Mini-Review

Cannabis in palliative care: current challenges and practical recommendations

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

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

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

Correspondence to: Claude Cyr, MD. Clinique La Cité Médicale de Montréal, 3500 Boulevard DeMaisonneuve west, suite 1520, Montreal, QC, H3Z 3C1, Canada. Email: claudecyrmd@gmail.com.

Abstract: Pain and symptom control challenges are common in palliative care, and the search for other therapeutic strategies is ongoing. Unfortunately, patients and their caregivers are receiving little information or support from healthcare providers regarding the increasingly popular cannabinoid-based medicines (CBM). Clinicians, meanwhile, feel understandably perplexed by the discrepancy between the available evidence and the rapid interest in which patients and their families have demonstrated for CBM. There is an urgent need to address the many challenges that are delaying the appropriate integration of CBM into clinical practice, notwithstanding the obvious need for a solid general knowledge of pharmacology, mechanism of action and available clinical evidence supporting its use. The authors will address these challenges and provide practical recommendations regarding patient assessment for the use of CBM. The authors will also make suggestions regarding patient expectations in order to define clear objectives, review the necessary precautions prior to initiating treatment, aid in selecting the appropriate strain and route of administration as well as establishing proper titration and monitoring protocols. The authors will also discuss the lesser known but potentially therapeutic psychoactive effects of cannabis. As this class of therapeutic agents are likely to play a major role in palliative medicine in the near future, clinicians would benefit from familiarizing themselves with CBM and we can expect that patients and their caregivers will appreciate receiving support in their search for safe and effective therapeutic alternatives.

Keywords: Medical cannabis; cannabinoids; palliative care; symptom control; quality of life; review

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Introduction

The need for palliative care is increasing at a rapid pace in the context of an aging population, and where 75% of deaths are caused by chronic and progressive conditions (1). Generally, subjects with terminal illnesses experience significant symptom burden that often increases in intensity over time. In cross-sectional studies, patients report 8–12 symptoms, with fatigue, pain, anorexia, cachexia, dyspnea, anxiety, and depression being particularly common (2,3).

There are many opportunities to improve palliative care

by utilizing both pharmacological and nonpharmacological means. Poor symptom control and/or intolerable adverse effects attributed to opioids and other medications encourage the search for other therapeutic strategies, such as cannabinoid-based medicines (CBM). These include approved pharmaceutical cannabinoids such as Nabilone (Cesamet®), Nabiximols (Sativex®), Dronabinol (Marinol®—no longer available in Canada) and medical cannabis products such as dried flowers or edible oils.

Integration of CBM into palliative care has been delayed by many obstacles, including a paucity of clinical research data, poor clinical knowledge on how to initiate and monitor cannabinoid treatments, and conflicting or confusing regulatory frameworks. This situation is further complicated by political and public opinions that either stigmatize cannabis use or claim cannabinoids of various formulations are highly effective in palliative care and for a range of other conditions. Furthermore, a survey published in 2017 of adult cancer patients at a major cancer center in Seattle, WA found high rates of active cannabis use (24% in the last year) and also showed that cancer patients desire but are not receiving information about cannabis from oncology healthcare providers (4). Interestingly, a more recent survey of 237 U.S. oncologists published in May 2018 showed that while only 30% felt sufficiently informed to make recommendations regarding CBM, 80% of oncologists conducted discussions about CBM with their patients and 46% recommended CBM clinically. Additionally, 67% viewed it as a helpful adjunct to standard pain management strategies, and 65% thought CBM were equally or more effective than standard treatments for anorexia and cachexia (5). Meanwhile, the Dutch government recently agreed to fully reimburse medical cannabis for terminally ill patients, beginning in January 2019 (6).

It is in this context that we have addressed these challenges through consensus from expert opinion and a review of the literature and organized them to reflect the patient consultation process.

Thus, this paper will:

- Review the current challenges when considering CBM in palliative care;
- Provide a brief overview of the current general knowledge of cannabis and cannabinoids in reference to these specific challenges; and
- Offer practical recommendations and clinical pearls regarding appropriate and supportive use of CBM in palliative care.

Current challenges when considering CBM in palliative care

Challenge 1: when is it appropriate to consider medical cannabis treatment for a palliative care patient?

Before considering the use of medical cannabis in palliative care, good clinical judgment should always determine if the timing and the indications for introducing this treatment are appropriate. For instance, it is essential to determine if there will be sufficient time to assess the potential therapeutic benefits of the cannabinoid treatment. Furthermore, in the terminal stages of cancer, delirium is a common finding and this could be exacerbated by the use of CBM.

Systematic reviews regarding the benefits of CBM for the management of pain reveal mixed recommendations (7-10). A recent review which aimed to assess the efficacy of CBM for relieving pain in patients with malignant disease demonstrated a significant analgesic effect in 15 of 18 trials as compared to placebo (11). However, a recent review from the College of Family Physicians of Canada (CFPC) recommended against the use of CBM as first or second line treatment to palliate cancer pain (strong recommendation) (12). According to the CFPC, clinicians could consider CBM for refractory cancer pain only after the following considerations have been met:

- Discussing the risks and benefits of CBM with patients;
- Patients have had a reasonable therapeutic trial of more than two prescribed analgesics and have persistent problematic pain despite optimized analgesic therapy;
- CBM are adjuncts to other prescribed analgesics.

