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CANNABIDIOL IN THE TREATMENT OF CHRONIC NEUROPATHIC PAIN IN CANCER PATIENTS

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Research Director, Sante' Cannabis.

MASCC/ISOO Annual Meeting on Supportive Care in Cancer

Vienna, June 29th 2018

Faculty Disclosure

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

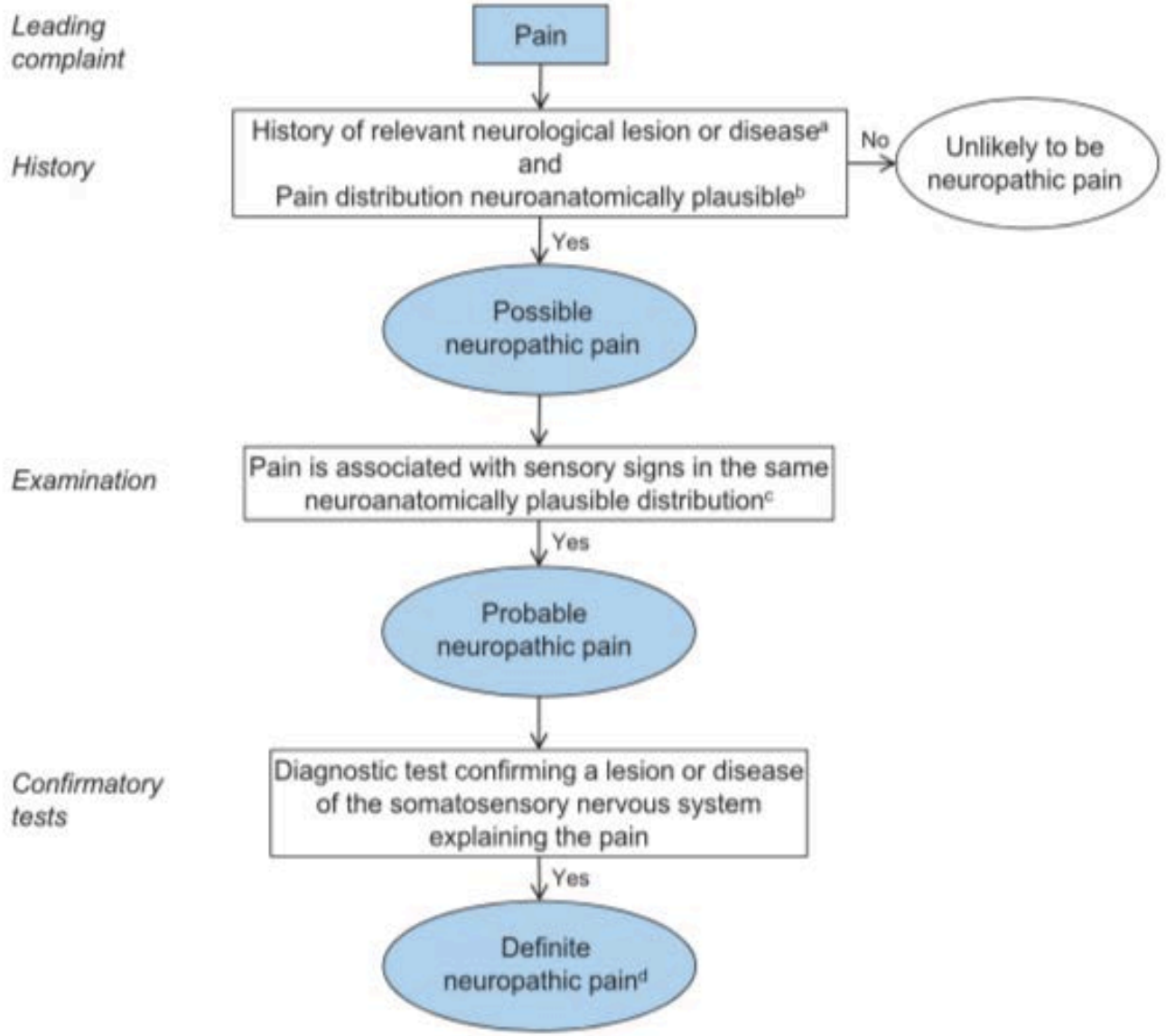
Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties / Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
Tetra Bio-Pharma Inc.			x					
Santé Cannabis		x						

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

Finnerup N, et al. Neuropathic pain: an updated grading system for research and c



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.

