



Position Statement on the Use of Medical Cannabis for the Treatment of Epilepsy in Canada

By the Canadian League Against Epilepsy Medical Therapeutics Committee, Invited Experts and Collaborators

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ABSTRACT: In Canada, recreational use of cannabis was legalized in October 2018. This policy change along with recent publications evaluating the efficacy of cannabis for the medical treatment of epilepsy and media awareness about its use have increased the public interest about this agent. The Canadian League Against Epilepsy Medical Therapeutics Committee, along with a multidisciplinary group of experts and Canadian Epilepsy Alliance representatives, has developed a position statement about the use of medical cannabis for epilepsy. This article addresses the current Canadian legal framework, recent publications about its efficacy and safety profile, and our understanding of the clinical issues that should be considered when contemplating cannabis use for medical purposes.

RÉSUMÉ: Énoncé de position quant à l'utilisation du cannabis médical dans le traitement de l'épilepsie. L'utilisation du cannabis à des fins récréatives a été légalisée au Canada en octobre 2018. Parallèlement à ce changement de politique, de récentes publication visant à évaluer l'efficacité du cannabis dans le traitement de l'épilepsie, de même qu'une sensibilisation médiatique accrue en ce qui concerne son utilisation, ont eu pour effet d'augmenter l'intérêt du grand public à son égard. Le Comité médical thérapeutique de la Ligue canadienne contre l'épilepsie (LCCE), de concert avec un groupe multidisciplinaire d'experts et des représentants de l'Alliance canadienne de l'épilepsie, a ainsi élaboré un énoncé de position en ce qui regarde

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l'utilisation du cannabis médical dans le traitement de l'épilepsie. Cet article entend donc aborder le cadre légal qui prévaut actuellement au Canada et examiner de récentes publications s'étant penchées sur le profil sécuritaire et sur l'efficacité du cannabis. De plus, nous voulons apporter un éclairage au sujet des aspects cliniques dont il faudrait tenir compte au moment d'envisager l'utilisation du cannabis à des fins médicales.

Keywords: Cannabinoids, CLAE, Statement, CBD, Epilepsy, Use

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INTRODUCTION

The marijuana plant, *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis* (for some considered a subspecies of *C. sativa*), contains more than 500 chemical species with more than 100 different phytocannabinoid (i.e. derived from the plant) compounds.¹ Two of these compounds – Δ -9-tetrahydrocannabinol (THC) and cannabidiol (CBD) – have generated the most interest in terms of their putative effectiveness as an anti-seizure agent. Most of the psychoactive properties of marijuana are mediated by THC. CBD is the most abundant nonpsychoactive cannabinoid in the marijuana plant. As a plant-derived oral solution, both CBD and THC have shown some anti-seizure effects in a number of laboratory models of seizures and epilepsy^{2,3} and in both open-label and randomized control trials (RCTs) in Dravet syndrome and Lennox-Gastaut syndrome.^{4–10} However, other studies have failed to replicate THC anti-seizure effect and a few showed pro-convulsant effects.³ There is some evidence that THC (recreational use) causes cognitive impairment and chronic psychiatric disturbances in adolescents and adults. For these reasons, the focus of most research and clinical use has been on another cannabinoid, namely, CBD.³

The potential beneficial effects of nonpurified medical marijuana with a high CBD-THC ratio has motivated discussions in recent years, leading to an increased demand for the high CBD and low THC cannabis herbal extract oil (CBD-THC oil) for both adults and children with drug-resistant epilepsy. This increased demand and specific issues about the use of cannabinoids in Canada¹¹ has prompted the Canadian League Against Epilepsy (CLAE) to develop a formal statement about its current position regarding the use of CBD-THC, particularly the oil formulation, for epilepsy. As the Canadian government uses the term cannabis to refer to regulated marijuana (for recreational or medical use), for the purpose of this statement, the term cannabis will refer to both regulated marijuana and its derivatives within the framework of federal, provincial, and territorial regulations for recreational or medical purpose. We have purposely avoided the term “hemp” as it is loosely used by the media, creating some confusion. According to the Industrial Hemp Regulations (SOR/2018-145, <https://laws-lois.justice.gc.ca/PDF/SOR-2018-145.pdf>), “industrial hemp” means a cannabis plant or any part of that plant in which the concentration of THC is 0.3% or less in the flowering heads and leaves. However, some commercially available high CBD-THC ratio hemp oils may not meet this specific legal criterion.

