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To cite this article: Sven Gottschling, Oyedeji Ayonrinde, Arun Bhaskar, Marc Blockman, Oscar D'Agnone, Danial Schecter, Luis David Suárez Rodríguez, Sherry Yafai & Claude Cyr (2020) Safety Considerations in Cannabinoid-Based Medicine, International Journal of General Medicine, , 1317-1333, DOI: [10.2147/IJGM.S275049](https://doi.org/10.2147/IJGM.S275049)

To link to this article: <https://doi.org/10.2147/IJGM.S275049>



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Published online: 01 Dec 2020.



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Safety Considerations in Cannabinoid-Based Medicine

This article was published in the following Dove Press journal:
International Journal of General Medicine

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Abstract: Cannabinoids are a diverse class of chemical compounds that are increasingly recognized as potential therapeutic options for a range of conditions. While many studies and reviews of cannabinoids focus on efficacy, safety is much less well reported. Overall assessment of the safety of cannabinoid-based medicines is confounded by confusion with recreational cannabis use as well as different study designs, indications, dosing, and administration methods. However, clinical studies in registered products are increasingly available, and this article aims to discuss and clarify what is known regarding the safety profiles of cannabinoid-based medicines, focusing on the medical and clinical safety evidence and identifying areas for future research. The two most well-studied cannabinoids are Δ^9 -tetrahydrocannabinol (THC), or its synthetic variants (dronabinol, nabilone), and cannabidiol (CBD). Across diverse indications, dizziness and fatigue are generally the most common adverse events experienced by patients receiving THC or combined THC and CBD. Patients receiving THC may experience adverse cognitive effects and impairment in psychomotor skills, with implications for driving and some occupations, while CBD may help to lower the psychotropic effects of THC when used in combination. Studies on dependency and addiction in a medical context are limited, but have shown inconsistent findings regarding misuse potential. Generally, the recommended route of administration is oral ingestion, as smoking medicinal cannabinoid products potentially releases mutagenic and carcinogenic by-products. There are several potential drug-drug interactions and contraindications for cannabinoid-based medicines, which physicians should account for when making prescribing decisions. The available evidence shows that, as with any other class of pharmaceuticals, cannabinoid-based medicines are associated with safety risks which should be assessed in the context of potential therapeutic benefits. Each patient should be assessed on an individual basis and physicians must rely on informed, evidence-based decision-making when determining whether a cannabinoid-based medicine could be an appropriate treatment option.

Keywords: cannabis, cannabinoid, safety, cannabidiol, Δ^9 -tetrahydrocannabinol

Plain Language Summary

Cannabinoids are drugs that are either found in the cannabis plant or made in a laboratory. There are many cannabinoids but researchers are mostly interested in CBD (cannabidiol) and THC (Δ^9 -tetrahydrocannabinol). Cannabinoids can help with several different diseases, but it is important to know how safe they are. Doctors need to know the facts about the pros and cons of cannabinoids so they know which patients they may be able to help.

Medicines with cannabinoids in them (cannabinoid-based medicines) either contain THC or CBD or both. They can be swallowed or inhaled (smoking or vaping). Because there are so many different types, it is hard to find out how safe they are. This article looks at what we know now and what researchers still need to find out.

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Many patients taking cannabinoid-based medicines get side effects, but very few get serious side effects. There are some groups of patients who should not take cannabinoids because they are more likely to get serious side effects. The most likely side effects for patients taking THC are feeling dizzy or tired. Patients who take THC might not be able to drive as they can have problems with moving and thinking clearly (cognitive effects). CBD does not cause these effects. Taking CBD and THC together might help reduce the cognitive effects of THC.

Cannabinoids can be helpful for treating some diseases, but we need more information to understand who they can help most and when it is best to use them.

Note on Terminology

Currently, terminology in this therapy area is non-standardized, with a variety of terms used interchangeably. In this article, we have defined and used the terminology below for clarity.

Cannabinoid-based medicine: medical therapy area pertaining to the use of cannabinoids with therapeutic intent.

Cannabinoid-based medicines: standardized products containing known cannabinoid constituents that are used under medical supervision with therapeutic intent.

Medical cannabis: cannabinoid-containing products derived from the cannabis plant used with therapeutic intent (whether clinically diagnosed or perceived), not necessarily a medical product nor used under medical supervision.

Cannabis use: recreational drug use with the aim of inducing euphoria or other cognitive effects (no therapeutic intent).

Introduction

Cannabinoids are a class of medicines that are increasingly recognized by global and national guidelines as potential treatment options for a range of conditions.^{1–7} Cannabinoids either occur naturally in the human body (endocannabinoids), are derived from the cannabis plant (phytocannabinoids), or are synthesized in the laboratory (synthetic cannabinoids) (Figure 1).^{8,9} Although approximately 150 cannabinoids have been identified,^{9,10} the two most well studied are Δ^9 -tetrahydrocannabinol (THC) (responsible for the euphoric effects associated with cannabis) and cannabidiol (CBD). These have different pharmacologic properties and have shown efficacy in clinical trials, either alone or in combination with each other.^{11–14}

The approved indications for specific cannabinoid-based medicines in either North American or European countries (among other countries) include: spasticity associated with multiple sclerosis (~1:1 THC:CBD oromucosal spray, known as nabiximols); AIDS/cancer cachexia or chemotherapy-induced nausea and vomiting (dronabinol or nabilone, respectively synthetic THC and a synthetic THC analog); and Lennox-Gastaut and Dravet syndromes (CBD).^{15–20} In addition to those mentioned above, other quality-controlled products with defined cannabinoid constituents are available in some countries and are prescribed for a range of other conditions, such as chronic pain (including neuropathic pain).

Cannabinoid-based medicines act on the human endocannabinoid system, a network of CB₁, CB₂, and other receptors distributed throughout the body. CB₁ receptors are congregated predominantly in the central and peripheral nervous systems, with a low concentration in the respiratory center in the brainstem, while CB₂ receptors are found largely in the immune and hematopoietic systems, as well as the brain, liver, endocrine pancreas, and bone.^{21–26} First discovered in 1992, endocannabinoids, such as anandamide or 2-arachidonoylglycerol, are produced naturally in the body and act on these receptors to regulate a variety of processes, including pain perception and neuroendocrine-immune pathways.^{22,27} Although current understanding of the endocannabinoid system is limited, it remains an important focus for research.