Bennet MI, et al. Prevalence and aetiology of neuropathic pain in cancer patients: a systematic review. Pain. 2012; 153: 359-65

Visovsky C, et al. Putting evidence into practice: evidence-based interventions for chemotherapy-induced peripheral neuropathy. 2007 Clin J Oncol Nurs; 11: 901–13.

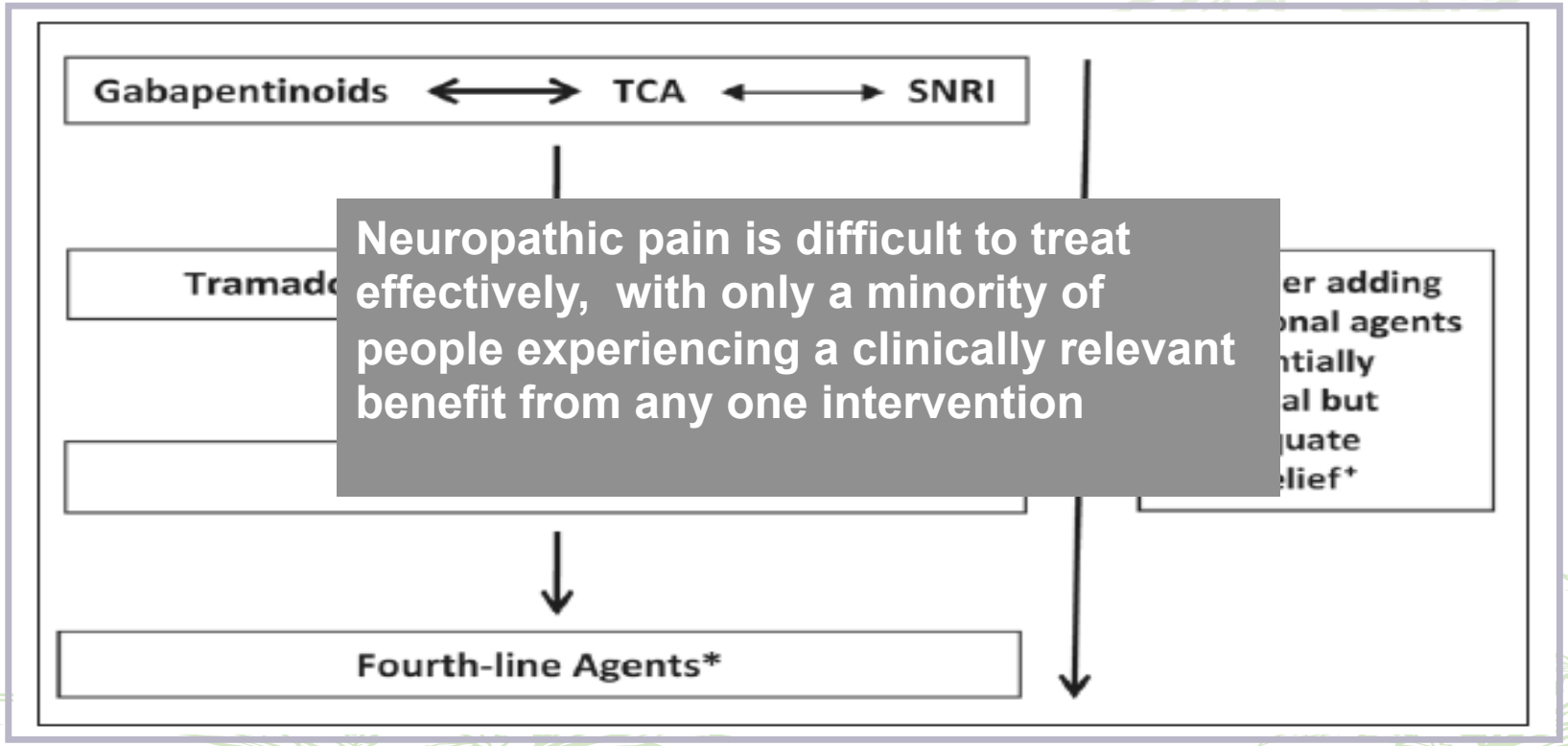
Yoon SY, Oh J. Neuropathic cancer pain: prevalence, pathophysiology, and management. Korean J Intern Med. 2018; doi: 10.3904/kjim.2018.162