The CFPC also recommends the approved CBM Nabilone or Nabiximols as the initial agents (strong recommendation), though only the latter has the indication for cancer pain by Health Canada.

While it is correct to argue that the effectiveness of CBM in treating pain in palliative care settings has not yet been well established in comparison to other therapies, the position of the CFPC is debatable for several reasons.

Despite the fact that most patients medicating with cannabis do so to reduce pain, a recent Israeli study on cannabis use in over 3,000 cancer patients showed a significant improvement in the control of other common symptoms, including sleep problems (70.8%), fatigue (55.9%), anxiety and depression (74.1%), and nausea and vomiting (54.7%). Only 18.7% of patients reported good

quality of life prior to treatment initiation, while 69.5% reported good quality of life at 6 months. Furthermore, 36% of patients stopped using opioids and less than 20% discontinued their cannabis treatment. Of these, only 19.3% stopped due to side effects (13). Thus, the clinical usefulness of CBM, still considered by many to be limited to pain control, appears to encompass a much broader range of symptoms encountered in palliative care settings. Considering these recent findings, now may be time to re-examine not only the role of CBM in symptom control, but also whether these compounds should be offered earlier in the course of a comprehensive palliative care strategy, particularly for patients who have had prior positive experience regarding the alleviation of symptoms other than pain.

Furthermore, if CBM were to be considered, we call into question as to whether the recommended CBM Nabilone and Nabiximols should be used as first line agents. Nabilone is a synthetic tetrahydrocannabinol (THC) analogue in oral form that is 10 times more potent than natural THC. It is approved for chemotherapy-induced nausea and vomiting and has been used off label for pain (14-16). Since it is often reimbursed by public and private insurance plans (at least in Canada), an initial trial with this product could reasonably be considered. However, this is not necessarily the case with Nabiximols, a whole plant extract from *Cannabis sativa* in the form of an oromucosal spray with a 1:1 ratio of THC and cannabidiol (CBD). In Canada, it is listed for the management of cancer pain, neuropathic pain and spasticity in multiple sclerosis (17,18). Although the purity and potency of unregulated cannabis products may often be unreliable or inaccurately labeled when compared with Nabiximols, Canadian law requires that medical cannabis provided by Licensed Producers must comply with many of the same standards expected from the pharmaceutical industry. Consequently, many available products from Licensed Producers exhibit a potency of the active cannabinoid compounds THC and CBD that are similar to Nabiximols. Since these are the two most abundant cannabinoids found in cannabis, and in all likelihood responsible for most of the primary therapeutic benefits, it may be surmised that dose-equivalent effects should be expected when using similar administration routes. Furthermore, since Nabiximols is seldom reimbursed and can often exceed the cost of a similar medical cannabis oil product by 80% or more, it is unclear why clinicians should impose this financial burden on their patients.

Finally, one could also argue against the use of unapproved cannabinoids on the grounds that official guidelines regarding the appropriate dispensing of these medical cannabis products have not been issued, leaving clinicians with little instruction on route of administration, dosage, titration and monitoring. However, considering the striking similarities between these products and the approved pharmaceutical forms of cannabinoid Nabiximols, it seems logical that comparable guidelines should be obtainable.

Challenge 2: how do we define the objectives of cannabinoid therapy and manage expectations?

Defining clear clinical objectives with patients and their families is of great importance in palliative care. As discussed earlier, the focus is often on the treatment of cancer pain, but many patients may want to address other common symptoms at end of life, such as anxiety, depression, nausea, anorexia or insomnia, which might also be relieved by CBM. Others may be seeking for a reduction or cessation of certain medications, and particularly for the opioid-sparing effects of CBM that have been observed in preclinical and early clinical studies (19). Furthermore, some evidence of potential synergistic relief of pain with concomitant use of opioids has been demonstrated without significantly altering plasma opioid levels (20). It is crucial to address these expectations and explain that individual responses to CBM can vary considerably. Some symptoms, including neuropathic pain, nausea and muscle spasms, have been studied in larger clinical trials, and consequently patients should be reminded that the evidence for the treatment of other symptoms is still inconclusive.

In cases where patients expect medical cannabis to act as a curative strategy for their advanced health condition, this delicate discussion leads into a topic in palliative care that bears mention: facilitation of a patient's right to access experimental treatments in line with their wishes and beliefs in the service of hope (21).

Preclinical evidence and a few case study reports have shown that cannabinoids might have disease-modifying effects. It is therefore not surprising that interest in using cannabis preparations to treat cancer has surged among patients and families. Several preclinical studies have demonstrated anti-tumor activity in cell cultures or animal models (22,23). In breast cancer, for example, cannabinoids have been shown *in vitro* to interact with multidrug resistant proteins, improving the effectiveness of antineoplastic medications (24), and emerging data has also shown that cannabis and cannabinoids do not negatively interact with

presently available chemotherapeutics (25).

However, there are no phase II or III clinical trials large enough to provide the necessary evidence to support the disease-modifying effects of medical cannabis with regards to cancer. Some believe this indication generally requires a 10-fold dose increase of cannabinoids normally used for symptom control (26), which may provoke significant side effects, though a recent phase II trial using Nabiximols in glioblastoma has shown promising results using lower doses of cannabinoids (27). There are also important financial considerations when purchasing much higher doses of concentrated cannabis oil extracts (i.e., "Rick Simpson oil" or "Phoenix Tears"), not available through Health Canada approved Licensed Producers. In addition, basic safety issues must be addressed regarding the use of any cannabis products, particularly if derived from petroleum-based solvents or containing other contaminants. If such a trial is to be pursued by the patient, it may require support from a healthcare provider experienced in CBM and should be conducted in close collaboration with the oncology healthcare team.