This position statement is based on a literature search, expert opinion, and consumer (epilepsy) representatives' input with final approval by the CLAE Board of Directors and Executive Committee; however, it may not necessarily represent the opinion of all CLAE members. It addresses three key elements: (1) the current legal framework for cannabis medical use, (2) the

published evidence for the anti-seizure efficacy of CBD-derived products, and (3) our current understanding of its utilization, doses, and safety with regard to both the short- and the long-term effects of cannabis use for medical purposes.

LEGAL CONSIDERATIONS OF CANNABIS FOR MEDICAL USE

The use of recreational cannabis in adults (defined as 18-year-old or older) was legalized in Canada on October 17, 2018. As per the Department of Justice website (<https://www.justice.gc.ca/eng/cj-jp/cannabis/>) and subject to provincial or territorial restrictions, the current legal framework (legalization and regulation) for cannabis use in adults is addressed in the Cannabis Act (S.C. 2018, c.16) and summarized in Table 1.

The Government of Canada has several online resources for the general public. A detailed explanation on how to access cannabis for medical purposes from a licensed producer can be found at <https://www.canada.ca/en/health-canada/services/getting-cannabis-from-licensed-producer/accessing-from-licensed-producer.html>. General information about the consumption of cannabis can be accessed at <https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/licensed-producers/consumer-information-cannabis.html>.

The process to access cannabis and its derivatives for medical purposes for Canadian patients was recently summarized by the Canadian Pediatric Society (CPS)¹² and by the Government of Canada (<https://www.canada.ca/en/health-canada/services/publications/drugs-health-products/understanding-new-access-to-cannabis-for-medical-purposes-regulations.html>). Cannabis for medical use was sanctioned by Health Canada in 2001. Since then multiple revisions occurred. The most up-to-date version of the Access to Cannabis for Medical Purposes Regulations (ACMPR, last amended on January 15, 2019) is available at <https://laws-lois.justice.gc.ca/PDF/SOR-2018-144.pdf> under Part 14.¹³

The process to obtain cannabis for medical purposes is summarized in Table 2.

Despite the legalization of the consumption of medical cannabis in Canada, there are no regulations regarding when it is appropriate to use medical cannabis. This leaves the final decision to the discretion of physicians in consultation with the person living with epilepsy and/or their care partners/parents. Table 3 includes a list of resources for physicians practicing in different provinces or territories in Canada with links to access provincial regulatory policies. These regulations do not apply to out-of-country utilization where the use of cannabis could be considered a criminal offense.

Of note, the Canadian Medical Association submitted a proposal to Health Canada to unify the cannabis regulations system for medical and recreational cannabis. If this were to happen, the maximum monthly cannabis supply allowed may

Table 1: Summary of regulations instituted in the Cannabis Act (S.C. 2018, c.16)***An adult (18 years old or older) is expected to:***

- Possess no more than 30 g of legal cannabis, dried or equivalent nondried form in public.
- Share no more than 30 g of legal cannabis with other adults
- Buy dried or fresh cannabis and cannabis oil from a provincially licensed retailer
- Be able to purchase cannabis online from federally licensed producers in provinces and territories without a regulated retail framework
- Grow, from licensed seed or seedlings, up to four cannabis plants per residence for personal use
- Make cannabis products, such as food and drinks, at home as long as organic solvents are not used to create concentrated products.
- Equivalents for 1 g of dried cannabis are the following:
 - 5 g of fresh cannabis
 - 15 g of edible product
 - 70 g of liquid product
 - 0.25 g of concentrates (solid or liquid)
 - 1 cannabis plant seed
- Not sell or provide cannabis for recreational use to any person under the age of 18 years or use a youth to commit a cannabis-related offense; doing so could result in criminal charges with a maximum penalty of 14 years in jail.

need to be modified as some medical doses may require larger amounts of cannabis (<https://www.cma.ca/sites/default/files/pdf/News/proposed-approach-regulation-cannabis-e.pdf>).

THERAPEUTIC CONSIDERATIONS

A pharmacological review of the anticonvulsant activity of the cannabinoids is beyond the scope of this document. For a detailed review we recommend the following references: Gaston and Friedman¹⁴ and Reddy and Golub.¹⁵ In addition, we refer the reader to Dow-Edwards and Silva¹⁶ for a review of the endocannabinoid system and its effects on brain plasticity during development.