Neuropathic pain drug treatment

CONSENSUS STATEMENT

Pharmacological management of chronic neuropathic pain: Revised consensus statement from the Canadian Pain Society

DE Moulin MD, A Boulanger MD, AJ Clark MD, H Clarke MD PhD, T Dao DMD PhD, GA Finley MD, A Furlan MD PhD, I Gilron MD MSc, A Gordon MD, PK Morley-Forster MD, BJ Sessle MDS PhD, P Squire MD, J Stinson RN PhD, P Taenzer PhD, A Velly DDS PhD, MA Ware MD, EL Weinberg MD, OD Williamson MBBS



Neuropathic pain is difficult to treat effectively, with only a minority of people experiencing a clinically relevant benefit from any one intervention

Pain Res Manag Vol 19 No 6 November/December 2014

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

PRECLINICAL STUDIES

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.

Pascual D, et al.. A cannabinoid agonist, WIN 55,212-2, reduces neuropathic nociception induced by paclitaxel in rats. Pain. 2005; 118: 23–34.

Naguib M, et al. MDA7: a novel selective agonist for CB2 receptors that prevents allodynia in rat neuropathic pain models. Br J Pharmacol. 2008; 155: 1104–1116.

CANNABIDIOL (CBD) IN CHRONIC NEUROPATHIC PAIN:
BRIEF SUMMARY OF THE EVIDENCE

British Journal of Pharmacology (2014) **171** 636–645

BJP British Journal of Pharmacology

RESEARCH PAPER

Cannabidiol inhibits paclitaxel-induced neuropathic pain through 5-HT_{1A} receptors without diminishing nervous system function or chemotherapy efficacy

Sara Jane Ward[1], Sean D McAllister[2], Rumi Kawamura[2], Ryuchi Murase[2], Harshini Neelakantan[3] and Ellen A Walker[3]

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.

The non-psychoactive phytocannabinoid cannabidiol (CBD) attenuates pro-inflammatory mediators, T cell infiltration, and thermal sensitivity following spinal cord injury in mice

Hongbo Li[a], Weimin Kong[b], Christina R. Chambers[a], Daohai Yu[c], Doina Ganea[b], Ronald F. Tuma[d], Sara Jane Ward[e,*]

Cellular Immunology 329 (2018) 1–9

”CBD treatment attenuated the development of thermal sensitivity following spinal cord injury and this effect may be related to protection against pathological T-cell invasion.”

Effects of Delta-9-Tetrahydrocannabinol and Cannabidiol on Cisplatin-Induced Neuropathy in Mice

Hannah M. Harris[1], Kenneth J. Sufka[1,2,3], Waseem Gul[3], Mahmoud A. ElSohly[3,4]

Planta Med 2016; 82: 1169–1172

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.

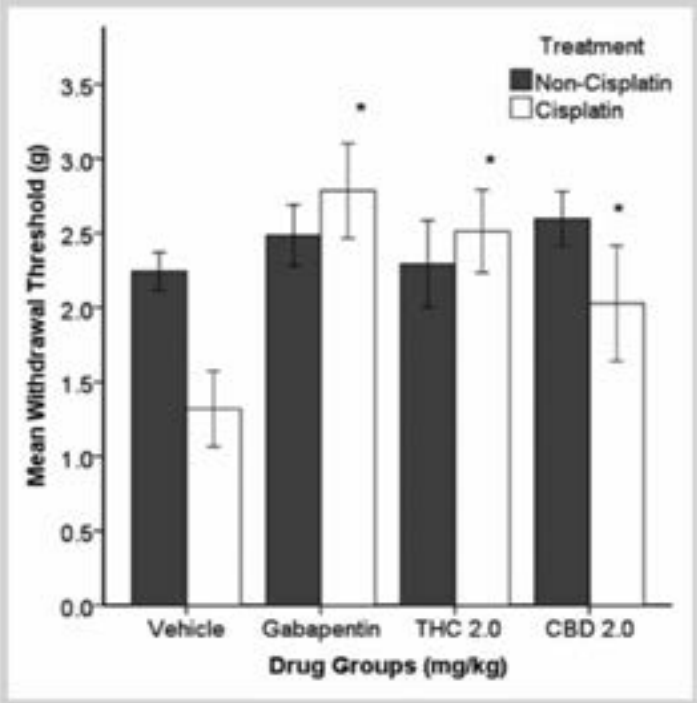


Fig. 2 Drug treatment effects of tactile allodynia on non-cisplatin and cisplatin mice. Values represent the mean paw threshold ± SE (n = 4–5 per group). *Denotes significant attenuation of tactile allodynia compared to the vehicle group ($p < 0.05$).