However, the patient and family should be reminded that a realistically achievable outcome of medical cannabis treatments is to potentially better cope with the emotional, existential or spiritual suffering associated with distressing physical symptoms or particularly complex psychosocial situations at the end of life.

Challenge 3: is there a difference between a naïve versus an experienced cannabis user?

It is essential to determine if the patient is naïve to cannabis or has had prior experience, as high tolerance to many of the psychoactive effects of cannabis has been documented in chronic heavy users, presumably due to CB1 receptor downregulation by THC (28). It also appears that the subjective "high" or euphoric effect of THC usually occurs at higher doses than necessary for pain control (29).

It is also likely that patients using cannabis from illicit sources may be unaware of the concentration of THC and CBD in the products that they have used, and a cautious titration period with approved medical cannabis should be employed, even with experienced users, in order to determine the optimal dose. However, therapeutic and/or side effects for experienced patients are often more predictable based on their previous experience.

For patients naïve to cannabis, it is preferable to start with the lowest possible dose and follow the general rule: "start low, go up slow and stay low" (30). For patients with contraindications to THC or who may be apprehensive or sensitive to its specific psychoactive effects, an initial trial of CBD rich formulations may also be considered, as these compounds are generally better tolerated. Otherwise, when starting with formulations containing THC, slow dose escalation will decrease the likelihood of side effects. For those patients who are already using high doses of cannabis (i.e., >3 g/day) and whose survival is estimated to be of several months or more, harm-reduction strategies should be considered, similar to the precautions used with opioids. For these patients, longer acting preparations (i.e., cannabis oils and Nabilone) should be recommended. This reduces the triggering of the pleasure reward pathway, which is typically encountered with the use of high potency, short-acting formulations (i.e., flowers administered through inhalation via smoking and vaping) and is associated with psychological dependence and chemical coping conditions. Furthermore, the concomitant use of CBD, which does not produce the psychoactive effects unique to THC, should be also encouraged as a harm reduction strategy.

Challenge 4: which precautions and/or contraindications should be considered before authorizing medical cannabis in the palliative care population?

In general, cannabis is a safe product. A prospective Canadian cohort study showed there was no difference in the risk of developing serious adverse events among patients receiving a standardized herbal cannabis product (12.5% THC) for a 1-year period, when compared to controls (31). However, medical cannabis users (median cannabis dose of 2.5 g/day) were at increased risk of mild to moderate non-serious adverse events (i.e., not impacting overall function or requiring discontinuation of medical cannabis), which is consistent with a previous systematic review (32). A more recent meta-analysis and systematic review concluded, however, that cannabinoids were associated with an increased risk of short-term adverse events (7).

THC side effects

- Drowsiness, dizziness, dry mouth, anxiety, euphoria, paranoia, toxic psychosis, tachycardia, orthostatic hypotension, slowed reaction time, headache, blurred vision, cognitive impairment, and depression. Cannabinoid hyperemesis syndrome (CHS) is a rare side effect of unclear origin, with roughly 80 reported cases, mostly in chronic cannabis users (33).

CBD side effects

- With standard dosing: dry mouth, drowsiness, light headedness, hypotension, fatigue.
- At high doses (20 mg/kg): diarrhea, vomiting, fatigue, pyrexia, somnolence, and abnormal results on liver-function tests (34,35).

According to Health Canada, the contraindications that apply to those considering using prescription cannabinoid-based therapies, such as Nabilone, Nabiximols or Dronabinol, also apply to those considering using medical cannabis (36). These precautions are generally well known and may be appropriate in a younger or otherwise functional patient population. However, a strict interpretation may be questionable in palliative care settings and we will briefly discuss the most relevant items here.

Cannabis should be used with caution in patients with severe cardiac or pulmonary disease due to occasional hypotension (or possible hypertension), reflex tachycardia and syncope caused by THC-rich products. To date, however, CBM have not been implicated in QT/QTc interval prolongation (37). In patients with significant hepatic or renal impairment, no specific studies have been done with CBM, though it can be expected that effects would be more exaggerated or prolonged in these patients. Given that cannabinoids are highly protein-bound in the plasma, it is unlikely they will be removed by hemodialysis (21). Concomitant use of sedative-hypnotics, opioids or other psychoactive drugs may have additive or synergistic CNS-depressive or psychoactive effects. Cannabis should also be avoided in patients with a personal or family history of psychotic disorders, although emerging data seems to indicate that CBD-rich formulations may be a safer alternative as they have antipsychotic and anxiolytic properties (38-40).

Challenge 5: what is clinically relevant from the scientific literature on the pharmacology of cannabinoids, including metabolism and potential for drug-drug interactions?

There are several published articles describing the pharmacological characteristics of the cannabis plant (41-44), which contains up to 545 chemical compounds, 114 of which are unique phytochemicals called cannabinoids that interact with the endocannabinoid system (ECS) (45). The remainder includes over 200 terpenoids, that give cannabis its characteristic odour, flavonoids, fatty acids, among others—all with potential medical uses. Some terpenoids have even been shown to bind with cannabinoid receptors and are particularly targeted as having possible synergistic or "entourage effects", though there is still little evidence to suggest a clear influence from these secondary compounds (46-48). *Table 1* lists the possible therapeutic effects of the most commonly found cannabis terpenoids.