A Cochrane review¹⁷ and a systematic review by the American Academy of Neurology¹⁸ (both published in 2014) concluded that there was a lack of adequate data from randomized, controlled trials of THC, CBD, or any other cannabinoid to support the use of these compounds in the treatment of epilepsy. Since these publications however, there have been four published randomized placebo-controlled clinical trials using a purified CBD oil (Epidiolex[®]) to treat two well-recognized and very specific drug-resistant pediatric epilepsy syndromes, namely, Dravet syndrome^{7,8} and Lennox-Gastaut syndrome.^{9,10} Epidiolex[®] is a CBD solution with a concentration of 100 mg/ml. Results to date show CBD to be beneficial in treating drug-resistant epilepsy, with a reasonable safety profile for short-term use in the above syndromes. When compared to placebo, there was an overall relative improvement in seizure frequency of 20%–25% for all seizure types.^{7–10,19} The first study in Dravet syndrome showed a statistically significant reduction only of convulsive seizures reported by the parents of affected children but not in other seizure types.⁸ Furthermore, 5% of all patients were seizure free on CBD treatment and 57% of patients had a seizure reduction of less than 50%. Common side effects were noted in more than 30% of patients, in particular gastrointestinal disturbance and

somnolence.⁸ CBD can increase the serum levels of some anti-seizure medications, particularly clobazam and its metabolite, which may have resulted in somnolence, at times severe, in some patients. Elevations in liver enzymes have also been reported.^{8–10}

Clinical trials in patients with Lennox-Gastaut syndrome showed a statistically significant improvement in the frequency of parent-reported drop seizures and overall seizures.^{9,10} Despite the statistically significant improvement, clinical significance is not clear since the median number of drop seizures decreased from 85 to 50 per month (from 3 to 2 seizures a day). CBD doses trialed were 10 and 20 mg/kg/day. Study limitations included the lack of blinding due to noteworthy side effects in the Epidiolex[®] group. There was also a relatively high incidence of seizure worsening, including status epilepticus (up to 15%) in patients on Epidiolex[®] when compared to placebo.^{9,10}

The results of the RCTs published to date do not readily translate to the Canadian experience as Epidiolex[®] (GW Pharmaceuticals, Cambridge, UK) is not available in Canada. In these studies, the maintenance dose used was between 10 and 20 mg/kg/day and only as an add-on therapy with other anti-seizure medication(s). The wide spectrum of CBD-containing products manufactured for medical purposes in Canada further precludes the ability to make any conclusions. Canadians mainly use oil formulations with a wide range of CBD-THC ratios. A recent, prospective open-label study in Dravet syndrome, using a cannabis oil product with a CBD-THC (50:1) performed in Canada,⁶ resulted in a median motor seizure reduction of 70.6%, a statistically significant improvement in quality of life, and a reduction in electroencephalographic spike activity over a 20-week period. The small sample size of 19 patients and unblinded intervention, however, were significant study limitations.⁶

Relatively long-term efficacy and safety was reported in an open-label ongoing expanded-access program study for the use of Epidiolex[®].⁴ Of the 607 enrolled patients, 89 (15%) withdrew due to lack of efficacy and 32 (5%) withdrew due to adverse events. Only 138 (23%) patients were followed until week 96. The 50%, 75%, and 100% reduction in convulsive seizures rates by week 12 of treatment were 52%, 31%, and 11%, respectively. These differences remained similar throughout until week 96 in those patients with available data. However, 23%–29% of patients had increased convulsive seizure frequency and 24%–27% had an increase in total seizures by the last visit at week 96 of those with available data.⁴ Thus, about 50% of patients with drug-resistant epilepsy (mainly Dravet syndrome or Lennox-Gastaut syndrome) will have a 50% or greater seizure reduction, 25% will not improve or will not tolerate the intervention, and 25% will have an increase in seizure frequency.

In Canada, the current commercially available CBD-THC cannabis oil for the treatment of epilepsy ranges from 12.5:1 to 50:1, with variable concentrations of milligram per milliliter. In the authors' experience, management decisions cannot simply be made by only considering a ratio. For instance, when comparing two different oil products with CBD-THC of 20:1 ratio, one product may contain 100:5 mg/ml of CBD-THC, while another may have 10:0.5 mg/ml. In both samples, the ratio is the same, 20:1 but the milligram amount of CBD and THC per ml is different. Due to these differences, CBD-THC cannabis oil products also have variable dried cannabis content. A recent

