Choosing and starting medical cannabis: from real world evidence to clinical practice

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- Expert on Medical Cannabis appointed by the Court of Quebec.
- Chair of Scientific Committee and Principal Investigator of the Quebec Cannabis Registry

McGill 51st ANNUAL COURSE IN DRUG THERAPY
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Montréal, Québec

REGISTRE CANNABIS QUÉBEC CANNABIS REGISTRY

Disclosures – Dr. Antonio Vigano

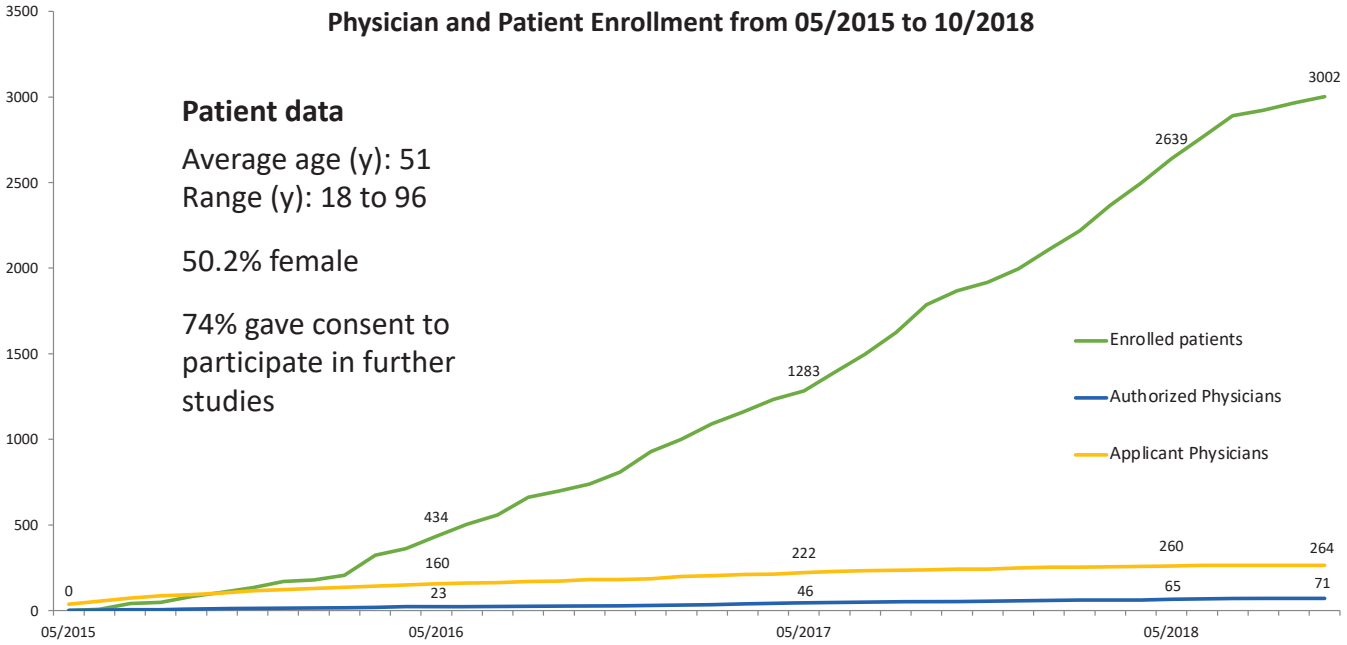
- Advisory Board Member: Spectrum Therapeutics/Canopy Health, Tilray, Tetrabiopharma, Syqe
- Former Research Director of Sante' Cannabis, Montreal, Canada
- Measures taken to mitigate potential sources of bias in this presentation: the information presented is explicitly evidence-based rather than based on recommendations for specific products