The number of clinical studies assessing the potential therapeutic benefits of cannabinoids is increasing, especially as cultural and legal barriers to research and access continue to ease. However, while there are several valuable reviews and commentaries on the efficacy of cannabinoids for a variety of indications,^{28–30} both short- and long-term safety are less well reported, despite these being critical factors in regulatory and prescribing decisions.

Many guidelines, recommendations, and reviews on cannabinoids do not differentiate data from studies in recreational and medical contexts when discussing safety, and this amalgamation of disparate data has led to confusion around the safety profiles of cannabinoid-based medicines.^{31–35} Studies of recreational cannabis use are associated with several confounding factors that may not be applicable to cannabinoid-based medicines. Recreational cannabis use may be associated with uncertain product compositions, with potentially a very high THC (or synthesized equivalent) content, and unknown impurities. Moreover, dosing may be unknown and

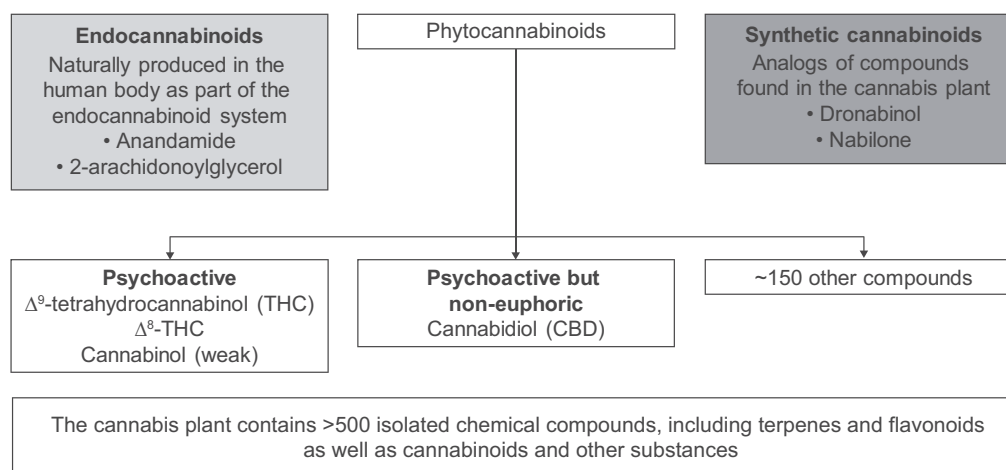


Figure 1 Types of cannabinoids.^{8,9}

uncontrolled, and usage may be accompanied by concomitant tobacco or other recreational drug use.³⁶ Recreational cannabis users are often aiming to take a large dose in order to induce euphoria and other psychoactive effects. In contrast, cannabinoid-based medicines are quality-controlled products with defined cannabinoid composition and standardized dosing, taken with the aim of achieving symptom relief. These products are administered under the direction of an informed, licensed healthcare professional, with appropriate monitoring procedures for concomitant medications and adverse events (AEs).

Although studies of recreational cannabis use can be of some value when medical literature is sparse, generalizing findings is challenging, as they are often based on subjective, unverifiable reports along with the associated factors described above. However, published data from studies in approved, registered products are increasingly available and can be leveraged to determine a more accurate picture of the safety profile of cannabinoid-based medicines in their intended therapeutic settings and patient populations.

Analyses of the overall safety of cannabinoid-based medicines are further confounded by variation in dosing and administration methods across products, study designs, and indications. While there are standardized doses for CBD in Lennox-Gastaut and Dravet syndromes, and in investigational studies,^{11,19,37} a commonly used dosing strategy for products containing THC is “start low, go slow, stay low”.³⁸ Patients, under supervision from their physician, start with a low dose of the cannabinoid-based medicine and gradually “titrate” until a balance between satisfactory symptom reduction and

minimal adverse effects is achieved (this practice is employed for a variety of approved medications³⁹). While this personalized approach is helpful for patients as individuals, lack of standardization, even within the same indication, represents a challenge for overall analysis of safety, and more studies to establish appropriate standard doses or dose ranges for each indication are needed. Additionally, while many cannabinoid-based medicines are administered orally, inhalation may be deemed appropriate in some cases and these different administration methods are associated with different pharmacokinetic characteristics. Although the general pharmacokinetic and pharmacodynamic properties of THC and CBD are broadly known,^{40,41} more studies are needed to understand further the effects of specific cannabinoid combinations on the intended patient populations.

The aim of this article is to discuss and clarify what is known regarding the safety profiles of cannabinoid-based medicines, focusing on the medical and clinical safety evidence and target areas for future research. We do not aim to comment on the regulations of individual countries, which vary widely, nor on the safety of recreational cannabis use.

This review is based on assessment and review of literature analyses of clinical trials and real-world studies of cannabinoid-based medicines, including registered products and other products used for medical purposes, together with multidisciplinary expert opinion and discussion. As well as ClinicalTrials.gov searches (Table 1), we qualitatively evaluated the literature based on PubMed searches including terms related to cannabis AND safety in the title or abstract.

Table 1 Safety Data from Phase 3 Randomized Controlled Trials in Registered, Approved Cannabinoid-Based Medicines