Table 2: Summary of the required steps to obtain cannabis for medical purposes

1. Canadian patients can obtain access to cannabis by visiting a licensed health-care practitioner;
2. The practitioner must complete a medical document if it is decided that cannabis is a good treatment option for this patient. The document, which could be obtained from Health Canada website (example in Figure 1. http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/marihuana/info/med-eng.pdf) must indicate:
 - The health-care practitioner’s given name, surname, profession, business address and telephone number and, if applicable, their facsimile number and e-mail address.
 - The province in which the health-care practitioner is authorized to practice their profession and the number assigned by the province to that authorization.
 - The given name, surname, and date of birth of the individual who is under the professional treatment of the health-care practitioner.
 - The address of the location at which the individual consulted with the health-care practitioner.
 - The daily quantity of dried cannabis, expressed in grams, that the health-care practitioner authorizes for the individual.
 - A period of use, specified as a number of days, weeks or months.
 - A medical document must be signed and dated by the health-care practitioner who is providing it and must include a statement confirming that the information in the document is correct and complete.
3. The physician can prescribe in the document up to 1 year of treatment.
4. The document is then presented by the practitioner to a licensed producer by regular mail or by fax. An updated list of current licensed producers for medical and recreational purposes can be found here <https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/industry-licensees-applicants/licensed-cultivators-processors-sellers.html>.
5. The producer can provide the patient with up to 30-day supply or up to a maximum weight of 150 g of dried cannabis or the equivalent amount if in another form.
6. A patient is able to request that a licensed producer transfers the medical document to another licensed producer. A patient does not have to obtain a new medical document in order to switch between two licensed producers; however, each licensed producer used must have a Medical Document or a faxed copy.

Medical Document Authorizing the use of Cannabis for Medical Purposes under the Access to Cannabis for Medical Purposes Regulations

Medical Document Authorizing the use of Cannabis for Medical Purposes under the Access to Cannabis for Medical Purposes Regulations

Help on accessing alternative formats, such as Portable Document Format (PDF), Microsoft Word and PowerPoint (PPT) files, can be obtained in the [alternate format help section](#).

For related information, please see Health Canada's [Information for Health Care Practitioners](#).

This document may be completed by the applicant's health care practitioner as defined in the Access to Cannabis for Medical Purposes Regulations (ACMPR). A health care practitioner includes medical practitioners and nurse practitioners. In order to be eligible to provide a medical document, the health care practitioner must have the applicant for the medical document under their professional treatment. Regardless of whether or not this form is used, the medical document must contain all of the required information, (see in particular s. 8 of the ACMPR).

Your health care practitioner may use this form to provide you authorization to use cannabis for medical purposes. Your health care practitioner may use a different form, but the required information as per section 8 of the ACMPR (outlined below) must be included.

Access via Health Canada licensed producers: Should you choose to access cannabis from a licensed producer, this form must be sent directly to the licensed producer of your choice. You may choose any licensed producer who is authorized to sell to registered clients. Please see the Health Canada website for a list of licensed producers. Should you wish to switch from one Health Canada licensed producer to another a new medical document will be required as licensed producers are required to keep the original medical document on file.

Access via production for own medical purposes: Should you choose to produce your own cannabis, or designate someone to produce it for you, the original of this document must be sent to Health Canada with your Registration Application Form.

Patient's Given Name and Surname:

Patient's Date of Birth (DD/MM/YYYY):

Daily quantity of dried marihuana to be used by the patient: grams / day

The period of use is day(s) or week(s) or month(s).

Note: The period of use cannot exceed one year

Health care practitioner's given name and surname:

Profession:

Health care practitioner's business address:

Full business address of the location at which the patient consulted the health care practitioner (if different than above):

Phone Number:

Fax Number (if applicable):

Email Address (if applicable):

Province(s) Authorized to Practice in:

Health Care Practitioner's Licence number:

By signing this document, the health care practitioner is attesting that the information contained in this document is correct and complete.

Health Care Practitioner's Signature: _____

Date Signed (DD/MM/YYYY):

Important Note for Authorizing Health Care Practitioner

If the patient chooses to produce cannabis for their own medical purposes or you are not submitting this document via secure fax do not initial the box below.

If your patient chooses to access cannabis for medical purposes via a licensed producer, this medical document can be submitted from the health care practitioner's office to the licensed producer by secure fax. If you choose to submit the medical document by secure fax, initial the statement below to acknowledge agreement.

I, the health care practitioner, acknowledge that the faxed medical document is now the original medical document and that I have retained a copy of this document for my records only.

Initial here:

Figure 1: Example of a medical document obtained from Health Canada (http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/marihuana/info/med-eng.pdf). The medical document could also be obtained from the licensed producer websites or the respective colleges of each province or territory.