REGISTRE CANNABIS QUÉBEC CANNABIS REGISTRY

QUEBEC CANNABIS REGISTRY: A FEW SNAPSHOTS

Enrollment

Physician and Patient Enrollment from 05/2015 to 10/2018



Patient data

Average age (y): 51
Range (y): 18 to 96

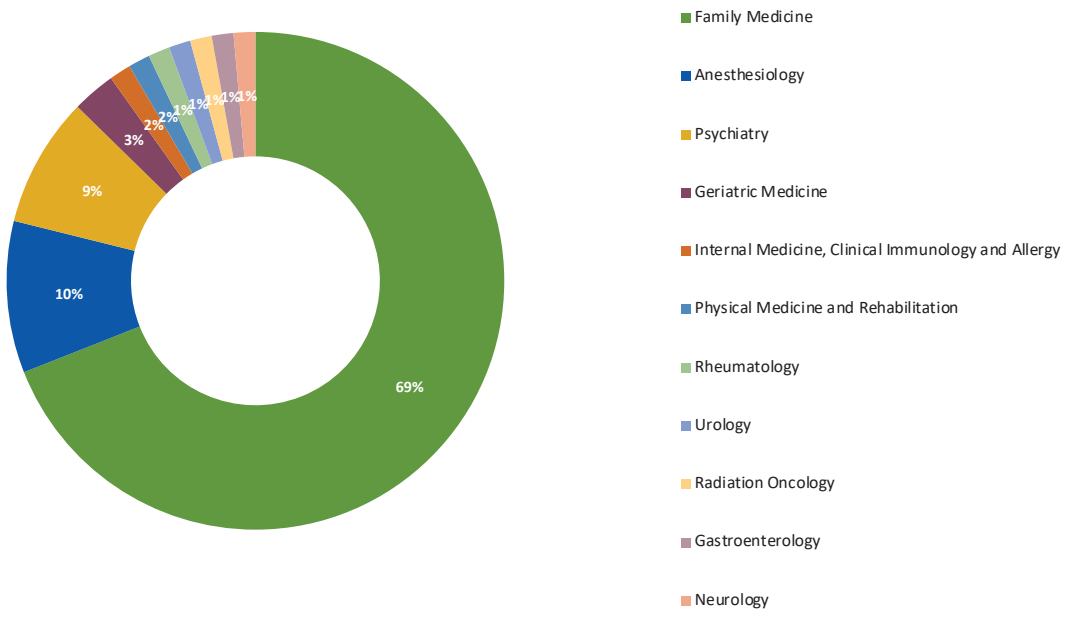
50.2% female

74% gave consent to participate in further studies

Unpublished data

Physician Enrollment

Medical specialty of Authorized Physicians (n=71)



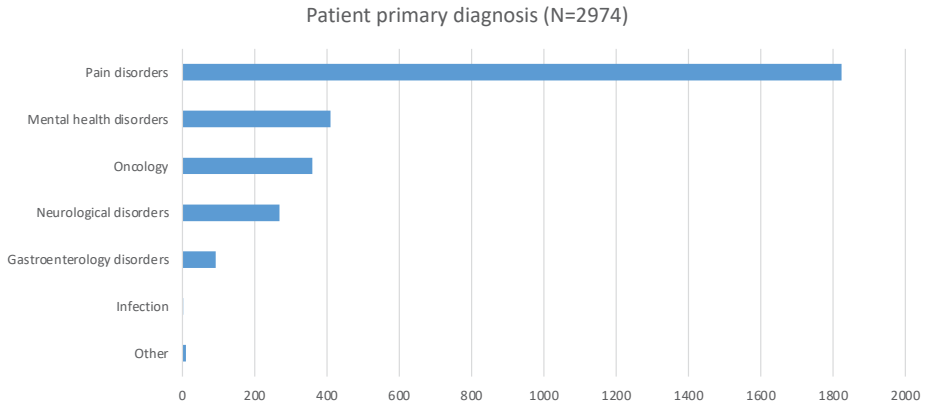
Unpublished data

Study Population

- **Total patients enrolled= 2,991**
- **Number of patients with 12 months follow-up=** 687 (median : 26 weeks)

Baseline Characteristics	Nbr. patients
Mean age (SD) (range)	51.0 (15.7) (18-96)
Proportion female (%)	50.2
Precaution and contraindication to MC (%)	670 (22.4)
History of ADD, OCD, BD	276 (41.2)
History of abuse	271 (40.4)
Personal or family psychosis	71 (10.6)
Unstable cardiopathy	32 (4.8)
Schizophrenia	18 (2.7)
Pregnant/breastfeeding	2 (0.3)
Alcohol use	
Regular	434 (15.0)
Occasional	1,322 (45.7)
Never	1,132 (39.1)
Illicit drug use	207 (6.9)