So far, studies have demonstrated efficacy of THC and CBD (41). THC binds as a partial agonist to G-protein-coupled cannabinoid receptors CB1 and CB2. It is thought to be responsible for most of the therapeutic effects attributed to cannabis, including mitigating pain, spasticity, nausea, insomnia and appetite loss. THC is also responsible for the unique psychoactive effects of cannabis through its actions at the CB1 receptor (49,50). These effects, which have been shown to be dose-related, can include distressing symptoms such as paranoia and anxiety, but may also produce euphoria or relaxation (30).

CBD, on the other hand, is generally well tolerated and does not appear to bind to either CB1 or CB2 receptors at physiologically meaningful concentrations, thereby averting the THC-mediated psychoactive effects (51). Results from preclinical studies suggest CBD has anti-inflammatory, analgesic, anti-nausea, anti-emetic, anti-psychotic, anti-ischemic, anxiolytic, and anti-epileptic effects (14). When used exclusively in certain conditions such as epilepsy and anxiety, large doses of CBD are often necessary (39,52-55). At lower doses, however, CBD may improve the tolerability and safety of THC by reducing many of the unwanted side effects (e.g., cognitive impairment, anxiety, paranoia, tachycardia) (15). Cannabinoids other than THC and CBD have yet to be adequately researched.

The metabolism of THC and CBD is not yet completely understood. It is carried out by the cytochrome P450 system (41), producing considerable variance in pharmacokinetics between the oral and inhaled route (see *Table 2*) (41,42,56). The CYP2C9 enzyme is thought to be responsible for the first-pass metabolism of THC. Another possible metabolic pathway for THC is through CYP3A4 enzymes. Interaction with potent CYP3A4 inhibitors, such as protease inhibitors, clarithromycin, ketoconazole, sildenafil and warfarin have been mentioned in the literature, but only as isolated case reports and do not seem to be clinically relevant (57-59).

Evidence for potential interaction between pharmaceutical CBD formulations (5–50 mg/kg/day) and antiepileptic drugs in adults and children has also been reported (52), and monitoring levels of clobazam and N-desmethylclobazam has been recommended (35,53,60).

Table 1 Cannabis terpenoid characteristics

Cannabis terpenoid	Possible pharmacological effect
Monoterpenes	
D-Limonene (commonly found in citrus essential oils)	(I) Anxiolytic
	(II) Antidepressant
	(III) Immunostimulating properties
	(IV) Anticancer (apoptosis in breast cancer cells)
Beta-Myrcene	(I) Potent anti-inflammatory (via prostaglandin E-2)
	Anxiolytic
	Analgesic (antagonized by naloxone)
	Sedating
	Muscle relaxant
	Hypnotic
	Blocks hepatic carcinogenesis by aflatoxin
Alpha Pinene	(I) Anti-inflammatory (via prostaglandin E-1)
	(II) Bronchodilator effect
	(III) Acetylcholinesterase inhibitor (may thereby aid with memory abilities)
	(IV) Anxiolytic
Linalool (common to lavender)	(I) Anti-inflammatory
	(II) Analgesic (via adenosine)
	(III) Anticonvulsant/anti glutamate
	(IV) Hypnotic
Sesquiterpenes: beta-Caryophyllene (common to black pepper and Copaiba balsam)	(I) Potent anti-inflammatory (via prostaglandin E-1)
	(II) Gastric cytoprotective activities
	(III) Selectively binds to CB2 receptors
Triterpenes: beta-Amyrin	(I) Anti-bacterial
	(II) Anti-fungal
	(III) Anti-inflammatory and anticancer properties

Challenge 6: what are the important considerations when selecting the appropriate medical cannabis strain and THC:CBD ratio?

Strain selection is one of the most perplexing issues regarding medical cannabis, since the commonly used but inaccurate vernacular system of distinguishing sativa and indica types of cannabis has developed independent of scientific and taxonomic classification systems. Although efforts are ongoing to adopt a more reliable system of science-based "chemovar" classification, there is little data to suggest specific *therapeutic* effects of the different cannabis strains (61). Small studies and anecdotal reports have suggested that sativa-dominant strains are characterized as uplifting and energetic, giving a feeling of optimism and well-being (62), while indica-dominant strains are described as calming and grounding and are said to result in relaxation, stress relief, and an overall sense of serenity (63). While this debate will surely continue for some time, there is little doubt that there is a significant overlap in therapeutic effects among the 700 or more cannabis

varieties in existence (64).

Standardized testing of THC and CBD content in regulated medical cannabis products has been established in a few countries, including Canada. However, many other jurisdictions still face inconsistent labeling information. Furthermore, a genetic analysis of 81 cannabis samples issued from licensed producers in Canada found that in 6 of 17 comparisons (35%), samples were more genetically similar to samples with different names than to samples with identical names (65). Consequently, the genetic identity of a cannabis strain cannot be inferred by its name or by its reported ancestry (66).

In summary, until standardized formulations become available, patients should focus primarily on THC and CBD. They should also be encouraged to try different chemovars with similar THC:CBD ratios and keep a detailed journal documenting their personal responses. While there seems to be a growing consensus regarding the benefits of using CBD with THC, much speculation remains about the ideal ratio that would optimize tolerability and efficacy. However, over 200 studies undertaken with Nabiximols has shown that a 1:1 ratio is usually well tolerated.