Table 3: List of provincial policies and regulations for the use of medical cannabis

Province or territory	Regulatory organization	Policy statement	Link	Issued or last update in:
Alberta	College of Physicians and Surgeons of Alberta	Related Standard of Practice: Cannabis for Medical Purposes	www.cpsa.ca/wp-content/uploads/2019/05/AP_Cannabis-for-Medical-Purposes_updated2019.pdf	March 2019
British Columbia	College of Physicians and Surgeons of British Columbia	Practice Standard: Cannabis for Medical Purposes	www.cpsbc.ca/files/pdf/PSG-Cannabis-for-Medical-Purposes.pdf	June 2019
Manitoba	College of Physicians and Surgeons of Manitoba	Standards of Practice of Medicine (Part 8; Section G; page 45)	www.cpshttps://cpsm.mb.ca/cjj39alckF30a/wp-content/uploads/Standards%20of%20Practice/Standards%20of%20Practice%20of%20Medicine.pdf#page=39 m.mb.ca/cjj39alckF30a/wp-content/uploads/ByLaws/By-Law-11.pdf	June 2019
New Brunswick	College of Physicians and Surgeons of New Brunswick	Medical Act, Regulations and Guidelines: Medical Marijuana Section	www.cpsnb.org/en/documents/index.php?option=com_edocman&task=document.viewdoc&id=41	September 2017
Newfoundland and Labrador	College of Physicians and Surgeons of Newfoundland and Labrador	Advisory to the Profession and Interim Guidelines: Marihuana for Medical Purposes	www.cpsnl.ca/web/files/CPSNL%20%20Medical%20Marihuana%20%20March%202014%20rev%201_0.pdf	March 2014
Northwestern Territories	Health and Social Services	None available	www.hss.gov.nt.ca/en	
Nova Scotia	College of Physicians and Surgeons of Nova Scotia	Professional Standard Regarding the Authorization of Marijuana for Medical Purposes	www.cpsns.ns.ca/wp-content/uploads/2017/12/Authorization-of-Marijuana-Medical-Purposes.pdf	December 2017
Nunavut	Department of Health and Social Services	None available	www.gov.nu.ca/health	
Ontario	College of Physicians and Surgeons of Ontario	Polices & Guidance: Cannabis for Medical Purposes	https://www.cpso.on.ca/Physicians/Policies-Guidance/Policies/Cannabis-for-Medical-Purposes	January 2019
Prince Edward Island	College of Physicians and Surgeons of Prince Edward Island	Polices: Prescribing of Medical Marijuana	http://cpspei.ca/wp-content/uploads/2017/03/Marijuana-Prescribing-Nov-3016.pdf	November 2016
Québec	Collège des médecins du Québec	Ordonnance de cannabis à des fins médicales	www.cmq.org/publications-pdf/p-1-2018-09-20-fr-ordonnance-cannabis-fins-medicales.pdf	September 2018
Saskatchewan	College of Physicians and Surgeons of Saskatchewan	Regulatory Bylaws for medical practice in Saskatchewan (Part 6; Section 19.2; page 62)	www.cps.sk.ca/iMIS/Documents/Legislation/Legislation/Regulatory%20Bylaws.pdf	June 2019
		Information on prescribing medical Cannabis for patients and physicians	www.cps.sk.ca/imis/CPSS/CPSS/Programs_and_Services/Medical_Marijuana/Medical_Cannabis.aspx	October 2018
Yukon	Yukon Medical Council	Standards of Practice: Marijuana for Medical Purposes	www.yukonmedicalcouncil.ca/pdfs/Marijuana_for_Medical_Purposes.pdf	September 2018

Summary of provincial prescribing regulations for medical cannabis. Notice that these regulations may include the use of medical cannabis for other purposes and not only for epilepsy. Each province has slightly different requirements and proceedings. Physicians working in different provinces should be familiar with local regulations. At the current time, Northwest Territories and Nunavut do not have prescribing regulations for medical cannabis, thus, physicians practicing in these areas should watch for new information or policies presented by regulatory entities or contact them directly for specific enquiries.

European study comparing the reported and the actual concentration in commercially available CBD oils supports this observation. In this study, authors carried an in-depth chemical profiling of cannabinoids, terpenes, and oxidation products of 14 commercially available CBD oils. Nine (64%) samples had concentrations differing from the declared amount with only five maintaining the optimal limits.²⁰ The maintenance dose (as used in the four RCTs) was 10–20 mg/kg/day. Depending on the patient's weight and the product used, this maintenance dose may require more than 150 g of dried cannabis per month, exceeding the legally allowed possession limit. In such cases, the practitioner may still authorize the appropriate dose, but the patient or parent/caregiver would have to order multiple batches

of supply from the licensed producer, so that they do not possess more than 150 g at any one time.