Single and combined effects of Δ⁹-tetrahydrocannabinol and cannabidiol in a mouse model of chemotherapy-induced neuropathic pain

British Journal of Pharmacology (2017) **174** 2832–2841

Kirsten M King[1,*], Alyssa M Myers[1,*], Ariele J Soroka-Monzo[1], Ronald F Tuma[1], Ronald J Tallarida[1,†], Ellen A Walker[2] and Sara Jane Ward[1]

"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

Citation: Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W. Cannabis-based medicines for chronic neuropathic pain in adults. *Cochrane Database of Systematic Reviews* 2018, Issue 3. Art. No.: CD012182. DOI: 10.1002/14651858.CD012182.pub2.

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.

Santé Cannabis registry: Safety data -1

Side Effects		Number of patients reporting at least one side effect 935 (N=4265)
Severity of side effect reported	Mild	864
	Moderate	67
	Severe	4
	Serious	0
THC:CBD ratio of suspected product		
	THC rich	51%
	THC:CBD	40%
	CBD-rich	9%
Route of administration of suspected product		
	Oral administration	68%
	Inhalation	30%
	Other	2%

Tolerated

Affect daily function, no medical intervention

Require medical intervention, Hospital visit, etc Non-life threatening

Medical intervention, Life-threatening

Sante' Cannabis registry: Safety data -2

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

Most Common

- Sedation
- Somnolence
- Dry Mouth
- Fatigue
- Euphoria, subjective 'high'

THC CBD

Occasional

- Postural hypotension
- Headache

THC CBD

- Dizziness
- Vasodilation
- Nausea

Rare

- Anxiety, panic attack
- Depression
- Cognitive impairment
- Tachycardia
- Ataxia
- Psychosis

Response individual and Dose-dependent

Mini-Review

Cannabis in palliative care: current challenges and practical recommendations

Claude Cyr[1], Maria Fernanda Arboleda[2,3], Sunil Kumar Aggarwal[4], Lynda G. Balneaves[5], Paul Daeninck[6], Andrée Néron[7], Erin Prosk[3], Antonio Vigano[2,3]

[1]Department of Family Medicine, [2]Department of Oncology, McGill University, Montreal, Canada; [3]Clinique Santé Cannabis, Montreal, Canada; [4]Department of Rehabilitation Medicine, University of Washington, Seattle, WA, USA; [5]College of Nursing, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada; [6]Department of Family Medicine, Max Rady College of Medicine, University of Manitoba, Winnipeg, Canada; [7]Pharmacy 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: claudecyrmd@gmail.com.

Journal: Annals of Palliative Medicine Manuscript ID: APM-18-147 doi: 10.21037/apm.2018.06.04

Status: approved by Health Canada and Currently Recruiting Patients

NIH U.S. National Library of Medicine

ClinicalTrials.gov

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Trial record **1 of 26** for: cannabis chronic pain

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Safety and Efficacy of Medical Cannabis Oil in the Treatment of Patients With Chronic Pain

