Bio-Pharma Inc.</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Santé Cannabis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- No, nothing to disclose
- Yes, please specify:
  - Principal investigator two clinical trials sponsored by Tetra Bio-Pharma
  - Contracted Research Director of Santé Cannabis
Neuropathic pain is...

- “Pain caused by a lesion or disease of the somatosensory system” (IASP 2011)
- A consequence of a pathological maladaptive response of the nervous system to ‘damage’ from a wide variety of potential causes
- Hypersensitivity symptoms (burning, tingling, and an electrical sensation) hyposensitivity symptoms (numbness and muscle weakness).

Mücke M et al. Cochrane Database of Systematic Reviews 2018
Neuropathic pain in cancer patients

• 18.7% to 21.4% of people with cancer have cancer-related neuropathic pain, as a result of either the disease or its treatment

• Chemotherapy-induced peripheral neuropathy (CIPN) occurs in 30–40% of patients but incidences can approach 75% with certain regimens

• The aetiologies of Neuropathic cancer pain include direct nerve invasion or nerve compression by the cancer, neural toxicity, chemotherapy, and radiotherapy.


Neuropathic pain is difficult to treat effectively, with only a minority of people experiencing a clinically relevant benefit from any one intervention.
Cannabis-Based Medicines and Neuropathic Pain

• In humans, several studies have demonstrated anti-neuropathic effects of Cannabis Based Medicines (CBMs): plant cannabis, Δ9-tetrahydrocannabinol (THC), or its synthetic analogues nabilone or dronabinol (Pinsger et al., 2006; Skrabek et al., 2008; Ware et al., 2010)

• However, several reports describe these effects as modest, while others have reported negative results (Wade et al., 2004; Johnson et al., 2010)

• Adverse events limit the tolerability and compliance with such treatments (mainly attributed to THC-rich products)
Cannabidiol and neuropathic pain: What is the mechanism?

5-HT1A receptor?
CBD binds as an agonist (potent anti-neuropathic effects with 5-HT1A agonists)

CB1?
Non-selective cannabinoid agonist WIN 55,212-2 reduced an established thermal hyperalgesia and tactile allodynia

CB2?
Activation of CB2 receptors has been shown to suppress established CIPN

Colpaert FC et al. 5-HT(1A) receptor activation: new molecular and neuroadaptive mechanisms of pain relief. Curr Opin Investig Drugs. 2006; 7: 40–47.


CANNABIDIOL (CBD) IN CHRONIC NEUROPATHIC PAIN:
BRIEF SUMMARY OF THE EVIDENCE
Cannabidiol inhibits paclitaxel-induced neuropathic pain through 5-HT$_{1A}$ receptors without diminishing nervous system function or chemotherapy efficacy

CONCLUSIONS AND IMPLICATIONS
Our data suggest that CBD is protective against PAC-induced neurotoxicity mediated in part by the 5-HT$_{1A}$ receptor system. Furthermore, CBD treatment was devoid of conditioned rewarding effects or cognitive impairment and did not attenuate PAC-induced inhibition of breast cancer cell viability. Hence, adjunct treatment with CBD during PAC chemotherapy may be safe and effective in the prevention or attenuation of CIPN.
Cisplatin produced a reduction in mean threshold for paw withdrawal indicative of neuropathy that was attenuated by gabapentin, THC and CBD, but NOT prevented by either cannabinoid.

These data demonstrate that THC and CBD alone can achieve analgesic effects against cisplatin neuropathy.
“CBD may be potent and effective at preventing the development of chemotherapy-induced peripheral neuropathy, and its clinical use may be enhanced by co-administration of low doses of THC.”
NO CLINICAL STUDIES PUBLISHED SO FAR FOR CBD-RICH PRODUCTS AND NEUROPATHIC PAIN IN CANCER PATIENTS

ALL AVAILABLE EVIDENCE IS FOR PRECLINICAL STUDIES ONLY

THC-RICH PRODUCTS…
Cannabis-based medicines for chronic neuropathic pain in adults

Objectives
To assess the efficacy, tolerability, and safety of cannabis-based medicines (CBMs) for conditions with chronic neuropathic pain in adults.