The variability between cannabis oil products is also a major topic of confusion as it has a direct impact on doses, costs, and side effects, particularly when switching suppliers. Of note, according to a published paper in Canada, a combination of CBD-THC (50:1 with 50:1 mg/ml) was used, tapering to smaller doses by the end of the 20-week period, achieving a mean dose of 13.3 mg/kg/day of CBD (range 7–16 mg/kg/day) and 0.27 mg/kg/day of THC (range 0.14–0.32 mg/kg/day)⁶ which could potentially support the use of a smaller daily dose of CBD (and THC). The cost of an appropriate daily CBD dose could range from CAD \$800 to \$1500 per month; regarding Epidiolex®, the cost for 100 ml is

US\$1297.84 (<https://www.drugs.com/price-guide/epidiolex>) and the yearly cost could be up to US\$32,500. At present, cannabis oil is not covered by any medical insurance companies, and the cost must be borne out of pocket by the patient or family/care partners. This situation is unlikely to change, unless more evidence is obtained to support the use of medical cannabis.

SAFETY CONSIDERATIONS

Much of the available data regarding the safety and side effect profile of cannabinoids, especially with long-term use, are obtained from studies examining the effects of recreational marijuana, which contains high levels of THC. Few studies assessed the long-term effects of purified CBD. In studies of pediatric patients with severe epilepsy, the short-term side effects of cannabis included diarrhea, gastrointestinal intolerance, fatigue, and severe somnolence. In an open-label study of purified CBD, status epilepticus was observed in 6% of patients.²¹ More chronic side effects, particularly of THC include impairment of memory, judgment, cognition and motor performance, and psychosis.²² The use of CBD alone seems to have a minor to moderate impairment effect on driving. Combining CBD with alcohol, however, is a major concern.²³ Cannabis use during pregnancy, especially on a daily basis, has been associated with adverse neonatal outcomes leading to neurophysiological and behavioral abnormalities.^{24,25} The potential exposure to pesticides, which are used to keep the marijuana plant healthy, is also of concern during pregnancy.²⁶ It is unknown whether cannabis for medical use could produce similar results.

An important point to consider is the pharmacological interactions between CBD and commonly used anti-seizure medications. It is important to be aware of potentially important and concerning serum level increases in anti-seizure medications, particularly *N*-desmethyloclobazam, eslicarbazepine, rufinamide, topiramate, and zonisamide. Altered liver enzyme levels are common when combining CBD and valproic acid; thus, close monitoring of liver function is key.²⁷ High levels of the biologically active clobazam metabolite (*N*-desmethyloclobazam) were reported when given concomitantly with CBD. Patients on this combination reported an over twofold increase in somnolence as compared to patients not on clobazam.⁴ Careful monitoring of this interaction is therefore essential to avoid the complications of excessive somnolence, particularly respiratory failure and accidents. Measuring clobazam and *N*-desmethyloclobazam levels in serum should be considered when side effects are noticed as CBD or THC levels in blood are not reliable indicators of toxicity. Currently there is no reliable serum level assay for CBD.

An additional important issue is the lack of consistency in CBD-THC concentrations from one batch of product to another as each marijuana plant possesses different concentrations of CBD and THC. The current regulations from Health Canada are attempting to address good production practices. However, there are no CBD-based products related to epilepsy treatment with a drug identification number at the present time (<https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/licensed-producers/additional-information-licensed-producers-under-access-cannabis-medical-purposes-regulations.html#a2>).

Information about the long-term side effects of purified CBD or combinations at different ratios of CBD-THC is lacking even when these products are appropriately dosed and medically supervised. Furthermore, the effect of CBD and/or THC on the

developing brains of neonates, infants and children is not clear. Well-designed studies investigating the long-term side effects of CBD and/or THC are lacking.

SUMMARY

Due to social media, patient and family advocacy groups, and Internet activity, there is significant public interest in cannabis as an alternative treatment of those living with epilepsy. CBD therapy offers a potentially promising alternative for patients who have failed to respond to many traditional anti-seizure medications, the ketogenic diet and/or surgical interventions. At present, the best data are available for two specific epilepsy syndromes: Dravet syndrome and Lennox-Gastaut syndrome. The extrapolation of these data to all seizure types or other epilepsy syndromes is difficult and not recommendable. The cost of treatment with reported maintenance doses is high. This therapy is not covered by medical insurance companies, provincial health programs, or the Ministry of Health and may place financial distress on already strained patients and their care partners/families. Although few RCTs are published, the reported findings are encouraging for Dravet and Lennox-Gastaut syndromes, showing significant improvements in seizure frequency in 20%–50% of patients. However, there exists a 20%–25% potential risk of significant side effects severe enough to warrant discontinuation. Furthermore, 15%–20% of patients do not show a decrease in seizure frequency. Information regarding the side effects of long-term use in humans and the risk in pregnancy is limited. Notably, the purified CBD oil (Epidiolex[®]) tested in the above described RCTs is not currently available in Canada. Canada remains dependent on a variety of products of differing quality and consistency.