Challenge 7: which method of administration of CBM will be best for a palliative care patient?

CBM may be administered in many forms, either through inhalation, oral preparations, oromucosal sprays, rectal suppositories, salves and topically delivered preparations. Other formulations such as high-potency concentrates and innovative delivery devices offering more accurate dosing (i.e., Syqe Medical™ inhaler, hmbldt™ dose pen) may be available to healthcare practitioners, according to local regulations (67).

Inhalation either by smoking combusted plant material or vaporization remain popular routes of administration, as the effects are quickly experienced, making titration easier. Though a large retrospective study found no association between cannabis smoking and lung cancer (68,69), smoking should be discouraged due to the obvious risks of bronchial inflammation (70,71). Patients can also be reminded that there is a significant loss through side stream combustion, which has been evaluated at approximately 50% of the THC content. Of the remaining inhaled smoke, another 50% is exhaled again, with some of the remaining smoke undergoing localized metabolism in the lung (70).

Vaporization of cannabis is becoming increasingly popular among medical cannabis users due to its perceived harm reduction through the release of a significantly lower percentage of noxious chemicals (42,72,73). When cannabis is given through this route, it vaporizes at a much lower temperature (175–225 degrees Celsius), and aerosolized active components can be inhaled without the generation of smoke (74), with significantly lower odor and carbon monoxide levels (75).

Orally administered cannabis extracts offer the advantage of more precise dosing, but many factors influence the time of onset, duration and intensity of effects. For example, hepatic first-pass metabolism transforms much of the Δ9 THC into 11-OH THC, a possibly more potent form, thus requiring a low starting dose and careful titration.

Table 2 indicates the differences between inhaled and oral routes of administration (41,42,56).

Table 3 summarizes the more relevant evidence regarding the use of cannabinoids for palliative care symptoms. In addition, suggestions for the type of cannabinoid and the most effective route of administration are also included, based on clinical experience and previous published evidence (96).

Challenge 8: what is considered a safe approach for dose initiation and titration?

Exact doses vary widely and depend upon individual patient need and tolerance of side effects. Furthermore, THC is also considered to have a wide safety margin, where non-lethal oral doses of up to 3,000 mg/kg have been observed in monkeys (97). Consequently, some patients will unintentionally overload their system and expose themselves to unwanted side effects and increased tolerance. Many cannabis-naïve patients will experience adverse events with a starting dose as low as 5 or 10 mg of THC. A recent trial assessed the dose-related effects of THC on emotional responses to acute psychosocial stress. In this study, a dose of 7.5 mg of THC dampened negative emotional responses without influencing performance while 12.5 mg resulted in a slight but significantly increased negative affect overall (98).

An often referenced study involving titration protocols in cancer pain by Johnson *et al.* using Nabiximols vs THC or placebo, showed that 43% of patients taking the THC:CBD extract Nabiximols achieved a 30% or greater improvement in their pain score at a median dose of 8.75 sprays per day (≥25 mg of THC per day) (84). Another study on chronic neuropathic pain showed that a single inhalation of 25 mg

Table 2 Differences between inhaled and oral cannabinoid administration

Characteristics	Inhaled	Oral
THC and CBD concentrations in available products sold in Canada	THC: <1–30%; CBD: <1–20%	THC: <1–30 mg/mL (maximum concentration); CBD: <1–25 mg/mL or more (no maximum concentration)
Titration characteristics	Quick titration	Lengthier titration
Ease of dosing	More challenging with higher potency strains	More precise with standardized preparations (oils, tinctures)
Average bioavailability of THC	10–25%	10% (variable 6–20%)
Active metabolites	Δ9-THC > 11-OH-THC	Δ9-THC < 11-OH-THC
Psychoactivity	THC-mediated	THC-mediated*
First onset of effects	3–10 minutes	60–90 minutes
Peak concentration	2–10 minutes	1–3 hours
Peak psychoactive effects: euphoria, depersonalization, sensory perceptions	15 minutes	3 hours
Peak cognitive effects: short-term memory, attention, concentration	15 minutes	5 hours
Duration of effects	2–4 hours	8–12 hours or more
Dosing frequency	5–6/day	1–3/day

*, 11-OH THC may be more psychoactive than Δ 9 THC. THC, tetrahydrocannabinol; CBD, cannabidiol.

of herbal cannabis containing 9.4% THC (equal to 2.5 mg of THC) TID for 5 days reduced the intensity of pain, improved sleep and was well tolerated (29).

Therefore, as these studies suggest, many experts now believe that the threshold for the medical benefits of THC is far lower than previously thought. A sub-psychoactive dose as little as 2.5 mg of THC or less, with or without CBD, may offer many of the therapeutic benefits of cannabis, while avoiding intoxication. Moreover, the different pharmacokinetics between inhaled and oral routes may not play a significant role in the overall effects at this starting dose (99). Patients can maintain this dose for 2–3 days and then titrate accordingly.

Regarding CBD-rich cannabis dosing, some authors recommend starting with lower doses than those seen in clinical studies with CBD isolate, starting with 5–20 mg CBD per day of oral preparations, in two or three divided doses (30).

Challenge 9: can some of the psychoactive effects of cannabis be beneficial in palliative care?