See Contacts and Locations

Verified November 2017 by Santé Cannabis

ClinicalTrials.gov Identifier:
NCT03337503

First Posted: November 9, 2017
Last Update Posted: November 9, 2017

Principal Investigator:
Antonio Vigano, MD, MSc

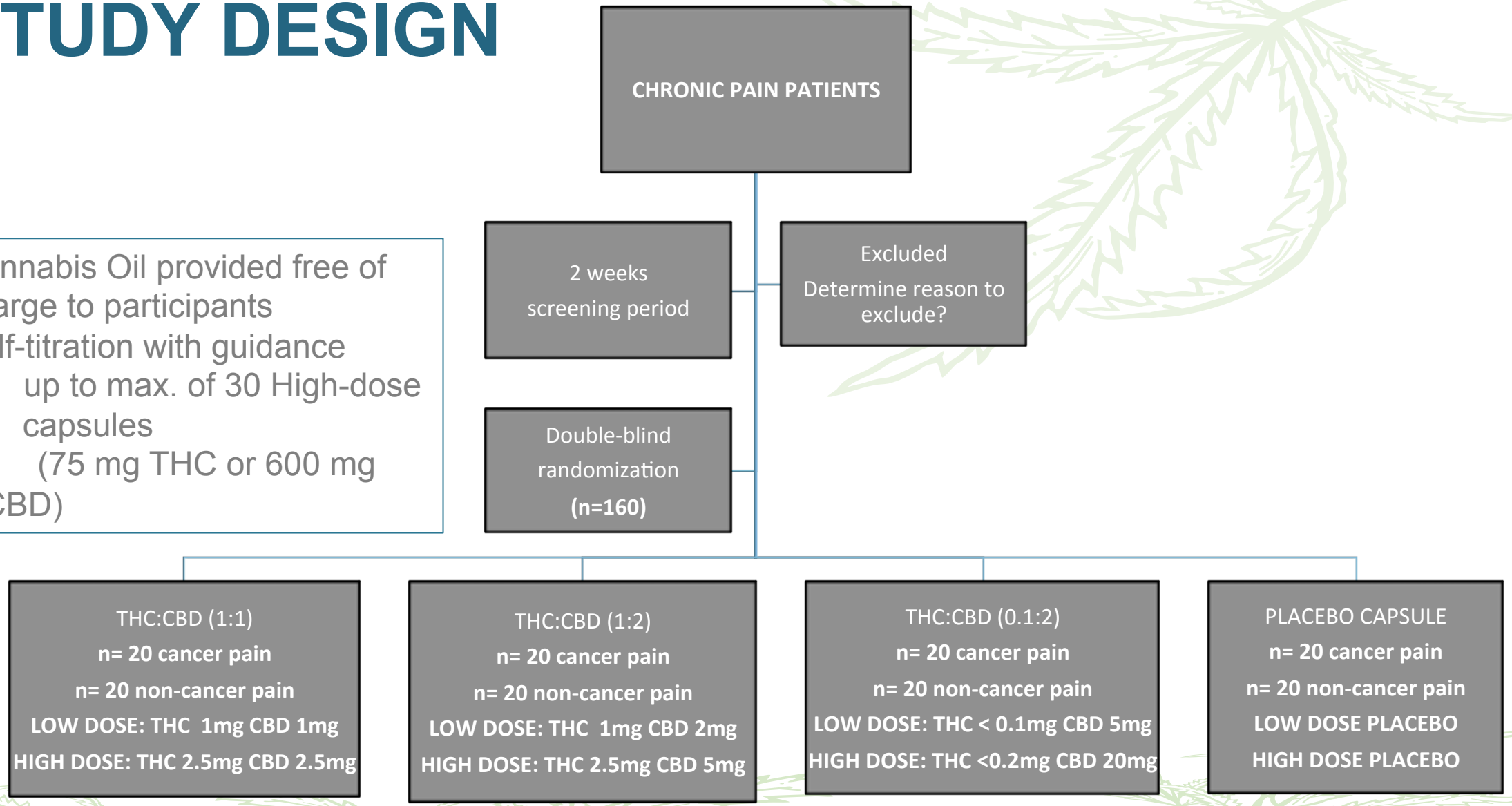
Primary objective:
To evaluate the effect of different doses and ratios of medical cannabis oil to improve uncontrolled chronic cancer and non-cancer pain

Study duration
Main study component 18 weeks in duration including the following:

- ✓ A 6-week treatment period
- ✓ A 12-week open-label extension phase

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)



WHAT ARE WE MEASURING?

Improvement of uncontrolled cancer and non-cancer chronic pain

EFFECT OF DIFFERENT DOSES AND RATIOS OF CANNABIS OIL

- Symptom burden
- Safety and tolerability
- Cognition and mood
- Effect to change amount of concurrent medications

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 effectives of CBD vs CBD-rich phyto-products

Questions and Answers

antonio.vigano@mcgill.ca

Acknowledgments

2019
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MASCC Multinational Association of Supportive Care in Cancer
ISOO International Society of Oral Oncology

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