PATIENT DIAGNOSES

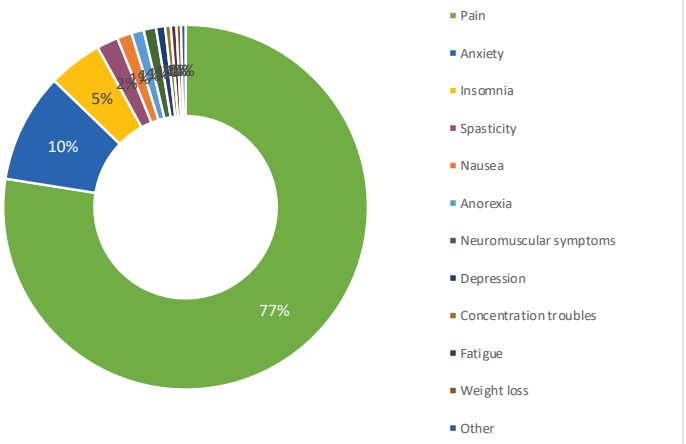


Unpublished data

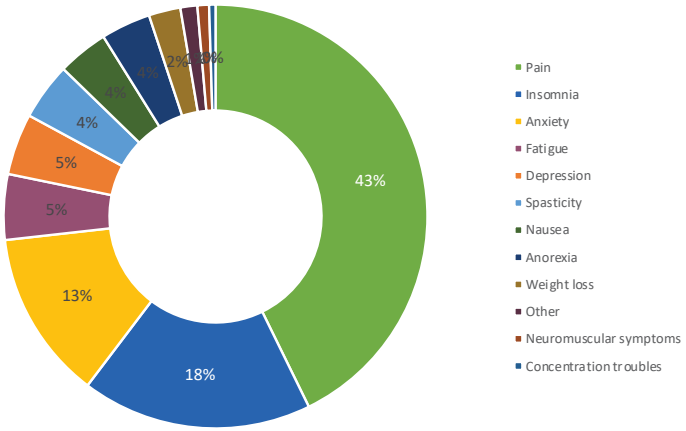
REGISTRE CANNABIS QUÉBEC CANNABIS REGISTRY

Patient indications (baseline)

Primary indication for which MC was prescribed (n=2954)



Indications (all) for which MC was prescribed (n=2954)



Unpublished data

REGISTRE CANNABIS QUÉBEC CANNABIS REGISTRY

FROM REAL WORLD EVIDENCE TO CLINICAL PRACTICE: A CLINICAL CASE

CLINICAL CASE

M.M. Male, 69 year old
- Married, lives with his wife (primary caregiver)

Primary diagnosis:
Non-small-cell lung cancer (NSCLC) since August 2016
Stage 4 (mets to sacrum, right iliac bone and ileum)
Cancer history: CMT, RDT, vertebrectomy - sacrectomy
Current treatment: Pemetrexed and bisphosphonates
Secondary diagnoses:
- Controlled hypertension (diagnosed in 1998)
- Dyslipidemia (2005)

Uncontrolled cancer pain

TREATMENT AGREEMENT WITH THE PATIENT

- All appropriate 1st and 2nd line pharmacological treatments should be tried and or monitored by referring MD
- Cannabinoids should be complementary (not alternative) to conventional treatments
- Agree to continuously review with patient objectives and expectations for medical cannabis treatment
- Confirm patients' commitment to avoid use of Société Québécoise Du Cannabis or street products

1. **What would be the initial assessment of the patient regarding medical cannabis?**

2. Which would be your treatment objectives?

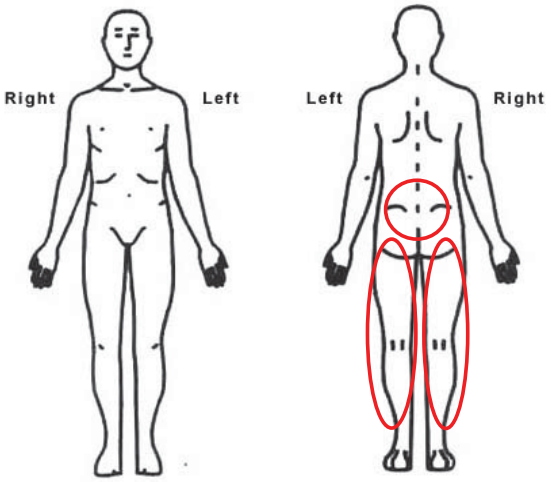
3. What would be your cannabis treatment plan? THC vs CBD? Inhaled versus oral administration? Starting dose? Frequency? Maximum daily allowance in medical document?

4. Monitoring/side effects follow-up?

CLINICAL CASE ASSESSMENT

Primary symptom: CANCER PAIN
Pain characteristics:

- Location(s): lumbar spine, lower limbs
- Chronic, cancer, mixed pain (peripheral neuropathic and nociceptive somatic pain mechanism)
- Current intensity (NRS): 7/10
- Incident pain intensity: 10/10 (stabbing pain mainly when standing up)



CLINICAL CASE ASSESSMENT

Edmonton Symptom Assessment System:
(revised version) (ESAS-R)

Please circle the number that best describes how you feel NOW:

No Pain	0	1	2	3	4	5	6	(7)	8	9	10	Worst Possible Pain
No Tiredness *(Tiredness = lack of energy)*	0	1	2	3	4	(5)	6	7	8	9	10	Worst Possible Tiredness
No Drowsiness *(Drowsiness = feeling sleepy)*	0	1	2	(3)	4	5	6	7	8	9	10	Worst Possible Drowsiness
No Nausea	0	1	2	3	4	5	6	(7)	8	9	10	Worst Possible Nausea
No Lack of Appetite	0	1	2	(3)	4	5	6	7	8	9	10	Worst Possible Lack of Appetite
No Shortness of Breath	0	1	(2)	3	4	5	6	7	8	9	10	Worst Possible Shortness of Breath
No Depression *(Depression = feeling sad)*	0	1	2	(3)	4	5	6	7	8	9	10	Worst Possible Depression
No Anxiety *(Anxiety = feeling nervous)*	0	1	2	3	4	5	(6)	7	8	9	10	Worst Possible Anxiety
Best Wellbeing *(Wellbeing = how you feel overall)*	0	1	2	3	4	5	6	(7)	8	9	10	Worst Possible Wellbeing
No _____ Other Problem *(for example constipation)*	0	1	2	3	4	(5)	6	7	8	9	10	Worst Possible _____

Other symptoms experienced

- **Insomnia**: poor quality of sleep, difficulty falling and staying asleep
- **Fatigue**
- **Nausea**
- **Anxiety**

PATIENT ASSESSMENT - CLINICAL

- **Physiological Status**
  - Age, frailty, renal or liver failure
- **Functional Status**
  - Activities of daily life, sleep quality, work
- **Mental Status**
  - Mood/anxiety, psychosocial issues, abuse potential
- **Medication Status**
  - Current (type, dose, effectiveness, side-effects
  - Treatment history, sufficient trial of 1st , 2nd line conventional medications

CLINICAL CASE ASSESSMENT

Functional status:

- Moderate limitation for daily life activities
- ECOG PS 2/4

CLINICAL CASE ASSESSMENT

Emotional status:

- Frustration, anger, irritability
- Good family and/or friend support

CLINICAL CASE ASSESSMENT

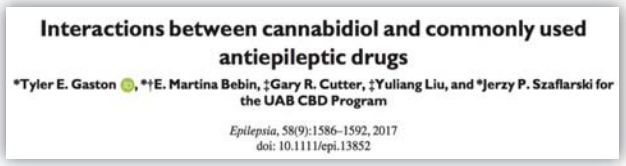
Allergies: Penicillin (rash)

Current Medications:

- Methadone 7.5 mg PO BID; Breakthrough dose: 2.5 mg Q 4h PRN
- Celebrex 100 mg BID
- Pregabalin 300 mg PO BID
- Acetaminophen 1 g PO TID

Potential drug-drug interaction?

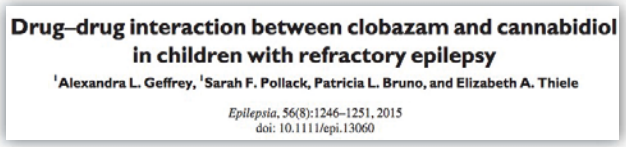
- Can be both at the pharmacokinetic and pharmacodynamic levels.



Interactions between cannabidiol and commonly used antiepileptic drugs

*Tyler E. Gaston, *†E. Martina Bebin, ‡Gary R. Cutter, ‡Yuliang Liu, and *Jerzy P. Szaflarski for the UAB CBD Program

Epilepsia, 58(9):1586–1592, 2017
doi: 10.1111/epi.13852



Drug–drug interaction between clobazam and cannabidiol in children with refractory epilepsy

[1]Alexandra L. Geffrey, [1]Sarah F. Pollack, Patricia L. Bruno, and Elizabeth A. Thiele

Epilepsia, 56(8):1246–1251, 2015
doi: 10.1111/epi.13060

- Evidence for potential interaction between pharmaceutical CBD formulations (5–50 mg/kg/day) and antiepileptic drugs in adults and children
- Monitoring levels of clobazam and N-desmethylclobazam has been recommended

Gaston, T.E., Bebin, E.M., Cutter, G.R., Liu, Y., Szaflarski, J.P. and (2017), Interactions between cannabidiol and commonly used antiepileptic drugs. Epilepsia, 58: 1586-1592. https://doi.org/10.1111/epi.13852

Geffrey, A.L., Pollack, S.F., Bruno, P.L. and Thiele, E.A. (2015), Drug–drug interaction between clobazam and cannabidiol in children with refractory epilepsy. Epilepsia, 56: 1246-1251

cancers

MDPI

Article

Cannabis Consumption Used by Cancer Patients during Immunotherapy Correlates with Poor Clinical Outcome