Cannabinoids may produce unique effects, which were known primarily through traditional medicinal and cultural uses and in anecdotal reports from patients and caregivers (21). These effects include euphoria and relaxation, aversive memory extinction, increased focus of attention, enhanced sensory perception and introspective abilities, and temporary dissociative states (100). Understandably, practitioners may feel somewhat perplexed about how to best manage these unique properties often considered as the "intoxicating" effects of cannabis. We will briefly discuss the issues regarding the most common psychoactive effects associated with cannabis and encourage practitioners to engage in an open discussion with their patients in order to better understand the therapeutic aspects of their experiences.

Stimulation of cannabinergic activity in certain parts of the brain is known to play a key role in memory extinction of aversive memories and anxious thoughts or behaviours (101). A recent study also showed that chronic cannabis use is associated with blunted stress reactivity and lower cortisol levels when exposed to an acute stress test (102). There is also some evidence of the benefit of cannabinoid use in those with recognized post-traumatic stress disorder (PTSD) (103). Targeting the ECS may, therefore, offer potential benefit in

Table 3 Recommendations for using cannabinoids in symptom management

Symptom	Evidence	Cannabinoid/route of administration suggested for symptom control
Nausea and vomiting	(I) Antiemetic effects when CB1 receptors activated by THC (76)	THC-rich products: inhaled
	(II) Dronabinol: superior anti-emetic activity versus neuroleptics in cancer patients (77)	
	(III) Synergistic effect for dronabinol and prochlorperazine (78)	
	(IV) Non-inferiority for dronabinol versus 5-HT3 antagonists (79)	
	(V) CBMs greater activity in suppressing anticipatory nausea in preclinical model (80)	
Pain	(I) Dronabinol:	THC-rich products
	10 mg better tolerated than 20 mg	THC/CBD 1:1
	Mild analgesic effect comparable to 60 mg codeine	Inhaled: breakthrough or pain crisis (benefit from immediate effect)
	Adverse reactions (20 mg): dizziness, somnolence, ataxia, and blurred vision (81,82)	Oral: persistent pain ("long acting" effect)
	(II) Nabiximols:	
	Low dose (1–4 sprays/day), medium dose (6–10 sprays/day), high dose (11–16 sprays/day)	
	Analgesia with low and medium dose *vs.* placebo. Poor drug tolerability with high dose (83,84)	
	(III) Natural cannabinoids:	
	Reduction in pain intensity, opioid-sparing potential, synergism effect with opioids (19,20,85,86)	
	(IV) Improvement in pain measures with the use of cannabinoids compared with placebo (7)	
	(V) Benefit from the use of inhaled cannabis treatments for neuropathic pain (87)	
	(VI) Prevention of chemotherapy induced neuropathy in preclinical studies (88)	
Appetite stimulation	(I) Dronabinol: increased appetite and weight stability in HIV/AIDs and dementia (89-91)	THC-rich products: inhaled or oral
	(II) Dronabinol versus megestrol acetate for cancer-associated anorexia: findings in favor of megestrol (92)	
	(III) THC (2.5 mg) versus THC (2.5 mg) + CBD (1 mg) versus placebo: no significant improvements in survival, weight, or other nutritional variables (93)	
	(IV) Increased weight with smoked cannabis in HIV in experienced marijuana smokers (91)	
	(V) Improved taste, smell and food enjoyment using oral dronabinol (94)	
Insomnia	(I) Positive association between cannabinoids and improved sleep quality (7,85)	THC-rich products
	(II) Lack of evidence in cancer/palliative care population	Inhaled: sleep induction
		Oral: sleep maintenance
Depression and anxiety	(I) Nabiximols:	Anxiety: CBD-rich
	High doses have negative effect in depression	Depression:THC-rich or THC/CBD 1:1
	Positive results for anxiety disorders (7)	Inhaled: panic attacks or anxiety
	(II) CBD-rich products recommended for patients with psychiatric disease (38-40,95)	Oral: for persistent symptoms
	(III) THC may exacerbate many conditions (i.e., schizophrenia, psychosis, bipolar disorder)	

THC, tetrahydrocannabinol; CBD, cannabidiol.

Table 4 Clinical pearls or tips when prescribing medical cannabis

Possible situation	Tips or suggestion
Patient is naïve to medical cannabis. Which product should we recommend initially?	We suggest starting with a product that contains THC/CBD 1:1 ratio, as this will allow a better tolerance of possible THC side effects
If using an oral product containing a THC:CBD ratio of 1:1, what is the maximum recommended initial dose in a naïve patient?	Since THC is the compound that will cause most of the unwanted side-effects, we suggest an initial dose of 2 mg THC + 2 mg CBD 1–2 hours before bedtime, and if tolerated slowly escalate the dose in increments of a maximum of 2 mg per day until therapeutic benefit or side effects are noted. Otherwise, a morning dose (BID) or a 3 times per day (TID) schedule could be added if needed
If using oral THC-rich or CBD-rich products, what is the maximum recommended initial dose of THC or CBD in a naïve patient?	In most cases, start with 2 mg of THC or 5 mg of CBD at 1–2 hours before bedtime, and if tolerated try to slowly escalate the dose, until therapeutic benefit or side effects are noted
How should patients be initiated to an inhaled product?	Patients should start with a single inhalation, pausing briefly for 10–15 minutes between inhalations to ascertain either therapeutic and/or adverse effect
Should patients hold their breath in order to maximize absorption when inhaling cannabis?	No. Inhaled cannabinoids are rapidly absorbed. Breath holding is not necessary and increases exposure to unwanted by-products. Patients should be advised to inhale fully but naturally and exhale in a relaxed way
Patient reports fatigue, depression and/or insomnia with the CBD-rich product. What is the next step?	Try to reduce CBD dose, and consider a THC/CBD 1:1 product, or a THC-rich product (consider "sativa" varieties and terpenoids that could give stimulating effect such as Limonene and Pinene)
Patient is reporting palpitations, increased drowsiness and/or dizziness	Consider reducing THC dose since this is generally related to the possible cardiac and anxiogenic effects of THC
Patient does not feel any effect (therapeutic or otherwise) one hour after taking his very first oral dose. Should he take another dose?	No! Peak effect with the oral route may take 3 hours or more. We suggest taking a single dose on the first few days of treatment and adjusting the dose only after 2 or 3 days. Even in the absence of therapeutic effects, this approach will allow to build tolerance for potential adverse effects, particularly in more frail patients
Are there increased safety risks when patients use high-potency products?	Yes. A single inhalation of cannabis containing 25% THC could contain a dose capable of producing unwanted side-effects in a cannabis naive patient. We recommend starting with a product containing a low to moderate THC content (10% or less)