NCT Number and Citation	Product	Indication	Patient Population ^a	Dosing	Proportion of Patients with AEs and Serious AEs	Other Safety Observations	Comments
NCT02224690 Thiele EA et al 2018 ¹²	Epidiolex (oral)	Lennox-Gastaut syndrome	Children and adults (2–55 years) (n=171)	20 mg/kg/day	<ul style="list-style-type: none"> • AEs reported in 86% (all-cause, any severity) with Epidiolex vs 69% with PBO • 78% vs 97% of AEs were mild or moderate with Epidiolex vs PBO 	<ul style="list-style-type: none"> • Common AEs (>10%) with Epidiolex: diarrhea, somnolence, pyrexia, decreased appetite, vomiting • Common AEs (>10%) with PBO: vomiting • Most common related serious AEs with Epidiolex: increased ALT, increased AST, increased GGT 	<ul style="list-style-type: none"> • Double-blind, PBO controlled
NCT02224560 Devinsky et al 2018 ⁴⁴	Epidiolex (oral)	Lennox-Gastaut syndrome	Children and adults (2–55 years) (n=225)	10 mg/kg/day or 20 mg/kg/day	<ul style="list-style-type: none"> • AEs reported in 94% in 20 mg Epidiolex group vs 84% in 10 mg Epidiolex vs 72% in PBO group • 89% of AEs (overall) considered mild or moderate 	<ul style="list-style-type: none"> • Common AEs (>10%) with Epidiolex: somnolence, decreased appetite, diarrhea, upper respiratory tract infection, pyrexia, nasopharyngitis, vomiting, status epilepticus • Common AEs (>10%) with PBO: upper respiratory tract infection, pyrexia, vomiting • Related serious AEs with Epidiolex: elevated AST, elevated ALT, elevated GGT, somnolence, increased seizures, non-convulsive status epilepticus, lethargy, constipation, worsening chronic cholecystitis 	<ul style="list-style-type: none"> • Double-blind, PBO controlled
NCT01610700 Wade et al 2004 ¹³	Sativex (oromucosal spray)	MS	Adults (≥18 years) (n=160)	Max. dose in 24 h: 130 mg THC/120 mg CBD	<ul style="list-style-type: none"> • Not available 	<ul style="list-style-type: none"> • Common AEs (>10%) with Sativex: dizziness, fatigue, application site discomfort 	<ul style="list-style-type: none"> • Double-blind, PBO controlled • Very limited safety information reported
NCT01610687 Wade et al 2006 ⁴⁸ (safety extension of study NCT01610700)	Sativex (oromucosal spray)	MS	Adults (≥18 years) (n=137)	Max. dose in 24 h: 130 mg THC/120 mg CBD	<ul style="list-style-type: none"> • Not available 	<ul style="list-style-type: none"> • Most common possibly, probably, or definitely related AEs (>10%): oral pain, dizziness, diarrhea, nausea • Related serious AEs: seizures, vomiting, impaired balance, diarrhea 	<ul style="list-style-type: none"> • No PBO arm (open-label extension)

NCT01610713 Wade et al 2004 ¹³ (open-label extension of study NCT01610700, results of both studies reported in same article)	Sativex (oromucosal spray)	MS	Adults (≥18 years) (n=160)	Max. dose in 24 h: 130 mg THC/120 mg CBD	<ul style="list-style-type: none"> As per NCT01610700 	<ul style="list-style-type: none"> As per NCT01610700 	<ul style="list-style-type: none"> No PBO arm (open-label extension)
NCT01606137 Serpell et al 2013 ^{47,b}	Sativex (oromucosal spray)	MS: spasticity/pain	Adults (≥18 years) (n=146)	Max. dose per day: 130 mg THC/120 mg CBD	<ul style="list-style-type: none"> AEs reported in 95% (all-cause) Majority of AEs considered mild or moderate 	<ul style="list-style-type: none"> Common AEs (>10%): dizziness, MS aggravated, headache, nausea, vomiting, diarrhea, fatigue, urinary tract infection, nasopharyngitis, muscle spasms Related serious AEs: aspiration pneumonia, abnormal liver function test, convulsions, dizziness, paraesthesia, tremor, nausea, delusion perception, and paranoia 	
NCT01599234 Collin et al 2010 ⁴³	Sativex (oromucosal spray)	MS: spasticity	Adults (≥18 years) (n=337)	Max. dose in 24 h: 65 mg THC/60 mg CBD	<ul style="list-style-type: none"> AEs reported in 93% in Sativex group vs 78% in PBO group Most AEs considered mild or moderate 	<ul style="list-style-type: none"> Common AEs (≥10%) with Sativex: dizziness, somnolence, muscle spasticity, fatigue, asthenia, nausea, dry mouth, urinary tract infection, vertigo Common AEs with PBO (≥10%): dizziness, fatigue, nausea, urinary tract infection Related serious AEs with Sativex: psychiatric disorders, urinary tract infection 	<ul style="list-style-type: none"> Double-blind, PBO controlled
NCT00702468 Notcutt et al 2012 ⁴⁵	Sativex (oromucosal spray)	MS: spasticity	Adults (≥18 years) (n=36)	THC 27 mg/mL/CBD 25 mg/mL at current effective dose	<ul style="list-style-type: none"> AEs reported in 83% in Sativex group vs 78% in PBO group Most AEs considered mild or moderate 	<ul style="list-style-type: none"> Common AEs (>10%) with Sativex: fatigue, pain, muscle spasticity, muscle spasms, back pain, musculoskeletal stiffness, urinary tract infection, diarrhea Common AEs (>10%) with PBO: pain, muscle spasticity, trigeminal neuralgia, muscle spasms, depressed mood Serious AEs with Sativex: pain in hip/thigh, lumbar spine stenosis (unrelated to treatment) 	<ul style="list-style-type: none"> PBO controlled, parallel group Randomized withdrawal study design

(Continued)

Table 1 (Continued).

NCT Number and Citation	Product	Indication	Patient Population ^a	Dosing	Proportion of Patients with AEs and Serious AEs	Other Safety Observations	Comments
NCT00681538 Novotna et al 2011 ⁴⁶	Sativex (oromucosal spray)	MS: spasticity	Adults (≥18 years) (n=241)	Max. dose in 24 h: 32.4 mg THC/30 mg CBD	<ul style="list-style-type: none"> • AEs reported in 53% in Sativex group vs 49% in PBO group 	<ul style="list-style-type: none"> • Common AEs (≥5%) with Sativex: vertigo, fatigue, urinary tract infection, muscle spasms • Common AEs (≥5%) with PBO: diarrhea, urinary tract infection, muscle spasms 	<ul style="list-style-type: none"> • Patients entered 4-week single-blind treatment phase prior to double-blind phase • Limited safety information
NCT00711646 Collin et al 2007 ⁴²	Sativex (oromucosal spray)	MS: spasticity	Adults (≥18 years) (n=189)	Max. dose in 24 h: 129.6 mg THC/120 mg CBD	<ul style="list-style-type: none"> • AEs reported in 82% in Sativex group vs 71% in PBO group • Most AEs considered mild or moderate 	<ul style="list-style-type: none"> • Common AEs (> 10%) with Sativex: dizziness, fatigue, urinary tract infection • Common AEs (> 10%) with PBO: dizziness, oral pain • Serious AEs (possibly related) with Sativex: vomiting 	<ul style="list-style-type: none"> • Double-blind, PBO controlled