Gil Bar-Sela [1,2,*], Idan Cohen [1], Salvatore Campisi-Pinto [3], Gil M. Lewitus [3], Lanuel Oz-Ari [2], Ayellet Jehassi [4], Avivit Peer [5], Ilit Turgeman [5], Olga Vernicova [1], Paula Berman [3], Mira Wollner [5], Mor Moskovitz [5] and David Meiri [3,*]

Cancers **2020**, *12*, 2447; doi:10.3390/cancers12092447

34 cancer patients using cannabis while being treated with immune checkpoint inhibitors, as compared to 68 treated with immunotherapy alone showed:
↓ time to tumor progression
↓ overall survival
↓ immune-related adverse events

Bar-Sela, G.; Cohen, I.; Campisi-Pinto, S.; Lewitus, G.M.; Oz-Ari, L.; Jehassi, A.; Peer, A.; Turgeman, I.; Vernicova, O.; Berman, P.; Wollner, M.; Moskovitz, M.; Meiri, D. Cannabis Consumption Used by Cancer Patients during Immunotherapy Correlates with Poor Clinical Outcome. *Cancers* **2020**, *12*, 2447. https://doi.org/10.3390/cancers12092447

CONSIDER…

Medical assessment:

Past History

- Has the patient been prescribed cannabinoids?
- Has the patient used cannabis?

Precautions

- Confirm relative and absolute contraindications
- Review potential adverse effects and risk factors

CLINICAL CASE ASSESSMENT

Recreational use of other substances:

Alcohol: social
Cigarettes: quit 15 years ago. Used to smoke 1 pack per day
Other drugs: Never
History of or potential for medication abuse or dependence: No

CLINICAL CASE ASSESSMENT

Previous use of cannabis:
Current street dried cannabis use since last summer
Smokes 1-2 joints per day (0.5-1 gram per day)
Has tried edibles (cookies)

Beneficial/therapeutic effects:

- ✓ Improved mood and stress
- ✓ Reduced pain
- ✓ Less nausea

Side effects: None

RELATIVE AND ABSOLUTE CONTRAINDICATIONS

- **Unstable or uncontrolled cardiac conditions**
  - Ischemia, arrhythmia, uncontrolled hypertension (avoid THC)
- Severe liver or renal dysfunction? (reduce THC and CBD dose)
- Severe pulmonary disease (avoid inhaled cannabis)
- **Personal history of psychosis, schizophrenia, bipolar disorders (avoid THC)**
- **Allergy or hypersensitivity to cannabinoids**
- **Patients less than 18 years of age (THC should not be prescribed or limited as much as possible)**

NB: Psychiatric and cardiovascular contraindications relate primarily to THC, and not to the non-intoxicating cannabinoids like CBD.

Information for Health Care Professionals: Cannabis (marihuana, marijuana) and the cannabinoids [Health Canada, 2013] [Internet]. aem. 2013 [cited 2017 Oct 24]. Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-use-marijuana/information-medical-practitioners/information-health-care-professionals-cannabis-marihuana-marijuana-cannabinoids.html

PRECAUTIONS

- Respiratory conditions (asthma, COPD) should avoid smoked cannabis
- **Activities requiring coordination**
  - Driving, Reduced mobility, Vertigo, dizziness
- Known hypersenstivity to THC
- **Hx of substance dependence or abuse**
- **Abuse potential (risk of Cannabis Use Disorder)**
- **Possible interactions with other medications and ETOH (pharmacokinetics and pharmacodynamics aspects)**
- Patients who are pregnant or breastfeeding
- Patients under 25 years of age

Information for Health Care Professionals: Cannabis (marihuana, marijuana) and the cannabinoids [Health Canada, 2013] [Internet]. aem. 2013 [cited 2017 Oct 24]. Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-use-marijuana/information-medical-practitioners/information-health-care-professionals-cannabis-marihuana-marijuana-cannabinoids.html

CLINICAL CASE DISCUSSION…

1. What would be your initial assessment of the patient regarding medical cannabis?
2. **Which would be the treatment objectives?**
3. What would be your cannabis treatment plan? THC vs CBD? Inhaled versus oral administration? Starting dose? Frequency? Maximum daily allowance in medical document?
4. Monitoring/side effects follow-up?

TREATMENT OBJECTIVES

<u>"MC not a miracle but different degrees of success for" :</u>

- Symptom control
  - **Pain, anxiety**, nausea, anorexia, mood, **insomnia**, etc.
- **Functional improvement**
- Weight gain or control
- Potential reduction of medication use
- Health related quality of life (HRQoL) vs. disease modification in cancer patient

CLINICAL CASE DISCUSSION…

1. What would be your initial assessment of the patient regarding medical cannabis?
2. Which would be your treatment objectives?
3. **What would be your cannabis treatment plan? THC vs CBD? Inhaled versus oral administration? Starting dose? Frequency? Maximum daily allowance in medical document?**
4. Monitoring/side effects follow-up?