THC, tetrahydrocannabinol; CBD, cannabidiol.

reducing the psychological trauma associated with terminal illness diagnosis and invasive treatments.

Cannabis has long been used as an enhancer, heightening sensory perceptions and awareness, including increased appreciation of music, tastes, scents, or other aesthetic pleasures. It could also help to heighten awareness of moment-to-moment presence, a state that is all the more critical when one's days are numbered. This could very well play an important therapeutic role for certain patients faced with the despair of a terminal illness, and the loss of function that typically accompanies it. The potential contribution to spiritual growth and development may help to create "a good death" or "tending to dignity by way of the senses" as stated by Dr. B. J. Miller (21).

When taken at much higher doses, cannabis is one of the many drugs that can induce temporary dissociative-like states, which can create a "distancing" from pain experience, without relieving it through a direct mechanism. Though many patients may not be receptive to these types of effects, some may consider them as a safer and more desirable option than opioids when overwhelmed with unbearable physical and or psychological symptoms, which can happen at the end of life.

Practical recommendations and clinical pearls

Common questions and recommendations to assist the palliative care or multidisciplinary team considering medical cannabis treatment are summarized in *Table 4*.

Conclusions

CBM will undoubtedly play a larger role in palliative care

medicine in the years to come but there are still hurdles preventing a safe and unencumbered system of access for patients. One notable obstacle lies in the fact that CBM are still not considered as approved treatments for any condition for reasons aforementioned. Large scale randomized control trials, still considered the authoritative arbiter to prove medical efficacy, are largely inaccessible to cannabis researchers for a variety of legitimate reasons. While modern pharmaceutical companies can no longer rely on expert testimonials and case reports to make broader claims about newly synthesized products, the historically safe profile of the cannabis plant could make data from other clinical trials more admissible in order to formulate reliable clinical practice guidelines.

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Footnote

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Erratum

Erratum to cannabis in palliative care: current challenges and practical recommendations

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

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

Correspondence to: Claude Cyr, MD. Clinique La Cité Médicale de Montréal, 3500 Boulevard DeMaisonneuve west, suite 1520, Montreal, QC, H3Z 3C1, Canada. Email: claudecyrmd@gmail.com.

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Cannabis in palliative care: current challenges and practical recommendations

The authors of this article would like to make some corrections in two sections as some omissions and errors were unfortunately overlooked during the editing process. Some additional pharmacological details have also been included, and may be of use for clinicians who wish to delve deeper into these issues.

Challenge Section 5: what is clinically relevant from the scientific literature on the pharmacology of cannabinoids including metabolism and for potential drug-drug interactions?

In this section, warfarin is mentioned as a potent CYP 3A4 inhibitor when in fact it has little or no influence on 3A4. Rather, the cited article points to a possible interaction between cannabidiol (CBD) in its "therapeutic" form and warfarin. This anecdotal reaction is caused by cannabidiol's inhibitory effect on CYP 2C9, which increases warfarin's effect (1).

Cannabidiol is a substrate of the hepatic cytochrome P-450 system and several isoforms are involved in its transformation (CYP 3A4 and CYP 2C19 predominantly and CYP1A1, CYP1A2, CYP2C9, CYP2D6, CYP3A5 secondarily) (1-7). Cannabidiol is also an important metabolic inhibitor of several CYPs and may even auto-inhibit its own metabolism. Therapeutic doses of isolated CBD may therefore influence the elimination of other drugs administered concomitantly. Furthermore, the sequence in which drugs are initiated can also influence the outcome (adding cannabis to an existing drug regimen versus adding a drug to a stable dose of cannabis). However, in clinical practice, one must keep in mind that drug interactions are complex mechanisms that do not necessarily produce serious clinical consequences for the patient even if the interaction is considered pharmacologically significant (1,4). According to the current state of knowledge, this is probably the case with cannabinoids, at least and when using smaller dose ranges that are generally recommended in most clinical conditions.

Furthermore, many factors influence serum concentrations of a particular drug, including CYP activities and their genetic polymorphisms, epigenetic changes, and other exogenous factors. These factors influence the metabolic activity of CYP substantially and are a major source of variability in pharmacokinetics and in the response of individuals to drugs (2,4,5). Also, there is a known discrepancy in the literature between drug interactions resulting from direct experimental observations and those found after systemic drug administration in individuals. While some preclinical studies have shown clear effects by direct interaction, the same substances do not necessarily produce a notable effect after systemic administration.