Notes: Search strategy: ClinicalTrials.gov search for: Epidiolex (synonyms: cannabidiol); dronabinol (synonyms: Marinol, Syndros, tetrahydrocannabinol, delta-9-THC); nabilone (synonyms: Cesamet); Sativex (synonyms: marijuana, cannabis). Note that synonyms were generated automatically by ClinicalTrials.gov. Inclusion criteria: interventional studies; Phase 3 studies; studies in approved product indications^c; adult or mixed pediatric and adult populations; studies with published data. Exclusion criteria: observational, registry and expanded access studies; early Phase 1 and 2, Phase 4, and Phase N/A studies; studies in pediatric-only populations; studies in pediatric-only populations; studies without a published manuscript. Search date: November 7, 2019. ^aAccording to inclusion criteria, not analysis set; ^bSafety listed as primary outcome measure in ClinicalTrials.gov entry; ^cEpidiolex: Lennox-Gastaut and Dravet syndromes; dronabinol: anorexia associated with AIDS or cancer; nabilone: anti-emetic or analgesic for neuropathic pain; Sativex: spasticity associated with MS.

Abbreviations: AE, adverse event; ALT, alanine transaminase; AST, aspartate aminotransferase; CBD, cannabidiol; GGT, gamma-glutamyl transferase; Max., maximum; MS, multiple sclerosis; PBO, placebo; THC, Δ^9 -tetrahydrocannabinol.

Adverse-Event Profiles

Overall analysis of traditional measures of drug safety, such as number and type of AEs, is challenging for cannabinoid-based medicines given the substantial differences between cannabinoids, individual product composition, study designs (particularly non-standardized dosing and administration), indications, and populations studied. Strategy and findings from a ClinicalTrials.gov search for randomized, controlled, Phase 3 clinical trials of cannabinoid-based medicines for approved indications are shown in Table 1, and illustrate that these challenges are apparent even across major clinical trials. Interestingly, there were no clinical trials found for dronabinol or nabilone that met the inclusion criteria for this search (Table 1).^{12,13,42–48}

However, many additional safety data from both randomized controlled trials and real-world evidence studies are available. A pragmatic approach is needed to assess these data and draw key safety findings, which are outlined below.

Across clinical trials, the most common AEs reported by patients receiving THC alone (including plant-derived THC, dronabinol, and nabilone) were generally dizziness, drowsiness/somnolence and fatigue, dry mouth, nausea/vomiting, and effects on cognitive function (eg, perception disorders, euphoria, confusion); balance and coordination problems were also commonly reported.^{14,28,49–57} The most common AEs remained broadly similar across diverse patient populations, including those with cachexia due to AIDS,¹⁴ multiple sclerosis,⁴⁹ chronic pain conditions including neuropathic pain,^{28,55,57} chemotherapy-induced nausea/vomiting,⁵¹ medication overuse headache,⁵² or sleep in fibromyalgia.⁵³

The AE profile of CBD is different to THC, with common AEs across clinical trials and real-world studies including diarrhea, somnolence, pyrexia, decreased appetite, vomiting, upper respiratory tract infection, and breakthrough epilepsy symptoms, noting that randomized controlled trials and real-world evidence studies of CBD are almost all in patients with rare forms of epilepsy using doses of 5–20 mg/kg daily.^{11,12,58–61} The most notable serious AE was elevated liver enzymes (ie, alanine transaminase, aspartate aminotransferase, and gamma-glutamyl transferase^{11,12}). However, dosing regimens for CBD in other conditions such as chronic pain have not yet been determined, with preclinical data suggesting a much lower therapeutic dose than that required for treating seizures, accompanied by a more favorable safety profile.⁶²

The most common AEs reported with nabiximols treatment (2.7:2.5 mg THC:CBD oromucosal spray, maximum of 12 sprays per day¹⁸) in patients with multiple sclerosis include dizziness, fatigue, somnolence, nausea, and application site discomfort,¹³ with few patients experiencing cognitive AEs.⁴⁸ Elevated liver enzymes did not appear to be a key safety signal, perhaps due to the relatively low dose of CBD compared with that used to treat patients with epilepsy. In patients prescribed other cannabis plant extracts containing both THC and CBD for other indications, the AE profile appeared generally similar to that of THC.

Overall, although many patients receiving cannabinoid-based medicines experienced AEs, the incidence of serious AEs was generally not significantly different compared with control individuals, with no serious AEs reported in some studies.^{28,29,63} AE profiles from real-world studies broadly correlate with those of clinical trials and are generally dose dependent, with dizziness, dry mouth, and somnolence commonly reported.^{64,65}

The “start low, go slow, stay low” dosing titration method may help to mitigate some AEs by finding a patient-specific balance between efficacy and tolerability.³⁸ Individual titration will depend on the cannabinoid combination, indication, concomitant medications, demographic characteristics, and patient’s previous experience with the medication. However, more studies in specific indications are needed to establish the frequency and intensity of AEs, and to optimize dosing for relevant patient populations.

Real-World Medical Use Patterns

Although the majority of clinical trial data are in the approved indications, real-world studies show that patients are using cannabinoid-based medicines to treat a range of other conditions (Figure 2),^{64,66} with chronic pain accounting for approximately 30–80% of patients.^{64,66–68} Additionally, and despite limited evidence of efficacy, mental health conditions were found to account for 27% and sleep disorders for 9.7% of cannabinoid-based medicine use in registered Canadian patients.⁶⁶ Given that almost half (45.5%) of patients with chronic pain conditions also suffer from sleep disorders and that alleviation of pain may lead to improved sleep quality, cannabinoid-based medicines may have a role in treating both these symptoms.^{35,69}

Although not specifically indicated for chronic pain, some chronic pain guidelines include cannabinoid-based medicines in recommended treatment algorithms,^{3,4} and the common