MEDICAL CANNABIS FORMULATIONS

Dried cannabis

% w/w THC : CBD

- THC-rich
- THC:CBD
- CBD-rich

Cannabis oil (also via spray)

- mg/mL (THC : CBD)

Cannabis oil capsules

- mg (THC : CBD) per capsule

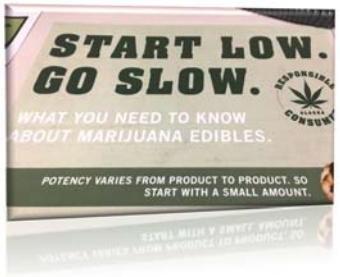
DOSING AND STRAIN SELECTION

- Type of preparation (oils vs inhalation): similar to opioid approach, depends on symptom type and behavior
- Role of synthetic cannabinoids: Nabilone (pain at night, insomnia, harm reduction) and Sativex (incidental pain, appetite stimulation, if private insurance coverage)
- Chemovars (THC:CBD ratio and potency): previous experiences, type of symptom, emotional component?, harm reduction?
- Cultivars (*Indica:* relaxation, stress relief, and overall sense of serenity vs. *Sativa:* uplifting and energetic) primarily during the day or at night?

McCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. Eur J Intern Med 2018
Available from: https://www.medicaljane.com/2013/07/25/cannabis-indica-as-explained-by-medical-jane/
Available from: https://www.medicaljane.com/2013/07/22/cannabis-sativa-as-explained-by-medical-jane

DOSING AND STRAIN SELECTION

- Exact dose: no magic recipe, process to find "sweet spot"
- Naïve patient: normally start with THC 1-2.5 mg and CBD 5 mg QHS (for indica products, qAM for sativa ones) and then escalate the dose



Naïve vs Regular cannabis user?
Is it different?

Consensus Recommendations on Dosing and Administration of Medical Cannabis to Treat Chronic Pain: Results of a Modified Delphi Process Arun Bhaskar, Alan Bell, Michael Boivin, Wellington Briques; Matthew Brown; Hance Clarke; Claude Cyr; Elon Eisenberg; Ricardo Ferreira de Oliveira Silva; Eva Frohlich; Peter Georgius; Malcolm Hogg; Tina Ingrid Horsted; Caroline A. MacCallum; Kirsten R. Müller-Vahl; Colleen O'Connell; Robert Sealey; Marc Seibolt; Aaron Sihota; Brennan Smith; Dustin Sulak; Antonio Vigano; Dwight E. Moulin, Journal of Cannabis Research 2021 (in press)

DIFFERENCE BETWEEN INHALED AND ORAL ADMINISTRATION

- Oral ingestion is convenient but unpredictable.
- Inhalation is often portrayed as a controversial route but can the preferred method for many patients as a quicker titration is possible.

Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. Clin Pharmacokinet 2003; 42:327–60

Borgelt LM et al. The pharmacologic and clinical effects of medical cannabis. Pharmacotherapy 2013; 33:195–209

DIFFERENCE BETWEEN INHALED AND ORAL ADMINISTRATION

	Inhaled	**Oral**
Onset of action	fast acting	delayed onset of action
Ease of titration	easier to titrate	cautious titration
Active metabolites	Δ9 THC > 11-OH THC	Δ9 THC < 11-OH THC
Psychoactivity	+++	+++
Ease of microdosing	more challenging with higher potency strains	more precise with standardized preparations (oils, tinctures)
First onset of effects	3-10 minutes	60 - 90 minutes
Peak concentration	3-10 minutes	1 - 2 hours
Peak psychoactive effects	15 minutes	3 hours
Peak cognitive effects [86,87]	15 minutes	5 hours
Duration of effects	2 - 4 hours	8 - 12 hours or more
Dosing frequency	5 - 6/day	1 - 3/day
Suggested symptom management	Nausea, appetite stimulation, sleep induction, seizure or spontaneous neuropathic pain episodes	Persistent symptoms such as chronic pain, sleep maintenance, spasticity