Selection criteria
- Randomised, double-blind controlled trials of chronic neuropathic pain
- Medical cannabis, plant-derived and synthetic cannabinoids against placebo or any other active treatment
- Chronic neuropathic pain in adults, at least two weeks duration and 10 subjects per arm
- 16 studies included, of 2 to 26 weeks duration with 1750 total participants.
RESULTS - EFFICACY

• CBMs probably increased the number of people achieving pain relief of 30% or greater compared to placebo: **moderate quality evidence** (39% versus 33%; NNTB 11 (95% CI 7 to 33).

• Number of people achieving 50% or greater pain relief compared to placebo: **low-quality evidence**
  (21% versus 17%; NNTB 20 (95% CI 11 to 100);

• Patient Global Impression of Change (PGIC): **low-quality evidence**
  (26% versus 21%; NNTB 11 (95% CI 6 to 100);
RESULTS – ADVERSE EVENTS

• CBMs caused increased withdrawal rate due to adverse events (10%) vs placebo (5%); NNTH 25 (95% CI 16 to 50); moderate-quality evidence.
• Insufficient evidence to determine if CBMs increase the frequency of serious adverse events compared with placebo; low-quality evidence.
• CBMs may increase nervous system adverse events compared with placebo (61% versus 29%; NNTH 3 (95% CI 2 to 6); low-quality evidence).
• Psychiatric disorders occurred in 17% of participants using CBMs and in 5% using placebo; NNTH 10 (95% CI 7 to 16); low-quality evidence.
• No information about long-term risks in the studies analysed.
<table>
<thead>
<tr>
<th>Side Effects</th>
<th>Number of patients reporting at least one side effect 935 (N=4265)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severity of side effect reported</strong></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>864</td>
</tr>
<tr>
<td>Moderate</td>
<td>67</td>
</tr>
<tr>
<td>Severe</td>
<td>4</td>
</tr>
<tr>
<td>Serious</td>
<td>0</td>
</tr>
<tr>
<td><strong>THC:CBD ratio of suspected product</strong></td>
<td></td>
</tr>
<tr>
<td>THC rich</td>
<td>51%</td>
</tr>
<tr>
<td>THC:CBD</td>
<td>40%</td>
</tr>
<tr>
<td>CBD-rich</td>
<td>9%</td>
</tr>
<tr>
<td><strong>Route of administration of suspected product</strong></td>
<td></td>
</tr>
<tr>
<td>Oral administration</td>
<td>68%</td>
</tr>
<tr>
<td>Inhalation</td>
<td>30%</td>
</tr>
<tr>
<td>Other</td>
<td>2%</td>
</tr>
</tbody>
</table>
Sante’ Cannabis registry: Safety data -2

Possible Side-Effects expected from the literature (all THC-attributed, unless noted)

<table>
<thead>
<tr>
<th>Most Common</th>
<th>Occasional</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>Postural hypotension</td>
<td>Anxiety, panic attack</td>
</tr>
<tr>
<td>Somnolence</td>
<td>Headache</td>
<td>Depression</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>Dizziness</td>
<td>Cognitive impairment</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Vasodilation</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Euphoria, subjective 'high'</td>
<td>Nausea</td>
<td>Ataxia</td>
</tr>
</tbody>
</table>

**Response individual and Dose-dependent**

THC

CBD
Cannabis in palliative care: current challenges and practical recommendations

Claude Cyr¹, Maria Fernanda Arboleda²,³, Sunil Kumar Aggarwal⁴, Lynda G. Balneaves⁵, Paul Daeninck⁶, Andrée Néron⁷, Erin Prosk³, Antonio Vigano²,³