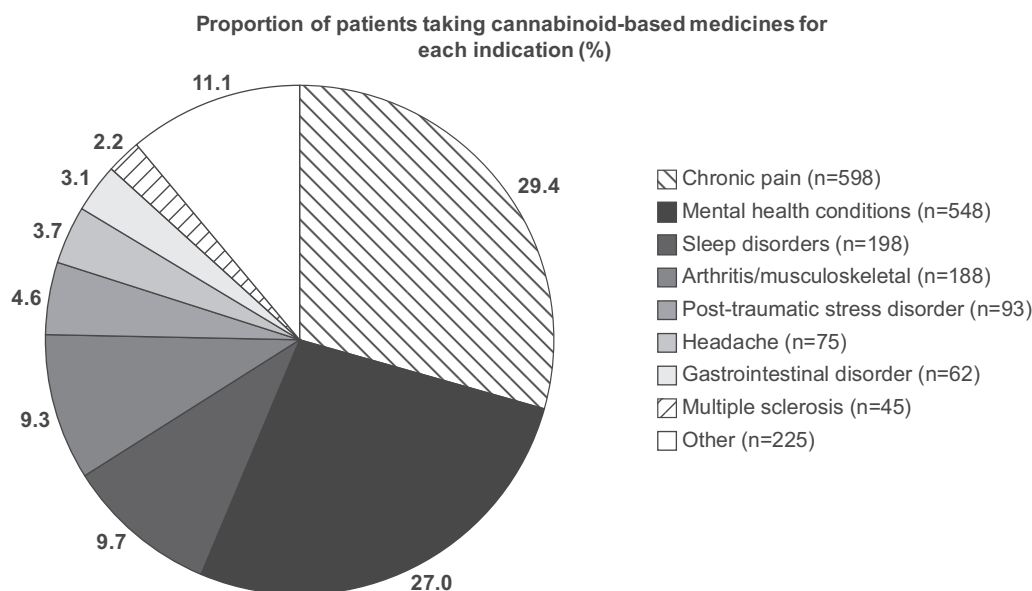


Figure 2 Patient-reported primary indications for cannabinoid-based medicine uptake in Canada. Adapted under the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0/>) from Baron EP, Lucas P, Eades J, Hogue O. Patterns of medicinal cannabis use, strain analysis, and substitution effect among patients with migraine, headache, arthritis, and chronic pain in a medicinal cannabis cohort. *J Headache Pain*. 2018;19(1):37.⁶⁶

AEs associated with cannabinoids seem generally comparable to those seen with other established treatments for chronic pain (Table 2).⁴ Although there are no studies that directly compare the overall safety profiles of cannabinoid-based medicines with other pain therapies, data from non-clinical studies indicate that there are potentially clinically meaningful differences in mortality and dependency (both in favor of cannabinoids), which warrant further investigation.^{70,71} This constitutes an important area for future research.

These findings represent a clear unmet need for clinical trials to assess the efficacy and safety of standardized cannabinoid-based medicines in the conditions in which they are being used and to compare them with existing standards of care. Meanwhile, existing real-world data could be leveraged to address urgent questions surrounding these therapeutic needs.⁷²

Concomitant Medication Use and Contraindications

There is a theoretical risk of drug–drug interactions between some cannabinoids and some concomitant medications.^{73,74} However, these have not been well studied in clinical practice and more drug–interaction studies are urgently needed to establish the extent of any interactions, including dose-dependent effects, especially with common medications that patients may be receiving alongside cannabinoids. Caution

should be exercised with any concomitant medication that is metabolized by the CYP450 complex, due to pharmacokinetic interactions with THC or CBD;^{75–77} however, the exact mechanisms of these interactions and their clinical relevance remain unknown. Current recommendations regarding concomitant medications are shown in Table 3.^{73,77,78}

Products approved and licensed for specific indications by national regulatory bodies (Epidiolex®, Sativex®, Marinol®, Syndros®, and Cesamet®) have clearly defined contraindications,^{15,16,18–20} and physicians should check the latest prescribing information to ensure compliance. For cannabinoid-based medicines that are not licensed for a specific indication, guidelines recommend contraindications based on currently available evidence (Table 4).⁷³ It should be noted that some of these rely on data from recreational cannabis use studies; therefore, it is not always clear which cannabinoid is relevant for the contraindication. In addition to regulatory compliance, safety should always be considered in the light of the specific cannabinoid and individual risk–benefit evaluation. For example, patients aged <25 years may be at risk of long-term cognitive effects from THC; however, for pediatric patients with refractory chemotherapy-induced nausea and vomiting, the potential benefits of THC-based treatments such as dronabinol or nabilone may outweigh the risks.⁷⁹ The currently known contraindications do not seem excessive or severely restrictive in the context of other treatments for similar indications.⁸⁰

Table 2 Common Adverse Effects of Treatment Options^a for Neuropathic Pain

Treatment	Common Adverse Effects
Tricyclic antidepressants (amitriptyline, nortriptyline, desipramine)	Drowsiness, confusion, orthostatic hypotension, dry mouth, constipation, urinary retention, weight gain, arrhythmia
Serotonin–noradrenaline reuptake inhibitors (venlafaxine, duloxetine)	Venlafaxine: nausea, dizziness, drowsiness, hyperhidrosis, hypertension Duloxetine: sedation, nausea, constipation, ataxia, dry mouth
Anticonvulsants (gabapentin, pregabalin, carbamazepine)	Gabapentin and pregabalin: drowsiness, dizziness, peripheral edema, blurred vision Carbamazepine: drowsiness, dizziness, blurred vision, ataxia, headache, nausea, rash
Controlled-release opioid analgesics (morphine, oxycodone, fentanyl, hydromorphone)	Nausea, vomiting, sedation, dizziness, urinary retention, constipation
Tramadol	Ataxia, sedation, constipation, seizures, orthostatic hypotension
Lidocaine (topical)	Virtually no systemic side effects
Nabiximols (~1:1 THC:CBD oromucosal spray)	Dizziness, fatigue, nausea, euphoria
Nabilone (synthetic THC analog)	Dizziness, drowsiness, dry mouth

Notes: ^aTreatments included according to the Canadian Pain Society consensus statement on the pharmacologic management of chronic neuropathic pain. Adapted under the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>) from Moulin DE, Boulanger A, Clark AJ et al. Pharmacological management of chronic neuropathic pain: Revised consensus statement from the Canadian Pain Society. *Pain Res Manag.* 2014;19(6): 328–335.⁴

Abbreviations: CBD, cannabidiol; THC, Δ^9 -tetrahydrocannabinol.