SO THE IDEAL TREATMENT PLAN FOR THE PATIENT (CLINICAL CASE) WOULD BE…

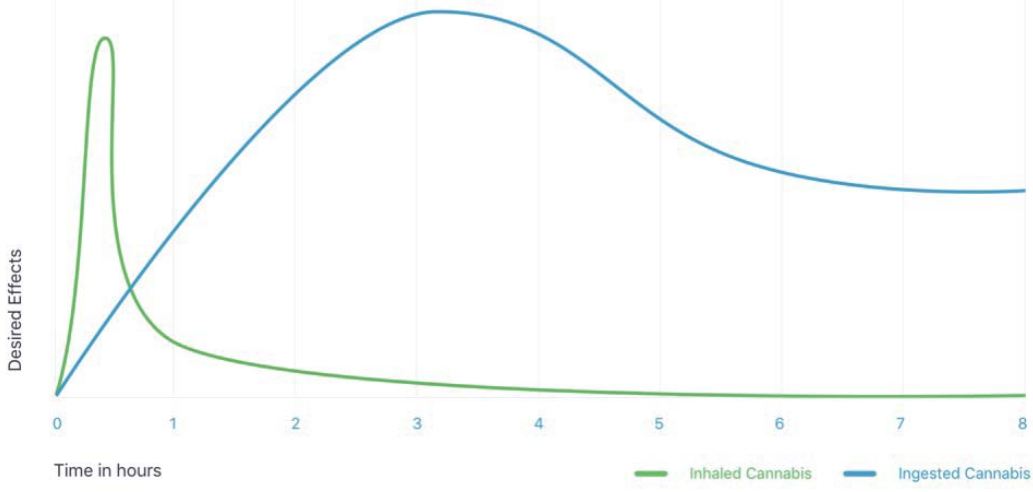
1. For this patient consider harm reduction (prevent tolerance/dependence)

2. Start with a THC/CBD 1:1 Product
   THC potential impact over pain, insomnia, nausea
   CBD potential impact over pain (anti-inflammatory effect) and anxiety mainly + harm reduction

3. Choose a THC/CBD 1:1 oil for his background pain ("long acting effect"), sleep maintenance, anxiety (i.e. 0.2 ml QHS and then titrate BID, TID accordingly)

4. Choose a THC-rich or THC/CBD 1:1 inhaled dried cannabis (ideally using vaporizer) for breakthrough pain ("short acting effect"), sleep induction, improve nausea (i.e. 1-2 inhalations and titrate according to symptoms)

TREATMENT PLAN
CLINICAL CASE



TREATMENT PLAN CLINICAL CASE

5. Still room for NABILONE! (i.e. 0.25-0.5 mg PO QHS) for insomnia, nausea and pain

Increase dose slowly according to therapeutic benefit and side effects

Syrup in some cases will be easier to titrate (i.e. 0.1 mg per ml)

6. Do not forget the **therapeutic contract** from the get go

CLINICAL CASE DISCUSSION…

1. What would be your initial assessment of the patient regarding medical cannabis?

2. Which would be your treatment objectives?

3. What would be your cannabis treatment plan? THC vs CBD? Inhaled versus oral administration? Starting dose? Frequency? Maximum daily allowance in the medical document?

4. **Monitoring side effects/follow-up?**

MONITORING SIDE EFFECTS (FIRST, DO NOT HARM!)

Clinically-Observed Side-Effects
Can often be avoided with careful titration and close follow-up (Start low, go up slow, keep low)

Most Common	Occasional	Rare
• **Sedation** • **Somnolence** • **Dry Mouth**	• Euphoria • Postural hypotension • Dizziness • Vasodilation • Headache • Nausea • Fatigue • Tachycardia	• Anxiety, panic attack • Depression • Cognitive impairment • Ataxia • Psychosis

McCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. Eur J Intern Med 2018

REGISTRE CANNABIS QUÉBEC CANNABIS REGISTRY

Adverse events (AE)/12 months

- 79 AE reports in 77 pts (2.6%)
  - 63 non serious
  - 15 serious
  - 1 death
- Most commons AE
  - Non serious: dizziness (5.7%), nausea (5.7%), somnolence (5.1%)
  - Serious: myocardial infarction (2 cases, 9.1%)
- Causality assessed for 11/15 serious AE
  - *Possible:* 2 (pneumonia, increased intraocular pressure)
  - *Probable*: 8 (tachycardia, loss of consciousness, dry mouth, loss of confidence, hot flushes, asthma, rash, pruritus)
  - *Certain*: 1 (suicidal ideation)
- Death case for myocardial infarction assessed as *unlikely*

Unpublished data

Notes d'évolution

AMBULATORY SERVICES
Progress notes

Admission-Visite/Visit: 2018-03-06 13:30
Site: RVH **Emplacement**/Location:

Nom de la clinique
Name of clinic Supportive and Palliative Care Clinic - Medical cannabis

Date 2018-03-06 AA/YY-MM-JJ

ASSEMENT for medical cannabis - Follow-up visit

69 yo, Stage 4 NSCLCa diagnosed in August 2016, no futer systemic treatment or active oncology follow-up. Cauda equina involment secondary to sacral mets.

Current Treatment : Aphria capilano 0.3 ml (2.8 mg THC) PO TID oil and Nabilone syrup.