RECOMMENDATIONS

We recognize that recent publications herein examined show some benefits of purified CBD oil (Epidiolex[®]) in patients with Dravet syndrome and Lennox-Gastaut syndrome with daily seizures. ***In our opinion, purified CBD oil without THC may be considered as an add-on treatment of patients with these two specific epilepsy syndromes and daily seizure frequency utilizing the reported dose (10–20 mg/kg/day) only when those patients have failed two appropriately prescribed and utilized anti-seizure medications.*** However, evidence is lacking for the remaining epilepsy syndromes and epilepsies not otherwise classified as well as for the other products currently available in Canada, containing a combination of CBD-THC (i.e. vaporizing, edibles, smoking, and others including CBD-THC oil).

Should a patient or a parent/guardian opt to use cannabis, we strongly recommend that this decision be made in consultation with their health-care provider to ensure their safety. We recommend that the treatment with CBD-THC cannabis oil be managed by a physician knowledgeable and experienced with epilepsy care and anti-seizure medications, preferably with experience in CBD-THC cannabis oil. The product should be procured from a Health Canada-approved licensed producer. It is important that physicians carry out an appropriate baseline assessment of the patient, ensuring no contraindications prior to starting the therapy and that potential drug interactions are monitored for, and appropriate laboratory evaluations are obtained. Physicians involved in the care of these patients should also be equipped

with or have rapid access to the necessary medical infrastructure and personnel to manage potential complications should they arise.

We encourage clinicians and researchers to continue to seek further knowledge and education about this therapeutic approach. The authors also encourage government and not-for-profit entities to support and fund research in this area to reduce the potential biases associated with industry-sponsored trials.²⁸ The recent US Food and Drug Administration approval of Epidiolex® in the USA for its use in certain epilepsy syndromes is noted.

The authors recognize that further clinical studies are underway to address the aforementioned limitations in Canada. This statement will be reviewed and modified in the future as more data and knowledge become available.

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STATEMENT OF AUTHORSHIP

JPA, compiled all feedbacks from co-authors, wrote the first draft of the manuscript and produced the final version of the manuscript after revisions and editing were made. CB, PMB, JGB, CSC, MBC, MDG, PF, DF, RH, MJ, NJ, LLJ, MK, JCL, BMC, RML, MCN, DN, AR, JMR, CS, JFT-Z, LW, and MZ equally discussed the topic and provided themes to be considered for the generation of the first draft, reviewed the manuscript at different stages, provided constant feedback, and collaborated with manuscript editing.