Cannabis-Use Disorder and Cannabis-Withdrawal Syndrome

While dependency is a normal physiologic reaction to many pharmaceutical products, and tolerance and withdrawal symptoms might be expected in patients on long-term medications for chronic conditions, substance-use disorder is generally characterized by continued use despite harm or risky behavior, cravings, and impaired control.⁸¹ Diagnostic criteria for cannabis-use disorder and cannabis-withdrawal syndrome are clearly defined elsewhere.⁸¹ However, available tools to detect substance-use disorder designed for recreational drug use may not be suitable for assessing problematic medication use in patients.^{82,83}

Table 3 Current Monitoring Recommendations for Concomitant Medications^{a,73,77,78}

Medication Class	Theoretical Effect	Clinical Recommendation
Anticholinergics, eg, amitriptyline	Additive tachycardia and/or hypertension	Monitor
CNS depressants, eg, alcohol, barbiturates, benzodiazepines, opioids	Additive effects including cognitive impairment BUT may be used in combination with opioids or benzodiazepines with the aim of reducing reliance on these medications	Monitor
CYP1A2 substrates, eg, acetaminophen, duloxetine, estrogen	Increased serum concentration of substrates	Monitor
CYP3A4 inducers/inhibitors, eg, St. John's Wort, erythromycin	Reduces/increases (respectively) serum concentration of cannabinoids	Monitor
CYP2C9 inhibitors, eg, fluconazole	Increases serum concentration of cannabinoids	Monitor
Disulfiram	Enhances adverse-effect profile (data from 2 case reports only)	Monitor
Nicotine	Additive tachycardia and stimulant effects	Monitor
Some anti-cancer therapies, eg, PD-1/PD-L1 inhibitors	Reduces response to treatment	Generally avoid

Notes: ^aMany data supporting these recommendations are in studies of recreational cannabis use and should be interpreted with caution. Individual interactions of THC and CBD may differ and this list is not exhaustive.

Abbreviations: CBD, cannabidiol; CNS, central nervous system; PD-1/PD-L1, programmed death-1/programmed death ligand-1; THC, Δ^9 -tetrahydrocannabinol.

The majority of data on cannabis-use disorder are in recreational use, with associated confounding factors of concomitant use of other recreational drugs and smoking. Data from recreational cannabis use studies indicate a prevalence of 18–34%.^{71,84} This is lower than estimated figures for opioid or alcohol users,⁷¹ with a much smaller estimated global burden.⁸⁵ Additionally, recreational cannabis use does not appear to be associated with increased mortality

Table 4 Recommended Contraindications for Cannabinoid-Based Medicines Based on the Current State of Evidence^{a,35,73}

Contraindication	THC or CBD ^b	Reason
Known sensitivity	THC/CBD	Existing sensitivity to cannabinoids
Aged <25 years ^c	THC	Increased risk of addiction or schizophrenia
Hepatitis C	THC/CBD	Linked to progression of fibrosis/steatosis
Pregnant/breastfeeding	THC/CBD	Various serious/long-term adverse effects on offspring
Personal or family history of psychosis or schizophrenia	THC ^d	Increased risk of earlier onset of psychosis in those already at risk of developing schizophrenia
Previous substance-abuse disorder	THC/CBD	Increased risk of developing cannabis-use disorder

Notes: ^aTable relates to cannabinoid-based medicines that are not licensed for a specific indication. Products approved and licensed for specific indications by national regulatory bodies have clearly defined contraindications and physicians should check the latest prescribing information to ensure compliance; ^bNot necessarily known which cannabinoid is contraindicated; ^cIn some cases of strong clinical need, it may be appropriate to prescribe products containing THC for patients aged <25 years if the benefits outweigh the risks; ^dSome preliminary research shows that CBD may be beneficial in treating schizophrenia.

Abbreviations: CBD, cannabidiol; THC, Δ^9 -tetrahydrocannabinol.

compared with the general population.⁸⁵ However, these data should be interpreted cautiously and cannot be extrapolated to standardized, quality-controlled products administered (often orally) under medical supervision.

Although studies on cannabis-use disorder and cannabis-withdrawal syndrome in a therapeutic context are limited, available data seem to show that incidence of cannabis-use disorder in patients receiving cannabinoid-based medicines is generally low.^{65,86} A review of nabilone found no concerns with abuse potential⁸⁶ and long-term registry data for nabiximols showed no signals of dependence or abuse.⁶⁵ A recent study showed that nabiximols may be effective in treating existing cannabis dependence,⁸⁷ while preliminary research indicates a potential role for CBD in treating heroin withdrawal.⁸⁸

Withdrawal symptoms in patients with neuropathic pain treated with dronabinol (sleep disturbance, excitability, nervousness, and increase of neuropathic pain) were found to be mild and transient.⁵⁷ Withdrawal symptoms with cannabinoids generally start within 1–2 days and resolve within

1–2 weeks of treatment discontinuation.⁷³ It is important to note that the presence of withdrawal symptoms does not necessarily constitute a diagnosis of cannabis-withdrawal syndrome.⁸¹

In addition, patients receiving cannabinoid-based medicines generally do not increase their dose over time, once the therapeutic dose has been achieved.⁸⁹ This is in contrast to opioid use, where dose escalation and addiction are not uncommon.^{38,80} In terms of toxicity, one model found that the estimated ratio of toxicologic threshold (based on median lethal dose [LD50] values) to standard daily human intake for THC was much higher than for many other substances, including all opioids studied,⁹⁰ which may partly explain why cannabis use is not associated with increased mortality. Indeed, official statistics for England and Wales in 2018 showed that opiates were a factor (not necessarily directly attributable) in 2208 deaths registered in 2018, compared with 210 for paracetamol and 22 for cannabis, noting that these values do not differentiate medical from recreational use (Figure 3).⁷⁰ Based on data in recreational cannabis use (with unknown product composition), acute overdose is associated with agitation, hyperemesis, tachycardia, drowsiness, and psychological disturbances that can include psychosis.^{91,92}

More high-quality medical research is needed to determine the incidence of cannabis-use disorder in patients treated with cannabinoid-based medicines, including identifying which combinations of cannabinoids, doses, and individual-use patterns cause these effects in which patients. This will decrease reliance on recreational cannabis use data in this area, with its associated confounding factors.

Psychiatric and Cognitive Effects

While both THC and CBD are psychoactive (ie, they act on the central nervous system to alter brain function), CBD does not induce euphoria or measurably impair psychomotor skills.^{73,93,94} CBD exhibits anxiolytic and neuroprotective properties,^{93,95} and is approved in some countries to treat children with Lennox-Gastaut or Dravet syndromes.¹⁹

Current evidence indicates that THC is anxiolytic at low doses and anxiogenic at higher doses, with unique dose–response curves.^{35,73,96–98} Interestingly, CBD (and other cannabis plant constituents such as cannabiol, terpenes, and flavonoids) may help to lower the psychotropic effects of THC when used in particular combinations^{35,99–101} and understanding this important interaction between these two cannabinoids should be a priority for further clinical research.