Followed for pain, nausea, anxiety and sleep.

Clinical impression: overall improvement in pain control and sleep quality despite underdosing nabilone

- ***New symptoms :no***
- ***Side effects :no***
- ***Changes in treatment plan :not for now***

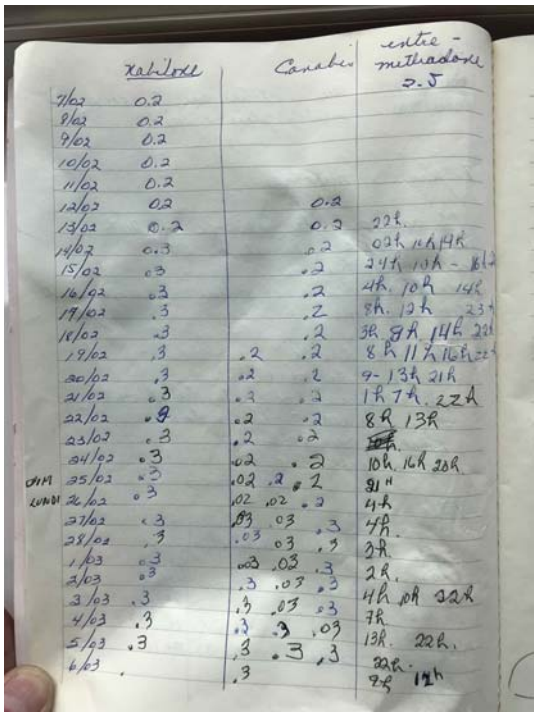
Nursing notes : Patient accompanied by wife and brother in law, in a wheelchair

Upcoming cannabinoid treatment plan : gradual titration upward of both nabilone (from 0.2 mg at hs) and cannabis oil from (2.8 mg of THC TID)

Follow-up in one month.

Team : Bacis, Christodoupoulos, Vigano

Opioid sparing effect….



Notes d'évolution

AMBULATORY SERVICES
Progress notes

SAINT-LAMBERT, PQ J4P 1A9
Admission-Visite/Visit: 2018-04-03 15:30
Site: RVH **Emplacement**/Location:

Nom de la clinique
Name of clinic Supportive and Palliative Care Clinic - Cannabis Pilot Project

Date 2018-04-03 AA/YY-MM-JJ

Assessment for Medical Cannabis – Follow-up Visit (2 month Follow-Up visit)

69 year old, male, Stage 4 NSCLC diagnosed in August 2016. No current oncologic treatment. Cauda equine involvement secondary to sacral mets.

Today patient comes with his wife and brother in law. He reports to be feeling very nauseaous.

Patient is currently taking Nabilone Syrup 0.5 mg (5 ml) PO QHS and CAPILANO cannabis oil (THC/CBD 1:1) 0.4 ml TID at 6:00 am, 2:00pm and 10:00 pm (3.7 mg THC / 5.4 mg CBD per dose).

Treatment objectives:

1. **Pain:** he reports improvement of lower limb pain with cannabis oil dose. Still stabbing pain in his lumbar area related to previous spine surgery
2. **Insomnia:** patient reports improvement of sleep quality and quantity after increasing nabilone dose to 0.5 mg QHS
3. **Nausea:** Still affecting him mainly early in the morning. Cannabis oil is not helping at all.
4. **Lack of appetite:** patient reports that lack of appetite has not improved with cannabis

Pressure sore has improved with CLSC nurse treatment at home.

Side effects: No

New symptoms: No

New plan:

1. Increase Nabilone: 1-2 ml AM and keep 5 ml QHS
2. Continue CAPILANO 0.4 ml TID
3. Recommended startign THC-rich Dried Cannabis Bienville from APHRIA (Inhaled) with vaporizer (PAX 2) for immediate effect for nausea and lack of appetite with inhaled route of administration. Start with 1-2 inhalations according to symptoms and slowly titrate up the number of inhlations
4. Metonia 5 mg PO Q 4 hours regular while awake for nausea
5. Follow-up in 1 month

Team:

Christodoupoulus, Arboleda, Vigano

Take home messages

- Pain, insomnia and anxiety are the most frequent indications for medical cannabis in Quebec
- Medical cannabis is complementary not alternative to conventional tx's
- Structured approach to patient assessment and management is necessary for medicinal cannabis
- This approach makes also possible real world data research, which is a source of evidence for the safety and effectiveness of medical cannabis

REGISTRE CANNABIS QUÉBEC CANNABIS REGISTRY

Centre universitaire de santé McGill — McGill University Health Centre

Thank you!

antonio.vigano@mcgill.ca

www.registrecannabisquebec.com