REFERENCES

- Husni AS, McCurdy CR, Radwan MM, et al. Evaluation of phytocannabinoids from high-potency Cannabis sativa using in vitro bioassays to determine structure–activity relationships for cannabinoid receptor 1 and cannabinoid receptor 2. *J Med Chem Res.* 2014;23(9):4295–300.
- Friedman D, Devinsky O. Cannabinoids in the treatment of epilepsy. *New Eng J Med.* 2015;373:1048–58.
- O'Connell BK, Gloss D, Devinsky O. Cannabinoids in treatment-resistant epilepsy: a review. *Epilepsy Behav.* 2017;70(Pt B): 341–48.
- Szafarski JP, Bebin EM, Comi AM, et al. CBD EAP study group. Long-term safety and treatment effects of cannabidiol in children and adults with treatment-resistant epilepsies: Expanded access program results. *Epilepsia.* 2018;59(8):1540–48. doi: 10.1111/epi.14477. Epub July 12, 2018.
- Devinsky O, Verducci C, Thiele EA, et al. Open-label use of highly purified CBD (Epidiolex®) in patients with CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndromes. *Epilepsy Behav.* 2018;86:131–37. doi: 10.1016/j.yebeh.2018.05.013. Epub July 11, 2018.
- McCoy B, Wang L, Zak M, et al. A prospective open-label trial of a CBD/THC cannabis oil in Dravet syndrome. *Ann Clin Transl Neurol.* 2018;5(9):1077–1088. doi: 10.1002/acn3.621. eCollection September 2018.
- Devinsky O, Patel AD, Thiele EA, et al. GWPCARE1 Part A Study Group. Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome. *Neurology.* 2018;90(14):e1204–e1211. doi: 10.1212/WNL.0000000000005254. Epub March 14, 2018.
- Devinsky O, Cross JH, Laux L, et al. Cannabidiol in Dravet Syndrome Study Group. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. *N Engl J Med.* 2017;376(21):2011–20. doi: 10.1056/NEJMoa1611618.
- Devinsky O, Patel AD, Cross JH, et al. GWPCARE3 Study Group. Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome. *N Engl J Med.* 2018;378(20):1888–97. doi: 10.1056/NEJMoa1714631.
- Thiele EA, Marsh ED, French JA, et al. GWPCARE Study Group. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet.* 2018;391(10125): 1085–96. doi: 10.1016/S0140-6736(18)30136-3. Epub January 26, 2018.
- McLachlan RS. Marijuana: a time-honored but untested treatment for epilepsy. *Can J Neurol Sci.* 2015;42(2):88–91. doi: 10.1017/cjn.2015.11. Epub February 26, 2015.
- Rieder MJ. Canadian Paediatric Society, Drug Therapy and Hazardous Substances Committee. Is the medical use of cannabis a therapeutic option for children? *Paediatr Child Health.* 2016; 21(1):31–34.
- Consolidation of Cannabis Regulations. SOR/2018-Last amended on January 15; 2019. Available at: <https://laws-lois.justice.gc.ca/PDF/SOR-2018-144.pdf>; accessed May 19, 2019.
- Gaston TE, Friedman D. Pharmacology of cannabinoids in epilepsy. *Epilepsy Behav.* 2017;70(Pt B):313–8.
- Reddy DS, Golub VM. The pharmacological basis of cannabis therapy for epilepsy. *J Pharmacol Exp Ther.* 2016;357(1): 45–55.

16. Dow-Edwards D, Silva L. Endocannabinoids in brain plasticity: cortical maturation, HPA axis function and behavior. *Brain Res.* 2017;1654(Pt B):157–64.
17. Gloss D, Vickrey B. Cannabinoids for epilepsy. *Cochrane Database Syst Rev.* 2014;5(3):CD009270.
18. Koppel BS, Brust JCM, Fife T, et al. Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 2014;82(17):1556–63.
19. Elliott J, DeJean D, Clifford T, et al. Cannabis-based products for pediatric epilepsy: a systematic review. *Epilepsia.* 2019; 60(1):6–19.
20. Pavlovic R, Nenna G, Calvi L, et al. Quality traits of “Cannabidiol Oils”: cannabinoids content, terpene fingerprint and oxidation stability of European commercially available preparations. *Molecules.* 2018;23(5). pii: E1230.
21. Devinsky O, Marsh E, Friedman D, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. *Lancet Neurol.* 2016;15(3):270–78. Erratum in: *Lancet Neurol.* 2016 Apr;15(4):352.
22. Volkow ND, Swanson JM, Evins AE, et al. Effects of cannabis use on human behavior, including cognition, motivation, and psychosis: a review. *JAMA Psychiatry.* 2016;73(3):292–7.
23. Williamson EM, Evans FJ. Cannabinoids in clinical practice. *Drugs.* 2000;60(6):1303–14.
24. Calvigioni D, Hurd YL, Harkany T, Keimpema E. Neuronal substrates and functional consequences of prenatal cannabis exposure. *Eur Child Adolesc Psychiatry.* 2014;23(10): 931–1.
25. Petrangolo A, Czuzoj-Shulman N, Balayla J, Abenhaim HA. Cannabis abuse or dependence during pregnancy: a population-based cohort study on 12 million births. *J Obstet Gynaecol Can.* 2019;41(5):623–30.
26. Leung MCK, Silva MH, Palumbo AJ, Lohstroh PN, Koshlukova SE, DuTeaux SB. Adverse outcome pathway of developmental neurotoxicity resulting from prenatal exposures to cannabis contaminated with organophosphate pesticide residues. *Reprod Toxicol.* 2019;85:12–18.
27. Gaston TE, Bebin EM, Cutter GR, et al. Interactions between cannabidiol and commonly used antiepileptic drugs. *Epilepsia.* 2017;58(9):1586–92. doi: 10.1111/epi.13852. Epub August 6, 2017.
28. Burnham EL, Eakin MN, Pakhale S. Ethics of health research supported by for-profit cannabis companies: what have we learned from Big Tobacco? *Ann Am Thorac Soc.* 2019; 16(3):396–7.