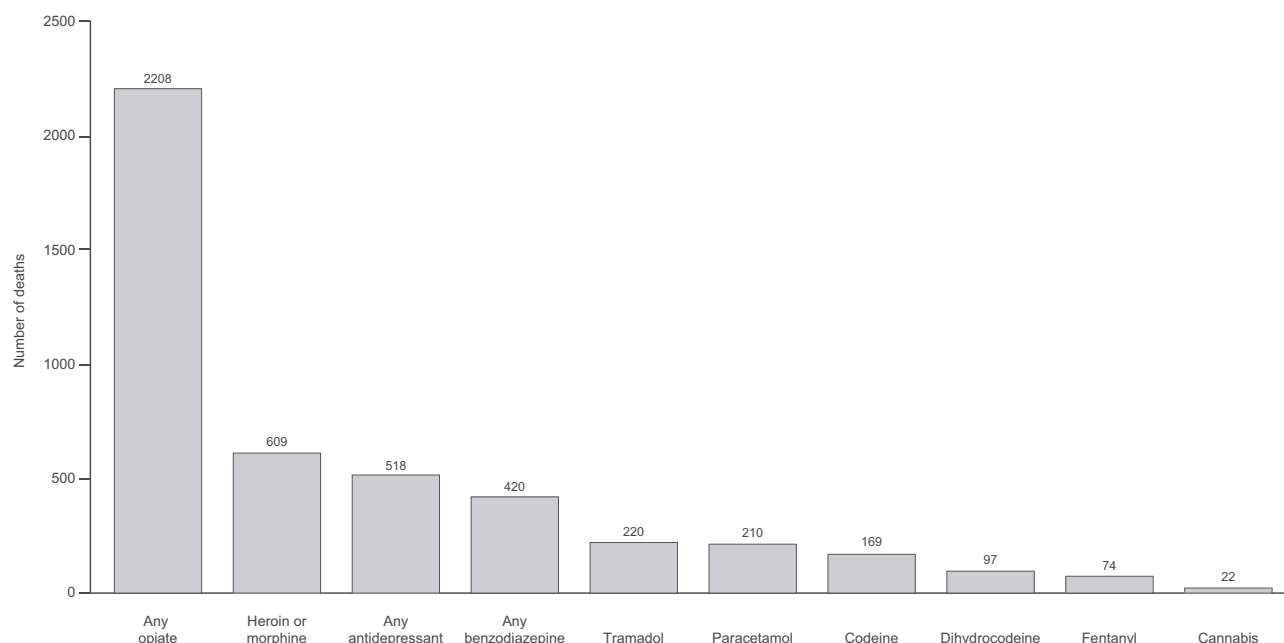


Figure 3 Number of deaths related to selected drugs, where the drug name was listed on the death certificate, England and Wales, 2018. *Data from the Office for National Statistics, accessed February 20, 2020: all deaths relating to drug poisoning in England and Wales registered in 2018, where a drug was mentioned on the death certificate. Any opiate includes unspecified opiates and excludes paracetamol compounds. Codeine and dihydrocodeine not from compound formulations (eg, co-codamol). Paracetamol includes paracetamol compounds. Office for National Statistics. Deaths related to drug poisoning, England and Wales. 2019. Available from: (<https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathsrelatedtodrugpoisoningenglandandwalesreferencetable>). Public sector information licensed under the Open Government Licence v3.0 (<http://www.nationalarchives.gov.uk/doc/open-government-licence/version/3/>).⁷⁰

Studies in recreational cannabis use show that early, frequent, and heavy use of high-potency THC may have long-term effects in the developing brain and is linked with earlier onset of psychosis in those with an individual or familial risk of psychosis or schizophrenia.^{35,73,96,102} Some synthetic cannabinoids produced illicitly for recreational use that bind to the same receptors as THC are associated with atypical psychosis and long-term cognitive impairment. However, other evidence suggests no association between adolescent cannabis use and structural brain differences in adulthood.¹⁰³ Currently, products containing THC or its analogs should not be prescribed for patients aged <25 years⁷³ unless there is a strong clinical need that cannot be met by other treatment options and the benefits outweigh the risks.^{35,79}

Due to a short-term decrease in psychomotor skills alongside potential cognitive and motor reflex impairments, patients may not be safe to drive or operate heavy machinery after taking medicines containing THC, with one review recommending abstinence from driving for 8 hours.^{104,105} Although the extent of impairment may depend on the dose, individual patient, route of consumption, concomitant medications, and rate of metabolism, a study in recreational cannabis use showed

that long-term cannabis users were impaired even when they had not consumed cannabis for at least 12 hours.¹⁰⁶ In addition to respective national laws, the patient's occupation and location are, therefore, important considerations when assessing whether a cannabinoid-based medicine is a suitable option. Further studies are needed to clarify the risk of prolonged psychomotor impairment in the therapeutic setting and establish any dose-dependent relationships.

Respiratory and Cardiovascular Safety

Smoking cannabinoid-based medicines is not recommended, as many by-products of pyrolysis are mutagenic and carcinogenic, and may exacerbate existing asthma or chronic obstructive pulmonary disease,³⁵ however, one large pooled analysis found no overall association between cannabis smoking and lung cancer.¹⁰⁷

Vaporization carries less respiratory risk, as the product is heated to a lower temperature (without combustion) than smoking and, therefore, does not produce the same level of toxic by-products.⁷³ Oral ingestion carries the least respiratory risk, with no known association between ingestion of cannabinoids and respiratory adverse effects. In

contrast to opioids, cannabinoids carry a low risk of respiratory depression due to the lack of endocannabinoid CB₁ receptors in the respiratory control centers in the medulla.^{23,80}

The existing literature assessing cardiovascular risk is in recreational cannabis use and shows conflicting findings.^{108,109} Recreational cannabis use is associated with a variety of cardiovascular effects such as tachycardia and dose-dependent peripheral vasodilation;^{32,110,111} however, it is unknown whether these effects are experienced by relevant medical populations receiving controlled doses and this is an important area for future research.