¹Department of Family Medicine, ²Department of Oncology, McGill University, Montreal, Canada; ³Clinique Santé Cannabis, Montreal, Canada; ⁴Department of Rehabilitation Medicine, University of Washington, Seattle, WA, USA; ⁵College of Nursing, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada; ⁶Department of Family Medicine, Max Rady College of Medicine, University of Manitoba, Winnipeg, Canada; ⁷Pharmacy Department, CHUM (Centre Hospitalier de l’Université de Montréal), Montreal, Canada

Contributions: (I) Conception and design: C Cyr, MF Arboleda, A Vigano, LG Balneaves, E Prosk, SK Aggarwal, P Daeninck; (II) Administrative support: C Cyr, MF Arboleda, E Prosk; (III) Provision of study materials: C Cyr, MF Arboleda, SK Aggarwal; (IV) Collection and assembly of data: C Cyr, MF Arboleda, E Prosk; (V) Data analysis and interpretation: C Cyr, MF Arboleda, SK Aggarwal, LG Balneaves, P Daeninck, E Prosk, A Vigano; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors

Correspondence to: Claude Cyr, MD. Clinique La Cité Médicale de Montréal, 3500 Boulevard Maisonneuve west, suite 1520, Montreal, QC, H3Z 3C1, Canada. Email: claudecyrm@gmail.com.
**Principal Investigator:**
Antonio Vigano, MD, MSc

**Primary objective:**
To evaluate the effect of different doses and ratios of medical cannabis oil to improve uncontrolled chronic cancer and non-cancer pain

**Study duration**
Main study component 18 weeks in duration including the following:
- A 6-week treatment period
- A 12-week open-label extension phase

**Status:** approved by Health Canada and Currently Recruiting Patients
STUDY DESIGN

- Cannabis Oil provided free of charge to participants
- Self-titration with guidance
  - up to max. of 30 High-dose capsules
    (75 mg THC or 600 mg CBD)

THC:CBD (1:1)
- n= 20 cancer pain
- n= 20 non-cancer pain
- LOW DOSE: THC 1mg CBD 1mg
- HIGH DOSE: THC 2.5mg CBD 2.5mg

THC:CBD (1:2)
- n= 20 cancer pain
- n= 20 non-cancer pain
- LOW DOSE: THC 1mg CBD 2mg
- HIGH DOSE: THC 2.5mg CBD 5mg

THC:CBD (0.1:2)
- n= 20 cancer pain
- n= 20 non-cancer pain
- LOW DOSE: THC < 0.1mg CBD 5mg
- HIGH DOSE: THC < 0.2mg CBD 20mg

PLACEBO CAPSULE
- n= 20 cancer pain
- n= 20 non-cancer pain
- LOW DOSE PLACEBO
- HIGH DOSE PLACEBO

2 weeks screening period

CHRONIC PAIN PATIENTS

Excluded
Determine reason to exclude?

Double-blind randomization (n=160)
WHAT ARE WE MEASURING?

- Improvement of uncontrolled cancer and non-cancer chronic pain
- Symptom burden
- Safety and tolerability
- Cognition and mood
- Effect to change amount of concurrent medications

EFFECT OF DIFFERENT DOSES AND RATIOS OF CANNABIS OIL

CURRENTLY RECRUITING PATIENTS
FUTURE DIRECTIONS

Completion of Phase 2 study:
Analysis of cancer-pain group to determine safety/efficacy of each treatment

Limitations:

1. **Sample size:** Not controlled for neuropathic pain, only small sample of cancer-related neuropathic pain patients will be recruited
   • Considering a sub-protocol to investigate larger sample of subjects with cancer-related neuropathic pain

2. **CBD:** CBD-rich capsule contains trace THC and other phytocannabinoids
   • Comparison with synthetic, or pure, isolated CBD to determine relative effectiveness of CBD vs CBD-rich phyto-products