Exposure time is another factor affecting the results of interaction studies. After repeated drug exposures, plasma and

tissue concentrations rise to higher levels than after a single dose. It has also been observed that reciprocal exchanges occur between cannabinoids and cannabinoid receptors, which could lead to changes in signaling and regulatory mechanisms of hepatic cytochromes (5,6). Although much has been observed over the last 30 years concerning the effects and metabolic fate of cannabinoids, many questions remain unanswered.

Inter-species differences in CYP systems create an important barrier for evaluating interactions in clinical settings. Data can be obtained from animals, *in vitro*, *in vivo*, *ex vivo*, after a single or multiple doses. This makes for a complex risk evaluation with every individual patient. However, results from most preclinical studies on drug interactions with delta-9 THC and CBD match their corresponding *in vitro* experiments. Consequently, cannabinoids are now generally regarded as cytochrome inhibitors (2,4-6).

Cannabinoids have emerged as a powerful drug class for the treatment of inflammatory and autoimmune diseases due to their immunosuppressive properties. Significant clinical and experimental data on their use as anti-inflammatory agents exist in many autoimmune disease settings, and some interesting studies with cannabidiol are underway, evaluating their potential role in transplant rejection (current clinical trials, phase II studies). Clinicians must, therefore, be very cautious as cannabidiol, a potent inhibitor of CYP 3A4 (and P-glycoprotein inhibitor—*in vitro* and *in vivo* studies) may very well impact on cyclosporine and tacrolimus metabolism (8-10).

The distinction between cannabis in its smoked form versus oral form also needs to be pointed out. The potential interactions with cannabis smoke are similar to those for tobacco, which implies a possible interaction with CYP 1A2. Polycyclic aromatic hydrocarbons are probably to blame for this effect (2,3,6). Clozapine, duloxetine and theophylline are examples of substrates that could undergo induction interaction and thus lose their effectiveness if the patient is a persistent smoker (monitor consumption ≥2 joints/week) (4).

In summary, there is currently little evidence-based data on how to manage the use of cannabis with other drugs. For the time being, frail patients or those with polypharmacy issues should be advised that delta-9 THC and cannabidiol may result in drug interactions that may impact the efficacy and safety of their other medications.

Challenge 8: what is considered a safe approach for dose initiation and titration

Again, we would like to clarify and modulate our statement on the concept of the lethal dose of cannabis. This issue remains very controversial, as cannabis has a historically wide margin of safety (11). For obvious ethical reasons, we do not have experimental studies to determine the lethal dose in humans and the few reported cases of fatalities with cannabis use often involve individuals who have used the inhaled form and suffered from multiple comorbidities, including cardiovascular conditions (11). Recently, however, the unexpected deaths of two otherwise healthy young men prompted Hartung *et al.* to suggest that smoked cannabis may have caused fatal cardiovascular complications. However, the blood levels of THC in these individuals were considered to be in the low range, which suggests that the cause of death would less likely be caused by an overdose of THC.

Animal studies as well as clinical studies conducted with approved cannabinoid drugs reveal a low risk of toxicity. Indeed, the virtual absence of CB receptors in the respiratory center in the brainstem explains this safety margin. This data is reassuring when using cannabis at therapeutic doses and with standardized formulations used for medical purposes. However, when side effects are considered, the risk assessment for cannabis and drugs of abuse is often poorly characterized (anecdotal cases, subjective impressions, animal studies) as opposed to data obtained for registered drugs or other consumer products. Thus, the most important pitfall in our knowledge with substances of abuse (including cannabis), is the lack of dose-response toxicology data in humans (12).

Consequently, the lethal half dose (LD50) for THC in humans which has been estimated to be around 30 mg/kg, remains under scrutiny (13). If this were truly the case, however, we must take caution with the rapid emergence of concentrated THC extracts known as “wax”, “dabs”, or “butane hash oil” which can contain up to 80% THC; one tenth of an ounce of these products can contain 2000 mg of THC (13). Lachenmeier *et al.* reported another method for comparative risk assessment of drugs using the margin of exposure (MOE) approach. The MOE is defined as the ratio between the toxicological threshold (benchmark dose) and estimated human intake. Median lethal dose values from animal experiments were used to derive the benchmark dose. Human intake was calculated for individual scenarios and population-based scenarios, with cannabis having an estimated MOE >10,000 (12).

Finally, we recommend that clinicians remain aware that, in contrast with regulated medical cannabis and synthetic

cannabinoids approved by the pharmaceutical industry, there exists a parallel market providing untested medical cannabis products that may produce unpredictable effects. This is especially the case for untested CBD-only products that have actually been shown to contain varying amounts of THC. Furthermore, when using supraphysiologic doses of therapeutic cannabis products, the endocannabinoid system may become overloaded that can provoke hazardous side effects, including acute psychosis, anxiety attacks, hypotension and even syncope and falls. The recent arrival of pure synthetic cannabinoid agonists (K2, Spice) are up to 100 times more powerful than natural THC and much more harmful than cannabis even at smaller doses. They are often consumed by youth to foil drug testing or because they are perceived to be harmless derivatives of a natural product. Thousands of cases of acute toxicity are reported annually with these unregulated products (12,14).

We regret the error and any inconvenience it might have caused.

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