Reproductive Safety

Men and women are known to exhibit different endocannabinoid responses.³⁵ Although the majority of available data on the reproductive safety of cannabinoids in humans are in recreational cannabis use, there is ample evidence that cannabinoid-based medicines may impact on both male and female reproductive systems.

In women, while data on sexual behavior and reproductive diseases are limited, use of cannabinoid-based medicines in pregnancy and breastfeeding may be associated with a variety of serious and long-term adverse effects in the offspring.^{35,73,112,113} Although no currently approved cannabinoid-based medical products have been studied in pregnant women, preclinical studies of CBD, nabilone, and dronabinol found dose-related developmental toxicity, noting that some findings were at much higher exposure levels than the human therapeutic dose.^{15,16,19,20} Although pregnancy is not specifically listed as a contraindication in the prescribing information for these products,^{15,16,19,20} guidelines currently contraindicate all cannabinoid-based medicines in pregnant and breastfeeding women.⁷³ However, some real-world studies in recreational cannabis use suggest that it is not an independent risk factor for adverse neonatal outcomes.¹¹⁴ As an estimated 12% of pregnant women in the US use cannabis or cannabinoid-containing products in the first trimester¹¹⁵ many to treat severe nausea and vomiting^{116,117} informed patient–practitioner conversations are needed to discuss and educate on the risks and benefits of cannabinoid-based medicines compared with other lifestyle and pharmacologic options.

In men, recreational cannabis use may be associated with increased risk of testicular cancer, and has also been linked to reduced sperm count, motility, and libido, and to erectile dysfunction.^{35,118–120} However, preclinical studies

of nabilone in rats showed no effect on fertility or reproductive performance.¹⁶

As the majority of data on reproductive safety are in recreational cannabis use, more preclinical and high-quality long-term clinical studies are needed to assess fully the risks, including which cannabinoids are responsible for specific adverse effects.

Potential as Adjunctive Therapy

Cannabinoids and opioids used in combination may augment the analgesic effects of opioids.¹²¹ In patients with chronic pain, some open-label and real-world studies have found that initiation of cannabinoid-based medicines may lead to a reduction in opioid use, which could have implications for opioid sparing.^{64,122–124} In real-world studies, 97% of patients with chronic pain reported that they were able to decrease their opiate dose and 92% found the side effects more tolerable with cannabinoids compared with opiates¹²³ while 14.4% of elderly patients ceased to use opioid analgesics within 6 months.⁶⁴ Another study found that initiation of cannabinoid-based medicines was associated with 17-fold higher odds of ceasing opioid prescriptions within 21 months.¹²⁵ Due to the synergy between cannabinoids and opioids, patients receiving both therapies should be closely monitored for increased adverse effects.

There is also evidence that prescribing cannabinoid-based medicines may reduce the use of benzodiazepines and non-steroidal anti-inflammatory drugs.^{52,64,126}

Conclusions and Future Directions

Robust analysis of the safety of cannabinoid-based medicine is challenging due to disparities in formulation, dosing, administration method, indication, and confusion with recreational cannabis use. Further high-quality research is needed to establish the safety profile of each individual cannabinoid formulation for the indications in which it is being used, from which treatment guidelines and algorithms based on credible and validated medical evidence can follow.

However, while the evidence base continues to evolve, the existing safety data can be leveraged to draw some key conclusions.⁷² As cannabinoid-based medicines are currently used to treat a range of conditions, ongoing pharmacovigilance and real-world studies provide important data sources that complement randomized controlled clinical trials.

The available evidence shows that, as with any other class of pharmaceuticals, cannabinoid-based medicines are

associated with risks, which need to be assessed in the context of potential therapeutic benefits. Individual, evidence-based decision-making is required by physicians to determine whether a cannabinoid-based medicine could be an appropriate treatment option for their patients. Healthcare professionals should always bear in mind their local legal framework and access procedures when recommending or prescribing cannabinoid-based medicines.

Abbreviations

AE, adverse event; CBD, cannabidiol; THC, Δ^9 -tetrahydrocannabinol.

Acknowledgments

Medical writing assistance was provided to the authors by Helena Cant, MChemPhys, of Complete HealthVizion, McCann Health Medical Communications, and funded by Spectrum Therapeutics, Ontario, Canada. The first draft was prepared based on detailed discussion and input from the authors and revised in accordance with their critical feedback.

Author Contributions

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors. All authors contributed to the conception and design of the manuscript and data interpretation, and critically revised the manuscript for important intellectual content. The authors take full responsibility for the scope, direction, and content of the manuscript, and have approved the submitted manuscript. They received no compensation related to the development of the manuscript.

Funding

This review was sponsored and funded by Spectrum Therapeutics, Ontario, Canada. The sponsor was involved in the conception and design of the article. Medical writing assistance was funded by Spectrum Therapeutics, Ontario, Canada. Neither honoraria nor payments were made for authorship.

Disclosure

Sven Gottschling has received consultancy fees from Bioevents, Bionorica, Biotest, Boehringer Ingelheim, Cogitando, Experten-Futur, Grünenthal, Hexal, IQQ Institut, Kyowa Kirin, MedConcept, Novartis, Roche, Sandoz, Spectrum Therapeutics, and Tilray.

Oyedemi Ayonrinde has no disclosures to declare.

Arun Bhaskar has received consultancy fees from Spectrum Therapeutics.

Marc Blockman has received consultancy fees from Spectrum Therapeutics.

Oscar D'Agnone has received consultancy fees from Spectrum Therapeutics.

Daniel Schecter is a former employee of Spectrum Therapeutics, a former employee of Canopy Growth Corp from February 2019 to March 2020 and has provided consulting services both prior and after this, was previously Chief Medical Advisor of AusCann, and received honoraria from and provided consulting services for the following: Aleafia Health Inc, Shoppers Drug Mart, Khiron, Tilray, and Organigram, outside the submitted work.

Luis David Suárez Rodríguez has received consultancy fees from Spectrum Therapeutics and funding from the Asociación Mexicana de Medicina Cannabinoide AC, and reports personal fees and non-financial support from Asociación Mexicana de Medicina Cannabinoide AC, outside the submitted work; and is the current President of the Asociación Mexicana de Medicina Cannabinoide AC.

Sherry Yafai has received consultancy fees from Canopy Growth.

Claude Cyr has received consultancy fees from Aurora, Shoppers/Inventiv, Spectrum Therapeutics, and Tilray.

The authors report no other potential conflicts of interest for this work.

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